EARTHJUSTICE
BECAUSE THE EARTH NEEDS A GOOD LAWYER

November 16, 2026

SUBMITTED VIA EMAIL

Assistant Administrator Douglas Troutman
Troutman.douglas@epa.gov
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, DC 20460

Re: Unsealed records requiring submission under FIFRA § 6(a)(2) and relevant to EPA's registration review decision on paraquat, Docket No. EPA-HQ-OPP-2011-0855

Dear Assistant Administrator Troutman:

On behalf of Alianza Nacional De Campesinas, California Rural Legal Assistance Foundation, Center for Biological Diversity, Farmworker Association of Florida, Inc., Farmworker Justice, Pesticide Action and Agroecology Network, and Toxic Free North Carolina, we write to supplement Earthjustice's August 4, 2023, letter (Docket No. EPA-HQ-OPP-2011-0855-0313), concerning adverse information about paraquat disclosed in multi-district litigation (MDL) against Syngenta and Chevron regarding paraquat's connection to Parkinson's Disease. In that letter, we noted that the sealed records in *Hoffmann et al. v. Syngenta Crop Prot. LLC*, No. 17-L-517 (Ill. Cir. Ct., 20th Jud. Cir.)—later centralized into the federal MDL, *In re: Paraquat Products Liability Litigation* (MDL No. 3004)—indicated the existence of potentially relevant documents concerning adverse effects information that is reportable under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) § 6(a)(2), 7 U.S.C. § 136d(a)(2). Recent reporting has made many sealed records from a separate MDL in Pennsylvania state court—*In re: Paraquat Products Litigation,* Master Docket / Case ID: No. 220500559—public.[1] Consistent with the concerns we shared in our letter, these documents contain important information relevant to paraquat's neurological toxicity and its connection to Parkinson's Disease, both of which are considerations before EPA as it undergoes registration review for paraquat. In these materials, Syngenta admits that it has no record of submitting several reportable materials to EPA under § 6(a)(2).

After our August 2023 letter, EPA sent a request to paraquat registrants to submit outstanding reportable information or certify compliance within 60 days on December 8, 2023. Docket No. EPA-HQ-OPP-2011-0855-0319. EPA's February 14, 2024, memorandum stated that all nineteen active registrants, including Syngenta Crop Protection LLC, confirmed full compliance and had no new information to report. Docket No. EPA-HQ-OPP-2011-0855-0325. However, Syngenta's January 24, 2025, amended admissions in the state court MDL, taken

[1] *See Syngenta's Secrets – What the company didn't tell the EPA about its "blockbuster" paraquat pesticide*, THE NEW LEDE, Sept. 21, 2026, https://www.thenewlede.org/2026/09/syngentas-secrets-paraquat-pesticide/.

together with deposition transcripts and other discovery materials, now bring that assurance into question. *See* Attachments A-F.

As explained below, we request EPA take three actions. First, EPA must evaluate the information from these materials together with paraquat's full epidemiological and toxicological record, including research that has been published since EPA's 2021 registration review decision, to determine whether paraquat continues to satisfy FIFRA's registration standard. 7 U.S.C. § 136a(c)(5), (g). Second, EPA must require Syngenta to submit the identified information and reconcile its admissions with its previously reported assurance of § 6(a)(2) compliance in December 2023 and assess any penalties accordingly. Third, the revealed records show that a document-by-document response from EPA and Syngenta is warranted, not just another general assurance of § 6(a)(2) compliance. We therefore request that EPA direct Syngenta to submit all relevant MDL materials and that EPA post the materials on the paraquat regulations.gov docket in advance of its stakeholder paraquat roundtable, with redactions if necessary, so that the public can access the information informing EPA's critical paraquat registration review decision.

I. The newly available Syngenta documents reflect a registrant pattern to deceive regulators and the public about the dangers of their products and is enabled by EPA's loose § 6(a)(2) enforcement.

The newly available Syngenta documents highlight the need for EPA to be vigilant in monitoring and enforcing § 6(a)(2) compliance. They reveal the same modus operandi followed by Monsanto in connection with Roundup, where litigation documented analogous conduct to conceal adverse effects information from EPA. For example, both Syngenta and Monsanto embarked on what they called "Freedom to Operate" campaigns in which they tried to control and manipulate the information made available to government agencies regulating their products.[2] The pervasiveness of this practice is reflected in their use of the same terminology to describe their advocacy campaigns.[3]

Further, both companies embarked on concerted campaigns to disparage and downplay adverse studies. For example, to counter independent studies containing information on paraquat's adverse effects, both companies contracted scientists who would let the company surreptitiously exercise editorial control.[4] Both companies then used these science-for-hire favorable studies to influence EPA and other regulators.[5] In fact, a published study tracked the influence of a Monsanto ghost-written article on glyphosate—the active ingredient in

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[2] *See Syngenta's Secrets – What the company didn't tell the EPA about its "blockbuster" paraquat pesticide*, THE NEW LEDE, Sept. 21, 2026, at https://www.thenewlede.org/2026/09/syngentas-secrets-paraquat-pesticide/; *Science journal retracts study on safety of Monsanto's Roundup: 'Serious ethical concerns': Paper published in 2000 found glyphosate was not harmful, while internal emails later revealed company's influence*, THE GUARDIAN, Dec. 5, 2025, https://www.theguardian.com/us-news/2025/dec/05/monsanto-roundup-safety-study-retracted.

[3] *Id*.

[4] *Id.*

[5] *Id*.

Roundup—and found it among the most cited glyphosate studies in government policy documents, Wikipedia, and academic publications over a period of 25 years, even after Monsanto's role in ghost-writing the paper had been revealed.[6] Even though the journal that issued the study retracted it upon finding it was ghost-written, the study's influence has permeated regulatory decisions for decades.[7] That is, even if a regulator like EPA expressly disavows reliance on a ghost-written article, or the journal retracts it, the article may have shaped other studies before the agency, extending its influence far beyond the specific article. In light of such misleading registrant behavior, EPA must take affirmative steps to ensure registrant compliance with § 6(a)(2).

II. EPA must evaluate the complete universe of information before its paraquat registration review decision.

EPA's registration review responsibility is independent of its determination on whether Syngenta complied with § 6(a)(2). Under 40 C.F.R. § 155.53(a), EPA must consider whether new data or information warrant a new risk or risk-benefit assessment or further review of registrations as it determines whether paraquat continues to satisfy FIFRA's registration standard. *Id*.; 7 U.S.C. § 136a(c)(5), (g). The records discussed below address critical aspects of paraquat's risks: paraquat's ability to reach and persist in the brain, adverse effects on dopaminergic neurons, occupational exposure associated with Parkinson's Disease, a foreign regulator's adverse assessment, and measured exposure during agricultural use. After its review of these materials, EPA should explain whether these materials change its assessment of the paraquat–Parkinson's Disease relationship, the assumptions used to estimate occupational exposure, the adequacy of protective equipment and other label restrictions, or its assessment of remaining uncertainty. Because the records identified below are highly relevant to the question of paraquat's adverse effects, any conclusion EPA reaches on paraquat's registration review without assessing these materials will be immediately cast into doubt.

III. The state court MDL records contain several pieces of information related to adverse effects from paraquat that Syngenta has no record of submitting to EPA as required under § 6(a)(2).

FIFRA § 6(a)(2) imposes a continuing obligation on registrants to submit "additional factual information" regarding a pesticide's unreasonable adverse effects on the environment. 7 U.S.C. § 136d(a)(2). Information is reportable under § 159.195(a) when the registrant knows or reasonably should know that, if correct, it could raise EPA's concerns about continued

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[6] Alexander A. Kaurov and Naomi Oreskes, *The afterlife of a ghost-written paper: How corporate authorship shaped two decades of glyphosate safety discourse*, Environmental Science & Policy 171:104160, Sept. 2025. https://www.sciencedirect.com/science/article/pii/S1462901125001765?via%3Dihub&__cf_chl_tk=7smrkfNPhd2fiIWKFqQpmr8e46Z_2YX9vU6OjoRj_2k-1792788222-1.0.1.1-a4TII2N5jWmedKzbSj0Xoe_e_3xHPZeSUBNAHbrBg_E.

[7] *Science journal retracts study on safety of Monsanto's Roundup: 'Serious ethical concerns': Paper published in 2000 found glyphosate was not harmful, while internal emails later revealed company's influence*, THE GUARDIAN, Dec. 5, 2025, https://www.theguardian.com/us-news/2025/dec/05/monsanto-roundup-safety-study-retracted.

registration or appropriate registration conditions, alone or together with other information. The state court MDL record contains several materials that are subject to § 6(a)(2). We highlight a subset of examples below to demonstrate to EPA why it must assess whether Syngenta is in full compliance with its § 6(a)(2) obligation and initiate enforcement actions based on Syngenta's past § 6(a)(2) violations.

a. Expert reports produced before and during the MDL

Relevant opinions and conclusions from employees, retained experts, experts whose views the registrant requested, and other qualified experts are all reportable information under § 6(a)(2). 40 C.F.R. § 159.158(a). Section 159.195(a) separately requires registrants to submit information which it knows, or reasonably should know, would concern EPA about continued registration or its terms if the information were correct. 40 C.F.R. § 159.195(a). This provision expressly includes unexpected bioaccumulation and information calling a submitted study's validity into question as examples of information that must be provided. *Id.* § 159.195(a)(1),(5). As explained below, Syngenta found no records of submitting two expert materials that it commissioned: a memorandum on paraquat's movement through the brain by Dr. Ted Lock, and an internal presentation on the same topic by Dr. Joan Abbott.

i. Dr. Ted Lock's Memorandum (Attachment A)

At Syngenta's request, Dr. Lock—who Syngenta admits is a qualified expert on the transport of chemicals through the blood-brain barrier—produced an expert technical assessment about a central issue in paraquat's neurological toxicity, fitting the memorandum squarely within the purview of reportable information under § 6(a)(2). 40 C.F.R. § 159.158(a). *See* Syngenta responses to Requests for Admission (RFAs) 50–52 (Attachment C). Dr. Lock's memorandum, "*How does the herbicide paraquat enter the brain?*" (December 21, 2007), found that paraquat can enter dopaminergic neurons in the substantia nigra of C57BL/6 mice at concentrations sufficient to cause cell death. *See* RFA 52.

Here, sections 159.158(a) and 159.195(a) reach expert evaluations that could alter EPA's understanding of a pesticide's risks, including Dr. Lock's memorandum. Notably, EPA's *Systematic Review of the Literature to Evaluate the Relationship Between Paraquat Dichloride Exposure and Parkinson's Disease* cited an earlier study, co-authored by Dr. Lock, that "described the rat [blood brain barrier] as an effective impediment to paraquat entry into the brain."[8] Dr. Lock's subsequent work, which Syngenta improperly withheld from EPA, contradicts that finding and confirms that paraquat does cross the blood brain barrier. The circulation of paraquat within the body and brain is a central issue in EPA's analysis of paraquat's neurological toxicity. Dr. Lock's findings examining paraquat entry into and death of dopaminergic neurons would therefore broaden EPA's understanding of paraquat's risks. Yet Syngenta states it could find no record of submitting the memorandum to EPA under § 6(a)(2). RFA 55. Instead, Syngenta defends its decision by citing Dr. Lock's later uncertainty about experimental artifacts and the maturity of the blood-brain barriers in the studies/animals. RFA 52. But Dr. Lock's later uncertainty on his own findings does not justify withholding data or

[8] *Systematic Review of the Literature to Evaluate the Relationship Between Paraquat Dichloride Exposure and Parkinson's Disease* at 57 (June 26, 2019).

information that is otherwise required to be reported. Rather, Dr. Lock's initial adverse assessment in his memorandum and any findings indicating later uncertainty are materials that belong coupled before EPA.

Accordingly, EPA should obtain Dr. Lock's memorandum, its references, and, if Syngenta invokes section 159.158(b)(1)'s "clearly erroneous" exception to evade reporting this memo given Dr. Lock's later disagreement, Dr. Lock's written correction as required by section 159.158(b)(1)(ii).

ii. Dr. Joan Abbott's internal presentation (Attachment B)

Syngenta invited Dr. Joan Abbott—also an expert on the transport of chemicals through the blood-brain barrier—to present her findings on paraquat's slow brain clearance and potential long-term toxicity on April 20, 2009. RFA 58; *see generally* RFAs 56–61. Based on her literature review, Dr. Abbott concluded that very slow paraquat clearance from the rodent brain suggested intracellular sequestration in the central nervous system and potential long-term toxicity. RFA 60. She also shared concerns about carrier-mediated uptake combined with slow clearance. RFA 61.

Brain uptake, persistence, and possible long-term toxicity bear directly on whether repeated paraquat exposure can produce neurological harm. Dr. Abbott's presentation therefore fits within the reporting requirements of §§ 159.158(a) and 159.195(a) as it covers unexpected bioaccumulation and information suggesting a greater risk than EPA previously believed. Yet, here again, Syngenta admits it has no record of submitting the presentation as part of its § 6(a)(2) obligations. RFA 62. Syngenta's admissions suggest it did not report Dr. Abbott's presentation as Dr. Abbott relied on public literature and a contrary 2013 study and requested further studies. RFAs 60-61. But none of those statements establish that Dr. Abbott's adverse assessment was exempt under § 6(a)(2) when Syngenta received it. In fact, the exception for published literature only covers specified publications and recognized scientific database abstracts; it is not a blanket exception for an unpublished retained-expert evaluation merely because the expert referenced published information. 40 C.F.R. § 159.158(b)(3). Therefore, EPA should obtain the full presentation and any explanatory materials and determine whether the complete reportable information was available to Syngenta and not submitted under the applicable timeline in 40 C.F.R. § 159.155(a).

b. <u>Operator exposure studies and detailed worker incident reports</u>

Registrants are required to submit studies of the toxicity of a pesticide if the studies present adverse effects different from or greater than those reflected in information previously submitted to EPA, including "effects at a lower dose, after shorter exposure, at greater frequency, or in a different species or exposure route." 40 C.F.R. § 159.165(a)(1)(i)-(v). Additionally, § 159.170 requires registrants to submit information about human studies supporting a possible correlation between pesticide exposure and adverse effects, regardless of the registrant's view of the association's significance. This provision further requires registrants to submit exposure monitoring studies that indicate higher risk or exposure than previously known by EPA. *Id*. Lastly, § 159.184 governs pesticide incident reports, including severity categories, information requirements, accumulation periods and aggregate reporting. *Id*. § 159.184. This provision requires registrants to submit pesticide incident information where the registrant is aware of the

exposure, the present or potential adverse effect, and could obtain details about the incident, such as location, pesticide, and a named contact regarding the incident. *Id*. § 159.184(a)(1)–(3).

Syngenta's admissions show it had multiple operator exposure studies demonstrating valuable adverse effects information that it has no record of submitting under § 6(a)(2). RFA 121. One set of authors produced multiple operator exposure reports that are especially crucial for EPA to have as they are collectively considered the "most modern, guidance-compliant studies available and are the ones of choice for assessment of absorbed dose for risk assessment purposes under the specific conditions of habitual use." Botham Dep. Tr. at 319:6–10 (Attachment D). For example, in one biomonitoring report titled "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following repeated days' habitual use in vines. TNO Report V6420/02. 15th May 2007b[,]" researchers measured excreted paraquat in operators after repeated days of habitual use of Formulation R-Bix (A9409AL) in vines in France. *Id*; *see also* Dixon Dep. Tr. 224:12–15 (Attachment E). The report showed two workers with exposures exceeding the European Acceptable Operator Exposure Level (AOEL) "by 116 and 780 percent[.]" Dixon Dep. Tr. at 212:5–212:8; *Id.* at 210:21–214:14; RFA 124. Yet Syngenta admitted that it only submitted a "very brief" aggregated summary of the study's findings and failed to provide EPA with additional information like the operators' specific exposure levels. RFA 124; Dixon Dep. Tr. at 218:19–21; 222:12–223:21. But an aggregate incident entry fails to communicate measured internal doses, application conditions, or the implications of unexpectedly high exposures. These records show that while Syngenta submitted a categorized incident entry to satisfy § 159.184, Syngenta did *not* satisfy the independent monitoring study submission obligation in § 159.165(a). And though the European AOEL is not itself a U.S. legal limit, Syngenta should have submitted the exposure incident details, including specific exceedances, so that EPA could compare that information with the information it relies upon in its registration review decision.

In another example, the same authors published a subsequent report titled "Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following a single day's habitual use in bananas. TNO Report V6420/04. 16th August 2007c." RFAs 125, 128. This study measured excreted paraquat in workers after a single day's habitual use in bananas in Martinique and found the operators measured exposures exceeding the European AOEL yet again. Dixon Dep. Tr. 224:5–224:11; RFA 128. Here, again, Syngenta could not confirm that it submitted this report, nor the worker exposure levels as part of its § 6(a)(2) obligations. RFA 128. Lastly, the same authors produced "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following three consecutive days' use in bananas with PPE according to label recommendation. TNO Report V6420/06. 6th September 2007a" in which a worker showed paraquat excretion for *four days* post application. Botham Dep. Tr. at 316:22–317:4. Consistent with the other reports, Syngenta could not confirm that it submitted this report as part of its § 6(a)(2) reporting requirements either. RFA 135.

EPA has stated that "in evaluating human health, EPA looks first for information directly evaluating the potential for effects to people, including epidemiological data."[9] EPA "uses

[9] EPA Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides at 3 (Dec. 28, 2016).

incident data to inform risk assessment/risk management activities," which "forms an integral part of our registration review activities."[10] There is thus no question that reports of paraquat exposure and excretion in exposed workers is relevant to EPA's analysis of paraquat's health risks. And the above studies are just a few examples of several studies and reports uncovered in the state court MDL materials. EPA should confirm it has them in addition to the following worker exposure reports and studies in its possession, and if not, acquire and review them, and determine whether Syngenta timely complied with its § 6(a)(2) reporting obligations:

- "Brouwer, D.H. and Roussel, C.-H. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following a single day's habitual use in vines. TNO Report V6420/01. 15th May 2007" RFA 118.
- "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following three consecutive days' habitual use in bananas. TNO Report V6420/05. 29th August 2007d" RFA 129.
- "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following a single day's habitual use in lucerne. TNO Report V6420/03. 11th June 2007e" RFA 132.

i. Syngenta's internal compilation of operator exposure studies

The Brouwer studies are part of a compilation of 22 studies gathered by Syngenta employees Graham Chester and Andy Cook in December 2009 titled "Paraquat Operator Exposure - A review of operator exposure studies." RFA 150; Botham Dep. Tr. at 312:8–317:9. The compilation and its underlying factual information are reportable information. 40 C.F.R. § 159.152(a). And because the compilation not only contains information about paraquat operator exposure effects, but also information on paraquat's fate and transport through the body, Syngenta should have submitted this information to EPA under 40 C.F.R. § 159.170. Yet Syngenta has no record of submitting this compilation to EPA despite the compilation containing materials that are highly relevant to EPA's assessments of paraquat's risks. RFA 150. For example, one study in the compilation titled "Report No. WER-006: Findlay, et al. PARAQUAT: WORKER EXPOSURE DURING APPLICATION OF GAMOXONE WITH A CONTROLLED DROPLET APPLICATION (CDA) MICRON 'HANDY' SPRAYER" showed paraquat in urine samples from 18 out of 20 workers following label-recommended PPE (protective gloves and face shield) when mixing and loading. *See* Botham Dep. Tr. at 314:16–315:15.

It is unclear whether the compilation includes other reports that have surfaced through the MDLs. These reports include:

- "REPORT NO: CTL/P/1467 PARAQUAT: PENETRATION THROUGH PROTECTIVE CLOTHING MATERIALS FROM A MALAYSIAN 'GRAMOXONE' FORMULATION" RFA 138.
- "REPORT NO: CTL/L/168O PARAQUAT: ABSORPTION THROUGH WELLINGTON AND TROOPER BOOT FROM GRAMOXONE" RFA 141.

[10] *Id.* at 37.

Accordingly, EPA must obtain this compilation, review every report and study in it and ensure it has them in its possession, and assess whether Syngenta timely complied with its § 6(a)(2) obligations regarding this compilation.

c. International regulatory findings

EPA guidance provides that "Information derived from studies or incidents occurring outside the United States is reportable if the information is relevant to a pesticide registration held by the registrant possessing the information and if the information is otherwise reportable under section 6(a)(2)."[11] Further, EPA considers all reportable information from outside the U.S. "to be reportable unless an expert concludes that differences between the formulation of product involved in the foreign information and product registered in the United States make the information irrelevant to the product registered in the United States."[12]

i. ANVISA Technical Reassessment Opinion No. 08 (Attachment F)

The Brazilian Health Regulatory Agency ("ANVISA") issued a series of technical assessments assessing the link between Parkinson's Disease and paraquat. These assessments address the same active ingredient and linkage at issue in EPA's registration review decision and contain precisely the kind of information that could raise concerns about continued registration under 40 C.F.R. § 159.195(a). Syngenta's admissions confirm that ANVISA's evaluation in its "Technical Reassessment Opinion No. 08/GGTOX/Anvisa (June 13, 2016)" raised concerns about potential mutagenic and neurotoxic effects, acute toxicity, and a missing antidote. RFA 204. In its Technical Reassessment Opinion No. 08, ANVISA concluded that "based on the currently-available [] strong weight of evidence (animal studies and epidemiological studies) indicating that Paraquat is associated to the triggering of Parkinson's Disease in humans." Dixon Dep. Tr. at 324:1–9. Yet Syngenta has no record of submitting this key technical assessment nor the other ANVISA assessments as part of its § 6(a)(2) obligation. RFA 109. *See also* Dixon Dep. Tr. 320:4–321:21; 322:6–9; 324:9–12; and 325:15–22 (explaining that Mr. Dixon received an English version of the report before a February 2017 meeting with EPA but did not believe it had ever been submitted.).

Because ANVISA's findings pertain to adverse effects from paraquat exposure, they constitute reportable information under § 6(a)(2) and § 159.195(a) and are relevant to EPA's determinations during registration review. Accordingly, EPA should obtain not only ANVISA Technical Reassessment Opinion No. 08, but all other ANVISA assessments uncovered in the MDL records:

- ANVISA "TECHNICAL REASSESSMENT OPINION NO. 01 of 2015/GGTOX/Anvisa Analysis of the technical reassessment note of the active ingredient paraquat elaborated by Fiocruz" RFA 106.

[11] U.S. EPA, Pesticide Registration Notice 98-3, *Notice to Manufacturers, Formulators, Producers, Distributors, and Registrants of Pesticide Products* (Apr. 3, 1998), https://www.epa.gov/sites/default/files/2014-04/documents/pr98-3.pdf, at 13.
[12] *Id*.

- ANVISA "REASSESSMENT TECHNICAL OPINION No.13/CREAV/GEPOS/GGTOX/ANVISA — version 2, dated January 5th, 2017." RFA 113.

ii. Mexican Social Security Institute Parkinson's Disease determination for former employee of Syngenta

Section 159.184(a) requires registrants to submit information about possible pesticide exposure and a present or potential adverse effect when the registrant has or could obtain the basic incident identifiers. 40 C.F.R. § 159.184(a). Physicians at the Mexican Social Security Institute (IMSS) concluded that a former Syngenta employee, Alberto Grimaldo Orozco, developed Parkinson's Disease from occupational exposure to paraquat. RFA 47. In 2009, the IMSS issued a report concluding that Mr. Orozco's occupational inhalation and dermal exposure to paraquat was broadly associated with Parkinson's Disease and warranted an occupational-disease determination. RFAs 43–47. Yet, despite admitting that it received the diagnosis from the IMSS, Syngenta has no evidence of submitting the IMSS conclusion about Mr. Orozco to EPA. RFAs 48–49. *See also* Dixon Dep. Tr. at 344:12–16, 346:5–14.

Mr. Orozco's diagnosis was reportable information under 40 C.F.R. § 159.184(a)(1)–(3) because: Syngenta was made aware after it received the IMSS report (*id.* § 159.184(a)(1)); Mr. Orozco had developed Parkinson's Disease (*id.* § 159.184(a)(2)); and Syngenta could have easily obtained identification information on its former employee (*id.* § 159.184(a)(3)). While Syngenta disputes the scientific support and details of the finding, such questions do not alleviate Syngenta's reporting obligations under § 6(a)(2). Indeed, EPA's guidance on "extraterritorial adverse effect information," includes incidents and provides that if a registrant questions whether it needs to report information, the "registrant can inquire from the 6(a)(2) Officer whether particular information should be reported."[13] Accordingly, EPA must obtain Mr. Orozco's diagnosis, incident details, and assess the paraquat product's relevance to U.S. registration formulations, and whether Syngenta should have reported the incident to EPA under § 6(a)(2).

d. Specific information on paraquat's linkage to Parkinson's Disease

Under 40 C.F.R. § 159.195(a)(5), registrants must submit "*Any* information which might tend to invalidate a study submitted to [EPA] to support a pesticide registration." (Emphasis added.) In the past, EPA has dismissed inhalation as an exposure pathway with neurological effects, but the MDL contains records that support EPA reconsidering its position, and that Syngenta has no record of submitting under its § 6(a)(2) duty. For example, as we stated in comments to EPA's supplemental analysis on paraquat's registration review decision, multiple studies support finding inhalation as an exposure pathway with results affecting the brain.[14]

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[13] U.S. EPA, Pesticide Registration Notice 98-3, *Notice to Manufacturers, Formulators, Producers, Distributors, and Registrants of Pesticide Products* (Apr. 3, 1998), https://www.epa.gov/sites/default/files/2014-04/documents/pr98-3.pdf, at 13.

[14] *See* California Rural Legal Assistance Foundation et al., Comments on EPA's Preliminary Supplemental Consideration of Certain Issues in Support of Its Interim Registration Review Decision for Paraquat, Docket No. EPA-HQ-OPP-2011-0855, https://www.regulations.gov/comment/EPA-HQ-OPP-2011-0855-0537 at 18.

MDL materials reveal there is additional support for assessing inhalation as an exposure pathway that can result in adverse effects, and EPA should therefore acquire the following studies and reports:

- Joanne Kilgour, "CTL/HR2357/SUMMARY/REPORT PARAQUAT 200G/L SPRAY STRENGTH SOLUTION: PRELIMINARY INVESTIGATIONS OF THE 4-HOUR ACUTE INHALATION TOXICITY IN THE RAT" RFA 156–161; *see also* Botham Dep. Tr. at 185–213; 189:21–193:7; 195:21–196:5 (stating Syngenta's internal § 6(a)(2) referral committee considered submitting this "unusual finding" to EPA but decided against it).
- "CTL/JV1806/REPORT: PHASE SEPARATED GRAMOXONE (A14380A): PREDICTION OF ACUTE SKIN IRRITATION USING THE INTEGRITY FUNCTION TEST" RFA 86.
- "CTL/R/1463 XENOBIOTICS LINKED TO PARKINSON'S DISEASE" RFA 89.

Additional state court MDL materials also appear helpful to EPA in assessing paraquat's association with Parkinson's Disease, but Syngenta likewise admits it has no submission records for these materials:

- "PRODUCT SAFETY TECHNICAL EVALUATION: Claimed links Between Exposure to Paraquat and Development of Parkinson's Disease – A Consideration of the Potential Implications for Reference Doses Draft: September 2009" RFA 92.
- "Paraquat SL (A3879EX) Acute Toxicity in Beagle Dogs with Toxicokinetic Analysis - Contemporary Control Study" RFA 165; Dixon Dep. Tr. 255:9–12; *see also* Dixon Dep. Tr. at 253:1–256:7 (explaining why this study required "unexpected" euthanization of subject dogs after exposure to paraquat).

EPA should thus obtain and review the studies and reports discussed above and determine whether Syngenta acted in accordance with § 6(a)(2)'s reporting requirements.

IV. The available information more than justifies the cancellation of paraquat's registrations.

Syngenta's failure to provide the materials it should have under FIFRA's reporting requirements does not excuse EPA's failure to act upon the information that it already has. In particular, FIFRA authorizes EPA to initiate pesticide cancellation if a pesticide "generally causes unreasonable adverse effects" "when used in accordance with widespread and commonly recognized practice." 7 U.S.C. § 136d(b). EPA has more than enough information to make that finding and to ban paraquat, as more than 70 other countries—including China, India, Brazil, and the members of the European Union— and multiple states have already done.[15]

[15] PIRG, *This toxic herbicide is banned in 70 countries, but still legal in America* (Dec. 19, 2024), https://pirg.org/articles/this-toxic-pesticide-is-banned-in-70-countries-but-still-legal-in-america/; Suchetana Choudhury, "India proposes nationwide ban on Paraquat Dichloride, marking watershed shift in crop protection policy" (Jul. 15, 2026), https://agrospectrumindia.com/news/8/34439/india-proposes-nationwide-ban-on-paraquat-dichloride-marking-watershed-shift-in-crop-protection-policy.html.

Even without the undisclosed Syngenta studies and reports, "[a] plethora of studies have shown that exposure to paraquat is correlated positively with [Parkinson's disease] in humans."[16] Epidemiological studies have found that people who apply paraquat, who work in the fields where paraquat is sprayed, or who live near those fields experience increased rates of Parkinson's disease.[17] Laboratory animals exposed to paraquat experience trembling, motor defects, and other hallmarks of Parkinson's disease.[18] In vitro and animal studies explain the biological mechanisms underlying this connection. Paraquat causes oxidative stress in cells, resulting in degradation of neurons that produce dopamine, a neurotransmitter that regulates movement and balance. Parkinson's disease is characterized by a loss of dopamine producing neurons.[19]

Paraquat is also associated with a range of other harms, from thyroid cancer and Non-Hodgkin Lymphoma to respiratory distress and kidney disease. In its 2021 registration review decision, EPA found that, even after accounting for all required mitigation, paraquat still threatens the health of farmworkers. Since then, the evidence of paraquat's unreasonable risks has only continued to mount. While EPA must enforce § 6(a)(2)'s reporting requirements, the available information is more than sufficient to establish paraquat's unreasonable risk and, in the absence of voluntary cancellations, to begin long overdue cancellation proceedings.

V. Conclusion

As we stated in our August 2023 letter, EPA must have this information before it during registration review, otherwise, any determination it makes will be flawed from the outset. This time, however, EPA cannot merely request § 6(a)(2) compliance confirmation from registrants and take that at face value. Syngenta's previous compliance assurance in particular is problematic because at the time of its assurance, the records here show that Syngenta did indeed have reportable information arising out of litigation that it had not submitted to EPA. These concerns are substantiated by ethics expert reports in the MDL that highlight Syngenta's questionable compliance practices.[20] The inconsistency between Syngenta's previous assurance and the state court MDL records warrants imposing penalties for withholding § 6(a)(2) required information, as EPA has done before.[21] Accordingly, we request that EPA:

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[16] Luciana Anselmi et al., *Ingestion of Subthreshold Doses of Environmental Toxins Induces Ascending Parkinsonism in the Rat*, 4 NPJ Parkinson's Disease Art. No. 30, at 5 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6160447/pdf/41531_2018_Article_66.pdf.
[17] California Rural Legal Assistance Foundation et al., Comments on EPA's Preliminary Supplemental Consideration of Certain Issues in Support of Its Interim Registration Review Decision for Paraquat at 9.
[18] *Id.*
[19] *Id.*
[20] *See* Expert Report of Timothy L. Fort, JD, PhD, https://www.thenewlede.org/wp-content/uploads/2026/09/E187-2024-EXPERT-REPORT-OF-TIMOTHY-L.-FORT.pdf at 7.
[21] *See,* e.g., Consent Agreement In the Matter Of E. I. du Pont de Nemours and Company and U.S. EPA, FIFRA Docket No. FIFRA-03-2014-0217 (Sept. 15, 2014), https://www.epa.gov/sites/default/files/2014-09/documents/dupontimprelis-cafo.pdf; and Consent Agreement In re: Makhteshim Agan of North America Inc., d/b/a ADAMA, FIFRA

- Require Syngenta to produce the relevant adverse effects information disclosed in litigation pursuant to § 159.195(c), including Dr. Ted Lock's memorandum; Dr. Joan Abbott's presentation; the IMSS diagnostic, report, and resolution; the ANVISA technical assessments, and any other unreported information relevant to paraquat's adverse effects, including any underlying information EPA needs to evaluate these materials;
- Investigate whether a § 6(a)(2) penalty is warranted in this instance. For each record Syngenta submits, EPA should determine the date Syngenta first possessed the reportable information, the relevant registration, any claimed reporting exception and supporting facts, and assess whether Syngenta violated its § 6(a)(2) obligations;
- Evaluate the complete information before issuing its next registration review determination; and
- Place this letter and its attachments in the paraquat registration review docket so that it is publicly available and do so in advance of the paraquat roundtable.

Please provide a written response within 60 days describing EPA's actions to secure the identified information, its findings concerning prior submissions or lack thereof under § 6(a)(2), and how it will incorporate these materials into paraquat's registration review. EPA must ensure that its registration review decision rests on a complete and critically evaluated record.

Respectfully submitted,

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Docket No. FIFRA-HQ-2016-5006 (May 5, 2016), https://www.epa.gov/sites/default/files/2017-03/documents/adama-cafo.pdf.

ATTACHMENT A

How does the herbicide paraquat enter the brain?

Paraquat (1,1'-dimethyl- 4,4'-bipyrilium) is an organic di-cation at physiological pH and will not readily cross cell membranes. However, paraquat has been shown to concentrate in lung cells, where it enters via a polyamine transport system and in kidney cells where it undergoes active transport via an organic cation transport system. These transport systems are not species specific have been observed in experimental animals such as rats, mice, dogs and monkeys as well as in humans.

Recent studies have demonstrated paraquat entry into the brain of a particular strain of mouse C57Bl6 where it causes selective injury to dopaminergic neurones in the substantia nigra as judged by loss of neurotransmitter, reduced neuronal cell counts and behavioural changes (Brooks et al., 1999; Thiruchelvam et al., 2000; McCormack et al., 2002). Surprisingly, it also has been shown that neutral amino acids such as L-valine when administered to mice at the same time as paraquat will reduce paraquat entry into the substantia nigra and prevent the neuronal cell injury (Shimizu et al., 2001; McCormack et al., 2003). While the amino acids D-valine or L-lysine had no effect. This data suggests that paraquat may enter the brain via a neutral amino acid transport system, which is very surprising and currently cannot be rationalised, although in time an explanation will no doubt be found.

What is the evidence to support the notion that paraquat enters cells via a organic cation transport (OCT) system? Three OCT's have been isolated, cloned and expressed in cells and characterised. OCT1 was first cloned by Grundemann et al., (1994) and subsequently its substrate specificity and electrogenic properties determined in rat and human kidney. OCT1 is responsible for the uptake of a wide variety of organic cations (OC) into epithelial cells such as renal tubule cells and hepatocytes. OCT-1 transports OC such as MPP^+, TEA, quinine, choline and polyamines such as spermine and spermidine, while paraquat is poorly transported. OCT1 is also expressed in murine kidney (Mori et al., 1997; Mooslehner & Allen (1999). Okuda et al., (1996) cloned, expressed and characterised a novel rat kidney OC transporter, OCT-2. OCT-2 was shown to stimulate the uptake of TEA, and this was markedly inhibited by cimetidine, procainamide and quinidine. Human homologues of OCT1 and OCT2 have also been cloned and functionally characterised (Gorboulev et al., 1997; Zhang et al., 1997), and OCT2 has been reported in murine kidney (Eraly et al., 2003). Kekuda et al (1998) then isolated a cDNA from rat placenta, which when expressed heterologously, mediates the transport of a wide spectrum of OC. This was designated OCT- 3, and found to be abundantly expressed in the placenta and moderately expressed in the intestine, heart and brain. Three other OCT members OCTN1, OCTN2 and OCTN3 have been identified. OCTN1 & 2 seems to be involved in carnitine and acetylcarnitine transport in spermatozoa (Kobayashi et al., 2007). OCTN2 has been shown to be present in brain capillary endothelial cells where it transports carnitine and acetylcarnitine into the brain (Kido et al, 2001). While, OCTN1 appears to be a more general cation transporter for a number of cationic drugs such as desipramine, dimethylamiloride, cimetidine, procainamide and is localised in rat kidney and brain (Wu et al., 2000). All three OCTN's have been detected in murine brain (Lamhonwah et al., 2007).

Recently OCT-1, 2 & 3 have been stably transfected into the human kidney epithelial cell line (HEK) and the transport of paraquat into these cells examined (Chen et al., 2007). No uptake was seen with OCT3 and very little with OCT1; the major transporter appeared to be OCT2. They demonstrated for the first time that the

di-cation paraquat is a substrate for OCT 2 with a Km of 114 ±23 μM and a Vmax of 174 ± 37pmol/min/mg protein. Consistent with these finding they showed that paraquat was more cytotoxic to HEK cell containing OCT2 (EC_{50} 23μM) compared to those with a mock transporter (EC_{50} 417μM) i.e. 18-times more sensitive.

In the kidney, OCT are located on the basolateral membrane transporting chemicals into renal tubule cells, in order for chemicals to undergo active secretion by the kidney they also need to undergo transport at the brush border membrane into the tubule lumen. This phenomenon has been observed and widely reported but the transporters involved were only relatively recently identified by Otsuka et al (2005) who reported that a human transport protein MATE1 (multidrug and toxin extrusion 1) mediated the final excretion step for organic cations. This was followed by the identification of MATE2 which appears to be present primarily in the kidney (Masuda et al., 2006). MATE 1 is present, primarily but not exclusively, in the kidney of rats, humans, rabbits and mice (Hiasa et al., 2006; Zhang et al., 2007; Kajiwara et al., 2007). Chen et al., (2007) expressed MATE1 in HEK cells and studied the transport of paraquat and showed uptake that obeyed saturation kinetics with a Km of 212 ±19 μM and a Vmax of 289 ± 46pmol/min/mg protein. As with the OCT2 cells they demonstrated that paraquat was more toxic to those cells containing MATE1 compared to those without it (EC_{50} 125μM versus 717 μM). This seminal paper thus showed that paraquat can enter cells via OCT2 and leave via MATE1.

What relevance does this have to the brain? The brain is a protected organ such that many foreign chemicals are excluded by the blood-brain barrier, which basically comprised of endothelial cells lining the blood vessels having very tight junction. However, the brain need substrates such as glucose, amino acids and neurotransmitters to function and these enter the brain by a range of transport systems located on capillary endothelial cells. There are currently 17 members of the human SL6 transporter family involved in the transport of amino acids, monoamines, GABA, osmolytes and creatine plus 10 members of the OCT and OAT (organic anion transporters). Thus foreign compound are generally excluded from the brain unless: they mimic a natural substrate e.g methylmercury-cysteine mimics methionine; are lipid soluble and can enter by diffusion or unless they enter in those regions of the brain where the blood brain barrier is leaky. These include the olfactory region, circumventricular region, area postrema and hypothalamus.

Paraquat can enter cells via OCT2 and OCT2 has been detected in the choroid plexus of the rat (Sweet et al., 2001). OCT2 & 3 are expressed in rat brain predominantly in regions located at the brain CSF fluid border, in the leptomeninges such as the choroid plexus and surrounding the ventricles. OCT3 is also located to these regions but also extends to monoaminergic pathways such as raphe nuclei, stratium and thalamus. A low level of expression was also detected in the granule cell layer of the cerebellum and in the granule layer and pyramidal cells of the hippocampus in the CA1-3 regions (Amphoux et al., 2006). OCT2 has also been detected in human brain, northern blotting showing it present in the thalamus, hippocampus, nucleus caudatus but below the limit of detection in the substantia nigra (Busch et al., 1998). In situ hybridisation with hOCT2-specific cRNA showed hybridisation in pyramidal cells of the human cerebral cortex and hippocampus (Busch et al, 1998) Functional studies indicate that in the brain OCT2 and OCT3 from rat and human appear to have a role in monoamine transport with a preference for histamine and adrenaline (Busch et al., 1998; Amphoux et al., 2006).

In summary, little information is available on OCT in the brain; however it is an area of active research and with time more detailed information will become

available. Paraquat can enter cells via an OCT2 transporter or in the case of the CSF – blood barrier leave the brain via this transporter. At the present time it is unclear how this may be linked to damage to the substantia nigra of the C57Bl6 mouse. OCT2 is present in rat, mouse and human kidney and rat and human brain but studies in mouse brain have not been reported. OCT3 has been detected in the striatum of rat brain, however Chen et al., (2007) reported that paraquat is not a substrate for this transporter. Thus the picture is far from clear. In addition, just to confuse the issue, Shimuza et al., 2001 and McCormack et al., 2003 showed that large doses of substrates for the neutral amino acid system (e.g. L-valine) could prevent paraquat entry and hence neuronal cell loss in the substantia nigra of C57Bl/6 mice, indicating a role for this transport system. Whether paraquat does indeed enter the brain via the neutral amino acid transport system is unclear and in time another explanation for this observation may be found. What is now beyond doubt is that paraquat can enter dopaminergic neurons in the substantia nigra of C57Bl6 mice in sufficient concentration to cause cell death.
OCT's appear to be fairly well conserved across mammalian species such that paraquat would be expected to undergo transport in a similar manner across species. The basis for the particular sensitivity of the C57Bl6 mouse, assuming it is a transport issue, may be due to a number of factors such as an absence of MATE1 or 2 to facilitate removal or a lower level of antioxidants to protect again the injury produced.

Dr E A Lock
20th December 2007

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Grundemann et al., (1994) *Nature* **372,** 549-552
Hiasa et al., (2006) *Am J Physiol Cell Physiol* **291,** 678-686
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Kido et al., 2001 *J Neurochem.***79,** 959-69.
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Mori et al., (1997) *FEBS Lett.***417,** 371-374
Okuda et al., (1996) *Biochem. Biophys. Res. Commun.* **224,** 500-507
Otsuka, et al., (2005) *Proc. Natl. Acad Sci USA* **102,** 17923-8
Shimizu et al., (2001) *Brain Res.* **906,** 135-142
Sweet et al., (2001) *J Biol. Chem.* **276,** 4161-9
Thiruchelvam et al., (2000) *J Neurosci.* **20,** 9207-14
Wu et al., (2000) *Biochim, Biophys. Acta* **1466,** 315-327

Case ID: 220300429

SYNG-PQ-20758520

ATTACHMENT B

CNS barriers: critical interfaces for CNS entry of paraquat

N Joan Abbott

BBB Group, King's College London

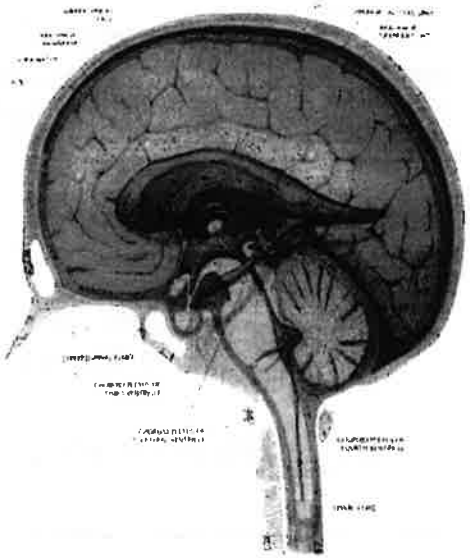


Syngenta Discussion
Marlow
20 April 2009

Botham, Philip
Exhibit_98
6/19/2020

BRAIN FLUID COMPARTMENTS

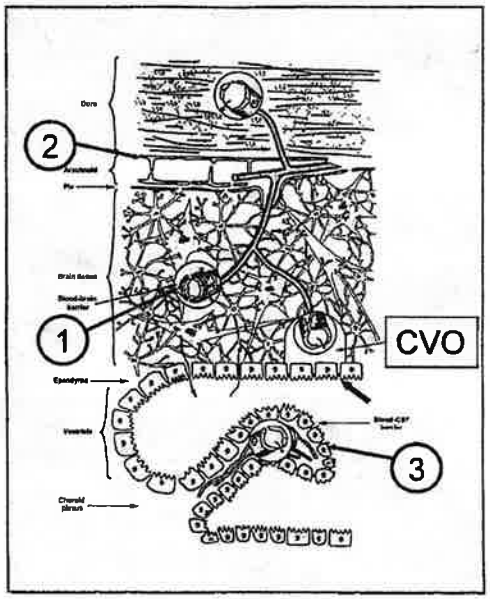
- Blood
- Cerebrospinal fluid (CSF)
- Interstitial fluid (ISF = ECF)



Spector & Johnson 1989, Scientific American

TOPICS

- CNS barriers, BBB, BSCB
- Neurovascular unit and BBB
- CNS barrier development
- Routes across brain endothelium
- CNS drug metabolism
- Regional and species differences
- Paraquat and CNS barriers
- Future perspectives



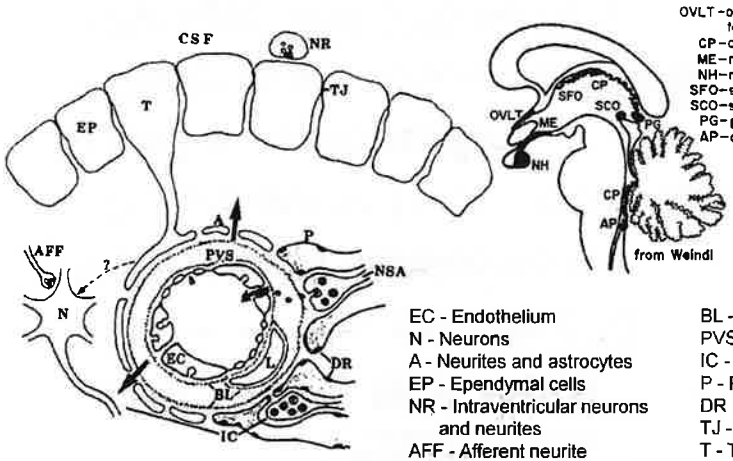
SITES OF CNS BARRIERS

1. Brain parenchymal capillary endothelium
2. Arachnoid epithelium
3. Choroid plexus epithelium

CVO : circumventricular organs

Segal and Zlokovic 1990, modified by A Reichel

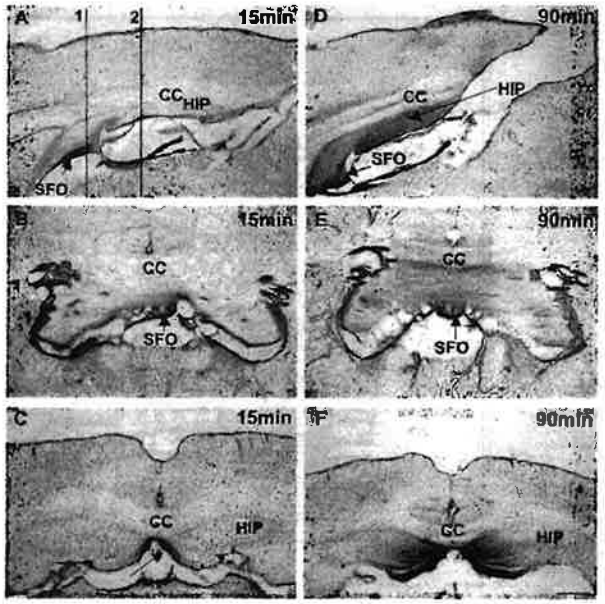
CIRCUMVENTRICULAR ORGANS (CVO)



OVLT - organum vasculosum lamina terminalis
CP - choroid plexus
ME - median eminence
NH - neurohypophysis
SFO - subfornical organ
SCO - subcommissural organ
PG - pineal gland
AP - area postrema

EC - Endothelium
N - Neurons
A - Neurites and astrocytes
EP - Ependymal cells
NR - Intraventricular neurons and neurites
AFF - Afferent neurite
NSA - Neurosecretory axon
BL - Basal lamina
PVS - Perivascular space
IC - Interstitial compartment
P - Pituicyte
DR - Dynorphin receptor
TJ - Tight junction
T - Tanycyte
L - Leptomeningeal cell

Prescott & Brightman, 1998. In: Introduction to the BBB, Ed WM Pardridge, CUP pp270-289



HRP tracer distribution in brain after iv injection

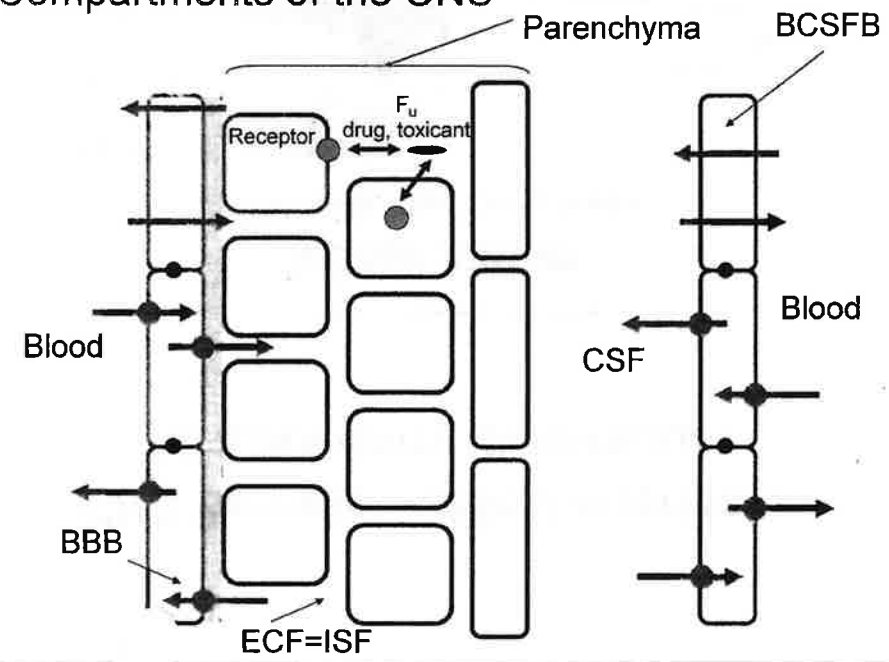
..often in regions adjacent to CVOs

Mouse
SFO: subfornical organ (CVO)

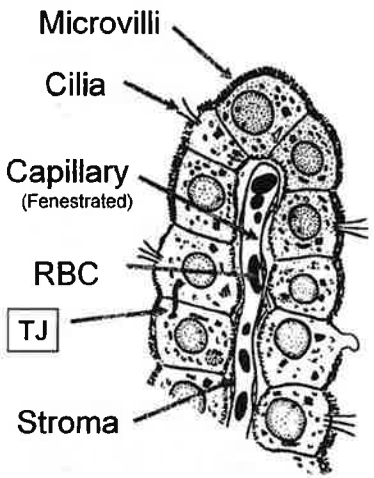
CC: corpus callosum
HIP: hippocampus

Ueno 2007 Curr Med Chem 14: 1199

Compartments of the CNS



CHOROID PLEXUS EPITHELIUM

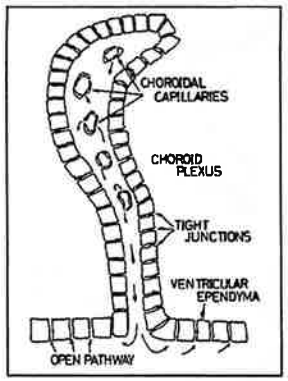


Anatomical barrier site:

- Leaky endothelium
- Moderately tight epithelium
- Microvilli and basal infoldings increase surface area
- Apical:basal specializations

Functions: CSF secretion, ionic regulation, xenobiotic exclusion, secretion of peptides

Plasma and CSF solutes



The functional leak or extracellular pathway.
Possible sites:
- CP stroma
- pial vessels

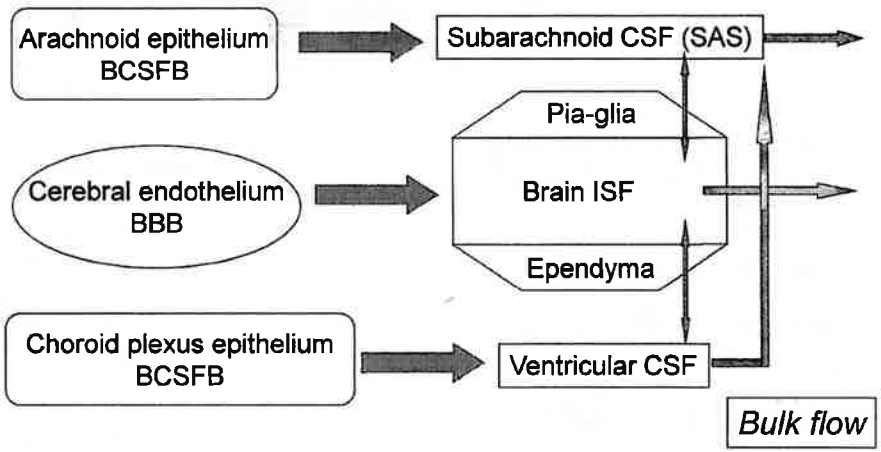
Typical plasma and cerebrospinal fluid concentrations for some selected solutes

Solute	Units	Plasma	CSF	Ratio
Na^+	mM	140	141	~1
K^+	mM	4.6	2.9	0.63
Ca^{++}	mM	5.0	2.5	0.5
Mg^{++}	mM	1.7	2.4	1.4
Cl^-	mM	101	124	1.23
HCO_3^-	mM	23	21	0.91
Osmolarity	mOsmol	305.2	298.5	~1
pH		7.4	7.3	
Glucose	mM	5.0	3.0	0.6
Total amino acid	µM	2890	890	0.31
Leucine	µM	109	10.1-14.9	0.10-0.14
Arginine	µM	80	14.2-21.6	0.18-0.27
Glycine	µM	249	4.7-8.5	0.012-0.034
Alanine	µM	330	23.2-32.7	0.07-0.1
Serine	µM	149	23.5-37.8	0.16-0.25
Glutamic acid	µM	83	1.79-14.7	0.02-0.18
Taurine	µM	78	5.3-6.8	0.07-0.09
Total Protein	mg/ml	70	0.433	0.006
Albumin	mg/ml	42	0.192	0.005
Immunoglobulin G (IgG)	mg/ml	9.87	0.012	0.001
Transferrin	mg/ml	2.6	0.014	0.005
Plasminogen	mg/ml	0.7	0.000025	0.00004
Fibrinogen	mg/ml	325	0.00275	0.000008
α 2-macroglobulin	mg/ml	3	0.0046	0.0015
Cystatin C	mg/ml	0.001	0.004	4.0

Compiled from various sources, values mostly human.

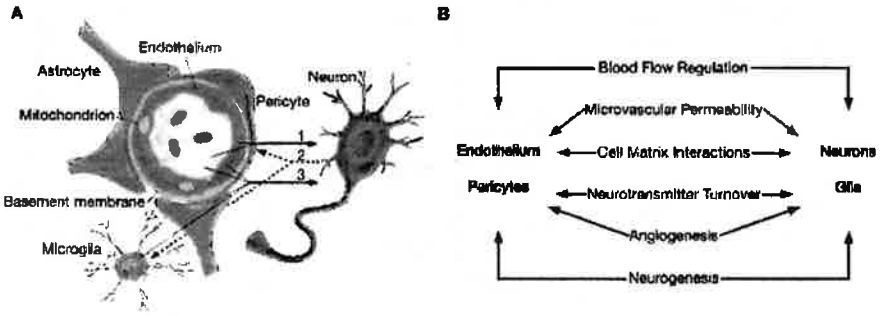
SYNG-PQ-00471702

Barriers and compartments



SYNG-PQ-00471703

Neurovascular Unit (NVU): Cell associations

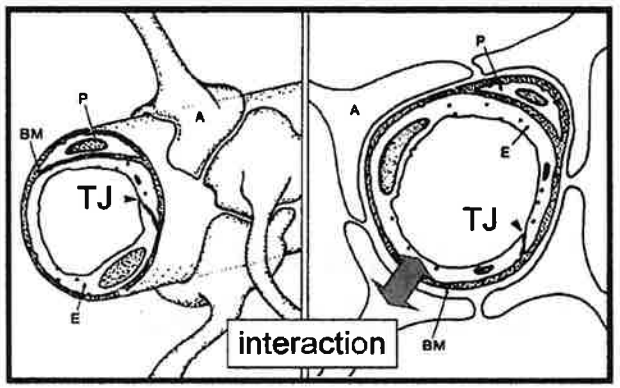


Key barrier features: Tight junctions, transporters, enzymes
- Cooperation between cell types of NVU

Zlokovic 2008 Neuron 57:178-201

SYNG-PQ-00471704

Blood-Brain Barrier Structure







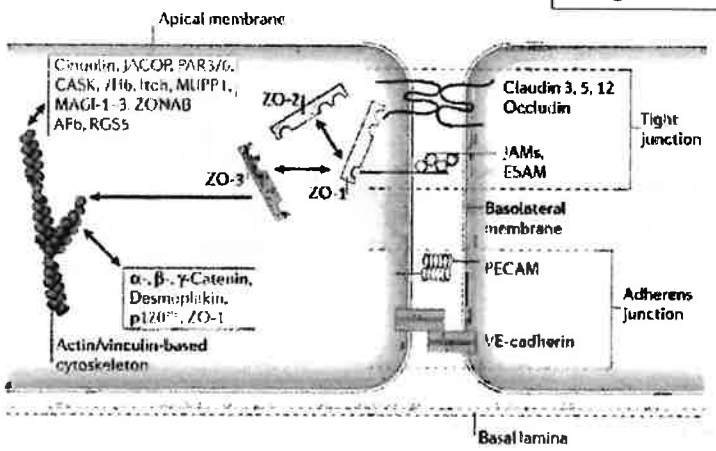
A = astrocyte E = endothelial cell
P = pericyte BM = basement membrane

+ other cell types: microglia, macrophages, leukocytes

SYNG-PQ-00471705

Molecular structure of BBB tight junctions

Regulatory sites



Tight junction

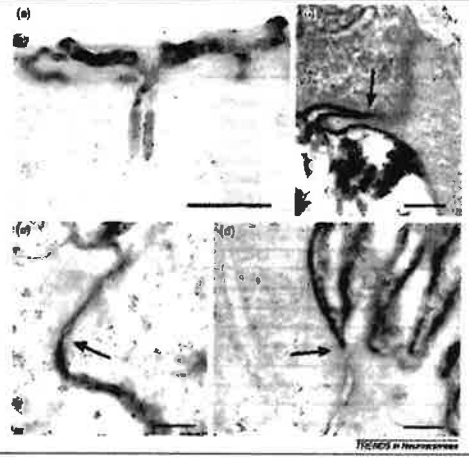
Adherens junction

Abbott et al 2006 Nat Rev Neurosci 7:41

DEVELOPMENT OF CNS BARRIERS

Development of BBB – at the time of vessel ingrowth

Tight junctions (TJ)



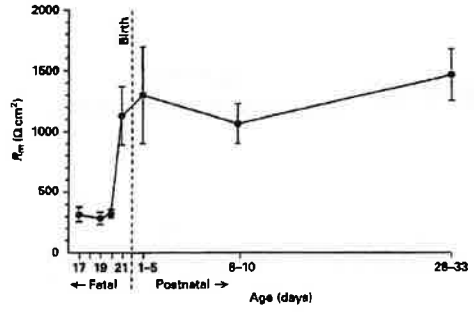
Newborn opossum

Wnt signalling : angiogenesis + barrier development

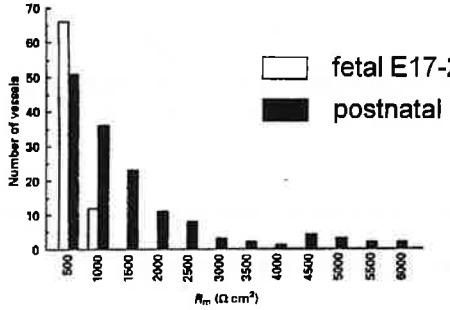
3 kDa biotin-dextran amine 30 min IP

Saunders et al. 2008. TINS 31:279

Tightening of BBB in rat pial vessels at birth: tight junctions



TEER: transendothelial electrical resistance R_m



fetal E17-20

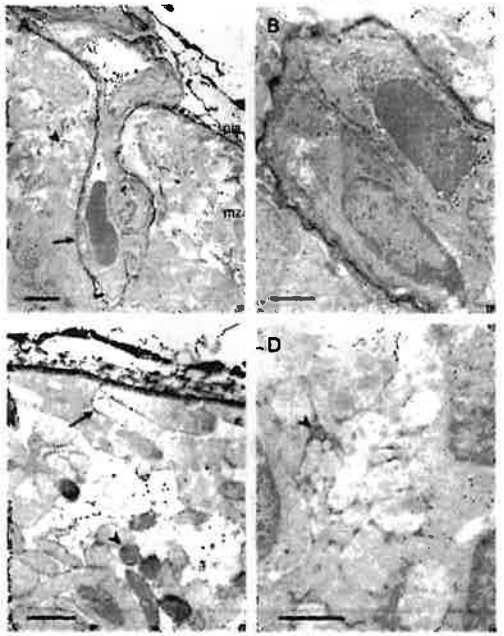
postnatal E21 and older

Butt et al. 1990 J Physiol 429:47

Evidence for well-developed perinatal BBB

- BBB to proteins and macromolecules present in fetal and neonatal brain (1,2,3,4,5,6,7)
- TJs develop between E11 and E17 in mouse, are barrier to proteins (6,7)
- Efflux transporters mdr1a,mdr1b and mdr2 appear between E13 and E18 in mouse (8)
- High electrical resistance present at E21 in rat (9)
- Permeability to ^{86}Rb declines from 42.5 to 12.2 $uL.g^{-1}.min^{-1}$ from E21 to P2 (3)
- K_{in} for mannitol is between 0.19 and 0.22ul.$uL.g^{-1}.min^{-1}$ at one week in rat (same as adult) (7)
- **Occludin and claudin-5 expressed in brain capillaries of 14 week human fetus with same cellular distribution as adult (10)**
- **Work with stillborns and perinatal deaths showed BBB to trypan blue present in human from 12 weeks gestation, comparable to adult (11)**

(1) Ballabh et al. (2001); (2) Olsson et al. 1968; (3) Tauc et al. (1984; (4) Saunders 1992; (5) Moos and Möllgård 1993; (6) Keep et al. 1995; (7) Preston et al. 1995; (8) Scheingold et al. 2001; (9) Butt et al. 1990; (10) Virgintino et al. 2004; (11) Gröntoft 1964



Perinatal CNS barriers – BBB effective, but some leak from choroid plexus or brain surface (pial) vessels

Biotin ethylenediamine tracer (BED, 286Da) 25 min after i.p. injection

Opossum P5 (~=E19 rat)

Ek et al. 2006
J Comp Neurol 496:13

FUNCTIONS OF BBB & BSCB

* 1. Control molecular traffic, keep out toxins (precise connectivity: low cell death)

* 2. Ion homeostasis - optimal neural signalling

3. Low protein environment, limit proliferation

* 4. Separate CNS:PNS neurotransmitter pools; allow non-synaptic signalling

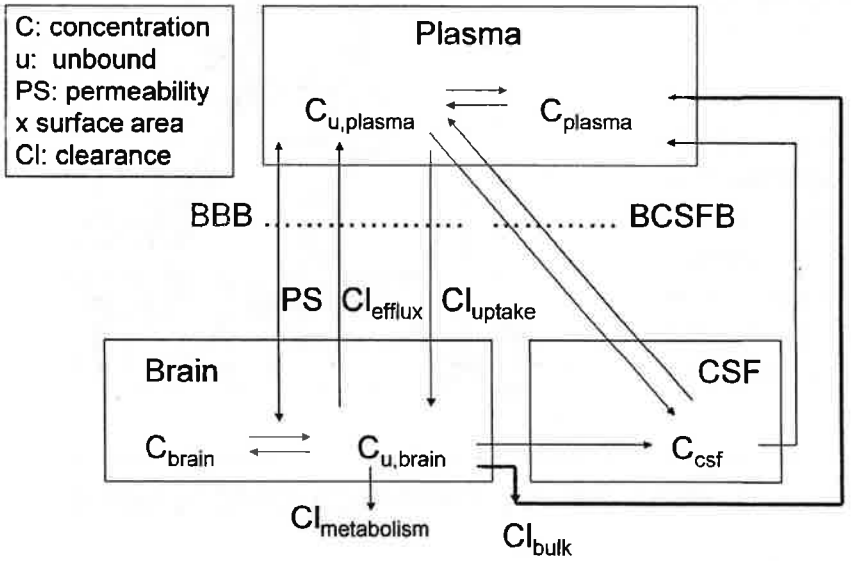
5. Immune surveillance with minimal inflammation, cell damage

Selective advantage

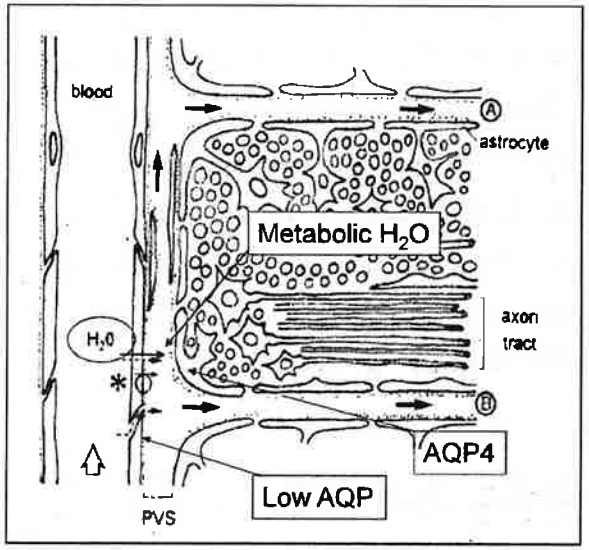
* *Functions needing tightest endothelium*

Compartmental analysis: CNS Drug distribution

C: concentration
u: unbound
PS: permeability x surface area
Cl: clearance



Perivascular space – flow of interstitial fluid (ISF)



*brain endothelial Na,K,ATPase

PVS, perivascuar space

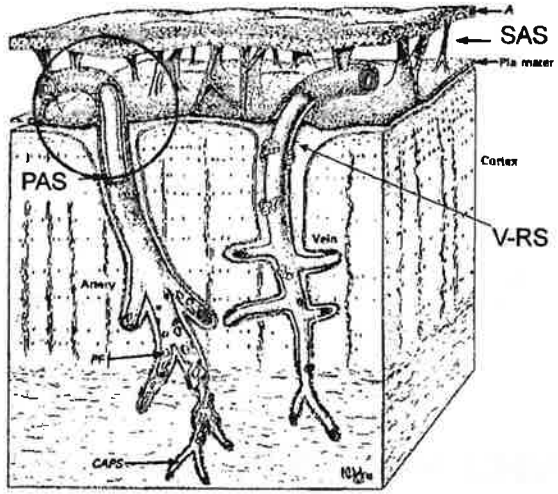
Source of H_2O :
- Plasma
- Metabolism

+ some recycled CSF

Abbott 2004 Neurochem Int 45:545

SYNG-PQ-00471714

Perivascular channels for ISF flow: human



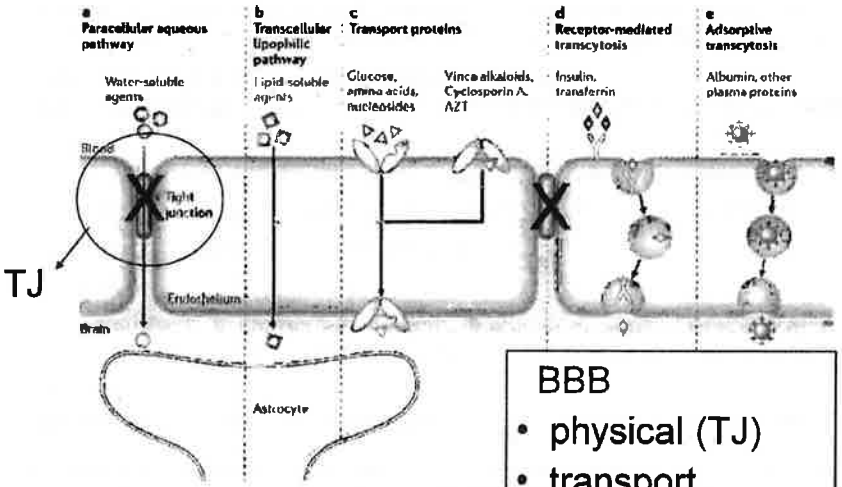
Relation of subarachnoid space (SAS), Virchow-Robin space (V-RS), and periarterial space (PAS) in human brain

A, arachnoid
PF, perforations
CAPS, capillaries

Zhang et al 1990 J Anat 170:111

SYNG-PQ-00471715

Pathways across the blood-brain barrier

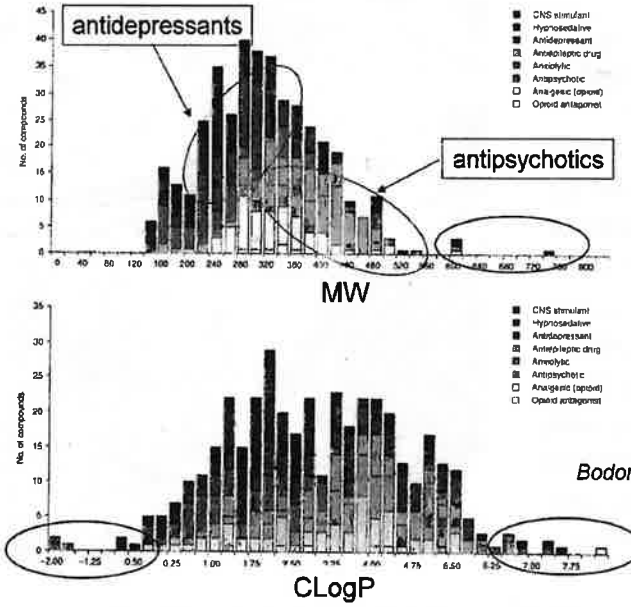


BBB
- physical (TJ)
- transport
- enzymatic

Abbott et al [illegible] Nat Rev Neurosci 7:41

SYNG-PQ-00471716

CNS drugs : Molecular weight and lipophilicity

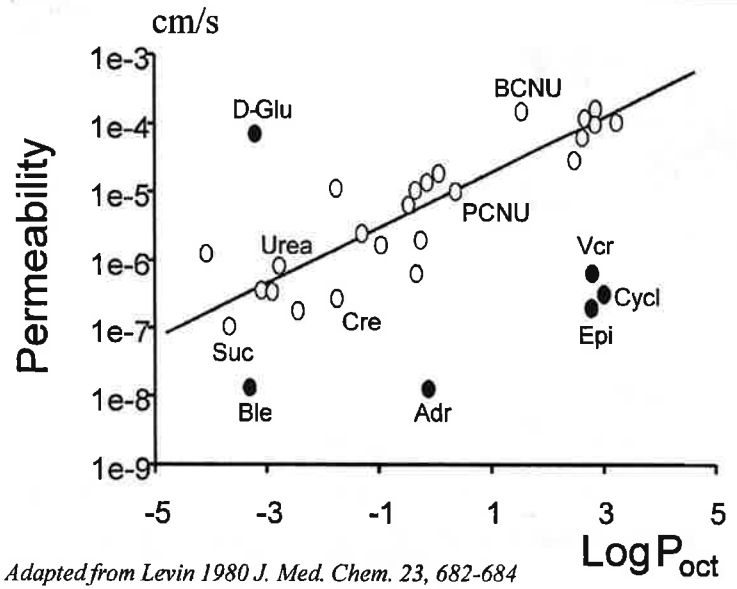


Learning from successful drugs : Darwinian approach

Bodor: Am J Drug Del 1: 2003

SYNG-PQ-00471717

BBB permeability and lipid solubility



Adapted from Levin 1980 J. Med. Chem. 23, 682-684

PC properties benefiting CNS penetration

Common properties of CNS drugs

• small	< 400-500
• lipophilic	log $D_{7.4} \geq 2$
• neutral	uncharged at pH7.4
• slim (x-sectional area)	$A_D < 80A^2$

Deteriorating properties

• Polarity	PSA > 60 A^2
• Lewis base strength	
• Hydrogen-bonding	esp. HBA, β^H_2
• Branching	
• # of rotatable bonds	

HBA > AR ~ HBD ~ κ > mw ~ logP > RotB

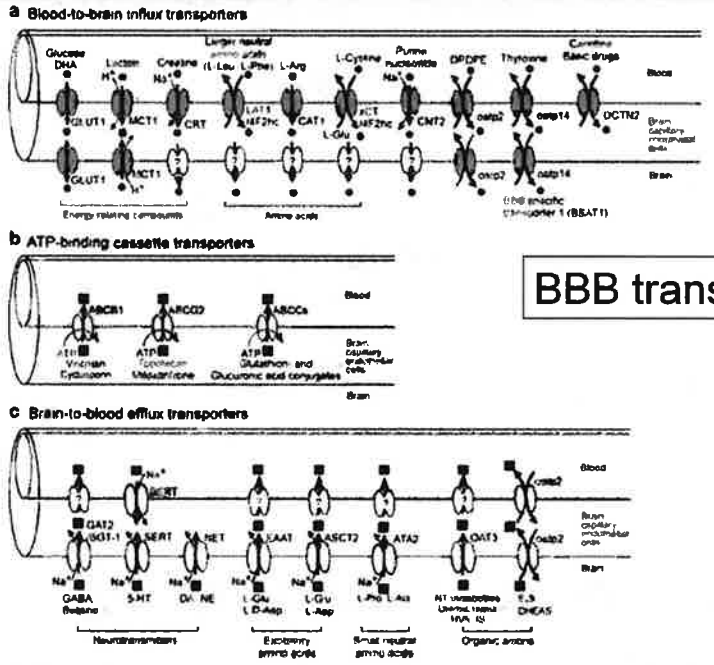
HBA - hydrogen bond acceptors
AR - aromatic density
HBD - hydrogen bond donors
κ - branching index
mw - size
logP - lipophilicity
RotB - No of rotatable bonds (flexibility)

Improving properties

- optimimum lipophilicity *and* relatively high membrane diffusivity
- presence of polarizable surface electrons,
  e.g. conjugated or aromatic substructures or larger halogens
- aromatic density

Pardridge (1998)
Fischer et al. (1998)
Ajay et al. (1999)
Norinder et al. (1998)
Lombardo et al. (1996)
Clark (1999)

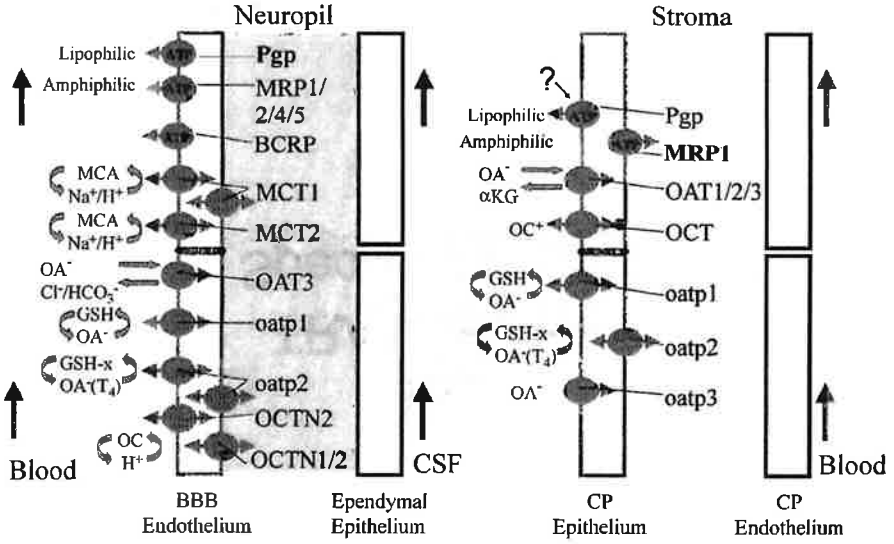
BBB TRANSPORT Specific carriers



BBB transporters

Ohtsuki 2007
Pharm Res
24:1745-58

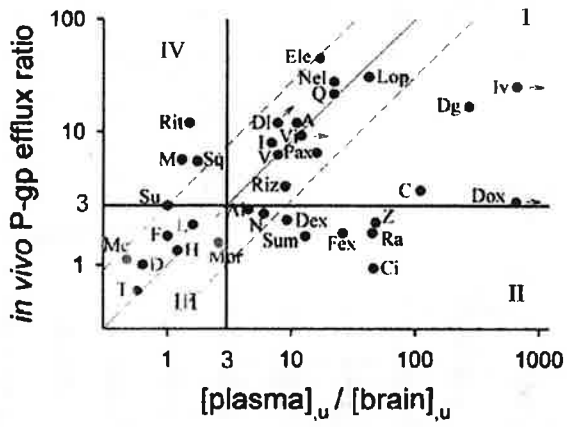
Efflux transporters in the BBB and B-CSF-B



Begley 2004 In Sharma & Westman volume (Spinal Cord)

SYNG-PQ-00471722

Measurements to segregate drugs



Quadrants I-IV

Quadrant III
Enter brain, not Pgp substrate

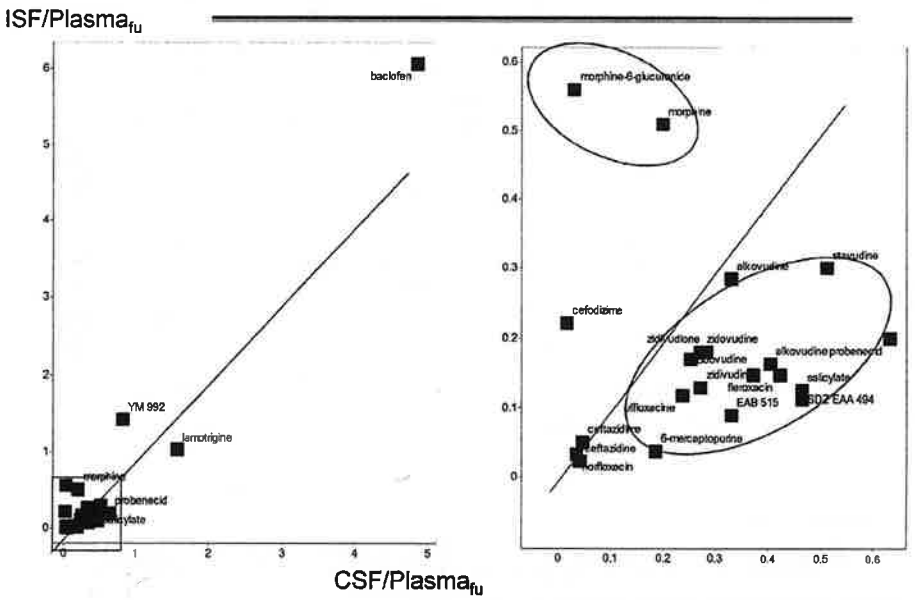
As yet unidentified transporters?

Dobson & Kell 2008: Nat Rev Drug Disc 7:205

Kalvass et al. 2007 Drug Metab Dispos 35:660

SYNG-PQ-00471723

Comparison of ISF(microdialysis) with CSF



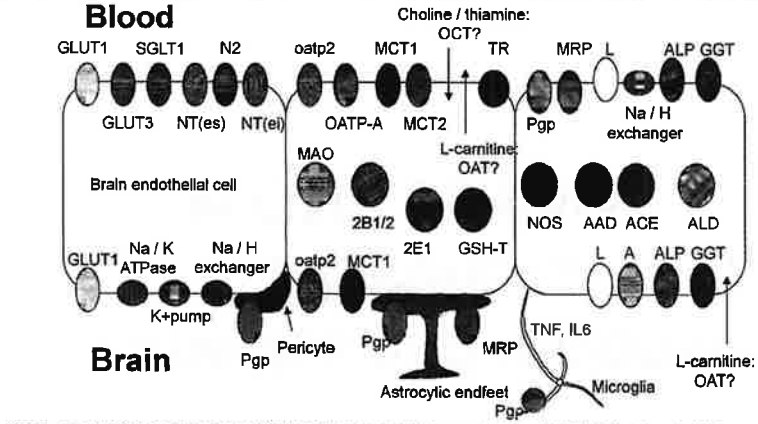
Data : Shen et al. 2004 Adv Drug Del Rev 56: 1825

SYNG-PQ-00471724

Drug metabolism in BBB and choroid plexus

SYNG-PQ-00471725

Transporters and enzymes of the BBB



Transporters: GLUT1-glucose transporter; SGLT1-sodium-dependant glucose transporter; N2, NT(es), NT(ei)-nucleoside transporters; Oatp2-rat organic anion transporter polypeptide 2; OATP-A-human organic anion transporting polypeptide-A; MCT1, 2-monocarboxylic acid transporters; TR-receptors for transferrin, insulin, leptin, lectins IGF's; Pgp-P-glycoprotein (MDR1); MRP-multidrug resistance associated protein; L-amino acids L-system (LAAT); A-amino acids A-system; Na^+/H^+ exchanger -Sodium-proton exchanger; ALP-alkaline phosphatase; GGT-γ-glutamyl-transpeptidase; OCT-organic cation trasnporter; OAT-organic anion transporter; Na^+/K^+-ATPase-sodium-potassium ATPase; K^+-pump - potassium pump. Agents : TNFα, IL-6 - cytokines.
Enzymes : MAO-monoamine oxidase; 2B1/2-CYP enzymes: 2E1-CYP enzyme; GSH-T-GSH-S-transferase; NOS-nitric oxide synthase; AAD-aromatic acid decarboxylase; ACE-angiotensin converting enzyme; ALD-aldehyde dehydrogenase

From: Mertsch & Maas (2002) Curr. Med. Chem. - Central Nervous System Agents 2, 187

Metabolic conversion in the CNS

Phase 1 (Functionalisation)

MAO [1] : flavone dependant mono-oxygenases [2] : cytochromes P450 [1, 2, 3]
NADPH-cytochrome P450 reductase [1, 3] : epoxide hydrolases [1, 2, 3]

Phase 2 (Conjugation)

UDP-glucuronyltranferases [1,2,3] : glutathione S-transferases [1,2,3]
sulphotransferases [2,3] : catechol O-methyltransferases [1,2,3]

Phase 3 (Export)

ATP-dependant transport of drugs and metabolites catalysed by Pgp [1,2] and MRP [1,2,3] and also by OAT, OCT and oatp [1,2]

1 BBB endothelium
2 Parenchyma (neurones and glia)
3 CP epithelium

Adapted from Minn 2000

Drug metabolizing enzyme activity in brain, liver

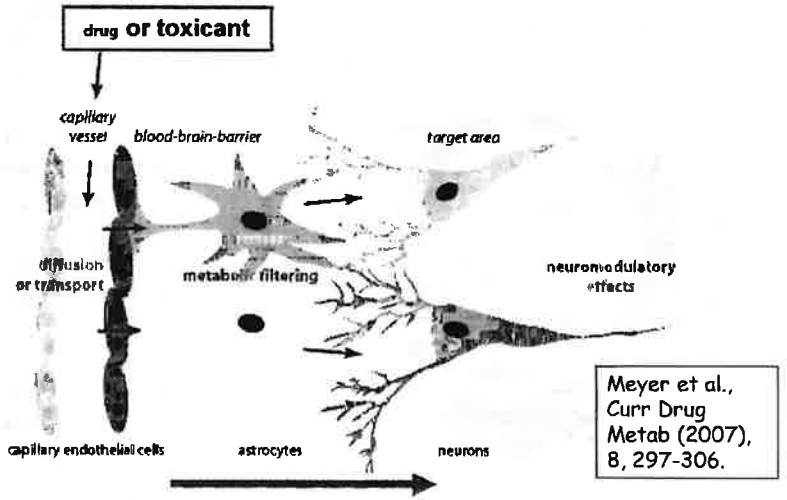
Ratio of drug metabolism activity compared to brain cortex homogenate

Enzyme	Isoform	Brain Microvessels	Choroid plexus	Olfactory Bulb	Liver
Monoamine Oxidase	B	8.6 (rat) 0.2 (human)	low		2.9
Cytochrome P450	1A and 2B	3.9	20	4.2	>100
NADPH-450 reductase		1.3	2.4		<0.1
UGT	1A6	1.5	~65		~50
Epoxide Hydrolases	Micro-somal	5.4	35	0.9	34
Glutathione-S-Transferase	TSO	1.8	2.1	1.8	6.2

UGT – Uridine diphosphate glucuronosyltransferase

Data from: Minn (2000, Pers.comm.)

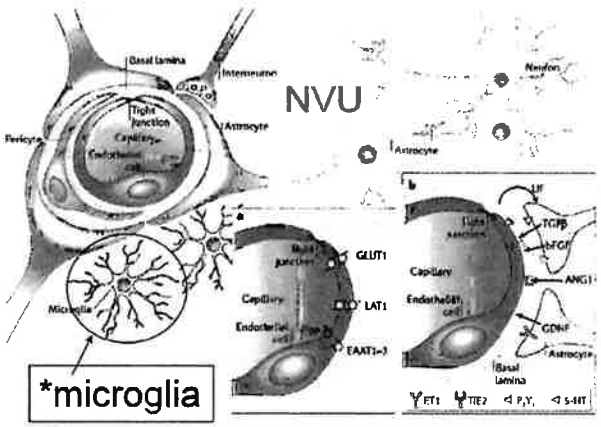
Summary: BBB enzymes as metabolic filter



Meyer et al., Curr Drug Metab (2007), 8, 297-306.

Downstream signalling: (dis)integrated brain network function?

Glial maintenance of BBB phenotype



*microglia

➢Tox context

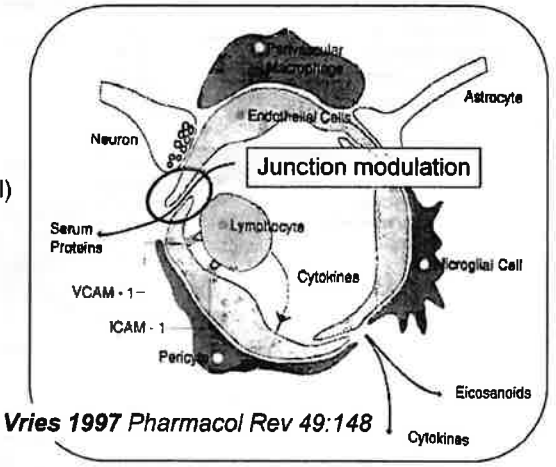
Abbott et al 2006 Nature Rev Neurosci. 7:41

Induction:
Junctions
Transporters
Enzymes
Receptors

Receptors:
- Signalling within Neurovascular Unit (NVU)
- Regulating **permeability** and transport

The BBB is involved in many CNS pathologies

- Traumatic brain injury
- Hypertension
- Diabetes
- Ischaemia, hypoxia
- Inflammation
- Migraine
- Pain (inflammatory, surgical)
- Multiple sclerosis
- HIV-encephalitis
- Cerebral malaria
- Bacterial meningitis
- Brain tumours
- Epilepsy
- Depression
- Schizophrenia
- Age-related dysfunctions
- Alzheimer's disease
- Parkinson's disease
- **Environmental toxins?**



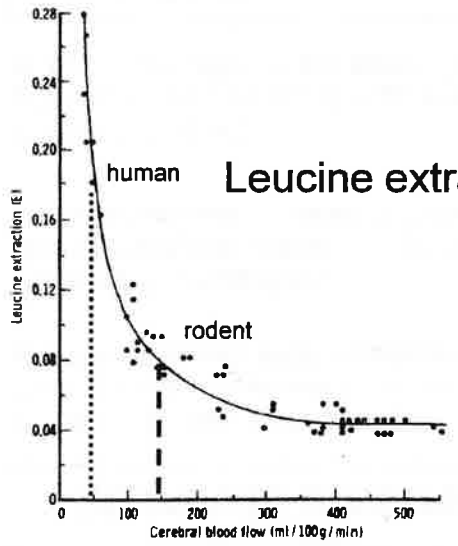
***de Vries 1997** Pharmacol Rev 49:148*

Characteristics of brain endothelium

Inflammation, ROS implicated in many

Species and regional differences in CNS barriers?

Effect of species differences in blood flow



CBF
Human~0.5ml/g/min
Rat, mouse ~1.5ml/g/min

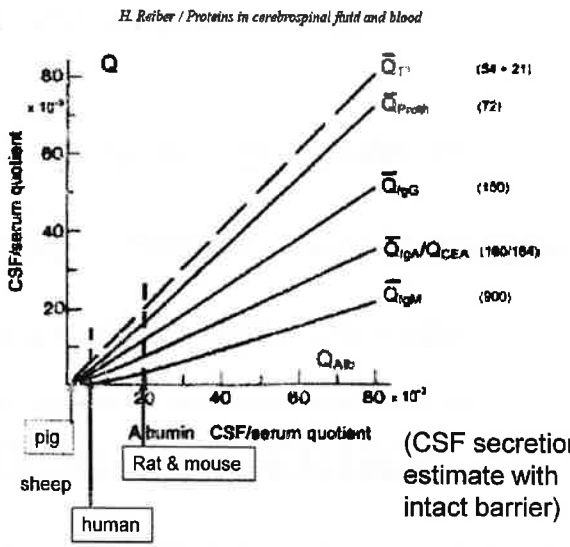
Leucine extraction

Slower flow, greater extraction during CNS transit

Sage 1981 J Neurochem 36:1731

Species differences

Using CSF to estimate brain concentration



(CSF secretion estimate with intact barrier)

Species differences

Cationic amino acid transporter, no CAT2 & 3 in human??

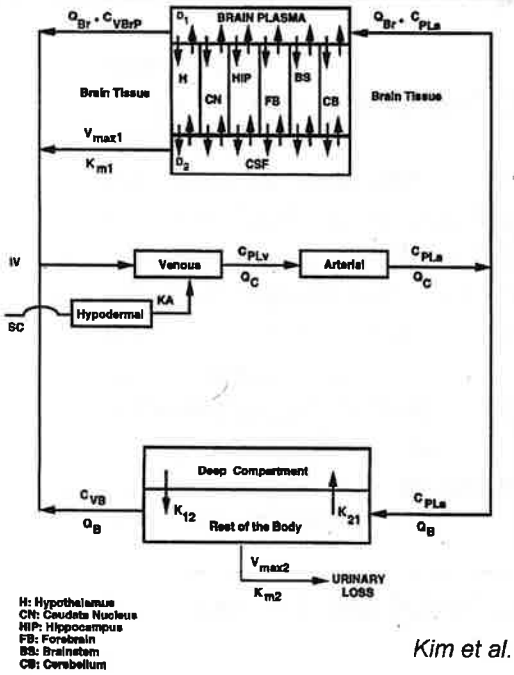
OAT1 OAT 3 (human CP)
Oat3 (rat BBB)

OCTN1 OCTN2 (human)
Octn1 octn2, octn3 (rodent)

MDR1 (human)
mdr1 mdr2 (rodent)

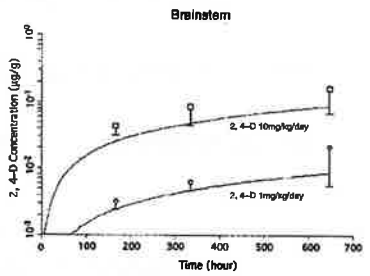
MRP1 4 5 6 (low3) (human)
mrp1 4 5 (low 2 & 3) (rodent)

Löscher and Potschka. Blood-Brain Barrier Active Efflux Transporters: ATP-Binding Cassette Gene Family. NeuroRx. 2005 January; 2(1): 86–98
Kusuhara H, Sugiyama Y. Active efflux across the blood-brain barrier: role of the solute carrier family. NeuroRx. 2005 Jan;2(1):73-85.



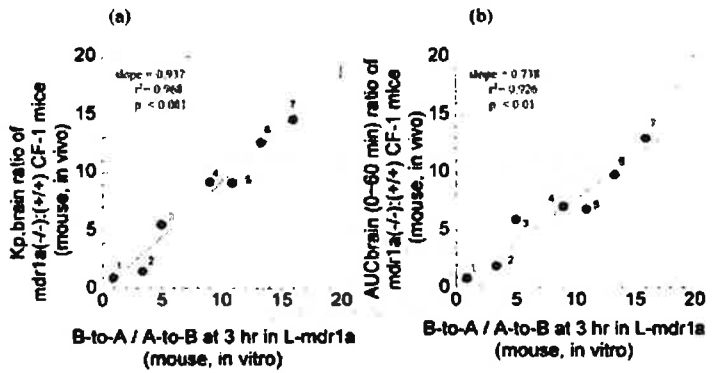
Physiologically-based pharmacokinetic (PBPK) modelling

Low-dose, long-term exposures of organic acid toxicant in brain. 2,4-dichlorophenoxyacetic acid (2,4-D)



Kim et al. 2001 Env Toxicol Pharmacol 9:153

Good correspondence mouse *in vivo* and *in vitro* Pgp function



➢Basis for cross-species PBPK modeling

Yamazaki et al. 2001 JPET 296:723

Species differences: summary

1. Vascular: territories, CBF
2. CSF: secretion rate, leakiness of CP/subarachnoid vessels, scaling for size
3. Plasma binding of drugs – will affect 'free unbound' concentration, PK
4. BBB passive permeability – well conserved
5. Regional differences – may be some variation
6. 'Housekeeping' transport systems – similar if not identical (may affect rank order of uptake, efflux)
7. Metabolising enzymes – may differ in isoforms, activity
8. PBPK helpful for modelling species and regional differences

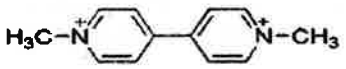
PARAQUAT AND CNS BARRIERS

PARAQUAT PROPERTIES

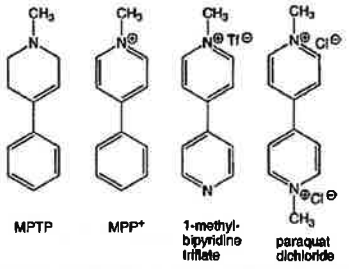
- 1,1-Dimethyl-4,4'-bipyridinium dichloride
- Para-substituted quaternary bipyridyl di-cation
- Non-selective herbicide. ICI - Syngenta (Gramoxone)
- One of most toxic herbicides (>40mg/kg)

PARAQUAT (PQ) CHEMISTRY



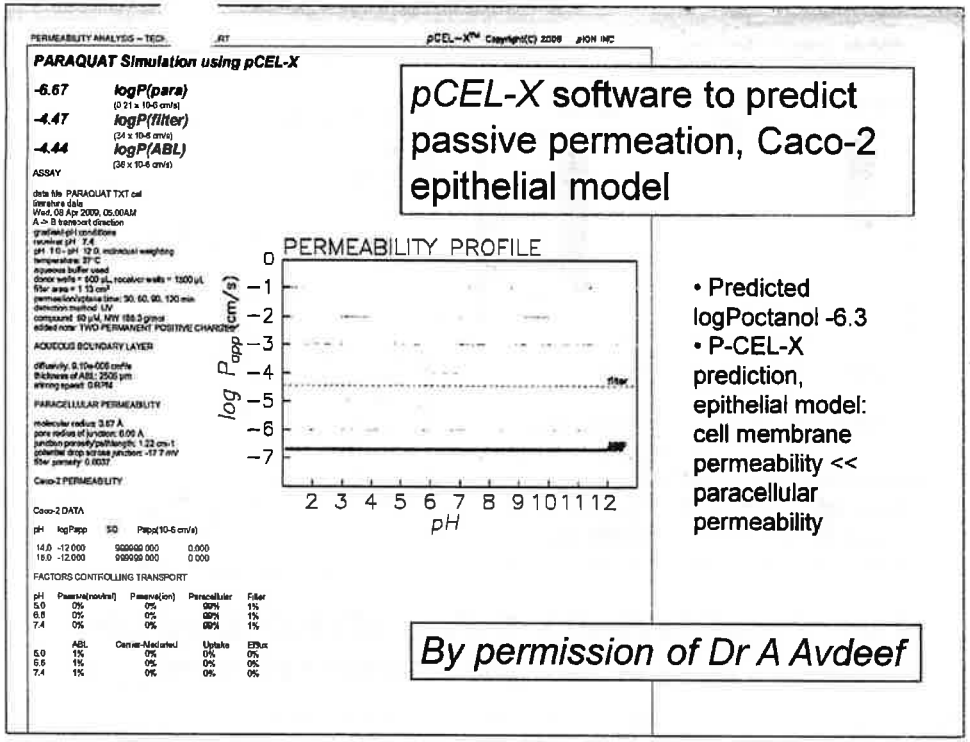


Similarities of PQ structure with MPP^+, neurotoxic metabolite of MPTP



Does paraquat cause a Parkinson-like syndrome?

Bartlett et al. 2009 Brain [illegible] 1259: 74



pCEL-X software to predict passive permeation, Caco-2 epithelial model

- Predicted logPoctanol -6.3
- P-CEL-X prediction, epithelial model: cell membrane permeability << paracellular permeability

By permission of Dr A Avdeef

SYNG-PQ-00471742

PARAQUAT PROPERTIES

- Permanently dicharged highly soluble cation
- Predicted logPoctanol -6.3
- *P-CEL-X* prediction – epithelial/BBB model – cell membrane permeability << paracellular permeability.
- PQ oral bioavailability low -~10%.
- Not subject to metabolism in body, rapidly excreted in urine
- If enters brain appreciably, expect this to by via transporter(s) or leak into CSF
- What about efflux?

SYNG-PQ-00471743

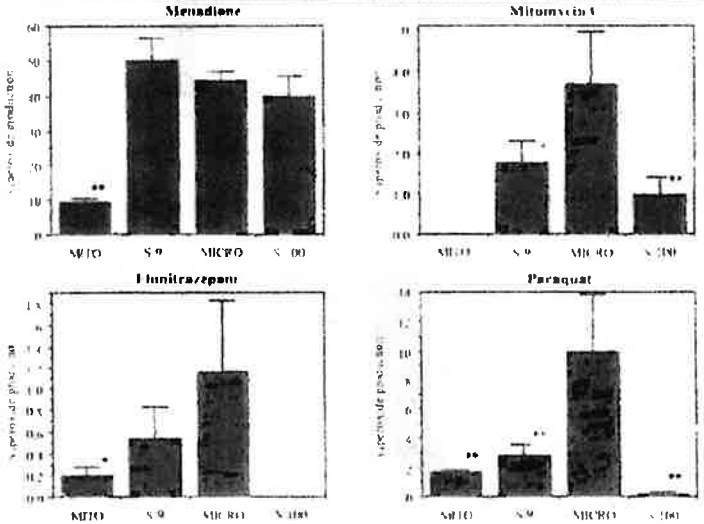
Does Paraquat (PQ) get into the CNS ?

Early work

- Smith et al. 1990 Lung toxicity PQ related to polyamine transporter (PAT), uptake into alveolar Type II cells
- Shin et al. 1985. Detectable polyamine transport rat BBB: BUI putrescine, spermidine, spermine 5.3-6.1% (baseline ~2%) 34% of this is carrier-mediated. But saturated at normal blood polyamine levels.
- Corasaniti et al. 1991. HPLC. PQ able to cross rat BBB, dose-related, entry higher in young (2 wks) and old (12,24 month) *cf.* 3 month.

SYNG-PQ-00471744

Superoxide production by brain and microvessels

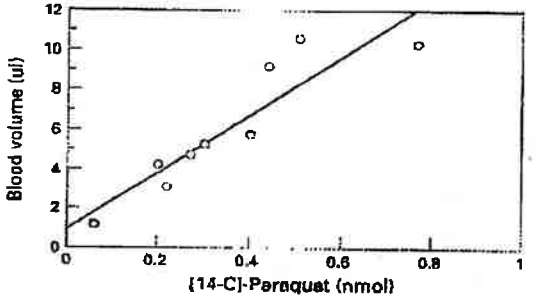


PQ on brain microvessels: $O_2^{\cdot-}$ production stimulated by NADH nucleotide cofactor

Ghersi-Egea et al. 1991 Toxicol Appl Pharmacol 110:107

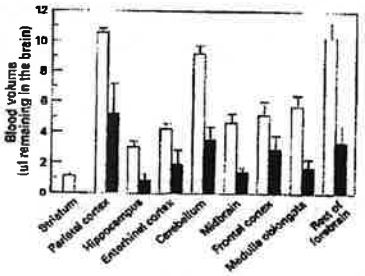
SYNG-PQ-00471745

A.



Paraquat distribution in brain related to regional blood volume (inulin space, ul)

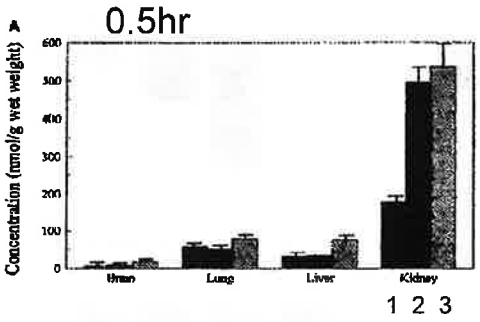
B. Inulin distribution (blood volume): black, perfused

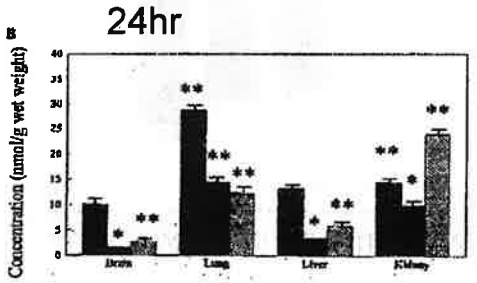


PQ remaining in brain at 24 hr mainly associated with vascular elements ?

Naylor et al. 1995 Hum Exp Toxicol 14:587

SYNG-PQ-00471748





Age-dependent entry [^{14}C] paraquat to brain

20mg/kg s.c.(median lethal dose), rat

1: neonate (10 day)
2: adult (3 month)
3: elderly (24 month)

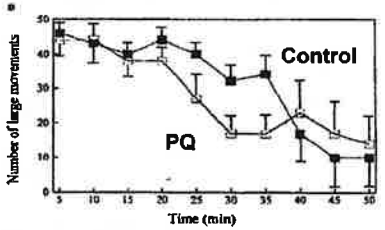
Initially in more permeable BBB regions, then in most of brain by 24 hr, especially in neonate

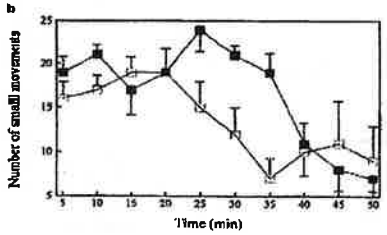
Widdowson et al 1996a Hum Exp Toxicol 15:231

SYNG-PQ-00471747

PD? Multiple paraquat oral dosing in rat caused no detectable change in behaviour or neurochemistry

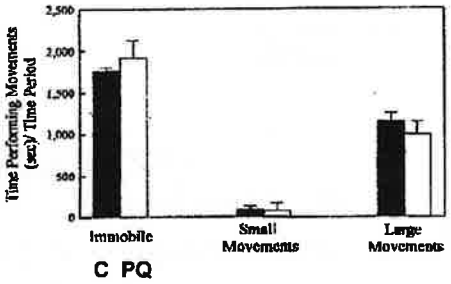
Locomotor activity





- 5mg/kg/day,14 days: conc in brain reached 10x higher than single dose.
- No change in behaviour, nigro-striatal neuronal cell death
- Neurochemistry, higher DA striatum

Time performing movements



Conclude: PQ not like MPP+

Widdowson et al. 1996b Hum Exp Toxicol 15:583

SYNG-PQ-00471748

Does Paraquat (PQ) get into the CNS ?

- Ghersi-Egea et al. 1991. PQ + other xenobiotics cause generation of ROS in brain cells and endothelium, via NADPH-cytochrome P450 reductase. Potential toxicity on BBB, neurons, glia, microglia etc.
- Naylor et al. 1995. BBB impedes ^{14}C PQ entry rat brain (c1/3 values HPLC method). Max entry (0.05% dose) within 1 hr, 13% residue at 24hr, associated with vascular elements? Especially pineal, lining of cerebral ventricles, olfactory bulb, hypothalamus, area postrema ('outside BBB or no BBB'). No evidence of neuronal damage.
- Widdowson et al, 1996a. ^{14}C PQ entry rat brain, greater and more sustained in 10 day old cf. 3 and 18 month old. Most entry in regions with more permeable BBB (dorsal hypothal, area postrema, an olfactory bulb), though more diffusely by 24hr.
- Widdowson et al. 1996b. PQ causes no detectable change in motor behaviour, neuronal cell death; increase in striatal dopamine concentrations due to PQ-induced stress?
- * Poduslo et al. 1996, 1998. Polyamine modification of proteins including growth factors improves CNS access, via polyamine transporter BBB?

SYNG-PQ-00471749

Does Paraquat (PQ) get into the CNS ?

- *Chen et al. 2007 Paraquat transported by renal hOCT2 (basolateral), hMATE1 (apical) (HEK-293 study). BBB expresses luminal OCT – would favour brain penetration. No MATE reported.
- Purisai et al. 2007. Microglial activation (LPS) priming – exacerbates PQ neurotoxicity against dopaminergic neurons.
- Gradinaru et al 2008. PQ upregulates choroid plexus UDP-glucuronosyltransferase UGT1A6.
- Bartlett et al. 2009. Rhesus macaque PET ^{11}C-PQ bolus injection 0.1-0.4ug/kg iv. Some in CSF, little detectable in brain.
- Prasad et al. 2009 Toxicokinetics and toxicodynamics of PQ accumulation in brain. Plateau after multiple doses.

PARAQUAT PROPERTIES

- 1,1-Dimethyl-4,4'-bipyridinium dichloride
- Para-substituted quaternary bipyridyl di-cation
- Non-selective herbicide. ICI - Syngenta (Gramoxone)
- One of most toxic herbicides (>40mg/kg)

- Permanently dicharged highly soluble cation
- Predicted logPoctanol -6.3
- P-CEL-X prediction – epithelial/BBB model – cell membrane permeability << paracellular permeability.
- PQ oral bioavailability low -~10%.
- Not subject to metabolism in body, rapidly excreted in urine

- If enters brain appreciably, expect this to by via transporter(s).
- Evidence for significant entry in rodents: rat, mouse. Primates?
- Candidates: L1, polyamine transporter, OCT? Problem – efflux transport? No metabolism in brain.

CONCLUSIONS

- PQ enters rodent brain rapidly, cleared slowly
- BBB uptake transporters L1 (+OCT? PAT?) + leak into CSF implicated
- No metabolic breakdown in CNS
- No clear efflux transporter from CNS
- Very slow clearance suggests intracellular sequestering in CNS – potential for long-term toxicity
- Similarities between species in CNS barrier organisation and uptake transporters mean it is likely that similar toxicokinetics and dynamics will apply in humans. Low dose PQ bolus PET study in primates may not be sufficiently sensitive to show CNS distribution
- CNS barriers more leaky/vulnerable in neonate, possibly also in old age
- Entry PQ into brain can be increased by other toxicants, e.g. DTCs
- Neuronal damage by PQ exacerbated by LPS/infection – priming role of microglial activation
- Need more studies of mechanisms for CNS uptake (BBB, CP) and efflux/clearance of PQ, in combination with other potential compounding factors; PBPK

➢ *Combination of carrier-mediated uptake with very low clearance and known toxicity: problematic profile*

Acknowledgements

The BBB Group KCL

BBB physiology, development, toxicology, pathology

- David Begley, Paul Fraser, Jane Preston, Mike Bradbury
- Arthur Butt, Nacho Romero, Andreas Reichel, Alex Easton, Rob Rist, Diana Dolman, Adjanie Patabendige
- Sarah Fredriksson, Siti Yusof

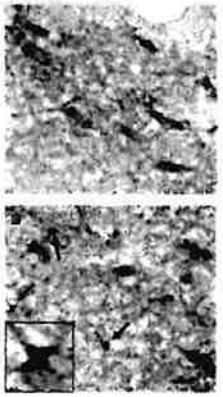
Collaborators

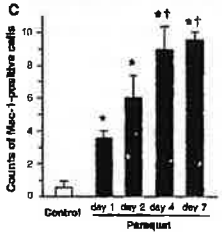
- KCL - Ken Smith, Catherine Rice-Evans, Marcus Rattray
- St Thomas' Hospital - Graham Hughes
- Budapest - Ester Domotor, Ildiko Sipos, Vera Adam-Vizi
- Cleveland - Damir Janigro
- Boston - Alex Avdeef (pION)

Supported by:

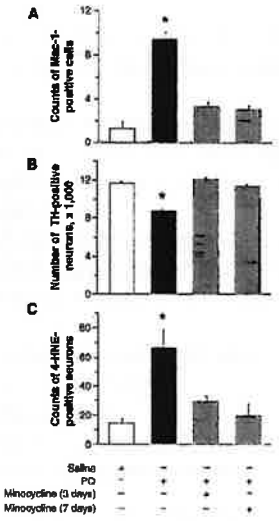
- The Wellcome Trust, BBB Consortium with Industry, UK MS Society and UCB

Microglial activation: priming event leading to PQ-induced dopaminergic cell degeneration

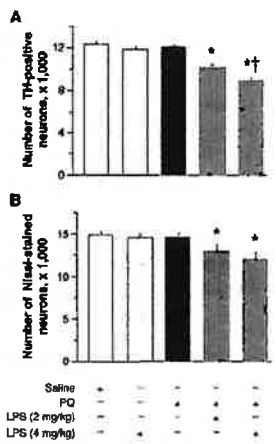




1. Activated microglia



2. Protection by minocycline



3. LPS + PQ: neurotox

Purisai et al. 2007 Neurobiol Dis 25:392

Drug and xenobiotic-induced upregulation of choroid plexus metabolic enzymes

Table 1 1-Naphthol UGT1A6 and NADPH-cytochrome P450 reductase enzymatic activities in rat choroid plexus isolated after an in vivo treatment with either: 3-methylcholanthrene, phenobarbital, dexamethasone, cyclosporine or paraquat

Treatment	1-Naphthol UGT1A6 specific activity (nmol/h per mg protein)	NADPH-cytochrome P450 reductase specific activity (nmol cytochrome *c* reduced/min per mg protein)
Control	115.32 ± 24.17	24.55 ± 8.27
3-Methylcholanthrene (50 mg/kg i.p. daily, for 2 days)	354.25 ± 85.44*	25.08 ± 7.17
Phenobarbital (80 mg/kg i.p. daily, for 3 days)	127.15 ± 40.11	26.12 ± 9.85
Dexamethasone (50 mg/kg i.p. daily, for 4 days)	110.45 ± 29.08	25.58 ± 10.05
Cyclosporine (30 mg/kg i.g. daily, for 6 days)	125.87 ± 34.49	23.66 ± 7.85
Paraquat (25 mg/kg i.p. daily, for 2 days)	257.51 ± 49.66*	26.54 ± 9.92

Results are given as mean ± SD, $n = 10$; n number of animals

i.p. Intraperitoneal administration, *i.g.* intragastric administration

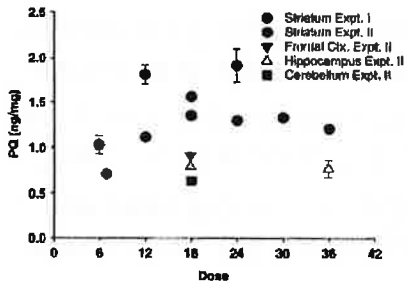
* Significantly different from control rats ($P < 0.001$, Student t test)

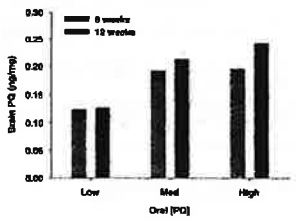
PQ: upregulation of choroid plexus UGT1A6 UDP-glucuronosyltransferase

Gradinaru et al. 2008 Arch Toxicol. Nov 21

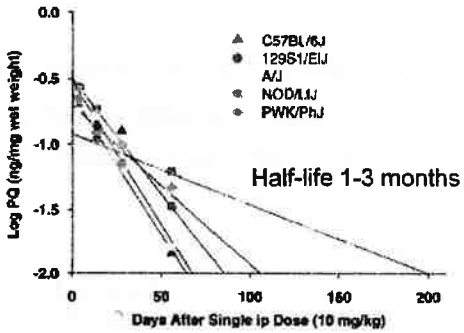
Paraquat toxicokinetics and toxicodynamics in mouse brain

1. Concentration in brain

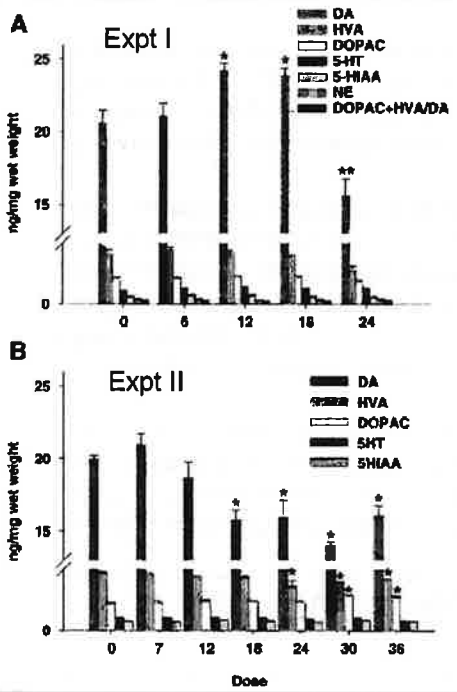




2. Strain differences in clearance



Prasad et al. 2009 Exp Neurol 215:358

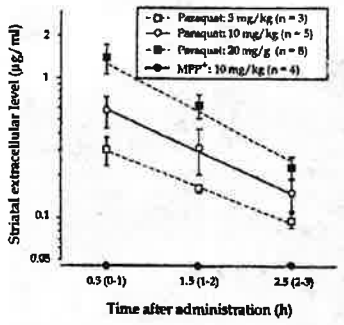


Paraquat toxicokinetics and toxicodynamics in mouse brain

3. Effects on striatal neurochemistry, 7 days after dose 10 mg/kg ip C57BL/6J (B6J)

Prasad et al. 2009 Exp Neurol 215:358

Paraquat crosses the rat BBB



Brain microdialysis, HPLC-UV detection

No detectable MPP^+ entry

Dose	n	Serum concentration (nmol/ml)	Striatal extracellular level (nmol/ml)	Ratio
Paraquat				
5 mg/kg	3	1.42±1.50	0.28±0.06	0.208±0.064
10 mg/kg	5	3.88±0.79	0.36±0.09	0.126±0.031
20 mg/kg	8	8.04±2.41	0.49±0.09	0.085±0.023**
MPP⁺				
10 mg/kg	4	11.62±4.84*	Not detected	-

Shimizu et al. 2001
Brain Res 906: 135

Paraquat crosses BBB by L1 (LAT1) amino acid carrier

	n	Striatal extracellular paraquat level 0–1 h	1–2 h	2–3 h	Serum paraquat 3 h	Ratio*
Paraquat (control)	8	4.50±1.06	2.03±0.38	0.74±0.13	8.04±2.41	0.085±0.023
Paraquat +L-valine	8	1.32±0.29**	0.71±0.13**†	0.06±0.23	11.74±2.80	0.032±0.006††
Paraquat +L-lysine	8	3.47±0.90	1.90±0.26	0.84±0.26	7.59±1.74	0.100±0.028

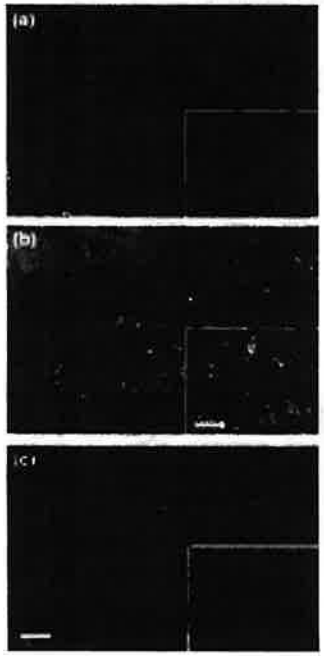
Transport inhibited by L-valine, L-lysine.

	n	Ipsi lateral (pmol)	Contra lateral (pmol)
Paraquat (50 μM)	5	172.5±53.9	ND*
Paraquat (50 μM) with Na^+-free Ringer's solution	5	76.3±6.8*	ND
Paraquat (50 μM) with putrescine (50 μM)	3	169.1±60.5	ND
MPP^+ (10 μM)	5	23.1±8.2	ND

Locally injected PQ:
Striatal neurone
PQ uptake
Na^+-dependent, not blocked by putrescine
?not PAT

Shimizu et al. 2001
Brain Res 906: 135

➢ *PQ crosses 3 membranes*



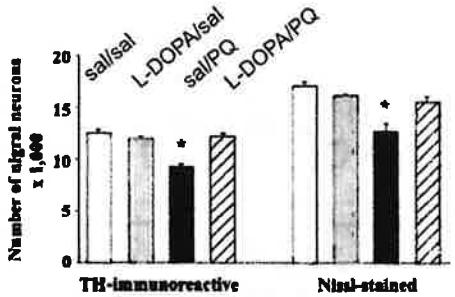
saline/ saline

saline/ PQ

L-val/ PQ

Paraquat entry to brain reduced by competing L1 transporter substrates

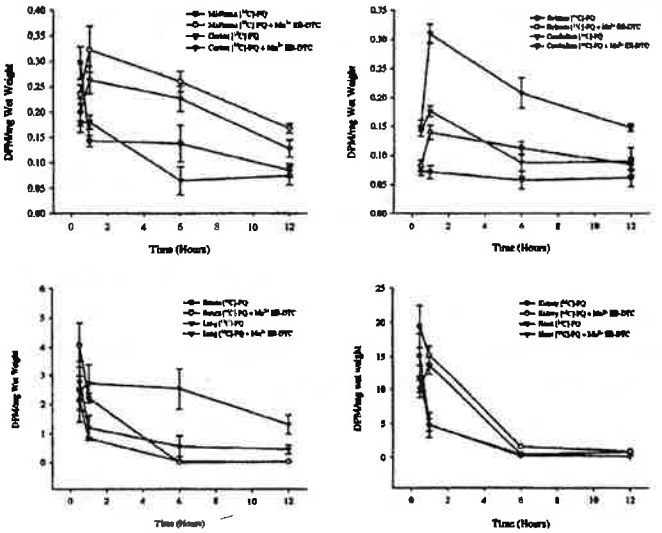
30mg/kg PQ ip. Antibody to detect PQ.
L-DOPA, L-valine, L-phenylalanine pretreatment (30 min) reduced brain entry PQ



L-DOPA protects against PQ neurotoxicity

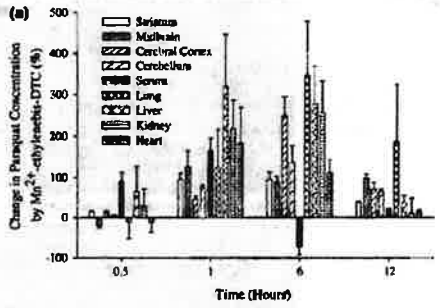
McCormack J Neurochem 2003 85:82

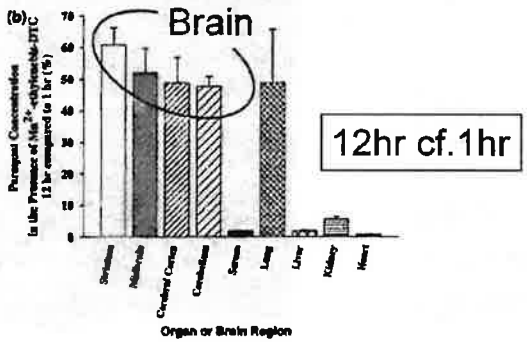
^{14}C PQ brain entry increased by Mn^{2+}-ethylenebis-DTC



DTC: Dithiocarbamate pesticide

Barlow et al. 2003
J Neurochem 85:1075





12hr cf.1hr

^{14}C PQ brain entry increased by Mn^{2+}-ethylenebis-DTC

Residual PQ in brain cleared slowly

➢ DTC inhibits efflux transporter?

Barlow et al. 2003
J Neurochem 85:1075

SYNG-PQ-00471754

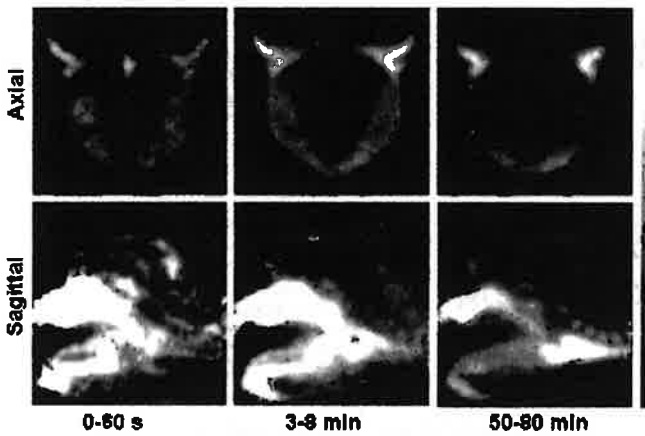
Does Paraquat (PQ) get into the CNS ?

- Shimizu et al. 2001. Rat brain microdialysis/HPLC-UV. Detectable entry PQ but not MPP+; BBB intact after PQ treatment. Uptake PQ BBB inhibited by L1 substrates: L-valine, L-lysine. Uptake into striatal neurones Na^+-dependent, not PAT.
- McCormack & Di Monte 2003. 30mg/kg PQ. Antibody to detect PQ. L-DOPA, L-valine, L-phenylalanine pretreatment reduced brain entry PQ. PQ entry BBB via L1 amino acid carrier.
- Barlow et al. 2003 ^{14}C PQ enters brain, peak levels ~1hr, certain dithiocarbamates increase brain uptake PQ - by inhibiting efflux transporter?

SYNG-PQ-00471755

[^{11}C] Paraquat in primate: low CNS distribution

PET study Rhesus macaque



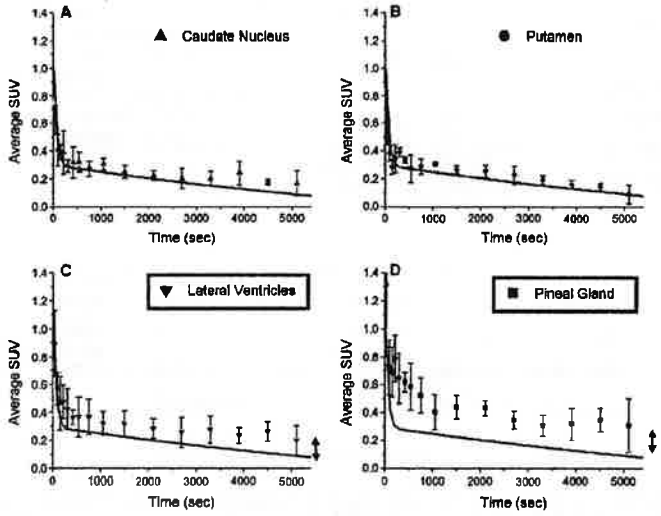
Single bolus injection PQ 0.1-0.4ug/kg iv

Rapid CNS entry, clearance.

Bartlett et al. 2009 Brain Res 1259: 74

SYNG-PQ-00471758

[^{11}C] Paraquat in primate: low CNS distribution



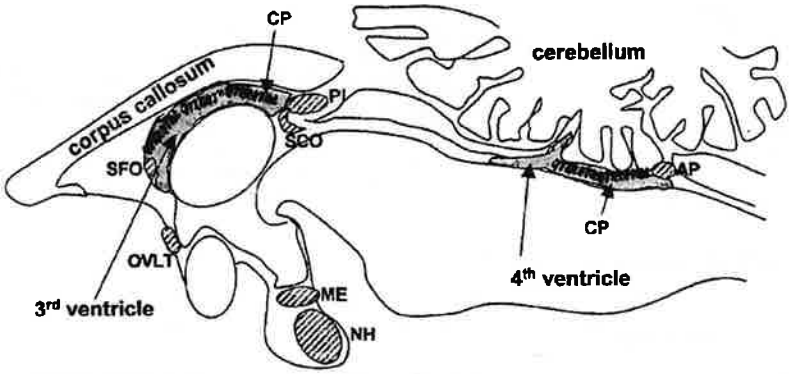
Standardized uptake values (SUV)
n=4 subjects

+ fitted plasma SUV curve (scaled to 5% CBV)

Bartlett et al. 2009 Brain F 259: 74

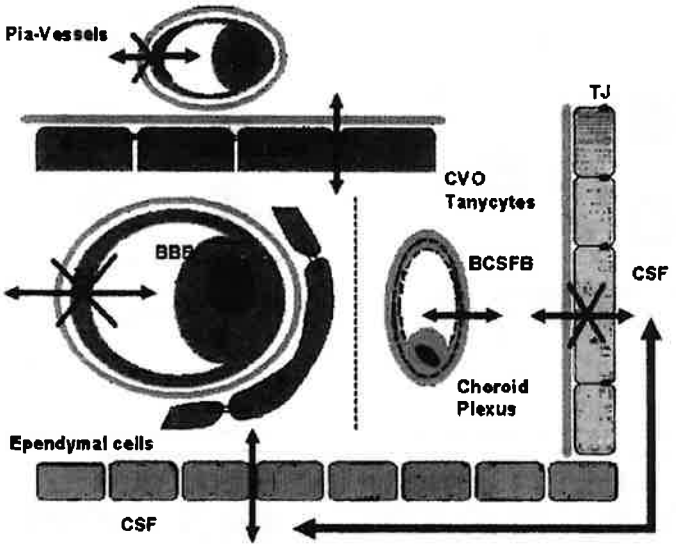
SYNG-PQ-00471757

CIRCUMVENTRICULAR ORGANS IN RAT



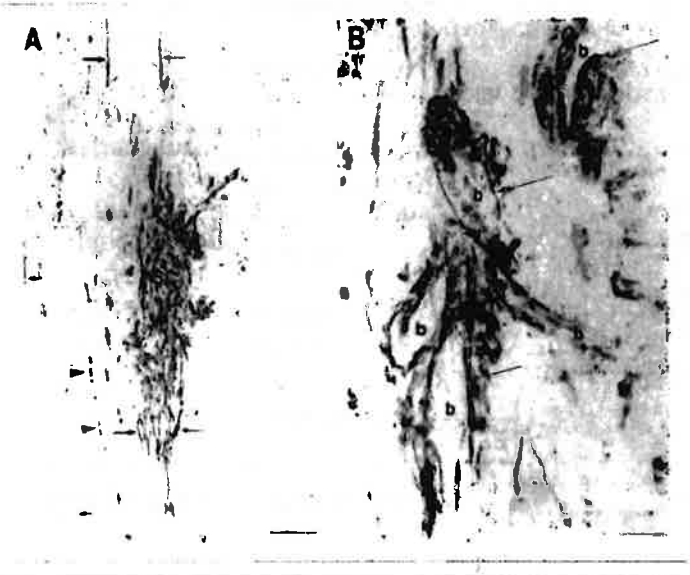
Ueno 2007 Curr Med Chem 14: 1199

CNS interfaces and barriers



Wolburg et al. 2009 Cell Tissue Res 335:75

Migration of grafted Schwann cells along perivascular spaces

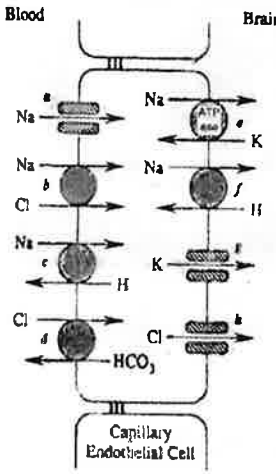


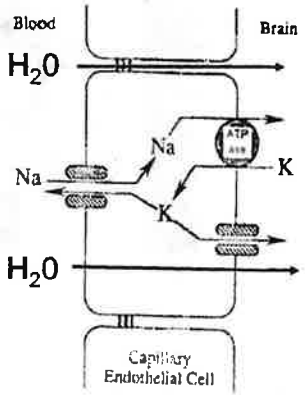
b,
blood vessel

PVS – also migration route for malignant cells

Li & Raisman 1997 Exp Neurol 149:397

Source of ISF ? Model of ion transporters and channels in brain endothelium



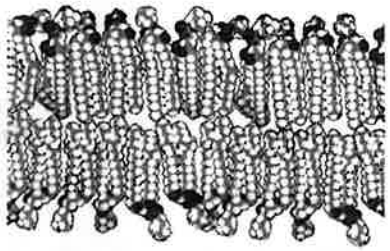


Schielke & Betz 1992

SYNG-PQ-00471770

Properties of the brain endothelial cell membrane

Anna Seelig 2007 J Mol Neurosci 33:32



Flexibility of membrane lipid chains

- Lipid bilayer: liquid crystalline state, crystals perpendicular to surface
- Aniosotropic (*cf.* isotropic octanol, hexadecane).
- Average order fatty acyl chains: high close to head group, low in centre of membrane.
- ↑Order: high % lipids with small polar headgroups (PE, SM, cholesterol).
- ↓Order: high % unsaturated fatty acyl chains, increased concentrations amphiphilic guest molecules (e.g. drugs).
- Transmembrane proteins good match with lipid bilayer properties – hardly influence bilayer properties.

SYNG-PQ-00471771

Properties of the brain endothelial cell membrane

Anna Seelig 2007 J Mol Neurosci 33:32

- Lateral packing density (Π_M) mN/m: intestinal barrier 28, BBB 35
- Energy required for membrane insertion $\Delta W = A_D.\Pi_M$ (cross-sectional area x packing density).
- Lipid:water partition coefficient ↓ with ↑A_D and (Π_M).
- Molecules spanning half membrane (long chain FA, lipids) move by flip-flop.
- Charged molecules can insert, but only uncharged form can cross hydrophobic core.
- For CNS entry: limiting cross-sectional area ~AD70-80Å^2, ionization constant pK_a = 4 (acids) – 10 (bases).

SYNG-PQ-00471772

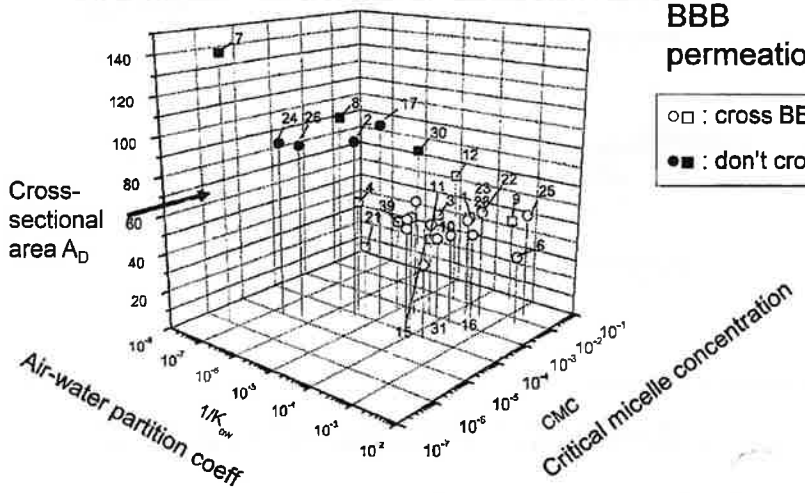
Properties of the brain endothelial cell membrane

Anna Seelig 2007 J Mol Neurosci 33:32

3-D calibration diagram for BBB permeation

○□ : cross BBB

●■ : don't cross

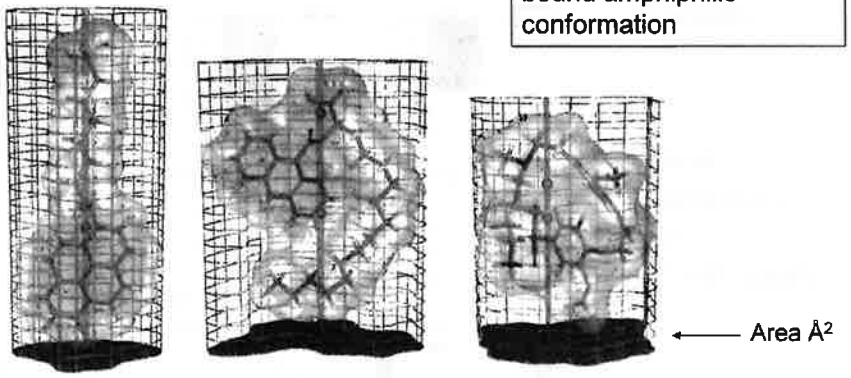


SYNG-PQ-00471773

Shapes of Fatty Acids *vs.* Verapamil

Anna Seelig 2007 J Mol Neurosci 33:32

Molecules in membrane-bound amphiphilic conformation

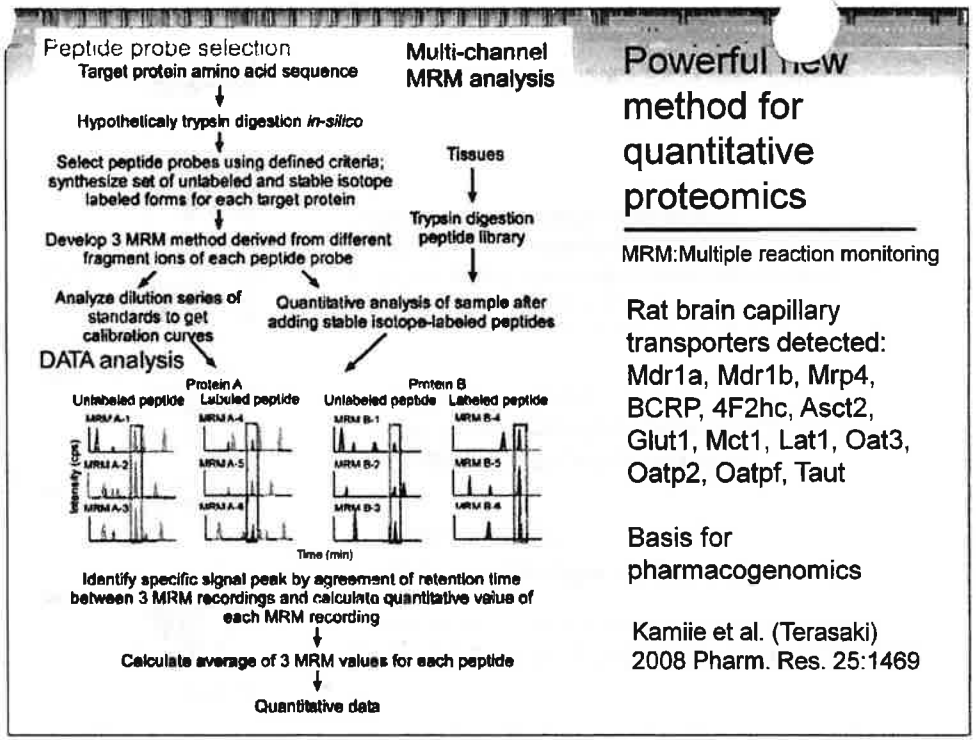


Area Å²

Pyrene nonanoic Acid (14) (high passive influx)

Antroyloxystearic acid (15) (low passive influx)

Verapamil (12) (Pgp efflux)



Powerful new method for quantitative proteomics

MRM:Multiple reaction monitoring

Rat brain capillary transporters detected: Mdr1a, Mdr1b, Mrp4, BCRP, 4F2hc, Asct2, Glut1, Mct1, Lat1, Oat3, Oatp2, Oatpf, Taut

Basis for pharmacogenomics

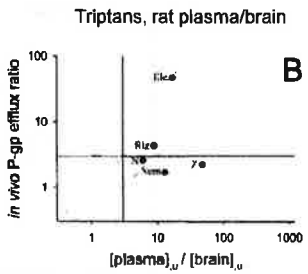
Kamiie et al. (Terasaki) 2008 Pharm. Res. 25:1469

Efficacy with low brain penetration

Triptans
- Zolmitriptan and sumatriptan
- $Brain_u/Plasma_u$ = 0.02, 0.08

(Kalvass et al 2007 Drug Metab Dis 35, 660-666)

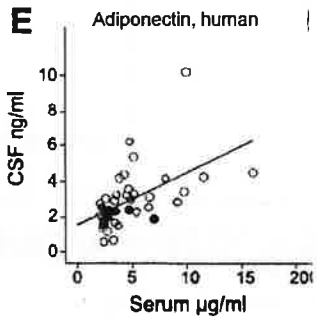
Reasons?
- Removal by CSF bulk flow
- Non-CNS target (vascular)?



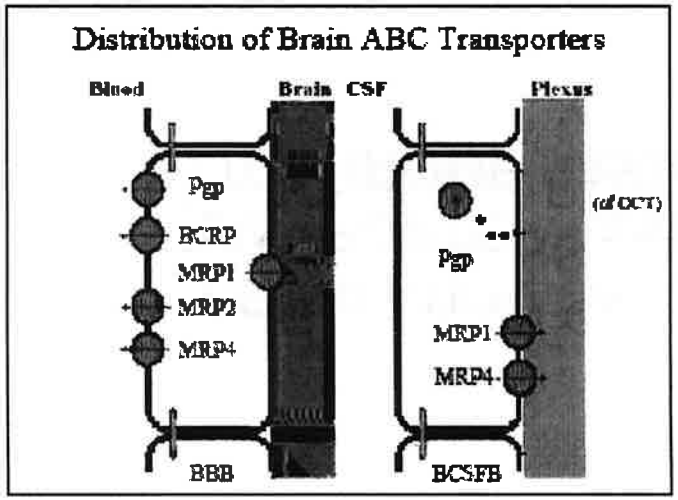
Adiponectin 150kDa
- i.v. injection = weight loss in leptin-deficient obese mice
- Detected in CSF 3hrs after i.v.
- CSF/serum = 0.001

(Neumeier et al 2007 Am J Physiol Endo & Metab 293, E965-E969)

Reasons?
- Small blood-CSF barrier penetration
- Sites of action AdipoR in hypothalamus and paraventricular nucleus close to CSF
- Rapid degradation (therefore difficult to detect)?

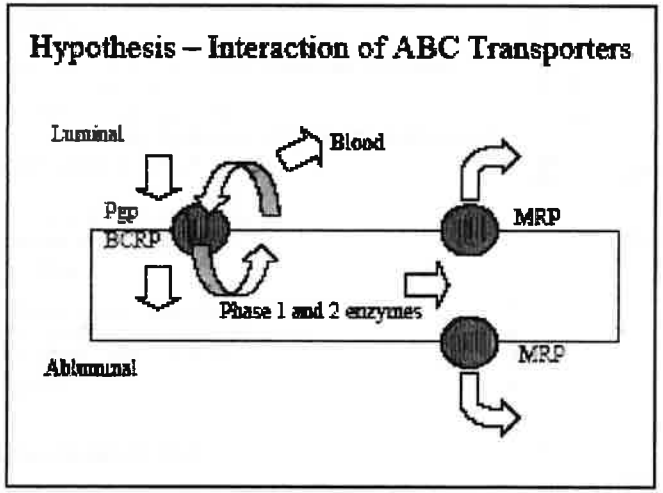


Functional drug efflux transporters, rat



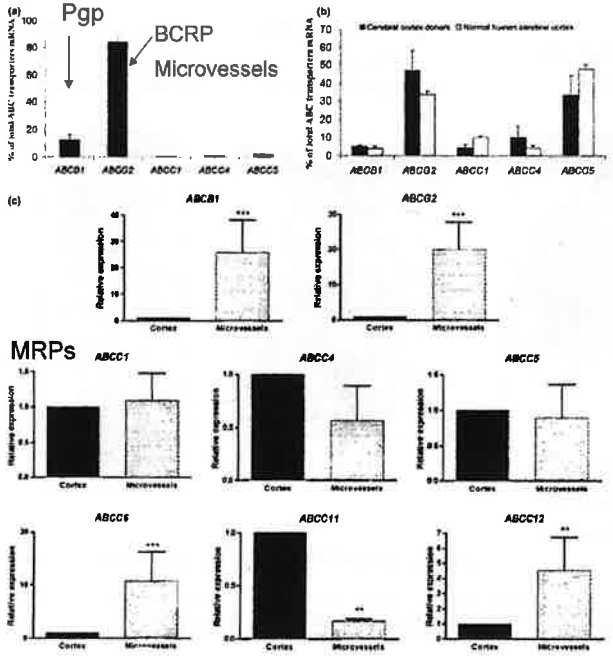
G Fricker

ABC Transporters: efflux and metabolism



G Fricker 2007

REGULATION OF TRANSPORTERS and CYTOCHROME P450s

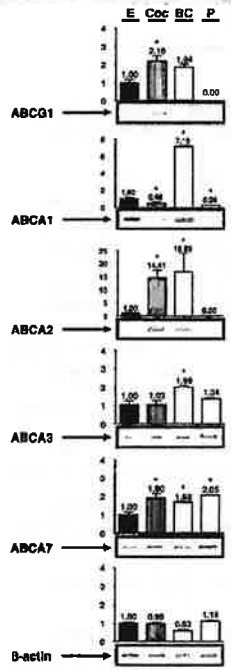


Cortex

Human brain: ABC transporter genes

Relative expression

Dauchy et al. 2008 J Neurochem 107:1518



Role of BBB in cerebral sterol homeostasis

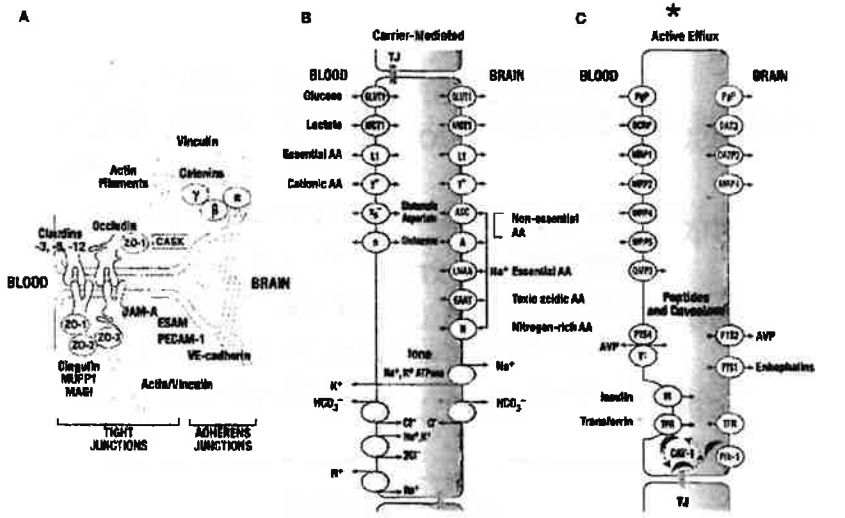
ABC Transporter expression bovine BCEC

- Coculture with astrocytes (Coc)
- with bovine capillary extracts BC)
- with pericytes (P)

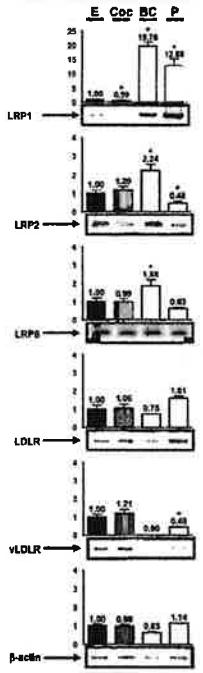
ABCG1: cholesterol efflux
ABCA1: ApoE- dependent cholesterol release
ABCA7: ApoA1-dependent cholesterol release
ABCA2, 3,7 induced by cholesterol

Gosselet et al. 2009 Brain Res. 1249:34

Regulation of transporter expression



Zlokovic 2008 Neuron 57:178-201



Receptors of the LDL-R family

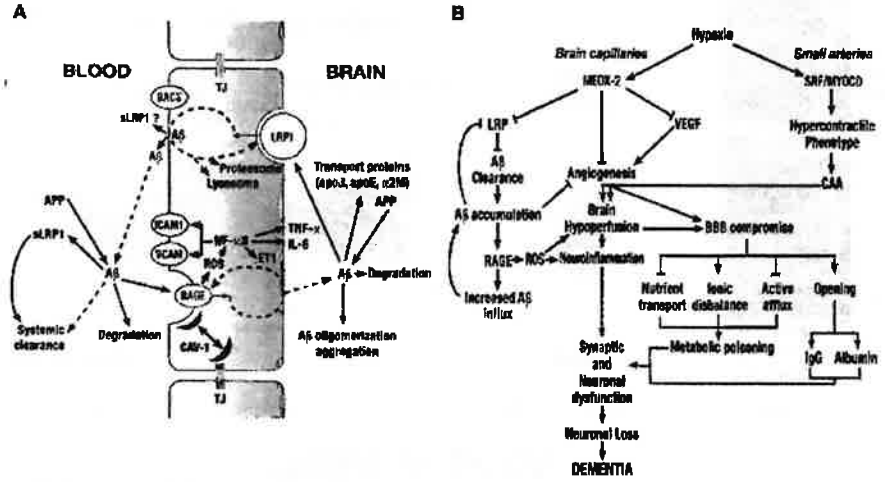
Lipoprotein receptor expression bovine BCEC

- Coculture with astrocytes (Coc)
- with bovine capillary extracts BC)
- with pericytes (P)

Gosselet et al. 2009 Brain Res. 1249:34

Role of BBB in Alzheimer's Disease : Aβ transport

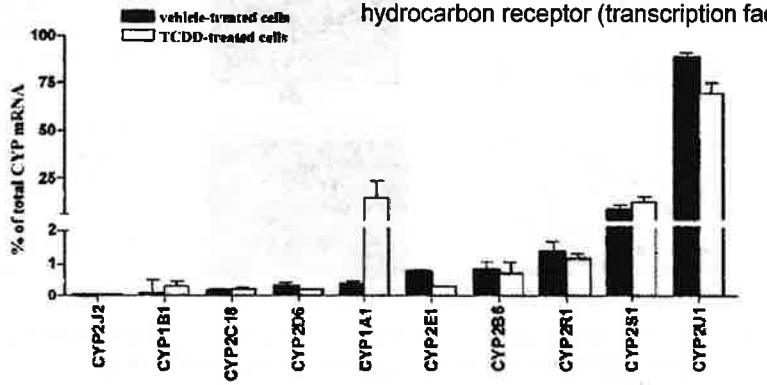
Modulation in hypoxia



Zlokovic 2008 Neuron 57:178-201

Expression profiles of CYP genes in hCMEC/D3 cells

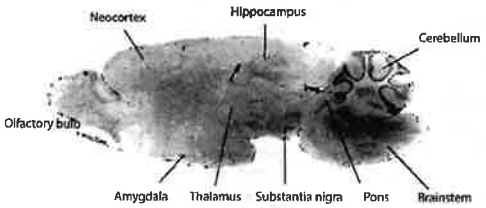
TCDD - agonist for AhR – aryl hydrocarbon receptor (transcription factor)



Dauchy et al. 2009 Biochem Pharmacol 77:897

P450 in brain

Mouse brain



CYP2C29, phenytoin-treated mouse

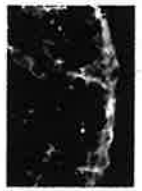
BBB



CYP2B1 (Rat)

Pons – Pia Mater





Regions with strong P450 expression:

Barrier regions (Blood-brain barrier & CSF- brain barrier)
Steroidogenic & steroid-metabolising regions of the brain

RP Meyer et al., Curr Drug Metab (2007), 8(4), 297-306.

SYNG-PQ-00471788

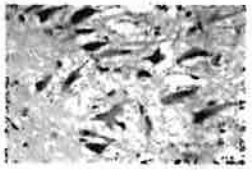
P450 & AR in human hippocampus

Androgen receptor- and CYP3A4-expression are enhanced in hippocampal pyramidal neurons of patients with temporal lobe epilepsy (TLE)

CA2 pyramidal neurons

Patient with TLE, treated with carbamazepine

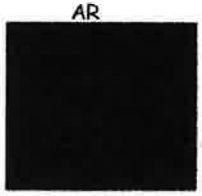


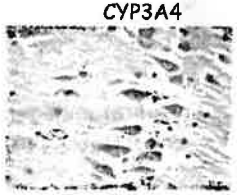


AR

CYP3A4

Control patient, (accident victim) untreated, no neurological symptoms





N. Killer et al. Epilepsia (2009) in press

SYNG-PQ-00471787

SUMMARY

- Wnt signalling important in angiogenesis, development of BBB phenotype
- Significant regulation of expression (and activity) for active efflux transporters
- Some reported regulation of other solute transporters
- Regulation of receptor-mediated transcytosis
- Regulation of cytochrome P450s

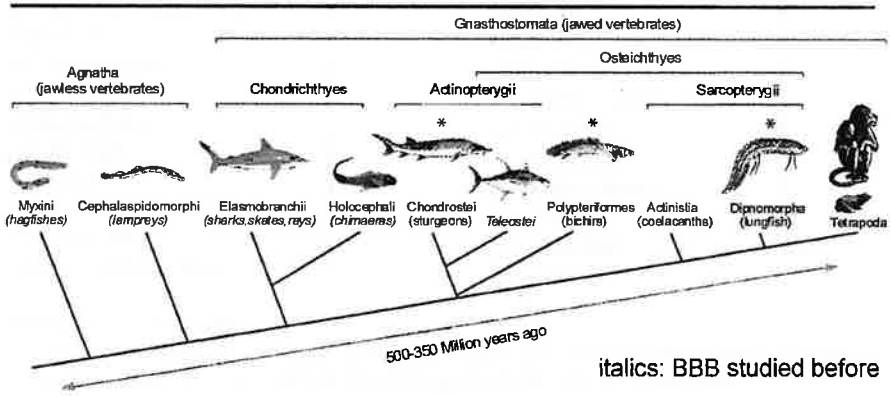
➢ *Physical, transport and enzymatic barrier – all regulated*

SYNG-PQ-00471786

SPECIES DIFFERENCES

SYNG-PQ-00471789

Evolution of BBB

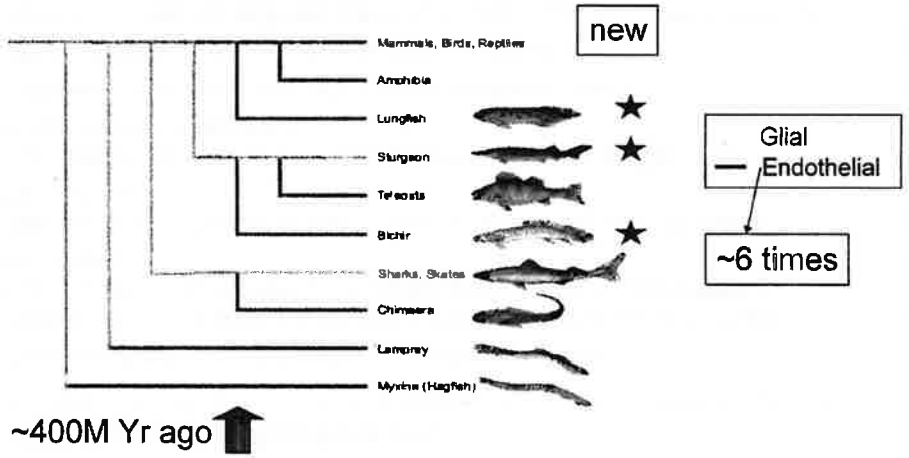


italics: BBB studied before

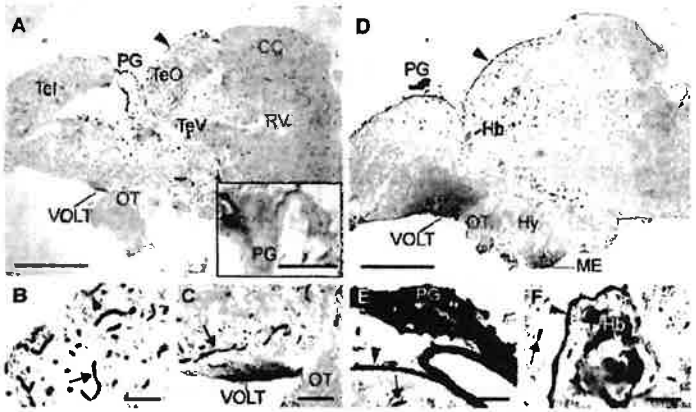
*New studies : Sturgeon, Bichir, Lungfish

Bundgaard & Abbott (2008) Glia 56 (7):699-708

Shift of barrier layers during evolution



Adult Zebrafish BBB (Teleost, endothelial)



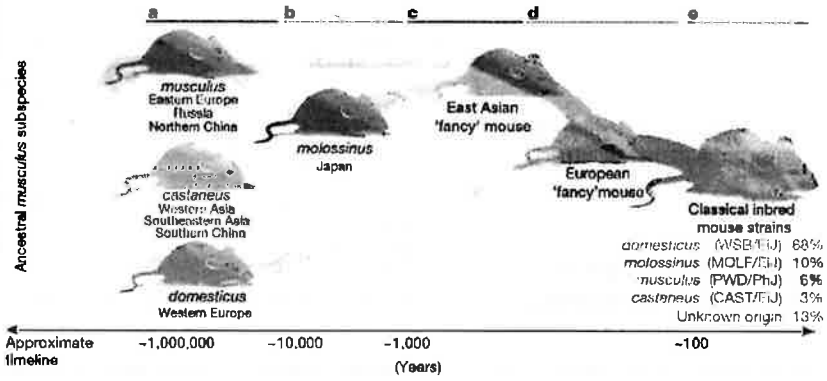
Tight junction proteins:
ZO-1
Claudin 5

HRP

Sulfo-NHS-biotin

Jeong et al. 2008
Brain Res Bull 75:619

Limited origin of inbred mice strains



Frazer et al. 2007 Nature 4448:1050

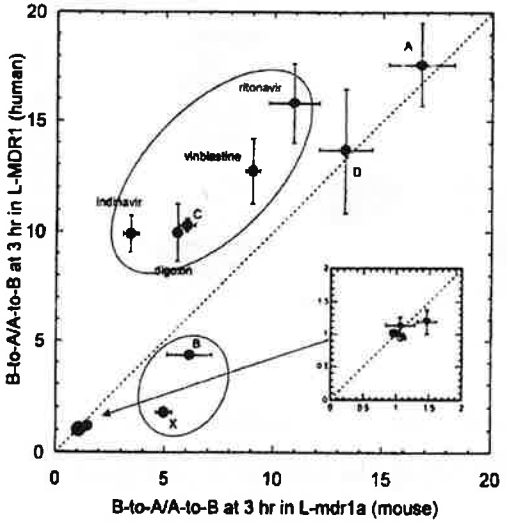
Variables in uptake

Age
↓Pgp (Toornvliet et al 2004)

↑Body mass index (↑venous pressure)
Reduced CSF drainage, elevated CSF drug concentration
(Seyfert et al 2002)

Pathology
'Sticky' lumen – binds protein, increases Vi
(Poduslo et al 2007)
BBB breach (AD etc)

Differences human and mouse Pgp drug specificity



Basal to apical vs Apical to basal transport ratios

Transfected LLC-PK1 porcine renal epithelial cell line

Yamazaki et al. 2001 JPET 296:723

Regional differences

Leucine transport (rat)
Vmax Highest in cortex (greater capillary surface area?)
No differences in Km or Kd (*Smith et al J Cereb Blood Flow Metab. 1985 5:300)*
Blood flow (rat)
Highest in grey matter, caudate nucleus & occipital lobe (0.030ml/g/s)
Lowest in cerebellum and white matter (0.018ml/g/s) but highest sucrose space (*Rapoport et al 1979)*

Sucrose space (rat)
Olfactory bulb 4.68%
medulla
cerebellum
frontal lobe
Parietal grey
pons
occipital lobe
colliculus
thalamus + hypothalamus
hippocampus
caudate nucleus
white matte 1.14%

Blood flow
Parietal grey 0.040 ml/g/s
Colliculus
caudate nucleus
occipital lobe
frontal lobe
thalamus + hypothalamus
hippocampus
pons
medulla
white matter
Olfactory bulb
cerebellum 0.017 ml/g/s

Species differences

- Evolution of BBB – insights into origin mammalian barrier
- Need to document, understand species differences among mammals and human, to build in to modelling (including PBPK) and to avoid problems in extrapolation
- Take into account history of specific animal models, e.g. rodents, mouse strains, KO etc
- Size differences – will lead to scaling factors, especially for CBF, fluid compartments and dynamics
- Differences in anatomy and territory of cerebral vasculature
- PK (concentration *vs* time curve plasma); protein binding
- Passive permeability BBB well conserved. Justification for *in vitro* and animal models, PAMPA
- Uptake transporters – some differences, e.g. amino acid transporters, but functionally similar
- Efflux transporters – most variability especially MRPs (may be linked to metabolic differences)

** Note - some reported differences may relate to techniques used, se* *ity*

Species differences

- Disease models – many, few mimic closely the clinical condition – e.g. stroke, multiple sclerosis, Alzheimer's. Differ among themselves, and between species
- How to choose model? Need to check against human disorder to decide on relevance. May get mechanistic information from animal models, but finally require validation and methods to monitor therapy in humans (e.g. imaging, biopsies, post-mortem, blood and CSF sampling, microdialysis in patients)
- Some treatments effective in rodent models, not in humans (e.g. stroke therapies, AD..) Check and understand better the timeframe, window for intervention, balance of elements in pathology
- New therapeutic targets in early stages of disease, including BBB. Couple with early diagnosis of BBB disorder.
- Extrapolation, toxicology etc. Warrants BBB Club Symposium on this topic. Examples of current practice from companies?

BBB MODULATION

Agents that increase permeability

	BBB	Perineurium
Histamine (H_2), 5HT, bradykinin	+	-
Arachidonic acid	+	-
A23187	+	-
Bile salts (DOC)	+	+
Non-ionic detergents	+	+
Reactive oxygen species (ROS)	+	+
*Nitric oxide (NO high)	+	+
*Glutamate	+	?
*ATP, ADP, AMP	*+	?
*ET-1, Substance P	+	?
*Cytokines, *MIPs	+	?
*VEGF	+	?

*Secreted by astrocytes

Agents that decrease BBB permeability

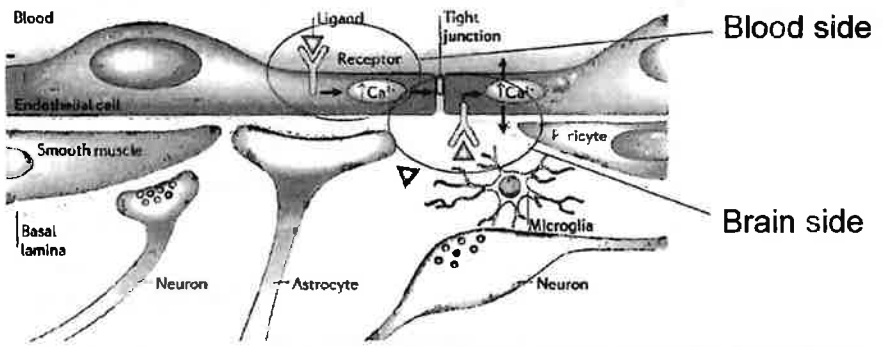
↑cAMP
- Histamine (H_1, high)
- Adrenomedullin
- Noradrenaline
- Dopamine
- Adenosine A2

Nitric oxide (NO, low)
Bradykinin? (low)

Corticosteroids
Fluvastatin

➢ BBB can be tightened by endogenous and exogenous agents

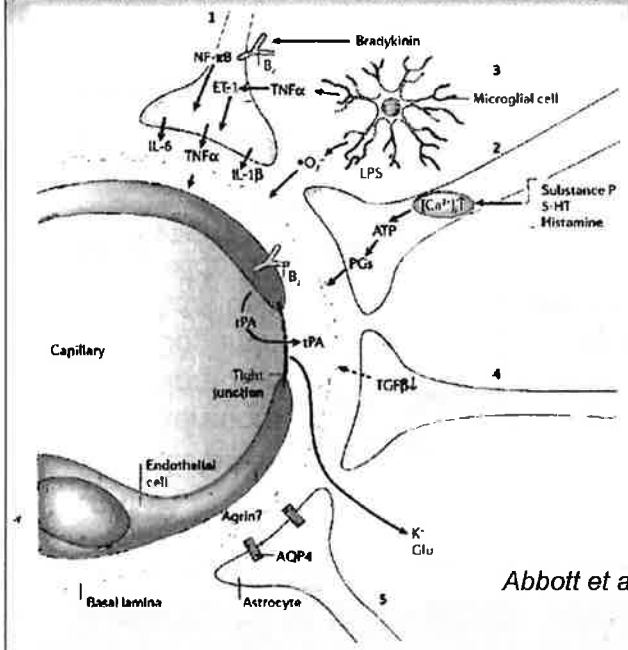
Source of modulating influences at BBB



Abbott et al 2006 Nature Rev Neurosci 7:41

- Physiology, pathology
- Therapeutic BBB modulation for drug delivery

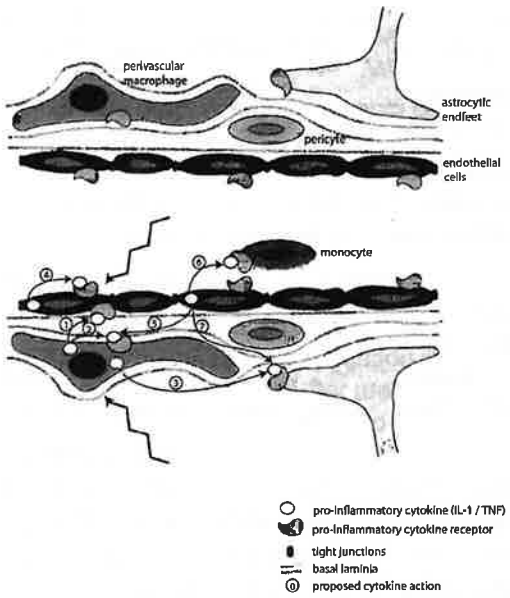
SYNG-PQ-00471802



Role of astrocytes and microglia in BBB modulation in pathology

Abbott et al 2006 Nature NS Revs

SYNG-PQ-00471803



Signalling within the *perivascular space: role in pathology

**especially post-capillary venules*

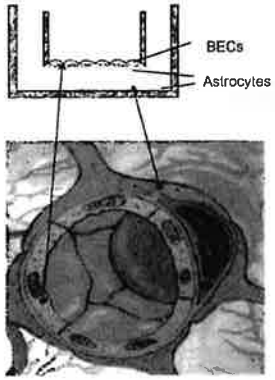
Konsman et al. 2007 Clin. Sci. 112, 1-25

SYNG-PQ-00471804

In vitro Models of the Blood-Brain Barrier

- **ECV304: Endothelial-epithelial phenotype, co-cultured with C6 glioma cells.** Hurst and Fritz. (1996) *J. Cell Physiol.* **167:** 81-88; Easton & Abbott (2001) *Brain Res.* **953**:157
- **Primary rat brain EC (RBEC) cultured with rat astrocytes.** Abbott et al. (1992) *J. Cell. Sci.* **103:** 23-37. Perrière et al. (2005) *J Neurochem* **93**:279.

S Fredriksson



Cross Section Brain Microvessel

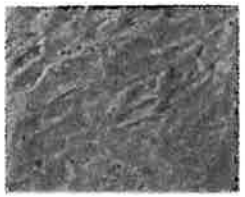




Glial cells

WPI EVOM STX-100
TEER 50-600 ohm.cm^2

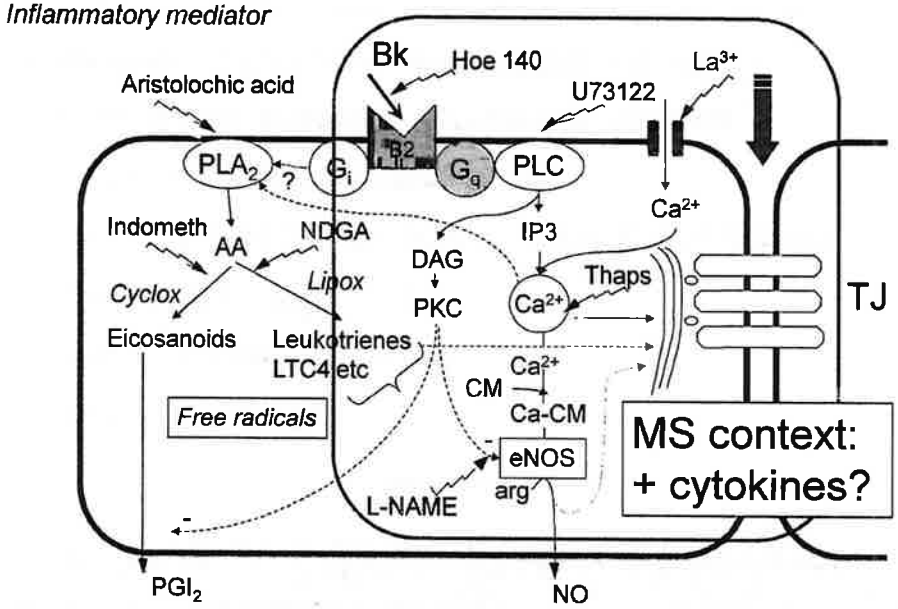
Use at ~4 weeks +



Endothelial cells

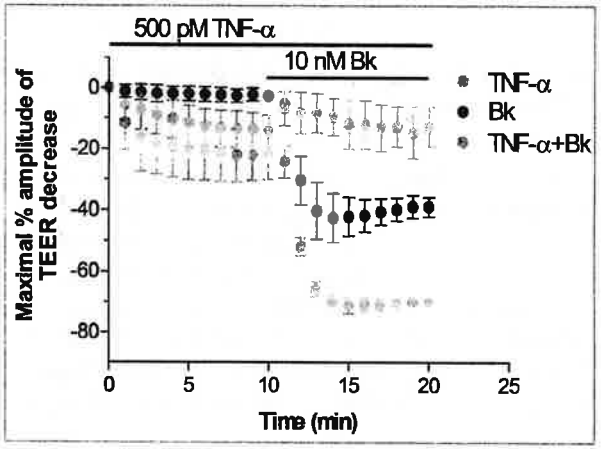
SYNG-PQ-00471805

Bradykinin modulation of rat brain endothelial cells



SYNG-PQ-00471806

Effect of TNFα on bradykinin response ?



Cytokine modulation

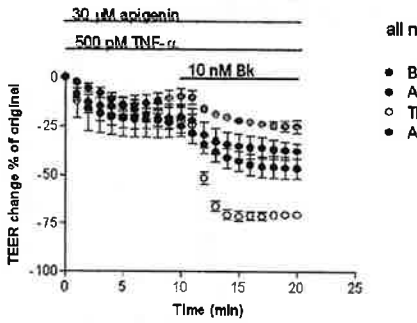
TNF-α augments Bk-induced TEER decrease

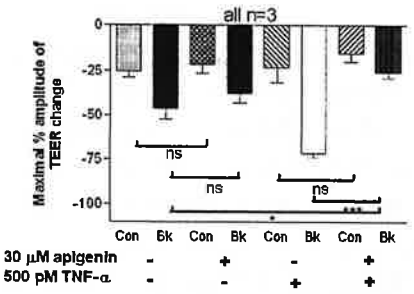
Can this be blocked ?

S Fredriksson

Mean ± SEM n=3

SYNG-PQ-00471807





all n=3

- Bk
- Apigenin+Bk
- TNF-α+Bk
- Apigenin+TNF-α+Bk

In vitro BBB

Flavonoid (flavone) Apigenin blocks augmenting effect of TNFα on Bk response

Mean ± SEM n=3

S Fredriksson

SYNG-PQ-00471808

Functions of BBB & BSCB: Effects of barrier breakdown?

1. Control molecular traffic, keep out toxins (precise connectivity: low cell death)
2. Ion homeostasis - optimal neural signalling
3. Low protein environment, limit proliferation
4. Separate CNS:PNS neurotransmitter pools; allow non-synaptic signalling
5. Immune surveillance with minimal inflammation, cell damage

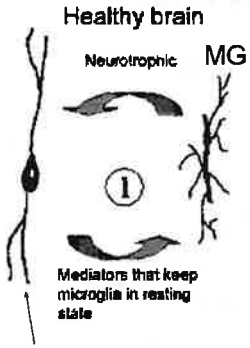
Disturbed CNS barriers : increased neuronal damage

SYNG-PQ-00471809

MICROGLIA (MG)

- Resident immunocompetent cells of brain
- Derived from monocytes/macrophages
- Quiescent, resting morphology: dendritic
- Contribute to BBB induction in endothelium
- Activated in pathology - amoeboid





Vilhardt 2005 Int J Biochem Cell Biol 37:17

MICROGLIA AND THE BBB

- Resident immunocompetent cells of brain
- Derived from monocytes/macrophages
- Contain COX_2
- Synthesise prostaglandins: PGH_2-synthetase
- Target for NSAIDS: Indomethacin and aspirin block PGE_2 release with LPS

Resting microglia
↓ ← cytokines/adenosine
Proliferation
↓ ← chemokines
Migration and differentiation
↓
Activated = Macrophages (phagocytic)

FOCUS on ENDOTHELIAL ACTIVATION

Triggering stress:

- Viral or bacterial infection
- LPS, TNFα, IFNγ, IL-1β
- Anti-endothelial antibodies, immune complexes
- Injury, trauma, thrombin, toxins
- Heat shock, exercise, ischaemia, hypoxia
- Regional differences within CNS – leads to vulnerable sites? *(nerve roots, brain stem, subventricular zone)*

Pattern of endothelial activation in MS

- ↑ Adhesion molecules including ICAM-1, E-selectin, leukocyte traffic, access encephalitogenic T cells, attack neuronal and glial antigens, can lead to demyelination and neuron/axon loss
- ↑ Protein traffic, mitochondrial activity, ROS
- ↑ Secretion IL-1β, IL-6, PGE_2, SubsP
- Activation macrophages, microglia
- Opening endothelial TJ, loss of homeostasis, entry of toxins
- Mechanism(s) – may involve TNFα, IL-1β, NFκB…

➢ *If transient, mild, get BBB resealing, protection against further stress (pre-conditioning, requires endothelial-astrocyte interaction)*

➢ *If severe or chronic, get positive feedback cascades, neuronal damage…*

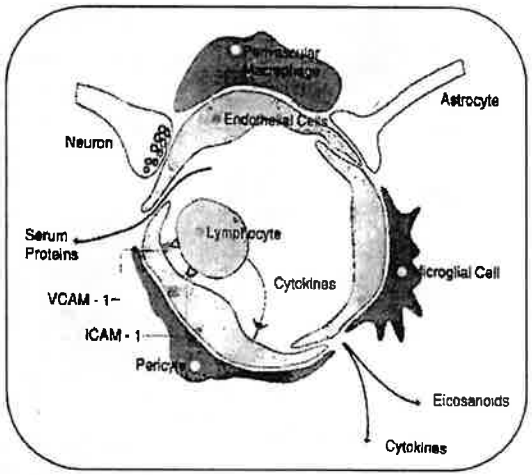
➢ *Hypothesis* : MS is a chronic BBB diseases

Therapies for BBB in CNS pathologies

BBB as target

Aim to maintain healthy BBB, and to repair BBB if damaged.

- Block reactive-oxygen species (ROS)-mediated damage
- Block leukocyte attachment and migration
- Block cytokine production



Characteristics of the brain endothelium

Value in MS – other CNS disorders?

The BBB in CNS pathologies

- Traumatic brain injury; BK ⇒ astrocyte release IL-6, BBB opening
- Hypertension; focal BBB opening
- Ischaemia, Stroke; disturbed BBB ion transport, two phase BBB opening, upregulation AQP4 astrocytes
- Inflammation, pain; changes in TJ, BBB permeability
- Multiple sclerosis; BBB opening, changes in laminin
- HIV-related dementia; BBB disruption
- Bacterial meningitis, encephalitis, sepsis; LPS ⇒ ROS, IL-6, IL-1β
- Brain tumours; Changes in TJs and glial endfeet
- Epilepsy; Changes in TJs and expression of MDR proteins
- Alzheimer's disease; changed expression Glut-1, AQP4, reduced P-gp ⇒ reduced Aβ efflux
- Parkinson's disease; reduced efficacy P-gp

➢ *Target and strategies for therapy*

CONCLUSIONS

- Damage to CNS barriers may be triggering or exacerbating event in CNS pathologies (MS, lupus, epilepsy...)
- Chronic low-grade BBB dysfunction could explain many features of disease progression
- Need better and earlier diagnostic tests for barrier damage; treat at-risk individuals
- Target prophylaxis and therapies to CNS barriers

➢ ***Future perspectives***

Acknowledgements

The BBB Group KCL

BBB modulation, physiology and pathology

- Paul Fraser
- Alex Easton, Diana Dolman, Lais Mendonca, Janet Taylor
- Sarah Fredriksson, Adjanie Patabendige, Siti Yusof

Collaborators

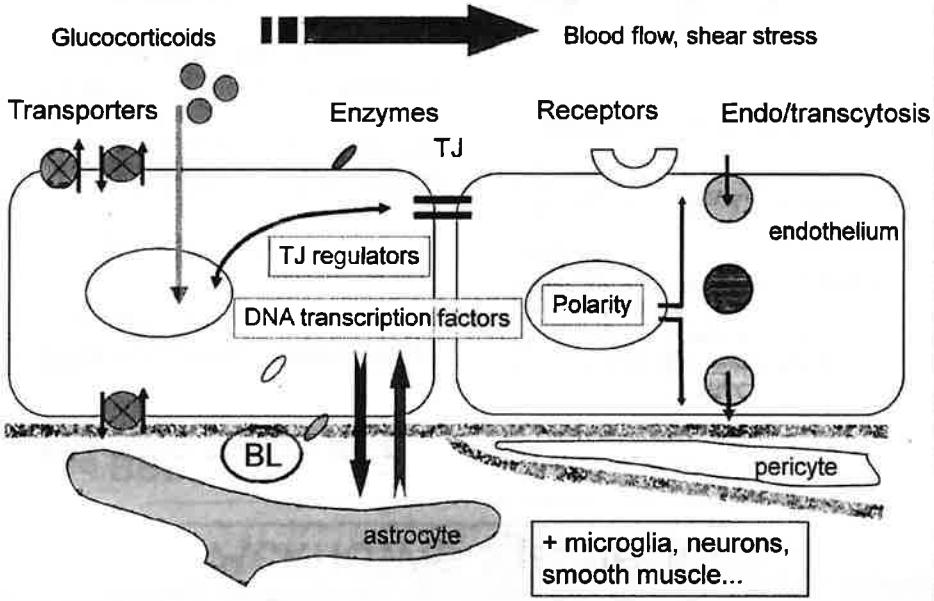
- KCL - Ken Smith, Catherine Rice-Evans, Marcus Rattray
- St Thomas' Hospital - Graham Hughes
- Budapest - Ester Domotor, Ildiko Sipos, Vera Adam-Vizi
- Cleveland - Damir Janigro

Supported by:

- The UK MS Society and UCB

BBB FUNCTION and DEVELOPMENT

BBB INDUCTION : SUMMARY



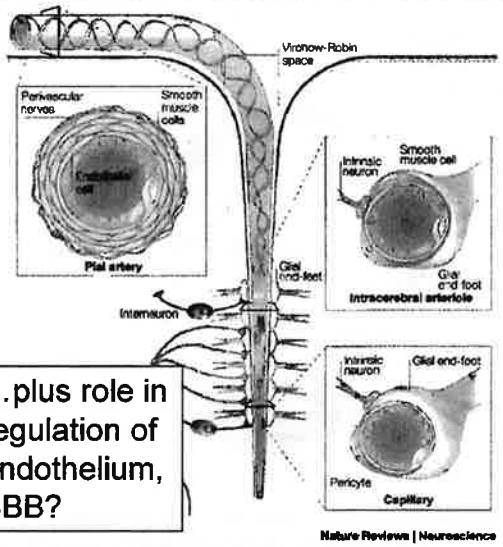
The Neurovascular Unit

Artery, arteriole, capillary

Neurons
Glial cells
Endothelial cells
+ *associated cells*

Role in regulation of regional blood flow : *Neural activity increases flow*

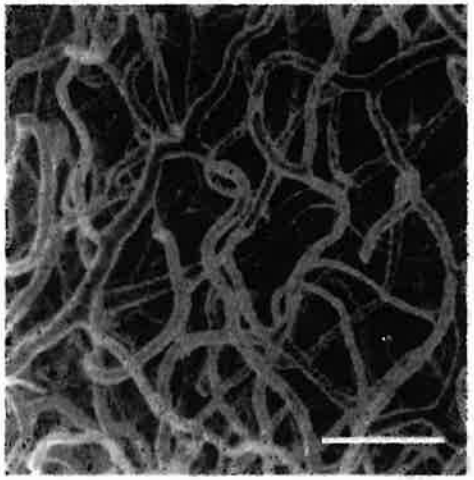
…plus role in regulation of endothelium, BBB?



Iadecola 2004 Nat Rev Neurosci 5:347

BRAIN MICROVESSELS

Cast of rat thalamus



Human brain: ~ 1200 g
Capillary length: ~ 650 km
Endothelial volume: ~ 1 ml
Mean distance: ~ 40 µm
Lumen diameter: ~ 3 µm
Surface area: ~ 12 m^2

Rat Brain: ~ 2 g
Endothelial volume: ~ 1 µl

Scanning EM
Bar = 50µm

THE CONCEPT OF A BLOOD-BRAIN BARRIER



Paul Ehrlich 1914
d.20/08/1915



T. cruzei From: "die blut" Frankfurt 2001

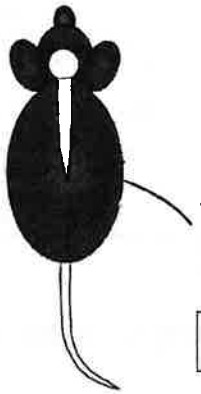


Trypan Blue (C60D)

SYNG-PQ-00471822

GOLDMANN'S 1st and 2nd EXPERIMENTS

1st (Ehrlich)



Trypan Blue
intravenous
injection

body stained
CNS unstained

2nd

Trypan Blue
intrathecal
injection

body unstained
CNS stained



SYNG-PQ-00471823

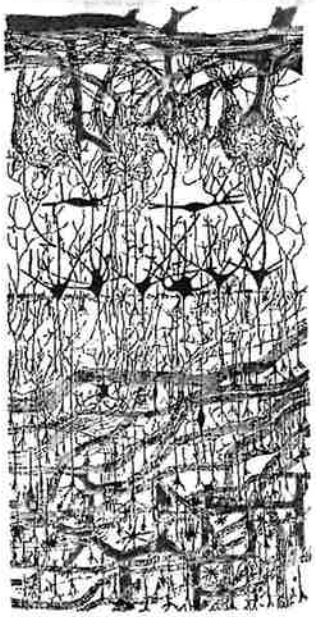
Critical role of synapses in integrated CNS function

Golgi 1875: regional specialisations in synaptic zones :
dog olfactory bulb

- *High activity*
- *High vascularity*

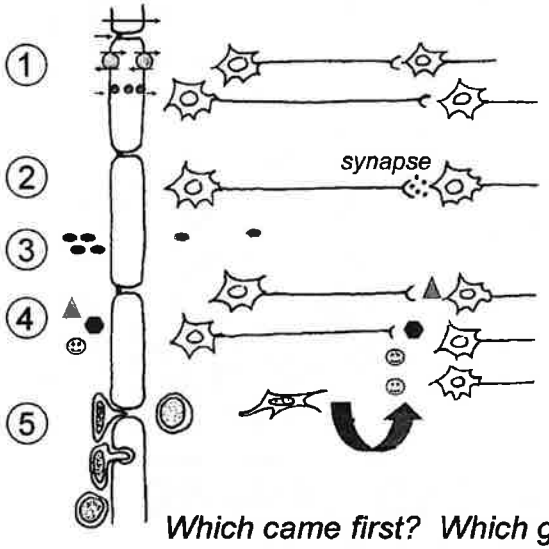
⇒

∴Need barrier



SYNG-PQ-00471824

FUNCTIONS OF BBB



Molecular traffic

Ion regulation

Low protein

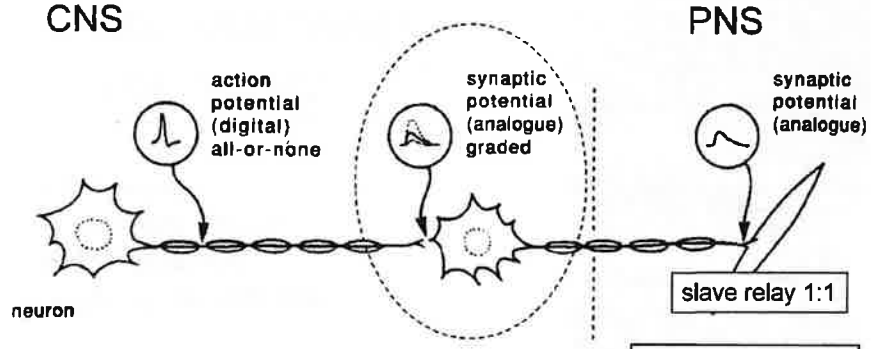
Signalling

'Silent' immune surveillance

Which came first? Which gave most advantage?

SYNG-PQ-00471825

SIGNALLING IN THE NERVOUS SYSTEM

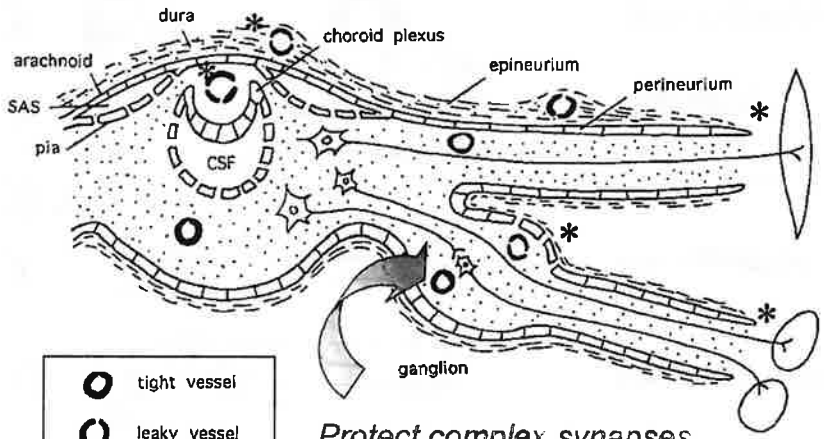


- Greatest need for ionic homeostasis around CNS synapses

Key selective advantage : evolution of BBB

SYNG-PQ-00471826

Barriers in CNS and PNS



Protect complex synapses, sense organs

Relevance to drug delivery, pathologies

SYNG-PQ-00471827

KING'S College LONDON

Myth 1

The BBB in the neonate is immature and leaky compared with that of the adult

SYNG-PQ-00471828

Development of BBB

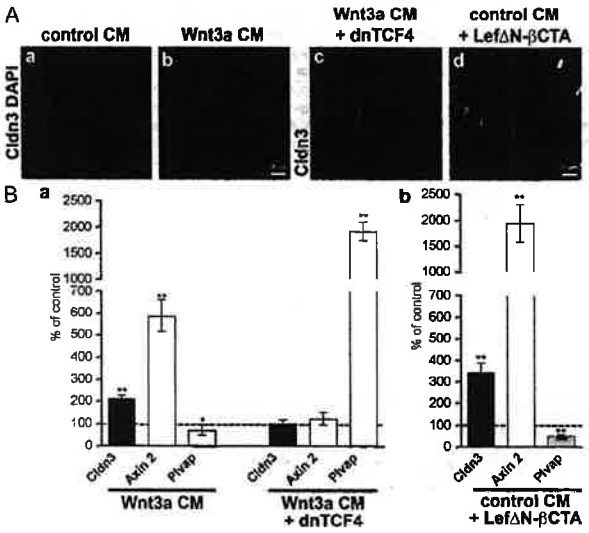
1. Evidence for leaky perinatal BBB

Injected Tracer Horseradish Peroxidase (HRP)	Species	Stage	Body wt g	Injection volume (% blood vol.)	Increase in plasma protein
Wakai and Hirokawa (1981)	Chick	E9	1.56	5-10%	2x
Risau et al. (1986)	Mouse	E13	0.083	100-300%	1%
Vorbrodt et al (1986)	Mouse	Newborn	1.4	100%	2-3x
Stewart and Hayakawa (1987)	Mouse	E15	0.26	Not stated	4x

From: Saunders 1992

SYNG-PQ-00471829

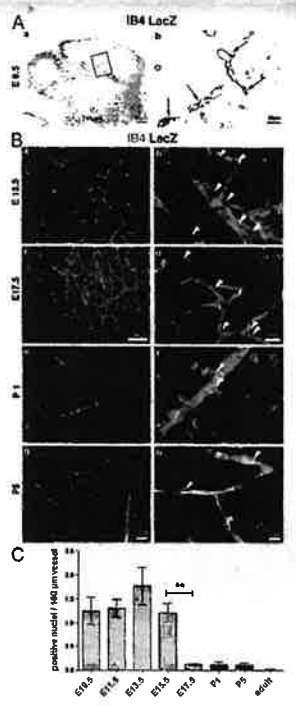
Tight junctional Claudin-3 upregulation by β-catenin



Claudin-3 upregulation requires transcriptionally active rather than junctional β-catenin in mouse brain endothelial cells in vitro

Liebner et al. J. Cell Biol. 2008:183:409-417

Cldn3 up-regulation requires transcriptionally active rather than junctional β-cat in MBEs in vitro. (A, a–c; and B, a) MBEs were either treated with Wnt3aCM or control CM and infected with dnTCF4 adenovirus or a control. (A, a–c) IF stainings for Cldn3. dnTCF4 abrogated the effect of Wnt3aCM on junctional Cldn3. Quantitative RT-PCR for Cldn3 (n = 3; **, P = 0.0095), Plvap (n = 3; *, P = 0.035), and Axin2 (n = 3; **, P = 0.004) with Wnt3aCM and for Plvap (n = 3; **, P = 0.002) with control CM and dnTCF4. (A, d; and B, b) MBEs infected with LefΔN-βCTA lentivirus or a control. Junctional localization of Cldn3 increased in IF stainings. Quantitative RT-PCR for Cldn3 (n = 3; **, P = 0.002), Plvap (n = 3; **, P = 0.008), and Axin2 (n = 3; **, P < 0.0001). Controls are set as 100% (dashed lines). Green nuclei show an anti–VS-TAG (c) and an anti–HA-TAG (d) staining of dnTCF4 and LefΔN-βCTA, respectively, confirming infection of the target cells. Error bars represent SEM.



Wnt signalling in angiogenesis

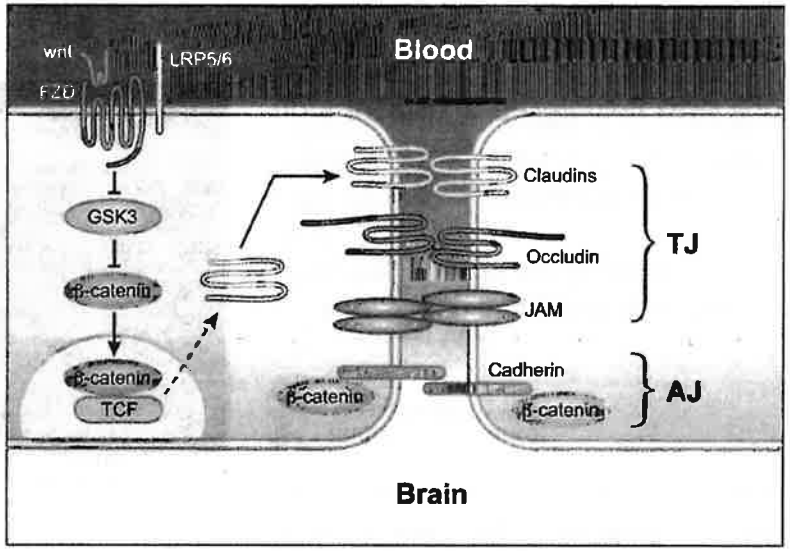
Mouse brain
IB4 : endothelial marker
LacZ : Wnt

- Canonical Wnt signaling active in endothelial cells during brain angiogenesis
- Becomes progressively down-regulated during vessel maturation
- Corresponds to period of Claudin-3 upregulation in developing BBB tight junctions

Liebner et al. 2008 J. Cell Biol. 183:409-417

Canonical Wnt signaling is active in ECs during brain angiogenesis and becomes progressively down-regulated during vessel maturation. (A) LacZ whole-mount stained (blue) E9.5 BAT-Gal embryos sectioned and counterstained for Isolectin B4 (IB4; red). Panel b is a higher magnification of the boxed area in panel a. Arrows point to nuclear LacZ reporter gene staining. (B, a–d) Whole-mount hindbrain staining for LacZ (reflection; red) and IB4 (green) of BAT-Gal embryos (E13.5 and 17.5) analyzed by confocal microscopy. Arrowheads indicate LacZ-positive nuclei. (B, e–h) Staining of brain cryosections from postnatal BAT-Gal pups (P1 and P5) for LacZ (immunofluorescence [IF], red) and IB4 (green). Arrowheads indicate LacZ-positive nuclei. Positive nuclei outside the vascular system indicate active Wnt signaling in the brain parenchyma. (C) Quantification of LacZ-positive nuclei per 100-µm vessel length shows a significant decrease from E15.5 to 17.5 (five fields per hindbrain; three brains; **, P = 0.0003). Error bars represent SEM.

Wnt signaling and the BBB



Polakis J. Cell Biol. 2008:183:371-373

SYNG-PQ-00471834

Wnt signaling and the BBB. Depiction of the primary constituents of the tight junction (TJ) and the adherens junction (AJ) at the interface between endothelial cell plasma membranes. Activation of Wnt receptors FZD and LRP5/6 inhibits GSK3 to stabilize β-catenin that in turn enters the nucleus to activate T cell factor (TCF)–dependent transcription. This drives Cldn3 gene activation either directly or indirectly (dashed line arrow), and the resulting Cldn protein reinforces the tight junction. JAM, junctional adhesion molecule.

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Enzyme-Replacement Therapy from Birth Delays the Development of Behavior and Learning Problems in Mucopolysaccharidosis Type IIIA Mice

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ABSTRACT

Mucopolysaccharidosis type IIIA (MPS IIIA; Sanfilippo syndrome) is a lysosomal storage disorder characterized by severe CNS degeneration, resulting in behavioral abnormalities and loss of learned abilities. Early treatment is vital to prevent long-term clinical pathology in lysosomal storage disorders. We have used naturally occurring MPS IIIA mice to assess the effects of long-term enzyme-replacement therapy initiated either at birth or at 6 wk of age. MPS IIIA and normal control mice received weekly i.v. injections of 1 mg/kg recombinant human sulfamidase until 20 wk of age. Sulfamidase is able to enter the brain until the blood-brain barrier completely closes at 10–14 d of age. MPS IIIA mice that were treated from birth demonstrated normal weight, behavioral characteristics, and ability to learn. MPS IIIA mice that wer[illegible]d from birth performed significantly better in the Morri[illegible]ze than MPS IIIA mice that were treated from 6 wk of age or left untreated. A reduction in storage vacuoles in cells of the CNS in MPS IIIA mice that were treated from birth is consistent with the improvements observed. These data suggest that enzyme that enters the brain in the first few weeks of life, before the blood-brain barrier matures, is able to delay the development of behavior and learning difficulties in MPS IIIA mice. (*Pediatr Res* 56: 65–72, 2004)

Abbreviations

BBB, blood-brain barrier
ERT, enzyme-replacement therapy
LSD, lysosomal storage disorder
MPS, mucopolysaccharidosis
rhNS, recombinant human sulfamidase

SYNG-PQ-00471836

ATTACHMENT C

IN THE COURT OF COMMON PLEAS OF PHILADELPHIA COUNTY
FIRST JUDICIAL DISTRICT OF PENNSYLVANIA
CIVIL TRIAL DIVISION

IN RE: PARAQUAT PRODUCTS LIABILITY LITIGATION ***APPLICABLE TO ALL CASES***	**May Term, 2022** **No. 559**

SYNGENTA CROP PROTECTION, LLC AND SYNGENTA AG'S AMENDED RESPONSES AND OBJECTIONS TO PLAINTIFFS' THIRD SET OF REQUESTS FOR ADMISSION

Defendants Syngenta Crop Protection, LLC and Syngenta AG ("Syngenta") provide the following Amended Responses and Objections to Plaintiffs' Third Set of Requests for Admission served on August 2, 2024 ("Responses"). Syngenta's investigations are ongoing, and Syngenta reserves the right to update these Responses should additional information become available. Syngenta designates these Responses Confidential pursuant to the August 19, 2022 Protective Order. Subject to its General Objections below, Syngenta responds as follows.

REQUESTS FOR ADMISSION

REQUEST FOR ADMISSION NO. 1:

Admit that Syngenta has never submitted a request to the EPA to amend its product labeling to include a warning that Paraquat is neurotoxic.

RESPONSE TO REQUEST FOR ADMISSION NO. 1:

Syngenta objects to this Request as vague and ambiguous as to the undefined word "neurotoxic" and to the ambiguous phrase "submitted a request." Subject to and without waiving its objections, Syngenta admits that it has not provided information on its paraquat labels indicating that paraquat is neurotoxic, for the reasons outlined below.

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Syngenta states that the contents of its product label and the label's communications to workers are and have always been focused on the safe use of paraquat products. That approach is consistent with EPA guidance, and Syngenta's product labels have been approved by the EPA.

The EPA's review of pesticide labeling is governed by EPA's Title 40 CFR Part 156 of the Code of Federal Regulations ("CFR"), "Labeling Requirements for Pesticides and Devices," and the EPA's regulations govern what is included on each product label. Syngenta further states that the EPA requires that hazard information on labels be supported by scientific data, and the scientific data, including the EPA's own findings, do not support inclusion of such a warning on the label for any of Syngenta's paraquat-containing products.

REQUEST FOR ADMISSION NO. 2:

Admit that Syngenta has never submitted a request to the EPA to amend its product labeling to include information regarding the association between Paraquat exposure and Parkinson's disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 2:

Syngenta objects to this Request as vague and ambiguous as to the undefined word "association" and to the ambiguous phrase "submitted a request." Subject to and without waiving its objections, Syngenta admits that it has not provided information on its paraquat labels indicating that paraquat is associated with an increased risk of Parkinson's disease, for the reasons outlined below.

Syngenta states that the contents of its product label and the label's communications to workers are and have always been focused on the safe use of paraquat products. That approach is consistent with EPA guidance, and Syngenta's product labels have been approved by the EPA.

The EPA's review of pesticide labeling is governed by EPA's Title 40 CFR Part 156 of the Code of Federal Regulations ("CFR"), "Labeling Requirements for Pesticides and Devices," and

the EPA's regulations govern what is included on each product label. Syngenta further states that the EPA requires that hazard information on labels be supported by scientific data, and the scientific data, including the EPA's own findings, do not support inclusion of such a warning on the label for any of Syngenta's paraquat-containing products.

REQUEST FOR ADMISSION NO. 3:

Admit that Syngenta has never submitted a request to the EPA to amend its product labeling to include a warning that exposure to Paraquat may cause or contribute to Parkinson's disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 3:

Syngenta objects to this Request as vague and ambiguous as to the phrase "cause or contribute to" and to the ambiguous phrase "submitted a request." Subject to and without waiving its objections, Syngenta admits that it has not provided information on its paraquat labels indicating that paraquat may cause or contribute to Parkinson's disease for the reasons outlined below.

Syngenta states that the contents of its product label and the label's communications to workers are and have always been focused on the safe use of paraquat products. That approach is consistent with EPA guidance, and Syngenta's product labels have been approved by the EPA.

The EPA's review of pesticide labeling is governed by EPA's Title 40 CFR Part 156 of the Code of Federal Regulations ("CFR"), "Labeling Requirements for Pesticides and Devices," and the EPA's regulations govern what is included on each product label. Syngenta further states that the EPA requires that hazard information on labels be supported by scientific data, and the scientific data, including the EPA's own findings, do not support inclusion of such a warning on the label for any of Syngenta's paraquat-containing products.

REQUEST FOR ADMISSION NO. 4:

Admit that Syngenta has never warned consumers in the United States that Paraquat can cause Parkinson's disease.

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RESPONSE TO REQUEST FOR ADMISSION NO. 4:

Syngenta objects to this Request as vague and ambiguous as to the undefined word "warned" and the ambiguous phrase "can cause." Subject to and without waiving its objections, Syngenta states that it does not agree with the premise of the Request, i.e. that paraquat can cause Parkinson's disease, given that the scientific findings reached by independent, peer-reviewed research do not conclude that paraquat causes Parkinson's disease. Syngenta further states that the scientific data, including the EPA's own findings, do not support the statement that paraquat can cause Parkinson's disease. Moreover, "[a] consensus exists in the scientific community that the available evidence does not warrant a claim that paraquat causes Parkinson's disease." Douglas L. Weed, *Does paraquat cause Parkinson's disease? A review of reviews*, Neurotoxicology Vol. 86 (Sept. 2021).

Syngenta admits that it has never warned consumers in the United States that Paraquat can cause Parkinson's disease because such a conclusion is not supported by the scientific evidence. But Syngenta denies that it has never informed consumers about the alleged link between Paraquat and Parkinson's disease through various mediums, including a section on its website that has discussed an alleged link between Paraquat and Parkinson's disease, which currently includes a section titled "Does paraquat cause Parkinson's disease?" *See* Syngenta, *Paraquat*, https://www.syngenta.com/en/paraquat-in-the-media#parkinsons-disease (last accessed Oct. 29, 2024). Syngenta has included information about these allegations on its website for years and, whenever there are updates, has included information regarding the state of the science for consumers to review. To the extent this Request suggests that paraquat causes Parkinson's disease, Syngenta denies.

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REQUEST FOR ADMISSION NO. 5:

Admit that Syngenta has never warned consumers in the United States that Paraquat exposure may be associated with Parkinson's disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 5:

Syngenta objects to this Request as vague and ambiguous as to the undefined word "warned" and the vague and ambiguous phrase "may be associated." Subject to and without waiving its objections, Syngenta denies this Request. Despite the fact that "[a] consensus exists in the scientific community that the available evidence does not warrant a claim that paraquat causes Parkinson's disease," Douglas L. Weed, *Does paraquat cause Parkinson's disease? A review of reviews*, Neurotoxicology Vol. 86 (Sept. 2021), Syngenta has included information about the alleged association between paraquat and Parkinson's Disease on its website for years and, whenever there are updates, has included information regarding the state of the science for consumers to review. *See* Syngenta, *Paraquat*, https://www.syngenta.com/en/paraquat-in-the-media#parkinsons-disease (last accessed Oct. 29, 2024). . To the extent this Request suggests that paraquat causes Parkinson's Disease, Syngenta denies.

REQUEST FOR ADMISSION NO. 6:

Admit that Syngenta has never warned consumers in the United States that Paraquat is neurotoxic.

RESPONSE TO REQUEST FOR ADMISSION NO. 6:

Syngenta objects to this Request as vague and ambiguous as to the undefined words "warned" and "neurotoxic." Subject to and without waiving its objections, Syngenta states that it does not agree with the premise of the Request, which seems to suggest that Paraquat is neurotoxic in all circumstances, regardless of dose, method of use, and other related variables. Syngenta denies that Paraquat is neurotoxic to humans using Paraquat consistent with label instructions.

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Syngenta further incorporates its Response to Request for Admission No. 1. Syngenta denies that it has never informed consumers about the alleged link between paraquat and Parkinson's disease, and Paraquat's toxicity profile more generally. For example, Syngenta has included a section on its website that has discussed an alleged link between paraquat and Parkinson's disease, which currently includes a section titled "Does paraquat cause Parkinson's disease?" *See* Syngenta, *Paraquat*, https://www.syngenta.com/en/paraquat-in-the-media#parkinsons-disease (last accessed Oct. 29, 2024). Syngenta has also included information about Paraquat's toxicity profile on its website. *See e.g.*, https://web.archive.org/web/20170617102740/http://paraquat.com/safety/safety-to-humans (noting that "Paraquat is not a neurotoxicity hazard" while noting that Paraquat "is toxic by the oral route," among others). Syngenta has included human health and safety information about Paraquat on its website for years and, whenever there are updates, has included information regarding the state of the science for consumers to review.

REQUEST FOR ADMISSION NO. 7:

Admit that Syngenta never warned Plaintiff Douglas Nemeth that Paraquat is neurotoxic.

RESPONSE TO REQUEST FOR ADMISSION NO. 7:

Syngenta objects to this Request as duplicative of Plaintiffs' Third Requests for Admission Nos. 1-6. Subject to and without waiving its objections, Syngenta admits that it never included a warning on its product labels that Paraquat is neurotoxic for the reasons explained in its Responses to Request for Admission Nos. 1-6.

REQUEST FOR ADMISSION NO. 8:

Admit that Syngenta never warned Plaintiff Douglas Nemeth that Paraquat exposure may be associated with Parkinson's disease.

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RESPONSE TO REQUEST FOR ADMISSION NO. 8:

Syngenta objects to this Request as duplicative of Plaintiffs' Third Requests for Admission Nos. 1-6. Subject to and without waiving its objections, Syngenta admits that it never included a warning on its product labels that Paraquat may be associated with Parkinson's disease for the reasons explained in its Responses to Request for Admission Nos. 1-6.

REQUEST FOR ADMISSION NO. 9:

Admit that Syngenta never warned Plaintiff Keith Lutz that Paraquat is neurotoxic.

RESPONSE TO REQUEST FOR ADMISSION NO. 9:

Syngenta objects to this Request as duplicative of Plaintiffs' Third Requests for Admission Nos. 1-6. Subject to and without waiving its objections, Syngenta admits that it never included a warning on its product labels that Paraquat is neurotoxic for the reasons explained in its Responses to Request for Admission Nos. 1-6.

REQUEST FOR ADMISSION NO. 10:

Admit that Syngenta never warned Plaintiff Keith Lutz that Paraquat exposure may be associated with Parkinson's disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 10:

Syngenta objects to this Request as duplicative of Plaintiffs' Third Requests for Admission Nos. 1-6. Subject to and without waiving its objections, Syngenta admits that it never included a warning on its product labels that Paraquat may be associated with Parkinson's disease for the reasons explained in its Responses to Request for Admission Nos. 1-6.

REQUEST FOR ADMISSION NO. 11:

Admit that Syngenta never warned Plaintiff Donald Mabs that Paraquat is neurotoxic.

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RESPONSE TO REQUEST FOR ADMISSION NO. 11:

Syngenta objects to this Request as duplicative of Plaintiffs' Third Requests for Admission Nos. 1-6. Subject to and without waiving its objections, Syngenta admits that it never included a warning on its product labels that Paraquat is neurotoxic for the reasons explained in its Responses to Request for Admission Nos. 1-6.

REQUEST FOR ADMISSION NO. 12:

Admit that Syngenta never warned Plaintiff Donald Mabs that Paraquat exposure may be associated with Parkinson's disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 12:

Syngenta objects to this Request as duplicative of Plaintiffs' Third Requests for Admission Nos. 1-6. Subject to and without waiving its objections, Syngenta admits that it never included a warning on its product labels that Paraquat may be associated with Parkinson's disease for the reasons explained in its Responses to Request for Admission Nos. 1-6.

REQUEST FOR ADMISSION NO. 13:

Admit that Syngenta never warned Plaintiff David Steele that Paraquat is neurotoxic.

RESPONSE TO REQUEST FOR ADMISSION NO. 13:

Syngenta objects to this Request as duplicative of Plaintiffs' Third Requests for Admission Nos. 1-6. Subject to and without waiving its objections, Syngenta admits that it never included a warning on its product labels that Paraquat is neurotoxic for the reasons explained in its Responses to Request for Admission Nos. 1-6.

REQUEST FOR ADMISSION NO. 14:

Admit that Syngenta never warned Plaintiff David Steele that Paraquat exposure may be associated with Parkinson's disease.

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RESPONSE TO REQUEST FOR ADMISSION NO. 14:

Syngenta objects to this Request as duplicative of Plaintiffs' Third Requests for Admission Nos. 1-6. Subject to and without waiving its objections, Syngenta admits that it never included a warning on its product labels that Paraquat may be associated with Parkinson's disease for the reasons explained in its Responses to Request for Admission Nos. 1-6.

REQUEST FOR ADMISSION NO. 15:

Admit that Syngenta never warned Plaintiff Wesley Lewis that Paraquat is neurotoxic.

RESPONSE TO REQUEST FOR ADMISSION NO. 15:

Syngenta objects to this Request as duplicative of Plaintiffs' Third Requests for Admission Nos. 1-6. Subject to and without waiving its objections, Syngenta admits that it never included a warning on its product labels that Paraquat is neurotoxic for the reasons explained in its Responses to Request for Admission Nos. 1-6.

REQUEST FOR ADMISSION NO. 16:

Admit that Syngenta never warned Plaintiff Wesley Lewis that Paraquat exposure may be associated with Parkinson's disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 16:

Syngenta objects to this Request as duplicative of Plaintiffs' Third Requests for Admission Nos. 1-6. Subject to and without waiving its objections, Syngenta admits that it never included a warning on its product labels that Paraquat may be associated with Parkinson's disease for the reasons explained in its Responses to Request for Admission Nos. 1-6.

REQUEST FOR ADMISSION NO. 17:

Admit that Syngenta never warned Plaintiff Stacey McGrath that Paraquat is neurotoxic.

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RESPONSE TO REQUEST FOR ADMISSION NO. 17:

Syngenta objects to this Request because Plaintiffs have voluntarily discontinued their case against Defendants with respect to Plaintiff McGrath.

REQUEST FOR ADMISSION NO. 18:

Admit that Syngenta never warned Plaintiff Stacey McGrath that Paraquat exposure may be associated with Parkinson's disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 18:

Syngenta objects to this Request because Plaintiffs have voluntarily discontinued their case against Defendants with respect to Plaintiff McGrath.

REQUEST FOR ADMISSION NO. 19:

Admit that Syngenta never warned Plaintiff Phyllis Welsh that Paraquat is neurotoxic.

RESPONSE TO REQUEST FOR ADMISSION NO. 19:

Syngenta objects to this Request because Plaintiffs have voluntarily discontinued their case against Defendants with respect to Plaintiff Welsh.

REQUEST FOR ADMISSION NO. 20:

Admit that Syngenta never warned Plaintiff Phyllis Welsh that Paraquat exposure may be associated with Parkinson's disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 20:

Syngenta objects to this Request because Plaintiffs have voluntarily discontinued their case against Defendants with respect to Plaintiff Welsh.

REQUEST FOR ADMISSION NO. 21:

Admit that Syngenta never warned Larry Bowen that Paraquat is neurotoxic.

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RESPONSE TO REQUEST FOR ADMISSION NO. 21:

Syngenta objects to this Request because Plaintiffs have voluntarily discontinued their case against Defendants with respect to Plaintiff Bowen.

REQUEST FOR ADMISSION NO. 22:

Admit that Syngenta never warned Plaintiff Larry Bowen that Paraquat exposure may be associated with Parkinson's disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 22:

Syngenta objects to this Request because Plaintiffs have voluntarily discontinued their case against Defendants with respect to Plaintiff Bowen.

REQUEST FOR ADMISSION NO. 23:

Admit that Syngenta never warned Plaintiff Stephen Skelton that Paraquat is neurotoxic.

RESPONSE TO REQUEST FOR ADMISSION NO. 23:

Syngenta objects to this Request as duplicative of Plaintiffs' Third Requests for Admission Nos. 1-6. Subject to and without waiving its objections, Syngenta admits that it never included a warning on its product labels that Paraquat is neurotoxic for the reasons explained in its Responses to Request for Admission Nos. 1-6.

REQUEST FOR ADMISSION NO. 24:

Admit that Syngenta never warned Plaintiff Stephen Skelton that Paraquat exposure may be associated with Parkinson's disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 24:

Syngenta objects to this Request as duplicative of Plaintiffs' Third Requests for Admission Nos. 1-6. Subject to and without waiving its objections, Syngenta admits that it never included a warning on its product labels that Paraquat may be associated with Parkinson's disease for the reasons explained in its Responses to Request for Admission Nos. 1-6.

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REQUEST FOR ADMISSION NO. 25:

Admit that Syngenta never warned Plaintiff Randy Parsley that Paraquat is neurotoxic.

RESPONSE TO REQUEST FOR ADMISSION NO. 25:

Syngenta objects to this Request because Plaintiffs have voluntarily discontinued their case against Defendants with respect to Plaintiff Parsley.

REQUEST FOR ADMISSION NO. 26:

Admit that Syngenta never warned Plaintiff Randy Parsley that Paraquat exposure may be associated with Parkinson's disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 26:

Syngenta objects to this Request because Plaintiffs have voluntarily discontinued their case against Defendants with respect to Plaintiff Parsley.

REQUEST FOR ADMISSION NO. 27:

Admit that Syngenta has never conducted any chronic animal toxicity studies on Paraquat formulations containing surfactants.

RESPONSE TO REQUEST FOR ADMISSION NO. 27:

Syngenta objects to this Request as vague and ambiguous with respect to the undefined phrase "chronic animal toxicity studies." Syngenta further states that it complies with the testing requirements for formulated products established by regulatory agencies, including short-term studies on the products and also by conducting numerous chronic-exposure animal studies on non-formulated paraquat. Scientifically, these chronic toxicity experiments are designed to study exposure to paraquat that is several orders of magnitude higher than any method of occupational exposure. The high doses of the active ingredient used in these studies not only assess the toxicity of paraquat itself but also any toxic effects which may be increased by the presence of other substances found in the formulations, such as surfactants, which could increase the absorption of

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paraquat. Syngenta further states that it has also conducted studies specifically to investigate the presence surfactants on dermal absorption. *See* Ward, R.J., *Paraquat: In Vitro Absorption From a 200k 1-1 SL Formulation Through Human Epidermis* (2004); Clowes, *Paraquat: 200 g/l SL Formulation:* In Vitro *Absorption of Paraquat Through Human Epidermis* (2000). Those studies concluded that the addition of a non-ionic surfactant to the paraquat formulation does not meaningfully increase dermal absorption of paraquat. *See id.* These findings are consistent with biomonitoring studies, which also demonstrate that applicators who use surfactants per the label do not exhibit meaningfully different exposures. *See* Meier, *Paraquat: Worker Exposure During Mixing, Loading and Application of Gramoxone Extra to Pecans Using Vehicle Mounted, Ground Boom Equipment* (1995). Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not identified chronic-exposure animal studies that it conducted using paraquat formulations containing surfactants.

REQUEST FOR ADMISSION NO. 28:

Admit that Syngenta has never conducted any neurotoxicity studies on Paraquat formulations containing surfactants.

RESPONSE TO REQUEST FOR ADMISSION NO. 28:

Syngenta objects to this Request as vague and ambiguous with respect to the undefined phrase "neurotoxicity studies." Subject to and without waiving its objections, denied.

REQUEST FOR ADMISSION NO. 29:

Admit that Syngenta is not precluded by any applicable law, regulation, or ordinance from conducting an animal study on paraquat formulations containing surfactants.

RESPONSE TO REQUEST FOR ADMISSION NO. 29:

Syngenta objects to this Request to the extent that it calls for a legal conclusion regarding applicable laws and regulations of testing of paraquat products that are not the subject of this

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lawsuit. Syngenta further states that it conducts toxicity tests in accordance with applicable laws, including tests on formulated products. Syngenta further objects to this Request to the extent that it is intended to imply that Syngenta has not conducted animal studies on paraquat formulations containing surfactants, because it has done so as evidenced by in its Response to Request for Admission No. 27. Subject to and without waiving its objections, Syngenta admits that it is not aware of a law, regulation, or ordinance that would preclude it from conducting an animal study with paraquat formulations containing surfactant.

REQUEST FOR ADMISSION NO. 30:

Admit that Syngenta has never conducted any chronic animal toxicity studies assessing the effect of Paraquat on dopaminergic neurons in the brain.

RESPONSE TO REQUEST FOR ADMISSION NO. 30:

Syngenta objects to the undefined phrase "chronic animal toxicity studies" as vague and ambiguous. Syngenta further objects to this Request to the extent that it seeks information that is the subject of expert testimony. Subject to and without waiving its objections, Syngenta admits that it has tested dopaminergic neurons in the brains of animals under various conditions and dosing regimens, including in the brains of C57BL mice.

REQUEST FOR ADMISSION NO. 31:

Admit that cyanide is routinely detected in Paraquat technical.

RESPONSE TO REQUEST FOR ADMISSION NO. 31:

Syngenta objects to this Request as vague and ambiguous as to the undefined term "routinely." Subject to and without waiving its objections, Syngenta admits that there can be residual cyanide in the technical grades of paraquat produced via the ammonia cyanide process. Syngenta tests for this in the final product storages, wherein the upper acceptable limit for free

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cyanide is 0.2g/kg (i.e., 200 parts per million). Syngenta typically detects amounts half of this value. Syngenta states that the cyanide content would be further diluted to some degree, depending on the exact formulation process and recipe.

REQUEST FOR ADMISSION NO. 32:

Admit that EPA employee Thurston Morton attended the University of Rhode Island with Syngenta's Head of Regulatory for North America, John Abbott.

RESPONSE TO REQUEST FOR ADMISSION NO. 32:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Thurston Morton" who "attended the University of Rhode Island" without providing additional identifying information. Subject to and without waiving its objections, Syngenta admits that John Abbott testified that a Thurston Morton attended a program at the University of Rhode Island for some indeterminate amount of time while Mr. Abbott was receiving his Ph.D. from the University of Rhode Island. Abbott Dep. Tr. 125:21-126:23. Syngenta further states that Mr. Abbott testified that he had "very limited interactions with" this Thurston Morton and that he did not "stay in touch" with Mr. Morton after their "limited interactions" at the University of Rhode Island. *Id.*

REQUEST FOR ADMISSION NO. 33:

Admit that EPA employee Thurston Morton was one of the authors of the Paraquat Human Health Risk Assessment dated June 26, 2019.

RESPONSE TO REQUEST FOR ADMISSION NO. 33:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Thurston Morton" who is an "EPA employee" without providing additional identifying information. Syngenta further objects to "the Paraquat Human Health Risk Assessment" as vague and ambiguous. Syngenta also objects to this Request to the

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extent that this information is equally available to Plaintiffs. Subject to and without waiving its objections, Syngenta admits that a Thurston Morton is listed as one of persons that sent a memorandum titled "Paraquat Dichloride: Draft Human Health Risk Assessment in Support of Registration Review," found at https://bit.ly/3AjVPKz, to the Office of Pesticide Programs at the EPA.

REQUEST FOR ADMISSION NO. 34:

Admit that EPA employee Thurston Morton was one of the authors of the HED Response to Comments on the Paraquat: Response to Comments on the Draft Human Health Risk Assessment dated September 4, 2020.

RESPONSE TO REQUEST FOR ADMISSION NO. 34:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Thurston Morton" who is an "EPA employee" without providing additional identifying information. Syngenta further objects to "HED Response to Comments on the Paraquat: Response to Comments on the Draft Human Health Risk Assessment dated September 4, 2020" as vague and ambiguous. Syngenta also objects to this Request to the extent that this information is equally available to Plaintiffs. Subject to and without waiving its objections, Syngenta states that, based on a reasonable investigation to date, it has not identified such a response dated September 4, 2020, but it has identified such a publication dated September 24, 2020. *See* SYNG-PQ-PA-00017310. Syngenta thus denies the Request as written.

REQUEST FOR ADMISSION NO. 35:

Admit that EPA employee Thurston Morton was one of the authors of the HED Response to Comments on the Proposed Interim Decision for Registration Review and updated Occupational Handler Exposure and Risk Estimates for Paraquat dated June 22, 2021.

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RESPONSE TO REQUEST FOR ADMISSION NO. 35:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Thurston Morton" who is an "EPA employee" without providing additional identifying information. Syngenta further objects to "HED Response to Comments on the Proposed Interim Decision for Registration Review and updated Occupational Handler Exposure and Risk Estimates for Paraquat dated June 22, 2021" as vague and ambiguous. Syngenta also objects to this Request to the extent that this information is equally available to Plaintiffs. Subject to and without waiving its objections, Syngenta admits that an individual named Thurston Morton is listed as one of the persons that sent a memorandum titled "**Paraquat:** HED Response to Comments on the Proposed Interim Decision for Registration Review and updated Occupational Handler Exposure and Risk Estimates," dated June 22, 2021.

REQUEST FOR ADMISSION NO. 36:

Admit that EPA employee Thurston Morton applied for a job at Syngenta while he was an employee with the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 36:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Thurston Morton" who is an "EPA employee" without providing additional identifying information. Subject to and without waiving its objections, Syngenta admits that an individual named Thurston Morton applied for a role at Syngenta in February 2023 and a different role in June 2023. Syngenta further states that, based on a reasonable investigation, Mr. Morton was not ultimately hired by Syngenta.

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REQUEST FOR ADMISSION NO. 37:

Admit that EPA employee Thurston Morton spoke to Syngenta's Head of Regulatory for North America, John Abbott, about working at Syngenta while Thurston Morton was an employee with the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 37:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Thurston Morton" who is an "EPA employee" without providing additional identifying information. Syngenta further objects to this Request to the extent that it asks for information outside of Syngenta's possession, custody, and control. Subject to and without waiving its objections, Syngenta admits that John Abbott testified that an individual named Thurston Morton "expressed an interest" in working at Syngenta while Mr. Morton was an employee of the EPA. Abbott Dep. Tr. 124:4-125:20. Based on a reasonable investigation, Syngenta states that Mr. Morton was never hired by Syngenta.

REQUEST FOR ADMISSION NO. 38:

Admit that Carolina Vaccari is the lead author of the published study: Paraquat and Parkinson's disease: a systematic review and meta-analysis of observational studies J Toxicol Environ Health B Crit Rev 2019;22(5-6):172-202.

RESPONSE TO REQUEST FOR ADMISSION NO. 38:

Syngenta admits that Carolina Vaccari is the first author listed in the cited study.

REQUEST FOR ADMISSION NO. 39:

Admit that Carolina Vaccari communicated with Syngenta employees about working at Syngenta prior to the publication of Paraquat and Parkinson's disease: a systematic review and meta-analysis of observational studies J Toxicol Environ Health B Crit Rev 2019;22(5-6):172202.

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RESPONSE TO REQUEST FOR ADMISSION NO. 39:

Syngenta admits that Carolina Vaccari communicated with Syngenta employees about the possibility of working at Syngenta at least as early as 2017, when she was considered for a role as a product safety analyst. *See, e.g.*, SYNG-PQ-19352267.

REQUEST FOR ADMISSION NO. 40:

Admit that Carolina Vaccari was hired by Syngenta after the publication of Paraquat and Parkinson's disease: a systematic review and meta-analysis of observational studies J Toxicol Environ Health B Crit Rev 2019;22(5-6):172-202.

RESPONSE TO REQUEST FOR ADMISSION NO. 40:

Syngenta admits that Carolina Vaccari started working for Syngenta after the publication of the article referenced in Request No. 40. Syngenta admits that it hired Carolina Vaccari for a role in Syngenta's product-safety group in Brazil; she started in that role in December 2019. Syngenta states that it appears that "Paraquat and Parkinson's disease: a systematic review and meta-analysis of observational studies J Toxicol Environ Health B Crit Rev 2019;22(5-6):172-202" was published in September 2019.**REQUEST FOR ADMISSION NO. 41:**

Admit that EPA staff toxicologist Jennifer Ryman-Rasmussen attended a meeting between Syngenta and the EPA in March 2010 where Syngenta presented information and data relating to Paraquat and Parkinson's Disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 41:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Jennifer Ryman-Rasmussen" who is an "EPA staff toxicologist" without providing additional identifying information. Syngenta further objects to this Request as vague and ambiguous as it asks about meeting attendees at a "March 2010" meeting "between Syngenta and the EPA" where "Syngenta presented information and data relating to Paraquat and Parkinson's Disease." Subject to and without waiving its objections, Syngenta states that, based on a reasonable investigation to date, it has not identified evidence of a Ms. Ryman-Rasmussen attending such a meeting in March 2010, but admits that a Ms. Ryman-Rasmussen

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attended a May 2010 meeting that meets the description contained in the Request. *See* SYNG-PQ_06518293. Syngenta thus denies the Request as written.

REQUEST FOR ADMISSION NO. 42:

Admit that Jennifer Ryman-Rasmussen applied for a job at Syngenta in 2011.

RESPONSE TO REQUEST FOR ADMISSION NO. 42:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Jennifer Ryman-Rasmussen" without providing additional identifying information. Subject to and without waiving its objections, Syngenta admits that it appears from SYNG-PQ-ATR-04534099 and SNYG-PQ-ATR-07876571 that Ms. Ryman-Rasmussen applied for a job at Syngenta in 2011, though it has not been able to find information in its HR system verifying that to be true. Syngenta further notes that, in the potential job application it identified, Ms. Ryman-Rasmussen states: "I am applying to Syngenta because of Syngenta's reputation for good science and quality work[.]" SYNG-PQ-ATR-04534099. Syngenta further states that Ms. Rasmussen was never hired.

REQUEST FOR ADMISSION NO. 43:

Admit that Alberto Grimaldo Orozco was a former employee of Syngenta.

RESPONSE TO REQUEST FOR ADMISSION NO. 43:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Alberto Grimaldo Orozco" without providing additional identifying information. Syngenta further objects to this Request as irrelevant. Subject to and without waiving its objections, Syngenta admits that an Alberto Grimaldo Orozco, D.O.B. 09/17/1965, was a former employee of Syngenta and Zeneca Mexicana.

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REQUEST FOR ADMISSION NO. 44:

Admit that Alberto Grimaldo Orozco worked at Syngenta or its predecessor companies between 1994 and 2009.

RESPONSE TO REQUEST FOR ADMISSION NO. 44:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Alberto Grimaldo Orozco" without providing additional identifying information. Syngenta further objects to this Request as irrelevant. Subject to and without waiving its objections, Syngenta admits that an Alberto Grimaldo Orozco, D.O.B. 09/17/1965, worked at Zeneca Mexicana beginning around 1994 or 1995, and at Syngenta from 2000 to 2009.

REQUEST FOR ADMISSION NO. 45:

Admit that Alberto Grimaldo Orozco was Head of Quality Control at Syngenta's San Luis Potosi formulation plant in Mexico.

RESPONSE TO REQUEST FOR ADMISSION NO. 45:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Alberto Grimaldo Orozco" without providing additional identifying information. Syngenta further objects to this Request as irrelevant. Subject to and without waiving its objections, Syngenta admits that Alberto Grimaldo Orozco, D.O.B. 09/17/1965, was Chief of Quality Control at a Syngenta San Luis Potosi plant in Mexico for some amount of time.

REQUEST FOR ADMISSION NO. 46:

Admit that Alberto Grimaldo Orozco, a former employee of Syngenta was diagnosed with Parkinson's Disease in 2008.

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RESPONSE TO REQUEST FOR ADMISSION NO. 46:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Alberto Grimaldo Orozco" without providing additional identifying information. Syngenta further objects to this Request as irrelevant. Syngenta further objects to this Request to the extent that it requests information that is outside Syngenta's possession, custody, or control. Subject to and without waiving its objections, Syngenta admits that in 2009 it received an initial medical diagnostic from the Mexican Social Security Institute (IMSS), which stated that Alberto Grimaldo Orozco, D.O.B. 09/17/1965, had been diagnosed with Parkinson's disease.

REQUEST FOR ADMISSION NO. 47:

Admit that physicians with the Mexican Social Security Institute (IMSS) concluded that Alberto Grimaldo Orozco's occupational exposure to Paraquat contributed to his development of Parkinson Disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 47:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Alberto Grimaldo Orozco" without providing additional identifying information. Syngenta also objects to the phrase "contributed to his development" as vague and ambiguous. Syngenta further objects to this Request to the extent that it requests information that is outside Syngenta's possession, custody, or control. Syngenta further objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that in 2009 it received an initial medical diagnostic from the Mexican Social Security Institute (IMSS), which stated that Alberto Grimaldo Orozco, D.O.B. 09/17/1965, had been diagnosed with Parkinson's disease. Syngenta admits that the medical resolution mentioned exposure to pesticides generally. Syngenta

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further explains that the diagnostic did not include any scientific support for the theory that pesticides contribute to the development of Parkinson's disease. Syngenta also admits that the Institute Mexicano del Seguro Social San Luis Potosi drafted a report that after reviewing a body of contemporaneous literature, concluded that "there was a broad association in the worker between inhaled dermal exposure of paraquat in work activities and Parkinson's disease, for it is determined it is a working disease." SYNG-PQ-MDL-000423618, at -20. Syngenta further explains that the report does not specify which worker it is referring to. Syngenta further states that the report noted this worker's exposure to diquat and pyrethroid insecticides. *See id.* Unless specifically admitted herein, denied.

REQUEST FOR ADMISSION NO. 48:

Admit that Syngenta never informed the EPA of the finding of the Mexican Social Security Institute (IMSS) that Alberto Grimaldo Orozco's occupational exposure to Paraquat contributed to his development of Parkinson Disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 48:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Alberto Grimaldo Orozco" without providing additional identifying information. Syngenta also objects to the phrases "informed the EPA" and "contributed to his development" as vague and ambiguous. Syngenta also objects to this Request to the extent that it suggests that Syngenta was under a legal obligation to "inform[ ] the EPA" of a particular finding. Syngenta further objects to this Request as misleading because it suggests the Mexican Social Security Institute ("IMSS") found that paraquat specifically contributed to his development of Parkinson's disease.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation, it has not found evidence of submitting an IMSS finding about Mr. Orozco to the

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EPA. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 49:

Admit that Syngenta never reported Alberto Grimaldo Orozco's diagnosis of Parkinson's Disease to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 49:

Syngenta objects to this Request as vague and ambiguous to the extent that it asks for information about an individual named "Alberto Grimaldo Orozco" without providing additional identifying information. Syngenta also objects to the phrase "reported . . . to the EPA" as vague and ambiguous. Syngenta further objects to this Request to the extent that it suggests that Syngenta had a duty to report a particular finding to the EPA. Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence of submitting an IMSS finding about Mr. Orozco to the EPA. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never

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cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 50:

Admit that Dr. Ted Lock is a qualified expert on the transport of chemicals through the blood-brain barrier.

RESPONSE TO REQUEST FOR ADMISSION NO. 50:

Syngenta objects to this Request as vague and ambiguous as to the phrases "qualified expert" and "transport of chemicals through the blood-brain barrier." Syngenta also objects to this Request as a it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion. Subject to those objections, Syngenta admits that Dr. Ted Lock has the expertise to analyze studies on the transport of chemicals through the blood-brain barrier.

REQUEST FOR ADMISSION NO. 51:

Admit that Syngenta invited Dr. Ted Lock to provide his opinions on the ability of Paraquat to pass through the blood-brain barrier.

RESPONSE TO REQUEST FOR ADMISSION NO. 51:

Syngenta objects to this Request as vague and ambiguous as the Request does not specify a time period. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion. Subject to and without waiving its objections, Syngenta admits that Dr. Ted Lock was asked by Syngenta to conduct an analysis on scientific literature as it relates to paraquat transporters in 2007.

REQUEST FOR ADMISSION NO. 52:

Admit that Dr. Ted Lock provided a memorandum to Syngenta on December 21, 2007 titled "How does the herbicide paraquat enter the brain?" containing his opinion that "What is now beyond doubt is that paraquat can enter dopaminergic neurons in the substantia nigra of C57B16 mice in sufficient concentration to cause cell death."

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RESPONSE TO REQUEST FOR ADMISSION NO. 52:

Syngenta objects to this Request to the extent that it mischaracterizes a document by selectively quoting, omitting, or emphasizing certain language or by drawing related inferences or by stating related opinions. Syngenta also objects to this Request as improper and misleading because it omits testimonial evidence from Dr. Ted Lock's deposition that provides additional context for the statement. Subject to and without waiving its objections, Syngenta admits that Dr. Lock provided the memorandum referenced in the Request and that it contains the quoted statement. Syngenta further states that Dr. Lock also testified during his deposition that the statement was made based on his review of the literature, and that "[a]t that time we had really serious questions around whether that was real. And I – I think – my view on it now is I'm not sure that it's real, that I think it was an artifact of the experimental work." E. Lock Dep. Tr. at 40:7-20. Dr. Lock continued: "there are a number of studies that have been done where paraquat has been administered to very young animals where the blood brain barrier is not intact so that more paraquat can enter the brain and potentially produce effects. But when the blood brain barrier is intact I believe, from the work we've done, that very little of the paraquat enters." *Id.* at 41:22-42:5.

REQUEST FOR ADMISSION NO. 53:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether Dr. Ted Lock's December 21, 2007 memo titled "How does the herbicide paraquat enter the brain? should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 53:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing

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statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this memorandum to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 54:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether Dr. Ted Lock's December 21, 2007 memo titled "How does the herbicide paraquat enter the brain?" should be reported to the EPA under FIFRA section 6(a)(2).

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RESPONSE TO REQUEST FOR ADMISSION NO. 54:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this memorandum to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 55:

Admit that Syngenta never submitted Dr. Ted Lock's December 21, 2007 memo titled "How does the herbicide paraquat enter the brain?" to the EPA.

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RESPONSE TO REQUEST FOR ADMISSION NO. 55:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the memorandum located at SYNG-PQ-20758517 as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 56:

Admit that Dr. Joan Abbot is a qualified expert on the transport of chemicals through the blood-brain barrier.

RESPONSE TO REQUEST FOR ADMISSION NO. 56:

Syngenta objects to this Request as vague and ambiguous as to the phrases "qualified expert" and "transport of chemicals through the blood-brain barrier." Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a

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legal conclusion. Subject to and without waiving its objections, Syngenta admits that Dr. Joan Abbot has the expertise to analyze studies on the transport of chemicals through the blood-brain barrier.

REQUEST FOR ADMISSION NO. 57:

Admit that Syngenta invited Dr. Joan Abbot to provide her opinions on the ability of Paraquat to pass through the blood-brain barrier.

RESPONSE TO REQUEST FOR ADMISSION NO. 57:

Syngenta objects to this Request as vague and ambiguous as the Request does not specify a time period. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion. Subject to and without waiving its objections, Syngenta admits that Dr. Joan Abbott was asked to present on information regarding certain chemicals and the blood-brain barrier in 2009.

REQUEST FOR ADMISSION NO. 58:

Admit that Dr. Joan Abbott provided a powerpoint to Syngenta dated April 20, 2009 (SYNG-PQ-00471694) containing her opinion that Non-ionic detergents increase the permeability of the blood-brain barrier.

RESPONSE TO REQUEST FOR ADMISSION NO. 58:

Syngenta objects to this Request to the extent that it mischaracterizes a document by selectively quoting, omitting, or emphasizing certain language or by drawing related inferences or stating related opinions. Syngenta also objects to the phrase "Non-ionic detergents" as vague and ambiguous. Subject to and without waiving its objections, Syngenta admits that Dr. Joan Abbott provided a 143-slide PowerPoint presentation to Syngenta dated April 20, 2009 regarding a number of topics, including central nervous system barriers, blood-brain barriers, neurovascular units, regional and species differences, and future perspectives. Syngenta also admits that on one

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particular slide of her presentation, Dr. Abbott appears to have presented information on certain agents that may increase permeability. Syngenta denies that it was Dr. Abbott's opinion that "Non-ionic detergents increase the permeability of the blood-brain barrier" because it is unclear whether she was referring to the increase in permeability of the blood-brain barrier or the perineurium. The document speaks for itself.

REQUEST FOR ADMISSION NO. 59:

Admit that non-ionic surfactants are non-ionic detergents.

RESPONSE TO REQUEST FOR ADMISSION NO. 59:

Syngenta objects to the phrases "non-ionic surfactants" and "non-ionic detergents" as vague and ambiguous. Subject to and without waiving its objections, Syngenta denies that all non-ionic surfactants are non-ionic detergents.

REQUEST FOR ADMISSION NO. 60:

Admit that Dr. Joan Abbott provided a powerpoint to Syngenta dated April 20, 2009 (SYNG-PQ-00471694) containing the opinion that the slow clearance of Paraquat from the brain suggests intracellular sequestering in the central nervous system and the potential for long term toxicity.

RESPONSE TO REQUEST FOR ADMISSION NO. 60:

Syngenta objects to this Request to the extent that it mischaracterizes a document by selectively quoting, omitting, or emphasizing certain language or by drawing related inferences or stating related opinions. Syngenta also objects to the phrases "slow clearance of Paraquat," "intracellular sequestering," and "the potential for long term toxicity as undefined, vague, and ambiguous. Subject to and without waiving its objections, Syngenta admits that Dr. Joan Abbott provided a 143-slide PowerPoint presentation to Syngenta dated April 20, 2009 regarding a number of topics, including central nervous system barriers, blood-brain barriers, neurovascular

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units, regional and species differences, and future perspectives. As part of her presentation, Dr. Abbott referenced a number of studies that were already in the public literature at the time that appear to have suggested that paraquat clears slowly from the rodent brain. Based on Dr. Abbott's review of the contemporaneous literature, she concluded that the "[v]ery slow clearance suggests intracellular sequestering in CNS – potential for long-term toxicity," . SYNG-PQ-00471764. To be clear, Syngenta denies that Dr. Abbott formed an independent basis to conclude that the slow clearance of paraquat from the brain suggests intracellular sequestering in the central nervous system and the potential for long term toxicity. Notably, Dr. Abbott also concludes on the same slide that there is a "[n]eed [for] more studies of mechanisms for CNS uptake (BBB, CP) and efflux/clearance of PQ, in combination with other potential compounding factors; PBPK." *Id.* Following Dr. Abbott's presentation, Syngenta continued to conduct mouse injection studies to better assess the pharmacokinetics and neurotoxicity of paraquat. For example, in 2013, Dr. Charles Breckenridge published a peer-reviewed study that found the injection of "near-lethal doses of PQ" failed to show the "constellation of effects" that would suggest neuron death in the relevant part of the brain. *See* Charles Breckenridge, et al., *Pharmacokinetic, neurochemical, stereological and neuropathological studies on the potential effects of paraquat in the substantia nigra pars compacta and striatum of male C57BL/6J mice* (2013) ("Breckenridge 2013"). While Dr. Breckenridge found that paraquat administered by intraperitoneal ("i.p.") injection to the C57BL/6J mice entered the brain and it was then slowly eliminated, Dr. Breckenridge concluded that "the totality of the evidence from this research program indicates there was no consistent stereological evidence of a loss of TH+ staining in the SNpc of male C57BL/6J mice administered PQ at near-lethal doses. Neurochemical changes were always observed following MPTP treatment, but there were never any changes in DA levels or DA turnover in the striatum after PQ treatment.

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There was clear evidence of neuropathological changes in the SNpc and the striatum after MPTP treatment in three separate studies, but there was no evidence that PQ had any effect on a broad range of indicators of cell death, in both the SNpc and the striatum." Id.

REQUEST FOR ADMISSION NO. 61:

Admit that Dr. Joan Abbott provided a powerpoint to Syngenta dated April 20, 2009 (SYNG-PQ-00471694) containing the opinion that the combination of carrier-mediated uptake of Paraquat into the brain with very low clearance and known toxicity created a problematic profile.

RESPONSE TO REQUEST FOR ADMISSION NO. 61:

Syngenta objects to this Request to the extent that it mischaracterizes a document by selectively quoting, omitting, or emphasizing certain language or by drawing related inferences or stating related opinions. Syngenta also objects to the phrases "carrier-mediated uptake," "very low clearance," "known toxicity," and "problematic profile" as undefined, vague, and ambiguous. Subject to and without waiving its objections, Syngenta admits that Dr. Joan Abbott provided a 143-slide PowerPoint presentation to Syngenta dated April 20, 2009 regarding a number of topics, including central nervous system barriers, blood-brain barriers, neurovascular units, regional and species differences, and future perspectives. As part of her presentation, Dr. Abbott references a number of studies that were already in the public literature at the time that appear to have suggested that a combination of carrier-mediated uptake and slow clearance would create a "problematic profile." SYNG-PQ-00471764. To be clear, Syngenta denies that Dr. Abbott formed an independent basis to conclude that a combination of carrier-mediated uptake and slow clearance would create a "problematic profile." Notably, Dr. Abbott also concludes on the same slide that there is a "[n]eed [for] more studies of mechanisms for CNS uptake (BBB, CP) and efflux/clearance of PQ, in combination with other potential compounding factors; PBPK." *Id.* Following Dr. Abbott's presentation, Syngenta continued to conduct mouse-injection studies to

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better assess the pharmacokinetics and neurotoxicity of paraquat. For example, in 2013, Dr. Breckenridge published a peer-reviewed study that found the injection of "near-lethal doses of PQ" failed to show the "constellation of effects" that would suggest neuron death in the relevant part of the brain. *See* Breckenridge 2013. While Dr. Breckenridge found that paraquat administered by i.p. injection to the C57BL/6J mice entered the brain and it was then slowly eliminated, Dr. Breckenridge concluded that "the totality of the evidence from this research program indicates there was no consistent stereological evidence of a loss of TH+ staining in the SNpc of male C57BL/6J mice administered PQ at near-lethal doses. Neurochemical changes were always observed following MPTP treatment, but there were never any changes in DA levels or DA turnover in the striatum after PQ treatment. There was clear evidence of neuropathological changes in the SNpc and the striatum after MPTP treatment in three separate studies, but there was no evidence that PQ had any effect on a broad range of indicators of cell death, in both the SNpc and the striatum." *Id*.

REQUEST FOR ADMISSION NO. 62:

Admit that Syngenta never submitted Dr. Joan Abbott's April 20, 2009 powerpoint presentation (SYNG-PQ-00471694) to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 62:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that Dr. Abbott's 2009 PowerPoint presentation was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

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Subject to and without waiving its objections, and based on a reasonable investigation, Syngenta admits that it does not have record of submitting the PowerPoint presentation located at SYNG-PQ-00471694 as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 63:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from Dr. Joan Abbott's April 20, 2009 (SYNG-PQ-00471694) powerpoint presentation should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 63:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as

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it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this PowerPoint presentation to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 64:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the opinions from Dr. Joan Abbott's April 20, 2009 powerpoint presentation (SYNG-PQ-00471694) should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 64:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear

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whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this PowerPoint presentation to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 65:

Admit that Syngenta never submitted the study report titled IHR 213 – TOXICITY TESTS ON GRAMOXONE FOR REGISTRATION IN THE U.S.S.R to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 65:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this study report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

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Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat. Syngenta further explains that the cited report was completed in 1967, and the EPA did not assume responsibility for regulating pesticides until 1970. Furthermore, FIFRA's Section 6(a)(2)—which defines and describes a registrants' reporting requirements—was not enacted until 1972.

REQUEST FOR ADMISSION NO. 66:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from IHR 213 - TOXICITY TESTS ON GRAMOXONE FOR REGISTRATION IN THE U.S.S.R should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 66:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal

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Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat. Syngenta further explains that the cited report was completed in 1967, and the EPA did not assume responsibility for regulating pesticides until 1970. Furthermore, FIFRA's Section 6(a)(2)— which defines and describes a registrants' reporting requirements—was not enacted until 1972.

REQUEST FOR ADMISSION NO. 67:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from IHR 213 - TOXICITY TESTS ON GRAMOXONE FOR REGISTRATION IN THE U.S.S.R should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 67:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine

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internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat. Syngenta further explains that the cited report was completed in 1967, and the EPA did not assume responsibility for regulating pesticides until 1970. Furthermore, FIFRA's Section 6(a)(2)—which defines and describes a registrants' reporting requirements—was not enacted until 1972.

REQUEST FOR ADMISSION NO. 68:

Admit that Syngenta never submitted the study report "CTL/R/373-The Effect Of Surfactants On The Toxicity And Intestinal Absorption Of – Paraquat" to the EPA.

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RESPONSE TO REQUEST FOR ADMISSION NO. 68:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this study report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1976. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 69:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "CTL/R/373-The Effect Of Surfactants On The Toxicity And Intestinal Absorption Of – Paraquat" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 69:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine

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internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1976. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 70:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "CTL/R/373-The Effect Of Surfactants On The Toxicity And Intestinal Absorption Of – Paraquat" should be reported to the EPA under FIFRA section 6(a)(2).

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RESPONSE TO REQUEST FOR ADMISSION NO. 70:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1976. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

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REQUEST FOR ADMISSION NO. 71:

Admit that Syngenta never submitted the study report "CTL/R/375: THE EFFECTS OF SURFACTANTS ON THE TOXICITY AND GASTROINTESTINAL ABSORPTION OF PARAQUAT" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 71:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this study report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1976. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 72:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "CTL/R/375: THE EFFECTS OF SURFACTANTS ON THE TOXICITY AND GASTROINTESTINAL ABSORPTION OF PARAQUAT" should be reported to the EPA under FIFRA section 6(a)(2).

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RESPONSE TO REQUEST FOR ADMISSION NO. 72:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1976. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

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REQUEST FOR ADMISSION NO. 73:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "CTL/R/375: THE EFFECTS OF SURFACTANTS ON THE TOXICITY AND GASTROINTESTINAL ABSORPTION OF PARAQUAT" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 73:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1976. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with

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its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 74:

Admit that Syngenta never submitted the study report "CTL/P/448: TOXICOLOGICAL COMPARISON OF NEW WETTER SYSTEMS FOR PARAQUAT FORMULATIONS" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 74:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this study report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1979. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

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REQUEST FOR ADMISSION NO. 75:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "CTL/P/448: TOXICOLOGICAL COMPARISON OF NEW WETTER SYSTEMS FOR PARAQUAT FORMULATIONS" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 75:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objections to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1979. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and

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followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 76:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "CTL/P/448: TOXICOLOGICAL COMPARISON OF NEW WETTER SYSTEMS FOR PARAQUAT FORMULATIONS" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 76:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1979.

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Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 77:

Admit that Syngenta never submitted the study report "CTL/L/1428 PREEGLOX-L: PHARMACO-KINETIC STUDY IN THE RAT" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 77:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this study report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1986. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

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REQUEST FOR ADMISSION NO. 78:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "CTL/L/1428 PREEGLOX-L: PHARMACO-KINETIC STUDY IN THE RAT" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 78:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1986. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the

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EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 79:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "CTL/L/1428 PREEGLOX-L: PHARMACO-KINETIC STUDY IN THE RAT" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 79:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1986. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has

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similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 80:

Admit that Syngenta never submitted the study report "CTL/P/4501 PARAQUAT: IN VITRO ABSORPTION FROM A 200g SL FORMULATION THROUGH HUMAN EPIDERMIS" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 80:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this study report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1994. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

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REQUEST FOR ADMISSION NO. 81:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "CTL/P/4501 PARAQUAT: IN VITRO ABSORPTION FROM A 200g SL FORMULATION THROUGH HUMAN EPIDERMIS" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 81:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objections to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1994. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and

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followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 82:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "CTL/P/4501 PARAQUAT: IN VITRO ABSORPTION FROM A 200g SL FORMULATION THROUGH HUMAN EPIDERMIS" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 82:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1994.

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Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 83:

Admit that Syngenta never submitted the study report "CTL/JV/1599 RESEARCH/REPORT PARAQUAT: SKIN IRRITATION OF BIPYIRIDYL FORMULATIONS – IN VITRO ASSESSMENT USING RABBIT SKIN" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 83:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this study report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA

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has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 84:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "CTL/JV/1599 RESEARCH/REPORT PARAQUAT: SKIN IRRITATION OF BIPYIRIDYL FORMULATIONS – IN VITRO ASSESSMENT USING RABBIT SKIN" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 84:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA

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guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 85:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "CTL/JV/1599 RESEARCH/REPORT PARAQUAT: SKIN IRRITATION OF BIPYIRIDYL FORMULATIONS – IN VITRO ASSESSMENT USING RABBIT SKIN" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 85:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was

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considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 86:

Admit that Syngenta never submitted the study report "CTL/JV1806/REPORT: PHASE SEPARATED GRAMOXONE (A14380A): PREDICTION OF ACUTE SKIN IRRITATION USING THE INTEGRITY FUNCTION TEST" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 86:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this study report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA

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has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 87:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "CTL/JV1806/REPORT: PHASE SEPARATED GRAMOXONE (A14380A): PREDICTION OF ACUTE SKIN IRRITATION USING THE INTEGRITY FUNCTION TEST" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 87:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA

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guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 88:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "CTL/JV1806/REPORT: PHASE SEPARATED GRAMOXONE (A14380A): PREDICTION OF ACUTE SKIN IRRITATION USING THE INTEGRITY FUNCTION TEST" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 88:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was

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considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 89:

Admit that Syngenta never submitted the study report "CTL/R/1463 XENOBIOTICS LINKED TO PARKINSON'S DISEASE" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 89:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this study report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA

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has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 90:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "CTL/R/1463 XENOBIOTICS LINKED TO PARKINSON'S DISEASE" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 90:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA

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guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 91:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "CTL/R/1463 XENOBIOTICS LINKED TO PARKINSON'S DISEASE" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 91:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was

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considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 92:

Admit that Syngenta never submitted the report "PRODUCT SAFETY TECHNICAL EVALUATION: Claimed links Between Exposure to Paraquat and Development of Parkinson's Disease – A Consideration of the Potential Implications for Reference Doses Draft: September 2009" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 92:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that the referenced report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA

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has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 93:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "PRODUCT SAFETY TECHNICAL EVALUATION: Claimed links Between Exposure to Paraquat and Development of Parkinson's Disease – A Consideration of the Potential Implications for Reference Doses Draft: September 2009" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 93:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was

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considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 94:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "PRODUCT SAFETY TECHNICAL EVALUATION: Claimed links Between Exposure to Paraquat and Development of Parkinson's Disease – A Consideration of the Potential Implications for Reference Doses Draft: September 2009" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 94:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA

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under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 95:

Admit that Syngenta never submitted the Exponent study report "Dose-Response Analysis of the Paraquat and Maneb Model for Parkinson's Disease Using Human-Relevant Paraments. Project Number PS2608" to the EPA. (See SYNG-PQ-01988076).

RESPONSE TO REQUEST FOR ADMISSION NO. 95:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over

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time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 96:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from Exponent's report "Dose-Response Analysis of the Paraquat and Maneb Model for Parkinson's Disease Using Human-Relevant Paraments. Project Number PS2608" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 96:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the

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right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 97:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether Exponent's report "Dose-Response Analysis of the Paraquat and Maneb Model for Parkinson's Disease Using Human-Relevant Paraments. Project Number PS2608" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 97:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA

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under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 98:

Admit that Syngenta never submitted Exponent's report "An Examination and Analysis of the Role of Paraquat and Maneb in Induced Neurodegeneration of the Substantia Nigra at Representative Human Exposure Doses, Final Report, Project Number PS2608" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 98:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over

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time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 99:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether Exponent's report "An Examination and Analysis of the Role of Paraquat and Maneb in Induced Neurodegeneration of the Substantia Nigra at Representative Human Exposure Doses, Final Report, Project Number PS2608" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 99:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA

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under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 100:

Admit that "An Examination and Analysis of the Role of Paraquat and Maneb in Induced Neurodegeneration of the Substantia Nigra at Representative Human Exposure Doses, Final Report, Project Number PS2608" has never been abstracted in a recognized database of scientific and medical literature such as Medline, EMBASE, Toxline or Index Medicus.

RESPONSE TO REQUEST FOR ADMISSION NO. 100:

Syngenta objects to this Request insofar as this information is equally available to Plaintiffs. Syngenta further objects to this Request as vague, ambiguous, and unduly burdensome as it asks about whether a report "has never been abstracted in a recognized database of scientific and medical literature." Syngenta further objects to this Request to the extent that it asks for historical information that is no longer available or accessible. Syngenta also objects to the extent that this Request asks for information outside of Syngenta's possession, custody, and control. Subject to and without waiving its objections, Syngenta states that, based on a reasonable investigation to date, it has not been able to determine whether the referenced study, "An Examination and Analysis of the Role of Paraquat and Maneb in Induced Neurodegeneration of the Substantia Nigra at Representative Human Exposure Doses, Final Report, Project Number PS2608" has never been abstracted in a recognized database of scientific and medical literature

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such as Medline, EMBASE, Toxline or Index Medicus. In light of the foregoing, Syngenta can neither admit nor deny this Request.

REQUEST FOR ADMISSION NO. 101:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether Exponent's report "An Examination and Analysis of the Role of Paraquat and Maneb in Induced Neurodegeneration of the Substantia Nigra at Representative Human Exposure Doses, Final Report, Project Number PS2608" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 101:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to

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these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 102:

Admit that Syngenta never submitted Exponent's report "Sensitivity Analyses of the Tanner et al. Case-Control Study of Parkinson's Disease in the Agricultural Health Study, September 10, 2013" to the EPA. (See SYNG-PQ-36932783).

RESPONSE TO REQUEST FOR ADMISSION NO. 102:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta admits that the referenced report was submitted pursuant to a request from the EPA, separate and apart from any adverse event reporting. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies additional information responsive to this Request. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations

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under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 103:

Admit that Syngenta never informed the EPA that it obtained additional data from the Farming and Movement Evaluation (FAME) study within the Agricultural Health Study and conducted a sensitivity analysis to assess the results and conclusions.

RESPONSE TO REQUEST FOR ADMISSION NO. 103:

Syngenta objects to this Request phrase "informed the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request as vague and ambiguous as it asks about "additional data" that Syngenta purportedly obtained without citing or referencing what data Plaintiffs are asking about. Syngenta further objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion. Subject to and without waiving its objections, Syngenta incorporates its response to Request for Admission No. 102. Syngenta further admits that it sent raw data used in the referenced analysis, which Syngenta interprets as the document referenced in Request for Admission No. 102, that it has in its possession to the EPA. Syngenta reserves the right to update this response should additional information become available.

REQUEST FOR ADMISSION NO. 104:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether Exponent's report "Sensitivity Analyses of the Tanner et al. Case-Control Study of Parkinson's Disease in the Agricultural Health Study, September 10, 2013" should be reported to the EPA under FIFRA section 6(a)(2).

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RESPONSE TO REQUEST FOR ADMISSION NO. 104:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that this Committee considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted.

REQUEST FOR ADMISSION NO. 105:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether Exponent's report "Sensitivity Analyses of the Tanner et al. Case-Control Study of Parkinson's Disease in the Agricultural Health Study, September 10, 2013" should be reported to the EPA under FIFRA section 6(a)(2).

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RESPONSE TO REQUEST FOR ADMISSION NO. 105:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that this Committee considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted.

REQUEST FOR ADMISSION NO. 106:

Admit that Syngenta never submitted the translated study report from the Brazilian regulatory agency (ANVISA) titled "TECHNICAL REASSMENT OPINION NO. 01 of 2015/GGTOX/Anvisa Analysis of the technical reassessment note of the active ingredient paraquat elaborated by Fiocruz" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 106:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA

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through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 107:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the study report from the Brazilian Regulatory Agency (ANVISA) titled "TECHNICAL REASSMENT OPINION NO. 01 of 2015/GGTOX/Anvisa Analysis of the technical reassessment note of the active ingredient paraquat elaborated by Fiocruz" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 107:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period

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of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 108:

Admit that the study report from the Brazilian Regulatory Agency (ANVISA) titled "TECHNICAL REASSMENT OPINION NO. 01 of 2015/GGTOX/Anvisa Analysis of the technical reassessment note of the active ingredient paraquat elaborated by Fiocruz" has never been abstracted in a recognized database of scientific and medical literature such as Medline, EMBASE, Toxline or Index Medicus.

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RESPONSE TO REQUEST FOR ADMISSION NO. 108:

Syngenta objects to this Request insofar as this information is equally available to Plaintiffs. Syngenta further objects to this Request as vague, ambiguous, and unduly burdensome as it asks about whether a report "has never been abstracted in a recognized database of scientific and medical literature." Syngenta further objects to this Request to the extent that it asks for historical information that is no longer available or accessible. Syngenta also objects to the extent that this Request asks for information outside of Syngenta's possession, custody, and control.

Subject to and without waiving its objections, Syngenta states that, based on a reasonable investigation to date, it has not been able to determine whether the technical assessment opinion from the Brazilian Regulatory Agency (ANVISA) titled "TECHNICAL REASSMENT OPINION NO. 01 of 2015/GGTOX/Anvisa Analysis of the technical reassessment note of the active ingredient paraquat elaborated by Fiocruz" has never been abstracted in a recognized database of scientific and medical literature such as Medline, EMBASE, Toxline or Index Medicus. In light of the foregoing, Syngenta can neither admit nor deny this Request.

REQUEST FOR ADMISSION NO. 109:

Admit that Syngenta never submitted the translated study report from the Brazilian regulatory agency (ANVISA) titled "TECHNICAL REASSESSMENT OPINION NO. 08/GGTOX/Anvisa, of June 13, 2016 Analysis of the contributions to the proposed reassessment of the active ingredient Paraquat supported by the Technical Reassessment Opinion no. 01 of 2015/GGTOX/Anvisa, object of the Public Consultation no. 94 of October 8, 2015" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 109:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that

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it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 110:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the study report from the Brazilian Regulatory Agency (ANVISA) titled "TECHNICAL REASSESSMENT OPINION NO. 08/GGTOX/Anvisa, of June 13, 2016 Analysis of the contributions to the proposed reassessment of the active ingredient Paraquat supported by the Technical Reassessment Opinion no. 01 of 2015/GGTOX/Anvisa, object of the Public Consultation no. 94 of October 8, 2015" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 110:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member

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communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 111:

Admit that the study report from the Brazilian Regulatory Agency (ANVISA) titled "TECHNICAL REASSESSMENT OPINION NO. 08/GGTOX/Anvisa, of June 13, 2016 Analysis of the contributions to the proposed reassessment of the active ingredient Paraquat supported by the Technical Reassessment Opinion no. 01 of 2015/GGTOX/Anvisa, object of the Public Consultation no. 94 of October 8, 2015" has never been abstracted in a recognized database of scientific and medical literature such as Medline, EMBASE, Toxline or Index Medicus.

RESPONSE TO REQUEST FOR ADMISSION NO. 111:

Syngenta objects to this Request insofar as this information is equally available to Plaintiffs. Syngenta further objects to this Request as vague, ambiguous, and unduly burdensome

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as it asks about whether a report "has never been abstracted in a recognized database of scientific and medical literature." Syngenta further objects to this Request to the extent that it asks for historical information that is no longer available or accessible. Syngenta also objects to the extent that this Request asks for information outside of Syngenta's possession, custody, and control.

Subject to and without waiving its objections, Syngenta states that, based on a reasonable investigation to date, it has not been able to determine whether the technical assessment opinion from the Brazilian Regulatory Agency (ANVISA) titled "TECHNICAL REASSESSMENT OPINION NO. 08/GGTOX/Anvisa, of June 13, 2016 Analysis of the contributions to the proposed reassessment of the active ingredient Paraquat supported by the Technical Reassessment Opinion no. 01 of 2015/GGTOX/Anvisa, object of the Public Consultation no. 94 of October 8, 2015" has never been abstracted in a recognized database of scientific and medical literature such as Medline, EMBASE, Toxline or Index Medicus. In light of the foregoing, Syngenta can neither admit nor deny this Request.

REQUEST FOR ADMISSION NO. 112:

Admit that Syngenta never submitted the translated study report from the Brazilian regulatory agency (ANVISA) titled "REASSESSMENT TECHNICAL OPINION No.13/CREAV/GEPOS/GGTOX/ANVISA — version 2, dated January 05th, 2017. It analyzes the proposals submitted by the Reassessment Task Force of the Active Ingredient Paraquat (file No. 291144162) and its questions to Reassessment Technical Opinion No. 08/GGTOX/Anvisa, from June 13th, 2016 (file No. 460883166)" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 112:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects

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to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 113:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the study report from the Brazilian Regulatory Agency (ANVISA) titled "REASSESSMENT TECHNICAL OPINION No.13/CREAV/GEPOS/GGTOX/ANVISA — version 2, dated January 05th, 2017. It analyzes the proposals submitted by the Reassessment Task Force of the Active Ingredient Paraquat (file No. 291144162) and its questions to Reassessment Technical Opinion No. 08/GGTOX/Anvisa, from June 13th, 2016 (file No. 460883166)" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 113:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of

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communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 114:

Admit that the study report from the Brazilian Regulatory Agency (ANVISA) titled "REASSESSMENT TECHNICAL OPINION No.13/CREAV/GEPOS/GGTOX/ANVISA — version 2, dated January 05th, 2017. It analyzes the proposals submitted by the Reassessment Task Force of the Active Ingredient Paraquat (file No. 291144162) and its questions to Reassessment Technical Opinion No. 08/GGTOX/Anvisa, from June 13th, 2016 (file No. 460883166)" has never been abstracted in a recognized database of scientific and medical literature such as Medline, EMBASE, Toxline or Index Medicus.

RESPONSE TO REQUEST FOR ADMISSION NO. 114:

Syngenta objects to this Request insofar as this information is equally available to Plaintiffs. Syngenta further objects to this Request as vague, ambiguous, and unduly burdensome

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as it asks about whether a report "has never been abstracted in a recognized database of scientific and medical literature." Syngenta further objects to this Request to the extent that it asks for historical information that is no longer available or accessible. Syngenta also objects to the extent that this Request asks for information outside of Syngenta's possession, custody, and control.

Subject to and without waiving its objections, Syngenta states that, based on a reasonable investigation to date, it has not been able to determine whether the technical assessment opinion from the Brazilian Regulatory Agency (ANVISA) titled "REASSESSMENT TECHNICAL OPINION No.13/CREAV/GEPOS/GGTOX/ANVISA — version 2, dated January 05th, 2017. It analyzes the proposals submitted by the Reassessment Task Force of the Active Ingredient Paraquat (file No. 291144162) and its questions to Reassessment Technical Opinion No. 08/GGTOX/Anvisa, from June 13th, 2016 (file No. 460883166)" has never been abstracted in a recognized database of scientific and medical literature such as Medline, EMBASE, Toxline or Index Medicus. In light of the foregoing, Syngenta can neither admit nor deny this Request.

REQUEST FOR ADMISSION NO. 115:

Admit that Syngenta never submitted the report "CEHC 2540: THE ACUTE INHALATION TOXICITY OF CC-15400 (SX-1711) IN RATS" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 115:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

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Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1986. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 116:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "CEHC 2540: THE ACUTE INHALATION TOXICITY OF CC-15400 (SX-1711) IN RATS" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 116:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as

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it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1986. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 117:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "CEHC 2540: THE ACUTE INHALATION TOXICITY OF CC-15400 (SX-1711) IN RATS" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 117:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the

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term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta states that the referenced report was completed in 1986. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 118:

Admit that Syngenta never submitted the report "Brouwer, D.H. and Roussel, C.-H. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following a single day's habitual use in vines. TNO Report V6420/01. 15th May 2007" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 118:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects

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to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 119:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "Brouwer, D.H. and Roussel, C.-H. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following a single day's habitual use in vines. TNO Report V6420/01. 15th May 2007" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 119:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal

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Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 120:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "Brouwer, D.H. and Roussel, C.-H. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following a single day's habitual use in vines. TNO Report V6420/01. 15th May 2007" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 120:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee

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member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 121:

Admit that Syngenta never submitted the report "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following repeated days' habitual use in vines. TNO Report V6420/02. 15th May 2007b" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 121:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that

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it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 122:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following repeated days' habitual use in vines. TNO Report V6420/02. 15th May 2007b" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 122:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of

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communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta denies that Syngenta's PRF Approach Committee never considered whether the results from "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following repeated days' habitual use in vines. TNO Report V6420/02. 15th May 2007b" should be reported to the EPA under FIFRA section 6(a)(2). Syngenta further states that its PRF Approach Committee did consider whether to report this study to the EPA and ultimately referred the study to its US PRF Committee. *See, e.g.*, SYNG-PQ-06528530; SYNG-PQ-02415384, at -02415412 to -02415416; M. Dixon Dep. Ex. 17.

REQUEST FOR ADMISSION NO. 123:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following repeated days' habitual use in vines. TNO Report V6420/02. 15th May 2007b" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 123:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee

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member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta denies that Syngenta's US PRF Committee never considered whether the results from "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following repeated days' habitual use in vines. TNO Report V6420/02. 15th May 2007b" should be reported to the EPA under FIFRA section 6(a)(2). Syngenta further states that its US PRF Committee did consider whether to report this study to the EPA. *See, e.g.*, SYNG-PQ-02415384, at -02415412-16; M. Dixon Dep. Ex. 17.

REQUEST FOR ADMISSION NO. 124:

Admit that Syngenta never informed the EPA that two workers involved in the study "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following repeated days' habitual use in vines. TNO Report V6420/02. 15th May 2007b" had measurable Paraquat exposures in excess of the Acceptable Operator Exposure Level.

RESPONSE TO REQUEST FOR ADMISSION NO. 124:

Syngenta objects to this Request because it suggests that Syngenta had an obligation to inform the EPA that two workers involved in the cited study had "measurable paraquat exposure in excess of the Acceptable Operator Exposure Level." Syngenta further objects to the term "Acceptable Operator Exposure Level" as undefined, vague, and ambiguous. Syngenta further objects to the phrase "informed the EPA" as vague and ambiguous. Syngenta also objects to this

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Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta denies that it never informed the EPA about an incident with two workers involved in the study "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following repeated days' habitual use in vines. TNO Report V6420/02. 15th May 2007b." *See* SYNG-PQ-02415384 The exposures were classified as H-E, which is the classification for human exposure incidents where there were no known health impacts. This classification is consistent with the EPA's guidance regarding 6(a)(2) reporting. Syngenta admits that it did not include additional information about the workers' exposure levels. Syngenta states that it was not required to share any further details of the exposure with the EPA. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 125:

Admit that Syngenta never submitted the report "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following a single day's habitual use in bananas. TNO Report V6420/04. 16th August 2007c" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 125:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that

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it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 126:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following a single day's habitual use in bananas. TNO Report V6420/04. 16th August 2007c" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 126:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of

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communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has found evidence that this study was considered by Syngenta's Potentially Referrable Findings Approach Committee and its US Potentially Referrable Findings Committee. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies any additional information relevant to this Request. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 127:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following a single day's habitual use in bananas. TNO Report V6420/04. 16th August 2007c" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 127:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing

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statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has found evidence that this study was considered by Syngenta's Potentially Referrable Findings Approach Committee and its US Potentially Referrable Findings Committee. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies additional information relevant to this Request. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 128:

Admit that Syngenta never informed the EPA that two workers involved in the study "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following a single day's habitual use in bananas. TNO Report V6420/04. 16th August 2007c" had measurable Paraquat exposures in excess of the Acceptable Operator Exposure Level.

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RESPONSE TO REQUEST FOR ADMISSION NO. 128:

Syngenta objects to this Request because it suggests that Syngenta had an obligation to inform the EPA that two workers involved in the cited study "had measurable paraquat exposure in excess of the Acceptable Operator Exposure Level." Syngenta further objects to the term "Acceptable Operator Exposure Level" as undefined, vague, and ambiguous. Syngenta also objects to the phrase "informed the EPA" as vague and ambiguous. Syngenta also objects to this Request to the extent that it calls for expert testimony. Syngenta also objects to this Request to the extent that it misrepresents findings in the cited study. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of informing the EPA that two workers involved in the cited study "had measurable paraquat exposure in excess of the Acceptable Operator Exposure Level," as this Request states. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 129:

Admit that Syngenta never submitted the report "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following three consecutive days' habitual use in bananas. TNO Report V6420/05. 29th August 2007d." to the EPA.

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RESPONSE TO REQUEST FOR ADMISSION NO. 129:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting this report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 130:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following three consecutive days' habitual use in bananas. TNO Report V6420/05. 29th August 2007d." should be reported to the EPA under FIFRA section 6(a)(2).

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RESPONSE TO REQUEST FOR ADMISSION NO. 130:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

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REQUEST FOR ADMISSION NO. 131:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following three consecutive days' habitual use in bananas. TNO Report V6420/05. 29th August 2007d." should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 131:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited

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or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 132:

Admit that Syngenta never submitted the report "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following a single day's habitual use in lucerne. TNO Report V6420/03. 11th June 2007e" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 132:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

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REQUEST FOR ADMISSION NO. 133:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following a single day's habitual use in lucerne. TNO Report V6420/03. 11th June 2007e" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 133:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving

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obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 134:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following a single day's habitual use in lucerne. TNO Report V6420/03. 11th June 2007e" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 134:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to

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these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 135:

Admit that Syngenta never submitted the report "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following three consecutive days' use in bananas with PPE according to label recommendation. TNO Report V6420/06. 6th September 2007a" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 135:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

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REQUEST FOR ADMISSION NO. 136:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following three consecutive days' use in bananas with PPE according to label recommendation. TNO Report V6420/06. 6th September 2007a" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 136:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta states that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving

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obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 137:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "Brouwer, D.H., Roussel, C.-H. and Links, I. Formulation R-Bix (A9409AL): Measurement of excreted paraquat in workers following three consecutive days' use in bananas with PPE according to label recommendation. TNO Report V6420/06. 6th September 2007a" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 137:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA

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guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 138:

Admit that Syngenta never submitted the report "REPORT NO: CTL/P/1467 PARAQUAT: PENETRATION THROUGH PROTECTIVE CLOTHING MATERIALS FROM A MALAYSIAN 'GRAMOXONE' FORMULATION" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 138:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA

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has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 139:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "REPORT NO: CTL/P/1467 PARAQUAT: PENETRATION THROUGH PROTECTIVE CLOTHING MATERIALS FROM A MALAYSIAN 'GRAMOXONE' FORMULATION" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 139:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA

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guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 140:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "REPORT NO: CTL/P/1467 PARAQUAT: PENETRATION THROUGH PROTECTIVE CLOTHING MATERIALS FROM A MALAYSIAN 'GRAMOXONE' FORMULATION" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 140:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was

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considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 141:

Admit that Syngenta never submitted the report "REPORT NO: CTL/L/168O PARAQUAT: ABSORPTION THROUGH WELLINGTON AND TROOPER BOOT FROM GRAMOXONE" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 141:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA

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has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 142:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "REPORT NO: CTL/L/168O PARAQUAT: ABSORPTION THROUGH WELLINGTON AND TROOPER BOOT FROM GRAMOXONE" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 142:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA

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guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 143:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "REPORT NO: CTL/L/168O PARAQUAT: ABSORPTION THROUGH WELLINGTON AND TROOPER BOOT FROM GRAMOXONE" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 143:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was

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considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 144:

Admit that Syngenta never submitted the report "Campbell, et al., 2014, PARAQUAT PBPK MODEL FOR CROSS-SPECIES DOSIMETRY Date: 04/10/2014" (SYNG-PQ-04225646) to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 144:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA

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has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 145:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "Campbell, et al., 2014, PARAQUAT PBPK MODEL FOR CROSS-SPECIES DOSIMETRY Date: 04/10/2014" (SYNG-PQ-04225646) should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 145:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA

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guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 146:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "Campbell, et al., 2014, PARAQUAT PBPK MODEL FOR CROSS-SPECIES DOSIMETRY Date: 04/10/2014" (SYNG-PQ-04225646) should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 146:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was

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considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 147:

Admit that Syngenta never submitted the report "REPORT NO: CTL/L/2109 PARAQUAT: ANALYSIS OF URINE AND PLASMA SAMPLES FROM A MALAYSIAN OPERATOR EXPOSURE STUDY" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 147:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA

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has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 148:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "REPORT NO: CTL/L/2109 PARAQUAT: ANALYSIS OF URINE AND PLASMA SAMPLES FROM A MALAYSIAN OPERATOR EXPOSURE STUDY" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 148:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA

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guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 149:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "REPORT NO: CTL/L/2109 PARAQUAT: ANALYSIS OF URINE AND PLASMA SAMPLES FROM A MALAYSIAN OPERATOR EXPOSURE STUDY" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 149:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was

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considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 150:

Admit that Syngenta never submitted the report "December 2009 Paraquat Operator Exposure: A review of operator exposure studies Author: Graham Chester & Andy Cook" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 150:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA

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has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 151:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "December 2009 Paraquat Operator Exposure: A review of operator exposure studies Author: Graham Chester & Andy Cook" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 151:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA

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guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 152:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "December 2009 Paraquat Operator Exposure: A review of operator exposure studies Author: Graham Chester & Andy Cook" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 152:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was

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considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 153:

Admit that Syngenta never submitted the report "Report No. WER-006: Findlay, et al. PARAQUAT: WORKER EXPOSURE DURING APPLICATION OF GAMOXONE WITH A CONTROLLED DROPLET APPLICATION (CDA) MICRON 'HANDY' SPRAYER" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 153:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA

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has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 154:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee never considered whether the results from "Report No. WER-006: Findlay, et al. PARAQUAT: WORKER EXPOSURE DURING APPLICATION OF GAMOXONE WITH A CONTROLLED DROPLET APPLICATION (CDA) MICRON 'HANDY' SPRAYER" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 154:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal PRF Committee meetings or if this Request is seeking information about any passing statement between any internal PRF Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal PRF Committee member communicated to any other internal PRF Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was

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considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 155:

Admit that Syngenta's internal 6(a)(2) Committee never considered whether the results from "Report No. WER-006: Findlay, et al. PARAQUAT: WORKER EXPOSURE DURING APPLICATION OF GAMOXONE WITH A CONTROLLED DROPLET APPLICATION (CDA) MICRON 'HANDY' SPRAYER" should be reported to the EPA under FIFRA section 6(a)(2).

RESPONSE TO REQUEST FOR ADMISSION NO. 155:

Syngenta objects to the term "considered" as undefined, vague, ambiguous, and overbroad as Syngenta does not know whether this refers to, for example, formal discussions during routine internal 6(a)(2) Committee meetings or if this Request is seeking information about any passing statement between any internal 6(a)(2) Committee members at any point during an undefined period of time. It is not feasible to investigate everything that any internal 6(a)(2) Committee member communicated to any other internal 6(a)(2) Committee member through any potential medium of communication during an undefined period of time. Syngenta further objects to the term "internal 6(a)(2) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that, based on a reasonable investigation to date, it has not found evidence that it considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the

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right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 156:

Admit that Syngenta never submitted the report "CTL/HR2357/SUMMARY/REPORT PARAQUAT 200G/L SPRAY STRENGTH SOLUTION: PRELIMINARY INVESTIGATIONS OF THE 4-HOUR ACUTE INHALATION TOXICITY IN THE RAT" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 156:

Syngenta objects to the phrase "submitted . . . to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been

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responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 157:

Admit that Syngenta's internal Potentially Referrable Findings (PRF) Committee determined that the results from "CTL/HR2357/SUMMARY/REPORT PARAQUAT 200G/L SPRAY STRENGTH SOLUTION: PRELIMINARY INVESTIGATIONS OF THE 4-HOUR ACUTE INHALATION TOXICITY IN THE RAT" should be reported to the EPA under FIFRA section 6(a)(2) because the clinical effects noted were treatment related and because of death in extremis of one animal at a very low concentration

RESPONSE TO REQUEST FOR ADMISSION NO. 157:

Syngenta objects to the phrase "determined that the results . . . should be reported to the EPA" as vague and ambiguous. Syngenta also objects to the terms "clinical effects," "treatment related," and "very low concentration" as undefined, vague, and ambiguous. Syngenta further objects to the term "internal Potentially Referrable Findings (PRF) Committee" as undefined, vague, and ambiguous because it is not clear whether this term refers to Syngenta's PRF Approach Committee, US PRF Committee, or some other internal Syngenta committee. Syngenta objects to this Request to the extent that it mischaracterizes a document or the roles of the various committees at play. Syngenta also objects to this Request as it calls for expert testimony. Finally, Syngenta objects to this Request as it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that Zeneca's Central Toxicology Laboratory's Potentially Referrable Findings (PRF) Committee considered this study. *See* Phil Botham Ex. 26 (September 17, 2024). Syngenta states that Dr. Phil Botham referred to this committee as the "PRF Approach Committee" that "would hand its recommendations over to the US committee." P. Botham Dep. Tr. 191:21-192:9 (September 17, 2024). Syngenta admits that the Central Toxicology Laboratory's Potentially Referrable Findings (PRF) Committee referred

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this study to the US Potentially Referrable Findings Committee. *See* Phil Botham Ex. 26 (September 17, 2024). Syngenta states that the document speaks for itself. Syngenta further admits that, based on a reasonable investigation to date, it has not found evidence that the US Potentially Referrable Findings Committee considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and developed and followed processes designed to comply with its evolving obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat. Unless specifically admitted herein, denied.

REQUEST FOR ADMISSION NO. 158:

Admit that Syngenta rejected the recommendation of the PRF Committee to report the results of "CTL/HR2357/SUMMARY/REPORT PARAQUAT 200G/L SPRAY STRENGTH SOLUTION: PRELIMINARY INVESTIGATIONS OF THE 4-HOUR ACUTE INHALATION TOXICITY IN THE RAT" to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 158:

Syngenta objects to the terms "rejected," "PRF Committee," and "report the results" as undefined, vague, and ambiguous. Syngenta objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta also objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation to date, Syngenta admits that it has not found evidence that the US Potentially Referrable Findings

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Committee considered submitting this report to the EPA under 6(a)(2). Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 159:

Admit that "CTL/HR2357/SUMMARY/REPORT PARAQUAT 200G/L SPRAY STRENGTH SOLUTION: PRELIMINARY INVESTIGATIONS OF THE 4-HOUR ACUTE INHALATION TOXICITY IN THE RAT" examined the inhalation toxicity of Paraquat combined with a non-ionic surfactant and found that a rat died at a dose of Paraquat ten times lower than what would be expected if no surfactant was used.

RESPONSE TO REQUEST FOR ADMISSION NO. 159:

Syngenta objects to the term "non-ionic surfactant" and the phrase "ten times lower than" as vague and ambiguous. Syngenta further objects to the extent that this Request suggests the rat's death can be definitively attributed to its dose of paraquat.

To the extent this Request mischaracterizes "CTL/HR2357/SUMMARY/REPORT PARAQUAT 200G/L SPRAY STRENGTH SOLUTION: PRELIMINARY INVESTIGATIONS OF THE 4-HOUR ACUTE INHALATION TOXICITY IN THE RAT" and conclusions by selectively omitting or emphasizing certain language or by drawing related inferences, they are denied.

Subject to and without waiving its objections, Syngenta admits the study examined the acute-inhalation effects of a paraquat-Agral formulation on rats, and that evidence of the cause of

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the rat's death was inconclusive. Syngenta states that the document speaks for itself. If not specifically admitted herein, denied.

REQUEST FOR ADMISSION NO. 160:

Admit that Syngenta advises users in the U.S. to mix a non-ionic surfactant with Paraquat prior to spraying Paraquat.

RESPONSE TO REQUEST FOR ADMISSION NO. 160:

Syngenta objects to the phrase "non-ionic surfactant" as vague and ambiguous. Subject to and without waiving its objections, Syngenta admits that its U.S. labels recommend that users add a non-ionic surfactant to the spray mixture prior to spraying paraquat.

REQUEST FOR ADMISSION NO. 161:

Admit that Syngenta did submit to the EPA a different 4-Hour Acute Inhalation Toxicity study in the Rat titled "HR2533 Sponsor Report Number: Study Title: PARAQUAT DICHLORIDE TECHNICAL MATERIAL - 4-HOUR ACUTE INHALATION TOXICITY STUDY IN RATS" that examined only the inhalation toxicity of Paraquat without a surfactant.

RESPONSE TO REQUEST FOR ADMISSION NO. 161:

Syngenta objects to the phrases "submit to the EPA," "a different," and "surfactant" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that the referenced study was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

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Subject to and without waiving its objections, Syngenta admits that "HR2533 Sponsor Report Number: Study Title: PARAQUAT DICHLORIDE TECHNICAL MATERIAL - 4-HOUR ACUTE INHALATION TOXICITY STUDY IN RATS" was submitted to the EPA. Syngenta further states that, based on a reasonable investigation, it has not been able to determine the exact formulation used in the study "HR2533 Sponsor Report Number: Study Title: PARAQUAT DICHLORIDE TECHNICAL MATERIAL - 4-HOUR ACUTE INHALATION TOXICITY STUDY IN RATS" from the details provided in the in the study. Syngenta further states that the purity of the test substance used in the study was 33.4% weight per weight paraquat cation and 46.1% weight per weight paraquat dichloride and that "the neat test material was diluted in deionized water to provide a 0.5%v/v solution (groups 1 and 3) and a 1.0%v/v solution for group 2." SYNG-PQ-21944254.

REQUEST FOR ADMISSION NO. 162:

Admit that the formulation of Paraquat used in study HR2533 which did not contain a surfactant was ten times less fatal than the formulation of Paraquat used in study HR257 which did contain a surfactant.

RESPONSE TO REQUEST FOR ADMISSION NO. 162:

Syngenta objects to the phrases "surfactant" and "ten times less fatal" as vague and ambiguous. Syngenta further objects to this Request as incomplete and misleading as written. Subject to and without waiving its objections, notes that it was unable to identify a study titled "HR257." In light of the foregoing, Syngenta denies this request as written.

REQUEST FOR ADMISSION NO. 163:

Admit that the formulation in the study "Paraquat SL (A3879EX) Acute Toxicity in Beagle Dogs with Toxicokinetic Analysis -Contemporary Control Study" contained a surfactant.

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RESPONSE TO REQUEST FOR ADMISSION NO. 163:

Syngenta objects to the phrase "surfactant" as vague and ambiguous. Subject to and without waiving its objections, Syngenta admits that the formulation in the study "Paraquat SL (A3879EX) Acute Toxicity in Beagle Dogs with Toxicokinetic Analysis - Contemporary Control Study" contained a surfactant. SYNG-PQ-05608996.

REQUEST FOR ADMISSION NO. 164:

Admit that three out of twelve dogs died after ingesting the surfactant-containing Paraquat formulation in the study "Paraquat SL (A3879EX) Acute Toxicity in Beagle Dogs with Toxicokinetic Analysis -Contemporary Control Study".

RESPONSE TO REQUEST FOR ADMISSION NO. 164:

Syngenta objects to the phrase "surfactant-containing Paraquat formulation" as vague and ambiguous. Subject to and without waiving its objections, Syngenta admits that two animals dosed with 0.64 mL A3879EX/kg were euthanized in extremis on Day 5. The remaining two animals in this group appeared normal, with no significant observations noted in the period after treatment. Syngenta admits that one additional animal dosed with 1.28 mL A3879EX/kg was euthanized in extremis on Day 4. All other animals survived the trial period. SYNG-PQ-06700353.

REQUEST FOR ADMISSION NO. 165:

Admit that the study "Paraquat SL (A3879EX) Acute Toxicity in Beagle Dogs with Toxicokinetic Analysis -Contemporary Control Study" was not submitted to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 165:

Syngenta objects to the phrase "submitted to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that

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it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, and based on a reasonable investigation, Syngenta admits that it does not have record of submitting the referenced report as part of FIFRA's 6(a)(2) process. Syngenta's investigation into this Request is ongoing, and Syngenta reserves the right to supplement this Request if it identifies information suggesting that this information was considered or submitted. Syngenta further states that FIFRA has evolved over time and EPA guidance regarding 6(a)(2) has similarly evolved; Syngenta has consistently been responsive to these changes and complied with its obligations under FIFRA 6(a)(2), and the EPA has never cited or sanctioned Syngenta for failing to comply with its 6(a)(2) disclosure obligations with respect to paraquat.

REQUEST FOR ADMISSION NO. 166:

Admit that the formulation in the study "Paraquat SL (A7813K) Acute Toxicity in Beagle Dogs with Toxicokinetic Analysis -Contemporary Control Study" did not contain a surfactant.

RESPONSE TO REQUEST FOR ADMISSION NO. 166:

Syngenta objects to the phrase "surfactant" as vague and ambiguous. Subject to and without waiving its objections, Syngenta admits that the formulation in the study "Paraquat SL (A7813K) Acute Toxicity in Beagle Dogs with Toxicokinetic Analysis - Contemporary Control Study" did not contain a surfactant.

REQUEST FOR ADMISSION NO. 167:

Admit that only one out of twelve dogs died after ingesting the non-surfactant-containing Paraquat formulation in the study "Paraquat SL (A3879EX) Acute Toxicity in Beagle Dogs with Toxicokinetic Analysis -Contemporary Control Study"

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RESPONSE TO REQUEST FOR ADMISSION NO. 167:

Syngenta objects to the phrase "non-surfactant-containing Paraquat formulation" as vague and ambiguous. Subject to and without waiving its objections, Syngenta denies that one out of twelve dogs died after ingesting the non-surfactant-containing paraquat formulation in the study "Paraquat SL (A3879EX) Acute Toxicity in Beagle Dogs with Toxicokinetic Analysis - Contemporary Control Study."

REQUEST FOR ADMISSION NO. 168:

Admit that the study "Paraquat SL (A7813K) Acute Toxicity in Beagle Dogs with Toxicokinetic Analysis -Contemporary Control Study" was submitted to the EPA.

RESPONSE TO REQUEST FOR ADMISSION NO. 168:

Syngenta objects to the phrase "submitted to the EPA" as vague and ambiguous. For example, it is not clear whether this Request asks solely about information submitted to the EPA through the 6(a)(2) submission process, or whether this Request also encompasses more informal correspondence and notification processes. Syngenta also objects to this Request to the extent that it suggests that this report was reportable under FIFRA Section 6(a)(2). Syngenta further objects to this Request to the extent that it calls for expert testimony. Finally, Syngenta objects to this Request to the extent that it calls for a legal conclusion.

Subject to and without waiving its objections, Syngenta admits that the study "Paraquat SL (A7813K) Acute Toxicity in Beagle Dogs with Toxicokinetic Analysis -Contemporary Control Study" was submitted to the EPA. *See* SYNG-PQ-02400408.

REQUEST FOR ADMISSION NO. 169:

Admit that surfactants will normally increase the absorption of paraquat and hence increase its toxicity.

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RESPONSE TO REQUEST FOR ADMISSION NO. 169:

Syngenta objects to the phrases "surfactants" and "absorption of paraquat" as vague and ambiguous. Syngenta further objects that this Request calls for expert testimony.

Subject to and without waiving its objections, Syngenta states there are numerous distinct types of surfactants, and hundreds of distinct surfactants within each type. In addition to the type of surfactant, the route of exposure (e.g., oral or dermal) also impacts how surfactants may impact paraquat absorption—if at all. Multiple studies have shown that non-ionic surfactants do not significantly impact dermal absorption. *See e.g.*, SYNG-PQ-19339827; SYNG-PQ-02107996. In light of the foregoing, Syngenta denies that surfactants will normally increase the absorption of paraquat and hence increase its toxicity.

REQUEST FOR ADMISSION NO. 170:

Admit that Syngenta never informed the EPA that the use of a dust mask filter or fabric mask may exacerbate the product user's exposure to Paraquat.

RESPONSE TO REQUEST FOR ADMISSION NO. 170:

Syngenta objects to the phrases "informed the EPA" and "may exacerbate" as vague and ambiguous. Syngenta further objects to this Request to the extent that it suggests Syngenta had a legal obligation to "inform the EPA" about the contents of this Request. Syngenta further objects to this Request because it is more appropriately the subject of expert testimony Subject to and without waiving its objections, Syngenta states that it cannot admit or deny the Request as written given the many ambiguities in the Request. Syngenta is willing to meet and confer with Plaintiffs regarding the need for this Request.

REQUEST FOR ADMISSION NO. 171:

Admit that the Paraquat that was initially marketed and sold in the United States was manufactured using a High Temperature Sodium (HTS) process.

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RESPONSE TO REQUEST FOR ADMISSION NO. 171:

Syngenta objects to the phrase "High Temperature Sodium (HTS) process" as vague and ambiguous. Syngenta further objects to this Request to the extent that it seeks information that is not in Syngenta's custody or control, or otherwise maintained in the ordinary course of business. Given the passage of more than 55 years since paraquat first became available for sale in the United States, as well as the numerous corporate changes that resulted in the creation of the Syngenta entities that are defendants in the present suit, it is impossible for Syngenta to answer this Request completely, and Syngenta must necessarily rely on the limited historical information available. As a result, Syngenta makes this response based on the information available to it at this time and reserves the right to modify or supplement this Response if further information is discovered.

Subject to and without waiving its objections, Syngenta admits that it manufactured paraquat at a High Temperature Sodium (HTS) plant between 1961 and 1964. Syngenta further states that it stopped operating its HTS paraquat plant between 1964-1966.

REQUEST FOR ADMISSION NO. 172:

Admit that the Paraquat that was initially marketed and sold in the United States contained terpyridines.

RESPONSE TO REQUEST FOR ADMISSION NO. 172:

Syngenta objects to the phrase "terpyridines" as vague and ambiguous. Syngenta further objects to this Request to the extent that it seeks information that is not in Syngenta's custody or control, or otherwise maintained in the ordinary course of business. Given the passage of more than 55 years since paraquat first became available for sale in the United States, as well as the numerous corporate changes that resulted in the creation of the Syngenta entities that are defendants in the present suit, it is impossible for Syngenta to answer this Request completely, and Syngenta must necessarily rely on the limited historical information available. As a result,

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Syngenta makes this response based on the information available to it at this time and reserves the right to modify or supplement this Response if further information is discovered.

Subject to and without waiving its objections, Syngenta admits that terpyridines are a potential impurity that may be produced by the High Temperature Sodium (HTS) process. Syngenta stopped operating its HTS paraquat plant in between 1964-1966. By way of further response, given the passage of time, Syngenta cannot confirm or deny whether paraquat containing terpyridines was marketed and sold in the United States during that time.

REQUEST FOR ADMISSION NO. 173:

Admit that terpyridines are extremely toxic in minute quantities.

RESPONSE TO REQUEST FOR ADMISSION NO. 173:

Syngenta objects to the phrases "terpyridines," "extremely toxic," and "minute quantities" as vague and ambiguous. Syngenta further objects to this Request to the extent that it calls for expert testimony. Subject to and without waiving its objections, Syngenta states that it cannot answer this Request as drafted.

REQUEST FOR ADMISSION NO. 174:

Admit that terpyridines are neurotoxic.

RESPONSE TO REQUEST FOR ADMISSION NO. 174:

Syngenta objects to the phrases "terpyridines" and "neurotoxic" as vague and ambiguous. Syngenta further objects that this Request calls for expert testimony. Subject to and without waiving its objections, Syngenta states that it is willing to meet and confer with Plaintiffs about the necessity of an RFA Response from Syngenta on this scientific topic as opposed to expert testimony.

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REQUEST FOR ADMISSION NO. 175:

Admit that death can occur from dermal exposure to Paraquat.

RESPONSE TO REQUEST FOR ADMISSION NO. 175:

Syngenta objects to "dermal exposure" as vague and ambiguous. Subject to and notwithstanding its objections, Syngenta admits that, in certain laboratory conditions that involved significant dermal exposure, dermal exposure has resulted in laboratory animal death. Syngenta further states that those experiments involved extreme levels of exposure that far exceed dermal exposure in humans.

REQUEST FOR ADMISSION NO. 176:

Admit that Paraquat is a skin irritant.

RESPONSE TO REQUEST FOR ADMISSION NO. 176:

Syngenta objects to the phrase "skin irritant" as vague and ambiguous. Subject to and without waiving its objections, Syngenta admits that repeated, prolonged exposure to paraquat concentrate can be irritating to the skin, but diluted, spray-strength material is not considered a significant skin irritant.

REQUEST FOR ADMISSION NO. 177:

Admit that non-ionic surfactants are skin irritants.

RESPONSE TO REQUEST FOR ADMISSION NO. 177:

Syngenta objects to the phrases "non-ionic surfactants" and "skin irritants" as vague and ambiguous. Subject to and without waiving its objections, Syngenta states there are hundreds of non-ionic surfactants with distinct physicochemical properties that may bear on skin irritation. In light of the foregoing, Syngenta can neither admit nor deny this Request.

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REQUEST FOR ADMISSION NO. 178:

Admit that Paraquat is corrosive to the skin.

RESPONSE TO REQUEST FOR ADMISSION NO. 178:

Syngenta objects to the phrase "corrosive to the skin" as vague and ambiguous. Subject to and without waiving its objections, Syngenta admits that repeated, prolonged exposure to paraquat concentrate can be corrosive to the skin, but diluted, spray-strength material is not considered corrosive to the skin.

REQUEST FOR ADMISSION NO. 179:

Admit that non-ionic surfactants are corrosive to the skin.

RESPONSE TO REQUEST FOR ADMISSION NO. 179:

Syngenta objects to the phrases "non-ionic surfactants" and "corrosive to the skin" as vague and ambiguous. Subject to and without waiving its objections, Syngenta states there are hundreds of non-ionic surfactants with distinct physicochemical properties that may bear on whether the compound is considered corrosive to the skin. In light of the foregoing, Syngenta can neither admit nor deny this Request.

REQUEST FOR ADMISSION NO. 180:

Admit that there were a total of 34 reported nosebleeds from Syngenta employees working in Paraquat manufacturing plants between September 1966 and March 1968. (See SYNG-PQ-02518937).

RESPONSE TO REQUEST FOR ADMISSION NO. 180:

Syngenta objects to this Request as misleading and seeking irrelevant information. The total of 34 reported nosebleeds in SYNG-PQ-02518937 includes workers exposed to Bipyridyl. Subject to and without waiving its objections, Syngenta admits that there were a total of 34

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reported nosebleeds from Syngenta employees working in paraquat manufacturing plants between September 1966 and March 1968.

REQUEST FOR ADMISSION NO. 181:

Admit that Syngenta received reports of fatal Paraquat poisoning through inhalation by 1973.

RESPONSE TO REQUEST FOR ADMISSION NO. 181:

Syngenta objects to the phrase "fatal Paraquat poisoning through inhalation" as vague and ambiguous. Subject to and without waiving its objections, Syngenta denies that, by 1973, it received reports of fatal paraquat poisoning through inhalation in occupational settings by those using paraquat according to its labeled instructions. Syngenta further denies that it has received any reports of fatalities solely through inhalation.

REQUEST FOR ADMISSION NO. 182:

Admit that Syngenta studies have confirmed that spray particles of Paraquat can be deposited in the oro-nasal region of a product user.

RESPONSE TO REQUEST FOR ADMISSION NO. 182:

Syngenta objects to the phrases "spray particles," "deposited," and "product user" as vague and ambiguous. Subject to and without waiving its objections, Syngenta admits that, due to its local irritant properties, nosebleeds attributable to irritation of the nasal mucosa have been reported in studies evaluating paraquat in occupational use. Syngenta further states that paraquat's particle size during application is too large to result in significant respiration.

REQUEST FOR ADMISSION NO. 183:

Admit that Paraquat can bypass the blood-brain barrier when absorbed through the nasal membrane.

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RESPONSE TO REQUEST FOR ADMISSION NO. 183:

Syngenta objects to this Request as vague and ambiguous with respect to the phrase "blood-brain barrier" which is not defined, and which may refer to a complex set of tissues or transport processes within the brain and surrounding tissues. Syngenta further objects to the undefined phrase "nasal membrane." Syngenta further objects that the word "bypass" is neither defined nor clear on its face. In addition, Syngenta objects to this Request as overbroad, as it seeks information regarding paraquat "bypass[ing]" the blood-brain barrier generally, and not the subject of Plaintiffs' claims, which is Parkinson's disease. Syngenta further objects to the extent that this Request asks for conclusions that are more properly the subject of expert testimony.

Subject to and without waiving its objections, Syngenta admits that small amounts of paraquat can enter the brains of people who have been exposed to lethal or near-lethal doses of paraquat that are thousands of times higher than those encountered by paraquat users under normal conditions and that overwhelm the body's natural defenses. Syngenta further admits that research has shown that even where humans are exposed to near-lethal doses of paraquat, they do not develop any signs of parkinsonism. Syngenta also specifically denies that paraquat has been found in the brains of humans using paraquat for its intended purpose and in accordance with the label instructions.

REQUEST FOR ADMISSION NO. 184:

Admit that Syngenta sells and/or has sold pesticides containing the ingredient Maneb (manganese ethylene bisdithiocarbamate).

RESPONSE TO REQUEST FOR ADMISSION NO. 184:

Syngenta objects to this Request on the grounds of relevance as no plaintiff in this case alleges that he or she used paraquat in conjunction with Maneb. Syngenta further objects that this Request is overbroad and unduly burdensome because it is not limited by geographic scope and

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thus includes pesticides sold in states and countries not at issue in this case. Subject to and without waiving its objections, Syngenta admits that it has sold products containing the ingredient manganese ethylene bisdithiocarbamate.

REQUEST FOR ADMISSION NO. 185:

Admit that Maneb, when used on its own without other pesticides, does not cause Parkinson's Disease in humans.

RESPONSE TO REQUEST FOR ADMISSION NO. 185:

Syngenta objects to this Request on the grounds of relevance as no plaintiff in this case alleges that he or she used paraquat in conjunction with Maneb. Syngenta objects that this Request calls for improper expert testimony. Subject to and without waiving its objections, Syngenta admits that manganese ethylene bisdithiocarbamate does not cause Parkinson's disease.

REQUEST FOR ADMISSION NO. 186:

Admit that Syngenta has never included a warning for Parkinson's Disease or neurotoxicity on any of the labels of its pesticides containing maneb.

RESPONSE TO REQUEST FOR ADMISSION NO. 186:

Syngenta objects to this Request on the grounds of relevance, given that Plaintiffs allege that paraquat caused their Parkinson's disease and there are no allegations in this case that Plaintiffs used paraquat in conjunction with Maneb. Syngenta further objects to the phrase "warning for Parkinson's disease" as vague. Subject to and without waiving its objections, Syngenta admits that it has not included a warning regarding neurotoxicity or Parkinson's disease on labels for products containing manganese ethylene bisdithiocarbamate.

REQUEST FOR ADMISSION NO. 187:

Admit that Syngenta has never included a warning for Parkinson's Disease on any label of any pesticide product it sells or has sold.

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RESPONSE TO REQUEST FOR ADMISSION NO. 187:

Syngenta objects on the grounds of relevance to the extent that this Request concerns products other than paraquat. Syngenta further objects to this Request as misleading, given that the EPA has determined that there is "insufficient epidemiological evidence of a clear associative or causal relationship" between paraquat exposure and the development of Parkinson's Disease. Syngenta denies that such a warning would be appropriate. Subject to and without waiving its objections, Syngenta admits that it has never submitted a request to the EPA to include a warning related to Parkinson's disease on any product label.

REQUEST FOR ADMISSION NO. 188:

Admit that Syngenta has never included a warning for Parkinson's Disease on any label of any pesticide product it sells or has sold.

RESPONSE TO REQUEST FOR ADMISSION NO. 188:

Syngenta objects on the grounds of relevance to the extent that this Request concerns products other than paraquat. Syngenta further objects to this Request as misleading, given that the EPA has determined that there is "insufficient epidemiological evidence of a clear associative or causal relationship" between paraquat exposure and the development of Parkinson's Disease. Syngenta denies that such a warning would be appropriate. Subject to and without waiving its objections, Syngenta admits that it has never submitted a request to the EPA to include a warning related to Parkinson's disease on any product label.

REQUEST FOR ADMISSION NO. 189:

Admit that Syngenta sells pesticides containing the following active ingredients: Abamectin, Acibenzolar-S-methyl, Pydiflumetofen, Ametryn, Atrazine, Azoxystrobin, benoxacor, Benzovindiflupyr, Bicyclopyrone, Bromoxynil Octanoate, ChlorantraniIiprole, Chlorothalonil, Clodinafop-ropargyl, Cloransulam-methyl, copper OH, Cyantraniliprole, Cyproconazole, Cyprodinil, Cyromazine, Dicamba, Difenoconazole, Difenoconazole + Fludioxonil, Diquat dibromide, Emamectin benzoate, Fenoxaprop-P-ethyl, Florasulam, Fluazifop-P-butyl, Fluazinam,

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Fludioxonil, Flumetralin, Fluroxypyr 1-methylheptyl ester, Fluxofenim, Fomesafen, Glyphosate, Lambda-cyhalothrin, Mancozeb, Mandipropamid, MCPA, Mefenoxam, Mesotrione, Metribuzin, Oxathiapiprolin, Pasteuria nishizawae-Pn1, Picarbutrazox, Pinoxaden, Primisulfuron-methyl, Prometryn, Propiconazole, Prosulfuron, Pydiflumetofen, Pyroxasulfone, S-Metolachlor, Sedaxane, Simazine, Sodium Salt of Dicamba, Sodium Salt of Fomesafen, Spinosad A, Spinosad D, Sulfentrazone, Tefluthrin, THIABENDAZ, Thiabendazole, Thiamethoxam, Triasulfuron, Trifloxysulfuron-sodium, and Trinexapac-ethyl, Zinc (Zn).

RESPONSE TO REQUEST FOR ADMISSION NO. 189:

Syngenta objects on the grounds of relevance; the compound at issue in this case is paraquat, any other compounds Syngenta may or may not sell are irrelevant. Syngenta further objects that this Request is overbroad and unduly burdensome because it is not limited by geographic scope and thus includes pesticides sold in states and countries not at issue in this case. Syngenta further objects to the undefined phrase "active ingredients" as vague and ambiguous.

Subject to and without waiving its objections, Syngenta admits that it currently sells crop protection products containing the following active ingredients: Abamectin, Acibenzolar-S-methyl, Pydiflumetofen, Ametryn, Atrazine, Azoxystrobin, benoxacor, Benzovindiflupyr, Bicyclopyrone, Bromoxynil Octanoate, ChlorantraniIiprole, Chlorothalonil, Clodinafop-ropargyl, Cloransulam-methyl, copper OH, Cyantraniliprole, Cyproconazole, Cyprodinil, Cyromazine, Difenoconazole, Difenoconazole + Fludioxonil, Diquat dibromide, Emamectin benzoate, Fenoxaprop-P-ethyl, Florasulam, Fluazifop-P-butyl, Fluazinam, Fludioxonil, Flumetralin, Fluroxypyr 1-methylheptyl ester, Fluxofenim, Glyphosate, Lambda-cyhalothrin, Mancozeb, Mandipropamid, MCPA, Mefenoxam, Mesotrione, Metribuzin, Oxathiapiprolin, Pasteuria nishizawae-Pn1, Picarbutrazox, Pinoxaden, Primisulfuron-methyl, Prometryn, Propiconazole, Prosulfuron, Pydiflumetofen, Pyroxasulfone, S-Metolachlor, Sedaxane, Simazine, Sodium Salt of Dicamba, Sodium Salt of Fomesafen (Fomesafen), Spinosada mixture of Spinosad A and Spinosad D, Sulfentrazone, Tefluthrin, Thiabendazole, Thiamethoxam, Triasulfuron, Trifloxysulfuron-

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sodium, and Trinexapac-ethyl, Zinc (Zn). Syngenta further admits that it currently sells pesticides containing the co-formulants copper OH and benoxacor.

REQUEST FOR ADMISSION NO. 190:

Admit that the following active ingredients do not cause Parkinson's disease: Abamectin, Acibenzolar-S-methyl, Pydiflumetofen, Ametryn, Atrazine, Azoxystrobin, benoxacor, Benzovindiflupyr, Bicyclopyrone, Bromoxynil Octanoate, ChlorantraniIiprole, Chlorothalonil, Clodinafop-ropargyl, Cloransulam-methyl, copper OH, Cyantraniliprole, Cyproconazole, Cyprodinil, Cyromazine, Dicamba, Difenoconazole, Difenoconazole + Fludioxonil, Diquat dibromide, Emamectin benzoate, Fenoxaprop-P-ethyl, Florasulam, Fluazifop-P-butyl, Fluazinam, Fludioxonil, Flumetralin, Fluroxypyr 1-methylheptyl ester, Fluxofenim, Fomesafen, Glyphosate, Lambda-cyhalothrin, Mancozeb, Mandipropamid, MCPA, Mefenoxam, Mesotrione, Metribuzin, Oxathiapiprolin, Pasteuria nishizawae-Pn1, Picarbutrazox, Pinoxaden, Primisulfuron-methyl, Prometryn, Propiconazole, Prosulfuron, Pydiflumetofen, Pyroxasulfone, S-Metolachlor, Sedaxane, Simazine, Sodium Salt of Dicamba, Sodium Salt of Fomesafen, Spinosad A, Spinosad D, Sulfentrazone, Tefluthrin, THIABENDAZ, Thiabendazole, Thiamethoxam, Triasulfuron, Trifloxysulfuron-sodium, and Trinexapac-ethyl, Zinc (Zn).

RESPONSE TO REQUEST FOR ADMISSION NO. 190:

Syngenta objects to this Request as vague and ambiguous. Syngenta also objects on the grounds of relevance; the compound at issue in this case is paraquat, and other unrelated chemicals are irrelevant. Syngenta further objects that this Request is overbroad and unduly burdensome because it is not limited by geographic scope and thus includes pesticides sold in states and countries not at issue in this case. Insofar as Syngenta sells products containing the referenced chemicals, *see* Response to Request for Admission No. 189, Syngenta admits that none of the products that it sells cause Parkinson's disease.

REQUEST FOR ADMISSION NO. 191:

Admit that the products listed on exhibit 1, which is a printout from Syngenta's website https://www.syngenta-us.com/crop-protection/all-products, are sold or have been sold by Syngenta.

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RESPONSE TO REQUEST FOR ADMISSION NO. 191:

Syngenta objects on the grounds of relevance to the extent that this Request concerns products other than paraquat. Syngenta denies that Exhibit 1 accurately represents the Syngenta-us.com website as a visitor would have seen it. Notwithstanding that, Syngenta admits that all the products at the link provided in this Request are products that are sold or have been sold by Syngenta in certain markets.

REQUEST FOR ADMISSION NO. 192:

Admit that none of the labels for the products listed on Exhibit 1, which is a printout from Syngenta's website https://www.syngenta-us.com/crop-protection/all-products, include a warning for Parkinson's disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 192:

Syngenta objects on the grounds of relevance to the extent that this Request concerns products other than paraquat. Syngenta further objects that this Request is misleading, insofar as it suggests that product labels should include a warning for Parkinson's disease where the scientific consensus does not support a causal relationship between any of these products and Parkinson's disease. Syngenta further objects to this Request as misleading, given that the EPA has determined that there is "insufficient epidemiological evidence of a clear associative or causal relationship" between paraquat exposure and the development of Parkinson's Disease. Syngenta denies that such a warning would be appropriate. Subject to and without waiving its objections, Syngenta admits that the products listed at the cited web page do not include labels with warnings for Parkinson's disease.

REQUEST FOR ADMISSION NO. 193:

Admit that, as of January 16, 2024, Syngenta was maintaining the registration of 833 different pesticide products approved for sale in the United States. SYNG-PQ-PA-00032122

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RESPONSE TO REQUEST FOR ADMISSION NO. 193:

Syngenta admits that on January 16, 2024, it submitted the cited document which references Syngenta paying fees to support 833 registrations. Syngenta further states that the document speaks for itself.

REQUEST FOR ADMISSION NO. 194:

Admit that none of the labels for the 833 different pesticide products listed on Exhibit 2 (SYNG-PQ-PA-00032122) registered by Syngenta, and approved for sale in the United States, include a warning for Parkinson's disease.

RESPONSE TO REQUEST FOR ADMISSION NO. 194:

Syngenta objects on the grounds of relevance to the extent that this Request concerns products other than paraquat. Syngenta further objects to this Request as misleading, given that the EPA has determined that there is "insufficient epidemiological evidence of a clear associative or causal relationship" between paraquat exposure and the development of Parkinson's Disease. Syngenta further objects that this Request is misleading insofar as it suggests that product labels should include a warning for Parkinson's disease without scientific consensus that would support a causal relationship between any of the products and Parkinson's disease. Syngenta denies that such a warning would be appropriate. Subject to and without waiving its objections, Syngenta admits that it has never submitted a request to the EPA to include a warning related to Parkinson's disease on any label.

REQUEST FOR ADMISSION NO. 195:

Admit that on August 2, 2019, an employee at the EPA informed Syngenta that it would be downplaying the potential risk of Paraquat to say that inhalation of Paraquat is unlikely. (See SYNG-PQ-MDL-000979557).

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RESPONSE TO REQUEST FOR ADMISSION NO. 195:

Syngenta objects to this Request as incomplete. Subject to and without waiving its objections, Syngenta admits that it received an email from an employee at the EPA on August 2, 2019. Syngenta further admits that the EPA emailed Syngenta with the subject line "EPA suggested improvements to Paraquat Training Program." In that email, an EPA employee stated, "At the beginning of the summer we discussed a few issues with the paraquat training that have been brought to our attention since it has gone live. The email is to follow up on that conversation and identify issues which the agency feels need to be addressed. . . . Thanks for your continued cooperation with the paraquat human health mitigation." The email included the following bullet: "Routes of exposure slide -- Inhalation is said to be unlikely . . . due to vapor pressure and droplet size. EPA asked registrants to remove this statement when we were having label language discussions because it sounds it's downplaying the potential risk, so it shouldn't have been added to the training." Except as admitted herein, denied.

REQUEST FOR ADMISSION NO. 196:

Admit that the document produced in discovery bates number SYNG-PQ-13102284-SYNG-PQ-13102406 is a true and accurate copy of a notebook of data and memoranda maintained by Syngenta scientists Dr. Ted Lock in the course of regularly conducted business activity and it was the regular practice of Dr. Lock to make such memorandum, report, record, or data compilation.

RESPONSE TO REQUEST FOR ADMISSION NO. 196:

Syngenta admits that the document produced in discovery Bates number SYNG-PQ-13102284–SYNG-PQ-13102406 is a true and accurate copy of a notebook containing copies of external studies and notes from Syngenta scientist Dr. Ted Lock. Syngenta denies that this notebook was maintained by Dr. Ted Lock in the course of regularly conducted business activity.

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By way of further response, Syngenta states that Dr. Lock's notebook summarizes both external and internal studies and their findings, which speak for themselves.

REQUEST FOR ADMISSION NO. 197:

Admit that on August 3, 2000, Dr. Ted Lock, a scientist employed by Syngenta stated "the Parkinson link will not diminish, we are stuck with it.!" (See SYNG-PQ-13102284, p. 69).

RESPONSE TO REQUEST FOR ADMISSION NO. 197:

Syngenta objects to this Request because it cherry-picks a single phrase from an isolated document and does not provide any context for it. Subject to and without waiving its objections, Syngenta states that on August 3, 2000, Dr. Ted Lock, a scientist employed by Syngenta, reviewed a 1998 Corasaniti study titled "Paraquat: a useful tool for the in vivo study of mechanisms of neuronal cell death." Dr. Lock stated "[o]verall, not a lot of new findings of concern, but it raises the profile of the neurotoxic effects of paraquat, as seen at *high doses* and *non relevant routes of exposure.*" SYNG-PQ-1302284 at pg. 69 (emphasis added). Syngenta admits that Dr. Lock concluded his analysis with the statement "the Parkinson link will not diminish, we are stuck with it.!" Except as specifically admitted here, denied.

REQUEST FOR ADMISSION NO. 198:

Admit that the document produced in discovery bates numbered SYNG-PQ-23457731 is a true and correct copy of a Letter from Mr. J.C. Gage to Dr. F.F. Snowdon, dated October 13, 1958; created and maintained in the course of regularly conducted business activity; and it was the regular practice of Syngenta to create and maintain such correspondence reporting data from Paraquat studies.

RESPONSE TO REQUEST FOR ADMISSION NO. 198:

Syngenta admits that the document produced with Bates number SYNG-PQ-23457731 is a true and correct copy of a Letter from Mr. J.C. Gage to Dr. F.F. Snowdon, dated October 13, 1958. Syngenta denies that this was created in the course of regularly conducted business activity.

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REQUEST FOR ADMISSION NO. 199:

Admit that on October 13, 1958, a Syngenta employee, Mr. J.C. Gage wrote to Dr. F.F. Snowdon reporting that "Dipyridyl appears to have a moderate toxicity mainly by affecting the central nervous system, and it can be absorbed through the skin." (See SYNG-PQ-23457731).

RESPONSE TO REQUEST FOR ADMISSION NO. 199:

Syngenta objects to this Request as incomplete and seeking irrelevant information. The "Dipyridyl" referenced in the cited document is not paraquat, and it has chemical properties that are substantially different than paraquat. Subject to its objections, Syngenta admits that the document contains the excerpted quoted language and otherwise speaks for itself.

REQUEST FOR ADMISSION NO. 200:

Admit that the document produced in discovery bates numbered SYNG-PQ-23457731 is a true and correct copy of a Letter from Mr. J.C. Gage to Dr. F.F. Snowdon, dated October 13, 1958 created and maintained in the course of regularly conducted business activity and it was the regular practice of Syngenta to create and maintain such correspondence reporting data from Paraquat studies.

RESPONSE TO REQUEST FOR ADMISSION NO. 200:

Syngenta admits that the document produced with Bates number SYNG-PQ-23457731 is a true and correct copy of a Letter from Mr. J.C. Gage to Dr. F.F. Snowdon, dated October 13, 1958. Syngenta denies that this was created in the course of regularly conducted business activity.

REQUEST FOR ADMISSION NO. 201:

Admit that the document produced in discovery bates numbered SYNG-PQ-01845525-SYNG-PQ-01845630 is a true and correct copy of a collection of memoranda created by Chevron and provided to Syngenta in the course of regularly conducted business activity and if it was the regular practice of Chevron to create and provide such memoranda regarding Paraquat to Syngenta.

RESPONSE TO REQUEST FOR ADMISSION NO. 201:

Syngenta admits that SYNG-PQ-01845525–SYNG-PQ-01845630 is a true and correct copy of a collection of memoranda collected by Chevron and provided to Syngenta. Syngenta

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denies knowledge about what Chevron's regularly conducted business activities entailed. Chevron is a separate entity and Syngenta cannot speak for its business activities.

REQUEST FOR ADMISSION NO. 202:

Admit that on March 6, 2008 a litigation hold was implemented by Syngenta "concerning retention of documents and emails relevant to potential future litigation involving claims that paraquat herbicide may be associated with the onset of Parkinson's Disease."

RESPONSE TO REQUEST FOR ADMISSION NO. 202:

Plaintiffs appear to be quoting from a copy of the litigation hold itself, which was produced to Plaintiffs pursuant to Federal Rule of Evidence 502(d). Syngenta specifically objects to the use of Rule 502(d) materials at trial or hearing in this matter on the grounds of privilege and relevance. Subject to and without waiving its objections, Syngenta admits that a litigation hold was issued on March 6, 2008.

REQUEST FOR ADMISSION NO. 203:

Admit that Paraquat may bind to glass surfaces and that therefore the analysis of the amount of paraquat in urine and blood samples will generate artificially low results if the samples are stored in glass tubes.

RESPONSE TO REQUEST FOR ADMISSION NO. 203:

Syngenta objects to this Request as vague and ambiguous with respect to the undefined phrases "may bind" and "artificially low results." Syngenta further objects to this Request to the extent that it is more properly the subject of expert testimony. Syngenta further objects to this Request to the extent that it asks Syngenta to generalize about the scientific conclusion that "samples will generate artificially low results" without reference to any specific study, including whether the glass was treated prior to the study to prevent absorption. Syngenta states that it is willing to meet and confer regarding Plaintiff's position regarding the necessity of this Request for Admission from Syngenta, rather than seeking this information from expert testimony.

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REQUEST FOR ADMISSION NO. 204:

Admit that Paraquat was banned in Brazil based on a 2016 technical evaluation conducted by Scientists in Brazilian's Regulatory Agency, Anvisa, that concluded that Paraquat was mutagenic and that Paraquat can cause Parkinson's disease in humans.

RESPONSE TO REQUEST FOR ADMISSION NO. 204:

Subject to its Objections, Syngenta states that Brazil began phasing out the use of paraquat products in September 2020, though farmers were permitted to use existing supplies through 2021. Syngenta admits that Brazil's decision to phase out paraquat products was based on a 2016 technical evaluation that recommended ending paraquat sales due to concerns about potential mutagenic and neurotoxic impacts, paraquat's acute toxicity, and the lack of an antidote for paraquat poisoning. Brazil is the only country in the world that purports to have conducted a scientific evaluation of whether paraquat has mutagenic or neurotoxic potential and to have concluded that it does. Other countries' regulators that examined potential neurotoxic impacts during the same time period as Brazil, such as Australia, or after Brazil's evaluation, such as the U.S. EPA, have concluded that the scientific evidence does not support a causal link between paraquat exposure and neurotoxic impacts.

REQUEST FOR ADMISSION NO. 205:

Admit that on July 11, 2007 the Court Of First Instance Of The European Communities voided the registration of Paraquat in the European Union, in part because Syngenta chose not to provide the European Commission "any data concerning the neurotoxicity of paraquat nor any reason why there was no need to provide information on this."

RESPONSE TO REQUEST FOR ADMISSION NO. 205:

Syngenta objects to this Request to the extent that it purports to characterize the reasoning behind a lengthy decision by selectively quoting a portion of a single sentence. Syngenta further objects to the selective quotation as improperly quoting the Court's ruling, which uses different language, specifically: "Moreover, it can be seen from the Draft Report that the notifier provided

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the rapporteur with no data concerning the neurotoxicity of paraquat, without giving any reason why information on that point was not necessary." Syngenta admits that the opinion of the Court of First Instance contains that language. Syngenta further states that, in 2007, a European Union judicial body issued a decision that annulled the existing EU paraquat registration. The reviewing court determined that the file for the initial registration was mishandled by the regulatory Commission and that it failed to consider all available evidence. The EU judicial body did not purport to conduct a regulatory review of paraquat safety or risk assessment based on a comprehensive review of the available scientific data. Certain non-EU countries also followed the EU's lead and terminated paraquat sales in order to align with the EU standards. The EU member countries impacted by this decision and other countries that aligned with the EU are as follows (though some of these countries made decisions about paraquat before or after the 2007 EU judicial ruling): Albania; Austria; Belgium; Bosnia & Herzegovina; Bulgaria; Croatia; Cyprus; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Latvia; Lithuania; Luxembourg; Macedonia; Malta; Montenegro; Netherlands; Poland; Portugal; Romania; Serbia; Slovakia; Slovenia; Spain; Sweden; Turkey; and United Kingdom. To the extent not specifically admitted herein, denied.

REQUEST FOR ADMISSION NO. 206:

Admit that Syngenta chose not to appeal the July 11, 2007 ruling of the Court Of First Instance Of The European Communities.

RESPONSE TO REQUEST FOR ADMISSION NO. 206:

Syngenta objects to this Request to the extent that it purports to characterize the appeals process for rulings of the Court of First Instance of the European Communities. Subject to and without waiving its objections, Syngenta admits that it did not appeal the July 11, 2007 ruling of

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the Court of First Instance of the European Communities. By way of further response, Syngenta incorporates its response to Request for Admission No. 205.

REQUEST FOR ADMISSION NO. 207:

Admit that if Syngenta applied to re-register Paraquat in the European Union then it would have had to provide the European Commission on data concerning the neurotoxicity of paraquat.

RESPONSE TO REQUEST FOR ADMISSION NO. 207:

Syngenta objects to this Request as vague and ambiguous as to the undefined word "neurotoxicity." Syngenta further objects to this Request to the extent that it calls for speculation, insofar as it asks Syngenta to admit to something that never happened. Syngenta further objects to this Request to the extent that it calls for legal conclusion. Subject to and without waiving its objections, Syngenta states that it cannot admit or deny this Request because it asks Syngenta to speculate regarding a re-registration process that never occurred. By way of further response, Syngenta states that it has continually, and would have continued to, provide necessary data to regulatory authorities under controlling regulatory regimes.

REQUEST FOR ADMISSION NO. 208:

Admit that Syngenta chose not to apply to re-register Paraquat in the European Union.

RESPONSE TO REQUEST FOR ADMISSION NO. 208:

Syngenta objects to this Request as vague and ambiguous. Subject to and without waiving its objections, Syngenta admits that it did not re-register paraquat in the European Union.

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GENERAL OBJECTIONS

1. Syngenta objects to these Requests as overbroad, unnecessarily duplicative, and not proportional to the needs of discovery in the case. Plaintiffs served over 200 Requests for Admission on Syngenta at the end of the discovery period, seeking detailed information regarding dozens of specific studies and hundreds of specific facts. Given the breadth of Plaintiffs' Requests, Syngenta is continuing to investigate and reserves the right to supplement its Responses if it identifies further responsive information.

2. Syngenta objects to these Requests to the extent that they seek information protected by the attorney-client privilege, work product doctrine, or any other applicable law, privilege, doctrine, or immunity. Any disclosure of information shall not be deemed, nor shall it constitute, a waiver of any such privilege or of any other ground for objecting to the discovery or admissibility of such material, its subject matter, or the information contained therein, nor shall such disclosure constitute a waiver of Syngenta's rights to object to the use of such information during this or any other proceeding.

3. Syngenta objects to these Requests to the extent that they purport to require Syngenta to assemble or produce information that is not already in existence and reasonably available in the form requested by Plaintiffs.

4. Syngenta's Responses reflect only the current state of Syngenta's knowledge and information regarding the information that Plaintiffs have requested. Further investigation may identify additional facts or information that could lead to additions to, changes in, or variations from, the Responses herein. Syngenta expressly reserves the right to supplement, amend, correct, clarify, or modify its Responses to the Requests as further information becomes available.

5. Syngenta objects to these Requests to the extent that they seek information or documentation that is equally available to Plaintiffs.

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Dated: January 24, 2025

Respectfully submitted,

/s/ Grace Brier

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Counsel for Defendants Syngenta Crop Protection, LLC and Syngenta AG

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CERTIFICATE OF SERVICE

I do hereby certify that a true and correct copy of the foregoing document has been served by means of electronic mail to all counsel registered for service in this action on January 24, 2025.

By: */s/ Grace C. Brier*
Grace C. Brier
Counsel for Defendants,
Syngenta Crop Protection LLC and
Syngenta AG

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ATTACHMENT D

Planet Depos
We Make It Happen™

CONFIDENTIAL

Transcript of Philip Botham, Ph.D., Corporate Designee

Date: September 17, 2024
Case: Paraquat Products Liability Litigation, In Re:

Planet Depos
Phone: 888.433.3767 | **Email:** transcripts@planetdepos.com
www.planetdepos.com
Michigan #8598 | Nevada #089F | New Mexico #566

Case ID: 220300429
Control No.: 26064959

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PHILADELPHIA COUNTY COURT OF COMMON PLEAS

TRIAL DIVISION

IN RE: PARAQUAT PRODUCTS LIABILITY LITIGATION,
This Document Relates to All Actions
Case No. 220500559

CONFIDENTIAL

Videotaped deposition of

DEFENDANT SYNGENTA

by and through its corporate representative

DR. PHILIP BOTHAM

Volume I
(pages 1 - 338)

London, England
United Kingdom

Tuesday, September 17, 2024

Job No. 553162

Reported stenographically by:
LEAH M. WILLERSDORF, RMR, CRR, FBIVR, ACR, QRR2, CLR

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Tuesday, September 17, 2024

09:24 a.m. to 5:59 p.m.
(British Summer Time)

VOLUME I of the videotaped deposition of SYNGENTA, by and through its corporate representative DR. PHILIP BOTHAM, held at the offices of Kirkland & Ellis LLP, 30 St. Mary Axe, London EC3A 8AF, England, United Kingdom, before Leah M. Willersdorf, Registered Merit Reporter and Certified Realtime Reporter, both with the US National Court Reporters Association, and Fellow of the British Institute of Verbatim Reporters, Accredited Court Reporter, Qualified Realtime Reporter (Level 2), and Certified LiveNote Reporter.

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Brian Brake	-	The Miller Firm (via Zoom)
Randi Ellis	-	Special Master
Jeremy Dineen	-	Videographer
Linda Fleet	-	Remote technician

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(On the record at 09:24 a.m.)

THE VIDEOGRAPHER: Here begins media number 1 in the videotaped deposition of Philip Botham, In Re: Paraquat Products Liability Litigation, in the Philadelphia County Court of Common Pleas.

Today's date is September 17, 2024. The time on the video monitor is 09:25 a.m.

The videographer today is Jeremy Dineen, representing Planet Depos.

Would counsel please voice-identify themselves and state whom they represent.

MR. DICKENS: David Dickens on behalf of the plaintiffs.

MR. TRAVERS: Jeffrey Travers on behalf of the plaintiffs.

MR. NARESH: Ragan Naresh on behalf of Syngenta.

MR. SMITH: Mark Smith, Syngenta.

MS. LAHASZOW: Kristin Lahaszow of Jones Day on behalf of defendant Chevron.

MS. BOSTON: Christina Boston from Troutman Pepper on behalf of FMC Corporation.

THE VIDEOGRAPHER: The court reporter today is Leah Willersdorf representing Planet Depos. Would the reporter please swear in the witness.

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THE STENOGRAPHER: Dr. Botham -- oh, sorry, before I do that.

Good morning. My name is Leah Willersdorf. I am a Registered Merit Reporter and a Certified Realtime Reporter.

Will counsel please stipulate that, in lieu of formally swearing in the witness, the reporter will instead ask the witness to acknowledge that their testimony will be true under the penalties of perjury, that counsel will not object to the admissibility of the transcript based on proceeding in this way, and that the witness has verified that he is, in fact, Dr. Botham.

MR. DICKENS: So stipulate.

MR. NARESH: Agreed.

THE STENOGRAPHER: Thank you.

Dr. Botham, do you hereby acknowledge that your testimony will be true under the penalties of perjury?

THE WITNESS: I do.

THE STENOGRAPHER: Thank you. Thank you, Counsel.

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DR. PHILIP BOTHAM,
having first agreed to tell the truth
under penalty of perjury, was examined
and testified as follows:

EXAMINATION ON BEHALF OF PLAINTIFFS

BY MR. DICKENS:

Q. Good morning, Dr. Botham.

A. Good morning.

Q. Can you please state your name for the record.

A. Philip Botham.

Q. And who is your current employer?

A. Syngenta.

Q. And I understand you've been put forward today as a witness to testify on behalf of Syngenta; is that your understanding?

A. That's correct.

Q. And to testify with respect to specific topics?

A. Yes.

Q. Have you had an opportunity to review those topics prior to today's deposition?

A. Yes, I have.

Q. And do you understand that in testifying for Syngenta on the designated topics, you're required

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to answer not based on information known to you personally, but also based on information known or reasonably available to Syngenta as a corporation?

A. That's my understanding, yes.

Q. And you understand that the matters you'll be testifying to for Syngenta includes actions and knowledge of Syngenta corporation as well as its predecessors, including AstraZeneca, Zeneca, Ciba-Geigy, Imperial Chemical Industries and its predecessors?

A. Yes, I do understand.

Q. And did you take that into account when preparing to testify today?

A. Yes, I did.

Q. What did you do to prepare for today's deposition?

A. Well, starting back in July, I've had a number of discussions with external counsel, Mr. Naresh and his colleagues, with also Mr. Smith, and looked at a large range of documents, which I think have provided the topics that are of interest to yourselves in this case, and I've also had some conversations with some other internal colleagues to help with making sure that I understand some of that information.

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Q. Do you have an understanding of what these lawsuits are about?

A. I think I do.

Q. Okay. What's your understanding?

A. Well, the -- my understanding is that these lawsuits are to represent individuals who have unfortunately developed Parkinson's disease and where it is believed that that disease may have been caused by their prior exposure to paraquat.

Q. Do you believe that your preparation has given you sufficient information to testify on behalf of Syngenta here today?

A. As much as I possibly can.

Q. You mentioned a review of documents. Were those documents that were specifically identified in the Notice of Deposition?

A. Yes.

Q. Did you review any additional documents outside of what was specified in that notice?

A. A few, but the majority were those that were provided in the notice.

Q. Now, you mentioned, other than counsel, you spoke to some colleagues. Which colleagues did you speak with?

A. I spoke to my colleague in the United

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States, Monty Dixon; a colleague in Basel, Ian Wheals; and another colleague in Basel, Clive Campbell.
That's the list.
Q. And what was the purpose of reaching out to Monty Dixon?
A. There were some specific questions about the company's interactions in the past with the US Environmental Protection Agency and I needed to understand, because he's been involved in those interactions, a little more about that. There were some issues around the formulations of paraquat that were marketed in the United States; I needed to know a little bit more about that.
With regard to -- yes, and I think that was the majority of what I spoke to Monty about.
Q. With respect to the regulations or regulatory matters with respect to the Environmental Protection Agency, what specifically did you discuss with Monty Dixon?
A. Well, we had a broad discussion about our, I guess you would say our philosophy of the way in which we've interacted with the US EPA over the years, and one or two specific discussions. But it was mostly so that I could be reassured, if you like, about the way in which we had had that relationship

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with the regulatory agencies.
Q. And what was the purpose of reaching out to Ian Wheals?
A. Ian Wheals was, 20 years ago or more now, the global regulatory manager and also the European regulatory manager for paraquat, and so there were, again, a few very specific documents where his name was on -- and I didn't really know as much about those as I needed to; so I think there were only two or three documents where we just needed to check the detail.
Q. And those were specific documents Ian Wheals was mentioned in or --
A. Yes.
Q. Is Ian Wheals still an employee at Syngenta?
A. He is.
Q. What was the purpose of reaching out to Clive Campbell?
A. Clive Campbell is the chief medical officer for Syngenta and has been for a number of years. So I wanted to discuss with him some detail about one or two documents with respect to the manufacture of paraquat and issues around the safety of the people involved in that manufacture. So that

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was the main thing. There were, again, one or two other smaller items.
Q. And those were the only three colleagues you spoke with for preparation for today's deposition?
A. Yes, I believe that's right.
Q. Now, you mentioned you reviewed some other documents other than what was included in the deposition notice. What documents in particular did you review?
A. Mainly for my own memory, I went back and looked at a few publications on paraquat and Parkinson's disease. I wouldn't be able to name all of them, but, as an example, I looked at a report from an organization called Exponent, and -- because I needed to recall the detail of that. So it was mainly scientific documents and publications.
Q. What document in particular related to Exponent did you review?
A. It was their report of a contract that they were involved in, sponsored by the UK government.
Q. Defra?
A. Yes, Defra.
Q. Now, I understand you've been deposed multiple times, correct?
A. I have.

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Q. And deposed multiple times as a representative for Syngenta, correct?
A. That's correct.
Q. Did you review your prior deposition testimony in preparation for today's deposition?
A. No, I did not.
Q. No deposition transcripts from previous depositions at all?
A. Not of my own. I believe on one occasion I was reminded of one or two little sections of my deposition, but I did not systematically review my own depositions.
Q. Did you review deposition transcripts of any other Syngenta employees or any other witnesses in this litigation?
A. I was given access to the depositions of two former Syngenta employees: Dr. Lewis Smith and Dr. Bob Scott.
Q. Any other depositions?
A. No, I don't believe so.
Q. And you reviewed those depositions specifically for preparation for today's deposition?
A. That's correct.
Q. Now, I see you brought something here with you today. What did you bring?

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A. These are some documents which we have put together as, essentially, aide-memoire information that relates to some of the topics that you were interested in. So it's just as an enabler of some of the detailed information that we may require.

Q. And are those notes that you specifically put together?

A. I've contributed to some of these. Others have been prepared, for example, by my colleague, Monty Dixon. So subject-matter experts have been involved.

Q. Okay.

MR. DICKENS: And we'll ask for a copy to mark those as an exhibit to today's deposition.

You're one step ahead of us. We'll go ahead and mark your notes as exhibit --

MR. TRAVERS: Is there another copy or is that it?

MR. NARESH: We just have that one.

MR. DICKENS: Exhibit 1 to today's deposition, and we'll just do the whole compendium.

(Exhibit 1 marked for identification.)

BY MR. DICKENS:

Q. In total, how long -- oh, I'm sorry.

THE STENOGRAPHER: It's okay.

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BY MR. DICKENS:

Q. In total, how long did you prepare for today's deposition?

A. I started around July 10 and have had regular meetings since then, so two months.

Q. Do you know roughly how many hours?

A. I would have to do a mental calculation. I would say 25, 30 hours.

Q. Now, is your current role at Syngenta still principal science advisor?

A. It is, yes.

Q. And you started in that position in 2017, correct?

A. That's right.

Q. Has there been any change in your role or job responsibilities as principal science advisor since your last deposition?

A. No.

Q. Now, paraquat's herbicidal properties were discovered in 1954; is that right?

A. Yes.

Q. And the discovery was made by scientists at ICI, or Imperial Chemical Industries?

A. That's correct.

Q. And I will just ask, as we go forward, if I ask a question you don't understand, please let me know and I'll rephrase; is that fair?

A. Mmm-hmm. Sorry.

Q. That's a yes?

A. Yes.

Q. Okay. And, therefore, if you go ahead and answer, I'll understand that you understood the question and answered fully and truthfully; is that fair?

A. That's fine.

Q. Now, scientists at ICI carried out a program of field testing on paraquat in the 1950s before putting paraquat on the market, right?

MR. NARESH: Objection to scope.

What topic?

MR. DICKENS: Topic 4.

MR. NARESH: Do you have the document?

MR. DICKENS: We do.

MR. NARESH: Oh, and can we have the stipulation I think we've done previously, that we don't have to go off the record to resolve objections in order to preserve them?

MR. DICKENS: That's correct, yes.

MR. NARESH: Okay.

MR. DICKENS: I'll go ahead and mark Exhibit 2 for the record.

(Exhibit 2 marked for identification.)

BY MR. DICKENS:

Q. Dr. Botham, I've handed you Exhibit 2 for the record. Is this a document you've seen before?

A. Yes, I have seen this document.

Q. And a document you reviewed in preparation for today's deposition?

A. This is one of the documents that I reviewed, yes.

Q. And the title of this document is "The Story of Gramoxone from 1947 to 1992," right?

A. That's correct.

Q. If you can turn to page 5 of this document -- it actually might be 4 but it looks like a 5 on the bottom there, but it's "History of Paraquat - Part 2 - Recognition" on the top.

Do you see that?

A. Ah, okay, right. Yeah, I'm there.

Q. Okay.

Now, this document discusses the history of paraquat, including prior to its coming onto the market, right?

A. It does.

Q. Okay. Now, it refers to field testing

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undertaken on paraquat before introducing paraquat to the market, not only in the United States but worldwide, right?

A. It does, yes.

Q. Okay. Now, you'd agree that during the time of the initial field tests on paraquat, very little was known about the properties of paraquat, including its toxicity and irritant effects, right?

A. The majority of the safety tests were certainly conducted shortly after that period.

Q. During the field tests in the 1950s, the earlier researchers experienced nosebleeds, lost fingernails, irritation to the eyes, right?

A. That's what the document says, certainly.

Q. Do you have any reason to dispute that that is correct?

A. No. It seems plausible.

Q. Did you do anything to confirm whether or not that was the case?

A. I did not.

Q. Do you have any reason to doubt the information mentioned here in this particular document?

A. I have no reason to doubt it.

Q. This document states:

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"The full extent of its toxicity and irritant effects were not known."

Do you see that?

A. Yes.

Q. "The early researchers had nosebleeds, lost fingernails, suffered conjunctivitis in their eyes before they learned to take the proper precautions."

Right?

A. That's what it says, yes.

Q. Now, in the early researching and testing of paraquat, the researchers also found the wings of airplanes used to spray paraquat in the field test being conducted on paraquat in Africa started to crumble away, right?

MR. NARESH: Objection to form.

THE WITNESS: Yes.

BY MR. DICKENS:

Q. And the airplane wings were crumbling because of the corrosive properties of paraquat, right?

A. That would be my assumption.

Q. Well, you have an understanding, right, that paraquat is corrosive to airplane wings, right?

A. I had no understanding of that, that that was the case, until I read this document.

Q. Do you know of other documents or experience where Syngenta researchers have found that paraquat is corrosive to metal airplane wings?

A. I have no other background on that subject at all.

Q. As you said, it doesn't surprise you that that is the case, correct?

A. Because paraquat does have corrosive properties, so, yes, it is plausible.

Q. You can put that document aside.

Syngenta's always known that paraquat is an acutely toxic compound, right?

A. Since the early 1960s, certainly, yes.

Q. Syngenta knew paraquat was acutely toxic, both from the findings in the field as well as animal studies that the company conducted?

A. Yes.

Q. Paraquat's capable of causing toxicity through the generation of reactive oxygen species?

MR. NARESH: Objection; scope.

What's the topic?

THE WITNESS: That is its mode of action --

MR. NARESH: Just wait.

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THE WITNESS: I'm sorry.

MR. NARESH: What's the topic?

I'll also note the last three questions are identical in substance to questions that Dr. Botham has previously been asked at depositions, to which plaintiffs' counsel have access to, which I don't think is consistent with our understanding of this deposition, which was that this deposition would be limited to new questions, not questions previously asked and answered by this witness on the same topics.

MR. DICKENS: Topic 17, I will state for the record, which is stating a foundation or laying a foundation for the questions I will be asking, but I can move on from there.

BY MR. DICKENS:

Q. We can agree that investigation field studies of paraquat began in the 1950s but wasn't sold for commercial use in the United States until 1965, correct?

A. That's right.

Q. Early animal studies showed paraquat could have an effect on the central nervous system, right?

A. There were some documents which suggested that, but I think the interpretation of those studies

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is not clear when you look at the actual wording of the documents.

Q. Are you aware of any early research showing paraquat having an effect on the central nervous system?

MR. NARESH: Objection; scope.

What's the topic?

MR. DICKENS: Topic 5.

I'll go ahead and mark Exhibit 3 for the record.

(Exhibit 3 marked for identification.)

MR. NARESH: This is 5B?

MR. DICKENS: 5B.

BY MR. DICKENS:

Q. I've handed you Exhibit 3. For the record, this is a study produced in Syngenta's production of documents in this litigation.

It's a study that you've seen before, correct, Doctor?

A. I don't recall having seen this one before.

Q. It's not a document you recall seeing in preparation for today's deposition?

A. It certainly, as far as I remember, is not part of the documentation that I was -- have been

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looking at over the last two months.

Q. Okay. Did you review all documents that were cited in the Notice of Deposition in preparation for today's deposition?

A. I believed I did.

Q. But this document, you don't recall seeing?

A. I don't think it was actually part of that, unless I have forgotten that. But I -- no, I don't think I've seen this.

Q. This study, titled "The effect of Gramoxone on the activity of the nervous system of laboratory animals."

Do you see that?

A. I do.

Q. A study from 1971?

A. Yes.

Q. Now, you mentioned earlier the studies or early studies with respect to paraquat and the central nervous system. Are the studies that you did review internal Syngenta studies?

A. No, not always. Some of them are external publications.

Q. And you're aware that those studies, or early studies in animals, did show signs of possible

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central nervous system effects, right?

A. "Possible" is the right word, but these were studies done at very high doses, and so it's possible that the interpretation of effects on the central nervous system was incorrect.

Q. Now, in this particular study -- and do you understand this to be a study conducted by outside researchers?

A. I assume so. I don't recognize the authors.

Q. And it's a document that appears to have been published in a journal, right?

A. Yes.

MR. NARESH: And, Dr. Botham, if you need a minute with the document, if you don't remember having looked at it, obviously take a minute to look at it, if you'd like to.

THE WITNESS: Okay.

BY MR. DICKENS:

Q. Now, the first paragraph in this study states that:

"The toxic influence of Gramoxone on the activity of the central nervous system is investigated in this work."

Correct?

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A. That's correct.

Q. If we can turn to page ending 7815 on the bottom right-hand corner, there's a "Discussion of results."

In the second paragraph, it states:

"It follows from the above results that Gramoxone acts on the central nervous system in two phases."

Do you see that?

A. I do.

Q. And it reports:

"In small doses, it amplifies processes of stimulation and inhibition in the central nervous system. In larger doses, it acts in the opposite way, weakening these processes."

Right?

A. That's what it says, yes.

Q. And it's specifically reporting that Gramoxone, in this study, according to the authors, does have an effect on the central nervous system, right?

A. As assessed with the methodology here, which I'm certainly not familiar with.

Q. Is the methodology any different than the methodology conducted by Syngenta in their early

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studies on the central nervous system effects?
MR. NARESH: Objection to form.
THE WITNESS: It looks different to me. It talks about methods which I have never really come across and I am, therefore, not sure about the suitability of these methods, even, for assessing the effects on the central nervous system. I'm not qualified to comment on that.
But certainly ICI, as far as I remember, didn't ever use this kind of methodology.
BY MR. DICKENS:
Q. Does Syngenta believe that the methodology used by the authors or researchers in this study is inappropriate to test the central nervous system effects on animals?
A. I would say that that would need to be reviewed by someone who is more expert in these matters than me.
Q. But I have you here today. Do you know whether or not Syngenta believes it's inappropriate, the methodology or research undertaken to test the central nervous effects in these animals?
A. I really have not been able to make a comment on that. I have never seen any other study using this methodology. So it's unusual.

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Q. Now, your familiarity with methodology in animal testing, is that from your experience with Syngenta?
A. It is.
Q. You're not a toxicologist?
A. I am a toxicologist.
Q. Okay. By your role with Syngenta, though, correct?
A. Yes.
Q. Is all of your experience with respect to toxicology involving animal studies based on your time and experience with Syngenta?
A. And its legacy companies, yes.
(Stenographer clarification.)
THE WITNESS: And its legacy companies.
THE STENOGRAPHER: "Legacy," thank you.
BY MR. DICKENS:
Q. The very last section of this page goes on:
"... it can be assumed that the observed changes in the activity of the nervous system can be ascribed to the dipyridyl component of Gramoxone."
Correct?
A. That's what it says, yes.
Q. And those were the findings of these

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particular authors, right?
A. That's right.
Q. And is it your understanding that Syngenta would have received a copy of this document if it was in its records and produced in this litigation?
A. Yes.
Q. Now, Syngenta knew, by the time of this study in 1971, that paraquat could get into the brain of humans, right?
A. There was certainly evidence that paraquat can get into the brain, yes, and there were some studies, postmortem studies, I believe, where -- from humans, where paraquat was measured.
Q. Okay. Postmortem studies being autopsies of individuals who died after ingestion --
A. Yes.
Q. -- of paraquat, right?
A. Yes.
Q. And Syngenta knew from the autopsies of those individuals who died after paraquat ingestion that paraquat could bypass the blood-brain barrier?
A. I don't -- they certainly didn't know that because of the evidence from the autopsies. I think the weight of evidence generally suggested that paraquat can get into the brain and that might include

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across the blood-brain barrier, but there were many other studies which addressed that point in more detail.
Q. Many other animal studies?
A. Mostly animal studies.
Q. And when you say many other animal studies that address that point, what animal studies are you referring to specifically?
A. Just as an example, some studies that were done in the 1990s by ICI as it was, Zeneca, were looking specifically at the ability of paraquat to be transported into the brain.
Q. Were those the Widdowson and Naylor studies?
A. That's correct.
Q. And those were undertaken in the 1990s, you said?
A. Those were in the 1990s, yes.
Q. Roughly 30 years after paraquat was in the market in the United States?
A. That would be right, yes.
Q. Were there any other studies prior to that time that was investigating the issue of whether or not paraquat could get into the brain?
A. I'm sure there were, yes. I'm afraid

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I don't have an encyclopedic knowledge of every study, but, yes, Widdowson was not the first -- the very first observation of that.

Q. And the other studies prior to Widdowson and Naylor, those were studies undertaken by Syngenta?

A. Some. Not all.

Q. Can you recall any studies undertaken by Syngenta prior to Widdowson and Naylor investigating whether or not paraquat could get into the brain of animals?

A. No, I don't recall specific examples right now.

Q. And we'll note for the record, Exhibit 3, "The effect of Gramoxone on the activity of the nervous system of laboratory animals," was identified in the Notice of Deposition at 5B.

Do you have any reason to dispute that?

MR. NARESH: I'll also note for the record that Dr. Botham answered all your questions on 5B.

MR. DICKENS: I'll go ahead and hand you Exhibit 4 for the record.

(Exhibit 4 marked for identification.)

BY MR. DICKENS:

Q. I've handed you Exhibit 4 for the record, which is a document identified in the Notice of

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Deposition, topic 5.

Is this a document you reviewed previously, Dr. Botham?

A. Yes, it is.

Q. And this is an autopsy of a poisoning victim; is that right?

A. That's correct.

Q. This is one of the postmortem studies that you were referring to in your earlier testimony, correct?

A. That's correct.

Q. This is an autopsy of an individual who was a farm worker, correct?

A. Yes, that's correct.

Q. And the autopsy took place in October of 1976, right?

A. That's right.

Q. Turn to page 2. The bottom of the page, there's an opinion on the cause of death.

Do you see that?

A. I do.

Q. The cause of death is related to paraquat ingestion.

Do you see that?

A. I do.

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Q. And then the next page, there's some histology listed, correct?

A. That's correct.

Q. And in this particular individual, there were effects on the brain that were listed, right?

A. There were.

Q. And those effects included degenerative changes in the cells in the substantia nigra, the Purkinje cells of the cerebellum, right?

A. That's correct.

Q. Substantia nigra, that's a structure of the brain that plays a role in controlling movement, mood, and other brain functions?

A. That's correct.

Q. Substantia nigra is a critical brain region for the production of dopamine?

MR. NARESH: Objection to the extent it calls for expert testimony.

THE WITNESS: It is correct, yes.

BY MR. DICKENS:

Q. Parkinson's disease is a progressive disorder caused by degeneration of nerve cells in the brain called the substantia nigra?

MR. NARESH: Same objection. Also, these are questions that Dr. Botham has been asked and

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answered previously as a corporate representative in prior deposition as to which plaintiffs' counsel have access.

(Stenographer clarification.)

MR. NARESH: ...previously as a corporate representative of Syngenta and that plaintiffs' counsel have access to.

THE STENOGRAPHER: Thanks.

BY MR. DICKENS:

Q. Is that correct?

A. Yes, correct.

Q. Now, "degenerative" means a continuous process where cells are damaged over time, correct?

A. That would normally be assumed from that phrase, yes.

Q. Do you know whether the findings of this autopsy were ever published in a scientific or medical journal?

A. I don't know.

Q. Did you do anything to determine whether or not the results of this autopsy were published in any way?

A. I don't recall looking for that.

Q. Do you know whether or not this autopsy or the other postmortem studies that you referred to were

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ever submitted to the United States Environmental Protection Agency?
MR. NARESH: Objection; scope.
THE WITNESS: I have no knowledge of that.
BY MR. DICKENS:
Q. There were findings of autopsies of paraquat poisoning cases that were published, though, weren't there?
A. Yes, there were.
Q. And almost all of them showed effects of paraquat on the brain, didn't they?
A. Certainly some did, yes.
Q. And when you say "some," the majority, right?
A. I take your word for it. I've not added them up.
(Exhibit 5 marked for identification.)
MR. DICKENS: I'll go ahead and hand you Exhibit 5 for the record.
Exhibit 5 is another document identifying topic 5 in the Notice of Deposition.
BY MR. DICKENS:
Q. Is this a document you've seen before, Doctor?
A. Yes, I believe so.

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Q. And this is a document that was prepared by Syngenta, correct?
A. Yes, I understand so.
Q. It's titled "Effects of Paraquat on the Brain - an annotated bibliography in three parts."
Right?
A. Correct.
Q. Now, this particular document identifies references in published literature where brain and the CNS were examined.
Is that your understanding?
A. That's correct.
Q. And there's a section here on the first page "Bibliography of references where the brain/CNS was examined and no effects were seen."
Right?
A. Yes.
Q. And there are three particular references in that section, right?
A. There are.
Q. Then there's, on the same page, a "Bibliography of references where the brain/CNS were examined and effects were seen."
Do you see that?
A. I do.

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Q. Okay. It goes on to list 14 particular publications where effects on the brain and CNS were seen, right?
A. Well, again, I haven't added them up, but, yes, I'm sure that looks like approximately the right number.
Q. And some of these, as on page 3, the Russell publication involves multiple cases where CNS and brain effects were seen, right?
A. Yes.
Q. Then on the page ending 9336, there's a section "Bibliography of references where details of postmortem paraquat brain concentrations were given."
Do you see that?
A. Yes, I do.
Q. And it goes on to list 14 more publications where brain concentrations of paraquat were given.
A. Yes, indeed, consistent with the answer I gave earlier.
Q. And those -- when it says "paraquat brain concentrations were given," these are instances, in fact, where paraquat was found in the brain of the individuals who died after ingesting paraquat?
A. Yes, that's correct.

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Q. Now, Syngenta would have known from at least the 1990s that a farmer spraying crops with paraquat was going to end up with paraquat in their brain, right?
MR. NARESH: Objection to form, foundation, scope.
THE WITNESS: What Syngenta knew is that -- as this report actually does also say, is that the paraquat poisoning results in a lot of different pathologies, and paraquat does enter a number of tissues. But it does include the brain, certainly.
BY MR. DICKENS:
Q. You mentioned other pathologies, but I think, as you just said, that does include effects on the brain as well, right?
MR. NARESH: Same objections as before.
THE WITNESS: Yeah, and the focus of this is on the brain, but certainly in many of these cases, other pathology was seen.
BY MR. DICKENS:
Q. Turn back to that page we had you on, the 9336, the "Bibliography of references where details of postmortem brain concentrations were given."
And specifically refer to the last publication on the document, by Cravey, "Poisoning by

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paraquat."
Do you see that?
A. Yes.
Q. That's a publication from 1978, right?
A. Yes.
Q. And it's referring to three human cases of fatal post-paraquat ingestion, right?
A. Correct.
Q. And these were deaths 22, 21 days, and 8 hours post ingestion, correct?
A. Correct.
Q. Now, it gives the actual postmortem paraquat concentrations for those three individuals, correct?
A. Correct.
Q. And they include 0.09, 6.3, 1.5, ug/grams respectively.
Can you tell us what that means in your understanding?
A. These are the concentrations expressed as micrograms per gram of brain tissue. So the brain would have been weighed, it would then have been analyzed for paraquat, and then the concentration of paraquat is expressed, as I've just indicated, micrograms of the pesticide per gram of brain tissue.

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Q. So these brain tissues, then, were reviewed, analyzed for paraquat post death, right?
A. That's right.
Q. And in these cases, it shows that paraquat remained in the brain 22 days and 21 days after ingestion, correct?
A. Yes.
Q. So paraquat remained in the brain 22 to 21 days after any exposure to paraquat in those particular cases?
MR. NARESH: Object to the form.
THE WITNESS: It did.
BY MR. DICKENS:
Q. And you understand that paraquat can accumulate in the brain, right?
A. We --
MR. NARESH: Objection to form, scope.
THE WITNESS: Yes, we do understand a little more now about, if you like, the kinetics of brain, of paraquat entry into the brain, yes.
BY MR. DICKENS:
Q. You say we know now. You would have known that back in 1978, right?
A. Well, I think we knewless then. I think we nowhave done more experiments to try to understand that in a little bit more detail; so, work that we've done in the last 10, 20 years has tried to understand exactly how much and how long paraquat may get into the brain.
Q. Well, you knew from this particular study published in 1978 that paraquat could stay in the brain at least 22 days after exposure, didn't you?
A. Yes, yes.
Q. And that was known back in 1978 that paraquat could stay in the brain for weeks after exposure to paraquat?
A. Yes.
MR. NARESH: Objection; asked and answered.
THE WITNESS: Sorry.
MR. DICKENS: I'll have marked Exhibit 6 for the record.
(Exhibit 6 marked for identification.)
MR. NARESH: Do you have a topic number handy?
MR. DICKENS: Exhibit -- sorry. Topic 42.
I've handed you Exhibit 6, which is from topic 42 in the Notice of Deposition, a document titled "Xenobiotics linked to paraquat disease," dated January 18, 2000, by a Ms. E.R.A. Ralph.

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BY MR. DICKENS:
Q. Do you see that?
A. I do.
Q. And this is a internal report from Central Toxicology Laboratory, right?
A. It is.
Q. And what is Central Toxicology Laboratory?
A. It is the toxicology laboratory which was owned by ICI and then Zeneca, and which closed in 2007 to 2010.
Q. At this time in 2000, it was the main research arm of what is now Syngenta, right?
A. It was the main toxicology safety assessment lab of Syngenta.
Q. And at this point in 2000, that lab undertook a report specific to xenobiotics and whether or not it's linked to Parkinson's disease, right?
A. Correct.
Q. And what's your understanding of what xenobiotics means?
A. Xenobiotics are -- they are external agents, such as chemicals, which can interact with the body, with the biology of a human being or with an animal.
Q. And this is Elizabeth Ralph. Do you know

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Elizabeth Ralph?
A. I don't know who Elizabeth Ralph was. I would be -- I've looked at this document before and I would be -- I would speculate that she may have been a temporary student at the Central Toxicology Laboratory.
MR. DICKENS: Okay. I'll move to strike everything after "I don't know who Elizabeth Ralph [is]."
MR. NARESH: I'll object to that motion as frivolous as part of the answer to the question.
BY MR. DICKENS:
Q. This was approved for issue by an A.R. Soames.
Do you see that?
A. I do.
Q. Do you know who that is?
A. Yes. Tony Soames was a pathology technician.
Q. And a circulation list here; do you see that?
A. I do.
Q. With individuals from the pathology department?
A. They were all from pathology, yes.

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Q. Okay. Now, there's a report number listed here, right?
A. That's correct.
Q. And report numbers show up on various Syngenta documents. What do the report numbers mean?
A. Well, the notation R, the R stands for "research" and the numbering is just the numbering which started at 1; so by the time it gets to 1463, that's the 1,463rd document under the research category.
Q. Okay. So these are officially commissioned reports or research for individuals at Syngenta to undertake, right?
A. They are reports of the research activities, which were very broad, conducted by many people at Central Toxicology Laboratory.
Q. Turn to page 8 of this document.
In the second paragraph, under "2.5 Epidemiology," it states:
"Soon after, epidemiological studies showed there to be a link between an increased incidence of Parkinson's disease and an agricultural lifestyle. Some reports directly link the increase in Parkinson's disease to herbicides and pesticides, and in particular paraquat."

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Right?
A. That's right.
Q. And it specifically cites to a reference of a study by Barbeau, "Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural cases."
Right?
A. It does, that's correct.
Q. You're certainly aware of that particular study?
A. I am.
Q. From 1987?
A. I am.
Q. Based on that study, Syngenta was aware that epidemiologists had linked paraquat to Parkinson's disease, right?
A. Yes. 1985 was the first epidemiological study which suggested that that -- there could be a link.
Q. Now, prior to that time, Syngenta itself did not undertake any epidemiological studies on paraquat and neurotoxicity, did they?
MR. NARESH: Objection to form. Can you define "epidemiological"?
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BY MR. DICKENS:
Q. Did Syngenta undertake any human studies to test whether or not paraquat was linked to neurotoxicity in humans?
A. I think the answer to that is yes. They were, strictly, not epidemiological studies, but there were certainly investigations of, as we've been discussing earlier, individuals exposed to paraquat, in some cases high concentrations of paraquat, and clinical observations were made on those individuals to see -- and that would include looking at the effects on the central nervous system.
So some of that work was published.
Q. What studies are you referring to?
A. Some of the worker -- so-called "worker exposure studies" from people using paraquat in the field, in parts of the Far East.
Q. So biomonitoring studies?
A. You could describe them as "biomonitoring," yes. I call -- I think they're better called "worker monitoring."
Q. Do you have an understanding -- in this document, for example, it references a category "epidemiology." Do you have an understanding what "epidemiology" means?

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A. I do, yes.
Q. And what is your definition of "epidemiology"?
A. It's the study of -- in human populations, generally in human populations, of the potential for a relationship between an exposure to, for example, an environmental agent or an agent in the diet to the development of a disease state.
Q. And there's different type of epidemiology studies, right?
A. There are.
Q. Cohort, case control studies, as examples?
A. That's correct.
Q. What category did those biomonitoring or worker exposure studies fall into from an epidemiological standpoint?
A. I'm not an epidemiologist, but I think that they would probably be described as observational studies.
Q. Now, you mentioned those studies taken in the Far East, those are studies that took place in Malaysia?
A. That's one of the countries, yes.
Q. And some other countries as well, right?
A. Yes.

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Q. What specifically did Syngenta do in those studies to figure out whether or not there were any central nervous system effects?
MR. NARESH: Object to scope.
What's the topic?
THE WITNESS: We --
MR. NARESH: Wait. Sorry.
THE WITNESS: Sorry.
MR. NARESH: What's the topic? I do believe these --
MR. DICKENS: It's topic 17.
MR. NARESH: -- questions have been asked previously of Dr. Botham, including in depos- -- well, in depositions that you have access to.
And which part of 17? There's --
MR. DICKENS: The actual subject of 17, which is "paraquat exposure studies and assessments including findings and information."
MR. NARESH: Well, that's not -- no, no, that's -- you've identified something like 60 or 70 different subparts to 17 and so, surely, it's one of those; so just tell me which one and then we can -- because there's a number of --
MR. DICKENS: It's not a requirement to tell you exactly which one.

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MR. NARESH: Well --
MR. DICKENS: The topic is --
MR. NARESH: -- hang on.
MR. DICKENS: -- exposure studies and assessments.
MR. NARESH: I'm sorry, I don't want to speak over you. We have had extensive back-and-forth on a subpart-by-subpart basis and reached a number of agreements on what is and what is not at issue. And so it does matter because half of the ones in 17 are, by agreement of counsel, not at issue in this deposition, so please tell me which one.
MR. DICKENS: So we could say -- once again, I don't believe it's necessary. We can ask whatever we want, but I don't have the numbers here. There are studies of Dunlop estate worker exposure to paraquat in Malaysia --
MR. NARESH: Okay. If you have specific questions, then you can ask those questions, but some of these -- you know, for example, we have an agreement that 17D, which is the Swan study from 1969, per a July 30 email from you-all, is not at issue in this deposition, right.
And so that's what I'm talking about, that a number of these you have said are not at issue in

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this deposition, and so if you have specific questions about studies that you've -- that, by agreement, are at issue here, I'm more than happy to let it go forward.
But, for example, a number of the ones on Malaysia you have said are not going to be questioned here, and I'm happy to show you the email if you'd like. It's from July 30 from Mr. Travers.
MR. DICKENS: Well, I don't think anything in our agreements prevents follow-up questions to answers given by the witness in this particular case, and so we're going to continue to ask follow-up questions as deemed appropriate. If he mentions his reliance on particular studies for his answers to any of the questions that we ask, nothing that we've talked about would preclude us from following up on those.
I'll continue to do so, unless I'm prevented by the Special Master or the Court. If you want to jump off and contact Randi Ellis, I'm happy to do so.
MR. NARESH: Look, let's see where this goes, but this is exactly the concern that I raised with you multiple times, that you're going to retread ground that has been asked and answered over the

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course of seven days of depositions with Dr. Botham.
(Stenographer interjection.)
MR. NARESH: This is exactly the concern that I've raised multiple times, that the subjects that you're asking about are exactly what was asked and answered of Dr. Botham in his seven prior days of deposition. This line of questioning has been asked of Dr. Botham repeatedly by multiple previous lawyers, as a corporate representative.
Let's see where it goes, but this is precisely what the point of incorporating prior depositions was intended to avoid, was answering these questions for a second or a third time just because you didn't like the prior answers, okay.
So let's see where this goes, but we will probably have to get Ms. Ellis on the phone once it is daylight in the Central Time Zone, and I need to make my record on this, so let's go for a while and then we'll call her at a break.
MS. ELLIS: You guys, I'm here.
MR. DICKENS: Hey, Randi.
MR. NARESH: I'm sorry.
MS. ELLIS: I'm listening.
MR. DICKENS: It's bright and early.
MS. ELLIS: I'm here. Yes, it is. Keep

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going.
MR. DICKENS: Okay.
BY MR. DICKENS:
Q. Doctor, what specifically did Syngenta do in the worker exposure studies to figure out whether or not there were any central nervous system effects?
MR. NARESH: Which studies are you talking about?
MR. DICKENS: I am talking about...
BY MR. DICKENS:
Q. You mentioned the biomonitoring exposure studies in the Far East, I believe you said, right?
A. Yes, yes.
Q. Okay. And so were you -- when you mentioned those studies in the Far East, were there any particular studies that you were referring to in your previous answer?
A. Yes. And, if I might, this is where, for example, I'm referring to my document folder that we mentioned at the beginning. So studies such as those authored by Howard and others. They indicate that there were clinical observations of those individuals which looked at a number of -- the health generally of those individuals, and that did include an assessment of any potential effects on the central nervous

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system.
Q. Was there any long-term follow-up of those individuals?
A. There was some follow-up. So it wasn't just a one-off in some cases. There were -- there was follow-up. It depends on your definition of "long-term."
Q. Well, tell me how long the follow-up, to your understanding, was in the studies that you're specifically relying on?
A. I don't recall exactly what that length of follow-up was. I seem to remember that it was certainly more than a year in one or two cases, but certainly not a decade; so it was -- it depends what your definition of "long-term" is.
Q. So not ten years, right?
A. No.
Q. Not five years, correct?
A. I don't think so, no.
Q. Dr. Botham, based on your understanding, you'd agree it would take far longer than a year for Parkinson's disease to develop, right?
MR. NARESH: Objection to form, vague.
THE WITNESS: Yes.
///

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BY MR. DICKENS:
Q. Last sentence of that paragraph:
"These conflicting reports suggest that a gene/environment interaction may well be very important in the etiology of Parkinson's disease. Purely genetic factors seem to be significant only in juvenile onset PD..."
Do you see that?
A. I do.
Q. And do you agree with that statement?
A. It's still generally true. Certainly, genetic factors are more prevalent in early onset Parkinson's disease. I wouldn't, today, describe it as "juvenile."
The gene/environment interaction is still very much an open book. It's not clear yet what -- how genes and environment may interact.
Q. And on the next page, under "Genetic factors," it states:
"Current understanding of the etiology of Parkinson's disease indicates purely genetic Parkinson's is rare, and causes early onset of the disease (before the age of 50)."
And that's what you were just referencing, right?

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A. That's correct.
Q. Under "Non-genetic factors":
"Oxidative damage caused by free radicals is currently held to be the main pathogenic factor in idiopathic Parkinson's disease."
For non-genetic factors. Right?
A. That's what it says. I wouldn't necessarily agree with that statement.
Q. Okay. What don't you agree with?
A. I don't think there's any evidence to say that in idiopathic Parkinson's disease that that is caused by the mechanism of oxidative damage. Idiopathic Parkinson's disease, by definition, means the mechanism, the origin of that Parkinson's disease is unknown.
Q. Will you agree that oxidative damage caused by free radicals is held to be the main pathogenic factor in environmental-caused Parkinson's disease?
MR. NARESH: Object to the form.
THE WITNESS: Even that, I would disagree with. It is one possible mode of action, but I would not agree with the view that it is the only one.
///

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BY MR. DICKENS:
Q. Now, this report in 2000 I think you mentioned was, to your understanding, by a research student with the pathology department?
A. I'm afraid that is speculation because I don't -- I'm not able to find any direct evidence for that.
Q. Was there ever any officially commissioned reports from Syngenta that was conducted by a neurologist on xenobiotics and the link to Parkinson's disease, to your understanding?
A. Not by a neurologist, no. We certainly employed external experts on epidemiology, for example, to look at the effect of -- the influence of xenobiotics and other factors that could be involved in Parkinson's disease.
Q. Turn to page 17. Section "Mechanisms of paraquat-induced cytotoxicity."
Do you see that?
A. I do.
Q. Do you know what "cytotoxicity" means?
A. It's the death of cells.
Q. It starts off:
"Once within a cell, paraquat cyclically reduced and reoxidized."

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That's something you agree with, right?
A. I do.
Q. And you've testified to that in prior depositions, correct?
A. Correct.
Q. It states later:
"... paraquat produces reactive oxygen species which [is] the classical theory of the etiology of Parkinson's disease..."
You agree with that statement, don't you?
A. Sorry, could you just repeat that?
Q. Yes.
"... paraquat produces reactive oxygen species which [is] the classical theory of the etiology of Parkinson's disease..."
MR. NARESH: I'm sorry, where? I'm not seeing it.
BY MR. DICKENS:
Q. It is the bottom section "4.2.3 Mechanisms of paraquat-induced cytotoxicity." Halfway in that paragraph.
MR. NARESH: Oh, do you see it?
THE WITNESS: Yes, I see it. But I don't agree -- I think as I explained, I don't agree with that. I think it is one possible mechanism but it

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certainly is not the classical theory of the etiology of Parkinson's disease. I think that is a misrepresentation.
BY MR. DICKENS:
Q. Now, you do agree paraquat produces reactive oxygen species, though, right?
A. Yes, I do.
Q. Okay. So it's the second part of that paragraph you don't agree with?
A. I agree, yes.
Q. Okay.
Turn to page 18. In the paragraph right before "The blood/brain barrier and paraquat," it begins:
"Paraquat can localize to neurones where neuromelanin is produced..."
Do you see that?
A. I do.
Q. And you agree with that?
A. Yes, it can.
Q. Turn to page 22 now.
At the top of that page, and this is referring to the Brooks study, which is discussed in the page earlier, but it states:
"The data seemed quite compelling;

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however, a few questions remain unanswered."
Right?
A. Yes.
MR. NARESH: Object on completeness.
BY MR. DICKENS:
Q. And then later on in "The future for paraquat research," the last sentence:
"Further studies must be done in different species to investigate the permeability of the blood/brain barrier to paraquat, and the role of genetics in determining susceptibility."
Right?
MR. NARESH: Object on completeness again --
THE WITNESS: Yes --
THE STENOGRAPHER: I'm sorry, I didn't hear that.
MR. NARESH: I'm objecting on completeness. It's missing the surrounding context.
THE WITNESS: Yes, some of these statements are actually what led me to speculate that this was written by a student because there are some very broad statements which I think -- you would expect a student who has perhaps not been an expert in this area for some time to write.

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So I think that some of these statements are too general and are not necessarily completely accurate.
MR. DICKENS: I move to strike.
BY MR. DICKENS:
Q. Doctor, my question specifically was all it does is state:
"Further studies must be done in different species to investigate the permeability of the blood/brain barrier to paraquat, and the role of genetics in determining susceptibility."
That's what it states, right?
A. Yes. That's an opinion, yes.
Q. Now, this report, this was commissioned by Syngenta specifically, right?
A. I really don't know how it was commissioned.
Q. It was given a report number, right?
A. It was certainly written up and issued as a report, yes.
Q. A report from Syngenta?
A. It was a report from the author as a -- I'm assuming, as the product of this lady's time in Central Toxicology Laboratory and the work that she clearly seemed to do mainly with reviewing the literature.

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Q. And specifically approved by a Syngenta employee, right?
A. Yes.
Q. Did you see anything in your review of documents to suggest that anyone at the time in 2000 within Syngenta disagreed with any of the statements in this document?
A. I don't have direct evidence that they were criticizing any of the content of this report. I think, like I've been doing, in 2000 I'm sure that if other people had read this, they may have had some questions about whether everything was actually fully accurate.
Q. Is it your understanding that individuals within Syngenta did not read this particular report?
A. I suspect it was read by a small number of people and maybe only the people who are on the circulation list.
Q. What did Syngenta do after 2000? What different studies in different species did Syngenta conduct to investigate the permeability of the blood-brain barrier?
A. Well, by then we had already done studies in rodents -- rats and mice -- and we didn't directly

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address the question of the permeability of the blood-brain barrier, but, subsequently, there were certainly studies done, for example, in the nonhuman primate, and now we're talking much later, where we were looking at the distribution of paraquat in the body of the nonhuman primate, including the brain.
Q. When were those nonhuman primate studies undertaken?
A. They were done in the time period of around 2016 to 2019, so published in 2019.
Q. So 19 years after this particular report?
A. That's correct.
Q. That was the Stevens study?
A. That's correct.
Q. You didn't measure paraquat in the brain in the Stevens study, right?
A. We did model the amount of paraquat that we expected to be in the brain, yes.
Q. Now, the earlier studies that were taken prior to this time, Widdowson and Naylor, those were in rats?
A. Yes.
Q. Rats lack neuromelanin?
A. I believe that's true, yes.
Q. Nonhuman primates possess neuromelanin?

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A. Yes, that's right.
Q. Humans do as well?
A. Yes.
Q. Now, with respect to Stevens, you mentioned there was modeling done. Modeling is not the same as directly measuring the amount of paraquat in the brain, right?
A. It's not, but today, in today's science, mathematical modeling is often as accurate as actually directly measuring substances, and we were using very modern modeling techniques.
Q. What are you relying on for your statement that mathematical modeling is often as accurate as actually measuring the amount of paraquat in the brain?
A. Well, we collaborated with people in the United States who were experts in this field, so it wasn't just Syngenta scientists that would be saying that. So we were working with a state-of-the-art research organization in mathematical modeling.
Q. So those individuals working in mathematical modeling told you that mathematical modeling is as accurate as actually measuring how much is in the brain?
A. It can be. You have to calibrate your

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mathematical model against actual data, so we -- and that is part of coming to the conclusion about the relative accuracy, and that's exactly what we did do.
Q. You could have directly measured the amount of paraquat in the brain in the Stevens study, right?
A. Yeah. In theory, yes. In practice, that would have been a very difficult experiment to do. Nonhuman primates are, of course, a highly protected species in laboratory animal experiments, and in order to do the ideal experiment, to answer your question, we would have had to have used significantly more nonhuman primates than we did and it would have not been possible -- we know it would not have been possible to get ethical approval to do those studies.
MR. DICKENS: I'll move to strike.
BY MR. DICKENS:
Q. Doctor, I didn't ask you whether or not it would be difficult to do so. I just simply asked, you could have directly measured the amount of paraquat in the brain in the Stevens study, right?
MR. NARESH: I'll object to that.
Go ahead.
THE WITNESS: I stick by my answer. We could have looked for paraquat in the brain, but it

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would have been meaningless without actually doing a proper, what I call a kinetic study and that would have required more animals.
BY MR. DICKENS:
Q. Now, do you understand that all the monkeys in the Stevens study were killed?
A. They were, yes.
MR. NARESH: Are you moving to a new document?
MR. DICKENS: I am, yeah. We can put that away.
MR. NARESH: We've been going for about an hour and 15.
MR. DICKENS: Yeah.
MR. NARESH: Take five, ten?
MR. DICKENS: Perfect. Whatever you need.
THE VIDEOGRAPHER: We are going off the record at 10:39.
(Break taken.)
THE VIDEOGRAPHER: We are back on the record at 10:52.
MR. DICKENS: Welcome back, Doctor. I'm going to hand you Exhibit 7 for the record.
(Exhibit 7 marked for identification.)
MR. NARESH: Which topic?

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MR. DICKENS: Topic No. 6.
MR. NARESH: Oh, it's 6GG?
MR. DICKENS: Yeah, I should have had those numbered -- or lettered.
BY MR. DICKENS:
Q. Doctor, I've handed you --
MR. NARESH: Wait, not GG. I'm still looking for it. Let me withdraw that for the record.
BY MR. DICKENS:
Q. -- Exhibit 7, which is a document identified in topic 6 of the Notice of Deposition, dated February 1, 1976.
Do you see that?
A. I do.
MR. NARESH: I'm sorry if I'm being dense, but where is this in topic 6?
MR. DICKENS: Q.
MR. NARESH: I have Q as a Syngenta Bates-numbered document, not a CUSA document.
MR. DICKENS: I don't know. It's the last one.
MR. NARESH: Let's go off the record for a second.
MR. DICKENS: We can go off the record.
THE VIDEOGRAPHER: We are going off the

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record at 10:54.
(Off the record.)
THE VIDEOGRAPHER: We are back on the record at 10:56.
BY MR. DICKENS:
Q. Okay. Doctor, I handed you a document dated February 1, two thousand -- sorry, 1976, relating to a paraquat toxicology meeting.
Do you see that?
A. I do.
Q. And this is a document you've reviewed before?
A. I've certainly looked at this in the last couple of months, yes.
Q. Okay. And this is actually a letter which was signed off by a Dr. Cavalli.
Do you see that?
A. That's correct.
Q. And do you understand Dr. Cavalli to be with Chevron?
A. Yes, he was.
Q. And Syngenta and Chevron had a contract or agreement with respect to the sale of paraquat in the United States?
A. Yes, that's correct.

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Q. And this states:
"The following is a summary of meetings between [himself]," Dr Cavalli, "and Ken Fletcher of CTL..."
Right?
A. Yes, that's right.
Q. And do you know who Ken Fletcher at CTL is?
A. He left before I joined CTL, but, yes, he was -- I can't remember whether he was medically qualified but he was certainly in the toxicology organization.
Q. If we can look at number 3 within this letter, it states:
"We discussed at some length the gaps in our knowledge of the chronic effects of paraquat exposure."
Do you see that?
A. Yes.
Q. "The animal studies available are old and do not meet the current standards. [...] Some are poorly done."
That's what's stated here, right?
A. That's what it says, yes.
Q. As a summary of a conversation held with

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Ken Fletcher of CTL, right?
A. Correct.
Q. "In fact, the cause of death from chronic exposure to paraquat could not be determined from these studies."
Right?
A. That's what it says.
Q. And that's an example of the studies being poorly done with respect to Dr. Cavalli, as he reports on this date, right?
MR. NARESH: Objection to form.
THE WITNESS: Yes. I don't know specifically which studies Dr. Cavalli is referring to, but that's what the record shows.
BY MR. DICKENS:
Q. Now, the documents -- or, sorry, the studies were old and poorly done, in part -- strike that.
The studies that were old and poorly done are referring to studies that were initially submitted by Syngenta and Chevron to the EPA in order to obtain registration, right?
MR. NARESH: Objection; foundation.
THE WITNESS: That's my assumption.
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BY MR. DICKENS:
Q. Before we move on from this document, if we can turn to number 10. It states:
"Dr. Fletcher described an unpublished case of paraquat poisoning by dermal absorption. An individual in Yugoslavia sprayed waist-high weeds and soaked his clothing."
Do you see that?
A. I do.
Q. And this is being reported by Dr. Fletcher, correct?
A. That's right.
Q. At the end of that paragraph:
"This individual died an unknown time later from what sounds like a typical paraquat death."
MR. NARESH: Object on the rule of completeness.
BY MR. DICKENS:
Q. "The case has not been published and no more details are available at present."
Do you see that?
MR. NARESH: Sorry, I didn't mean to cut you off. I'll object on completeness; it leaves out the middle sentences.
(Stenographer clarification.)

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MR. NARESH: I'm sorry, okay. I'll object on completeness; it leaves out the middle sentences.
THE STENOGRAPHER: Thanks.
THE WITNESS: So do you have a question?
BY MR. DICKENS:
Q. Yeah. That's what it says, correct?
A. Yes, it does.
Q. Now, at this time in 1976, Syngenta was aware of paraquat poisoning by dermal absorption, right?
A. Yes, it was.
Q. And death could occur by dermal absorption of paraquat, and that was known by Syngenta by 1976?
A. Yes. It would require a very extensive exposure by the dermal route, but it was certainly known.
Q. Okay. Now, this individual soaked his clothing while spraying. The clothes were not changed for two days, right?
A. That's right. That's what it says.
Q. "At this time, he was seen at the hospital for a skin rash. The following day he sprayed again, [...] resulting in severe chemical burns."
Correct?
A. Correct.

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Q. And is that an instance that you would say or consider as extreme exposure enough to cause death by dermal absorption?
A. Exactly. I think this is an example of what I've just been saying. You would not normally expect somebody to have such exposure as is described here.
Q. It appears he sprayed on two days, right?
A. Yes.
Q. Now, the case was not published and no more details were available.
Do you know whether or not this instance or death was reported to the United States Environmental Protection Agency?
A. I don't know that.
Q. Now, going back to the first page and the animal studies that are referenced as "old," "do not meet current standards" and "are poorly done," for those early animal studies, Syngenta contracted with a company Industrial Bio-Test Laboratories to conduct paraquat toxicity studies for the purposes of EPA registration, correct?
A. I understand that to be true, yes.
Q. And the EPA found that IBT tests to support the registration of pesticides were deficient and invalid.
Correct?
MR. NARESH: What's the topic?
MR. DICKENS: Topic 8. Sorry, not topic 8. 86.
MR. TRAVERS: And 85.
MR. DICKENS: And 85.
BY MR. DICKENS:
Q. I'll ask again. Doctor, the EPA found that IBT tests to support the registration of pesticides were deficient and invalid, right?
A. I believe that was the case, yes.
Q. Those tests relied on fraudulent data, right?
A. I've seen that phrase "fraudulent data." I've never actually understood or looked at, in detail, what the basis for that accusation of fraud is.
Q. Did you look at that issue in detail for preparation for today's deposition?
A. No, I did not.
Q. Did you look at any document specific to IBT in preparation for today's deposition?
A. No. Again, only through sort of tangential mention of the IBT studies. We did not go into that in any detail.
Q. Were you aware that IBT's president and founder, Joseph Calandra, along with other IBT employees, were found criminally responsible for their fraud in the role in falsifying scientific data?
A. I don't remember the name, but I do remember the incident being described to me in the past.
Q. The past; while you were working for Syngenta?
A. Yes. I'm not talking about in the last two months. I remember it being said in the more distant past.
MR. DICKENS: I'm going to hand you what we'll mark as Exhibit 8 for the record.
(Exhibit 8 marked for identification.)
BY MR. DICKENS:
Q. Doctor, I've handed you Exhibit 8, which is a document from the United States Environmental Protection Agency, "Summary of the IBT review program, from the office of pesticide programs," dated July 1983.
Right?
A. Correct.
Q. And this was -- report was approximately

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seven years after the last document we looked at where Syngenta and Chevron were discussing the fact that Syngenta studies were old and poorly done, right?

A. Yes.

Q. If you can turn to the first page. "The IBT Review Process" states:

"This report summarizes the findings of the joint program conducted by Environmental Protection Agency and the Health Protection Branch of Health and Welfare Canada to re-examine the health effects studies on pesticides tested by Industrial Bio-Test Laboratories (IBT)."

Right?

A. Yes.

Q. And that review:

"... revealed serious deficiencies in IBT tests [...] to support the registration of numerous pesticides."

Right?

A. Yes.

Q. Then it states:

"Exhibit A shows how many IBT and non-IBT tests are available to EPA in each testing category for the pesticide chemicals having some IBT-conducted studies in their database."

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Right?

A. Right.

Q. Now, if we can turn to Exhibit A, which begins on page 10. Page 10, it just states "Exhibit A - The Data Base for Industrial Bio-Test Chemicals" and then the very next page kind of gives a summary of Exhibit A. It states:

"The IBT studies are designated by the letter O. Studies in the EPA data base done by labs other than IBT are designated by the letter X."

Do you see that?

A. I do.

Q. Now, if we can find paraquat, it's alphabetical --

A. Yes.

Q. -- but there are no page numbers.

A. Yes.

Q. Let me know when you're there.

A. I'm there.

Q. Okay.

So there's paraquat listed and then there's various categories of studies, correct?

A. Yes, that's right.

Q. And if you can look in the column for neurotoxicity, there's one study presented, right?

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A. Yes, that's right.

Q. And that's an O, correct?

A. That's right.

Q. So that means that the neurotoxicity study submitted by Syngenta was conducted by IBT, right?

A. That's what that suggests, yes.

Q. And there were no other studies in EPA's database on neurotoxicity as of the date of this document in 1983, right?

A. I don't know that. This document doesn't show me that, so I can't comment.

Q. Well, we just looked, Doctor, at the part for section A, that describes what letter O and letter X mean, right?

A. Yes.

Q. It says:

"The IBT studies are designated by the letter O."

And:

"Studies in the EPA data base done by [other] labs [...] are designated by the letter X."

A. Okay, sorry. I misunderstood the question. Yes, that's true, I agree.

Q. So, for example, the other chronic effects for paraquat, there's an IBT study but some --

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A. Yes.

Q. -- other studies, right?

A. Now I understand. Yes, I agree.

Q. For neurotoxicity, however, there are no other studies other than the IBT, right?

A. That's what that suggests, yes.

Q. So the EPA's approval of paraquat in the 1960s was done with respect to one neurotoxicity study that was submitted in support of registration, right?

MR. NARESH: Object to the foundation and the form.

THE WITNESS: That's what that suggests, I agree.

BY MR. DICKENS:

Q. And that one study was conducted by IBT?

A. Right.

Q. The laboratory whose studies were found to be invalidated and relied on by fraudulent data by the EPA, right?

MR. NARESH: Objection; form, foundation.

THE WITNESS: That's what I understand, yes.

BY MR. DICKENS:

Q. So as of 1983, there were no valid neurotoxicity studies in the EPA's database supporting

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paraquat?
MR. NARESH: Objection to form and foundation.
THE WITNESS: That's what this would indicate.
BY MR. DICKENS:
Q. Now, Syngenta knew, even before the EPA's report, that there were issues in IBT's tests being conducted on behalf of Syngenta, right?
A. I don't -- I'm not familiar with the detail of that history. I'm sorry.
MR. DICKENS: I'll go ahead and hand you what we'll mark as Exhibit 9.
(Exhibit 9 marked for identification.)
BY MR. DICKENS:
Q. Exhibit 9 is a letter from an A.A.B. Swan to a J.C. Calandra, director of Industrial Bio-Test Labs, dated February 12, 1964.
Do you see that?
A. Yes.
Q. And it's regarding urinary estimation in dogs, right?
A. Yes.
Q. Now, was paraquat on the market in the United States in February 1964?

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A. I think -- isn't that shortly before?
Q. To the best of your knowledge.
A. Yeah, I think it was shortly before.
Q. And do you know who A.A.B. Swan is?
A. Yes. He was the director of the Central Toxicology Laboratory at that time.
Q. So the director of the Central Toxicology Laboratory is writing to the director of IBT, right?
A. Yes.
Q. And he's writing with respect to a dog study where they're testing urinary excretion of paraquat?
A. Yes.
Q. In the very last couple sentences in the third paragraph, the sentence beginning, "It is difficult to understand..."
Do you see that?
A. Yes.
Q. And so the director of Central Toxicology Laboratory writes:
"It is difficult to understand why dogs on such widely varying paraquat intakes (up to tenfold) should show no difference in the levels of urinary excretion, and I think it would be wise to defer killing the animals until we are satisfied that all

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doubts on the method of paraquat estimation have been resolved."
That's what is being reported to the director of IBT, right?
A. Yes.
Q. And you'd agree that it would be unusual for the paraquat intakes -- or, sorry, for the levels of urinary excretion to be the same for paraquat intakes that are tenfold different, right?
A. I would -- yes, I would agree.
Q. Do you know whether or not IBT did defer on killing the animals until they resolved or satisfied all doubts on the methods of paraquat estimation?
A. I don't immediately recall having seen any evidence for that, but perhaps you've got some documents which would substantiate that.
Q. You can put that to the side.
MR. DICKENS: I'll go ahead and hand you Exhibit 10 for the record.
(Exhibit 10 marked for identification.)
BY MR. DICKENS:
Q. I've handed you the exhibit dated May 11, 1966, correspondence from, once again, the director of CTL, A.A.B. Swan, to an R.A. Hamilton, and W.

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Johnston, or Johnstone, of Plant Protection Limited.
Do you see that?
A. Yes, I do.
Q. And what was Plant Protection Limited?
A. That was the division of ICI that was involved in crop protection chemicals.
Q. So both CTL and ICI, those are now what is known as Syngenta, right?
A. Yes.
Q. And so there's internal correspondence here specific to Chevron and the paraquat petition, right?
A. Yes.
Q. And in your understanding, this would be the petition to the United States to register paraquat?
A. That's correct.
Q. I direct your attention the third paragraph, beginning "In the petition..."
In this paragraph, the director of CTL notes that:
"In the petition for temporary tolerances presented in January 1965..."
Do you know what temporary tolerances he's referring to?

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A. I think it's a kind of interim step in the registration.
Q. Registration in the United States?
A. Yes, yes.
Q. In order to sell paraquat?
A. Yes.
Q. And it mentions work being done on inhalation toxicity by IBT.
Right?
A. That's right.
Q. And those were inhalation studies that were submitted to the United States for the registration in the United States to sell paraquat?
A. Right.
Q. He goes on at a subsequent "examination at IHRL..."
And what is that referring to?
A. That was the Industrial Hygiene Research Laboratory, which is what Central Toxicology used to be called.
Q. So that is kind of the predecessor of CTL?
A. That's correct.
Q. Is it in the same location in the UK?
A. It actually was in the south of England and then it moved to the north of England.

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Q. And so there was an examination of the IBT studies at IHRL -- sorry.
Examination of a sample of equipment that was used by IBT, and that led the scientists at Syngenta to believe that the work actually "underestimated the inhalation toxicity" of paraquat.
Right?
A. Yes, that's what it says.
Q. And that was actually confirmed by results of experimental work at IHRL in 1965, right?
A. Yes, I believe so. Yes.
Q. So Syngenta actually re-examined work by IBT and found that the studies they ran underestimated the amount of inhalation toxicity from paraquat?
A. That would appear to be the case, yes.
Q. And if we can turn the page --
MR. NARESH: I'll object on completeness; you left out the last sentence.
BY MR. DICKENS:
Q. Okay. It says:
"[IBT] were informed and agreed to do further work, in the light of which they issued revised reports..."
Right?
A. Yes.

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Q. So it was IBT, then, that did the additional work, correct?
A. This is what this suggests, yes.
Q. Okay. And they apparently issued revised reports in 1966, correct?
A. Right.
Q. Now turn the page. Now, at the bottom of that first paragraph, "In the event..."
Do you see that?
A. Yes.
Q. "In the event the old, unrevised Bio-Test work [was] submitted in the petition, together with the first half of the paper I presented at the Development Conference, as evidence for the proposed threshold limit value for respirable aerosol concentration. Thus, the greatest apparent discrepancy in results has been presented, and this could so easily have been avoided."
Right?
A. Yes.
Q. So what this is saying, from the director of Central -- or IHRL at the time, Dr. Swan, is the actual old IBT work that underestimated inhalation toxicity was actually submitted to the EPA, right?
A. Yes.

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Q. Instead of the new revised reports that were done at the request of Syngenta?
A. That would appear to be the case, yes.
Q. You can put that aside.
MR. DICKENS: I'll hand you Exhibit 11.
(Exhibit 11 marked for identification.)
BY MR. DICKENS:
Q. I'm actually going to direct your attention to what is the fifth page, ending 6541.
A. Yes.
Q. These are minutes from a Chevron/ICI meeting on October -- sorry, on August 31, 1977, right?
A. That's right.
Q. It includes various individuals from CTL and ICI, and then Chevron, right?
A. Yes.
Q. And it begins with a discussion of Industrial Bio-Test Laboratory, two-year rat and dog studies, correct?
A. Correct.
Q. "Dr. Cavalli..."
He's with Chevron, right?
A. Yes, he was at that time.
Q. And he told the meeting:

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"... IBT had severe problems at all levels within the organization apart from right at the top, during the '60s until mid '70s."
Right?
A. Yes.
Q. That was the very time that IBT was conducting testing and research for Syngenta in order to submit paraquat for registration in the United States?
A. Yes.
Q. And as we looked at before, this was the time that the only neurotoxicity study submitted with paraquat for registration in the United States would have been conducted by IBT?
(Stenographer clarification.)
MR. DICKENS: Yes.
BY MR. DICKENS:
Q. And as we looked at before, this was the time that the only neurotoxicity study that was submitted for registration in the United States for paraquat was conducted by IBT?
A. Yes.
Q. It goes on:
"This [has] led to a loss in faith in IBT by the FDA/EPA."

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Right?
A. Yes.
Q. Now, at the time paraquat was submitted for registration in the United States, the EPA did not exist, right?
A. I don't have that detailed history, so I can't comment on that.
Q. Anyway, FDA/EPA was asking, "a complete review of all IBT studies which supported petitions."
Right?
A. Yes.
Q. And Chevron actually conducted a review of those IBT studies?
A. Correct.
Q. And they reported at this meeting some of their findings, correct?
A. That's written down here, yes.
Q. And some of those findings from the two-year rat and dog studies were that the IBT study had no concept of recording of data?
A. Yes.
Q. It reported, based on Chevron's review, that no dates were recorded in the IBT studies, only month numbers.
Right?

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A. Yes.
Q. There was a poor identification of animals in the IBT studies, right?
A. Yes.
Q. One animal actually died four times in their study, correct?
A. Yes.
Q. And:
"Two-thirds of the experiment were individually housed and one-third had 5 per cage - no explanation and all data handled in the same manner..."
Right?
A. Yes.
Q. These are serious concerns that would invalidate the toxicology studies conducted by IBT, right?
A. They would certainly seriously question the quality of the study, yes.
Q. Well, one animal dying four times, I mean, that goes beyond questioning the study; it invalidates it, doesn't it?
A. I think certainly in terms of good laboratory practice and so on, yes, it would.
Q. I mean, just common sense says that an

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animal can't die four times?
A. Of course.
Q. And these two-year rat and dog studies, these were studies that would have been submitted to the EPA for registration of paraquat?
MR. NARESH: Objection; asked and answered.
THE WITNESS: Yes, I believe so.
BY MR. DICKENS:
Q. If we can turn to the next page. The second paragraph:
"As far as Chevron could ascertain, the raw data for both the rat and dog paraquat studies had been destroyed."
Right?
A. Yes.
Q. No longer existed?
A. Correct.
Q. All right. We can put that aside.
MR. DICKENS: I'll hand you Exhibit 12.
(Exhibit 12 marked for identification.)
MR. DICKENS: I've handed you Exhibit 12, which, for the record, is topic 109 of the Notice of Deposition.
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BY MR. DICKENS:
Q. These are notes on another ICI/Chevron meeting; this time in July 16, 1979, correct?
A. That's correct.
Q. Is this a document you reviewed in preparation for today's deposition?
A. It is.
Q. And this includes, once again, individuals from ICI as well as Chevron, right?
A. Yes, it does.
Q. Now, starting off on page 1, there's a discussion on "Toxicology - Dermal Trigger."
Do you see that?
A. Yes, I do.
Q. And the second sentence begins, "Dr. Rose," and that's a Dr. Michael Rose?
A. That's right, yes.
Q. He was with Syngenta?
A. He was at the Central Toxicology Laboratory, yes.
Q. And what was his role with the Central Toxicology Laboratory?
A. He was a biochemical toxicologist. He was a section head of that -- of biochemical toxicology in CLT.

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Q. It says:
"Dr. Rose drew attention to the ten known incidents of death arising from dermal exposure to paraquat."
Do you see that?
A. Yes.
Q. And we looked at the one case from Yugoslavia earlier that we discussed, right?
A. Yes.
Q. Dr. Rose is reporting here there was at least ten known incidents at this point in 1979 of deaths from dermal exposure, correct?
A. Yes, that's right.
Q. Several of those were accidents with the concentrate followed by inadequate remedial measures, right?
A. Yes.
Q. Then he goes on that:
"... three published incidents relate to spraying paraquat low volume at strengths, or with equipment, not recommended."
Right?
A. Yes.
Q. Do you know what strengths or equipment were being used in those particular cases?

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A. No, I don't.
Q. Do you know whether or not those strengths or equipment were contraindicated by Syngenta in any way?
MR. NARESH: I'll object to that. You just used a different word then, "contraindicated."
THE WITNESS: This suggests --
MR. NARESH: Let him rephrase.
MR. DICKENS: Let me ask it again.
BY MR. DICKENS:
Q. Were the strengths or equipment -- strike that.
Did Syngenta -- do you know whether or not these deaths were at strengths, or equipment, that Syngenta had warned should not be used in the spraying of paraquat?
A. Well, I think that is -- this suggests that the equipment and strengths that were used were not those recommended by Syngenta.
Q. There's a difference between recommended and telling someone not to use something, right?
A. Yes, but it is assumed that in saying "You should use paraquat in this way, this strength, this equipment," that is effectively an instruction for safe use.

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Q. That you should use something is directing them, while a recommendation is different; you'd agree with that?
A. The purpose of a product label is to give instruction as to how to best use a product, yes.
Q. And so that's a fair point. Do you know whether or not the strengths or equipment being used was specified on the label that it should not be used?
A. I can't comment on that. It will be unusual to say, "Don't do it this way." Normally, it's a positive statement saying to do it this way.
Q. All right. One worker, it mentions:
"... died following a leaking connection from a backpack container to a herbicide applicator and subsequent poor hygiene."
Do you see that?
A. Yes.
Q. A leaking backpack container would not be against recommendations on the label, correct?
A. It would -- the label would probably say that you should avoid that and what to do in the event that it happens.
Q. Syngenta certainly was aware by this point in 1979 of individuals wearing backpack containers having leaking incidents, right?

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A. Yes.
Q. Do you know what poor hygiene is being referred to here in this document?
A. I don't know specifically. You would -- it would suggest that, for example, the individual did not take action to decontaminate, to wash his clothing or himself.
Q. If you go down to the bottom of that page, under (ii) it says:
"Chevron have had up to a dozen cases in their packaging plants of accidents where workers have had quite severe dermal exposure and shown significant paraquat levels in blood and urine."
Do you see that?
A. Yes.
Q. "Four or five [of them] were hospitalized."
Right?
A. Yes.
Q. Were the Chevron workers, to your knowledge, exposed to paraquat in ways that were not recommended?
A. I can't comment on the working practices in Chevron packing plants, I'm afraid. I've no evidence to understand that.

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Q. Nonetheless, those individuals did have paraquat in their blood and their urine, right?
A. Yes. I mean, the assumption must be that there was some bad practice going on.
Q. And the assumption being the fact that there was paraquat in their blood and urine?
A. The fact that they were exposed at all to paraquat would be something you wouldn't expect in a packaging plant.
Q. Syngenta, by this point in 1979, had individuals working within their packaging plants who experienced adverse health effects from exposure to paraquat, such as severe nosebleeds, right?
A. Yes.
Q. Including dermal incidents as well, right?
A. I can't give you chapter and verse on that as regards packaging, but there were certainly incidents of dermal toxicity, yes.
Q. Including incidents of keratosis or skin issues?
A. That's different. So the keratosis was not in packaging plants; that was in manufacture.
Q. That's fair. So do you know whether or not there were any issues of dermal incidents in the actual packaging plants?

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A. I understand that there -- as you referred earlier, that there were some incidents, for example occasional nosebleeds. That's something that I've been told about, yes.
Q. But there were other incidents you are aware of of skin issues, such as keratosis, in the manufacturing plants of paraquat?
A. Where there was significant exposure in the early days of paraquat manufacture.
Q. Turn the page. It begins on top:
"[Syngenta] agreed to send details of these cases to Dr. Rose."
Do you see that?
A. Yes.
Q. Do you know whether that was done?
A. I do not.
MR. NARESH: Did you say "Syngenta agreed to..."?
MR. DICKENS: Oh, I might have. Let me ask again.
BY MR. DICKENS:
Q. It says:
"Chevron agreed to send details of these cases to Dr. Rose."
A. Yes. I'm sorry, I misheard you as well.

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Yes, correct.
Q. Do you know whether or not Chevron did send those to Dr. Rose?
A. No, I don't.
Q. Do you know whether or not Dr. Rose reviewed those cases and drafted a report in any way?
A. I don't recall that.
Q. Do you know whether or not Syngenta ever notified the United States EPA that Chevron workers in packaging plants had quite severe dermal exposure and ended up with paraquat in their blood and urine?
A. I don't know, but, in any case, that would be the responsibility of Chevron.
Q. In the next section, "Inhalation," there's a section here that's bracketed. It says:
"Irritation to mucus membrane and nosebleed has always been associated with exposure of workers to spray mist as a clear warning of exposure."
Right?
A. Yes.
Q. And you'd agree with that statement?
A. Yes.
Q. Turn two more pages to a section towards the bottom, "Other Paraquat Studies."
Do you see that?

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A. Yes.
Q. It mentions:
"According to Chevron, IBT dog studies tended to be well done and the only IBT study they have so far succeeded in validating is a dog study."
Right?
A. Yes.
Q. Now, we looked at earlier that the IBT dog studies were included in the group that was criticized in the Chevron/ICI meeting, right?
A. Right.
Q. So not all the dog studies were well done; we can agree on that?
A. Okay.
Q. Is that --
A. Yeah, I don't -- sorry, I would need to go back to just double-check that in that report, but yes.
Right. So this -- well, the report that we talked about earlier from the US EPA doesn't appear to specify dog studies.
Q. I was actually referring to Exhibit 11, and I'll put that back up here. It's hard to keep track of all these.
A. Yes, okay.

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Q. This is the one of the minutes of a meeting held August 31, 1977.
A. Yes.
Q. It's at page ending 6541.
A. Right.
Q. And the section we were looking at is "IBT two-year rat and dog studies."
Right?
A. Ah, right, okay. Yes. Mmm-hmm.
Q. So the issues they were reporting here relate to the two-year rat and the dog studies, correct?
A. Okay, yes.
Q. So we can turn back now and turn to the second-to-last page, page 6 of this document. There's a section "Proposed Label Changes" a little more than halfway down the page.
Do you see that?
A. Yes, I do.
Q. Now, at the time of the IBT scandal and the invalidation of those studies, paraquat was undergoing something known as a RPAR, or Rebuttable Presumption Against Registration in the United States, right?
A. Yes.

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Q. What's your understanding of what the Rebuttable Presumption Against Registration in the United States meant?
A. So this is one of the questions I had of Mr. -- of Monty Dixon because I wasn't sure myself, so how he described that was that the EPA would start from a position that a registration was not possible until -- essentially until there was a rebuttal to that and that rebuttal should be based on data, on studies, in order for them to allow registration.
Q. And that's a review that was initiated by EPA itself, right?
A. Yes.
Q. And it was initiated -- or they initiated the review of paraquat under this process because of concerns that paraquat may cause unreasonable adverse effects on people and the environment?
A. Yes.
Q. And that review was ongoing at this particular time, right, in 1979?
A. That's correct.
Q. And as discussed at this meeting between Chevron and ICI:
"... no attempt to discuss label changes should be made unless it became apparent that the

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technical case to rebut any particular trigger was failing to influence EPA and that otherwise the Agency was likely to issue an RPAR of paraquat."
Right?
A. Right.
Q. So, "We won't be discussing any labeling changes with the EPA until we know whether or not they're going to actually issue a Rebuttable Presumption Against Registration of paraquat in the United States"?
A. That would be my understanding of what was said here, yes.
Q. Okay. So at this time, then, based on meeting notes in 1979, ICI and Chevron knew that dermal exposure could result in significant paraquat levels in the blood and urine of humans, right?
A. Yes, when, essentially, there was a misuse of the product.
Q. Okay. It knew that once in the blood, paraquat could pass through the blood-brain barrier?
MR. NARESH: Objection; form.
THE WITNESS: Yes.
BY MR. DICKENS:
Q. It could accumulate in the brain?
A. Yes.

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Q. And there were death in users from exposure on the skin, as well as inhalation of paraquat?
A. Correct.
Q. You can put that aside.
MR. DICKENS: I'll hand you Exhibit 13 for the record.
(Exhibit 13 marked for identification.)
BY MR. DICKENS:
Q. I've handed you Exhibit 13, which is a statement read by Michael Rose to the US House of Representatives on June 28, 1979, right?
A. Yes.
Q. Michael Rose, once again, as you mentioned, was, it says here, a toxicology -- or a paraquat toxicology research manager in the Central Toxicology Laboratory of ICI, right?
A. Yes.
Q. And this is a statement Dr. Rose made to the US government?
A. To the House of Representatives, yes; a select committee thereof.
Q. Shortly after the meeting minutes that we just looked at between ICI and Chevron, right?
A. That's just before, yes.

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Q. Michael Rose tells the US Congress that ICI:
"... is one of the largest," I believe that should be, "companies in the world, with 145,000 employees and sales (in 1978) of around $9 billion in petrochemicals, plastics, fibers, dyes [...] as well as agricultural chemicals."
Right?
A. Correct.
Q. CTL at the time was staffed by 300 trained scientists; is that correct?
A. At the time, it was correct.
Q. How many trained scientists are in the Syngenta research laboratories currently?
A. Well, we don't do laboratory toxicology in-house anymore; that is outsourced. But the internal teams of what we now call product safety are around about 200 or so.
Q. And those scientists' job was to provide the ICI group with safety evaluation of all chemicals used by the company to ensure that both their employees and customers are not exposed to hazards.
Right?
A. Yes.
Q. And that's an accurate description of CTL

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in 1979?
A. Yes. It's not a complete description but it's a reasonable one.
Q. And it's what was reported to US Congress, right?
A. I'm sorry?
Q. It is what was reported to the US Government?
A. Yes, yes.
Q. Michael Rose goes on:
"All of this data, both experimental and epidemiological, confirm our view that there are no significant health hazards associated with the normal use of the product."
And that product being paraquat, right?
A. Yes.
Q. And that was the message, or public message, by ICI, or Syngenta, at this point, in June 1979, right?
A. Yes.
Q. That there were no significant health hazards associated with use of paraquat?
MR. NARESH: No, no. I'll object; misstates the document.
THE WITNESS: The keyword there is

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"normal use," by which we mean when it's used according to the label instructions. So that -- in other words, if you avoid the kind of exposures that we've been talking about, if you breathe in an aerosol, if you get it on your skin, of course there can be health effects.
But if used normally -- what it means by here is "normally" means as according to the instructions, there should be no health hazards. That was his intent, I think, in making this statement.
BY MR. DICKENS:
Q. You can put that aside.
Now, we talked about the Rebuttable Presumption Against Registration earlier. The EPA ultimately decided -- or ultimately issued its decision in 1982 that the data did not support a Rebuttable Presumption Against Registration for paraquat, didn't it?
A. I'm sorry, I don't have that date to hand so I'll take that as accurate.
Q. Do you understand whether or not, an RPAR, as they say, was -- ended up being issued by the EPA?
A. I don't know whether that happened.
MR. NARESH: I'll do a belated scope objection on that.

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(Exhibit 14 marked for identification.)
MR. DICKENS: I'm going to go ahead and hand you Exhibit 14 for the record.
MR. NARESH: Can you give me the topic number on this one?
MR. DICKENS: 105.
MR. NARESH: 105.
BY MR. DICKENS:
Q. I've handed you a document which is identified in topic 105 of the Notice of Deposition, a letter from a Maurice Green to a Dr. Braunholtz at ICI/Plant Protection Division dated June 3, 1980.
Do you see that?
A. I do.
Q. And is this a document you reviewed prior to this deposition?
A. Yes.
Q. And do you understand that Maurice Green was a former employee of ICI?
A. Yes. I've confirmed that that is the case.
Q. At this point in 1980, or June 3, 1980, he was no longer an employee with ICI, right?
A. That's correct.
Q. But he is writing to a former colleague of

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his, a Dr. Braunholtz, right?
A. Yes.
Q. Do you know who Dr. John Braunholtz is?
A. At that time, he would probably have been the director of research -- of R&D, research and development.
Q. Do you know what Maurice Green's role at Syngenta was while he was working there?
A. I don't know what his role was. I know that he was working in a part of ICI that was not the pesticide, the agriculture business. I think he was working in the chemicals business.
Q. He writes to John:
"I hope that you are well and that PPD is flourishing."
That's Plant Protection Division, right?
A. Correct.
Q. Last paragraph:
"I greatly enjoy my new job in Washington."
Right?
A. Yes.
Q. "My company exists to help any firms which have problems with the government authorities such as EPA, FDA, OSHA [...] over registration of products,

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[...] [including] toxic substances, hazards to consumers..."
Right?
A. Yes.
Q. Now, at this time in June 1980, Syngenta was having problems with government authorities as they were undergoing a Rebuttable Presumption Against Registration, right?
A. Yes; so you indicated.
Q. He goes on:
"We independently assess the size of the problem and make recommendations on what should be done about it, and we also handle all the negotiations with the government departments for our clients as we know all the protocol and the right form in which to present evidence and we also have an inside track to EPA."
Right?
A. That's what it says.
Q. So he's reporting to an old colleague at ICI that his new company assists chemical and pesticide manufacturers in issues they're having with the EPA, right?
A. Yes. And it says elsewhere that he also works directly for the EPA as well, so he had a -- his

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consultancy was -- had a number of different clients.
Q. And his inside track with the EPA, and which he had from actual working with them as well, and can be used to assist those manufacturers or registrants with the problems that they were having; that's what he's reporting, right?
A. My interpretation of this is that it would help a company like ICI/Syngenta to understand how to make representations and -- to the EPA in situations that we're describing now.
Q. Representations to deal with situations for the benefit of the registrants of pesticides such as ICI with paraquat, right?
A. At the end of the day, in order to make sure, I guess, that the EPA has the right information in the right form at the right time.
Q. It goes on:
"EPA also use us to assess the risks of products, effluents [...] from firms they suspect because they have neither the money nor the staff to do all the work themselves."
Right? So he's reporting the EPA doesn't have the work or staff to do the assessment of risks of pesticides?
A. Yes.

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Q. And that's why they call in his new company to assist in that process?
A. Yes.
Q. Another field Maurice Green is getting into is re-registration of pesticides, right?
A. Indeed.
Q. And he reports:
"They therefore settled," they being the EPA, "for reconsideration of the active ingredients only and issue of generalized registrations for these."
Right?
A. Yes, and this is part of that other role I was describing where the EPA are asking his agency to do some work.
Q. And it's your understanding that the EPA, in consideration of pesticides, considers the active ingredient and the registration of the active ingredient in the product, right?
A. They do, yes.
Q. So their concern for paraquat, for example, is -- or for Gramoxone, would be looking at the active ingredient being paraquat?
A. Yes, but regulatory authorities, including US EPA, also look at the formulated product as well as

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part of their registration process.
Q. Okay. And so the formulated product being what's actually in the container --
A. Yes.
Q. -- that's being sold to consumers?
A. Yes.
Q. And any of the ingredients within the actual container itself, right?
A. That would be part of their assessment of the formulated product, yes.
Q. Now, the reconsideration of the active ingredients, that proved to be beyond the scope of the present staff at EPA, according to Maurice Green, right?
A. That's what it says.
Q. So they handed the whole job over to Clement Associates, right?
MR. NARESH: Objection to foundation.
THE WITNESS: That's what it says.
BY MR. DICKENS:
Q. And do you have any reason to dispute that that was the case?
A. No.
Q. Clement Associates:
"... have a $5 million contract to develop

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the risk assessments for 78 existing pesticides. [...] the first one that EPA sent us was paraquat."
Right?
A. Yes.
Q. And so Maurice Green, then, would be handling the analysis and re-review of paraquat at Clement & Associates.
A. That seems to be the case, yes.
Q. So the former employee of ICI is reviewing whether or not paraquat should be re-registered based on the scientific information presented to the EPA?
A. Yes.
Q. And the last sentence on the last page says:
"We have already had the toxicological expertise in Clement to deal with the risk assessment..."
Correct?
A. Yes.
Q. And that's being Clement Associates have the toxicological expertise?
A. Yes.
Q. And he says:
"... I shall build up the facilities here to do the benefit assessment and the risk-benefit

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analysis."
Right?
A. Yes.
Q. So Maurice Green, the former employee of ICI, was going to do the risk-benefit analysis on paraquat for the EPA?
A. Yes. And, through today's lens, this all looks a little strange, that you would describe this, perhaps, today as a conflict of interest. But I can assume that, at the time, this was recognized by the EPA to be appropriate.
Q. Do you know whether or not the EPA knew that Maurice Green was a former employee of ICI?
A. I don't know, no.
Q. Did you see any evidence in your review or preparation for today's deposition that the EPA knew that a former employee of ICI would be doing the risk-benefit analysis for paraquat?
A. No, I've not seen that.
Q. And this risk-benefit analysis, this was specific to the Rebuttal Presumption Against Registration for the EPA, right?
A. Yes, and that, again, still now is normal practice. It's -- there always is a balance between what the benefit of a product is versus the potential

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risks.
MR. DICKENS: I'll hand you Exhibit 15.
(Exhibit 15 marked for identification.)
BY MR. DICKENS:
Q. I've handed you Exhibit 15 which, for the record, is topic 105 of the Notice of Deposition, which are minutes from a meeting of Chevron and ICI, June 30 to July 2 of 1980.
Do you see that?
A. I do.
Q. And there's a Summary section beginning with "Chevron," and this is less than 30 days from the initial correspondence from Maurice Green on June 3, 1980, right?
A. Yes, that's right.
Q. So within a month's time:
"Chevron now confidently learned that an RPAR will not issue on paraquat before early 1981 (latest date published by EPA is October 1980), and the chances of an RPAR being issued at all seems to be declining."
That's what they're discussing at this meeting, right?
A. Yes.
Q. "As we already know, Clement Associates

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have been assigned the job of reviewing the database on paraquat for EPA."
Right?
A. Correct.
Q. So at this point in June -- or June 30 or July 2 of 1980, less than 30 months after Maurice Green reaches out, Chevron/ICI now don't expect that a Rebuttable Presumption Against Registration will not issue for paraquat, correct?
A. Yes. Sorry, just to correct you. I think you said "months" there; I think you meant to say "days." But, yes, that is correct.
Q. And Chevron and ICI, within these minutes, specify the fact that Clement & Associates have been assigned to the job, right?
A. Yes.
Q. Now, one of the issues the EPA initially started the process of the RPAR for was concerns of the chronic toxicity of paraquat, right?
A. I believe so.
Q. If you can turn to page 6, the second paragraph:
"Messages received from Don Dye (Chevron's representative in Washington) are that pressures on paraquat seem to have relaxed somewhat."

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Right?
A. Yes.
Q. Once again, they reference the fact that the review of paraquat data has been turned over to Clement Associates.
Right?
A. Yes, correct.
Q. And it was discussed between ICI and Chevron that they learned of this independently through contact of one of their former employees, Maurice Green.
Right?
A. Yes.
Q. If we can go down underneath the Roman numerals:
"Reports received from Chevron, and independently through contacts at the Downing town Conference, are that Clement Associates are making a poor job of the reviews undertaken under contract from EPA."
Right?
A. Yeah. Sorry, where are you reading that? I'm just --
Q. It's that same page, under Roman numeral -- for paragraph (iv).

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A. Oh, yes. Yes, I see it. Yes, indeed.
Q. So what's being discussed with ICI and Chevron is not only does -- Clement & Associates reviewing the paraquat data, but they're not doing a very good job of it, right?
A. That's what that suggests.
Q. And it's your understanding that Clement Associates continued to undertake the paraquat review for the RPAR until the final decision was issued by the EPA, right?
A. I am not sure that I do know that.
Q. You're not sure you know that or you do?
A. No, I don't know for how long the company Clement actually did continue with that work. I can't remember seeing any dates.
Q. The next paragraph:
"It was agreed that neither ICI nor Chevron would supply Clement Associates with the data which had not been first sent to EPA. There seemed little value to be gained from discussions with the EPA paraquat RPAR manager until after Clement Associates had completed its reviews."
Right?
A. Okay.
Q. That's what it says?

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A. That's what it says.
Q. So ICI and Chevron wouldn't discuss with the actual EPA employee responsible for the Rebuttable Presumption Against Registration until Clement Associates completed its review of the risk-benefit analysis for paraquat, right?
A. Which seems very reasonable, until the EPA were able to be given full and complete information.
Q. Until -- EPA giving full and complete information as presented from Clement Associates, right, that's what you mean?
A. That's what that suggests, yes.
Q. So there would be no discussions with EPA related to paraquat until they knew how Clement Associates were going to come out on the side of paraquat?
MR. NARESH: Objection; form, foundation.
THE WITNESS: That's certainly an interpretation of what's said here.
BY MR. DICKENS:
Q. And as we saw on the first page:
"The chances of the RPAR being issued seems to be declining."
That was the understanding of ICI and Chevron at this point in 1980, right?

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A. Yes.
MR. NARESH: Objection; asked and answered.
THE WITNESS: And it gave some reasons for that further up on this same page, on page 6.
BY MR. DICKENS:
Q. And, indeed, an RPAR was not issued, right?
A. I believe that was true, yes.
Q. And it was not issued based on the review and risk-benefit analysis undertaken by Clement?
A. Indeed, and with a more complete and up to date set of studies and assessments.
MR. DICKENS: Do you want to take a quick break?
MR. NARESH: Sure.
THE VIDEOGRAPHER: We are going off the record at 12:06.
(Lunch break taken.)
THE VIDEOGRAPHER: We are back on the record at 12:46.
BY MR. DICKENS:
Q. Welcome back, Dr. Botham.
A. Thank you.
Q. We talked a little earlier in the deposition with respect to dermal absorption of paraquat. Now, absorption of paraquat through the skin is greatly increased in the presence of damaged or irritated skin, right?

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A. That's correct.
Q. And that includes skin with cuts, rashes, sores or other irritation?
A. Yes, mmm-hmm.
Q. And skin absorption's also greatly increased if the user wears the same clothing or PPE on multiple days, right?
A. Yes, and I think that we touched on some of the cases earlier which may have been -- where the toxicity may have been caused by that, so yes.
Q. Now, paraquat is a moderately strong irritant of the skin, is it not?
A. It is.
Q. Meaning that exposure to paraquat itself will irritate the skin, right?
A. Yes.
MR. DICKENS: I'll hand you what we'll mark as Exhibit 16.
(Exhibit 16 marked for identification.)
BY MR. DICKENS:
Q. I've handed you Exhibit 16, for the record, which is topic 17 in the Notice of Deposition, which is a memo dated June 29, 1977, "Paraquat Dichloride - Short-term dermal study in more than one specie."
Do you see that?

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A. Yes, I do.
Q. And it's from a I. Pratt to Michael Rose, correct?
A. That's correct.
Q. And this is a document you've seen prior to today?
A. Yes, it is.
Q. There's a "Results" section midway and it includes "Epidermal effects," right?
A. Yes.
Q. And "epidermal" meaning skin?
A. The epidermis is the layer just below the surface of the skin.
Q. And in that layer just below the skin:
"Paraquat produced changes typical of a moderately strong chemical irritant."
Right?
A. That's what the report says, yes.
Q. And, once again, this is in multiple species, right?

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A. Yes.
Q. And it says:
"Effects were more severe in occluded than in non-occluded skin."
That's what's being reported here, right?
A. That's correct.
Q. And "occluded" meaning covered, right?
A. Yes, that's right.
Q. So the effects when the skin was covered after -- well, strike that.
So in these studies, paraquat would be applied to the animal, right?
A. Mmm.
Q. And then there would be a measurement or a observation as to the effects on the epidermis in this instance, right?
A. Yes. So this was a pathological study, so the skin would be investigated under the microscope.
Q. And so in some of the animals, they covered the skin after applying paraquat; in some they did not, right?
A. That's right.
Q. And in the animals in which the skin was covered, the epidermal effects were more severe,

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right?
A. That seems to be the case, yes.
Q. And that's the case and has been the case with respect to all species studied in the dermal studies with paraquat by ICI or Syngenta, right?
A. Yes, yes.
MR. NARESH: Objection; form.
THE WITNESS: Excuse me, can I just take one minute. I forgot to switch my phone off, which was very bad of me.
MR. NARESH: Go right ahead.
THE WITNESS: I don't want to be causing a disturbance. So apologies for that.
MR. NARESH: Could you just do your last -- I think he was checking his phone. Could you just do your last Q&A again, please.
THE WITNESS: Yeah, just give me a second, Ragan, please.
Okay, ready to go.
BY MR. DICKENS:
Q. And in ICI or Syngenta dermal studies, ICI and Syngenta have found that effects are more severe in occluded rather than non-occluded skin?
A. Yes, yes.
Q. Okay. If you can turn the page, the

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second page, number (3) lists some follicular effects, right?
A. That's correct, yes.
Q. And this is reporting on damage to hair follicles, right?
A. That's right.
Q. And damage to the hair follicles, that was seen in all species, right?
A. Yes.
Q. The effect being:
"... particularly marked in the hair bulb and dermal papilla, the growing point of the hair."
Right?
A. Correct.
Q. And in some species, follicular effects were seen at lower dose levels, particularly when that skin was covered.
Right?
A. Yes, and there are probably -- the explanation for that is that the hair follicle is an easy route for substances to enter the skin.
Q. In fact, on the next page, under "Points of interest," number 2, it says just that, right?
A. Mmm.
Q. "... the early changes in the follicles

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indicate a very rapid penetration of the chemical by this route."
Right?
A. Yes, that's correct.
Q. And that is true with respect to all species tested by ICI or Syngenta in dermal studies, right?
A. Right.
Q. And the same would be true with respect to humans, correct?
A. Yes. I mean, there obviously is a big difference between humans and some of these species. Humans have far fewer hair follicles. We're not, basically, a hairy species, whereas a guinea pig and a rat are.
Q. But it's true that in the areas where there are hair follicles, those would be the areas that would be more prone to greater dermal absorption in humans when exposed to paraquat?
A. That is certainly plausible, yes.
Q. It goes on:
"[The] pattern of damage does not appear to have been seen frequently with chemical irritants, and the selective [section] of the hair bulb and dermal papilla, leaving the upper part of the follicle

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untouched, is unusual as far as I know."
Right?
A. Yes.
Q. And there's a statement that this may explain the nail bed effects that were known.
Right?
A. Yes.
Q. And so it's reporting that while there's very rapid penetration through the hair follicles, paraquat is acting differently than other chemical irritants, right?
A. That's what Dr. Pratt has suggested, yes.
Q. And who was Dr. Pratt?
A. Dr. Pratt was a pathologist, a senior pathologist.
Q. And he would have been the one responsible for this particular study?
A. It was a she, but yes.
Q. Oh, okay.
A. Yes.
Q. Thanks.
Now, dermal absorption through damaged skin, that will happen virtually immediately after exposure to paraquat, right?
A. It depends on the nature of the damage,

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how deep the damage is, so you can't generalize, but, obviously, a damaged skin will impact the amount and the time it takes for paraquat to get through.
Q. And so, say, a large opening or lesion on the skin, that penetration would occur rapidly?
A. It could do.
Q. Almost immediately?
A. Yes, it could do.
While less-damaged skin but still damaged would be more than intact skin?
A. Yes, because skin is actually a very effective barrier to paraquat. So intact skin, paraquat does not easily get across that barrier; the skin is a very effective barrier.
Q. And that was seen in studies conducted on paraquat, right?
A. Yes.
Q. And paraquat alone?
A. Yes.
Q. What's a non-ionic surfactant?
A. It's the kind of substance which is used in many different products, including pharmaceuticals as well as agrochemicals, other kinds of products, too, usually to improve what you might call the bioavailability of a substance; so it will help, in

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the case of a drug, to enable that drug to -- if it's a topical substance, to penetrate the skin to do its job.
Q. Surfactants are also known as or referred to as "wetters"?
A. They're called "wetters," yes; particularly in the agrochemical world they are, yes.
Q. And farmers and other users of paraquat in the United States have always been instructed to mix paraquat with surfactants prior to spraying?
A. That's right, and the instruction has been to use a non-ionic surfactant.
Q. And prior to spraying, paraquat users in the United States would have to manually mix paraquat, surfactants and water in a tank prior to spraying?
A. Just say that again.
Q. Yeah. Prior to spraying, in the United States paraquat users would have to manually --
A. Ah, right.
Q. -- mix paraquat, surfactants and water?
A. Yes, essentially and, of course, that's again meant to be done according to strict instruction on how you do that, where you do it and how you should protect yourself whilst doing that.
Q. The paraquat formulations sold in the

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United States, have they ever contained a non-ionic surfactant in the formulation itself?
A. In the United States, some of the products that have been sold have small amounts of non-ionic surfactant, and -- but they also come with the recommendation or instruction to then add further non-ionic surfactant in order to produce the substance that is then suitable for spraying.
Q. So regardless, the formulation of non-ionic surfactant would always need to be added?
A. That's really the only way in which it can effectively do its job as a herbicide.
Q. Which formulations in the United States have contained small amounts of non-ionic surfactant?
(Stenographer clarification.)
MR. DICKENS: Yeah.
BY MR. DICKENS:
Q. Which products in the United -- or which formulations in the United States have included small amounts of non-ionic surfactants?
A. It was one of the questions that I was discussing with Monty Dixon. I don't have that information to hand, but it's certainly true that we know what those products are.
Q. You know them from the statement of

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formulas for those particular --
A. I know them because Monty Dixon has confirmed that.
Q. Okay. But you don't know the names of those as you sit here today?
A. I've not got them immediately to hand. There are many different trade names that are used.
Q. Okay. Now, the purpose -- you mentioned the purpose of surfactants in things like pharmaceuticals. The purpose of adding surfactants with paraquat is to enhance the amount of paraquat that can penetrate into the plant or weed that you're trying to kill, right?
A. Yes. It's needed, really, to be an effective herbicide.
Q. And whilst surfactants increase the absorption in plants, it also has the same effect on humans, right?
A. Potentially, it could, but non-ionic surfactants are specifically recommended because that enhancing effect is not as significant as it would be with other types of surfactant.
Q. But you do agree that non-ionic surfactants will increase the dermal absorption of paraquat?

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A. There will be some degree of increase, yes.
Q. Now, non-ionic surfactants will also increase the speed by which paraquat can reach peak concentration in the blood, in humans, of paraquat?
A. They may have that. I'm not sure that I can immediately bring to mind a sort of, if you like, a systematic analysis of that, but, yes, theoretically, if you get faster or greater penetration of paraquat across the skin, that, in turn, could change the kinetics in the blood.
Q. And, in turn, that addition of non-ionic surfactants will also increase the toxicity of paraquat, right?
MR. NARESH: Object to the form.
THE WITNESS: Well, it might. It depends on the actual amount that gets across. I think you would still need a significant exposure to paraquat, with or without surfactants, in order to see toxicity. As we've said this morning, the toxicity is generally seen when there is poor hygiene or, as you said earlier, where people have been using it with cuts and abrasions and so on. So under normal use, you don't see that toxicity.
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BY MR. DICKENS:
Q. Non-ionic surfactants, added to paraquat, will require less paraquat exposure to result in toxicity, right?
A. In --
MR. NARESH: Objection to form.
THE WITNESS: In theory, yes.
BY MR. DICKENS:
Q. And Syngenta has known that since the 1960s, that paraquat with surfactant would be more toxic than paraquat alone?
MR. NARESH: Objection to form.
THE WITNESS: And since the 1960s, we've done toxicity studies on formulated product as well as the active ingredient.
BY MR. DICKENS:
Q. Now, the studies on paraquat with surfactants, those have not been submitted to the United States Environmental Protection Agency, have they?
MR. NARESH: Objection to scope.
THE WITNESS: Studies of paraquat with surfactant added, yes, absolutely. It's a requirement that certain types of toxicity studies are submitted to the EPA.

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BY MR. DICKENS:
Q. Okay. What toxicity studies have been submitted to the EPA comparing paraquat versus paraquat with a surfactant?
MR. NARESH: Objection to scope.
Which topic is this?
MR. DICKENS: Topic 17.
MR. NARESH: Where does it talk about EPA in topic 17?
My understanding is that topic 84 is about --
MR. DICKENS: Sorry.
MR. NARESH: -- submitting studies to the EPA.
MR. DICKENS: Probably topic 6, sorry.
MR. NARESH: Where is --
MR. DICKENS: "Communications to the EPA about the effect of surfactants on the absorption of paraquat into mammals."
MR. NARESH: Are you asking about one of these specific studies or just generally?
MR. DICKENS: I'm asking about the general topic that's listed in topic 6 that specifically says we'll be asking the witness about:
"Communications to the EPA about the

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effect of surfactants on the absorption of paraquat into mammals."

MR. NARESH: I'll maintain my scope objection.

If you know the answer to any of these, it's obviously -- answer truthfully whatever you know, but if you don't, then you don't.

THE WITNESS: What I know is that studies were submitted to the EPA on paraquat as paraquat, and some studies were submitted to the EPA of paraquat as a formulated product and, largely speaking, those were studies that are required under regulatory guidelines.

BY MR. DICKENS:

Q. So do you agree that studies comparing paraquat and paraquat with the surfactant should have been submitted to the EPA?

A. Those that are required, certainly, yes.

Q. Has Syngenta submitted dermal absorption studies to the EPA comparing the absorption rates of paraquat versus paraquat with a surfactant?

MR. NARESH: Same objection as before as to scope.

THE WITNESS: I know that dermal absorption studies have been done and that includes, again, studies with the active ingredient and with

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formulated product. I am not able right now to be able to say what studies have been submitted to the EPA.

MR. DICKENS: Go ahead and mark Exhibit 17 for the record.

(Exhibit 17 marked for identification.)

BY MR. DICKENS:

Q. Before you take Exhibit 17, are there -- in other countries in which Syngenta sold paraquat formulations, have there been paraquat formulations that did not require the addition of a non-ionic surfactant prior to spraying?

MR. NARESH: Objection; foundation.

Answer if you know.

THE WITNESS: Again, there have been many, many formulations of paraquat. My understanding is that the majority, if not all, the recommendation has been either to add surfactant, or they've been sold with non-ionic surfactant already part of the formulation.

BY MR. DICKENS:

Q. Okay. Do you know, if we wanted to find out what studies have been submitted to the EPA involving a comparison of paraquat with paraquat and surfactant formulations, where would we go to find

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that out?

A. Where would you go?

Q. Yeah.

A. I guess that information should be available from the EPA database.

Q. All right. Exhibit 17 is a document identified in topic 6 of the Notice of Deposition, "Toxicity tests on Gramoxone for registration in the USSR," dated April 1967.

Do you see that?

A. Yes.

Q. And the report is authored by K. Fletcher. We discussed Dr. Fletcher previously, right?

A. We did.

Q. It's the same doctor?

A. It's the same person.

Q. Turn to page 2. It says:

"The Russian authorities require the following additional information on the toxicology of Gramoxone or paraquat."

Right?

A. Yes.

Q. And one of the things required is a cutaneous LD50.

Right?

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A. Yes.

Q. "Cutaneous" meaning skin?

A. I assume that means a dermal LD50, yes. Skin.

Q. And LD50 is the median lethal dose?

A. That's right.

Q. And that's the dose required to kill half of the animals in a tested study or a tested population?

A. Yes, that's right.

Q. And LD50 is used to estimate the potential hazards of a chemical on humans?

A. Yes.

Q. And so this test was to determine in LD50 the amount of paraquat that would cause an effect or hazard to humans, right?

A. That's right.

Q. If you can turn to page 3.

Now, in this study, the cutaneous LD50, three solutions were tested, right?

A. It is the salt -- are you referring to -- yes, the dichloride and the dimethosulfate. Is that what you're referring to?

Q. So on the top of page 3 --

A. Oh, 3, I'm sorry. I'm sorry.

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Q. -- there's a section "Cutaneous LD50."
A. Yeah, okay. Yes, okay, got it.
Q. And it says three solutions were used: (1) Gramoxone, containing no wetter.
Right?
A. Right.
Q. And so that is just paraquat with no surfactant?
A. That's right.
Q. Paraquat with 5% wetting agent, right?
A. Yes.
Q. And it lists which surfactants are included: Ethomeen and Lissapol, right?
A. Yes.
Q. Those are both non-ionic surfactants?
A. I don't know. I'm not - unfortunately, I'm not a chemist with deep knowledge of surfactant chemistry. So I suspect so, but I don't know.
Q. And then Gramoxone with 10 percent wetting agent, right?
A. Right.
Q. And the study was run with each of these solutions on the backs of rabbits, right?
A. That's right.
Q. And there was steps taken to reduce the

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possibility of oral ingestion, right?
A. That's right.
Q. In (a), it gives the results of 400 mg/kg of paraquat with no surfactant was left on the skin for 24 hours, right?
A. Yes.
Q. And what were the results when no surfactant was added?
A. So it said on the fifth day, one animal died, although it says the cause of death wasn't discovered, and there was no obvious effects on the skin apart from mild erythema.
Q. So no surfactants, there's no observable effects on the skin of those animals, right?
A. Mild erythema, that's mild reddening of the skin.
Q. And one animal died on the fifth day; no cause of death was discovered, right?
A. That's right.
Q. Then they did the experiment using the surfactants with -- I mean, sorry, paraquat with the surfactants, right?
A. Yes.
Q. And it gives us information with respect to what occurred in those animals, right?

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A. Yes.
Q. And there were deaths with the rabbits that were exposed to both surfactant -- or both paraquat and the surfactants, right?
A. That's correct.
Q. Now, these animals, they followed for four weeks, right?
A. Right.
Q. And there were deaths with surfactants at a dose of 100 mg/kg?
A. With the 5 percent wetter only, interestingly, yes.
Q. Okay. And then deaths in the 5 percent wetter with 200 mg/kg, correct?
A. Yes.
Q. Deaths for both in 300 and 400 mg/kg, right?
A. That's right.
Q. And therefore the approximate dermal LD50 to rabbits of paraquat with wetter is therefore 200 mg/kg, right?
A. That's right. I don't know whether they've combined the 5 percent and 10 percent data to get that, but that's -- yes, that looks approximately right.

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Q. And that is a lower LD50 than it would be for Gramoxone alone -- I mean, Gramoxone being paraquat without the wetter?
A. Yeah, yeah. Well, strictly speaking, Gram- -- well, today, Gramoxone would actually be a description of a formulated product rather than the active ingredient, but I take that what's meant here is that "Gramoxone" meant pure -- essentially, pure paraquat.
Q. So I should ask better. The 200 mg/kg of the paraquat with the surfactant is lower than the LD50 would be for paraquat alone?
A. Right.
Q. Now, do you know whether or not this toxicity test was submitted to the EPA?
MR. NARESH: Objection to the scope.
This was specifically agreed not part of Dr. Botham's testimony and this question was asked of Mr. Dixon for whom this topic was designated.
THE WITNESS: Yeah, so I don't know the answer to that question.
BY MR. DICKENS:
Q. Paraquat never got approved in the USSR, right?
MR. NARESH: Objection to scope.

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THE WITNESS: I really don't know. I mean, this, again, we're going back a long time here, 1967, so I'm afraid I don't carry that historical record.
BY MR. DICKENS:
Q. At least from the time -- well, you began working on paraquat in 2008?
A. Thereabouts.
Q. From the time you began working on paraquat, has paraquat ever been registered in the USSR?
A. Well, I've got a list of where paraquat was and wasn't registered with me, so I can certainly check that point.
Q. Sure.
A. Yeah, so there's no mention here of the USSR.
Q. No mention of paraquat being registered?
A. No, it's not in the list of countries that I've got.
Q. Now, the study we just looked at was a study involving rabbits, right?
A. Yes.
Q. Now, paraquat with surfactants have been shown to have a lower LD50 in other species as well,

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right?
A. Yes, I believe that's true.
Q. And that includes rats?
A. Yes.
Q. Monkeys?
A. That's right, yes.
Q. Cats?
A. I think so.
Q. Dogs?
A. Yes.
Q. Has Syngenta ever conducted a study testing absorption in man in paraquat versus paraquat and surfactants?
A. It will have done work in -- using human skin, certainly.
MR. DICKENS: I'll hand you what we'll mark as Exhibit 18 for the record.
(Exhibit 18 marked for identification.)
MR. NARESH: Is this within topic 6?
MR. DICKENS: It is, yes.
MR. NARESH: Yeah.
BY MR. DICKENS:
Q. Doctor, I've handed you Exhibit 18, which is a correspondence dated May 26, 1972, titled "Paraquat Strategy."

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Do you see that?
A. I do.
Q. And it's from an A. Calderbank to a T.C. Frears, right?
A. Yes.
Q. Both are ICI employees at this time?
A. They are in the Plant Protection Division.
Q. And in this correspondence, they're talking about new marketing plans, right?
A. Yes.
Q. It says:
"You may be aware of fairly recent work at IHRL which has demonstrated that paraquat is much more toxic to some species when administered as 'Gramoxone,' with wetter than as the pure chemical."
Right?
A. Yes. Interestingly, making the point I was making earlier: "Gramoxone" is normally meant with wetter.
Q. But we can agree that as of 1972, ICI knew that paraquat with wetter was more toxic in some species than paraquat alone?
A. Indeed, and we've just recognized that in some of the studies that have been done, yes.
Q. And:

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"... we cannot be sure that the presence of wetters significantly increases the toxicity of paraquat to man - but at least it seems probable that the toxicity would be increased to a certain extent."
Right?
A. Yes, and that was, I guess, their hypothesis to say that the same could apply to man.
Q. And they said it is probable, in light of the information we have at this point in 1972, that it would be more toxic in man, right?
A. As I said, that was their hypothesis, yes.
Q. At no point prior to 1972 had Syngenta informed any consumers that the addition of a surfactant would make paraquat more toxic, right?
MR. NARESH: Objection; scope, foundation.
THE WITNESS: I don't know what -- by "consumers," I assume you mean farmers who were using the product. I can't comment on what kind of communications may have been made.
BY MR. DICKENS:
Q. Has Syngenta ever publicly stated in any form that the paraquat with a surfactant would be more toxic than paraquat alone?
MR. NARESH: Same objections.
THE WITNESS: Well, we've obviously

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disclosed the studies we've done, which have been comparing the toxicities, so, in that sense, that information is in the public domain.
BY MR. DICKENS:
Q. When you say "disclosed," do you mean published?
A. Published, submitted to the regulatory authorities; both.
Q. It goes on:
"Thus, it could be argued we are making a toxic product even more toxic by [re]formulating it with wetter."
Right?
A. Yeah, that's what it said.
Q. There were discussions and considerations of marketing a formulation of paraquat with a non-ionic surfactant in the United States that would not require the addition of more, right?
A. Yes.
Q. And that was in response to products like Roundup, including glyphosate, which had a non-ionic surfactant already mixed in?
MR. NARESH: Objection; scope, foundation.
THE WITNESS: I don't think that you can make a connection with Roundup; I don't think that

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this was in response to that.
BY MR. DICKENS:
Q. But nonetheless, ICI and Syngenta was considering a product that would not require the addition of a non-ionic surfactant?
A. That was one of the considerations, but, of course, you have to weigh up the benefit, does it do the job versus the potential increased risk.
Q. And that increased risk being that it would be more toxic to man with the surfactant?
A. It has the potential to be more toxic, yes.
Q. And so that was the risk on why the company decided not to move forward with that product, right?
MR. NARESH: Objection to form.
THE WITNESS: Because to move forward with a product that didn't contain surfactant or...
MR. NARESH: There was a "that" in your question that was a little confusing.
MR. DICKENS: Okay.
BY MR. DICKENS:
Q. So the question was specific to the reason why the company decided to not move forward with a product including paraquat and a non-ionic

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surfactant at a quantity sufficient where you didn't need to add more in. The reason why they didn't move forward was because of the potential toxic effect to humans?
A. I don't believe that that was the reason. I mean, certainly in the United States, as we said earlier, what has been sold and what is still sold today, generally, is a product which contains small quantities of surfactant to which you then have to add surfactant in order to be able to provide the product that works.
Q. And my question was a little different. Just with respect to, was ICI and Syngenta considering marketing a product where you would not need to add more non-ionic surfactant in? It would already be included.
A. Well, the challenge was obviously being thrown down in this memo, that's for sure. I don't know what -- whether any specific action was taken of that nature. I can only describe to you what actually was being sold and what is still being sold today.
Q. And the determination as to whether or not to market that product or continue with a product that you would not need to add more non-ionic surfactant would be a risk-benefit analysis?

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A. Undoubtedly, and if marketing a product which did not contain surfactant in the hands of a farmer and grower didn't do the job that they were expecting, then the benefit is clearly not -- no longer available to the farmer.
Q. Okay. And, as discussed in this memo in 1972, the adding of a wetter or a surfactant could be said that you were making a toxic product, paraquat, even more toxic, right?
MR. NARESH: Objection; asked and answered.
THE WITNESS: Yes, that's a true statement, that there is a higher hazard.
(Exhibit 19 marked for identification.)
MR. DICKENS: I'll hand you what we'll mark as Exhibit 19 for the record.
BY MR. DICKENS:
Q. Let me know when you're ready, Doctor.
A. Okay, yes.
Q. I've handed you an exhibit which was produced by Syngenta in this litigation, which is a group of correspondence, and this is a document you've reviewed in preparation for today's deposition?
A. I've certainly seen some of this document, yes.

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Q. And there was multiple correspondence with dates. I'm going to start on the very back page, which appears to be one of the earlier dates, but this is a letter written from a Stelzer to an Ospenson.
Do you see that?
A. Yes.
Q. And it's dated May 13, 1975 and titled "Paraquat plus surfactant."
Right?
A. Yes.
Q. And this is a correspondence from Chevron; is that right?
A. I think this is probably a correspondence within Chevron.
Q. Okay. They state:
"Our initial approach has been to work with PPD..."
And that's the Plant Protection Division?
A. That's right.
Q. That's an ICI division?
A. That's right.
Q. "... collecting the data necessary to register their export formula (JF1682), which contains 10% surface active agents."
First of all, "surface active agents"

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referring to surfactants?
A. Yes.
Q. And what is export formula JF1682?
MR. NARESH: Objection; foundation.
THE WITNESS: I assume it's a formulation which is available for export to other countries.
BY MR. DICKENS:
Q. And PPD or ICI at the time had formulas of -- or paraquat formulations that included as much as 10 percent surfactants, right?
A. Okay, mmm-hmm.
Q. And formulations that contained 10 percent surfactants with paraquat, would those be formulations where you would not be required to add more non-ionic surfactant prior to spraying?
A. Possibly so, yes. I mean, again, I'm not an expert in formulation technology, but that's -- certainly, there are formulations that have been produced which, indeed, do not require the addition of a further surfactant.
Q. And those formulations have been marketed and sold by Syngenta in other places around the world?
A. That's correct.
Q. And PPD supplied that information, right?
A. Yes.

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Q. And that included information on the dermal LD50 that we discussed earlier, right?
A. Yes.
Q. As well as skin irritation and eye irritation, correct?
A. Yes.
Q. He says:
"... a red flag concerning oral toxicity has come to light and I recommend we defer all plans to register and market a paraquat + surfactant product."
Correct?
A. Yes.
Q. Last sentence of the second paragraph:
"... R. Cavalli has informed me that CTL..."
That's Central Toxicology Laboratories, right?
A. It is, yes.
Q. "... has unpublished data on dogs showing that the addition of surfactant to paraquat increases the rate of, and degree of, absorption from the gut into the blood; mortality is also increased."
Right?
A. Yes.

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Q. And you've reviewed that data specifically with respect to the dogs, right?
A. We talked about that earlier, yes.
Q. And that data -- you mentioned that data on paraquat-plus-surfactant toxicity would be available through publication or submission to the EPA, right?
A. It normally would be the case.
Q. It would not be the case for unpublished data; we can agree on that?
A. Correct.
Q. And this study specifically was unpublished, right?
A. It's certainly suggestive of that, yes.
Q. Last sentence of the last paragraph:
"The addition of surfactant appears to make a bad situation worse."
Right?
A. Yes.
Q. "Unless PPD can produce data to contradict the above, I strongly recommend we discontinue the exercise toward registering a product with built-in surfactant."
Right?
A. Yes.

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Q. PPD never produced additional data to Chevron in order to register a product in the United States with built-in surfactant, correct?
MR. NARESH: Objection; foundation, scope.
THE WITNESS: I can't comment on that.
BY MR. DICKENS:
Q. Well, certainly, neither ICI, Syngenta or Chevron attempted to register a product in the United States that included paraquat and 10 percent wetter or surfactant?
A. I believe that's the case.
Q. And that's the case due to concerns about toxicity?
MR. NARESH: Objection to form, foundation, scope.
THE WITNESS: I think that will have been one factor but probably not the only one.
BY MR. DICKENS:
Q. The surfactant made the bad situation worse, right?
MR. NARESH: Same objections.
THE WITNESS: In theory, it could, yes. And let me reiterate, this is about hazard and not necessarily risk. You can still use a substance which has got built-in wetter safely, but obviously it

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increases -- because the hazard is increased under situations of bad practice, bad use, you can make the toxicity worse. That's true.
BY MR. DICKENS:
Q. You agree that surfactant with paraquat increases the hazard at least with respect to toxicity?
A. Yes.
Q. And that's true with respect to humans?
A. It is, yes.
Q. You agree, in the United States farmers and other users of paraquat mix the surfactant in with the paraquat, right?
A. That's my understanding.
Q. So you'd agree that the end-use product being sprayed by farmers is more toxic than the paraquat they're pouring out of the jug that they purchase in the United States?
MR. NARESH: Object to form, foundation, and scope.
THE WITNESS: It has greater hazard potential.
BY MR. DICKENS:
Q. It's more toxic?
A. Yeah.

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MR. NARESH: Same objections.
MR. DICKENS: I'll go ahead and hand you Exhibit 20 for the record.
(Exhibit 20 marked for identification.)
BY MR. DICKENS:
Q. Showing you Exhibit 20. Once again, a document from topic 6 in the Notice of Deposition, a memo from a Paul Dugard, July 22, 1982, "Paraquat Formulations: Methods for assessing relative hazards of skin contact."
This is a document you've seen before, correct, Doctor?
A. It is.
Q. And there is a section here, "Skin Absorption: Human in vitro," right?
A. Yes.
Q. And it references previous permeability experiments with surfactants and non-surfactants.
Right?
A. Yes.
Q. Permeability being absorption studies?
A. That's right. Permeability -- it would generally mean permeability across a biological surface, either the gut or the skin.
Q. Okay. And the studies he's referring to

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here, do you know whether or not they're referring to -- or the previous permeability experiments involved human skin?
A. I don't know whether the previous studies included human skin at that time. He's obviously now proposing that human skin could be used, and that's what I was referring to earlier in terms of the data that we did have available.
Q. Do you know whether or not there had been, by this point in July of 1982, dermal absorption studies using human skin?
A. No. That, I'm not absolutely sure about.
Q. He states that those previous studies show:
"... that surfactants alter stratum corneum permeability to paraquat without intervention of a biological response."
That's what he's saying in 1982, right?
A. Yes, that's correct.
Q. And who is Paul Dugard?
A. Paul Dugard was a toxicologist and he specialized in acute toxicity, short-term toxicity, and also, as this suggests, skin absorption. So this was his wheelhouse, this area.
Q. So this is his particular wheelhouse of

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skin absorption studies for ICI?
A. Yes.
Q. Now, stratum corneum, that's the outermost layer of the skin, right?
A. It is.
Q. And it's the part of the skin that protects the body from the outside environment?
A. That's right.
Q. And what Paul Dugard is saying here is that surfactants themselves will alter the permeability of the stratum corneum.
Correct?
A. Yes.
Q. So surfactants themselves allow more of the chemical or product to be absorbed into the skin through that alteration?
MR. NARESH: Objection to form, foundation.
THE WITNESS: That's right. It's one explanation for the phenomenon that we have just been discussing.
BY MR. DICKENS:
Q. So that's without intervention of a biological response; so, at the end of the day, it's saying surfactants will allow more paraquat to absorb

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into the skin, right?
A. That's correct.
MR. DICKENS: I'll hand you Exhibit 21 for the record.
(Exhibit 21 marked for identification.)
BY MR. DICKENS:
Q. This is a document from a P. Slade, dated June 20, 1973, the topic "Safer Gramoxone."
Do you see that?
A. Yes, I do.
Q. Is this, once again, a document you've reviewed in preparation for today's deposition?
A. Yes, I do recall this one.
MR. NARESH: Can you just remind me, I don't see it within 6. Is it within a different one?
MR. DICKENS: It is in 6.
MR. NARESH: It is. Oh, there it is. It's in a double. I got it, thank you. 6D.
BY MR. DICKENS:
Q. And this document's marked "Confidential," right?
A. Yes, it is.
Q. It begins:
"Following our recent correspondence about

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the problem of minimizing the hazards of Gramoxone..."
Right?
A. Yes.
Q. The second paragraph:
"... we have insufficient toxicological information at present to make a firm decision about the effect of replacing the existing wetting agents in Gramoxone with an alternative."
Right?
A. Yes.
Q. What he can say is that:
"... the LD50 of Gramoxone is about 5-10 times greater than pure paraquat..."
Right?
A. Yes. As he says, in some species but not all.
Q. And as you said earlier, the Gramoxone reference, that would be paraquat with the surfactant?
A. That's correct.
Q. So Gramoxone with surfactant in some species are five times -- sorry, the LD50, or the median lethal dose of paraquat with the surfactant is about five to ten times greater than paraquat alone?
A. Yes.
MR. NARESH: I'll object on the rule of

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completeness grounds.
But go ahead.
BY MR. DICKENS:
Q. And he says "the extent of [...] of paraquat from paraquat/wetter solutions in the dog..." and that's judged by both urinary and blood levels, right?
A. That's correct.
Q. And that would depend on the nature of the wetting agent present, right?
A. Yes.
Q. And he says:
"With several wetting agents, the amount of paraquat absorbed is very much less than occurs when the normal Gramoxone wetters are used."
Right?
A. Yes.
Q. "... the effect of these alternative wetters on the acute toxicity of paraquat has not been measured."
Right?
A. That's what it says.
Q. Now, the normal Gramoxone wetters being referred to at this point are non-ionic surfactants, right?

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A. That was my understanding, yes.
Q. And so there were other wetting agents available which would be -- have a lower dermal absorption than the non-ionic surfactants with the paraquat, right?
A. Indeed.
Q. Okay. And those alternative wetters had not been tested or studied by Syngenta or ICI?
A. That would appear to be the case.
Q. And at no point in the United States was there ever a recommendation other than to use paraquat with a non-ionic surfactant?
A. Correct.
Q. Do you know how much -- or what percentage of surfactant is to be mixed in the United States by farmers and other users prior to spraying?
A. I'm afraid I don't have that information to hand, no.
MR. DICKENS: I'm going to hand you Exhibit 22 for the record.
(Exhibit 22 marked for identification.)
BY MR. DICKENS:
Q. I've handed you Exhibit 22, which is a PSAC Toxicity Working Group Minutes, July 2, 1986.
Do you see that?

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A. I do.
Q. What's the PSAC refer to?
A. I can't remember what PSAC stands for, I'm sorry.
Q. There's individuals who were at that meeting, right?
A. Yes.
Q. Lewis Smith who you talk -- or read his deposition prior to today's deposition, correct?
A. Yes.
Q. He was with CTL?
A. Correct.
Q. He was a toxicologist with CTL?
A. That's right.
Q. Number 1 there, "Effect of wetters on paraquat toxicity," right?
A. Yes.
Q. The last two sentences state:
"Recent CTL studies using undiluted doses to rats suggest an approximate 2x increase..."
And then it gives a conclusion, right?
"CTL conclude that for man the elimination of wetters from the standard formulation would lead at least to a 2x reduction in toxicity, i.e., a 2x increase in minimum lethal dose."

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Right?
A. Yeah. I mean, I just want to point out that we've actually switched the area of attention here because I believe this is to do with GI tract absorption, so this is not to do with skin absorption.
Q. Okay. Do you have any reason to believe that skin absorp- -- or that GI absorption would be any different than absorption into other organs within the body?
A. Absolutely. It's quite conceivable that there would be differences in the -- well, obviously differences in the amount that could be absorbed but also differences in the effect that a surfactant could have because these are biologically very different barriers.
Q. Okay. The skin and the GI tract, right?
A. Yes, yes.
Q. Would you agree that surfactants can increase the absorption into the brain?
A. In theory, but I don't know that I have got direct evidence for that.
Q. Has Syngenta ever studied the amount of paraquat getting into the brain of paraquat versus paraquat with surfactants?
A. I don't recall seeing such data.

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Q. So, as far as you know, no study like that has ever taken place?
MR. NARESH: Object to the scope.
THE WITNESS: I don't believe so.
BY MR. DICKENS:
Q. Do you agree that the end-use product being used by farmers and other paraquat users in the United States includes paraquat plus a surfactant, right?
A. Yes.
MR. DICKENS: I'll go ahead and hand you Exhibit 23 for the record.
(Exhibit 23 marked for identification.)
MR. NARESH: What's the topic number?
MR. DICKENS: Topic 6.
BY MR. DICKENS:
Q. Sir, I've handed you a document which is identified in topic 6 of the Notice of Deposition, which is a study, "The Blood-Brain Barrier: Bottleneck in Brain Drug Development," by William Pardridge.
Do you see that?
A. Yes.
Q. And this is a document that you would have reviewed in preparation for today's deposition?
A. I think it was -- yes, I think it was part

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of that. I'm -- yes, I think so, yeah.
MR. NARESH: And, Dr. Botham, if counsel is going to ask you questions about it, feel free to -- I know it's been a long couple of months --
THE WITNESS: It has, yes, so --
MR. NARESH: -- so if you want to refresh yourself on it, take your time.
THE WITNESS: I am doing. Thank you.
Yeah, okay, I understand the gist of this.
BY MR. DICKENS:
Q. And this is a document produced by Syngenta in this litigation, with the date of January 2005.
Do you see that? At the bottom.
A. Yeah, yeah, at the bottom, yes. Got it. Mmm-hmm.
Q. Turn your attention to the page ending 7147.
There's a section here, "Blood-Brain Barrier Disruption," and then a subtopic, "Solvent/adjuvant-mediated BBB disruption."
Correct?
A. Yes.
Q. "BBB" being blood-brain barrier, correct?
A. Correct.

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Q. It states:
"The blood-brain barrier, like cell membranes in general, is subject to solvent-mediated disruption with chemicals [...] [including] tween 80, also known as polysorbate 80."
Right?
A. Yes.
Q. Tween 80 is a non-ionic surfactant?
A. It is, yes.
Q. And so there are studies that were done with chemicals and a non-ionic surfactant to determine whether or not those chemicals could bypass the blood-brain barrier, right?
A. Well, yes, I think that this is one of the mechanisms that was being either hypothesized or where there was maybe some evidence that adding a surfactant or a solvent might increase the ability of a drug to cross the blood-brain barrier in order to effect its disease treatment.
Q. And, in fact, for various, as indicated in this article, there have been studies which have suggested that the addition of a non-ionic surfactant does allow chemicals to bypass the blood-brain barrier, right?
A. I don't know whether the right word is

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"bypass." I think it can affect the ability of another agent to cross the blood-brain barrier.
Q. Okay.
A. I'm sure the mechanisms are more complicated than simply bypass.
Q. And Syngenta certainly had the capability -- or has the capability to undertake a study to determine whether or not the non-ionic surfactant added to paraquat would allow paraquat to by- -- or to cross the blood-brain barrier?
MR. NARESH: Object to the form, foundation.
THE WITNESS: Well, we had no reason to want to do such an experiment. The concern that we've been talking about up until this point has been the increased toxicity that might come from skin penetration or gut penetration.
To look at the blood-brain barrier would mean that we felt there was a hypothesis that the brain could be damaged and we still to this day, of course, do not believe that that is the case.
BY MR. DICKENS:
Q. Syngenta does not know how much paraquat with a surfactant will end up in the brain of humans, correct?

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MR. NARESH: Objection; scope, foundation.
THE WITNESS: We've not done differential experiments comparing paraquat with and without a surfactant in terms of how much may get into the brain.
BY MR. DICKENS:
Q. And those mathematical modeling that you referred to earlier, that was done with pure paraquat, right?
A. That was on the basis of the properties of the paraquat molecule itself.
Q. This document, in the second column on the same page, page 7, it's closer to the bottom but there's a sentence beginning "Tween 80..."
A. Yes.
Q. "Tween 80, also known as polysorbate 80, is frequently administered in CNS drug formulations."
That's central nervous system, right?
A. It is.
Q. "A dose of [the non-ionic surfactant] will cause blood-brain barrier disruption in mice."
Right?
A. Right.
MR. NARESH: Rule of completeness.
///

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BY MR. DICKENS:
Q. It gives as an example: oligopeptide normally does not cross the blood-brain barrier, but it's possible, following the co-administration of the non-ionic surfactant.
Right?
A. Yes, it's possible, but, I mean, I don't know whether they actually demonstrated that for real, but it's possible.
Q. Do you have any reason to dispute what is said in this particular article?
A. No, not at all. I mean, it's a reasonable hypothesis.
Q. So would you agree, then, that Syngenta knows paraquat can enter the brain of humans, right?
A. Yes.
Q. That the addition of the non-ionic surfactant will allow more paraquat to enter the brain of humans?
MR. NARESH: Objection to form, foundation and scope.
THE WITNESS: Again, that would be a hypothesis and we don't actually know whether that is the case because --
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BY MR. DICKENS:
Q. Because --
A. -- don't forget, humans, especially when we are talking about farmers who are using the product, will be exposed to very -- relatively low -- you know, very low concentrations of paraquat and surfactant. Here, you're -- this is -- you're talking about drug delivery, so you're talking about very high concentrations of both the surfactant and the pharmaceutical.
Q. And we don't know whether or not that's the case because Syngenta has never undertaken such a study, right?
MR. NARESH: Objection; asked and answered.
THE WITNESS: We have certainly not done that, for the reasons that I indicated: that we didn't believe that there was a hypothesis that required testing.
MR. DICKENS: I'm going to move -- why don't we take a five-, ten-minute break.
THE WITNESS: Okay.
THE VIDEOGRAPHER: We are going off the record at 13:55.
(Break taken.)

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THE VIDEOGRAPHER: We are back on the record at 14:07.
BY MR. DICKENS:
Q. Doctor, we were discussing the effect of surfactants on dermal absorption and toxicity, but surfactants also increase the risk of inhalation toxicity with paraquat, right?
A. In a similar way, yes, because of the effect on membranes.
Q. And it would increase the absorption and toxicity of both the respirable particles as well as toxicity of larger particles that may not reach the lungs?
A. Yes, that's true.
Q. And the surfactants can facilitate transport across mucus membranes in the upper respiratory tract?
A. Yes, because it's another membrane, as I've just been saying.
Q. And that's true with respect to humans as well, right?
A. Yes, indeed. Yes.
MR. DICKENS: I'm going to hand you Exhibit 24 for the record.
(Exhibit 24 marked for identification.)

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BY MR. DICKENS:
Q. Exhibit 24 is another document identified in topic 6 of the Notice of Deposition, which is a summary report of a four-hour acute inhalation toxicity study conducted by Syngenta in the rat; is that right?
A. Yes, that's right.
Q. And is this a document you reviewed in preparation for today's deposition?
A. It is, yes.
Q. And the report, on page 2, the author is a Joanne Kilgour; is that right?
A. Yes.
Q. She was an inhalation toxicologist at Syngenta?
A. That's right.
Q. She's the author and study director of this particular study, correct?
A. Correct.
Q. On the next page, page 2, in the Introduction it identifies the purpose of the study, and that was:
"... to expose rats to a spray strength paraquat under conditions simulating potential worst-case operator exposure."

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Right?
A. Yes.
Q. And "spray strength paraquat," that would be the strength of the paraquat that's actually being sprayed by operators, farmers, users of paraquat, right?
A. That's right, yes. So it's a diluted paraquat as a consequence, yes.
Q. And it's meant to simulate the worst-case operator exposure from an inhalation standpoint, right?
A. Yes.
Q. It mentions Agral 90 was mixed with the formulation.
Do you see that?
A. I do.
Q. Agral 90 is a surfactant, right?
A. It is.
Q. And a non-ionic surfactant?
A. Correct.
Q. And it was added to the formulation since it may be included in tank mixes for tractor operation, right?
A. That's right.
Q. And it may be included with the

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formulation in the United States as well, right?
A. Yes, potentially.
Q. So this study is testing the end-use product that would be sprayed by users in the United States, right?
A. If it was used in the United States, yes.
Q. Turn to the next page. Under "Study Design":
"A group of five male and five female [...] rats were exposed in a manner designed to simulate 'downwind' exposure to a commercial spray head operating in its normal mode."
Right?
A. Right.
Q. And the results include an achieved test atmosphere and has analyzed paraquat ion concentration.
Do you see that?
A. Yes, I do.
Q. And what was that "analyzed paraquat ion concentration" in this study?
A. 0.15 +/- 0.07 micrograms per liter.
Q. Now, this study was never completed, was it?
A. It's a preliminary study, so, yes, in that

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sense it was completed but it was not -- it was done at a single concentration, for example, so it was decided that this was sufficient information that was required at the time.
Q. And then the conclusion, there was the death of an animal in this study that was deemed by the inhalation toxicologist, Dr. Kilgour, to be unexpected.
Right?
A. Yes.
Q. And that's because previous regulatory studies had shown the MLC -- what does MLC stand for?
A. Median lethal concentration. It's the equivalent to the ML -- the median lethal dose that we've been talking about for oral and dermal studies.
Q. And it was at a concentration of 1 microgram per liter, right?
A. Yes.
Q. And so that was significantly below what that LD50 or median lethal concentration would be, right?
A. Yes, but it goes on to suggest that this may not actually have been associated with paraquat, actually. So it could have been a spontaneous finding for other reasons.

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Q. Okay. Based on this study, the company did not know whether or not it was because of paraquat with surfactant, right?
A. I think what this suggests, that it's actually unlikely to have been caused by paraquat. The weight of evidence would say that would have been very surprising to see paraquat toxicity at that concentration.
Q. And so this finding was unexpected. It was also a new finding for Syngenta due to the unexpected death at such a low concentration, right?
MR. NARESH: Objection to form and foundation.
THE WITNESS: Yes.
BY MR. DICKENS:
Q. Are you aware of any inhalation studies on paraquat and with a surfactant prior to this study, dated December 18, 2002?
A. There were, yes, I think a number of inhalation studies done prior to this date.
Q. Inhalation studies with paraquat and a surfactant as used to simulate spray conditions of a user or farmer?
A. Well, this was the unique feature here, so this was really trying to make it even more relevant

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to the farmer by generating the atmosphere in a way that might be the case when it's used in the field.

Q. And this was the first of that type of study that would have been more relevant to the farmer, in your words?

A. It --

MR. NARESH: Objection; foundation, and scope.

THE WITNESS: That was the intention.

BY MR. DICKENS:

Q. And it was the first study, correct?

MR. NARESH: Same objections. Asked and answered as well.

THE WITNESS: I have not seen any other studies of this type.

BY MR. DICKENS:

Q. Okay.

Second paragraph in the Conclusion:

"Since Agral is known to be a severe eye irritant and, by inference, may have exacerbated the known effects of paraquat in this study, no further work was done pending clarification on the use of Agral in the field."

Do you see that?

A. Yes.

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Q. Now, at any point in time did Syngenta, or ICI, instruct farmers to stop using Agral while spraying paraquat?

MR. NARESH: Objection; foundation, scope, form.

THE WITNESS: I don't know the answer to that question. I would need to ask other colleagues about that.

BY MR. DICKENS:

Q. Was there any other work done to clarify the use of Agral in the field with paraquat?

MR. NARESH: Same objections.

THE WITNESS: Similarly, I would need to be reminded if that was the case. I don't -- I actually don't know.

BY MR. DICKENS:

Q. In your preparation for today's deposition, did you see any documents that would have been relevant to the use of Agral in inhalation studies?

A. I've seen so many studies that I can't remember particularly at the moment.

Q. But as this study says, no further work was done, at least with respect to this study, right?

A. That's right.

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Q. Do you know whether or not Syngenta manufactures Agral?

MR. NARESH: Objection; scope, foundation.

THE WITNESS: I don't know, but I would doubt it.

MR. DICKENS: I'll go ahead and hand you Exhibit 25 for the record.

(Exhibit 25 marked for identification.)

MR. NARESH: What's the topic number?

MR. DICKENS: Topic 6, still.

MR. NARESH: Is it specifically referenced in 6?

MR. DICKENS: I believe so.

MR. TRAVERS: 6.

MR. NARESH: I'm not seeing it, but maybe I'm missing it.

MR. TRAVERS: It's another combined one on 6Y. It's the second one.

MR. NARESH: Got it, thank you.

BY MR. DICKENS:

Q. Doctor, the findings of the last study, the four-hour inhalation study with Agral that we looked at, that was referred to Syngenta's Potentially Referable Findings Committee, correct?

A. That's right.

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Q. Also known as the PRF Committee?

A. Correct.

Q. There was also a committee in the United States responsible for determining whether information would need to be reported to the US EPA, right?

A. Yes. The document you have just handed me is a minute of what's called the PRF Approach Committee, so it was -- this committee would hand its recommendations over to the US committee.

Q. And were you a member of the PRF Approach Committee?

A. I was for a period of time, yes.

Q. Okay. Now, this document is titled "Data submission for consideration by the CTL Potentially Referable Findings (PRF) Committee," right?

A. Yes.

Q. And what is the purpose of this particular document?

A. It's to summarize the findings in a study and why they may -- those findings may meet the criteria for referability under the US Regulation 6(A)(2).

Q. And this particular document was submitted by Dr. Kilgour on June 29, 2000, right?

A. That's right, because it was the

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responsibility of the study director to flag these.
Q. And so this was particularly flagged by Joanne Kilgour due to the death of an animal on day 3 post-exposure, right?
A. Yes.
Q. And you said it was an unusual finding. I believe you said, right?
A. Yes. And I think, you know, the report -- although it says here that the clinical observations are consistent with known effects of paraquat, I think the report itself doesn't actually come to that conclusion. There are clearly effects but I think the reason why Dr. Kilgour would have brought it to that committee was because it was not clear whether the effects were actually due to paraquat.
Q. And then, so from this data submission or this referral, what happens next?
A. If it's agreed that it is potentially referable, if the Approach Committee consider that it may meet the criteria, it is then submitted to the US PRF Committee, who is, if you like, the legally constituted committee within the US organization.
MR. DICKENS: I'll hand you Exhibit 26 for the record.
(Exhibit 26 marked for identification.)

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MR. DICKENS: Which is still topic 6 of the Notice of Deposition.
BY MR. DICKENS:
Q. Document 26 are minutes from the PRF Standing Committee meeting, July 18, 2000, right?
A. Yes.
Q. And you were present at this particular meeting?
A. Yes.
Q. As a member of the PRF Committee?
A. That's correct.
Q. As well as other toxicologists within Syngenta?
A. Yes. It was the senior group of toxicologists who comprised this committee.
Q. And the senior group of toxicologists at Syngenta considered the acute inhalation study by Dr. Kilgour that we just looked at, right?
A. It did.
Q. And it looked at that because of the referral to the PRF Committee by Dr. Kilgour?
A. Yes.
Q. The minutes note that the purpose of the study, once again, was to establish a meeting -- MLC?
A. The median lethal concentrate.

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Q. Thank you.
"...but was to investigate the acute toxicity of the spray strength solution."
We discussed that earlier, right?
A. Yes, we did, yes.
Q. It goes on:
"It was further noted that this test material had not previously been tested in an acute inhalation study, and so the finding should be treated as a 'new finding' under the CTL guidelines."
Right?
A. Yes. The CTL guidelines are what you would call very precautionary. So if in doubt, in other words, we're not -- in situations like this where we're not absolutely sure about what was going on, what was causing this effect, even in that situation we would normally refer or pass on to the US committee because, essentially, we feel that it's better to be open about that rather than to say, well, we can write this off.
Q. And are you aware of EPA guidelines that say if you're in doubt you should submit them to the EPA?
A. Well, it's not so much a guideline. I mean, it certainly comes from discussions which my

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US colleagues have had with the EPA, which is to say if you're in any doubt about whether you should submit, please do send them, and we will ascertain whether we feel it's something that is -- where we need to take any action.
Q. Have you ever had a role on the US committee determining whether something should be submitted to the EPA?
A. No, I've not been on -- in that committee.
Q. And so the senior group of toxicologists at Syngenta reviewed this and were unsure as to whether or not it should be reported; is that right?
A. This is the UK-based committee, the Approach Committee, that said that because it -- essentially, it's a new finding because we'd never even looked at this kind of formulation before, that if -- again, with the "If in doubt, refer," we chose to say to our US committee, "Consider referring."
Q. Consider referring to the EPA?
A. Yes.
Q. When you say "this formulation," that's paraquat with Agral, right?
A. Correct, yes.
Q. And so the PRF Committee, you're saying, "This is a new finding with paraquat plus Agral, so

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you should consider submitting to the EPA"?
A. Yes.
Q. And on the next page, top of the page, it does lay that out:
"... the clinical effects noted were treatment related..."
Do you see that?
A. Yes.
Q. So there was a determination by the senior toxicologist at Syngenta that the death of the mouse was indeed treatment related, right?
A. Yes. Which part of the treatment, if you like, was actually responsible was where we didn't -- we couldn't be sure.
Q. But it would have been the result of the paraquat plus the surfactant --
MR. NARESH: Objection --
BY MR. DICKENS:
Q. -- in some measure?
MR. NARESH: Objection; foundation, scope.
THE WITNESS: We actually don't know as to whether it was the paraquat or the Agral itself or the combination of the two. I mean, this was a preliminary experiment, as you've indicated, so you would need to do more work to really tease apart, if

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it really is treatment related, which -- that's what I meant by which part of the treatment may have caused the effect.
BY MR. DICKENS:
Q. Syngenta never did that additional work, did they?
MR. NARESH: Objection; scope, foundation.
THE WITNESS: I don't believe they did, no.
BY MR. DICKENS:
Q. And, as you said, then, the precautionary or the safer approach would be to refer this information so that it could be considered, right?
A. That's right.
MR. NARESH: Objection; asked and answered.
BY MR. DICKENS:
Q. It notes the death of one animal, a very low concentration and, because of that, the study should be referred.
We just discussed that, right?
A. Yes.
Q. We can put that aside.
MR. DICKENS: I'll hand you Exhibit 27.
(Exhibit 27 marked for identification.)

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MR. NARESH: Is this the whole document?
MR. DICKENS: It is, yes.
MR. NARESH: Is there a family member, do you know?
MR. DICKENS: I don't believe so.
MR. TRAVERS: I'll check.
MR. DICKENS: All right.
MR. NARESH: I suspect there's embedded documents that will probably show up in the family.
MR. DICKENS: We don't know.
MR. TRAVERS: It just comes up as one document when we search.
BY MR. DICKENS:
Q. I've handed you a document identified in topic 6 of Plaintiffs' Notice of Deposition, and this is a document you've reviewed prior to today; is that right?
A. You know, when I saw this just now I wasn't sure that I had seen this. I may have done, but, anyway, I can understand where it comes from.
Q. It mentions "RAD Strategy Meeting Minutes."
Do you know what RAD refers to?
A. Regulatory affairs department.
Q. And what is the regulator [sic] affairs

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department at Syngenta?
A. As it says on the tin, it's a department that deals with regulatory issues.
Q. Is that global regulatory issues?
A. I'm not quite sure at this particular time because we're talking about 2000, so it's just after Syngenta was formed, whether this was the European regulatory affairs department or whether it was the US one.
This is -- I'm not absolutely clear about that.
Q. You mentioned there was a separate committee in the United States to determine whether or not information should be submitted to the US regulatory agencies. Was the same true with respect to other countries?
A. Yes, that's right. So there was certainly, and still is, a process, which can be via committee, to look at referability in other countries.
Q. Okay. Now, the RAD, regulatory affairs department, strategy minutes, did consider the four-hour inhalation study that we've been discussing, right?
A. Yes.
Q. And it begins:

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"Europe would like to develop a reduced-strength formulation [...] to avoid labeling as toxic or very toxic based on long-term effects."
Right?
A. Yes.
Q. And you're aware of that?
A. Yes.
Q. Later on, it notes -- the study says that:
"It should be noted that the 200..."
Is that grams per liter?
A. It is.
Q. "... SL formulation contains surfactants (Agral)."
So that's a formulation of paraquat with surfactants, right?
A. Yes.
Q. "... and these may have a bearing on the tox profile."
"These" being the surfactants, right?
A. Yes.
Q. Now, the regulatory affairs department, is that made up of regulatory people within the United States?
A. Largely, yes.
Q. Are there toxicologists on the regulatory

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affairs department?
A. There certainly were at some point in time, yes.
Q. Were you on the regulatory affairs department at this time?
A. No.
Q. Do you know whether or not the senior scientists who were on the PRF Committee were on the regulatory affairs department?
MR. NARESH: At the time?
BY MR. DICKENS:
Q. At the time.
A. I don't know who exactly was on the -- I mean, let's assume that this was actually a US committee. I can't tell you, in 2000, exactly who those people were but there would certainly be some senior people in the regulatory affairs department.
Q. And the third paragraph states:
"The meeting considered that the study did not provide clear evidence of a paraquat-related effect."
Right?
A. Yes.
Q. That being the four-hour inhalation study?
A. That's the one we've just been talking

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about.
Q. The one that the senior group of scientists at Syngenta said was treatment related, right?
A. Treatment related, yes. This is actually specifically saying is it related to paraquat, and I think I've just answered that question: that this study itself, it wasn't really possible to determine whether those effects were due to paraquat or Agral, or a combination of the two, or to some other reason. So this committee obviously thought you can't say this is down to paraquat.
Q. The study's purpose was to determine inhalation toxicity of the end-use product being sprayed by farmers, right?
A. Yes.
Q. And that treatment, the end-use product is what resulted in the related effect of the death of an animal at a low concentration, right?
A. That's correct, but essentially for unknown reasons. We still don't understand that study.
Q. And no efforts were undertaken further to understand that study?
A. I don't believe so, and that's potentially

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because that particular formulation was not actually further developed. But I don't know precisely if that's true.
Q. Was the 200 gram per liter SL formulation different in any way than the formulation on the market in the United States at this time?
MR. NARESH: Objection; foundation, scope.
THE WITNESS: I don't know. I'd have to look at more detailed information to make -- to answer that question.
BY MR. DICKENS:
Q. It says:
"It does not appear that the findings meet the criteria for submission as a PRF given that the single mortality at one exposure concentration of 0.15 microgram per liter does not alter the existing classification of this formulation."
A. Mmm. Yeah.
Q. Do you see that?
A. Yes.
Q. Now, this is in direct contradiction to the findings of the PRF committee, right?
A. No, not really, because the -- when you actually translate what we've just been talking about into what the US committee does, and, actually, more

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important, what the US EPA does, what the US EPA wants these referable findings for largely is does this information have a bearing on our assessment of -- risk assessment of a substance, of a product. And that could include things like classification, and that will be true of other legislation, including Europe.

So I think the judgment here is that in spite of that, and in spite of not knowing whether it's due to paraquat or not, it wouldn't change, if you like, the risk profile of that formulation.

Q. That was a decision that the regulatory affairs department at Syngenta made, right?

A. That's right, yes.

Q. The EPA was not afforded the ability to make that determination on its own?

A. If it was not submitted, that would be the case.

Q. Do you know whether or not it was submitted?

MR. NARESH: Again, scope.

I believe these questions were asked of Mr. Dixon.

MR. TRAVERS: We might want to go off the record because we did a supplemental Notice of Dep.

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MR. DICKENS: Okay.

MR. NARESH: Well, his answer may be "I don't know," so --

MR. DICKENS: Okay.

MR. NARESH: -- I don't know what --

MR. DICKENS: Right.

MR. NARESH: -- his answer is on this, so we -- why don't --

MR. DICKENS: Yes.

MR. NARESH: -- you ask your question again, answer it, and then we'll see where we are.

BY MR. DICKENS:

Q. Do you know whether or not the study was submitted to the US EPA?

A. I don't know personally.

Q. The PRF Committee did find that it met the criteria for submission as a PRF?

MR. NARESH: Objection; asked and answered.

THE WITNESS: The Approach Committee did, yes.

BY MR. DICKENS:

Q. Do you know whether or not the US 6(A)(2) or PRF Committee considered this study?

A. Well, I'm saying, I'm wondering if this is

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actually the minute of their discussion or whether this is a minute of the European equivalent of that committee. That's not entirely clear to me.

Q. Okay. This committee found that:

"... the findings would not be referred to either in the US or Europe..."

Right?

A. Yes.

Q. So that was a determination by some committee that not only would it not be referred in the US, but it also wouldn't be referred in Europe, right?

A. Yes.

Q. Would that be a finding that the US 6(A)(2) or PRF Committee would make as to whether or not it would be referred in Europe?

MR. NARESH: Objection to scope, foundation.

THE WITNESS: No. The way in which this worked, as I understood it, was, and certainly during most of the time that I was on the PRF Committee, is that the US committee, PRF Committee, would essentially make their own decision based on their -- on the 682 regulations in the US.

There will be a separate process to look

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at referability elsewhere in the world. This almost looks like it's been mixed up, which I -- is somewhat unusual.

BY MR. DICKENS:

Q. Unusual in the process in which this particular issue was handled?

A. Well, unusual in the way in which it's been dealt with, because RAD does sound to me like it's the European regulatory affairs department, but I don't know for sure. And to actually say "it would not be referred either in the USA or Europe at this time," that's not what I've -- that's not been my experience generally, that they would be separate decisions.

Q. It says:

"CTL will be informed of this conclusion..."

That's the toxicologists?

A. Yes, we would always get feedback from these committees in order to -- just out of courtesy, just so we know what's happened to our recommendation.

Q. So feedback from the regulatory people?

A. Feedback from the -- yeah, from the PRF committees, mostly in the United States.

Q. So the committee who made this ultimate

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decision, whether it's the RAD or the PRF Committee, they would give feedback as to the design of the study to the inhalation toxicologists who conducted the study?

A. No, they would give feedback on whether or not they decided it, in their view, met the applicable reporting criteria in whatever region we're talking about and the reasons for that.

In the vast majority of cases, they agreed with the recommendation. In some, they might disagree, and here is an example of the latter.

Q. They did more in this instance, though, didn't they? They indicated that "further work to better understand the finding" would be needed and expressed concern about the study design."

Right?

MR. NARESH: Objection to form.

THE WITNESS: Sure, there's a much more detailed commentary on this than would normally have happened.

BY MR. DICKENS:

Q. So the regulatory department's making or expressing concerns about Dr. Kilgour's study design for inhalation toxicology study?

A. Well, you could interpret it that way and

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I don't think Dr. Kilgour would disagree because it was a preliminary study and, under normal circumstances, that might lead to another study where some of those issues would be addressed.

Q. You can put that away.

MR. NARESH: Can you make a representation about any of the metadata surrounding Exhibit 27: dates, custodians, anything like that?

MR. TRAVERS: Give me a second.

MR. NARESH: Just so we have something on the record on that.

MR. TRAVERS: Yeah.

MR. NARESH: I suspect the dates because --

MR. TRAVERS: July 24, 2001, Andy Cook's the custodian --

(Stenographer clarification.)

MR. TRAVERS: The document's metadata says it's dated July 24, 2001 and the custodian is Andy Cook.

THE STENOGRAPHER: Thanks.

THE WITNESS: We're talking about that document?

MR. NARESH: This one.

THE WITNESS: Right.

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MR. DICKENS: I'll go ahead and mark Exhibit 28 for the record.

(Exhibit 28 marked for identification.)

BY MR. DICKENS:

Q. Doctor, these are minutes and actions from an inhalation exposure meeting at CTL on April 12, 2001.

Do you see that?

A. Yes.

Q. Joanne Kilgour is in attendance?

A. Yes.

Q. The others are other toxicologists at Syngenta, correct?

A. They are. Apart from Sonia Ellis, I should say, by the way. Excuse me. Sonia Ellis was in the regulatory department.

Q. Okay. Okay. If we can turn to page 6 -- sorry, page 2, number 6.

Number 5, first of all, is "Review of spray strength data to check consistency."

Do you see that?

A. Yes.

Q. And there were studies done on diquat, right?

A. Yes.

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Q. And the study design, the same as paraquat, "although in this case a Reglone formulation was used."

Right?

A. Reglone is diquat.

Q. Okay. And Agral was added, correct?

A. That seems to be the case.

Q. And it says "What are the consequences for paraquat?"

Right?

A. Yes.

Q. And then, in the second action item, it's:

"... evaluate risk of doing a study to reinforce arguments."

Do you see that?

A. Yes.

Q. It states:

"It was agreed at the previous meeting that Agral is likely to have an adverse effect on any testing and [won't] be included."

Right?

A. Yes.

Q. So any further testing with respect to inhalation toxicity with paraquat would not include Agral because it would increase the adverse effects?

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A. Yes. And I -- what I don't know, but one would normally expect, is that that might therefore mean that Agral would not necessarily therefore be appearing in commercialized product.

Q. Yet it wouldn't appear in commercialized product because of the increased toxicity, so we'll just have the farmers add it in later, right?

MR. NARESH: Objection to form, foundation.

THE WITNESS: Well, I think that's a kind of an information trail which I would need more information on. I honestly don't know what has happened, or what happened and what has ever happened to the addition of Agral.

BY MR. DICKENS:

Q. Do you have any reason to believe Agral would act any different than any other non-ionic surfactant?

A. Well, non-ionic surfactants are not all the same, so inevitably you might expect there to be differences in their ability to do their job to act as a surfactant and, potentially, therefore in the effect they may have on toxicity.

Q. Has Syngenta ever conducted toxicity studies on multiple surfactants to determine which is

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the safest of the non-ionic surfactants when added with paraquat?

A. I'm not aware of, if you like, almost a systematic study which says, you know, here's a big bunch of non-ionic surfactants and here's what they all do. I think it's been much more directed towards we believe that we would like to add this to a formulation and we need to do an assessment of toxicity.

(Background interruption.)

MR. DICKENS: Brian, can you go on mute?

MR. NARESH: Let's go off the record. Let's go off the record for a minute.

MR. DICKENS: I think he got it.

All right. We'll go ahead and mark 29 for the record.

(Exhibit 29 marked for identification.)

MR. DICKENS: 29 is still within topic 6 of the Notice of Deposition. These are minutes from an inhalation exposure meeting, August 15, 2001, so several months after the last one.

BY MR. DICKENS:

Q. Do you see that?

A. Yes.

Q. And, once again, Joanne Kilgour, as well

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as other toxicologists, are present?

A. That's right.

Q. And then there's a section towards the end of page 1 that begins "Agral."

Do you see that?

A. I do.

Q. And it was judged that:

"... Agral (a wetter) is very likely to contribute to enhanced inhalation toxicity of paraquat..."

Do you see that?

A. Yes. To be clear, the second clause is important. So that wasn't based on that study that we were talking about earlier; it's a read-across from the fact that it has got greater irritancy to the eye.

Q. Certainly, Joanne Kilgour and the others would have been aware of the previous study, right? Sorry, the four-hour inhalation study conducted with paraquat and Agral?

A. Of course.

Q. "Its surfactant properties may also contribute directly to increased absorption."

Right?

A. Indeed. That's as we've been saying throughout this afternoon.

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Q. So the toxicologists at Syngenta believed that Agral, or the non-ionic surfactant, will enhance both the absorption as well as the inhalation toxicity of paraquat, based on the information that they had at the time?

A. Yeah, they've done a weight of the evidence to come to that conclusion.

Q. The next section's with respect to additional tests, and the last sentence:

"Given the high risk of doing further testing..."

And this is high risk of doing further testing with paraquat and Agral, right?

A. Right.

Q. "... it was agreed that the present strategy..."

Is that the Pauluhn approach?

A. Pauluhn, yes.

Q. What is the Pauluhn approach, if you know?

A. All I know is that Pauluhn was a very well-respected inhalation toxicologist and he had approaches for assessing the safety of materials. I'm not a deep technical expert in that area.

Q. "... the present strategy ([using] Pauluhn

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approach [...]) should be pursued in the first instance."
Right?
A. Yes.
Q. Let me turn to the next page, at the very bottom, "Draft Presentation on Classification for Inhalation Toxicity."
Right?
A. Yes.
Q. The second paragraph mentions the weakness for the Pauluhn approach, right?
A. Yeah.
Q. And that's cases where a.i. -- do you know what a.i. is referring to?
A. The active ingredient, so paraquat in this case.
Q. So where paraquat "exerts its toxic effect systemically."
What do you understand exerting toxic effects systemically is referring to?
MR. NARESH: Objection to form.
THE WITNESS: It means that the principal toxicity is one which comes from exposure through, essentially, the blood supply, so hence affecting other organs, whereas in the case I think what Pauluhn

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was talking about was substances which only had toxicity locally in the respiratory tract.
BY MR. DICKENS:
Q. Paraquat exerts its toxic effect systemically, right?
A. Yes, and locally.
Q. And so the Pauluhn theory would not be used in -- where the active ingredient, paraquat in this instance, would incur --
(Stenographer interjection.)
BY MR. DICKENS:
Q. Yeah. The Pauluhn theory would not be used for active ingredients like paraquat which exert its toxic effect systemically, right?
A. That's what they were recommending, yes.
Q. Do you know whether or not they used the Pauluhn approach for paraquat for inhalation toxicity?
A. I've not seen anything one way or the other on that. No, I don't know.
Q. Well, do you know whether or not a four-hour acute inhalation study was conducted by Syngenta on paraquat without Agral?
A. There were, you know, quite a number of four-hour acute inhalation studies done on paraquat formulations, and many of them would not have had

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Agral.
MR. DICKENS: Can we go off the record for a minute.
THE VIDEOGRAPHER: We are going off the record at 14:53.
(Off the record.)
THE VIDEOGRAPHER: We are back on the record at 14:57.
BY MR. DICKENS:
Q. Now, by the time of the four-hour acute inhalation study with paraquat and Agral we looked at, Syngenta was aware of reports of deaths following inhalation exposure to paraquat, right?
A. There were some reports, yes.
Q. And those reports included autopsies or postmortem reports as well, right?
A. Yes.
Q. And there were individuals -- or strike that.
MR. DICKENS: Why don't we just go ahead and mark Exhibit 30 for the record and I'll do 31 right behind it.
(Exhibit 30 marked for identification.)
(Exhibit 31 marked for identification.)
///

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BY MR. DICKENS:
Q. Let me know when you're ready.
A. Do you want me to look at both documents?
Q. I can start with 30 and then we'll move on to 31.
Exhibit 30 is a coroner's report, dated January 19, 1973 involving the death of an individual exposed to paraquat, right?
A. Yes, that's correct.
Q. Okay. And there was a premortem urine sample as well as a postmortem urine sample, correct?
A. Yes, that's right.
Q. And both of those urine samples showed paraquat in the urine of this particular individual?
A. Yes.
Q. And the death in the opinion was secondary to paraquat poisoning, at the bottom of page 1?
A. Yes, that's right.
Q. And that was signed by the coroner, a P.J. Bofin, right?
A. Correct.
Q. P.J. Bofin, the coroner, determined that the death was the result of inhalation exposure of paraquat?
A. Yes.

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MR. NARESH: I'm sorry to interrupt. Which topic are we in?
MR. DICKENS: 17.
THE WITNESS: Actually, just to correct myself, if I may, I'm just looking for where the coroner said it was definitely due to inhalation exposure to paraquat. He certainly says it was due to paraquat poisoning.
BY MR. DICKENS:
Q. Okay. Why don't we look at Exhibit 31. That might be able to help. 31 is a report from a visit to Ireland, February 28, 1973, right?
A. Yes.
Q. And it's A.W., is that Waitt?
A. A.W. Waitt, I -- yes, I don't know A.W. Waitt, but that's probably how it's pronounced.
Q. The visit was on February 28, 1973 but the report was drafted in March of 1973, right?
A. Yes.
Q. It was circulated to individuals, including Dr. Swan who we discussed earlier, right?
A. Yes. Yes.
(Stenographer interjection.)
BY MR. DICKENS:
Q. The purpose of the visit to Ireland was

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specific to the report of the death in the individual we looked at in Exhibit 30, correct?
A. Yes, it was.
Q. And the introduction states:
"... a verdict of paraquat poisoning as a result of inhaling the spray solution was brought by Dr. Bofin, the coroner in Dublin."
Right?
A. Yes, and I do remember that from reading these documents before and the reason for my correcting myself is that I'm still not sure from the autopsy report as to whether he was convinced that it was due to inhalation exposure. But that's what the record shows.
Q. Now, the purpose of this visit, ICI/Syngenta informed the coroner, as well as the head of the Poisons Information Centre in Ireland, that deaths could not result from inhalation of paraquat spray, right?
A. I think that there was a surprise in -- if that was the explanation, yes.
Q. "Dr. Woodcock," it mentions, "was not convinced that death could not result from the inhalation of paraquat spray and [...] expressed persisting doubts about the safety of the agricultural

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use of paraquat and encouraged ICI to do more work."
Do you see that?
A. Yes.
Q. And the purpose of sending someone out was to discuss paraquat with Dr. Bofin and Dr. Woodcock in an attempt to convince them that deaths could not result from paraquat inhalation, right?
A. I think it was rather like I'm doing now, to try and understand the strength of evidence that that was the cause of death.
Q. If you can turn to the next page, page 305, there's a meeting with Dr. Bofin.
Do you see that?
A. Yes.
Q. Dr. Swan explains -- so Dr. Swan accompanied or was on this visit from ICI, right?
A. Yes.
Q. And he explained the background of the visit and their intention "to carry out a demonstration to confirm earlier work that paraquat sprays were of no significant hazard."
Do you see that?
A. Yes.
Q. Was it Syngenta's position at this time in 1973 that paraquat sprays presented no significant

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hazard to users or farmers?
A. The view at this time was because of the size of the particles that are produced during paraquat spraying were very unlikely to achieve the systemic exposure that will be required to cause, in this case, a tragic death.
Q. And so that's referring to the respirable particles, right?
A. That's correct, yes.
Q. And so Syngenta's position was that because the particles were too large, they could not reach the lungs?
A. That was the position, yes.
Q. There's a difference between the respirable particles and particles that can be breathed in either intranasally or through the mouth, correct?
A. Yes, and those are described as inhalable.
Q. And those inhalable particles can cause toxic effects even if they don't reach the lungs?
A. They can cause local toxicity, yes.
Q. Nosebleeds and the such?
A. That's right.
Q. Now, do you have an understanding that intranasal or inhalable particles of paraquat can

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reach the brain in areas outside of the blood-brain barrier?
A. Well, we are now into the hypothetical because, again, theoretically, yes, because there is a direct route from the nose into the olfactory bulb in the brain, but, again, in terms of causing toxicity, that would depend on how much and for how long and so on.
So it's theoretically possible, but there was no direct evidence that it actually happened in practice with people who were using paraquat in its -- in the normal agronomic way.
Q. We've looked at the first page, Dr. Woodcock expressed doubts and encouraged ICI to do more work.
Do you know whether or not ICI did any work with respect to inhalation toxicity as a result of this report of a death in 1973?
A. I can't give you a direct link, as I sit here, between this incident and any further studies that were done. All I can say is that we continued to look at the toxicity of paraquat, including by the inhalation route, over a period of time beyond this.
Q. Now, regulatory agencies have expressed concerns about toxicity of exposure to the larger

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non-respirable particles of paraquat, right?
MR. NARESH: Objection; form, scope, foundation.
THE WITNESS: Yes.
BY MR. DICKENS:
Q. And that includes the US EPA?
A. Questions have been asked, yes.
Q. And you saw documents to that effect in preparation for today's deposition, right?
A. Yes, indeed.
Q. And you saw statements from the US EPA concerned that those non-respirable particles could result in chronic toxicity?
A. I'd need to be reminded exactly how they put that, so maybe you can help me with a document.
MR. DICKENS: Why don't I start with an earlier report. I'll go ahead and mark Exhibit 32 for the record.
(Exhibit 32 marked for identification.)
MR. DICKENS: For the record, this is identified in topic 5 of the Notice of Deposition.
BY MR. DICKENS:
Q. Dr. Botham, this is a document from the -- Health and Welfare Canada, dated October 23, 1989.
And do you understand specifically it is

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the head of reassessment division; do you see that?
A. That's right, yes, Dr. Riedel.
Q. And you understand this is the regulatory agency for Canada?
A. Yes.
Q. And at this time, paraquat formulations were registered for market and sale in Canada?
A. Yes.
Q. And in the first section, it references some acute and short-term inhalation studies.
Do you see that?
A. I do.
Q. And those studies that are listed, do you understand those studies to have been done on paraquat itself without a surfactant?
A. Yes, I think so.
Q. Now, it mentions:
"... Chipman submitted an acute inhalation toxicity study in the rat, May 30, 1988."
Right?
A. Yes.
Q. Do you know what they're referring to for "Chipman," as submitting an acute inhalation toxicity study?
A. Do you mean --

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Q. Like, who is Chipman --
A. Yeah. Well --
Q. -- I guess is the easy way to ask it?
A. -- I think my understanding is that Chipman was, essentially, the ICI Canada commercial organization.
Q. And the second page in the middle, there's a paragraph beginning, "The above comments..."
Do you see that?
A. Yes.
Q. "The above comments indicate that toxic effects resulting from an acute exposure may be underestimated from this study. However, signs of respiratory distress, neurotoxicity and damage to lung tissue were evident in the rats exposed to the low nominal exposure level of 0.185 micrograms per liter [in the] air."
Do you see that?
A. I do.
Q. Now, Health Canada is reporting -- Syngenta, first of all, would have received a copy of this letter back in the 1989 time frame, right?
A. Yes.
Q. And it's being reported that inhalation toxicity study -- and this was an inhalation toxicity

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that was submitted by another company or ICI?
A. Right, yes.
Q. Is it ICI?
A. It is I- -- it's another comp- -- I don't know whether it was owned by ICI, but, yeah, certainly very closely associated with ICI.
Q. It's within the Syngenta realm?
A. Exactly, yeah, yeah, yeah.
Q. So Syngenta submitted an inhalation study and the Health Canada regulatory agencies are saying there were signs of neurotoxicity in the rats with a low nominal exposure level, right?
A. That's what they said, yes.
Q. And that exposure level is right around what we saw in the four-hour acute inhalation study, correct?
A. Yes, and just to point out that this acute inhalation study was not, if you like, a standard acute inhalation study. So on the first page it says that this study was done to simulate practical use exposure level, so it wasn't trying to stress the system to do a medium lethal concentration as you would normally do.
Q. And even at that practical-use exposure levels, there were signs of neurotoxicity, right?

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A. Yes. I would need to have a look again at the report to see precisely what they meant by that because neurotoxicity can mean many different things.
Q. But certainly someone within Syngenta underlined neurotoxicity in this particular document, right?
MR. NARESH: Objection; foundation.
THE WITNESS: I don't know if it was somebody from Syngenta, but somebody's underlined it.
BY MR. DICKENS:
Q. This document actually refers to the "invalidated IBT studies," right?
A. Yes.
Q. Turn to the next page.
A. Mmm-hmm.
Q. Health Canada mentions:
"These studies are not considered adequate by present standards..."
And there's a toxicology data gap for short-term inhalation toxicity.
Right?
A. Yes.
Q. It mention that there was an 80 percent mortality over 14 days in one group of rats after a single exposure to 1 microgram per liter in the air.

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Right?
A. Well, that was in the repeat-dose study, I assume, was it? It occurred over 14 days in one group of rats -- oh, no, after single exposure, excuse me.
No, sorry, it was a delayed toxicity. Right.
Q. "Delayed toxicity" meaning toxicity that occurs after some time?
A. Yes.
Q. And paraquat is known to result in delayed toxicity, correct?
A. Yes.
Q. "The above information indicates that very low concentrations of paraquat aerosols may result in irritation and damage to the lungs, and that respiratory protective equipment should be worn when paraquat is applied in the form of sprays."
Do you see that?
A. I do.
Q. Now, in 1989, Syngenta was not warning farmers or other users to wear respiratory protective equipment, right?
A. Well, this is something that I discussed with Mr. Dixon, and I don't -- I've not got

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immediately to hand here, but there were certainly periods of time when we were recommending respiratory protection. I just don't have that date window at my fingertips.
Q. And when you say "respiratory protection," does that include a dust mask or a fabric mask?
A. An appropriate NIOSH-approved mask.
Q. And that could just be a fabric mask, right?
A. I'm not an expert in that, so I wouldn't know exactly what the constitution would be.
MR. DICKENS: I'll hand you what we will mark as Exhibit 33.
(Exhibit 33 marked for identification.)
MR. DICKENS: 33 is a memorandum from the EPA to Syngenta.
BY MR. DICKENS:
Q. Is that right?
A. Yeah -- this was from the Health Effects Division branch to another person in Health Effects Division, so this looks more like an internal memo.
Q. You're right and I apologize for that. So this is an internal memo on a review of paraquat incident reports for inhalation, right?
A. That's correct.

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Q. And Syngenta would have received a copy of this report that was internal, this memorandum prepared by the EPA at some point in time, correct?
A. That would seem to be the case, yes.
Q. And the date of the report is August 10, 2000?
A. Yes.
Q. If we can turn to the last page, page 8.
MR. NARESH: This is topic 17?
MR. DICKENS: Sorry. This is 17, correct.
BY MR. DICKENS:
Q. And in the conclusion, the EPA, after their review of paraquat incident reports and inhalation, note that:
"... Wessling and NIOSH reports suggest that large droplets that could get into the nasal mucosa may pose a serious hazard."
That's what the EPA is finding, right?
A. That's right, that's what it says.
Q. And:
"These droplets may be swallowed or absorbed across the nasal membrane."
Correct?
A. Yes.
Q. "Nasal exposure to non-respirable droplets

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could cause serious and perhaps fatal poisoning by paraquat."
Do you see that?
A. Yes.
Q. And this was reported to Syngenta in the year 2000, correct?
A. Yes.
Q. And is that a statement that Syngenta agrees with, that non-respirable droplets of paraquat could cause serious and perhaps fatal poisoning?
A. I think it was -- really, the data speaks for itself. The evidence is that in relatively rare cases this can happen and so it was a reinforcement of the need for further personal protective equipment, this tied to the respiratory tract.
Q. And that respiratory equipment was meant to prevent exposure from inhalation to farmers and other users of paraquat?
A. Yes.
MR. DICKENS: Keep going. I'll hand you Exhibit 34 for the record.
(Exhibit 34 marked for identification.)
MR. DICKENS: For the record, this is on topic 63 within the Notice of Deposition.
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BY MR. DICKENS:
Q. This is a multiple email chain produced by Syngenta in the litigation. I will start at the bottom, from Barry Elliott to Nick Sturgess, dated August 5, 2005.
Do you see that?
A. Yeah.
Q. And this is referencing Defra, correct?
A. That's right.
Q. And that's the report that you mentioned earlier in the deposition, that you had reached out to someone for further information; is that correct?
A. That's right, yes.
Q. And Defra had conducted a study investigating paraquat?
A. Yes. To be accurate, and this was probably true at this time, 2005, they were looking to place a contract which could include doing some studies which would involve exposing animals to paraquat, including by the intranasal route.
Q. Now, at this point in 2005, Defra was proposing this work. Had Syngenta ever undertaken studies to investigate the effect of paraquat through the intranasal route?
A. Not of -- no, we had not, no.

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Q. Certainly, Syngenta had the capabilities prior to 2005 to have undertaken a study investigating paraquat through the intranasal route?
A. We had the technical capability, yes.
Q. And there's a highlighted section from Defra related to possible entry into the brain via the olfactory bulb.
Do you see that?
A. Yes.
Q. And the olfactory bulb, that's the upper part of the nasal cavity?
A. Yes, and it is, as I said earlier, a potential route of entry into the brain which doesn't involve going through the blood-brain barrier.
Q. As Defra states:
"'Chemicals could [...] enter the brain without having to cross the blood-brain barrier.'"
Right?
A. Yes.
Q. And then on the top of the page, Nick Sturgess responds on that same day, and Nick Sturgess -- who is Nick Sturgess?
A. Nick Sturgess was our neurotoxicologist.
Q. So you say he is the neuro- -- was he the only neurotoxicologist with Syngenta at the time?

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A. At the time, I think yes, because the previous neurotoxicologist was Dr. Widdowson. I think Dr. Widdowson had left by that time.

Q. The second paragraph begins -- in the second paragraph:

"Having read through some of the information provided by Paul..."

And you understand that to be Paul Hext?

A. Yes, Paul Hext.

Q. And Paul Hext is an inhalation toxicologist?

A. Yes, he was the senior inhalation toxicologist.

Q. The neurotoxicologist, Nick Sturgess, at Syngenta, said:

"... my opinion is that there certainly is a potential for paraquat to be transported to the olfactory bulb if the nasal mucosal epithelium comes into contact with paraquat."

Right?

A. Yes.

Q. And the way the nasal mucosal epithelium would come into contact with paraquat is through intranasal exposure?

A. Yes.

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Q. Breathing it in?

A. Right, although let me just clarify there. When -- for example, here, there's a description of intranasal administration; again, that is an exaggerated way of applying a substance. It's not like you're asking the animals to breathe in naturally into the nose. You're actually, essentially, pushing a substance intranasally, so it gives exaggerated exposure compared to what human beings might be exposed to.

Q. But that is the accepted method of undertaking an intranasal exposure study, right?

A. It is, but it's rather like things like intraperitoneal exposure; it's accepted but it's also accepted to be not a physiological mechanism of exposure, if you like. It's an exaggerated exposure.

Q. And is it on that basis why Syngenta has never undertaken an intranasal exposure study involving paraquat?

A. I would say it was one reason, in that we didn't feel that an intranasal study was going to give any further information about actual human risk from exposure to paraquat and, also, you know, we were beginning at that time to do experiments using other routes of exposure.

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When we learned that Defra might be doing this, we -- it was another reason to say, well, let's see what they find. I mean, we -- there's no point in duplicating that kind of work.

Q. Okay. And do you know what they did find, Defra?

A. I don't believe they ever did such a study and that's why I looked at the record that I was telling you about before. So they ended up doing a lot of kinetic modeling and predicting what might happen had they done such a study, but from what I can gather, they never actually commissioned or did an intranasal toxicity study.

Q. Didn't you say earlier in the deposition that kinetic modeling could be as accurate if not more accurate than direct measurements?

A. It can be, yes. Yes.

Q. So you understand -- do you know what the kinetic modeling undertaken by Defra found with respect to intranasal exposure to paraquat?

A. I've got their report, certainly, yes.

Q. What did they find?

A. I'd need to -- I've not brought the report into the -- it's a very thick report, actually, so we'd need to look at that outside.

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Q. You've reviewed that in preparation for today's deposition?

A. I did.

Q. Later on, Nick Sturgess says:

"The mechanism involved seems to be the transfer along the olfactory nerve pathway via some form of axonal transport, directly to the olfactory bulb in the brain, thereby circumventing the blood-brain barrier."

Right?

A. Yes.

Q. That's what the neurotoxicologist at Syngenta is reporting as of August 2005, correct?

A. And I think it was -- that was really taking the example of manganese, so he was saying this is how manganese may actually reach the brain. Because he says whether the same would have happened -- could happen with paraquat is open to debate.

Q. And the kinetics of this transport process would be quite rapid, within minutes following introduction into the nasal cavity.

Right? That's what's being reported?

A. Yes, again, but this is all built on the experience or understanding of what happened with manganese, so it's not known what could happen with

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paraquat.
Q. And not known because no studies had been done at this point in August --
A. Not at this site, no -- not of this sort, no.
Q. And, in fact, Nick Sturgess refers to:
"... the lack of definitive quantitative experimental data measuring olfactory bulb concentrations of paraquat following nasal exposure."
Right?
A. Yes.
Q. You can put that aside.
MR. DICKENS: I'll hand you Exhibit 35 for the record.
(Exhibit 35 marked for identification.)
MR. DICKENS: Exhibit 35 is more email correspondence produced by Syngenta in this litigation. For the record, it's topic 63 in the Notice of Deposition.
BY MR. DICKENS:
Q. Once again, this is an email chain that you reviewed prior to today's deposition, right, Doctor?
A. It is, yes.
Q. And beginning once again on the bottom

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email, this is from a Matthew Jacobsen to Nick Sturgess, subject "Olfactory lobe and paraquat entry," dated September 5, 2005, right?
A. Yes.
Q. Okay. It states:
"Nick, I've been thinking about this one."
Specifically olfactory lobe and paraquat entry, right?
A. Yes.
Q. And he discusses, at the very bottom, axonal transport of paraquat, right, and he says that it is possible in his opinion -- or if it's possible, sorry?
A. Yeah. Look, I mean, my reading of this email from Matt is, essentially, it's Matt thinking aloud or contemplating a number of different scenarios that could be possible and, you know, you also have to read it in the context of what Nick had said in the previous email, that when you then try and do the translation to whether this could happen with paraquat, as against manganese, you're talking about massive volumes of paraquat needing to be -- if you like, to enter through the nasal cavity.
So it was a theoretical discussion.
Q. You say massive amounts would need to go

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into the nasal cavity. Syngenta does not know that, however, because they'd never conducted a test as to how much would need to be ingested intranasally in order to lead to affects on the brain?
A. Well, absolute -- yes, we -- but, equally, we do know that the amount of paraquat that is inhaled is, generally speaking, very low.
So I think it was a reasonable hypothesis that there would be a very big margin of safety, if you wish, from the likely volumes or amount of paraquat that somebody spraying the product would be exposed to versus that that would actually kind of generate the transport of paraquat in the way in which is being described.
Q. You agree that intranasal exposure does occur?
A. Nasal exposure, yes, that's right.
Q. We began the deposition talking about the nosebleeds in the very early research studies, right?
A. Indeed.
Q. And nosebleeds are the most common adverse effect that have been reported with respect to paraquat?
A. I don't know if it's the most common, but it's certainly common.

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Q. And the evidence of nosebleeds itself is evidence that individuals, farmers and other users of paraquat are getting paraquat into the nasal regions, right?
A. Yes, but we're talking about the lower -- I mean, the nosebleeds are coming from the lower part of the nose, so they're not coming from up here into the olfactory bulb, so it's exposure to -- you know, basically where you can feel yourself.
Q. You can't say how much paraquat is getting into the upper regions or the olfactory bulb in a farmer or individual who has experienced a nosebleed, right?
A. I can't sit here and give you a number, certainly.
Q. It says:
"If axonal transport of paraquat is possible, then it could enter from cuts in the skin and reach the CNS."
Central nervous system, right?
A. It's what I said before: This is thinking aloud; it's highly speculative thoughts, the kind of things that researchers do when they're talking to each other. So I don't think this is based on Matt saying "I know that this could definitely happen,"

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particularly when we're talking about axonal transport.
Q. Who is Matt Jacobsen?
A. He's a pathologist.
Q. And he's a pathologist discussing paraquat entry through the olfactory lobe --
A. Yes.
(Stenographer clarification.)
MR. DICKENS: Sorry.
BY MR. DICKENS:
Q. He is a pathologist at Syngenta discussing paraquat entry into the olfactory lobe with the neurotoxicologist?
A. Yes.
Q. "... then it could enter from cuts in the skin and, and reach the CNS [...] via the peripheral nerves, or from the ophthalmic nerve from a splash in the eye. I [may] have a little dig on anatomy, time permitting."
Right? That's what he's reporting at this point?
A. Right. But all of this, to repeat, highly speculative to imagine that you would get the transport of paraquat through nerves in the way in which it's been described into the brain.

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Q. And you're saying it would be speculative. Nick Sturgess responds -- or, sorry, forwards Matt Jacobsen's email to Barry Elliott, right?
A. Yes.
Q. And who is Barry Elliott again?
A. Barry at that time was the project manager in CTL for paraquat.
Q. Okay. It says:
"Barry, I have the attached response from Matt re the olfactory transport to the brain issue."
Do you see that?
A. Yes, and he said "theoretically possible." I suppose he's saying, like me, of course all things are theoretically possible, but, I mean, my reading of this is that it's highly theoretical.
Q. He says "I have the attached response from Matt...," indicating that Matt was responding to an inquiry with respect to olfactory lobe and paraquat entry, right?
A. Yes, yes.
Q. So the neurotoxicologist and Barry Elliott specifically reached out to Matt Jacobsen for his viewpoint as to this particular issue?
A. I don't know exactly how it went, how that conversation or inquiry was made, but I can imagine --

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I believe at this time that Matt Jacobsen may have been on a technical team, together with Nick Sturgess and Barry Elliott, who were focused on paraquat. So it probably happened within the context of the discussions within that team.
Q. And you mention -- he said it's theoretical, correct?
A. Yes.
Q. But he said:
"If we are worried about our position on this, then it is possible to do some experiments as Matt describes."
Right?
A. I think that's an off-the-cuff view on how easy it would be to do such experiments, particularly if we're talking about transmission through the nervous system. I think they would be extremely difficult to do, in practice.
Q. Well, he doesn't say anything in his email about the ease of doing those experiments, right?
A. No.
Q. Or the cost of doing those experiments?
A. No.
Q. He does mention that the problem with doing such an experiment is that any positive finding

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would be reportable.
Right?
A. Of course, yes.
Q. And that's reportable to the regulatory agencies?
A. Yes.
Q. So Nick Sturgess doesn't say, "This would be such a hard study," or "I don't know what the results would show." He's saying, "If we do get a finding, we have to tell regulatory agencies"?
A. Yeah, sure.
MR. NARESH: Objection to form.
Go ahead.
THE WITNESS: Look, this is something which, again, you've got to have a sense of the context of why these discussions go on. Of course people were concerned about generating data which were potentially referable. But they also were having, at the same time, conversations about are these experiments really going to tell us about the risk from paraquat.
So reporting is just one element of that decision about whether it makes any sense whatsoever to invest in doing studies of this sort.
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BY MR. DICKENS:
Q. It says:
"... do we really want to go there?"
Right?
A. Mmm.
Q. "A negative, however, would put it to bed pretty well."
So Nick Sturgess is saying, "If we did do this study and it was negative, we wouldn't have to be worried about this issue," right?
A. Well, sure, but then of course you can never prove a negative, so even that might be an exaggerated statement.
MR. DICKENS: I'll move to strike everything after "Well, sure."
BY MR. DICKENS:
Q. Isn't the question of paraquat entry through the olfactory lobe a question that Syngenta would want answered?
A. I think that we are starting -- were starting, and continue now to this day, to say that that might be relevant if we really thought that paraquat does cause, under the conditions of exposure that farmers and growers are subjected to in their work, that that could be causative in Parkinson's

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disease.
We do not believe that to be the case, and so these kind of experiments are really not necessary in that situation.
Q. But as Nick Sturgess says, you could run a study and get the answer pretty easily, right?
A. You could do many studies and get the answer easily, but let me just -- although you struck the previous one, I would say, you know, you can do many experiments and you don't see an effect and people will say, yes, but you didn't do this, you didn't have a high enough concentration, you didn't use the right species.
So it's very difficult to know when you get a definitive negative answer.
Q. Has a intranasal study ever been done by Syngenta --
MR. NARESH: Objection; asked and answered.
BY MR. DICKENS:
Q. -- on paraquat?
A. No.
Q. Syngenta did, though, however, get price estimates for an intranasal study, right?
A. We did.

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Q. And price estimates to run the exact intranasal study to determine the amount of paraquat entry through the olfactory lobe, right?
A. The kinetic component was part of that, yes.
Q. And that was through WIL Research?
A. That would have been an option for us, yes. That's where we got one of the price estimates.
MR. DICKENS: I'll hand you Exhibit 36 for the record.
(Exhibit 36 marked for identification.)
MR. NARESH: What's the topic number?
MR. DICKENS: Good question. Topic 35.
MR. NARESH: Thank you.
BY MR. DICKENS:
Q. Doctor, I've handed you a document from Syngenta's production, dated July 17, 2008. "Study Title: Evaluation of the effect of intranasal administration of paraquat in the C57B16 mice."
Right?
A. Yes.
Q. And this is a quotation for a study by WIL Research Laboratories, right?
A. It is.
Q. And the objective:

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"To evaluate the neurochemical and histological effects of paraquat on male and female [mice] following intranasal administration."
Right?
A. Correct.
Q. And under this study, there would be some brain neurochemistry, correct?
A. Yes.
Q. And in this study, WIL Research gave a price quote of $667,000 to run this study, right?
A. Yes.
Q. At no point did they ever say, "We can't do this particular study"?
A. No, they didn't, no.
Q. This study would have included sectioning of the brains for striatum and substantia nigra --
A. Yeah --
Q. -- and review --
A. -- the histology, yes.
Q. Okay. So there would have been stereology as to the effect of paraquat on the substantia nigra within the mouse brains?
A. That was the intention, yes.
Q. Following intranasal administration?
A. That's right.

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Q. And this was specific to identify whether or not intranasal exposure would have neurotoxic risks, right?

A. Right. So, again, a sense of context because I did look at this again myself. So this quotation was asked for as a consequence of a -- discussions we'd been having in what was then known as the Health Science Team about a number of potential experiments that we might do.

The reason why we asked for this is -- I think pretty self-evident from the discussions we've just been having, because it is a genuine experimental option; however, we, again, at that particular time, were still under the assumption that the Defra contract would have requested such a study to be done.

So one reason -- not the only reason -- why we didn't go ahead with this is because we thought it might be duplicating what was being done somewhere else.

Q. Now, Syngenta had communications with Defra with respect to the study that they were doing on paraquat, right?

A. As much as we were able, with confidentiality and conflict of interest.

Q. And, certainly, Syngenta could have asked

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Defra what type of intranasal study were they contemplating, right?

A. We were very careful about the nature of our communications. There were some communications with them, but we were not having ongoing detailed dialogue about the details of -- and, in fact, to be fair, even Defra were -- when I had a discussion, a little bit unclear exactly what was being done by the successful winner of that contract, Exponent.

Q. No one at Syngenta ever asked anyone at Exponent or with Defra as to what type of intranasal administration study they were conducting?

A. I don't personally remember having that kind of conversation and, to reiterate, we needed to take some care about, you know, being perceived as trying to have some influence over what Exponent were doing because, you know, we may have been sitting here today and you'd have been showing me emails to say, you know, "Why did you have these discussions?"

Q. You were on the ACP panel at Defra overseeing the study, were you not?

A. Not overseeing the study. No, I was not on the ACP. That's the Advisory Committee on Pesticides. That's the regulatory advisory committee. I was on a group, a sort of shadow group to that,

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called the Medical and Toxicological Panel, which included people from industry.

That was the legitimate interaction that we could have from industry with Defra and with the advisory committee. So I was not involved at all in the contract and the output of that contract from Defra, other than knowing a little bit about it from time to time in the Medical and Toxicological Panel meetings.

Q. Okay. You provided peer-review comments as to the Exponent study?

A. I was asked to comment on that, yes.

Q. And when was that?

A. I can't remember the date. It was around about this kind of time. I don't have the exact year to hand.

Q. Do you know whether it was before or after July of 2008?

A. I'd need to be reminded. I know that there is an email with my report on it. I just haven't got the date to hand.

Q. And you gave peer-review comments. Did that include peer-review comments specific to the intranasal findings in the Defra study?

A. I don't think I did because I don't

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think -- no, I think, again, I would just need to look at that to remind myself. I think it was more to do with the study that was done on some of the stereological information.

Q. Syngenta notified WIL Research that they would not be moving forward with the intranasal study prior to Defra's study being made available, right?

A. This is the interesting thing here because the Defra study, you might argue, was never really made fully available. It was never properly externally published, so I got hold of a report because of the links that I was -- just described. There were two presentations made, posters. That's all that ever appeared from that project.

Q. Okay. And understanding it wasn't publicly available, it certainly was available to Syngenta, right?

A. Eventually, yes.

Q. And did Syngenta notify WIL Research they would not be going forward with the intranasal administration study before or after receiving the report internally from Defra?

A. I can't remember. I would need to see the chronology of this again. I didn't manage to put all that chronology together as preparation, so I'm sorry

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I can't give you an answer today.
Q. Has Syngenta reached out to WIL Research or any other contract research organization to do an intranasal administration study after receiving the Defra results?
A. Not that I'm aware of.
MR. DICKENS: Okay. Why don't we take a break.
THE VIDEOGRAPHER: We are going off the record at 15:48.
(Break taken.)
THE VIDEOGRAPHER: We are back on the record at 16:05.
MR. DICKENS: Dr. Botham, I'm going to hand you what we'll mark as Exhibit 37 for the record. This is Topic No. 102 in the Notice of Deposition.
(Exhibit 37 marked for identification.)
BY MR. DICKENS:
Q. This document are minutes from a meeting to discuss the possibility for a paraquat symposium at IHRL, meeting taking place October 7, 1971.
Is that right?
A. It is.
Q. This is a document you reviewed in preparation for today?

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A. It is.
Q. And it lists individuals who were present, right?
A. Yes.
Q. Who are these individuals, just generally?
A. Well, they are people from various parts of the ICI organization. Different divisions of ICI.
Q. Okay. And what type of divisions are represented?
A. Well, it looks like we've got a representation from what was then called Mond Division, which is kind of the bulk chemicals business of ICI, Plant Protection people from IHRL, the predecessor of CTL, and possibly others as well.
I don't know everybody who was on this list.
Q. And the meeting was called because, in the next paragraph:
"Last year it [was] suggested that a round-table discussion on paraquat should be held with all registration authorities."
And is it your understanding that refers to regulatory authorities?
A. Yes, indeed.
Q. And:

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"IHRL had since heard that an outside body was considering a paraquat symposium and thought it would be far better if such a move came from within ICI, and [...] would be a more effective means of getting the paraquat information over to the authorities."
Right?
A. Yes.
Q. So there was a discussion or consideration as to whether or not ICI should have a meeting with regulatory agencies to discuss paraquat?
A. Yes.
Q. And this was with respect to discussion as to the toxicity risks as well as benefits of paraquat?
A. Yes, that's right. The document goes into that further down.
Q. It notes:
"It has been requested by PPL..."
And that's -- who is that, PPL?
A. Plant Protection Limited.
Q. Okay. What was Plant Protection Limited's role in the overall ICI in comparison to IHRL?
A. So Plant Protection Limited was the commercial part of ICI involved in crop protection.
Q. So PPL was the marketing division, if you

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will?
A. Yes. It also had some regulatory and other functions, but, yes, principally marketing.
Q. Okay. So PPL, the commercial component, requested "the symposium be restricted to the European sphere" because:
"... dealings with the Americas, Australia and the Far East have been running smoothly to date."
Right?
A. Yes, that's what it says.
Q. And:
"Dr. Fletcher visualized the proceedings as running along the lines of a scientific symposium."
Right?
A. Yes, that's right.
Q. Okay. And then there are some advantages and disadvantages of having such a symposium, right?
A. Yes.
Q. I'll have you turn to the second page. On the second page is listed some of the disadvantages of actually having this symposium with the regulatory agencies, right?
A. Yes.
Q. Number 1 -- and your understanding from these minutes are these would have been disadvantages

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that would have been discussed at the minute -- or the meeting of the ICI individuals, right?
A. That would be my assumption, yes.
Q. And the disadvantages, number 1:
"Too many facts may be unearthed..."
And:
"... we would have to be prepared to give information freely and without reservation."
Do you see that?
A. I do.
Q. And that's what was reported as a disadvantage for meeting with the regulatory agencies in the symposium, correct?
A. Yes.
Q. Implication being that ICI would like to hold some information back with respect to paraquat at that point in time, right?
A. I really wouldn't like to say what the specific issues are that might have been of concern at that time. I think that would be very speculative.
Q. Number 3:
"In some cases, i.e., safer paraquat formulations it is not economic to consider further work in certain directions. If we are talking to academic people and minutes are within the reach of

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the general public, will these people understand this placing of economics before safety?"
Right?
A. Yes.
Q. That's what the minutes state as discussed at this ICI meeting in 1971, correct?
A. Yes.
Q. Would the public and others understand us as a company putting economics or profit over safety?
A. Yes, and it's -- I mean, I'm always, shall I say, disappointed when I see statements like that, recognizing that we are talking about more than 50 years ago now when we were in a different world. It's not -- it's certainly not the kind of statement that Syngenta would make today or would have made in my -- most of my working lifetime.
Q. You weren't with Syngenta or ICI at this point in time, correct?
A. I was not, no.
Q. And ICI was the predecessor of Syngenta, correct?
A. Yes.
Q. And this was indeed a statement that was in the minutes of a meeting from 1971?
A. Correct.

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Q. And ICI was the company that was responsible for the sale and marketing of paraquat in the United States as of October 7, 1971?
A. Yeah. Those windows of when it was ICI and when it was Chevron and when it was both, I just don't have those dates to hand, so -- but yes.
MR. DICKENS: I'll hand you what we'll mark as Exhibit 38.
(Exhibit 38 marked for identification.)
MR. DICKENS: This is topic 97 in the Notice of Deposition.
BY MR. DICKENS:
Q. This is a document dated May 18, 1966, from a Dr. Swan to a Dr. Toland at Chevron.
Do you see that?
A. Yes.
Q. And we've discussed Dr. Swan and his role, correct?
A. Yes.
Q. There's other individuals listed on the top, including a Dr. Boon?
A. Yes. I don't know these individuals, but, yes, Dr. Boon and Mr. Cronshey are from Plant Protection Limited that we were talking about before.
Q. And Dr. Swan, he's with ICI at this time,

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right?
A. That's correct.
Q. And he writes to Dr. Toland at Chevron and states:
"We are puzzled and concerned that you are considering changing the label for paraquat at this moment, when the present label has been agreed with the US authorities and in the petition which is filed with the US F&DA is now presumably under consideration."
Right?
A. Yes.
Q. "It seems to [ICI] that the introduction of skull and crossbones implies [...] a greater hazard than exists."
Correct?
A. Yes.
MR. NARESH: I'll just object to completeness.
BY MR. DICKENS:
Q. And so --
MR. NARESH: Go ahead.
BY MR. DICKENS:
Q. -- ICI, at this point in time, did not agree with a proposal by Chevron to change the label

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to include, among other things, a skull and crossbones, right?

A. Yeah, I mean, when I looked at this document, I think I came to the conclusion, particularly if you read it towards the end, so on page 3 where you've got the words that are underlined, Dr. Swan was not disagreeing that we shouldn't be warning people who are using this product, and, essentially, the language that's underlined is effectively what the skull and crossbones tell you.

So for some reason he was objecting to that pictogram of representing the hazard, and it may have been because at that time paraquat could have been out of line with other products.

I really don't know because this is way before my time.

Q. Dr. Swan indicates that there is:

"... no reason to make a major point of the oral toxicity of paraquat."

Right?

A. Well, he's saying that it's important that we do make sure that people understand that it can be fatal if swallowed. So I don't think that he's -- that's what he's saying on the last page, on page 3, so I don't think he's trying to dismiss oral toxicity.

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Q. On the last page, he does state his concern about a possible consequence and he says:

"It appears to us that the possible consequences of the step you are contemplating are serious and could well prejudice the attitude of the F&DA to the petition for paraquat which they are at present reviewing."

Right?

A. Yes.

Q. And that's petition for registration, as far as you know?

A. Well, I assume so, yes. My reading of this is that, at the time, Dr. Swan may have been advised or thought that the appearance of skull and crossbones could actually affect that registration.

Q. And you didn't -- Dr. Swan didn't, and ICI didn't, want to prejudice paraquat in the eyes of the F&DA, correct?

A. Well, that's the way it's been written, certainly.

Q. And you understand the F&DA at that time was the regulatory agency that was responsible for approving registrations for pesticides?

A. Yeah, because the EPA has not actually come to pass at that time.

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MR. DICKENS: Exhibit 39 for the record.

(Exhibit 39 marked for identification.)

MR. DICKENS: This is topic 95 within the Notice of Deposition.

BY MR. DICKENS:

Q. This is another letter from Dr. Swan, this time dated February 12, 1969, to the manager of research and development at Chevron.

A. Yes.

Q. Do you see that?

A. Yes.

Q. Now, it begins saying:

"[We have] learned from Dr. Dye..."

We have seen Dr. Dye's name before. He was an individual at Chevron responsible for regulatory matters, right?

A. Okay.

Q. It says:

"[We have] learned from Dr. Dye that our discussion with Dr. Hayes was successful to the extent that he has given up [a] threat to withdraw registration of 'Gramoxone' in return for stronger label warnings..."

Right?

A. Yes.

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Q. And that would probably include the skull and crossbones.

A. Yes.

Q. It notes that Hayes -- and your understanding is Dr. Hayes is with the F&DA?

A. That was my assumption.

Q. "... had been strongly influenced by the misrepresentations of the Cornell newsletter item."

Do you see that?

A. Yes.

Q. And then he goes on, at the bottom, to say he had an opportunity to read copies of Chevron releases on paraquat and diquat which were handed over at a meeting.

Correct?

A. Yes.

Q. And those documents were handed over July 25 and addressed to all marketing personnel, right?

A. Yes.

Q. Now, Chevron at this time was in charge of the marketing of paraquat within the United States?

A. Right.

Q. And, according to Dr. Swan, ICI did not believe that those marketing documents adequately

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bring out considerable distinction on the toxicity of paraquat and diquat.
Do you see that?
A. Yes, that's one of his concerns, yes.
Q. And one of those "grossly incorrect statements," according to Dr. Swan, was that:
"... hazards of spray mist makes no distinction between large particles which impact in the nose and smaller 'respirable' particles which can reach the lungs..."
A. Yes.
Q. "... and which are not produced by low-pressure spray equipment."
Right?
A. Yes.
Q. And as we saw later on, years later, in the year 2000, the EPA actually wrote a memorandum saying that those larger particles could be serious and indeed fatal, right?
A. Yes.
Q. Dr. Swan also takes issue with the statement:
"Paraquat can be absorbed through the skin and can cause delayed systemic reactions, including damage to the lungs.'"

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Do you see that?
A. Yes. And again --
Q. Now --
A. -- for a sense of context, we have to remember this was written in 1969 when, really, what we now understand about how paraquat can cause toxicity was not fully understood, so the damage to the lung, for example, is a great example of that, that the lung can be damaged because of systemic exposure. There was, I think, a period of time when people thought, well, that might happen because of inhalation exposure.
And so I think some of this has to be recognized as not being -- as being written at a time when there was kind of an incomplete understanding.
Q. Well, Chevron obviously believed there was enough information in order to arm its marketing personnel with those statements to bring to users and distributors of paraquat, right?
A. Mmm-hmm.
MR. NARESH: Objection to form, foundation.
BY MR. DICKENS:
Q. That's a yes?
A. Yes.

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Q. And we can agree that paraquat can cause delayed systemic reactions, right?
A. Yes, and those are the kind of things that I've been describing, but it's because when you get absorption from whatever route into the bloodstream, that the lung is the target organ and that is a delayed toxicity.
Q. And Dr. Swan takes issue with the statement that:
"Diluted paraquat presents a greater potential hazard than some herbicides in that [its] toxic effects are cumulative and delayed.'"
Right?
A. Yes.
Q. Dr. Swan does not believe that that information should be told to the public at this point in time?
A. That was his view at the time. I presume he was, as it says there, comparing with other pesticides which must have had, in his view, a more significant toxicological profile.
Q. Now, ICI knew at this time, or around this time, that paraquat could cause cumulative and delayed toxic effects, right?
A. That was the emerging information, yes.

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Q. And not -- emerging as in right around this time that he wrote this letter in February 12 of 1969?
A. Yes.
Q. Dr. Swan also knew at this time that cumulative and delayed toxic effects were different than other herbicides, right?
A. Yes, and that is what I was referring to earlier, in that we now understand why -- what was happening.
Q. Okay. But he understood that right around this time, well, within a month of writing this letter in 1969, right?
A. To some extent, yes, but, I mean, that, I think, is really sort of making my point: You know, it was still the -- what was happening with paraquat was really just beginning to be fully understood and making sure there was a shared understanding at around about this time.
Q. Well, shared understanding not with anyone outside of ICI or Chevron, as he's indicating that these statements should not be included in the documents handed to the marketing personnel responsible for marketing paraquat within the United States, correct?

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MR. NARESH: Objection; foundation, form.
THE WITNESS: I mean, look, again, we're talking about 50 years -- well, yes, 50-odd years ago. I can't comment on why that was seen to be the right thing to do at that time.
BY MR. DICKENS:
Q. He ends that paragraph by saying:
"... I strongly suggest that this particular document [...] not be given any further circulation."
Right?
A. Yes.
MR. DICKENS: Moving to Exhibit 40.
(Exhibit 40 marked for identification.)
MR. DICKENS: For the record, this is topic 18 within the deposition notice.
BY MR. DICKENS:
Q. This is an internal ICI document, dated March 11, 1969, "ICI Pilkington-Sullivan Works: Delayed Irritant Effects."
Do you see this?
A. I do.
Q. And this is, roughly, almost exactly one month from Dr. Swan's letter to Chevron telling him not to further circulate the marketing documents,

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right?
A. Absolutely, yes.
Q. And one of those reasons he said don't circulate it is the comparison to other herbicides and the fact -- or the statement that paraquat's toxic effects could be cumulative and delayed.
Right?
A. Yes.
Q. This document, internal ICI document, states:
"Paraquat is, however, different from most corrosive chemicals because its effects are not immediate."
Right?
A. Yes.
Q. That's what ICI is telling each other in this particular document, right?
A. Yes.
Q. Pretty much exactly what Chevron was planning to tell individuals who would be purchasing paraquat, right?
A. But a very different scenario. Here, we've got people who are actually -- excuse me, are involved in the production of paraquat, and so their likely exposure would be significantly higher.

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Q. So at this point in time in 1969, Chevron and Syngenta did not have a full understanding as to what amount of paraquat would cause toxic effects in humans, right?
MR. NARESH: Objection; foundation.
THE WITNESS: Quantitatively, I guess the answer to that is yes, but, obviously, I think it was clear that, you know, the more you're exposed the more likely it is you are to get exposure. We were talking about this earlier on; so when you've got exaggerated exposure because of wet clothing or your skin is damaged, then, clearly, you get more toxicity.
So in that sense it was understood, but there were still things of which we didn't know at this time.
BY MR. DICKENS:
Q. Okay. And, as you mentioned, the individuals who'd be working in the -- is it the manufacturing plant?
A. Yes. Yes.
Q. Okay. There was specific guidelines implemented for the individuals who would be exposed to paraquat within those manufacturing plants, right?
A. Yes.
Q. And these would be all employees of ICI?

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A. That, I presume, is correct, yes. They are talking about apprentices, so they would be employed.
Q. So all employees of ICI who would be exposed to paraquat:
"... must undergo a medical examination at Pilkington-Sullivan Works."
That's the manufacturing plant, right?
A. Yes.
Q. "... before they commence work."
Right?
A. Yes.
Q. And that was due to concerns about the potential toxic effects of paraquat?
A. From my understanding of this, it was to see if there might be people who could be more susceptible to what were then the known toxicities of paraquat because, for example, they had a tendency to have compromised skin, skin irritation, or they had a history of nosebleeds, because that might increase their -- the exposure to paraquat.
Q. And, in fact, the apprentices had experienced incidents of delayed irritant effects from paraquat?
A. Yes.

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Q. And there was a concern that these individuals may not recognize the risk because of the fact that those effects were indeed delayed.
Right?
A. That's the concern, yes.
Q. So the concern is these individuals who splashed themselves or may get paraquat on them may not really know that there's a risk there because they may not see an immediate reaction on their body to paraquat?
A. Yeah, you don't get -- like you would do from a caustic soda, you don't get the immediate "Ouch, must wash that off" reaction, necessarily.
Q. So it's important, then, to warn those individuals within ICI of those delayed irritant effects?
A. Indeed.
Q. But according to ICI, it is not important to warn the actual users or farmers of delayed irritant effects, correct?
A. But, again, I don't know from the time, but the exposure situations would be different, the concentrations of paraquat would be different.
You know, here, we're talking about concentrated paraquat and unfortunately, at that time,

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of course, occupational hygiene standards which are not the same as they are today.
Q. Well, we can agree that Chevron thought it was important to warn users and farmers about the delayed irritant effects of paraquat?
A. I agree there was clearly a debate going on between Chevron and ICI about what should be done about that, and the record shows that it wasn't -- there wasn't an immediate agreement about that fact.
Q. Now, ICI also required anyone exposed to paraquat to receive individual -- or receive special individual instruction on the hazards of paraquat, right?
A. Yes.
Q. Now, when paraquat was initially registered in the United States, it could be sold for residential use, right?
A. My understanding, again from discussions with Monty Dixon, is that we've never actually sold a product in the United States for residential use. So there may have been a registration, but it was never sold.
Q. Okay. And that's based on information told to you by Monty Dixon?
A. Yes.

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Q. Did you undertake any review of documents to confirm that?
A. I received a confirmatory document to that effect, but I've not gone back and double-checked that.
Q. Do you know whether or not Chevron did stop the circulation of their documents provided to marketing personnel?
A. I've got no idea, no.
MR. DICKENS: I'll hand you what we'll mark as Exhibit 41.
(Exhibit 41 marked for identification.)
MR. DICKENS: This is a document produced by Syngenta in this litigation, which is a letter from Dr. -- or from a D.F. Dye to T.W. Reed, dated April 23, 1969.
BY MR. DICKENS:
Q. Do you see that?
A. Yes.
Q. It's referencing Geigy. Correct?
A. Yes.
Q. Do you know what Geigy Agricultural Chemicals's relationship with respect to paraquat would have been at this time in 1969?
A. Sorry, I've got no idea, no.

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Q. Do you know whether or not Geigy was a manufacturer of atrazine at this time?
A. I don't know.
Q. This is reporting:
"We [...] discussed Geigy's attitude [towards] paraquat."
Do you see that?
A. Yes.
Q. "John said that Geigy felt that paraquat was a potentially hazardous chemical and they were not doing any research on this product."
Right?
A. Yes.
Q. "Their marketing people have been advised to not promote or encourage the use of paraquat in any way."
Right?
A. Yes.
Q. "He advised that Geigy is very conservative with [respect] to highly toxic or hazardous chemicals."
Correct?
A. Yes.
Q. And we agree, at this point in 1969, paraquat would be considered a highly toxic and

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hazardous chemical, right?
A. We understand -- we understood its toxicity, as we've just been describing, yes.
Q. In fact, the marketing people at Geigy sent out a notice to their salesmen telling them not to encourage the use of paraquat with any of Geigy's products.
Correct?
MR. NARESH: Objection; foundation.
THE WITNESS: That's what this letter says.
BY MR. DICKENS:
Q. Part of the reason is they didn't want to increase their liability by having paraquat included with their own products, right?
MR. NARESH: Can I have a standing objection as to the whole questioning about this document as to foundation?
(Stenographer clarification.)
MR. NARESH: Can I have a standing objection as to foundation, as to any questioning about this document, or do you want me to object each time?
MR. DICKENS: That might be the last question, but you can have a standing objection.

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MR. NARESH: Okay.
THE WITNESS: I mean, this is an internal Chevron document. I can only say it is what it is. I mean, I've got no kind of further information about it.
BY MR. DICKENS:
Q. Did you undertake any efforts to discover Geigy's relationship to ICI at this time in 1969 when you reviewed this document in preparation for the deposition?
A. No, I did not do that.
Q. Did you look for any additional correspondence between Geigy and Syngenta with respect to paraquat?
A. Well, my colleagues who were, you know, helping with this may have tried to look for that. If they did, nothing was passed my way.
Q. All right. And I don't want any communications with counsel. When you say "my colleagues," are you referring to attorneys?
A. I'm talking -- exactly, yes.
Q. Okay. And so the only document with respect to Geigy that you reviewed for this deposition is the document right here before you as it applies to 1969?

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A. I believe this is the only one which includes Geigy, yes.
Q. Now, in 1969, the FDA and USDA were receiving letters from senators and congressmen making inquiries as to why they permitted paraquat, right?
A. So I understand, yes.
Q. And it was a determination that, with that bad publicity in 1969, that the paraquat would cost more, right?
MR. NARESH: Objection to form.
THE WITNESS: I can't remember what the evidence for that is, but there may be a document which you can remind me of.
MR. DICKENS: Mark Exhibit 42 for the record.
(Exhibit 42 marked for identification.)
MR. DICKENS: This document has been identified in topic 90 and 106 of the Notice of Deposition.
MR. NARESH: Very thorough of you to have two topics on it. Thank you for that.
BY MR. DICKENS:
Q. This is a letter produced by Syngenta in this litigation dated January 16, 1974, from a Warren Lewis to a Gerry Jenkins at Plant Protection Limited.

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Do you see that?
A. I do.
Q. And Plant Protection Limited, once again, was within ICI?
A. Yes. It's as we've discussed before, PPL, yes.
Q. And they are the marketing or commercial arm of ICI, right?
A. That's right.
Q. All right. And Chevron's writing to PPL and saying:
"[I have attached] a memo from our Lemac Hopkins to apprise you of the growing seriousness of the paraquat health-hazard situation in the United States."
Right?
A. Yes. Well, I believe this was specifically a concern in California.
Q. Okay.
A. And I should say, by the way, that I did ask if I could see a memo from Lemac Hopkins and no such document was provided, so I don't even know who or what Lemac Hopkins is.
Q. Were there any other documents that you requested for your preparation for this deposition

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that could not or were not provided to you?
A. I can't -- no. Very, very few. I mean, this was one that I particularly remember because of my question about Lemac Hopkins, but mostly things were made available.
Q. And at this point, he mentions:
"With glyphosate nearly on the scene and facts of efficacy and health hazard extremely widespread, we no longer have the usefulness and need for paraquat as a defensive argument."
That's what Chevron's telling ICI at this point, right?
A. It's certainly what Mr. Lewis's view was, yes.
Q. And glyphosate at this point in 1974 was not yet on the market but close, correct?
A. I don't know. I don't know the history of the dates of glyphosate, so I'll accept what you say.
Q. And glyphosate is the active ingredient within Roundup and Roundup products, right?
A. It is, yes.
Q. Manufactured by Monsanto?
A. At that time.
Q. All right. Glyphosate and glyphosate products are now the top-selling broad-spectrum

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herbicides?
A. I --
MR. NARESH: Objection; foundation and scope.
BY MR. DICKENS:
Q. If you know.
A. I don't know. I mean, that's not information that I've looked at.
Q. When it mentions "facts of efficacy and health hazard extremely widespread," that's specific to paraquat, right?
A. That's the context of this document, it would seem, yes.
Q. And because of glyphosate coming -- and you understand that glyphosate was considered as a safer and more effective herbicide?
A. Could you repeat that, please, because I was just -- my eye was caught by something which I was wanting to look -- do say it again.
Q. Do you have an understanding that glyphosate was considered, or generally considered, a safer and more effective broad-spectrum herbicide?
A. Right. So --
MR. NARESH: Objection to the form, foundation and scope.

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THE WITNESS: I mean, I certainly remember, even after this date, that glyphosate was seen to be a safer herbicide, certainly. Effective? Different question. Paraquat and glyphosate have different herbicidal properties, so they're not equivalent.
BY MR. DICKENS:
Q. But we can agree it's considered safe?
A. It has got a very different safety profile and certainly doesn't have some of the toxicity that paraquat has.
Q. And Syngenta itself manufactures glyphosate?
MR. NARESH: Objection; scope, foundation.
THE WITNESS: I don't know whether we manufactured it. We certainly sold it.
BY MR. DICKENS:
Q. It goes on:
"Paraquat is in serious trouble, particularly in California but also in other states. Paraquat, as you know, is an extremely well-known compound, and news of a hazardous nature travels fast."
Right?
A. Right.

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Q. Chevron tells ICI:
"If it sounds like we are alarmed, we are."
Right?
A. Yes.
Q. And then Chevron details some of the concerning information with respect to paraquat, including:
"... the building up clash head-on with previously held toxicological facts."
Right?
A. Yes.
Q. And some of those facts are that:
"Medics indicate that spray droplets are being inhaled - in spite of data to the contrary, because the claim is that conditions and methods of application and resulting particle size do not necessarily parallel those of previous studies."
Right?
A. I think Mr. Lewis, here, is not, clearly, a sort of technical expert. He's a market development individual. So I think he's not got a full understanding of the sort of things we've been talking about and the difference between inhalable and respirable.

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Q. But what he is reporting is that medics are reporting to Chevron that spray droplets are being inhaled, right? That's what's being reported here?
A. Yes.
MR. NARESH: Objection to form.
BY MR. DICKENS:
Q. And when you hear "inhale," you're talking about the respirable particles?
A. Well, it's difficult to know. When "Medics say spray droplets are being inhaled," I don't know if they mean getting into the lungs or whether they just mean getting into the nose.
Because there's a tendency for casual language sometimes to be used.
Q. Well, certainly, these medics aren't just calling Chevron up for no reason. These are individuals who are treating people who had been injured after spraying paraquat, right?
MR. NARESH: Objection; foundation, form.
THE WITNESS: Well, I assume that these were farmers, but he doesn't actually say so, yes.
BY MR. DICKENS:
Q. At least individuals exposed to paraquat, we can agree?
A. Yes.

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MR. NARESH: Same objections.
BY MR. DICKENS:
Q. They're apparently seeing medics after breathing in paraquat in spite of data and statements to the contrary by Chevron and Syngenta -- or ICI at this time?
A. By which you mean the warning labels to avoid that? Is that what you're...
Q. I'm saying at this point in time, ICI and Chevron were instructing farmers and other users of paraquat that there was no risk of inhalation or breathing in paraquat because of the particle size.
A. Yes, and that's why this is creating, I'm sure at the time, some confusion over the implications of particle size.
Q. And, in fact, as we discussed earlier, the Chevron document for the marketing personnel had specifically included information about spray mist and the inhaling of paraquat causing severe irritation to the nose and throat, right?
A. Yes.
MR. NARESH: Objection to form.
BY MR. DICKENS:
Q. And that's a statement that Dr. Swan at ICI said, "We should not be providing"?

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A. Yes, we've been through that, I agree.
MR. DICKENS: Exhibit 43 for the record.
(Exhibit 43 marked for identification.)
MR. DICKENS: And this is topic 17.
BY MR. DICKENS:
Q. This document is from a G.A. Willis, manager of Product Safety and Registration Group at ICI, dated February 14, 1983, deemed confidential, subject "Paraquat labeling USA."
Do you see that?
A. I do.
Q. This reports that:
"Chevron has obtained EPA's approval for detailed wording changes to the Ortho Paraquat CL labeling."
Do you see that?
A. I do.
Q. And that would have been the paraquat that was on the market in the United States at the time?
A. Yes, I assume that's what it would mean.
Q. And these detailed wording changes to the paraquat labeling was in response to a lawsuit that had been filed against Chevron, right?
A. That is my understanding of what this says, yes.

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Q. Move to page 2. Towards the bottom of the page, it says:
"As a result of these arguments and an overall re-evaluation of their wording, Chevron amended their labeling..."
And it gives how it was amended, right?
A. That's right.
Q. And it was arguments that were made within the lawsuit filed by a user who had experience in adverse effects that he alleged was from paraquat, right?
A. That's correct.
Q. You can turn the page to the top of page 3, ending in 20363. ICI claims that:
"The main driving forces for these changes were the Chevron lawyers and the Chevron Environmental Health Center."
Right?
A. Yes.
Q. And those lawyers had:
"... concerns for being able to defend Chevron in law as well as possible and CEHC is called upon to provide 'expert witnesses' for the toxicological aspects of the defense."
Right?

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A. Yes.
Q. And the defense of paraquat specifically?
A. Yes.
Q. Now, ICI provided some comments on the proposed rewording to Chevron, right?
A. They did.
Q. And ICI was not very happy because they did not believe there was a practical problem with dermal or inhalation poisoning using the product?
A. I think it was specifically with regard to the risk of fatality in that way, yes.
Q. At the very bottom of the page:
"One concern which has been expressed to me relates to the possibility of adverse impacts of Chevron's label."
And that's the label for paraquat in the United States, right?
A. Yes.
Q. So the label shared by Chevron and ICI with respect to being able to sell paraquat in the United States?
A. Yes.
Q. And, according to ICI, they've lived with the problem with US labeling being more severe than other places in the world:

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"... and the recent changes will accentuate the difference further."
Right?
A. That was clearly one of the concerns that Mr. Willis was suggesting.
Q. ICI notes:
"[The] changes do not alter the overall appearance of the label and they are likely to go unnoticed by all but those who make a specific effort to compare the old and new texts in detail."
Right?
A. I guess he was saying that these would be subtle changes.
Q. Those changes so subtle that unless someone held up the labels next to each other, they'd go unnoticed, right?
MR. NARESH: Objection to form.
THE WITNESS: That's certainly the inference from the way this was written.
BY MR. DICKENS:
Q. And written by a member of ICI, correct?
A. Yes.
Q. And those changes -- when it says the changes would go unnoticed, that includes by farmers or others who were spraying around -- spraying

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paraquat in the 1983 time frame?
A. Well, I guess so, yes. But, I mean, look, I knew and know Mr. Willis. I mean, I think he was really in no way saying that that change of wording, or the subtlety that we're talking about, would, in his view, take away the warning that would be required by farmers and growers to use paraquat safely.
So, Mr. Willis always was, and still is as far as I know, concerned about the health protection of people using the product.
Q. And that's what you say now. At this point in 1983, according to Mr. Willis's letter, he actually advises Chevron not to circulate a letter to distributors drawing attention to the label changes, right?
A. Yes.
Q. He's telling Chevron, these won't be -- these label changes would go unnoticed "unless we draw attention to them."
A. Yes.
Q. So we should not draw attention to them, right?
MR. NARESH: Objection to form.
THE WITNESS: Yes, and this is another one of those emails where, I think, again, looking

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through -- at this through today's lens, this is certainly not the way in which we would tackle this problem right now.
And I think also, as I said a few minutes ago, it probably doesn't actually give, you know, sufficient justice to the fact that Jeff Willis was certainly concerned about safety.
BY MR. DICKENS:
Q. Another situation of putting economics over safety?
MR. NARESH: Objection to form.
THE WITNESS: No, I don't think that -- I mean, there's very little discussion, if any, of economics in this. This was, really, whether the proposed changes that Chevron wanted to do were essentially an overreaction, that you didn't need to actually put that -- the word "fatal" in, as they were describing, in order to properly protect people.
BY MR. DICKENS:
Q. "I believe that without such a letter the label changes would pass mainly unnoticed."
Right?
A. That's what I mean by that's not the kind of wording that I think would be appropriate.
Q. Because that wording suggests that ICI and

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Jeff Willis did not want users and farmers to know that a label change would be made, right?
A. That's what that suggests, yes.
Q. But Chevron lawyers deem that circulation of the letter was mandatory to meet their legal obligations, right?
A. Yes.
Q. "If we are to use senior level inputs to modify Chevron's behavior pattern [...], I would place a high priority in seeking to persuade them not to circulate any such note."
Right?
A. Yes.
Q. Don't let people know a labeling change has been made.
MR. NARESH: Objection; asked and answered.
BY MR. DICKENS:
Q. Right?
A. Yes.
MR. DICKENS: Is now a good time for that break before we...
MR. NARESH: Yeah.
THE VIDEOGRAPHER: We are going off the record at 16:56.

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(Break taken.)
THE VIDEOGRAPHER: We are back on the record at 17:04.
BY MR. DICKENS:
Q. Dr. Botham, earlier in the deposition we were discussing the Defra study.
Do you recall that?
A. Yes.
Q. And you indicated you had reviewed Defra in preparation for today's deposition?
A. As much information as I could find.
MR. DICKENS: I'll go ahead and mark Exhibit 44 for the record.
(Exhibit 44 marked for identification.)
MR. NARESH: What topic number?
MR. DICKENS: The document itself is not specifically identified in the Notice of Deposition.
MR. NARESH: I'll do a standing scope, but if Dr. Botham can answer questions --
MR. DICKENS: You can have a standing objection.
MR. NARESH: Okay.
MR. DICKENS: What I've handed you, Exhibit 44, which -- is a document Evidence Project Final Report, Defra.

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BY MR. DICKENS:
Q. Is this the document you reviewed in preparation for today's deposition?
A. It's a different version of a document that I saw, I think. I've not seen one in this format.
Q. So you saw it in a different format but it has the same content and information?
A. Well, I would need to read this in more detail to -- but, probably, from just a very, very quick look at this.
Q. I just want to go over certain items that I believe you brought up with respect to Defra, and specifically on page 2 there's an "Executive Summary" listed here.
Do you see that?
A. Yes.
Q. And then there's Study 1 and it identifies a PBPK model, right?
A. Yes.
Q. And it says:
"Commercial Gramoxone, a paraquat formulation, was spiked with radiolabeled paraquat at a dose specific to the route of exposure and tested for good detection in a pilot study."

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Right?
A. Yes.
Q. And when it says "radiolabeled paraquat," what's that referring to?
A. It means that it's -- on the molecule of paraquat, it's got a radiotracer label on it so that you can quantify -- you can see where it gets to and quantify that.
Q. Okay. So you could see where -- you know, if paraquat, for example, can get into the brain, you'd be able to see that, right?
A. Yes. You would be able to measure it.
Q. And on the next page, that next line notes:
"At a designated time after dosing, the animals were sacrificed and the amount of paraquat in blood and brain was measured."
Right?
A. Yes.
Q. And then the next page for Study 1, it notes "Modeling Exposure"?
A. Yes.
Q. It says:
"The study was designed to generate data on which to fit a PBPK model of human field exposures

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to paraquat, using the brain as the target organ."
Right?
A. Yes.
Q. But in this study:
"Adult mice were given single doses of paraquat according to the three routes of exposure..."
A. Yes.
Q. Correct?
A. Yes.
Q. And so the purpose of this study was to generate data in order to generate a PBPK model for human field exposures to paraquat?
A. Yes, that's correct.
Q. And then two pages later, at the top of the page, after the animals were dosed, they were:
"... sacrificed [...] to create a 24-hour time course."
Right?
A. Yes.
Q. And then:
"After sacrifice, blood and brain samples were taken and measured for paraquat radioactivity."
Right?
A. Yes.
Q. So they actually did take samples of the

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brain in order to determine how much paraquat made it to the brain in these particular studies.
A. Okay.
Q. And that's your understanding?
A. Yes. And I can see now, the more I read this, there's actually more detail in this report than the one that I saw.
Q. And then on page 13 of 17 --
MR. NARESH: And, Dr. Botham, in light of your comment just now, you know, read as much or as little as you feel like you need to to be able to answer the questions, given the length and density of the document, in order to contextualize it as you need to.
BY MR. DICKENS:
Q. And I'm going to ask you about the paragraph "Future Work - Intranasal Transport," so if you need time to read it, just let me know when you're ready.
A. Okay, I've read that.
Q. What the study research scientists noted in the intranasal transport side is that:
"... intranasal dosing in the PBPK model portion of this study indicated a fast and extensive circulation of paraquat in the brain tissue - the

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amount of paraquat detected in the brain after intranasal exposure was tenfold higher than the model predicted based on systemic flow."
Right?
A. Yes.
Q. So the amount of paraquat that was found in the brain of the animals after sacrifice was actually ten times higher than what was expected through their use of the PBPK model?
A. That's right. And if I could add at this point, I mentioned earlier that there were a number of reasons why an intranasal study was something that we, in the end, didn't actually do, and there was -- one other reason, which this reminds me of, is that rather like with the intraperitoneal injection studies that we see frequently, which we did ourselves, intranasal administration of substances to animals was done in the PBPK section of this, is a very exaggerated mechanism of exposing the animals.
So it's not like a nasal drop. You know, you're literally forcing it up into the top of the nasal cavity, which is way exaggerating what would come from a normal exposure of an operator in the field, for example.
MR. DICKENS: I'll move to strike

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everything after, "That's right."
MR. NARESH: I'll object to that.
BY MR. DICKENS:
Q. The study authors report that:
"To better understand the risk, a study would be needed to examine the intranasal arterial hypothesis, including the pattern of paraquat distribution to the brain, and confirmation of the amount in the brain regions after intranasal administration."
Right?
A. Well, not unreasonable, yes. I mean, so they're not saying -- they're saying here they don't know how much got into the brain and where it went to.
Q. All they know is what was actually in the brain was tenfold higher than what was expected in their model?
A. Yeah, yeah.
Q. And they're saying in order to better understand the risk, additional studies would be necessary?
A. Yes.
Q. Syngenta has never undertaken any additional studies to investigate that risk?

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A. No.
Q. At this point in 2012, was Syngenta undertaking its own studies or is that farmed out to third parties?
A. In 2012, we were fully engaged in our very significant study, large study, using that intraperitoneal injection model, and the reason we were doing that, even though it does, again, exaggerate exposure, is because this was a study which we, in part, were seeing whether the findings that other scientists had made of an effect on the substantia nigra in the brain, following an IP administration of paraquat, whether that was something that could be replicated and, if so, at what kind of concentrations do you see that and are those concentrations relevant to human exposure.
Q. In 2012, did Syngenta have the ability to run a test through an inhalation chamber with animals?
A. It could have done, yes.
Q. It did not do that, right?
A. It did not do that.
Q. Page 4 once again of Defra, under "Modeling Exposure," the adult mice were given single doses of paraquat, three routes of exposure that were meant to be "relevant to human field conditions for

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pesticides," including intranasal.
Right?
A. Yes. But the intranasal, as I said earlier, nevertheless exaggerates the actual likelihood of that dose, whatever it is, of getting into the brain, for example.
Q. We can put that aside.
Dr. Botham, are you aware of a ECCO group within the toxicology department of Syngenta, or ICI?
A. Is that E-C-C-O, ECCO?
Q. Correct.
A. Yes, I've seen a document recently which had that on it.
Q. Okay. In preparation for today's deposition?
A. Yes.
Q. Do you know what ECCO stands for?
A. I can't remember, actually, no.
Q. Okay.
MR. DICKENS: I'll hand you Exhibit 45 for the record.
(Exhibit 45 marked for identification.)
MR. NARESH: What's the topic number, please?
MR. DICKENS: 23.

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BY MR. DICKENS:
Q. Okay. This is a document dated June 12, 1997, "Paraquat toxicology, ECCO meeting outcome."
Do you see that?
A. Yes.
Q. And it's provided on behalf of Andy Cook, who was currently on holiday at that time.
Do you see that?
A. Yes.
Q. Andy Cook had some responsibilities for paraquat?
A. Yes. So at this time he would have been the regulatory manager in Europe for paraquat.
Q. And in your prior deposition, you had spoken to Andy Cook in preparation for your deposition on behalf of Syngenta, right?
A. Yes.
Q. You did not speak to him in preparation for today's deposition?
A. I did not, no.
Q. And this document doesn't necessarily specify what the ECCO refers to. This doesn't jog your memory in any way, does it?
A. Well, you asked me what it stands for. So I don't know what E-C-C-O means. I think EC

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probably is to do with European Community. I mean, this is a group associated with the European Commission, so it's the European regulatory authorities and it was some kind of specialized meeting, which our regulatory people had access to.
Q. And it's related to a meeting between June 3 and 5 of 1997.
Do you see that?
A. Yes.
Q. And there's a PSD attendee, Ian Dewhurst.
Do you know who that is?
A. Yes, he was the toxicology lead in -- PSD is the Pesticides Safety Directorate. That's the UK regulatory authority for pesticides.
Q. Do you know whether or not Ian Dewhurst was involved in Defra at all?
A. Yes. Ian Dewhurst was one of the people who led on the project proposal, if you wish, or the call for tender.
Q. And he was apparently an attendee at this meeting with respect to the paraquat and toxicology issues in Europe, right?
A. Yes.
Q. And there's a section midway down page 1 of "Operator Exposure."

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Do you see that?
A. Yes.
Q. And we discussed earlier just operator exposure studies and you mentioned the ones that were done in the Far East, right?
A. Mmm-hmm.
Q. That's a yes, sorry?
A. Yes.
Q. Okay. And those operator exposure studies are designed to measure the amount of paraquat that a user or a farmer or operator of paraquat would be exposed to during spraying activities?
A. Yes.
Q. As well as mixing and loading, right?
A. Yes.
Q. Now, it mentions:
"NL raised a concern that the in vitro skin absorption study was unoccluded."
And we discussed occluded versus unoccluded with respect to dermal absorption studies, right?
A. We did.
Q. And the occluded, or covering, of the skin actually resulted in higher dermal absorption, right?

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A. Yes, and that was in the animal model that we were discussing earlier.
Q. Right. And because of that:
"The meeting considered that the absorption of paraquat through skin may increase if occluded ([or] clothing was present)."
Right?
A. Yes.
Q. And:
"... operator exposure studies (in Sri Lanka and USA) did not represent EU conditions [for] personal protection equipment as most workers wore shorts [and] shirt."
Right?
A. Right.
Q. And:
"It was considered possible that the exposure may [actually] be greater if long trousers were worn."
Right?
A. Yes.
Q. And so the ECCO group proposed that a new operator exposure study be undertaken, right?
A. Yes.
Q. Do you know whether or not that operator

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exposure study was undertaken?
A. I'm not sure whether that study was done specifically in response to that. It is 1997, so I suspect the answer is probably no because it's very close to the Court of First Instance judgment on paraquat.
Q. And that was with respect to an action brought by Sweden?
A. Yes.
Q. In which -- what did the -- what was your understanding of the Court of First Instance judgment on paraquat?
A. Well, this was Sweden leading on an objection to the way in which the European Commission had proceeded with regard to the re-registration of paraquat in the European Union. So it was a procedural objection.
Q. And the Court found that the procedure was sufficient, right?
A. The Court found that -- found in favor of Sweden and said that, really, the European Commission had not acted appropriately.
Q. Had not acted inappropriately?
A. Had not used -- had not followed the appropriate procedures.

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Q. We'll look at that probably tomorrow at this point.
MR. DICKENS: I will go ahead and mark Exhibit 46 for the record. Topic 17 on the Notice of Deposition.
(Exhibit 46 marked for identification.)
BY MR. DICKENS:
Q. Okay. I've handed you a document titled "Paraquat Operator Exposure - A review of operator exposure studies" by Graham Chester and Andy Cook, December 2009.
You've reviewed this document previously?
A. I did.
Q. Turn to page 3, Executive Summary.
It notes that:
"A total of 22 studies have been conducted to determine operator exposure to paraquat during the use of appropriate, recommended spray application equipment. Eleven of these studies have been published."
Right?
A. Yes.
Q. Now turn to the next page. In the Introduction, it notes the purpose of the review, and it was:

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"... intended to be a critical appraisal for the paraquat operator exposure studies in the published literature and those conducted by Syngenta and its legacy companies with a particular emphasis on scientific integrity and suitability for use in the quantitative assessment of risk of exposure to paraquat under typical conditions of use."

Right?

A. Yes.

Q. And then the summary, in the preamble, it notes that:

"There are two types of study: pre- and re-registration studies, and post-registration surveillance studies."

Correct?

A. Yes.

Q. The pre- and re-registration studies would have been "done in full compliance with the requirements of the product label."

Correct?

A. Yes, yes.

Q. And that would have included "recommended application rates, protective clothing and equipment," right?

A. Yes.

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Q. And the studies of the other type, or post-registration surveillance studies, would have been done according to those users' "typical or habitual working practices," right?

A. Yes, that's the phrase, "habitual"; so actually what happened in reality when they were -- people were using the product.

Q. So Syngenta, or whoever the individuals are who were conducting this study, would not intercede and instruct the users to wear particular types of clothing; it would be how they would normally typically apply paraquat, right?

A. That's correct. This was to look at what the reality was in the field.

Q. Turn to page 5.

Now, the second study here notes a recent European regulatory study on knapsack spray operators.

Right?

A. Okay.

Q. And that was in Spain in 1997.

A. Okay, right. Yes.

Q. That was the Findlay study?

A. Yes.

Q. And in the Findlay study all workers generally complied with the product label

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recommendation for protective gloves and face shield when mixing and loading.

Right?

A. Yes.

Q. And with the filing, the labeling recommendations, paraquat was found in the urine of 18 of the 20 workers involved in that study.

Right?

A. Yes.

Q. So at this point, the personal protective equipment worn by the workers in this study did not completely protect them from exposure to paraquat.

We can agree on that?

A. And that is not -- was not a surprising finding, yes.

Q. It then mentions:

"... a 2007 study in Martinique in knapsack spray operators..."

Right?

A. Yes, yes.

Q. And that's a Brouwer 2007 (a) study?

A. Yes.

Q. And that operator is wearing a standardized set of PPE on banana plantations, right?

A. Right.

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Q. And the prototype PPE included PVC trousers.

Do you know what PVC refers to?

A. Polyvinyl chloride; yeah, plasticized trousers.

Q. And a PVC poncho, long-sleeved shirts and a hat with a protective neck guard, right?

A. Yes.

Q. "In addition, gloves, long rubber boots and [...] disposable respiratory mask were worn throughout the three days..."

Right?

A. Yes.

Q. Okay. In that particular study, there were ten operators whose paraquat was mostly completed on the days of use after the last -- sorry, the excretion of paraquat was mostly complete on the days of use or within one day after the last of their three days of use.

Right?

A. Yeah.

Q. But one operator continued to excrete paraquat up to four days post application, right?

A. Okay.

Q. So one operator who was exposed to

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paraquat had paraquat in their body or in their system four days after their last exposure to paraquat, right?

A. That's right.

Q. Andy Cook and Graham Chester note:

"There was no clear explanation for this other than an observed incident of contamination..."

Right?

A. Indeed, yes.

Q. Now, this Brouwer study was not the only study undertaken by Brouwer for measuring the amount of paraquat that operators were exposed to, right?

A. Yes, that's right, yes. Brouwer worked for a contract research organization that was doing a number of different operator exposure studies.

Q. Okay. And operator exposure studies on behalf of Syngenta specifically, right?

A. That's right, yes.

Q. Page ending in -- oh. Page 7 of this document.

At the very bottom, it notes:

"In 2006-7, a series of related, habitual-use biological monitoring studies was done in vines and bananas in mainland France and Martinique..."

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Right?

A. Yes.

Q. And they were in compliance with the OECD guidance and GLP, correct?

A. Correct.

Q. And what is the significance of being in compliance with OECD and GLP?

A. Well, that it was, if you like, an approved protocol; so the methodology that was used would have -- would be acceptable as a good-quality study and backed up by the fact that it was done to good laboratory practice.

Q. The formulation used in those studies was R-BIX containing 100 grams of paraquat.

Do you know what was in the formulation of the R-BIX used in this particular study?

A. Do you mean what surfactants were in there?

Q. What surfactants or other ingredients other than the paraquat?

A. No, I can't tell you off the top of my head what else was there.

Q. Do you know whether or not there was a surfactant included in that study?

A. I don't.

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I suspect there was because it was called an SL formulation, which suggests that there would be surfactant in there.

Q. If you can turn to the next page, page 8. Right above 3.3, it notes:

"The French and Martinique studies are the most modern, guidance-compliant studies available and are the ones of choice for assessment of absorbed dose for risk assessment purposes under the specific conditions of habitual use."

A. Yes.

Q. Right?

A. Yeah.

Q. And that's being used by operators how they would typically apply paraquat?

A. That's what "habitual use" means, yes.

Q. And so these two studies were deemed to be the best for risk assessment purposes for how users were actually spraying paraquat, right?

A. Indeed, yes.

Q. And, once again, Graham Chester and Andy Cook are employees of Syngenta?

A. Yes. Andy Cook we've talked about before. Graham Chester was an employee of Syngenta up to a certain point in time. I don't know exactly when,

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but he was very much an expert in operator exposure studies.

Q. All right. At the very top of the page --

MR. NARESH: Still page 8?

MR. DICKENS: Page 8 still, yeah.

BY MR. DICKENS:

Q. -- it references the study involving a single day's use of paraquat in vines in France, right?

A. Yes.

Q. This is the French study that was part of what was deemed as the most modern guidance compliance studies for habitual use, right?

A. Yes.

Q. And the excretion of paraquat was calculated to be a mean absorbed dose of 8.54 micrograms per kilogram, right?

A. Yes.

Q. And that would equal 0.0084 milligrams per kilogram?

A. Yes.

Q. And what is the AOEL? What does that refer to?

A. The AOEL is deemed to be -- it's called a reference dose, so it's calculated from -- you start

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with a 'no effect' level in a toxicology study, a toxicity study. You then divide that by a safety factor, and that gives you an AOEL.

Q. And that is the acceptable amount that a human could be exposed to paraquat without causing adverse health effects, right?

A. Yes.

Q. And the AOEL for paraquat is 0.0005 --

A. That's --

Q. -- milligrams per kilogram, right?

A. That's correct, yes.

Q. So the excretion of paraquat in this study and the mean absorbed dose as determined by the study authors actually exceeded the AOEL, right?

A. Right. Now, my understanding is that that exceedance of the AOEL was restricted to two individuals; so not every individual had an exceedance of that AOEL.

Q. But two individuals with habitual use of paraquat exceeded the AOEL in this particular study, right?

A. That's right, yes.

Q. Okay. The study that was deemed the best choice for assessment of absorbed dose for risk assessment purposes?

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A. Mmm-hmm. Yes.

But those exposures, by the way, just to complete the answer, they did not exceed the 'no effect' level from the toxicity study. So there is that margin of safety which I described.

Q. Looking back at that last line where it's the 8.54, now, that indicates it's a geometric mean of the nine operators with quantifiable paraquat in their urine, right?

A. Yes.

Q. So it actually included all nine operators who were deemed to have paraquat in their urine, not just the two who exceeded the AOEL on their own, right?

A. I mean, I'm now wondering whether we -- I mean, there are so many different studies here.

Your calculation of 0. -- of 8.54 and then comparing that with the AOEL, and, you're quite right, it says the geometric mean.

My understanding was, and maybe it wasn't this particular study, so I'm getting rather late in the day here, was that there were only two individuals in one of these studies where there was exceedance of the AOEL.

Q. I actually want to turn back to page 6.

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At the very bottom, it references, under "Habitual Use Studies," a study in Sri Lanka in 1987 by Chester.

Right?

A. Yes.

Q. And is that Graham Chester who --

A. It's the same one, yes.

Q. And this is the Sri Lanka study that was referenced in that ECCO meeting that we looked at earlier?

(Stenographer clarification.)

BY MR. DICKENS:

Q. Yeah. This is the same Sri Lanka study that we looked at in that ECCO meeting?

A. Well, I assume it may have been. You can't make a direct assumption of that, but let's -- I think we can assume it probably was.

Q. And in that Sri Lanka study, blood samples were also taken of the individuals who were exposed to paraquat, right?

A. Yes.

Q. So this is a ICI, or Syngenta, operator exposure study, right?

A. Yes.

Q. And so Syngenta actually not only took

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urine samples but took blood samples of those individuals exposed to paraquat?

A. Yes.

Q. You can put that aside.

MR. DICKENS: I'll hand you 47.

(Exhibit 47 marked for identification.)

BY MR. DICKENS:

Q. This document refers to Dunlop Estate worker exposure studies to paraquat in Malaysia, right?

A. Yes.

Q. And the objective was:

"To obtain data on sprayman, carrier and tapper dermal and respiratory exposure..."

Right?

A. That's right.

Q. Now, there's a "Determination of dermal exposure," and it notes:

"Dermal exposure pads were attached to clothing (or skin, if exposed)..."

Right?

A. Yes, indeed.

Q. And that was on various locations on the individual?

A. Yes.

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Q. Now, they ran into some problems for dermal exposure, at the bottom of the page, in that:

"... saturation of the exposure pads to the lower leg and thigh..."

Or there was:

"... saturation to the exposure pads to the lower leg and thigh [of paraquat] as the worker walked through sprayed vegetation."

Right?

A. Yes.

Q. And so that:

"... necessitated removal of the pads after a relatively short period of spraying - sometimes as little as 30 minutes."

Right?

A. Mmm-hmm.

Q. So the legs and the pads within the legs of those individuals became so saturated with paraquat that they had to be removed, correct?

A. That's right.

MR. DICKENS: I want to look at another Malaysian study. This is Exhibit 48.

(Exhibit 48 marked for identification.)

BY MR. DICKENS:

Q. This is a report from a B.H. Woollen,

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"Paraquat: Analysis of urine and plasma samples from a Malaysian operator exposure study," May 26, 1998.

Do you see that?

A. Yes, indeed. That's 1988, actually.

Q. I said --

A. '98.

Q. -- '98? You're correct, 1988. And on the next page, it notes that:

"In February 1988, an exposure study was carried out in Malaysia involving knapsack spray operators who were exposed to paraquat."

A. Yes.

Q. Right. Now, this actual study, this was not included in the summary of operator exposure studies that we looked at in the previous exhibit by Graham Chester and Andy Cook, correct?

A. I would need to double-check that, but let's assume that you're correct for now.

Q. And in this case, much like the Sri Lanka study, they actually undertook both urine as well as plasma samples from the individuals?

A. Yes.

Q. And plasma being blood?

A. It's a component of blood.

Q. If you can turn to page ending in 7570,

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end of the first paragraph:

"It's noteworthy that while paraquat excretion declined rapidly at the end of the spraying period between days 3 and 4, the decline was much slower thereafter and paraquat was still detectable in urine on day 10 for six of the subjects."

Right?

A. Yeah. Yes.

Q. So there were individuals in this study who still had paraquat in their urine ten days after their last exposure, right?

A. I assume it's after their last exposure and that they weren't still subject to some form of exposure at that period in time, which is another alternative, of course.

Q. Now, with respect to plasma, it notes:

"Paraquat was detectable at low concentrations in 12 out of 50 samples collected during days 1 and 3 when spraying occurred, but not in samples collected on day 5."

Right?

A. Okay. Yeah, indeed.

Q. This study specifically indicates that paraquat was not only getting into the body and excreted through the urine but paraquat was actually

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getting into the blood of users who were spraying paraquat, right?

A. Well, indeed, in order to get into the urine it's highly likely that it will have gone via the circulation.

Q. And in this, they specifically measured the plasma paraquat concentrations in order to determine the total operator exposure to paraquat in Malaysia at this point in time, right?

A. I would need to understand that in a little bit more detail as to why they felt it was important to look at the plasma as well as the urine. I'm not sure that it was -- I wouldn't describe it in the way in which you had done, so I wouldn't like to say whether that was the intention and purpose here.

MR. DICKENS: Two last ones for today. Get up to 50. I'll hand you Exhibit 49 for the record.

(Exhibit 49 marked for identification.)

MR. DICKENS: For the record, this is topic 17 in the Notice of Deposition.

BY MR. DICKENS:

Q. This is an email chain, "For your personal information: Meetings in Malaysia," August of 2002, from a Martin Wilks, bottom of the first page.

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Do you see that?
A. I do.
Q. And then on the bottom of the second page, the first email in this email chain is from a Bruce Woollen to Martin Wilks and Mike Clapp, right?
A. Yeah.
Q. And he's reporting on meetings he had in Malaysia. Bruce Woollen, he was -- was he the neurotoxicol- -- okay.
Who is Bruce Woollen?
A. Right. Well, as in the previous document, which Bruce Woollen was an author on, he was our analytical expert, analytical chemistry expert.
Q. And he's noting that he spoke to individuals in Malaysia and they were wishing to carry out a paraquat exposure study, right?
A. An individual in Malaysia was wishing to do that and he was discussing this with other scientists in Malaysia.
Q. And that's because the Pesticides Safety Board were not prepared to accept previous ICI studies on the basis that they were not considered to be impartial, right?
A. That --
MR. NARESH: Object to the form.

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Go ahead.
THE WITNESS: Sorry. Yeah, that was the reason given, yes.
BY MR. DICKENS:
Q. And:
"A key influencer was the man who visited with Bala [...] 18 months ago. He had [...] taken a strong position that if Syngenta did commission an independent study, [...] paraquat measurements should be done in blood plasma."
Right?
A. Yes.
Q. If you turn to the page -- to the last page, the second paragraph:
"Having convinced Bala of these arguments, he tried to arrange a meeting with the key influencer in the hope that I could convince him that plasma measurements would be futile."
Right?
A. Yes.
Q. Bruce Woollen is attempting to get the -- any Malaysian exposure studies not to include a measurement of paraquat within the blood or plasma?
MR. NARESH: Objection to the form.
///

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BY MR. DICKENS:
Q. Is that your understanding?
A. Indeed, and probably for the same reason that I was saying it's not, to me, clear why plasma was -- plasma paraquat levels were measured in that previous study. The urine levels are the key parameter.
Q. Okay. Part of the reason, on page 1, email from Martin Wilks, the last paragraph on page 1:
"More importantly, there is a real danger of generating data which could cause a great deal of harm to the global paraquat position."
Right?
A. Yes.
Q. And paraquat being found in the blood or plasma of users was considered data which would cause great harm to Syngenta and its business with paraquat, right?
MR. NARESH: Objection to form.
THE WITNESS: I don't know whether the specific concern was about detecting paraquat in the blood. I'm not able to make a judgment about specifically Martin's concern.
BY MR. DICKENS:
Q. It states at the very end:

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"If additional work is unavoidable, we must try to maintain as much control as possible."
Right?
A. Yes.
Q. And that's in order to influence what is happening, right?
MR. NARESH: Objection to form.
THE WITNESS: I think it's -- as is -- has been the case in another -- a number of examples: we wanted to -- I guess the better word would be to collaborate in order to create -- if a study was to be done, it would be done using the best possible approach, using the best possible protocol.
MR. DICKENS: Let's look at the last of the day, Exhibit 50, which is topic 17, still, in the Notice of Deposition.
(Exhibit 50 marked for identification.)
BY MR. DICKENS:
Q. This is an email chain in May of 2007 which, once again, includes Bruce Woollen.
Do you see that?
A. Yes.
Q. Okay. Let's start on the first email, which is on the second page. It's an email sent to Bruce Woollen on May 30, 2007 and it appears that a

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group was planning to do an operator exposure with samples of urine and plasma from plantation workers for a chronic exposure study.
Right?
A. Yes.
Q. And this would have been an outside group who would have been doing this operator exposure study of chronic exposure to paraquat, right?
A. Yes.
Q. Turn back to page 1, Bruce Woollen writes back, right?
A. Yes.
Q. And in the third paragraph, he states:
"Regarding operator exposure studies, I would advise you against blood sampling."
Right?
A. Yes. And this actually says, in different language, exactly what I've been saying in the last -- with the last two exhibits: that the use of measurements in plasma are less meaningful than would be the case with urinary samples.
MR. DICKENS: I'll move to strike.
BY MR. DICKENS:
Q. Dr. Woollen notes, in the next paragraph:
"In all our biological monitoring studies

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in the last 20 years [...], we have always used urine and never blood sampling."
Right?
A. He said that, yes.
Q. That's not true, correct?
A. Well, when you look back and -- it's clear that he'd forgotten the study that we were looking at earlier, yes.
Q. He forgot both the Sri Lankan study as well as the Malaysian study that we looked at, right?
A. That's what we were looking at, yes. The Malaysian study I was -- is the one that I was referring to, yes.
Q. And in the report or review that was done by Chester and Cook, we looked at the fact that blood samples were taken in the Sri Lankan study, right?
A. Okay, yes.
Q. So now there's two studies, biomonitoring studies that were done by Syngenta prior to 2007 where they have measured blood sampling, right?
A. Yes.
Q. And so the comment in this statement, through Bruce Woollen, to this independent researcher, simply isn't true, right?
MR. NARESH: Object to the form, asked and

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answered.
THE WITNESS: Well, it's inaccurate, but I think he's also saying that, perhaps with the benefit of hindsight, he now believes that the measurement in urine is a much more robust way of assessing exposure to paraquat.
BY MR. DICKENS:
Q. Well, he actually gives us the reason for why he said that in his email to Martin Wilks on May 30, 2007, right?
A. Yes.
Q. He says:
"My efforts to try and influence Teh..."
And that's the individual who had emailed him, right?
A. Yes.
Q. "My efforts to try and influence Teh to influence his supervisor continue, both technically and to avoid a potential 'can of worms' from plasma analysis results."
Right?
A. Yes.
Q. There was fear that plasma results of paraquat in the blood would open up a can of worms?
MR. NARESH: Objection to form.

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THE WITNESS: Yes, because they are -- as is said here, they are a snapshot in time and you can -- they don't provide you with the robustness of conclusion that urine samples over a period of time provide.
MR. DICKENS: We can go ahead and end for the day.
THE VIDEOGRAPHER: We are going off the record at 17:59.
(Whereupon, the deposition concluded for the day, to resume on Wednesday, September 18, 2024 at 09:00 a.m.)

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CERTIFICATE OF WITNESS

I, PHILIP BOTHAM, declare that I have read the entire transcript of Volume I of my Syngenta Corporate Representative deposition, or the same has been read to me, and certify that it is a true, correct and complete transcript of my deposition given on Tuesday, September 17, 2024, save and except for changes and/or corrections, if any, as indicated by me on the attached Errata Sheet, with the understanding that I offer these changes and/or corrections as if still being questioned.

Signed_____
Philip Botham

Dated this.....day of.....20...

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CERTIFICATE OF STENOGRAPHER

I, LEAH M. WILLERSDORF, Registered Merit Reporter, Certified Realtime Reporter, Fellow of the British Institute of Verbatim Reporters, Qualified Realtime Reporter Level 2, and Certified LiveNote Reporter, do hereby certify that:

PHILIP BOTHAM appeared before me on Tuesday, September 17, 2024, agreed to tell the truth under the penalties of perjury, and was thereupon examined by counsel; the testimony of said witness was taken by me stenographically; the foregoing is a true and accurate record to the best of my knowledge, skill and ability; I am neither a relative nor employee of any party to the action in which this testimony was taken; I am neither relative nor employee of any attorney or counsel employed by any party thereto; and, further, I am not financially or otherwise interested in the outcome of the action.

LM Willersdorf
_____
LEAH M. WILLERSDORF
RMR, CRR, FBIVR, ACR, QRR2, CLR
(September 27, 2024)

Case ID: 220300429
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ATTACHMENT E



Case ID: 220300429
Control No.: 26064959

PHILADELPHIA COUNTY COURT OF COMMON PLEAS
TRIAL DIVISION

- - - - - - - - - - - - - - -X
IN RE: PARAQUAT PRODUCTS : LIABILITY LITIGATION : NO. 559
- - - - - - - - - - - - - - -X

VIDEOTAPED DEPOSITION OF MONTAGUE DIXON

WASHINGTON, D.C.

Thursday, July 11, 2024

9:04 a.m.

Job No.: 2024-948228

Pages: 1 - 456

Reported By: Okeemah S. Henderson, RPR

Case ID: 220300429
Control No.: 26064959

Deposition of MONTAGUE DIXON, held at the offices of:

KIRKLAND & ELLIS, LP
1301 Pennsylvania Avenue, NW
Washington, D.C. 20004
202-879-5000

Pursuant to Notice, before Okeemah S. Henderson, RPR, Notary Public in and for the District of Columbia.

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ALSO PRESENT:

RYAN J. HEATHCOCK, VIDEOGRAPHER
ALAN NADEL
PETER VAN DYKEN

C O N T E N T S

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*****

P R O C E E D I N G S

THE VIDEOGRAPHER: We're now on the record. My name is Ryan Heathcock. I am the videographer that has been retained by Lexitas. This is a video deposition for the Philadelphia Court -- County Court of Common Pleas, Trial Division. Today's date is Thursday, July 11, 2024, and the time on the video monitor is 9:04 a.m. Eastern.

This deposition is being held at 1301 Pennsylvania Avenue, Northwest, in Washington, D.C. This is in the matter of Paraquat Products Liability Litigation No. 559.

Our deponent today is Mr. Montague Dixon. All counsel you will be noted in the stenographic record, but at this time, would you all please identify yourself starting with the noticing attorney.

MR. DICKENS: David Dickens on behalf of Plaintiffs.

MR. TRAVERS: Jeffrey Travers on behalf of Plaintiffs.

MR. HONG: Don Hong, Kirkland & Ellis on

behalf of Syngenta. I also have Thomas Leahy on behalf of Syngenta and Alan Nadel of Syngenta.

THE VIDEOGRAPHER: Our court reporter today is Miss Okeemah Henderson and she will now swear in the witness.

MONTAGUE DIXON,

was called as a witness, and having been first duly sworn, was examined and testified as follows:

THE WITNESS: I do.

THE VIDEOGRAPHER: Counsel, you may proceed.

MR. HONG: Counsel, before you get started, given that this is noticed in multiple jurisdictions and different rules apply, objections as to form, we all agree we'll preserve those objections to a later date with no need to go off the record to attempt to resolve those objections contemporaneously and we'll preserve those until a later date.

MR. DICKENS: So stipulated. We agree.

EXAMINATION BY COUNSEL FOR PLAINTIFF

BY MR. DICKENS:

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Q. Good morning, sir.
A. Good morning, sir.
Q. Can you please state your name for the record.
A. Yes. My name is Montague Dixon.
Q. And Mr. Dixon, I understand you've been deposed before; is that right?
A. That is correct, sir.
Q. And deposed before in the Paraquat litigation?
A. That is correct, sir.
Q. So you understand the drill. I'll just ask, if I ask a question you don't understand, just let me know, and I'll do my best to rephrase; is that fair?
A. Yes, sir.
Q. And if you go ahead and answer, I'll presume you've answered -- or understood the question and answered fully and truthfully; is that fair?
A. Yes, sir.
Q. Where do you currently live?

A. Jamestown, North Carolina.
Q. And are you currently an employee of Syngenta?
A. I am.
Q. How long have you worked at Syngenta?
A. I started working at Syngenta at one of its legacy companies as a full-time employee in March of 1990, that company was known as Ciba-Geigy. In 1996 which company became Novartis and then ultimately, Novartis became Syngenta.
I've with the company and the legacy forms from 1990 until currently.
Q. Are you still currently employed by Syngenta?
A. Yes, sir.
Q. So you've been working for Syngenta or its legacy companies from 1990 until today?
A. Yes, sir, with a brief two summers in 1986 and 1987 as a lab assistant.
Q. Prior to -- I, kind of, want to go through your background prior to joining Ciba-Geigy in 1990, you received a bachelor's degree from the

University of North Carolina in 1989; is that --
A. That's correct.
Q. And a master's degree in chemistry in 2000?
A. Yes, sir.
Q. So you were working at -- I guess Novartis at the time you received your master's degree?
A. That would be correct.
Q. Prior to obtaining your master's degree -- in 1990 when you began working for Ciba-Geigy, what was your position?
A. My initial position was as a residue chemist. I held that position for approximately a year. I think the official title was assistant chemist but my focus was in our residue chemistry department.
Q. And were you working with pesticides at all while with Ciba-Geigy?
A. Yes, sir.
Q. What pesticides in particular?
A. It would be very, very difficult for me to remember going all the way back to 1990, sir.

Q. Fair to say you weren't working on Paraquat at the time?
A. I don't recall ever working on Paraquat in that role, sir.
Q. You mentioned Ciba-Geigy became Novartis in 1996. What was your role at Novartis?
A. So after one year in the resident chemistry group, before we became Novartis, I moved into our metabolism chemistry group; similar type of role just earlier in the analytical process, and I maintained that role until 2000, so from the formation of Novartis until Syngenta.
Q. When Novartis became Syngenta in the year 2,000, what was your job title for Syngenta?
A. Sure. I transitioned into a new role which was called the operator safety group, and I was an operator and safety specialist.
Q. And what did that job entail?
A. That involved multiple facets; participating and doing risk assessments to determine people's potential exposure based upon work practices or residential behaviors to

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products.
I also participated on task forces and also participated and conducted studies using the different algorithms and study methods to generate the data used in that type of work such at TTR studies, turf, transfer or residue studies, hand press studies or dyslogic (ph) portfolio residue studies.
Q. When you undertook risk assessments, were you out in the field?
A. To generate the data doing those type of studies that would be ultimately used in risk assessments, there would be some field work involved with that, sir. The risk assessments themselves, however, are done in the office.
Q. In generating the data, would you be personally spraying --
A. No, sir.
Q. Did you do any risk assessments on paraquat?
A. No, sir, not that I recall.
Q. Are you, yourself a licensed pesticide

applicant.
A. Yeah, if I may take a step back, I did handle an issue with paraquat in that role but it was not a classic risk assessment as in plugging values and generating MOE-type calculations, it was more dealing with an issue around requirements for a dust mist filter type respirator --
THE COURT REPORTER: I'm sorry for a --
THE WITNESS: I'm sorry, yes, ma'am.
THE COURT REPORTER: Just repeat what you just said?
THE WITNESS: Sure.
The COURT REPORTER: Dealing with issues around requirements for a --
THE WITNESS: Dust mist filter for a --
THE COURT REPORTER: Dust mist?
THE WITNESS: Yes, ma'am. Respirator.
So that wasn't the traditional type of risk assessment that that function would normally have.
BY MR. DICKENS:
Q. So that issue for the dust mist filter

respirator, that was specific to Paraquat?
A. That was, sir.
Q. And what was your role in that particular issue with the dust mist filter respirator?
A. I was contacted by our regulatory team and asked as somebody who works in the area of risk assessment to evaluate I believe it was California's request to include this type of facial covering.
I was asked to do an analysis to see if I could come up with recommendations to either mitigate that or to at least inform the regulatory team on that.
Q. And California's concern was specific to nosebleeds?
A. That is correct, sir.
Q. And nosebleeds reported to California in operators spraying Paraquat?
A. I'm not sure of the source of the reports, but it was concerning trying to reduce the potential for nosebleeds in operators.
Q. And that was something that was actually

reported to California themselves with respect to operators who were experiencing nosebleeds after exposure to Paraquat, right?
MR. HONG: Object to form. Lacks foundation, but you can go ahead and answer.
A. I'm not sure exactly where California would have gotten the information, but certainly, I was asked to address it based upon work for California for that -- that had -- California was requesting it and I was asked to address it.
BY MR. DICKENS:
Q. And you did, in fact, make recommendations with respect to how to mitigate that particular adverse effect, correct?
A. I would have done so in that role and recall that I provided reports and recommendations. I can't remember exactly what those were but that was my duty and I'm sure I would have responded to that.
Q. And we'll look at that in a minute. Did you in your role in operator of residential safety group, did you have any other issues with Paraquat

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that you dealt with?
A. Not that I can recall, sir.
Q. I believe I asked but we went back before I got an answer to the question, are you, yourself a licensed pesticide applicator?
A. No, sir.
Q. Have you, yourself ever sprayed Paraquat?
A. No, sir.
Q. Have you ever been in the vicinity of areas where Paraquat was sprayed?
A. I don't believe I have, sir.
Q. Have you ever seen anyone spray Paraquat?
A. I don't recall having ever seen anybody spray Paraquat, sir.
Q. Were you ever involved in any risk assessments or biomonitoring studies with Paraquat at any point in time in your career at Syngenta?
A. Not with Paraquat, sir.
Q. Now, you remained in the operator and residential safety group until 2006; is that right?
A. That is correct.

Q. And in 2006, you joined the federal regulatory team?
A. Yes, sir.
Q. You were an herbicide regulatory manager?
A. Yes.
Q. Was one of the herbicides you were responsible for Paraquat?
A. It was.
Q. And have you been responsible for Paraquat from 2006 until present?
A. Not until present, sir.
Q. When did you stop having any responsibility for Paraquat?
A. I transitioned to a new role in December of 2022 which is the role I'm currently in. As part of the transitioning, I was leading the herbicide regulatory team, so some time during the course of that summer, my responsibilities on Paraquat were transitioned to another team member.
Q. The summer of 2022?
A. Yes, sir.
Q. An who was that other team member?

A. Jordon Moseley. I did retain some consultancy. I believe I submitted a couple of documents in the 6(a)(2) arena still representing Paraquat, but he was the day-to-day manager of Paraquat starting in that summer.
Q. Is he still in that role or position today?
A. I believe he is, sir.
Q. Going back to 2006 or the 2006 to 2022 timeframe, what were your job responsibilities as herbicide regulatory manager?
A. They were multiple responsibilities; to work internally with business partners, product safety partners, other partners, formulation chemists, to maintain our license and registration of Paraquat, to look at potentially new uses or new formulations.
I also had our primary role of being the lead regulatory contact with EPA on that regulatory matters concerning Paraquat.
Q. And was that true throughout the entire time period of 2006 to 2022?

A. Until the summer of 2022, yes, sir.
Q. Do you also have role as a regulatory portfolio lead?
A. We use that term in our organization. Regulatory herbicide portfolio lead would be a more accurate description, that started in 2017, sir.
Q. And did your job responsibility or role change in 2017 when you transitioned to that position?
A. It did.
Q. In what ways?
A. I took on leadership of the other team members in that group. I went from being a team member to the team leader.
Q. Even as the team member, you were the main contact between Syngenta and the EPA?
A. For regulatory matters, yes, sir.
Q. And for regulatory matters even after you became team lead, you continued to serve as the main contact or conduit between Syngenta and EPA, correct?

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A. For regulatory matters, yes, sir.
Q. Did you have someone you reported to? Who would your supervisor in the 2006 to 2022?
A. There were multiple supervisors during that time frame, they included John Abbott, Dan Campbell, Jerry Wells and Charlie Pearson.
Q. So it's fair to say then between 2006 and the summer of 2022 with respect to Paraquat you were the Syngenta employee who would interact with the EPA most frequently?
A. Most frequently on regulatory matters.
Q. And you maintained ongoing relationships with EPA employees, correct?
MR. HONG: Object to form.
A. Working professional relationships, yes, sir.
BY MR. DICKENS:
Q. And you used those relationships to help navigate difficult issues involving Gramoxone?
MR. HONG: Object to form.
A. So certainly having the working relationships with EPA would use those -- would

contact and have discussions, so yes, sir.
BY MR. DICKENS:
Q. And difficult issues involving Gramoxone did come up between 2006 and 2022, correct?
A. Correct.
Q. And difficult issues you had to deal with the EPA with respect to, right?
A. Correct.
Q. And you were the one who was the main liaison between Syngenta and EPA on those matters?
MR. HONG: Object to form.
A. That would be correct, sir.
BY MR. DICKENS:
Q. So if there was an meeting to be conducted by Syngenta and EPA, it's likely you would have been the one to set up that meeting, right?
A. Most likely, yes.
Q. And would have attended those meetings?
A. Yes, sir.
Q. If there was a question somebody had at the EPA with respect to Gramoxone or any of the Paraquat products registered by Syngenta, EPA

would have come to you first, right?
MR. HONG: Object to form.
A. Most likely.
BY MR. DICKENS:
Q. And your interactions with EPA on behalf of Syngenta would have included communications related to the labeling of Paraquat?
A. That is correct, sir.
Q. Including what information would appear on the labeling for Paraquat?
A. That is correct.
Q. Including information and communications with respect to the safety information included, right?
A. The required regulatory safety information, yes, sir.
Q. And you would agree that the product registrant, in this case Syngenta with respect to its Paraquat products, Syngenta is ultimately responsible for the information on the label?
MR. HONG: Object to form.
A. We provide the information to the label,

that is correct.
BY MR. DICKENS:
Q. To your knowledge, has Syngenta ever informed the EPA that Paraquat may be neurotoxic?
MR. HONG: Object to form.
A. To my recollection, no, sir.
BY MR. DICKENS:
Q. To your knowledge, has Syngenta ever attempted to amend its Gramoxone labeling in the United State to warn users that a neurotoxicity hazard may exist from exposure to Paraquat?
MR. HONG: Object to form.
A. Syngenta, to my knowledge, has never believed there was a neurotoxicity issue, so we would not have amended a labeled for a concern we didn't believe existed.
BY MR. DICKENS:
Q. And you never actually submitted anything to the EPA to warn of that labeling, right?
MR. HONG: Object to form.
A. Specifically to neurotoxicity, sir?
MR. DICKENS: Correct.

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A. No, sir, not that I'm aware of.
BY MR. DICKENS:
Q. To your knowledge, has Syngenta ever attempted to amend its Gramoxone labeling in the United States to warn users that exposure to Paraquat may increase the risk of developing Parkinson's Disease?
MR. HONG: Object to form.
A. No, sir. Syngenta doesn't believe that to be the case, so we would have not made any type of amendments to the label along those lines.
BY MR. DICKENS:
Q. So the only amendments you would make to the labeling or suggest to the EPA to change the labeling is if you absolutely believed there is a link between the Paraquat use and the adverse effect; is that fair?
MR. HONG: Object to form. Mischaracterizes his testimony. You can answer the question.
A. Syngenta would amend the label, for example, as we did during the human health

mitigation to always make sure that our products we use in this most safe manner possible, and if we see opportunities to improve the safety, we would certainly amend the label to do so.
BY MR. DICKENS:
Q. The labeling for the human health mitigation, though, that was suggested initially by EPA, correct?
MR. HONG: Object to form.
A. Not suggested, per se. How that played out, sir, is we were contacted by -- I specifically was acted I believe by a Molly Clayton around 2013ish indicated they had received a letter from a California physician expressing some concerns around accidental ingestion.
She reached out to me to ask if Syngenta could start thinking about ways to further improve the product to prevent the risk of accidental ingestions, and through that, that started a series of dialogs that ultimately led to the human health safety mitigation decision.
BY MR. DICKENS:

Q. How did the labeling change with respect to the human health safety mitigation?
A. So we worked and developed what was called a counter card, and the counter card is something that Syngenta worked with the Agency to develop, and we included not only warnings in English, Spanish, we also developed pictures, Pictograms. We believe that was important safety information all around; do not transfer the material to an unlabeled container, keep it locked up, read the label, keep away from kids, important safety messages.
So we recommended that. The Agency agreed with those recommendations and we've actually provided that -- those images as well to the industry because we thought it was such an important mitigation massive.
Q. First of all, Molly Clayton, she's an EPA employee?
A. She was. I don't believe or cannot confirm she's with the Agency now. She would have been my contact early in the registration review

process.
Q. Do you know where she's at currently?
A. I cannot, sir. I don't know if she's retired or it's been 2013 probably since last we spoke, maybe 2014.
Q. So it's fair to say that the initial contact that was made with respect to the concerns over labeling and increasing the warnings on the labeling, that came from the EPA to you, correct?
A. Correct.
Q. And it wasn't you or anyone at Syngenta that reached out to the EPA and said we think we have a concern here and need to update our label?
A. That is correct.
Q. So EPA is the one who initiated that, indicated they were considering additional warning language and then the dialogue began?
A. Yes, sir.
Q. And you mentioned a closed container, right.
A. I didn't but that was part of that, sir.
Q. When you mentioned the -- fair enough.

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Closed container is something that would allow the mixing of Paraquat without becoming exposed during the mixing process, right?

A. So the primary driver for the closed container was to mitigate the risk associated with decanting the product into an unlabeled container. So that mitigation specifically was designed, for example, to indicate that the only way a closed system would work was that the material could be transferred from the company's packaging into the application equipment through a closed-loop type system.

Our system involved a locking cap that would go into the mixing chamber, so the only way you could open up the container is to have it in the lock, open it up, distribute the product; to get it off, you have to close it.

Now, one important clarity, just for full description of the closed system requirement, that only applies to containers less than 120 gallons. And again, that's based on the concept that people would be very unlikely to decant a product from a

very large container system but much more likely and potential from a small thing like a two-and-a-half-gallon jug where you could pour it out.

Q. Now, that closed-loop system, that technology was available back from the 1960s, right?

MR. HONG: Object to form. Calls for speculation.

BY MR. DICKENS:

Q. If you know?

A. No, sir.

Q. Do you know when the closed-loop system was available?

A. Well, there is no one such closed system. We worked very hard to develop the system that we had; it was based upon an earlier design for a different project, but we found it to be quite a daunting task ultimately to develop a system that would go on those containers that did not run the risk of leaking.

We ultimately were able to do that, but it

was a quite a significant engineering feat to get that done.

BY MR. DICKENS:

Q. It's fair to say that the closed-loop system -- well -- strike that. It's fair to say Paraquat was on the market for over 50 years before the closed-loop system was implemented, correct?

MR. HONG: Objection. Object to form. Calls for speculation.

A. I don't know what closed-loop systems would have been available throughout the history of Paraquat but we did not have a closed-loop system with Paraquat in the U.S. to the best of my knowledge until we went through the human health mitigation system.

BY MR. DICKENS:

Q. My question is a little different. So Paraquat was on the market when?

A. My understanding is from the -- some time in the '60s going forward.

Q. And it's fair to say that from some time

in the 1960s up until 2015, there was no safety measure in place for a closed-loop system?

MR. HONG: Object to form. Lacks foundation. You can answer the question.

A. Yes, sir. But when you say no safety measure in place, I'm not quite sure I'm understanding. There has been technology out there to do that. There was no mandated requirement for that.

BY MR. DICKENS:

Q. And then that's all I'm asking is is Paraquat was on the market for over 50 years before there was a mandate to require a closed-loop system for Paraquat?

MR. HONG: Object to form.

BY MR. DICKENS:

Q. Correct?

A. Yes. That mandate came as part of the human health mitigation, which would have been approximately I believe 2017, '18 approximately. It may have been late 2016, but that's the ballpark and it gave a multi-year time frame to

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shift the manufacturing to that.
Q. Now, you also mentioned counter cards, correct?
A. Correct, sir.
Q. Syngenta initially pushed back against the requirement to have counter cards when initially suggested by EPA; isn't that true?
A. That does not square with my recollection, sir. I believe we were supportive from the start with that, at least in my tenure.
Q. Well, when you say in your tenure, it wasn't until the EPA reached out and some time in 2013 before it was even considered, right?
MR. HONG: Object to form.
A. Certainly from my work experience when they reached out, that's when we started thinking about additional safety measures that went above and beyond what was required on the label.
BY MR. DICKENS:
Q. Does the counter card mention anything with respect to neurotoxicity?
A. To my recollection, no, sir.

Q. Does the counter card mention anything with respect Parkinson's Disease?
A. No, sir.
Q. The counter card with information on neurotoxicity was, in fact, recommended by a Brazilian regulatory agencies, correct?
A. I have a -- I was not in charge or responsible for our Brazilian work. I have a general awareness, but I'm not an expert in that.
Q. You were involved in presenting information with the EPA with respect to what Brazil was doing, right?
A. We certainly updated EPA that Brazil was evaluated Paraquat, yes.
Q. Did you ever update the EPA that Brazil was considering a counter card which included information on neurotoxicity?
A. To my recollection, no.
Q. Now, in the labeling discussions, you'd agree that the EPA relies on Syngenta for proposing use directions, precautions, and warnings for the labeling of its registered

Gramoxone products, correct?
A. I think that would be in the aggregate not a wholly correct, and the reason for that is when the registrants apply for products, apply for registered uses, they submit a proposed label, EPA reviews the label, EPA will make recommendations at times to change the label, and then part as the registration review -- reregistration review process they go through and issue what's called a proposed interim decision and then that lists specific label requirements to use patterns the EPA may require.
Q. When did you first become aware of an association between Paraquat and Parkinson's Disease?
MR. HONG: Object to form.
A. I would say to the earliest of my recollection would be when I moved into the regulatory manager role and became aware of some of the allegations and some of the work that was being done.
BY MR. DICKENS:

Q. And that was in 2006?
A. Yes, sir. I would say I moved to that role in September of 2006, so some time in that time frame moving forward.
Q. And from 2006 moving forward, you've been involved in handling issues related to Parkinson's Disease and specifically with respect to handling that with the EPA; is that right?
MR. HONG: Object to form.
A. So I would have been the liaison reaching out to EPA to set up meetings and make sure that we were able to come in and update our program as necessary.
BY MR. DICKENS:
Q. And the allegation with respect to Paraquat and Parkinson's Disease continue to this day; you're aware of that, right?
MR. HONG: Object to form.
A. I'm aware of the allegations and the literature around that, yes, sir.
MR. DICKENS: I'll hand you what we'll mark as Exhibit 1 to your deposition.

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(Exhibit 1 was marked.)
THE WITNESS: May I take a moment to look through this, sir?
MR. DICKENS: Yes.
THE WITNESS: Thank you. Okay. I think I'm ready, sir.
BY MR. DICKENS:
Q. At the top of Page 1 is an e-mail to you from a Chris Tutino dated August 13, 2021 with a subject, Paraquat talking points.
Do you see that?
A. I do.
Q. Who is Chris Tutino?
A. He was in our communications group, sir.
Q. He mention [As read] "Paul provided me with talking points below on the ID asked if there was anything more that you can say."
Do you see that?
A. I do.
Q. At this point in 2021, it notes that Paraquat is undergoing EPA's regular 15-year reregistration review.

Do you see that?
A. I do.
Q. And this is in '20. In '21, has EPA concluded its reregistration review?
A. Are you asking have they currently?
Q. Correct.
A. They issued a proposed interim decision which is part of that process.
Q. So part of that process but it's not completed yet?
A. It's not fully completed. No, sir.
Q. So its now been 18 years roughly that the reregistration review has been going on with respect to Paraquat?
A. I believe it started in 2011.
Q. So my math is terrible but 13 years, is that --
A. That's correct.
Q. There's some talking points on Page 2 that were sent over to you.
MR. HONG: And just are you referring to the Bates ending in 9613?

MR. DICKENS: That's correct.
MR. HONG: Just so the record is clear, it was not sent to Mr. Dixon.
BY MR. DICKENS:
Q. This e-mail chain was forwarded to you, correct, sir?
A. It is part of this e-mail chain, it appears.
Q. And in fact, the e-mail we initially looked at said "provide me with the talking points below." Right?
A. It does say that.
Q. So the talking points -- and that's Paul, specifically. That's Paul Minehart, right?
A. That is correct.
Q. And these are the talking points on Page 2 which are forwarded over to your attention?
A. Yes, sir.
Q. Who is Paul Minehart?
A. Paul Minehart was in our communications group, sir. I think he was the lead at one point.
Q. And when you say communications group,

that's a group responsible for communicating information about Syngenta products publically, right?
A. That's a fair statement, yes, sir.
Q. Basically can use these reactively.
Do you see that?
A. I do.
Q. And reactively means in response to questions, correct?
MR. HONG: Object. Objection. Lacks foundation but go ahead.
A. I'm not exactly sure what Paul's thinking there but that's my understanding of the term reactive.
BY MR. DICKENS:
Q. And that's a term that was used within Syngenta, right?
MR. HONG: Objection. Form.
A. That I can't speak to, sir. I see it in this e-mail.
BY MR. DICKENS:
Q. And then there's talking points. It

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states, "For more than 55 years, Syngenta Paraquat products have been approved by U.S. regulatory agencies as safe and effective."

Do you see that?

A. I do.

Q. And that is one -- a talking point of Syngenta at this time in 2021, right?

MR. HONG: Object to form.

A. I would answer yes. EPA has a federal obligation to ensure that before a product is registered, that it can be used safely as intended.

MR. DICKENS: I'll move to strike everything after yes.

BY MR. DICKENS:

Q. Sir, that's a message that is -- continues to be a talking point to this day, right?

A. Yes.

Q. The next bullet point under Paraquat overview, the last one, [As read] Syngenta committed to product stewardship on helping people stay safe."

Do you agree with that statement?

A. Can you tell me exactly, sir --

Q. Yeah, the last bullet point under Paraquat overview?

A. Paraquat overview. I'm sorry, yes. Yes, I agree with that point, sir.

Q. And that's a message that's not only told by Syngenta to the public but also a message that's communicated to the EPA, right?

A. It is a commitment that we live up to, so yes, sir.

Q. Then there's [AS read] "Paraquat litigation relating to Parkinson's."

Do you see that that?

A. Yes, sir.

Q. Third bullet point [As read] "There's no critical evidence that Paraquat, which has been wide whether I used for more than 55 years, causes Parkinson's Disease."

Do you see that?

A. I do see that.

Q. And that's a talking point and a message

to the public in 2021, right?

MR. HONG: Object to form.

A. That is a proposed talking point, sir.

BY MR. DICKENS:

Q. But that's not only a proposed talking point, that is actually what Syngenta was telling the public in 2021, right?

MR. HONG: Object to form.

A. I would like to see the final version of this, but I believe that is consistent with our position that Paraquat does not cause Parkinson's Disease.

BY MR. DICKENS:

Q. And not only your position, but you're saying there's no credible evidence that Paraquat causes Parkinson's Disease; is that the position of the company as you understand it?

MR. HONG: Object to form.

A. No, sir, I can't speak on behalf of Syngenta as the company, sir.

BY MR. DICKENS:

Q. Is that a message as far as you know that

was said publically that there is no credible evidence that Paraquat causes Parkinson's Disease?

A. I'm certainly not aware of all public statements, but I believe our position is consistent with the science it does not cause Parkinson's Disease, so I would certainly anticipate we would say that publically.

Q. And this is from the communications group once again; Paul Minehart, right?

A. That's who sent this e-mail, yes, sir.

Q. It mentions [As read] "No peer reviewed study including the largest study which included 38,000 farmers has ever concluded Paraquat causes Parkinson's Disease."

That's a -- Syngenta's public message in 2021; is that right?

MR. HONG: Object to form.

A. That's what the bullet point does say, sir.

BY MR. DICKENS:

Q. Do you know what the largest study involving 38,000 farmers is referring to?

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A. Not with definitive. I'm not an expert in that area. My assumption is it's the Ag health study.

Q. Now, you agree there are peer reviewed studies that have concluded or shown that Paraquat substantially increases the risk or association of Paraquat exposure on Parkinson's Disease?

MR. HONG: Object to form.

A. Can you please restate that, sir.

BY MR. DICKENS:

Q. Yeah. There have been studies that have shown a statistically significant increased risk of Parkinson's Disease after exposure to Paraquat?

MR. HONG: Object to form. Calls for expert testimony. Go ahead and answer.

A. And I'm certainly not an expert in that area. I do know there are studies that have alleged an increase. So but as far as the validity of the studies, I can't speak to them.

BY MR. DICKENS:

Q. Next one [As read] "EPA and other government -- government authorities have

extensively analyzed this issue and similarly found no evidence that Paraquat causes Parkinson's Disease."

Again, that's a public message from Syngenta in 2021, correct?

A. That is what the talking point says, yes, sir.

Q. And that is a public message of Syngenta to this day, right?

A. I can't speak on behalf of Syngenta, sir.

Q. Now, this talking point doesn't mention anything about the fact that Paraquat is banned in dozens of countries, does it?

A. No, sir.

Q. It doesn't mention that government authorities have extensively analyzed the issue and found evidence that Paraquat causes Parkinson's Disease, right?

MR. HONG: Object to form.

A. It does not state that, sir.

BY MR. DICKENS:

Q. And, in fact, that had occurred by 2021

that government authorities had analyzed the issue and found evidence that Paraquat causes Parkinson's Disease; you would agree with that?

MR. HONG: Object to form.

A. I can't say that I would agree with that, sir. I don't know all of the government analyses. I certainly know the agency EPA has evaluated and believes there's not a limited or there's not a sufficient evidence to establish a relationship between Paraquat and Parkinson's disease. I believe ANVISA has a similar thing, but I can't speak -- I was only responsible for U.S. EPA interactions.

BY MR. DICKENS:

Q. As you sit here today, are you aware of any government authority that has analyzed the issue and found that Paraquat causes Parkinson's Disease?

MR. HONG: Object to form. Assumes facts not in evidence. Go ahead and answer the question.

A. I'm not aware of any government that has

made a definitive conclusion. I do have a general awareness that Brazil was requiring statements around Parkinson's Disease so that would certainly seem to indicate that they looked at that issue.

BY MR. DICKENS:

Q. You actually reviewed ANVISA Brazil's report with respect to their analysis of Paraquat and Parkinson's disease in your role as herbicide regulatory manager between 2006 and 2022, did you not?

A. I certainly think I recall seeing that, yes.

Q. Next section, [As read] "Has Syngenta settled any lawsuit?" Mentions Syngenta settled claims at California and Illinois courts related to Paraquat. You are aware of that, right?

A. I am.

Q. You want to emphasize entering an agreement knowing applies Paraquat causes Parkinson's Disease or that Syngenta's done anything wrong; that's the position you maintain today, right?

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MR. HONG: Object to form. Where is that in the document, Counsel?
MR. DICKENS: It is the third bullet point.
MR. HONG: Got it.
A. That is the position in the bullet point. Yes, sir.
BY MR. DICKENS:
Q. And you'd agree that manufacture of a pesticide, like Syngenta, must take responsibility for assuring that its products are safe?
A. I agree.
Q. Now, you mention -- strike that.
We can put that away. You're familiar with the World Health Organization?
A. Broadly, yes.
Q. It's a United Nations --
THE COURT REPORTER: I'm sorry. Answer.
A. Broadly, yes.
BY MR. DICKENS:
Q. It's a United Nations organization dedicated to promoting health and safety around

the world?
A. Yes, sir.
Q. You'd agree it's a credible and well-respected organization?
A. I'm not an expert on it, but certainly I know of, heard of World Health Organization, so I would assume it's a credible organization.
MR. DICKENS: Let's go ahead and mark Exhibit 2.
(Exhibit 2 was marked.)
MR. DICKENS: I handed you exhibit --
A. May I take a quick second to read this.
MR. DICKENS: You sure can.
THE WITNESS: Thank you.
MR. DICKENS: Exhibit 2 is a -- for the record, a document that was marked as an exhibit in your earlier deposition and is a printout from Paraquat.com, Paraquat information center?
A. Yes, sir, it looks very familiar. I'm not going to read through it but in general I'm familiar with this.
BY MR. DICKENS:

Q. And I'm going to actually direct your attention to the third page, Bates number ending 8922.
A. 8922. Okay, sir.
Q. And before we get there, so Paraquat.com that is a Syngenta website, right?
A. That is my understanding.
Q. And this is a website where Syngenta posts information about Paraquat information including safety, right?
A. Yes, sir.
Q. And this is a website that consumers or users are directed to to find information with respect to Paraquat?
A. Correct.
Q. At the bottom of page 3, there's a question: Is Paraquat safe to farmers?
Do you see that?
A. Yes.
Q. The second paragraph beginning, In 2004, do you see that?
A. I do.

Q. It says [As read] "2004 Paraquat was again reviewed by leading international organizations including food and agriculture organization, UN joint meeting on pesticide residues, which is comprised of experts from the World Health Organization, right?
A. Yes, I'd like to read that paragraph real quickly. Okay. Yes, sir.
Q. It goes on [As read] "These experts support that when used as directed, there's no safety hazard associated with Paraquat." That's what is being told to consumers and the public with respect to, is Paraquat safe to farmers?
A. That's certainly what is stated there.
Q. So Syngenta is referring consumers to experts from the World Health Organization as concluding there's no safety hazard associated with the use of Paraquat, right?
MR. HONG: Object to form.
A. It's relaying the statement there that discusses the World Health Organization, yes, sir.
BY MR. DICKENS:

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Q. Now, the World Health Organizations called for the ban of Paraquat as part of the global strategy to combat Parkinson's Disease, right?

MR. HONG: Object to form.

A. I have no specific knowledge of that but if you're asserting that's the case, then I don't dispute that, sir.

MR. DICKENS: I'll go ahead and mark Exhibit 3 for the record.

(Exhibit 3 was marked.)

THE WITNESS: Are we done with this one, sir?

MR. DICKENS: We are.

BY MR. DICKENS:

Q. Again on top of Exhibit 3 is an e-mail from Chris Tutino to yourself on July of 2022.

At this point, have you taken on your new job position?

A. I -- this is about the time frame when I was transitioning to that new role roughly. I can't give you the specific date but that's the summer where I made that transition.

Q. He's forwarding WHO PQT understanding World Health Organization of Paraquat, right?

A. Yes, sir.

Q. He said, [As read] "Per my text call, see below."

Do you see that?

A. I do.

Q. Now, would you receive text messages from time to time from Syngenta employees with respect to Paraquat?

A. From time to time I would receive a text message. Typically it would be something, like, you know, Monty, can you give me a call.

Q. Did you have a company cell phone?

A. I do.

Q. Have you had a company cell phone from at least 2006 to the present?

A. Yes, sir.

Q. Is that where you would typically receive text messages from Syngenta employees?

MR. HONG: Object to form.

A. Yes, sir.

BY MR. DICKENS:

Q. Do you recall the text and call from Chris Tutino with respect to the World Health Organization?

A. I do not recall that. I'm looking at the document here. Clearly, he indicates that he did.

Q. And he's forwarding you an e-mail from a Jay Byrne at V Fluence. Do you see that?

A. I do.

Q. Do you know who Jay Byrne or a V Fluence is?

A. Does not ring a bell with me, sir.

Q. That e-mail forwards you [As read] "W-H-O World Health Organization launches global strategy to combat Parkinson's Disease, including a call to ban Paraquat as well as chlorpyrifos." Is that right?

A. Yes, sir.

Q. Goes on later on mentions that launches global strategy, may publish the technical brief entitled Parkinson's Disease and public health approach?

Do you see that?

A. Where is that, sir?

Q. It's in the text of the Page 1 under the WHO launches global strategy in that first two sentences?

A. Okay. I see that, World Health launches global strategy. Yes.

Q. The technical brief calls to ban pesticides and chemicals.

Do you see that?

A. I do see that. Yes, sir.

Q. With respect to this, you've reviewed the World Health Organization's technical brief; is that right?

MR. HONG: Object to form.

A. I do not recall reviewing that, sir. In my role as a U.S. regulatory person, I would have been more focused on U.S. and this most likely would have been reviewed in depth by our global regulatory team.

BY MR. DICKENS:

Q. But it's fair to say that at least with

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respect to the information provided to consumers there is -- on the Paraquat.com website, there's reliance on the World Health Organization for finding that there's no safety hazard associated with the use of Paraquat, right?

MR. HONG: Again, object to form. Assumes facts not the evidence.

THE WITNESS: Could you restate that please, sir?

BY MR. DICKENS:

Q. Exhibit 2, which we looked at earlier, Paraquat.com?

A. Right.

Q. Refers to World Health Organization, experts from the World Health Organization and their finding that no safety hazard associated with the use of Paraquat?

MR. HONG: I'm going to object to form. Assumes fact not in evidence. Go ahead and answer the question.

A. It does state that in the document, sir.

BY MR. DICKENS:

Q. And that's a document that's on -- that was on the website for that Syngenta would instruct users or consumers to go to on safety information, right?

A. In general, yes. I don't believe there's any direct references on our labels to that website.

Q. Has Syngenta ever taken any steps to warn users within the United States that the World Health Organization has called for a ban of Paraquat?

MR. HONG: Object to form. Lacks foundation. You can go ahead and answer the question.

A. I don't believe we have, and that would be unlikely. The U.S. EPA has its own regulatory process, so the work we do in the U.S. would be to satisfy the U.S. regulatory guidelines and make sure products are compliance with EPA's guidelines.

BY MR. DICKENS:

Q. Well, you're not saying, sir, that the EPA

prevents you from posting information on your website that the World Health Organization has called for a ban of Paraquat, are you?

MR. HONG: Object to form.

A. So actually if you make any links on the label to a website, that website becomes subject to EPA's labeling requirements. So I don't believe EPA would force a registrant to put a statement on their label that's -- you must go see the WHO for information. I don't think that's what EPA would do.

BY MR. DICKENS:

Q. Well, you've transitioned that to labeling, sir. The information we saw on Paraquat.com we just looked at was -- did the EPA approve that; the information on Paraquat.com with respect to the question: Is Paraquat safe for consumers?

MR. HONG: Objection. Lacks foundation.

A. So EPA would not be involved with any reviews of Paraquat.com, that is a global website. EPA would be focused on U.S. regulatory matters.

BY MR. DICKENS:

Q. Is there anything -- and you mentioned if there was a link to something on the labeling, the EPA would regulate that as labeling for the product, right?

MR. HONG: Object to form.

A. They reserve the right to do that.

BY MR. DICKENS:

Q. But certainly Syngenta could have outside of the labeling or linking to an unlabeling, informed users and consumers of World Health Organization's call to ban Paraquat for Parkinson's Disease, right?

MR. HONG: Object to form. Calls for speculation. Go ahead and answer.

A. I wouldn't want to speculate on how Syngenta would do that, sir.

BY MR. DICKENS:

Q. But if it wasn't linked to on the labeling, the EPA wouldn't prevent Syngenta from informing consumers about a potential health risks, right?

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MR. HONG: Object to form. Calls for speculation.
A. Yes, and EPA, I wouldn't want to speak on behalf of EPA.
BY MR. DICKENS:
Q. Has Syngenta ever informed consumers about their thoughts between the link on Paraquat and health effects without the EPA approval?
MR. HONG: Object to form.
A. Syngenta has been involved in publications, been involved Paraquat research, so that is a public presentation of the information we've generated.
BY MR. DICKENS:
Q. So EPA -- Syngenta can tell consumers on Paraquat.com that experts from the World Health Organization support that there's no safety hazard associated with the use of Paraquat, but can't tell them that World Health Organization experts found there is a safety hazard; is that your testimony?
MR. HONG: Object to form.

Mischaracterizes testimony.
A. As it's a global website, I wouldn't want to speak for Syngenta on that.
BY MR. DICKENS:
Q. You mention it's a global website. It's a website, once again, that Syngenta would instruct consumers and users within the United States to as well, right?
MR. HONG: Object to form.
A. I certainly would think it's in the realm of possibility there might be references there. I'm not familiar with us specifically directing people to any particular website, sir.
BY MR. DICKENS:
Q. Are you aware of whether or not Syngenta had a separate website specific to the United States?
A. We do have for our products region-specific websites, but that's, like, for the Syngenta product listing, there would be Syngenta USA website where you go and look at Syngenta products -- U.S. products. This would be

Syngenta Canada, so there are regional-specific websites directly associated with the Syngenta products.
MR. DICKENS: Hand you what we'll mark as Exhibit 3.
MR. HONG: I think it's Exhibit 4.
MR. DICKENS: I'm probably going to say three, three more times today but thank you. Exhibit 4.
(Exhibit 4 was marked.)
THE WITNESS: Sir, after we do this one, can I have a brief biological break?
MR. DICKENS: If course and this should not take long.
THE WITNESS: Okay. Thank you.
MR. HONG: Counsel, is this a produced document?
MR. DICKENS: It is not.
MR. HONG: Do you have a date then for this document?
MR. DICKENS: Per Page 3 it's in the 2022 time frame.

BY MR. DICKENS:
Q. Sir, he Exhibit 3 we did just look at mentions the technical brief entitled Parkinson's Disease, a public health approach, correct?
A. Yes, sir.
Q. I've handed you Exhibit 4, which is the technical brief Parkinson's Disease at Public Health Approach.
Turn your attention to Page 3 -- or Page 2 of this document. There's a copyright there, World Health Organization 2022.
Do you see that?
A. When you say Page 2 --
Q. Oh, I'm sorry. It's not Page 2. Page 3. I apologize.
A. Are we talking this page, sir?
Q. That's correct.
Just on the top, there's a World Health Organization says 2022?
A. Yes, sir.
Q. Now, turn two more pages to acknowledgments?

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A. Okay.
Q. It says, project coordination and editing?
A. I see that.
Q. Then they list some individuals who were involved including a Corell Shot (ph), Columbia, Linda -- why did I do this -- Nwabuobi at Weill Cornell Medical Center.
Do you see that?
A. I do.
Q. And then it mentions there's some expert reviewers, and in April of 2021, made vital contributions to the development of the Parkinson's Disease technical group.
Do you see that?
A. I do.
Q. And on the next page it mentions financial support and acknowledges financial support from the Edmond J. Safer Foundation (ph).
Do you know what that foundation is, by any chance?
A. I'm afraid I don't, sir.
Q. There's no financial support here from any

registrants or pesticide manufactures; you'd agree on that?
A. I -- it certainly doesn't state that.
Q. Okay. No one from chemical industries or anything along those lines?
A. This is the first time I've seen this document. I don't see any indication of anything other than what's there, sir.
Q. And when you received the e-mail and the text and the call from Chris Tutino with respect to the World Health Organization, you didn't go and try to review what the technical brief actually said?
MR. HONG: Object to form.
THE COURT REPORTER: I'm sorry. Review what the technical...
MR. DICKENS: Brief actually said.
A. I don't believe I did that, sir.
BY MR. DICKENS:
Q. Do you recall why Chris Tutino was contacting you then with respect to World Health Organization's findings?

MR. HONG: Object to form. Lacks foundation.
A. I wouldn't want to speculate.
MR. HONG: Then don't speculate, sir.
BY MR. DICKENS:
Q. Do you know why Chris Tutino was contacting you?
MR. HONG: Same objection. Call -- lacks foundation.
MR. DICKENS: What's the lack of foundation? I'm asking --
MR. HONG: You're asking him --
MR. DICKENS: If he knows?
MR. HONG: Yeah, isn't that what you just said?
MR. DICKENS: Yeah, do you know?
MR. HONG: If he knows if Chris Tutino was contacting him?
BY MR. DICKENS:
Q. Sir, you agreed Chris Tutino contacted you with respect to the World Health Organization findings in this technical brief, correct?

A. I received the e-mail that was presented as Exhibit 3, yes, sir.
MR. HONG: And that's a different question, Counsel.
MR. DICKENS: That foundation had already been established early in the deposition, but if you want me to do it every question, then we're going to have a problem here in this deposition, we'll probably be back another day.
BY MR. DICKENS:
Q. Sir, with respect to this particular technical brief, if we can turn our attention to what's actually on the very bottom, Page 13 of this actual brief.
A. Page number 13, sir? This one, sir.
Q. Yeah, it's prevention and risk reduction on the top.
A. Okay.
Q. And actually the page right before that begins, kind of, key actions.
Do you see that?
A. I do.

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Q. And these are key actions proposed by the World Health Organization, and then there's prevention and risk reduction.

Do you see that?

A. I do, yes, sir.

Q. [As read] "And for prevention and risk reduction for Parkinson's Disease, plant pesticides Paraquat, chlorpyrifos and chemicals trichloroethylene, which had been linked to Paraquat and develop safer alternatives as per guideline -- or guidance.

Do you see that?

A. I do.

Q. We can agree that the World Health Organization in this technical brief for prevention and risk reduction of Parkinson's Disease is recommending as a key action to ban Paraquat as its been linked to Parkinson's Disease, right?

MR. HONG: Objection to form.

A. That's what's stated there, sir.

MR. DICKENS: We can go ahead and take the

break.

THE WITNESS: Okay. Thank you.

THE VIDEOGRAPHER: Time is 10:03 a.m. we're now off the record. Microphones, everyone. (A break was taken from 10:03 a.m. to 10:15 a.m.)

THE VIDEOGRAPHER: This is the beginning of media unit No. 2 in the video recorded deposition of Mr. Montague Dixon. The time is 10:15 eastern. We are back on record. Counsel, you may proceed.

BY MR. DICKENS:

Q. Welcome back, Mr. Dixon. If you can bring back up Exhibit 3, which is the e-mail from Chris Tutino to you, World Health Organization and Paraquat.

A. Yes, sir.

Q. We've discussed on Page 1 the technical brief. If you can turn to Page 2. At the very top [As read] "WHO researchers note increase Parkinson's risk among those exposed to pesticides and note to study published JAMA Neurology."

Do you see that?

A. I do.

Q. And you're familiar with JAMA Neurology?

A. No, sir, I'm not.

Q. Do you understand that it's a journal?

A. It appears to me to be a science journal, yes, sir.

Q. [As read] "Note six action steps to address global disparities in Parkinson's Disease and World Health Organization priority."

Do you see that?

A. I do.

Q. And then it lists a number of individuals. Do you see that?

A. I do.

Q. For example, Nicoline Schiess with the Brain Health Unit of the World Health Organization, right?

A. Oh I'm sorry. The very first one, yes.

Q. Same thing with Rodrigo Cataldi, Ph.D with the Brain Health Unit of the World Health Organization?

A. Yes.

Q. Michael Okun, Department of Neurology and

associate editor of JAMA Neurology, right?

A. Yes, sir.

Q. On the next page there are the two individuals that we highlighted as the coordinating writers and editors of the technical brief that we looked at for Exhibit 4. Do you see that, Lynda Nwabuobi and Hiral Shah?

A. I do not see that highlighted but that's who we're talking about there, yes.

Q. And it mentions later on JAMA Neurology published online July 11, 2022?

A. I do see that, yes, sir.

Q. And then on two more pages from there, Bates number ending 55039, there's prevention and risk reduction?

A. I see that.

Q. And the second paragraph it begins, [As read] "Evidence linking exposure to pesticides with the risk -- "evidence linking exposure to pesticides with the risk of developing Parkinson's Disease is substantial and supported by multiple metaanalysis."

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Do you see that?
A. I do.
Q. Do you agree that evidence linking pesticides and Parkinson's Disease is substantial?
MR. HONG: Object to form.
A. I'm not a topological expert. My understanding really comes from what I've been monitoring, for example, with the Agency recently published, sir.
BY MR. DICKENS:
Q. Well, the public statements of Syngenta close to a year before this was that there was no credible evidence that Paraquat caused Parkinson's Disease, right?
A. I can't speak to the Syngenta public statements.
Q. You did receive a copy of the talking points --
A. I did, yes, sir.
Q. And you would agree that those talking points included a statement that there's no credible evidence that Paraquat causes Parkinson's

Disease?
A. I seem to recall that being in that talking point.
Q. I believe it's Exhibit 1?
A. Exhibit 1. I just want to make sure. Okay.
Q. These authors published in JAMA Neurology also say [As read] "Some of the most common used pesticides such as Paraquat and chlorpyrifos have been associated with an increased risk of Parkinson's disease and are banned in many countries, although not in the United States."
Do you see that?
A. I do.
Q. As you sit here today, are you able to say that the authors of this JAMA Neurology article are not credible?
A. I do not know these authors, so I can't speak to that.
Q. Would you agree that publications suggesting there's an association between Paraquat and Parkinson's Disease were considered a threat

to Paraquat?
MR. HONG: Object to form.
A. If you'd restate that please.
BY MR. DICKENS:
Q. Would you agree that statements and publications suggesting there was an association between Paraquat and Parkinson's Disease was considered a threat to Paraquat?
MR. HONG: Same objection.
A. A threat by who, sir?
BY MR. DICKENS:
Q. Just a regulatory threat to Paraquat.
A. Certainly Syngenta was monitoring what was going on and wanted to understand the science, so when Syngenta is aware of any issues around its products, it would do due diligent investigation to make sure that the products were safe. So if they were seeing those allegations, they would react to it.
BY MR. DICKENS:
Q. Syngenta was not only monitoring the issue but also developing strategy to diffuse potential

threats to Paraquat since the time you were an operator exposure specialist for the company?
MR. HONG: Object --
BY MR. DICKENS:
Q. Correct?
MR. HONG: -- to form. Lacks foundation.
A. I can't speak for Syngenta on that.
BY MR. DICKENS:
Q. Well, you knew that Parkinson's Disease was an inevitable threat to Paraquat all the way back to the early 2000s; isn't that right?
MR. HONG: Object to form.
A. My personally?
BY MR. DICKENS:
Q. Correct?
A. I first learned about these allegations probably in 2006 or '07, sir.
Q. You knew nothing about potential Paraquat and Parkinson's Disease before that time?
A. To the best of my recollection, no, sir, I was not familiar with Paraquat until I moved into the regulatory world other than that the issue

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around nosebleeds.
Q. You didn't attend meetings where Paraquat and Parkinson's Disease was discussed?
A. Certainly not prior to 2006.
Q. And prior to 2006, you didn't attend meetings where the company was discussing ways to combat allegations of Paraquat and Parkinson's Disease?
MR. HONG: Object to form.
A. Certainly prior to 2006, no, sir. Certainly none that I recall.
MR. HONG: Let's wait for a question, Mr. Dixon.
THE WITNESS: Okay.
BY MR. DICKENS:
Q. Now, part of your goal in your role with the company was to improve the public image of Paraquat to maintain the company's freedom to sell, right?
MR. HONG: Object to form.
A. I would not say I had a role in Paraquat's public image, my role was to ensure that we met

all the regulatory guidelines and requirements.
BY MR. DICKENS:
Q. And to maintain the freedom to sell, right?
A. Correct.
Q. And free to sell was a term used within the company?
A. I've heard license to sell, freedom to operate, yes, sir.
Q. And freedom to sell?
A. I don't specifically recall, but would not say that's out of the realm of possibility.
MR. DICKENS: Go ahead and mark Exhibit 5.
(Exhibit 5 was marked.)
THE WITNESS: I'll just scan this real quick. Okay. Thank you.
BY MR. DICKENS:
Q. Direct your attention to the e-mail on top of page from Mike Clapp to numerous individuals including yourself right, Mr. Dixon?
A. I do.
Q. And this e-mail is from October 4th, 2001,

right?
A. Yes, sir.
Q. So this is shortly after you became employed by Syngenta?
A. Correct.
Q. Certainly well before 2006, right?
A. Yes, sir.
Q. Who is Mike Clapp with the company in 2001?
A. My recollection is he was one of our senior scientists, sir.
Q. And he states [As read] "Agree there appears to be -- currently be no regulatory concern with respect to Paraquat registration in the U.S. However, there have continued to be new publications or presentations in scientific for our literature during 2001 as researchers promote their hazard models of predicting Parkinson's Disease which could alert EPA to further reviews at some time in the future."
Do you see that?
A. I do, yes, sir.

Q. And specifically, the subject here of this e-mail is specific to Paraquat, right?
A. Yes, sir.
Q. And one of the senior scientists in 2001 is bringing to individuals' attention that there are publications and scientific literature concerning pesticides and Parkinson's Disease, right?
MR. HONG: Object to form.
A. That is what's contained here, yes, sir.
BY MR. DICKENS:
Q. And there was a concern with the company all the way back now in 2001 that this could alert EPA to review whether or not there was an association between Paraquat and Parkinson's Disease; that's your understanding, right?
MR. HONG: Objection. Lacks foundation.
A. Certainly Mike Clapp seems to be indicating that, sir.
BY MR. DICKENS:
Q. And indicating it to various individuals including yourself, right?

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A. Right.
MR. HONG: Same objection.
BY MR. DICKENS:
Q. Later on in the middle, what appears to be the second paragraph is a sentence that begins, As you are aware?
A. Yes, I see that.
Q. Says [As read] "As you are aware, we need to promote Paraquat strengths to improve the perceived image to maintain not only the license to sell, but importantly the freedom to sell."
Do you see that?
A. I do see that.
Q. So those of you -- well, let me ask, those who were included in this e-mail, were they, including yourself, within a particular group with Syngenta at this time?
A. Sure. As I look across this e-mail, there seems to be a relatively wide diversity of individuals. So I see Leah Rosenheck, for example, she was my leader; this was when I was in the operating residential safety group.

I see Nina Heard who would have been in our dietary safety group. Nancy Tout who was our Canadian. I see different scientists, Jerry Wells who was a regulatory manager. So I would say a cross section of different functions within the organization.
Q. So this wide variety, this relatively wide group of individuals as a whole needs to promote the strengths of Paraquat to prove the image and maintain that freedom to sell, according to Mike Clapp, right?
MR. HONG: Object to form.
A. That's what Mike Clapp is writing here.
BY MR. DICKENS:
Q. And freedom to sell is to diffuse threats to the products so that they could be sold with no regulatory restrictions; is that fair?
MR. HONG: Object to form.
A. I'm not exactly sure what Mike meant by freedom to sell, sir.
BY MR. DICKENS:
Q. Did you ask him?

A. Not that I recall. I don't even recall this e-mail here, sir.
MR. DICKENS: Go ahead and mark Exhibit 6.
(Exhibit 6 was marked.)
BY MR. DICKENS:
Q. Exhibit 6 are minutes from June 9, 2003 Paraquat RDT regulatory science foresight meeting.
Do you see that?
A. I do.
Q. And it lists the attendees. You're included as an attendee at this particular meeting, right?
A. I -- yes, sir.
Q. And under the minutes, Ian Wheals --
A. I think that's how you say his name.
Q. -- welcomed the extended Paraquat regulatory development team and explained the emphasis of the June 9, 2003 session.
Do you see that?
A. Yes.
Q. So in 2003 you were part of the extended Paraquat regulatory development team, right?

A. Yes, sir.
Q. And as part of the Paraquat regulatory development team, you would have received copies of the minutes after they were taken?
A. Correct.
Q. And the emphasis of that particular session is, raising the level of regulatory science foresight with the intention to focus on topics including Parkinson's Disease neurotox hazard.
Do you see that?
A. I do.
Q. So at this stage in 2003, certainly you were aware of Parkinson's Disease and neurotoxicity hazards specific to Paraquat?
A. Based upon this document, I would have been aware at that time, yes sir.
Q. It also mentions operator exposure?
A. That is correct, that was the role I had at that time, sir.
Q. And operator exposure means exposure of Paraquat to the individuals who were actually

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using the product, right?
A. Correct.
Q. Goes on, [As read] "The objective is to move from a situation where we work predominantly reactively in discrete scientific disciplines to a situation where we have coherent strategy across all disciplines focusing on external influencing that proactively diffuses the potential threats that we face." Right?
A. Correct.
Q. That was the objective of this particular --
A. So stated there, yes, sir.
Q. And external influencing referred to influencing individuals outside the company to support the safety profile of Paraquat?
MR. HONG: Object to form.
BY MR. DICKENS:
Q. Correct?
A. I don't recall specifically but that's what the term external influencing would mean to me as I looked at it.

Q. And that's a term internal influencing used within Syngenta, right?
A. I've heard that term before, yes, sir.
Q. And that's how you know what that definition is is based on your time within Syngenta?
A. Correct.
MR. HONG: Object to form.
BY MR. DICKENS:
Q. And one of those potential threats being faced, as we discussed earlier, was that PD, Parkinson's Disease and neurotox hazards, right?
THE COURT REPORTER: I'm sorry. Parkinson's disease and.
MR. DICKENS: Neurotox hazards.
A. That certainly appears to be the focus here.
MR. DICKENS: Turn to Page 3 ending Bates number 23456?
THE WITNESS: Okay. I have that, sir.
BY MR. DICKENS:
Q. At the very top once again, Mike Clapp is

mentioned.
Do you see that?
A. I do.
Q. He gave a general introduction to set the context of the discussion on potential threats posed by Parkinson's Disease issues, right?
A. That's what's reported, yes, sir.
Q. This is the same Mike Clapp that we saw in 2001 had sent an e-mail to you and others noting the importance of promoting Paraquat strengths to maintain licence to sell and the freedom to sell, right?
MR. HONG: Objection to form. Mischaracterize the document. You can answer.
A. I believe that is the same Mike Clapp.
BY MR. DICKENS:
Q. In the chart below, there's NAFTA.
Do you see that?
A. I do.
Q. And that includes North America, right?
A. That would, yes, sir.
Q. And ultimately, when you became part of

the regulatory team, you were in charge of part of, kind of, the NAFTA group within Syngenta?
A. With NAFTA group within Syngenta but with specific U.S. responsibility.
Q. Discussed at this meeting, although Parkinson's Disease has not been raised as a regulatory issue at this time. I'll stop there. You would agree at this time the EPA had not raised with Syngenta concerns of Parkinson's Disease; is that fair?
MR. HONG: Object to form.
A. Based upon my recollection and knowledge, I think that's an accurate statement. I was not in the regulatory arena at that point, though, I was in the operator safety group, so a little different role.
BY MR. DICKENS:
Q. When you came into the regulatory role in 2006, did you go back and review what had been communicated to the EPA prior to you taking on that position?
A. On a case-by-case basis, not specific to

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this issue, but if I was going to do, for example, a submission of a revised CSF, which is confidential statement formula or other regulatory actions, columns, petitions or whatever, I would look at previous work to know what was previously said.

Q. Did you -- when you got your role in 2006, go back to see what Syngenta had submitted to the EPA with respect to Parkinson's Disease specifically?

A. I do not recall so doing so.

Q. Did you do so at any point between 2006 and 2022 go back to see what Syngenta had communicated to the EPA on Parkinson's Disease prior to your taking on the position in 2006?

MR. HONG: Object to form.

A. Later in that time frame we did go back and make some additional study submissions, and as part of that, I would have seen the history that we did up to that point.

BY MR. DICKENS:

Q. When -- when you say we went back and made

additional study submissions, what time frame was that?

A. Approximately 2019, sir.

Q. Are you referring to the Marks studies?

A. Yes.

Q. And in Marks studies, those were neurotoxicity studies that were conducted at Syngenta?

A. I believe at the CTL Laboratories, yes, sir.

Q. And CTL Laboratories, that's kind of, the scientific investigative arm of Syngenta?

MR. HONG: Object to form.

BY MR. DICKENS:

Q. To your understanding?

MR. HONG: Same objection.

A. CTL was where we had a very strong toxicology group of experts where our tox work would have been done.

BY MR. DICKENS:

Q. And Louise Marks she was a toxicology with Syngenta?

A. That's my understanding.

Q. And she conducted tests or studies where she administered Paraquat to mice; is that correct?

A. That is my understanding.

Q. And she found statistically significant reduction in dopaminergic neurons in those studies, didn't she?

MR. HONG: Object to form. Assumes fact not in evidence.

A. That's my understanding. I don't know the exact specifics of those studies. I couldn't speak about the specifics, but I believe there were findings.

BY MR. DICKENS:

Q. And those studies were conducted by Louise Marks in 2003 and 2005, right?

A. And that time frame sounds correct.

Q. And a report was drafted by Dr. Marks in 2007?

MR. HONG: Object to form. Lacks foundation.

A. I don't know that report specifically, sir.

BY MR. DICKENS:

Q. But you would agree that the reports from Louise Marks on her mice studies were not submitted to the EPA until December 2019, correct?

MR. HONG: Object to form.

A. The actually study reports were 2019.

BY MR. DICKENS:

Q. They weren't reported to the EPA until an attorney representing an individual with Parkinson's Disease sent a letter to Syngenta indicating they had not submitted relevant documents to the EPA for their consideration; isn't that correct?

MR. HONG: Object to form.

A. That's my recollection. The attorney requested that. We certainly had no reason not to submit them, so we did.

BY MR. DICKENS:

Q. You say you had no reason not to submit them, but you'd agree they were not submitted at

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the time they were completed?
A. I would agree with that.
Q. They weren't submitted until more than a decade after they were completed, correct?
A. That time frame sounds about right. Yes, sir.
Q. Prior to 2019, had you gone back and reviewed what Syngenta had submitted to the EPA with respect to Parkinson's Disease prior to that time in December of 2019?
MR. HONG: Object to form.
A. I was aware of our presentations of the research program, and I was aware that Syngenta had submitted a 6(a)(2) for the one of the Marks studies that had shown an effect that hadn't previously been reported in the public literature.
BY MR. DICKENS:
Q. When was that reported?
A. To the best of my recollection, I think that 6(a)(2) report was done in 2006.
Q. And it was submitted in 2006?
A. I believe that's correct, sir.

Q. And that study that was submitted in 2006 that you say something that hadn't been previously reported, what was that, to your knowledge?
A. And just for clarity, as part of the 69a)(2) process, registrants provided notification, they don't necessarily provide the study unless EPA requests the study for additional information. So that study would have been part of the 2019 studies as far as the formal study but the notification was in 2006. Okay.
Q. Okay. And that's fair. So the notification of EPA you mentioned is because there was something that wasn't previously reported. What was that something that was actually being noted -- EPA was being notified about?
MR. HONG: Object to form.
A. To the best of my recollection, there was a event seen at a dosing regimen that had not previously been seen or utilized.
BY MR. DICKENS:
Q. Do you know what that event was?
A. I would have to go back and look at the

report to be able to speak accurately on that, sir.
Q. We can agree that the studies where Dr. Marks found a statistically significant reduction in dopaminergic neurons the EPA was not notified of that until December of 2019, correct?
MR. HONG: Object to form.
A. To the best of my understanding, EPA was notified of that in 2019.
BY MR. DICKENS:
Q. And not before that?
A. Not that I'm aware of.
Q. Do you know the rational or reasoning as to why the EPA was not notified of those studies?
MR. HONG: Object to form.
A. My understanding is those studies were done to see if they could replicate data that had been previously published. The findings that were identified were consist with previous reported literature and as such, fall out of this reporting requirements of 6(a)(2).
BY MR. DICKENS:

Q. You'd agree Syngenta previously told the EPA that those study results could not be replicated, right?
MR. HONG: Object to form.
BY MR. DICKENS:
Q. Prior to December 2019?
A. I cannot speak to that, sir, I don't know.
Q. Going back to the exhibit we were on.
A. This one, sir, number 6?
Q. That's right. So we were looking at the NAFTA section?
A. Yes, sir.
Q. It says, [As read] "Although Parkinson's Disease has not been raised as a regulatory issue at this time, it is considered inevitable that at some point in the future we will have to respond to significant Parkinson's Disease related threat to our Paraquat business to the public image of the product if not the registration directly."
Do you see that?
A. I do.
Q. So we can agree as of 2003, Syngenta

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recognized that Parkinson's Disease was an inevitable threat to the Paraquat business?

MR. HONG: Object to form.

A. I would say that that's what Mike Clapp is stating here. That's Mike Clapp's statement.

BY MR. DICKENS:

Q. Understanding it's Mike Clapp's statement, there's nothing in the minutes to suggest that anyone disagreed with Mike Clapp, right?

MR. HONG: Object to form.

A. I would have to read through them closely here to see that. I'm not aware, but I would be happy to read through it and see. I'm not seeing any direct contradiction to what Mike is stating there, sir.

BY MR. DICKENS:

Q. In that next paragraph, it notes [As read] "The U.S. market has been selected as a model development of the Syngenta influencing strategy for Parkinson's Disease."

Do you see that?

A. Yes, I do.

Q. You were aware that United States would be the model for Syngenta's influencing strategy as it related to Parkinson's Disease as of 2003?

A. That's what is stated here.

Q. On the next page, mentions [As read] "Good contact, the evaluation of key research groups that have been established that predicted future research activity is being mapped."

Do you see that?

A. I do.

Q. Do you know what's being referred to as being mapped?

A. Not exactly the term mapped, sir.

Q. Are you aware of the term regulatory mapping being used within Syngenta?

A. I have certainly heard that term before.

Q. Do you know what it means?

A. I can give you my understanding of it.

Q. What's your understanding, that's all I'm asking.

A. Yes, sir. My understanding is when we doing regulatory mapping, we are looking at the

different regulatory bodies and how to position our products within the different regions.

Q. Then they mention particular research groups there. Do you see that?

A. I do, sir.

Q. One is DiMonte with the Parkinson's Disease Institute in California, right?

A. I do.

Q. You're aware that Dr. DiMonte had run tests which found a build up of alpha-synuclein in the brain in rogue (ph) studies, right?

A. As a layperson, I know Dr. DiMonte's name, I know he was very actively in this region, but I would have relied heavily on the toxicologist to interpret any of the work he's done, and at this point, I was not in a role where I would have been looking into that. I would have been purely in the operator safety space of that, sir.

Q. Same story with respect to Cory-Slechta?

A. Yes, sir.

Q. Now, in the talk within these minutes of influencing strategy and the regulatory threat of

Parkinson's Disease being inevitable, the only concern of Syngenta was the threat to the business itself, not the threat to human health, right?

MR. HONG: Objection. Lacks foundation.

A. I can't speak for Syngenta on that, sir.

BY MR. DICKENS:

Q. But there's nothing within these minutes that specifically notes steps to be taken with respect to safety to reduce exposure due to Parkinson's Disease or neurotoxicity threats, right?

MR. HONG: Object to form.

A. I don't see anything like that in the minutes.

BY MR. DICKENS:

Q. It's with respect to taking steps to mitigate threats to Paraquat business and its regulatory status, right?

MR. HONG: Object to form.

A. I wouldn't characterize it quite that way. What I see in here are different groups being asked to look at different areas to understand

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what's happening, so not wanting to speak beyond my own area, I know my focus would have been in the operator exposure area, sir.
BY MR. DICKENS:
Q. To look at different areas to understand what's happening in order to respond to significant Parkinson's Disease related threats, right?
MR. HONG: Object to form.
A. I think to understand the environment around Paraquat as a molecule and try to understand what's being published and understand what's out there so they can make appropriate, you know, investigations to understand the literature, which is something they were involved with.
BY MR. DICKENS:
Q. But Syngenta's influencing strategy weren't attempting to influence researchers to find that Paraquat was associated with neurotoxicity hazards, right?
A. I'm not aware of any discussions with researchers. I wouldn't have been part of those,

sir.
Q. Now, part of the reason there were threats to Paraquat during this time was there were concerns that users of Paraquat would move to safer and cheaper alternatives; is that correct?
MR. HONG: Object to form.
A. I cannot speak to that, sir.
BY MR. DICKENS:
Q. Well, you would agree that one of the reasons you didn't publically site negative opinions of Paraquat was you were trying to vigorously defend all registrations and uses of Paraquat, right?
MR. HONG: Object to form. Lacks foundation.
A. My role at the time would have been to analyze it from an operator and safety standpoint and provide inputs from there, sir.
BY MR. DICKENS:
Q. Would you agree that during your time Paraquat was vulnerable to cheaper alternative pesticides that had lower toxicity?

A. In which time frame, sir?
Q. Say 2006 to 2022?
A. Paraquat actually has a very unique biological profile with respect to wheat control, so there are very few alternatives to Paraquat, especially with the increase of resistant management or as a resistance management tool with the speed to desiccation, so there really are very few alternatives to Paraquat in the agronomic toolbox for U.S. growers.
Q. There were concerns and investigations done by Syngenta of alternatives on the market during your time between 2006 and 2022, right?
MR. HONG: Object to form.
A. I'm certainly not aware of those specific. That may have been in a different group, but I'm not aware of anything such as that.
BY MR. DICKENS:
Q. You would agree that there are pesticides on the market that have lower toxicity profiles?
A. Yes, I would certainly say that.
Q. And the EPA itself has indicated during

the human mitigation time period that one of the reasons was that there are alternatives that were safer, right?
A. I wouldn't want to characterize or speak on behalf of EPA. There are other nonselective herbicides, that is a true statement.
Q. Well, you don't have to speak on behalf of the EPA because the EPA told you and others at Syngenta that glyphosate and glufosinate were safer?
THE COURT REPORTER: I'm sorry. That --
BY MR. DICKENS:
Q. Glyphosate and glufosinate were safer.
A. I would -- I would have to see that communication from EPA to refresh my memory. My understanding is EPA fully feels like Paraquat is a safe product when used as intended.
MR. DICKENS: Move to strike.
MR. HONG: The entire answer?
MR. DICKENS: After refresh my memory.
Go ahead and hand you what we'll mark as Exhibit 7.

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(Exhibit 7 was marked.)
BY MR. DICKENS:
Q. There's an e-mail that you sent January 2016 and goes on to the second page?
A. Correct.
Q. Referring to an EPA meeting at Paraquat on January 6, 2016. Do you see that?
A. I do.
Q. And Syngenta participated in EPA requested meeting of all Paraquat technical registrants on January 6 of 2016, right?
A. Yes, sir.
Q. And do you recall this meeting?
A. I do. It was part of the human health mitigation work that we were doing.
Q. And that's what we discussed before, right?
A. Yes, sir. Correct.
Q. And so at this meeting, you attended in person, right?
A. Correct.
Q. Along with Jerry Wells?

A. It appears that it was Jerry Wells with me as well.
Q. What was Jerry Wells' position at Syngenta at the time?
A. I believe in 2016 he was my direct supervisor.
Q. It was EPA that initiated this meeting, right?
A. I believe that is correct.
Q. And EPA was reviewing proposals for additional stewardship members as additional issues came to their attention, right?
A. That is correct.
Q. And that's what we discussed it was actually EPA that called for these measures as they were notified of potential concerns related to the safety of Paraquat specifically, right?
A. Correct.
MR. HONG: Object to form.
BY MR. DICKENS:
Q. And the Agency, that's being the EPA, right?

A. Yes, sir.
Q. And they did a comparative analysis of the potential for occupational injuries from the application of Paraquat compared to other herbicides on the market, right?
MR. HONG: Counsel, sorry to interrupt. Can we take a quick break? This appears to be a attorney-client privileged document and I just want to check something.
So let's stop the examination on this document and can we take a 2 minute break so I can talk to the witness?
MR. DICKENS: Sure.
THE VIDEOGRAPHER: The time is 10:56. We're now off the record.
(A break was taken from 10:56 a.m. to 11:01 a.m.)
THE VIDEOGRAPHER: The time is 11:01 a.m. Eastern. We are now back on the record.
Counsel, you may proceed.
MR. HONG: Thank you, Counsel. I've had a chance to confer with the witness regarding Exhibit 7, and I'm going to retract my objection

to privilege and you can go ahead and question the witness on this document.
BY MR. DICKENS:
Q. Mr. Dixon, the Agency or the EPA undertook a comparative analysis of the potential for occupational injuries in the application of Paraquat with similar information for other herbicides on the market. You agree with that, right?
A. That is correct.
Q. And they reported the findings of that comparative analysis to you and others at Syngenta, right?
A. Correct.
Q. And on the next page are the findings of the EPA from that comparative analysis, correct?
A. Yes, sir.
Q. The overall incident rate for Paraquat products normalized by usage, Paraquat was seven times more likely to have an incident reported in glufosinate and 13 times more likely been glyphosate, right?

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A. That's what's stated, yes, sir.
Q. And glufosinate and glyphosate are herbicides registered by the EPA in the United States?
A. Yes, that is correct.
Q. And when examining incidents for high or moderate severity, Paraquat was 10 times more likely than glufosinate and 23 times more likely than glyphosate to have a moderate to severe effect, right?
A. That's what is stated, sir.
Q. Diquat fell out as not being statistically significant, right?
A. As stated, yes, sir.
Q. Diquat is another one of Syngenta's products?
A. It is.
Q. Now, the next sentence says, [As read] "Based upon that analysis, EPA developed additional proposed requirements." Right?
A. That is correct.
Q. And those proposed requirements included

closed system, right?
A. Correct.
Q. We talked about that?
A. Yes, sir.
Q. Prohibition of backpack and other hand-held applications, right?
A. Yes, sir.
Q. Limiting use of certified applicators and not allowing use by someone under the supervision of certified applicators, right?
A. Correct.
Q. And then adoption of stewardship proposals though not if not finalized presented in December of 2014. Do you see that?
A. Correct. Those were all proposed specifically to address the type of injuries that EPA was concerned about, that being eye irritation and skin irritation, those were the occupational injuries that these were supposed to address.
Q. And those -- the proposed requirements, those were ones that EPA themselves developed, right?

A. They developed, however, we certainly discussed those with the Agency and provided our support for and particularly the closed system of Syngenta.
Q. But once again, it wasn't a proposal that Syngenta brought to the EPA based on safety data the company had, right; it was the other way around, EPA brought it to Syngenta?
A. I believe the Agency proposed that, yes, sir.
Q. And at no time prior to the EPA's proposal did Syngenta ever propose to restrict Paraquat products to close systems?
MR. HONG: Object to form.
A. To the best of my recollection, that is a correct statement.
BY MR. DICKENS:
Q. And prior to the EPA's proposal to prohibit backpack and hand-held applications, Syngenta had never gone to the EPA and proposed to put that prohibition in place, right?
A. Not that I recall.

Q. And Syngenta never went to the EPA and proposed to limit use to certified applicators and not someone under the supervision, right?
MR. HONG: Object to form.
A. I do not recall that, no.
BY MR. DICKENS:
Q. Now, EPA brought to Syngenta information on their comparative analysis of glufosinate with glufosinate and glyphosate in 2016, but isn't it true that Syngenta had done an analysis of users or consumers on their thoughts about Paraquat compared to other herbicides?
A. I'm trying to recall. I know I took a look at some work associated with reports in the Poison Control Center database.
Q. Was that back in the time frame you were considering the dust mist filter?
A. No, sir. This would have been more in the 2012, '13 timeframe.
Q. And what specifically were you looking for?
A. Trying to quantify the number of potential

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fatalities. We were very concerned about the accidental ingestion situation and trying to understand the case reports around fatalities that were being captured by the AAPCC.

Q. With respect to comparatives and alternatives, you mentioned there are, I believe your testimony, are no real alternatives to Paraquat; that's your opinion, right?

MR. HONG: Object to form.

A. I would say that there are scenarios where Paraquat provides perhaps the only or at least one of the best solutions for the growers, perhaps saying the only would be too far.

Glyphosate has very well documented resistance now significantly set, for example, such as palmer amaranth, glyphosate can't take out, there's much more resistance to glufosinate.

So Paraquat has perhaps the lowest resistant profile of all the herbicides that are currently registered. I'm not an agronomic expert but that's my working understanding of that.

BY MR. DICKENS:

Q. You would agree that Syngenta was losing Paraquat business to glufosinate and glyphosate, right?

MR. HONG: Object to form. Lacks foundation.

A. I can't speak to that, sir.

MR. DICKENS: I'll hand you what we'll mark as Exhibit 8, which is a document from your custodial file.

(Exhibit 8 was marked.)

MR. HONG: Counsel, do you know if there's a parent document for this presentation?

MR. DICKENS: I don't believe there is.

BY MR. DICKENS:

Q. Mr. Dixon, I've hand you a document produced by Syngenta in your custodial file, a glufosinate market study dated January 2009.

Do you see that?

A. I do.

Q. And you're aware that Syngenta would conduct market studies from time to time with respect to their products as well as other

products, correct?

MR. HONG: Object to form.

A. That -- that seems reasonable.

BY MR. DICKENS:

Q. And you've seen market study data during your time with Syngenta between 2006 and 2022?

A. I don't recall seeing this one. I don't have any specific recollection but it's certainly possible.

Q. I'm going to turn your attention to Page 4. Part of the research -- one of the research goals was to gain an understanding of what glufosinate usage will look like as a result of the price decrease and that's specifically price decrease of glufosinate. Is that your understanding?

A. That's what is stated here, yes, sir.

Q. And part of that goal determine why growers have changed from Gramoxone to glufosinate. Do you see that?

A. Yes.

Q. So Syngenta, in its own market study,

determined that growers were changing from Gramoxone to Glufosinate?

MR. HONG: Object to form.

A. That appears to be the question being asked there.

BY MR. DICKENS:

Q. Also wanted to understand the perceptions of glufosinate and to evaluate growth satisfaction with Gramoxone and glufosinate, right?

A. Yes, sir.

Q. Now, if you can turn to Page 16. There are some advantages and disadvantages of Gramoxone. Do you see that?

A. I do.

Q. And under disadvantages includes requires a respirator, danger labeling, category one material requires a closed mixing system.

Do you see that?

A. I do, although I'm surprised about the requires a closed mixing system.

Q. Now, do you agree that closed mixing system was in place in California before it was

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federally?
MR. HONG: Object to form.
A. I certainly don't have a clear recollection of that, but the document here does state it requires a closed mixing system, and I'm assuming that's California specific based upon your statement here.
BY MR. DICKENS:
Q. And you'd agree that states can have different labeling requirements than the EPA?
A. Yes.
Q. And you're aware that California, from time to time, had implemented different labeling for pesticides than the federal label would have?
MR. HONG: Object to form.
THE COURT REPORTER: Than the federal --
MR. DICKENS: Federal label would have.
A. I believe that is correct.
BY MR. DICKENS:
Q. Now, requires a respirator for Gramoxone, at that stage in 2009 that was a does dust mask filter, right?

A. Yes.
Q. So that's essentially a fabric or cloth mask, correct?
A. Correct.
Q. Not one that involved cartridges or anything along those lines?
A. Correct.
Q. Did that change at some point in time?
A. As far as going forward from 2009?
Q. Correct.
A. I believe EPA's definition around it has changed but essentially the same respirator requirement remains today.
Q. Still the same cloth mask?
A. I believe it is still the N -- well, we carry it as an N-95, they've changed the definition. At one time it was called a particulate dust mist filter. I think there's other names that have been utilized but essentially it's the same type of mask.
Q. And that's something you were looking at all the way back in 2000, early 2000s, right?

A. That is correct.
Q. And that was the issue that you first worked on for Gramoxone after joining Syngenta?
A. Correct.
Q. Turn the page. Now, it lists some advantages, disadvantages of glufosinate.
Do you see that?
A. Yes.
Q. And one of the advantages, broader spectrum, more effective on broad leaves.
Do you see that?
A. I do.
Q. And then there's easy to use, do not need closed system, do not need respirator, category 3 material, and considered safer; caution label versus danger, right?
A. That's based upon the Cutox (ph) profile.
Q. And that was what was being perceived by those within the market study is that glufosinate was safer than Gramoxone, right?
MR. HONG: Object to form. Lacks foundation.

A. I am just now seeing this document and it looks like it was done by a research corporation, so I can't speak for them.
BY MR. DICKENS:
Q. You say you now just saw this document. Is there a reason why it would have been within your documents or custodial file that was produced to us by Syngenta if you hadn't previously used --
A. I certainly don't recognize it but this type of information would have been generated by our marketing team, and when we have functional meetings, presentations would be given, marketing team, regulatory team, biology team, so it ws probably in my possession as a result of having been part of a meeting where it would have been presented.
Q. In a meeting that it would have presented that you attended?
A. I probably attended. If not, was given notes afterwards.
Q. And so --
A. This is clearly not a regulatory document

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though, this would have been done by our marketing team.

Q. And the marketing team based on a study that they did to compare Gramoxone to one of its competitor herbicides, right?

MR. HONG: Object to form. Lacks foundation.

A. That appears to be the context of the document, sir.

BY MR. DICKENS:

Q. Okay. We can turn to Page 19, and provide some conclusions here. So some of the conclusions for glufosinate perceived to be more effective than Gramoxone and glyphosate resistant.

Do you see that that?

A. Correct.

Q. It's perceived to be safer than Gramoxone?

A. That's what's stated there, yes, sir.

Q. It's easier to use and safer than Gramoxone; that's how it was perceived, right?

A. That's what's stated.

Q. And that was, in your experience and at

the meetings you attended, a concern for Syngenta and its Gramoxone business, right?

MR. HONG: Object to form. Lacks foundation.

A. It's what's stated in the document here, sir.

BY MR. DICKENS:

Q. We discussed earlier -- we can put this aside -- part of your role with the company was to implement Syngenta's regulatory strategy, right?

A. Yes, sir.

Q. And to interface with the U.S. EPA?

A. Correct.

Q. One of the goals was to convince the EPA that Paraquat was not associated with Parkinson's Disease?

MR. HONG: Object -- object to form.

A. Our goal was to present the results of the research that we were doing on the allegation, sir.

MR. DICKENS: Before I move on, I'm going to -- just to clear it up, go ahead and mark

Exhibit 9 for the record.

(Exhibit 9 was marked.)

MR. HONG: We've been going for about an hour. Can we take a break after this one?

MR. DICKENS: Yes.

A. Sir, I have reviewed it.

BY MR. DICKENS:

Q. We can start off by turning to Page 2. Middle of the page there's an e-mail from David Scott to you, February 20, 2009, right?

A. Yes.

Q. And the subject is glufosinate study results and next steps.

Do you see that?

A. I do.

Q. And David Scott, who is he within the company?

A. My recollection is David at the time was the global Paraquat brand manager. Brand manager has a role where you're developing the products and marketing the products.

Q. And he is bringing to you information with

respect to glufosinate study results in 2009, right?

A. Yes, sir.

Q. Your understanding is that glufosinate 2009 study results that we just looked at in that PowerPoint slide, right?

A. That marketing information. I'm not exactly sure what study he's saying but looking at the follow up, it appears it's referring potentially to that directions research.

Q. And you're not aware of another glufosinate study that would have been conducted?

A. No, but just the glufosinate study is such a broad statement. I'm not sure if that's the one or if he was referring to another one.

Q. And you don't know, as you sit here today, whether or not there was another one?

A. I don't recall another one, sir.

Q. You would agree that the e-mail in this time frame 2009 corresponds with the 2009 PowerPoint slides that we just looked at, right ?

A. It appears similar, yes, sir.

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Q. Would it be typical for the company to have more than one glufosinate study in a year?
A. Possibly. Depends on the nature of the study. If we were exploring, for example, using glufosinate in the field, we might be doing mix type studies, we might be looking at formulation, so the term study really could encompass many different things.
Q. And David Scott is forwarding you study results and next steps and there's an e-mail prior to that, right?
A. Yes.
Q. If we can turn to Page 5.
A. Yes.
Q. Under next steps, one of the next step. Take another look at Gramoxone from a regulatory view. Do we really need to have the kind of restrictions? David Scott, right?
A. Yes, sir.
Q. And after this, David Scott is coming to you at this point in time, correct?
A. Correct.

Q. And if we can look up at some of the --
A. Although, just for clarity, it appears that it might have been Rosalind Moore that summarized that but David is in the e-mail chain, sir.
Q. And David Scott appears to be the one assigned to determine whether or not the current restrictions really need to be in place?
A. He was the global lead, so it appears he is the driver for that ask.
Q. Earlier on Page 5 includes for Syngenta thoughts and it summarizes some of those findings. And under Syngenta thoughts are Syngenta thoughts starts on Page 4, right ?
A. Yes.
Q. It's referring to, kind of, price comparisons and which one is more effective, right?
A. Yes.
Q. Which is similar to the information that was presented in the market study results, correct?

A. That appears to be correct.
Q. Now, David Scott brings you his e-mail and in his e-mail on Page 2 in the above meeting the question was raised, [As read] "If you could look again at the Paraquat PPE requirement in California to see if we can get it lifted." Correct?
A. Yes.
Q. Now, Syngenta, during the course of your history with the company, had tried to get the dust mask respirator removed as a PPE requirement from time to time, right?
MR. HONG: Object to form.
A. At the time I was in the operator exposure group that was a desire to see if we could justify removing that because of concerns it could actually exacerbate the risk of nosebleeds.
BY MR. DICKENS:
Q. The actual dust mask filter within Syngenta there was a recognition that that could actually make nosebleeds worse, right?
A. There was a concern it could potentially

do that.
Q. And a concern held by not just you, but scientists within Syngenta that the dust mask filter could actually trap particles on the face and in the nasal cavity making the situation worse, right?
A. That was part of -- what I would call part of the rational and discussions.
Q. Now, you would agree that a respirator with cartridges that could filter that out would not present the same problem, right?
MR. HONG: Object to form.
A. I would not agree with that; that's not the nature of the concern around the trapping the vapors. It was purely concerned about chemical hygiene and whether or not a user, for example, had an itchy -- an itch on their nose and they would take their gloved hand, rub their nose, put the mask back on therefore trapping it.
It wasn't about preventing the vapors from coming in, it was about dermal transfer, you know, rubbing an itchy nose. So whether it was a dust

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mist filter or cartridge respirator, you would have the same event.

MR. HONG: And for the record, Mr. Dixon was demonstrating on the video of the action he was just testifying about.

THE WITNESS: I'm sorry.

BY MR. DICKENS:

Q. So having nothing, then, is better than having something over it at that point in time?

MR. HONG: Object to form.

A. That was my understanding. The biggest concern was potentially trapping vapors in the nose by transferring them and rubbing your mouth, rubbing your face, putting residues there, now you've covered it up.

BY MR. DICKENS:

Q. Now, you agree that Paraquat being sprayed can be inhaled into the nasal cavity, right?

MR. HONG: Object to form.

A. I would agree. Certainly when somebody is making an application, there is a potential for vapors or mist to be inhaled.

BY MR. DICKENS:

Q. We'll look at inhalation but so we can take a break, let's move on from this document at least. So David Scott mentioned, [As read] Let's look again. Can we remove the PPE requirement from California." Right?

A. Yes, sir.

THE WITNESS: So are we moving from this one or we still on --

MR. DICKENS: Still on for now, then we'll take a break.

THE WITNESS: Okay. Sure.

BY MR. DICKENS:

Q. And then you respond back, [As read] "David, as you correctly surmised, there have been, over the past eight years or so, several thoughts in attempt to go at the PPE issue." Right?

A. Correct.

Q. And this is to reduce the amount of PPE that would need to be worn by users spraying Paraquat?

MR. HONG: Object to form.

A. My recollection is that was about the dust mist filter, not the other PPE.

BY MR. DICKENS:

Q. It mentions, [As read] "For the respirator, California's EPA took a further proactive step to try to mitigate the rare instances of nasal irritation evidenced by nasal bleeding." Right?

THE COURT REPORTER: Evidenced by nasal --

MR. DICKENS: Bleeding.

THE COURT REPORTER: If you could keep your voice up at the end. Thank you.

BY MR. DICKENS:

Q. Correct?

A. That's what it said, yes, sir.

Q. And you said rare instances there, but you're aware that Syngenta was familiar of nose bleeding all the way back to the 1960s as a potential adverse effect, right?

MR. HONG: Object to form. Lacks foundation.

A. That significantly predates my time in that role, so I wouldn't want to speak going back that far, sir.

BY MR. DICKENS:

Q. So you as the regulatory liaison between Syngenta and EPA, had no knowledge of any nosebleeds up until 2006?

MR. HONG: Same objection and also mischaracterizes prior testimony. Go ahead and answer.

A. I would have certainly been aware in 2000 when I was doing the work and concerns over the operator exposure role that I was in at that point.

BY MR. DICKENS:

Q. Did you have any knowledge of nasal irritation or nosebleeds prior to 2000 when you began working on the issue with the dust mask filter?

A. I certainly don't recall any.

Q. Did you go back and look to see whether or not that was a known adverse effect that was being

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experienced by users of Paraquat?
MR. HONG: Object to form.
A. That was so long ago, I don't recall exactly what I would have done other than what's been written.
BY MR. DICKENS:
Q. Now, you say, it's a rare instance, but Syngenta had undertaken a questionnaire of users and workers as to adverse effects that they've received over the years of using Paraquat, right?
MR. HONG: Objection. Lacks foundation.
A. I don't recall that document.
BY MR. DICKENS:
Q. You don't recall anything where -- a document where a questionnaire found that 25 percent of Paraquat users experienced nosebleeds?
MR. HONG: Same objection. Lacks foundation.
A. As I sit here today, I do not recall such a document, sir.
MR. DICKENS: Why don't we take a break,

you can look at it then.
THE WITNESS: Okay. Thank you, sir.
THE VIDEOGRAPHER: The time is 11:28 p.m. We are now off the record. Microphones everyone.
(A break was taken from 11:28 a.m. to 11:40 a.m.)
THE VIDEOGRAPHER: This is the beginning of media unit No. 3 in the video-recorded deposition of Mr. Montague Dixon. The time is 11:40 a.m. Eastern. We are back on the record.
Counsel, you may proceed.
MR. DICKENS: I'm going to hand what you we'll mark as Exhibit 10.
(Exhibit 10 was marked.)
BY MR. DICKENS:
Q. Exhibit 10 is an e-mail chain beginning with an e-mail from you to Greg Watson, May 30, 2001; is that right?
A. Yes, sir.
Q. And this is the time frame you were working on the dust mask filter respirator issue for Gramoxone, right?
A. Yes, sir.

Q. And as a Paraquat meeting follow-up investigation of alternative PPE for Paraquat, that was one of the duties that you were asked to investigate on behalf of the company, right?
A. That is correct.
Q. And Greg Watson was in Regulatory Affairs; is that correct?
A. Yes, sir.
Q. And you were reporting him the results of your investigation, right?
A. That is correct.
Q. And specifically on alternatives for preventing nasal irritation that had been reported for Paraquat use, correct?
A. Correct.
Q. And you consulted with a chemical hygienist and is that a chemical hygienist with Syngenta?
A. Yes.
Q. And you recommended increasing awareness of the users to potential nasal irritation problems?

A. Correct.
Q. And then from a worker protection standpoint, you recommended some various things that could be done to reduce incidences of nasal irritation, correct?
A. That is correct.
Q. And one of the things you recommended was require applications be made in a closed cab environment?
A. That is correct.
Q. And that's different than the closed-loop system we were talking about before?
A. That is correct, sir.
Q. Closed cab would be spraying within a tract or other enclosed spraying device where you would not be directly in the line of the Paraquat spray, right?
A. Correct.
Q. So you recommended we could have users spray with inside an enclosed tractor?
A. Correct.
Q. Was that ever implemented by Syngenta?

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A. Not -- no, sir, not in that time frame.
Q. Was it ever -- strike that. Did Syngenta in this time frame request the EPA to amend the labelling to require applications be made in the closed cabin environment?
MR. HONG: Objection. Lacks foundation.
A. I was not in regulatory at that time. I'm not aware of such a request.
BY MR. DICKENS:
Q. Are you aware of Syngenta ever recommending to the EPA that the labeling should be amended to require applications be made in closed cabin environments?
MR. HONG: Same objection.
A. I am not.
BY MR. DICKENS:
Q. One of your recommendations was utilization of a respirator equipped with an appropriate vapor cartridge, right?
A. Yes.
Q. And that's what we just discussed before is a vapor cartridge versus just a cloth mask,

right?
A. Correct.
Q. And you recommended to reduce nasal incidences -- or incidences of nasal irritation back in 2001 a respirator that used a vapor cartridge, right?
A. Correct.
Q. And at this point in time, did Syngenta request a labeling change to require a respirator with a vapor cartridge?
A. I'm --
MR. HONG: Objection. Lacks foundation.
A. I'm not aware of such a request.
BY MR. DICKENS:
Q. Are you aware of Syngenta ever requesting a labeling change with the EPA to require users to use a respirator with a vapor cartridge?
MR. HONG: Same objection.
A. I am not aware of one.
BY MR. DICKENS:
Q. Once again, you recognize in this e-mail that the dust mist type of mask, "It is our

belief", and when you say "our," being those within Syngenta?
A. I believe that would be correct.
Q. [As read] "That increases the potential for nasal irritation by trapping Paraquat residue in close proximity to the skin and nasal passages and thus potentially aggravating skin irritation." Right?
A. Yes, sir.
Q. Did you, during your time in regulatory, ever inform the EPA of your belief that the dust mask would actually increase nasal irritation?
MR. HONG: Object to form.
A. I don't recall any such communication.
BY MR. DICKENS:
Q. Now, you're aware at this point in time when you were undertaking that investigation in 2001 that the EPA itself was also concerned with nasal irritation and intranasal exposure of Paraquat, right?
MR. HONG: Object to form.
A. I can't say that I have an awareness of

that, sir.
BY MR. DICKENS:
Q. Well, are you aware, based on documents you received after becoming or taking your role in regulatory, that the EPA had previously been concerned with nasal irritation and intranasal exposure to Paraquat?
MR. HONG: Same objection.
A. Other than the work that I did in 2000, I don't recall any thoughts about that, sir.
MR. DICKENS: I'm going to hand you Exhibit 11 and I'll mark Exhibit 12 as well.
(Exhibits 11-12 were marked.)
THE WITNESS: Sir, I'm ready.
BY MR. DICKENS:
Q. Exhibit 11 is e-mail chain in which you're involved. First one an e-mail from you to Jeff Stabnau, March 31, 2014.
Do you see that?
A. Yes.
Q. And you're asked if you could obtain an August 10, 2000 memorandum from a Jerome Blondell

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regarding Paraquat incident reports involving inhalation.

Do you see that?

A. I do.

Q. Jeff Stabnau did, in fact, send you that requested memorandum, right?

A. He did.

Q. Put that aside. Exhibit 12 appears to be that memorandum?

A. Yes, it does.

Q. And this is indeed a memorandum that you did review, right?

A. Yes.

Q. Do you recall why you requested to obtain a copy of this memorandum?

A. Not specifically, sir.

Q. You don't know why in April of 2014 you would have wanted to see this particular document?

A. This would have been during the human health mitigation work that we were doing, so I believe it would have been associated with that, trying to understand that situation.

Q. Do you know whether or not you would have reviewed this back in 2001 when you were looking at the dust mask filter requirement for Paraquat?

A. I don't recall so doing.

Q. And this is a review of Paraquat incident reports from inhalation that was compiled by the EPA itself, right?

A. That's the title of the document, sir. I believe that's correct.

MR. HONG: Mr. Dixon, since you're going to get questions on this document, why don't you take time to review the document because it's a nine page document, single spaced. So take a minute or two to review it.

MR. DICKENS: We can go off the record while he does that.

THE VIDEOGRAPHER: The time is 11:50. We are now going off the record.

(Off record.)

THE VIDEOGRAPHER: The time is 11:52 -- excuse me, 11:53 a.m. Eastern. We are now back on the record.

Counsel, you may proceed.

BY MR. DICKENS:

Q. Mr. Dixon, you had an opportunity to review the memorandum marked as Exhibit 12; is that right?

A. Yes, sir.

Q. And once again, this is a document that you would have reviewed at least during the human mitigation review of Paraquat, right?

A. Correct.

Q. If you can turn to page 6 in the right-hand corner Bates ending 4335?

A. 4335?

Q. Correct.

A. Okay. Sir.

Q. There's a chart EPA prepared with medical outcome and percent inhalation for various categories.

Do you see that?

A. Are we talking table --

Q. Sorry. Table 8. I apologize. Human Paraquat exposures reported to Poison Control

Centers where medical outcome was determined.

Do you see that?

A. Yes, I see that.

Q. The EPA determined that out of the moderate medical outcomes, 31 percent were due to inhalation exposure, right?

A. Let me make sure I understand. I knew the parenthesis are that but just to make sure I understand that. Percent inhalation. I see the header on that, yes, sir.

Q. And major medical outcomes, 50 percent related to inhalation, correct?

A. That's what's stated.

Q. And total 26.4 of all incidences were determined to be from inhalation exposure?

A. And that's what's listed, yes, sir.

Q. Based on these numbers, EPA concluded that inhalation can be a significant risk for symptoms of Paraquat intoxication, right?

A. They state that inhalation can be a significant risk in that last paragraph, so that's their statement, yes, sir.

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Q. Turning to next page, Page 7.
A. Sir, are you 7 or 8? My next page is 8.
Q. I'm on page 7 if yours is 8 -- oh, I'm sorry. I'm talking 7 in the top right-hand corner, which appears to be a difference for some reason on the lower left-hand corner.
A. Thank you.
Q. The last paragraph they reference a Wesseling study in 1997, correct?
A. Yes, sir. May I just read that paragraph just to make sure I understand what he says.
Q. Sure. So they note the Wesseling and then later on the paragraph starting with however and they cite Ames, 1993?
A. Yes.
Q. They cite Ames 1993 study which suggest [As read] "The possibility of intoxications from inhalation of droplets from other types of spraying." Do you see that?
A. I do.
Q. And that's referencing specifically inhalation of droplets during natural spraying

activities?
A. I haven't read the Ames study, so I can only go by what it says here which is the possibility of inhalation or the inhalation of droplets. So based on what it says, that's all I can understand.
Q. Inhalation of droplets from spraying, right?
A. From other types of spraying, yeah.
Q. And not any type of hygiene issues or anything along those lines?
A. I don't think you can separate that, sir.
Q. So in your mind and with respect to this inhalation issue, spraying and you touching of the face would be considered one of the same?
A. From my previous role, one of the key learnings I had when I was doing occupational and residential studies and observations is even with workers making the same application, their work practices would directly influence how much, for example, they might get on -- did they take their gloves off when they went to the bathroom or when

they sprayed, did they walk backwards through the treated foliage or did they go to the end of the row and back out.
So that's what I'm saying -- I'm saying spraying -- you have to break it down into how the person made the application.
Q. In your previous role, though, you never actually saw anybody ever spray Paraquat, right?
A. Not Paraquat, sir.
Q. So you never witnessed anyone taking their mask off, touching their face personally?
A. No, sir, and in this particular study, this is in another country, too, so the agronomic practices are different in different countries as well.
Q. Are you aware of Syngenta-sponsored studies in which nosebleeds were found?
A. I don't have a specific recollection, so I can't say definitively yes or no.
Q. Do you know whether or not there had been nosebleeds in individuals in the United States who did not take their mask off and touch their nose

or around their nasal region?
MR. HONG: Object to form. Lacks foundation.
A. I don't know.
BY MR. DICKENS:
Q. So you don't know one way or the other whether or not nosebleeds are being caused by touching the face versus inhalation of spray droplets, correct?
MR. HONG: Object to form.
A. I do know.
BY MR. DICKENS:
Q. Last sentence of that paragraph suggests that [As read] "Absorption through the nasal mucosa and gastrointestinal absorption after swallowing may have contributed to an internal dose sufficient to contribute to lethality in their two cases. In addition, there may have been unobserved absorption through minor skin lesions." Right?
A. That's what's stated, sir.
Q. Then there's the conclusion on the next

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page of the EPA, right?
A. Yes, sir.
Q. EPA states [As read] "Both the Wesseling and NIOSH reports suggest large droplets that could get into the nasal mucosa, may pose a serious hazard." That's the conclusion of the EPA, right?
A. I believe in that same sentence they also say this is unlikely as well. Let me read that sentence just to make sure I'm remembering that correctly.
On the other hand, [As read] "Assessments of exposures this is NIOSH and Howard and others suggest that respirable levels sufficient to cause poisoning cannot occur under normal circumstances."
So that's the sentence right above that one there, sir.
Q. And I agree, but there is a difference, sir, between respirable levels and large droplets, right?
A. I'm not a tox expert, but I believe that

to be the case.
Q. Respirable means the amount that's getting into the lung, correct?
A. There's a certain particle size there, yes, sir.
Q. And that would be enough to cause an acute lung injury, which is also a concern with Paraquat, correct?
A. I have a layman's understanding. I'm not a toxicologist but that's my understanding.
Q. And so when Syngenta typically talks about inhalation with the EPA, for example, they're talking about the respirable levels that could actually get into the lung, correct?
MR. HONG: Object to form. Lacks foundation.
A. It's my understanding and from my previous work, the position has been that the respirable part that the sprays don't produce respirable particles that get into the deep lung.
BY MR. DICKENS:
Q. And therefore what Syngenta tells EPA and

others is that because the droplets aren't at small enough to be respirable, there is no inhalation risk, right?
MR. HONG: Object to form. Lacks foundation.
A. That's been my understanding of EPA's position from 2000 to just recently, and I believe that's the position we've also held.
BY MR. DICKENS:
Q. But in this sentence that I highlighted, they're not talking about respirable droplets, right; they're talking about large droplets?
A. Let me read that sentence again just to make sure. That is stated there, yes, sir.
Q. And you would agree that droplets can be large enough that they may not get to the lungs but still be trapped in the nasal mucosa, right?
A. I'm not an expert in that area, but I do believe that you could have droplet that you could inhale.
Q. And those large droplets that get into the nasal mucosum, they may pose as serious hazard;

that's what the EPA is saying, right?
A. That's the statement in the document, sir.
Q. And they conclude at the very last of that conclusion, [As read] "Nasal exposure to nonrespirable droplets of Paraquat could cause serious and perhaps fatal poisoning by Paraquat." Right?
A. And that's what is stated in the document, sir.
Q. And within Syngenta, the position of the company was that non -- was wearing a dust mask filter would exacerbate the effects of nonrespirable droplets, correct?
MR. HONG: Object to form. Lacks foundation.
A. Could you please restate.
BY MR. DICKENS:
Q. Within the company, Syngenta's position was that wearing a dust mask filter would exacerbate the effects of nonrespirable droplets in the nasal mucosa.
MR. HONG: Same objection. Lacks

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foundation.
A. I'm not being clear from a tox perspective. Out position was it had the potential to trap vapors in the nose and potentially irritate the nose more, so that was my understanding of the concern.
BY MR. DICKENS:
Q. And the same would be true with respect to droplets within the mask that were then trapped within the nasal mucosa, right?
MR. HONG: Same objection.
A. Could you please restate.
BY MR. DICKENS:
Q. The same would be true with respect to droplets that contact the mask and are then trapped within -- on the face within the nasal mucosa?
MR. HONG: Same objection.
A. Within the mask different than being trapped on the outside of the mask.
BY MR. DICKENS:
Q. Correct. Is it your position that the

mask completely prevents Paraquat droplets from getting through the masks and into the nasal region?
MR. HONG: Same objection.
A. I don't have the knowledge to answer that.
BY MR. DICKENS:
Q. You can put that away. Now, you agree, sir, that Syngenta knew before even receiving the Blondell report that Paraquat particles deposited in the upper respiratory system could lead to market toxic effects, right?
MR. HONG: Objection. Lacks foundation.
A. I wouldn't want to speak on behalf of Syngenta on that, sir.
BY MR. DICKENS:
Q. Well, you've received documents while at Syngenta involving inhalation studies conducted by Syngenta, right?
A. Correct.
Q. Including reports of inhalation studies and its toxicity?
A. Correct.

Q. And you'd agree that those reports on inhalation studies and their toxicity show that toxicity can occur even if it's non-respirable particles, right?
MR. HONG: Object to form.
A. I'm not a tox expert. I don't recall those conclusions, sir.
MR. DICKENS: Go ahead and mark Exhibit 13 and 14 for the record.
(Exhibits 13-14 were marked.)
BY MR. DICKENS:
Q. I'm just going to -- so Exhibit 13 is an e-mail from a Doug Wolf to you and others dated October 31, 2022, correct?
A. Yes, sir. And is there more to it than just this?
Q. I believe it's just attaching two documents?
A. Okay.
Q. Correct?
A. Looks like this 2521. Yes.
Q. And those documents are Review of

Inhalation Toxicology Studies by Paul Hext, right?
A. That's what this appears to be. I might note that at this point, I was no longer actively engaged in managing their Paraquat. I see that I'm on this e-mail but at this point, Jordon would have been the lead on that.
Q. Would you have reviewed this particular document at the time?
A. I honestly don't recall reviewing it. At that point, my -- my role was to let him take the lead. So I don't recall reviewing it, to be honest with you, sir.
Q. Did you know Paul Hext in any way?
A. No, sir, I do not.
Q. Okay. Did you review, prior to this point 2022, any of the inhalation toxicology findings of Paul Hext or any other toxicologist at Syngenta?
A. I certainly don't recall anything from Mr. Hext directly or minutes of Mr. Hext. I did make a submission as part of our public comments of an inhalation tox study somewhere around 2013, '14 in that period. So I would have reviewed that study.

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Q. Do you know whether or not any reviews of inhalation toxicology drafted by Paul Hext were submitted to the EPA at any point in time?

MR. HONG: Object to form. Lacks foundation.

A. Sir, off the top of my head, I do not know.

BY MR. DICKENS:

Q. Did you do anything to determine whether or not reviews of inhalation toxicology on Paraquat were submitted to the EPA for their consideration?

MR. HONG: In all time, Counsel or just...

BY MR. DICKENS:

Q. Let's start at all time?

MR. HONG: Object to form.

A. In public comments addressing the EPA's proposal for -- the proposed or medication decision, we made a argument in which I relied upon information from Andy Cook about the particle size, making the same argument EPA had changed its inhalation paradigm to introduce a different

approach.

And so I made comments in the public response addressing inhalation there.

BY MR. DICKENS:

Q. Comments being that inhalation toxicity is not a concern because the droplets are non-respirable?

A. That's my recollection of the argument, sir.

Q. Did you say -- indicate to the EPA in your comments or at any other time that non-respirable droplets can also result in increased toxicity?

MR. HONG: Object to form.

A. I don't recall any such statement being made by myself.

BY MR. DICKENS:

Q. At any point in time from 2006 to 2022?

A. I don't believe so.

Q. At any point in time in your comments or otherwise from 2006 to 2022, did you ever inform the EPA that toxicologists -- inhalation toxicologists within Syngenta had found that

non-respirable droplets of Paraquat can cause toxicity?

MR. HONG: Object to form. Assumes facts not in evidence.

A. I don't recall any such communication.

MR. DICKENS: Put that aside. I hand you Exhibit 15.

(Exhibit 15 was marked.)

THE WITNESS: I'm fairly familiar with this one.

BY MR. DICKENS:

Q. This is a document December 16, 2019 submission of 60 day comments in response to the draft human health ecological risk assessment signed by you, correct?

A. That's correct.

Q. And these are the comments that you just referenced?

A. Yes, sir.

Q. I'm going to refer to Appendix 2, which is after page 59.

A. Can you tell me the header, sir?

Q. Yes. So it is Paraquat lack of potential for inhalation toxicity for aqueous formulations.

THE WITNESS: Let me see if I can find that.

MR. DICKENS: If you can find 59, it's about three pages after.

MR. HONG: And just so the record is clear, the witness's testimony was concerning comments in 2013 and 2014, I just checked the record, not 2019. So I want to make sure we get a clean record.

A. This appears to be a report from Dr. Cook.

BY MR. DICKENS:

Q. Is that Andy Cook?

A. That would be correct, sir.

Q. July 21, 2009?

A. Yes, sir.

Q. He is with product safety at Syngenta?

A. He is now retired but was at that time.

Q. And do you know whether he's a doctor or not?

A. I believe he has his Ph.D., yes, sir.

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Q. And these are comments that were submitted in December, 2019 but they appear to be 2009 comments?

A. This appears that's the date the document is dated, yes, sir.

Q. And counsel for the record noted that you were referring to comments made in the 2014 time frame with respect to inhalation.

Are there comments different than what was submitted here in 2019 to the EPA for comments on inhalation toxicity that you're aware of?

A. I'm afraid that confuses me.

Q. Okay?

A. My response to you was based upon this.

Q. Okay. Thank you, that's helpful. So these are the only comments you're aware of with respect to inhalation toxicity to the EPA?

A. Let me look back. Given the documents over the years, my recollection is not perfect. This is the one I was speaking about there. I don't know if there were earlier documents.

Q. And the comments to the EPA, that is a way

to present Syngenta's opinion to the EPA on these various issues, right?

A. Yes, sir, it's part of the reregistration review process where EPA starts off with a preliminary problem formulation, they identify areas they're interested in. They then would issue a data call in if they felt there was sufficient data.

Then at that point, they do their work, publish what's called a draft human health and a draft ecological risk assessment, that starts a comment period where registrants or other people in the public can review the comment, make public comments back and that's what these would be.

These would be our review of what EPA had assessed in the human health and ecological risk assessment.

Q. So then let's look at Syngenta's opinion with respect to inhalation toxicity as told to the EPA. So Syngenta tells the EPA, [As read] "There is no inhalation hazard when an operator handles the formulation concentrate."

Do you see that?

A. I do.

Q. [As read] "Based on the low vapor pressure of Paraquat, operator exposure from volatilized Paraquat in the air after spray application is negligible." Correct?

A. That is correct.

Q. And that is the position of Syngenta?

MR. HONG: Object to form.

A. Yes, sir.

BY MR. DICKENS:

Q. Later on, [As read] "Inhalation theory supports the fact that large droplets do not pose an inhalation risk since they are not inhalable or respirable and are therefore orally adsorbed rather than inhaled." Correct?

A. So where exactly are we -- oh, I see. I just found it. Thank you.

Q. Okay. And with respect to this side, the inhalation risk, you're only talking here about the risk for lung toxicity; is that fair?

A. Inhalation risk assessments are based upon

lung toxicity, yes, sir.

Q. So this section is only dealing with lung toxicity and how much is being breathed in, correct?

A. Based upon how the inhalation risk assessments are done and the fact that it's used against a inhalation hazard end point, specific lung toxicity, that's what this would be addressing; primarily what is the impact on the target organ; in this case, the lung.

Q. So large droplets not pose an inhalation risk meaning large droplets don't pose a risk of lung toxicity, that's what you're informing the EPA of at this point in time, correct?

MR. HONG: Object to form.

A. In this case inhalation -- I would say we are informing exactly what it says here, does not pose an inhalation risk as they are not inhalable or respirable. I -- this is a report from Andy. It states what it states, sir.

BY MR. DICKENS:

Q. It cites to Hext 2002, right?

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A. Yes, sir.
Q. Was there ever any report, did you see here in the comments or otherwise of findings of animal studies or rodent studies which showed non-respirable droplets poised a toxicity risk?
A. That is out of my area of expertise. I would have relied on our subject matter tox experts to do that type of analysis.
Q. Was Andy Cook one of those tox experts?
A. He had a background in toxicity. At this point he had moved to become a global regulatory manager but prior to that he was the global Paraquat toxicologist.
THE COURT REPORTER: I'm sorry. Can you repeat that a little slower, please.
THE WITNESS: I'm sorry.
THE COURT REPORTER: Everyone slow down.
THE WITNESS: Okay. Yes, so Andy Cook, who at the time was the global regulatory manager, in his previous role had been the global Paraquat lead toxicologist.
BY MR. DICKENS:

Q. In this comment section in dealing with Paraquat, this is only dealing with Paraquat as the active ingredient, right?
MR. HONG: Object to form.
A. No, sir. When EPA does these risk assessments, they are looking at end use products, so it's not just the active ingredient but also the use patterns and you also potentially have mitigations based on formulation type.
BY MR. DICKENS:
Q. And when you say formulation, for say Gramoxone what are you talking about?
A. Product formulation. So when a pesticide is registered, there's different forms; it could be solid, it could be liquid, soluble concentrate. The active ingredient is one part of a composition. The rest of the composition would be co-formulants, water and other additives.
Q. With respect to the Gramoxone that's been registered in the United States, that does not include a surfactant, correct?
MR. HONG: Object to form.

A. I would need to take a look at the formulations. We've had multiple formulations, each have different compositions, so I don't have the formulations memorized.
BY MR. DICKENS:
Q. Well, let's talk about the time that you were the liaison between EPA for Syngenta. During 2006 to 2022, did any Gramoxone products on the market include a surfactant?
A. Not having the CSF's in front of me, it's hard to give a specific answer. I will say that during my time frame we had Gramoxone Inteon, Gramoxone SL 2.0, and Gramoxone SL 3.0.
I could try to determine and take a look at CSF's. My recollection would be really their complex formulation, so I just don't have them memorized.
Q. It's relevant to questions of toxicity whether or not the product contains a surfactant? Do you agree?
MR. HONG: Object to form. Lacks foundation.

A. With respect to the acute toxicity of formulations, the formulations are tested so the composition of the formulations are factored into the acute toxicity profiles that are required to register products. That's how PPE is determined, for example.
BY MR. DICKENS:
Q. Understood. You agree that surfactants increase toxicity of Paraquat, right?
MR. HONG: Object to form. Calls for expert.
A. Yes, I have no foundation to comment on that, sir.
BY MR. DICKENS:
Q. You've never seen anything that suggest that?
A. I am not a tox expert. I can only speak on what I know, sir.
Q. It's fair to say that -- well, do you know whether or not the labeling for Paraquat on the products that were on the market when you were in charge of regulatory matters from 2006 to 2022

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instructed users to mix Paraquat with a surfactant?

MR. HONG: Object to form.

A. It's certainly possible because our product labels do have mixing instructions and sequence from adding things into the tank, so that is possible.

BY MR. DICKENS:

Q. But you don't know?

A. I -- specifically I would have to look at the label to refresh my memory. I haven't looked at these labels in a couple of years now.

Q. Gramoxone Inteon that -- Syngenta informed the EPA that that was a safer product than what was previously on the market, correct?

A. Correct.

Q. Safer from a toxicity standpoint, correct?

A. Specifically targeted at oral toxicity from ingestion, yes, sir.

Q. Is that safer Gramoxone Inteon still on the market?

A. No, sir.

Q. Syngenta made a determination to pull Gramoxone Inteon and replace it with another product?

A. We did replace Gramoxone Inteon with Gramoxone SL 2.0 but before doing, we did tox test to show they had equivalent toxicity and the metric doses that were used for the original Inteon standard which was 128 milligrams per kilogram in the rat species.

Our alginate supplier had indicated they were not going to be able to provide additional alginate which was a key component of the Inteon, and so we tested a similar formulation, same loading and determined that at the 2 tox metrics we were looking at, our non-Inteon two pound product had equivalent plasmary (ph) end of the curve as our Inteon formulation once we satisfied that safety standard.

MR. DICKENS: Move to strike everything after did replace.

BY MR. DICKENS:

Q. With respect to we were talking

inhalation, do you have an understanding that surfactants also reduce particle size?

MR. HONG: Object to form.

A. Yes, sir. I'm not a formulation chemist, so I don't know all the roles surfactants play.

BY MR. DICKENS:

Q. Well, it's fair to say that if the labeling for Paraquat did instruct users to mix with a surfactant, that the EPA would not be taken into consideration the toxicity of the Paraquat and the tank mix after the fact?

MR. HONG: Object to form. Lacks foundation.

A. Yeah, I can't speak on EPA's approach there.

BY MR. DICKENS:

Q. Well, do you know whether or not the EPA looks at toxicity of tank mixes in reregistration reviews?

A. I can't speak for EPA on that, sir.

Q. You don't know whether it's specific to the active ingredient or not?

A. The registration review?

Q. Correct.

A. The registration review is specific to the active ingredient but the approach EPA takes is I'm not an expert on EPA's internal working.

Q. But you do agree that with respect to the registration and the review of the safety of the product, the EPA looked at the active ingredient, right?

A. That is the role of EPA in that, yes, sir.

Q. So the registrant is registrant of Paraquat, right? I mean, that's what they're looking from a toxicity standpoint?

A. Of Paraquat and the formulation.

Q. Turn your attention to several pages after the last page which concludes the conclusions?

A. The one where we were past, sir?

Q. Yes.

A. So we have the page and the reference. I'm assuming you're going past the reference?

Q. So go back one more, right before Andy Cook's name on that page. That one right there.

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A. Okay.
Q. There's a section, Exposure Measurements From Paraquat Biological Monitoring Studies.
Do you see that?
A. Yes, sir.
Q. It states [As read] "Biological monitoring studies offer a higher tier of assessment and Paraquat is an ideal candidate for such studies." Right?
A. I see that.
Q. States, [As read] "Operator exposure biomonitoring studies enable assessment of the total absorbed dose, integrating the total exposure received from all routes including inhalation." Right?
A. I see that.
Q. And it references a Findlay study? Findlay study.
A. That would have been Malcolm Findlay. He was one of our scientists many years ago.
Q. And did he conduct biomonitoring studies for Syngenta?

A. It appears based upon this statement he conducted a Spanish Paraquat knapsack biomonitoring study.
Q. This is the study that is specifically referenced by Syngenta to the EPA on exposure measurements, right?
A. Not sure, sir. There were biomonitoring studies done in the U.S. Those I'm aware of. I'm not sure beyond this reference here where else this is referenced.
Q. Well, it says, [As read] "This is study provides further data demonstrating low systemic exposure of Paraquat from all route of exposure. This study is the Findlay study, right?
A. Yes, sir.
Q. And this Findlay study being relied on by Syngenta, are you aware whether or not Syngenta had any biological monitoring studies that weren't submitted to the EPA?
A. I believe there would be biomonitoring studies not submitted to EPA if they were not done within the U.S., and the reason for that is that

the agronomic practices, the formulations, there's no really way for EPA to make a meaningful comparison of a application practice that doesn't mimic U.S. application practices.
The formulations are different, the work or activities are different, the exposure durations would be different, the clothing would be different, so it makes it really impossible to compare, for example, a person doing a knapsack application study in a rubber plantation to somebody doing a aerial application to a soybean field.
THE COURT REPORTER: Aerial application to a...
THE WITNESS: Soybean field.
BY MR. DICKENS:
Q. Sir, where was the Findlay study conducted?
A. It says here Spain, if this is the one you're referring to. It says Spanish, so I'm assuming it's Spain.
Q. So certainly Syngenta is relying on

biological monitoring studies conducted outside the United States, aren't they?
A. I would say not relying but referencing.
Q. Well, relying in the comments to say that there's low systemic exposure to Paraquat, they're only relying on one study in this particular comments, right?
A. In this particular section of the comment.
Q. And that is a study conducted outside the United States.
A. Yes.
Q. And there are other biological monitoring studies conducted outside the United States that's not being relied on by Syngenta, correct?
A. Yes.
Q. And that's because they'll show higher systemic exposure of Paraquat, right?
MR. HONG: Object to form.
A. I cannot speak to why they didn't -- weren't submitted. I gave you the rationale as to why EPA could not make meaningful data on that.
BY MR. DICKENS:

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Q. You believe EPA could make meaningful data of the Findlay study conducted outside the United States?

MR. HONG: Object to form.

A. I would not make that conclusion. I think this is just building the weight of evidence.

BY MR. DICKENS:

Q. Well, wouldn't the submission of other biomonitoring studies also build the weight of evidence with respect to exposure measurements of Paraquat biological monitoring studies?

MR. HONG: Objection. Calls for speculation. You can answer the question, sir.

A. Sure. For those other studies, the relevant subject matter experts would evaluate those and determine whether or not they would have meaningful information to submit.

BY MR. DICKENS:

Q. When you say experts, experts within Syngenta?

A. Syngenta experts would be determining what Syngenta would submit, yes, sir.

Q. So Syngenta employees themselves would determine whether or not this is an appropriate study to submit to the EPA?

MR. HONG: Object to form.

A. Syngenta subject matter experts evaluate the studies to see whether or not they would comply with EPA requirements.

BY MR. DICKENS:

Q. And they did that with Findlay, correct?

A. In this particular case, I cannot say.

Q. But you can say that Syngenta specifically points to this in comments to the EPA, right?

A. I can say it points to comments. I cannot say with confidence that the Findlay study itself was submitted. It's referenced in the comments.

Q. You can put this aside?

MR. HONG: It's almost 12:40. Do you want to keep going?

MR. DICKENS: We can take a lunch break now if you want.

THE VIDEOGRAPHER: The time is 12:36 --

MR. HONG: Are we still on the record?

THE VIDEOGRAPHER: I have not taken us off.

MR. HONG: Do you need to take a lunch break now or keep going.

THE WITNESS: Why don't we take the lunch break right now and then circle back, if that's okay.

MR. HONG: Okay.

THE VIDEOGRAPHER: The time is 12:37. We are now off the record.

(A lunch break was taken from 12:37 to 1:16 p.m.)

THE VIDEOGRAPHER: This is the beginning of media unit No. 4 in the video-recorded deposition of Mr. Montague Dixon. The time is 1:16 p.m. Eastern. We were now back on the record.

Counsel, you may proceed.

BY MR. DICKENS:

Q. Welcome back, Mr. Dixon.

A. Thank you.

Q. Would you agree that the Federal Insecticide Fungicide and Rodenticide Act or FIFRA imposes on the registrant the duty to keep the EPA

informed on information relating to the registrant's pesticide products?

MR. HONG: Object to form.

A. That's a very broad statement. I would say my understanding of FIFRA is that it sets forth all of the requirements that the registrants must follow and certainly within their certain reporting requirements.

BY MR. DICKENS:

Q. And in those reporting requirements is a duty to report information concerning unreasonable adverse effects of pesticide products?

A. I believe that is correct, sir.

Q. You would agree the EPA itself does not conduct studies or tests on pesticides that are registered, right?

MR. HONG: Object to form.

A. I can't speak to what research EPA does, so I'm not sure on that, sir.

BY MR. DICKENS:

Q. You don't know if the EPA conduct studies on Syngenta products?

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A. I'm not aware of EPA conducting studies on Syngenta products.
Q. And with respect to Paraquat then, the EPA would rely on information submitted by Syngenta with respect to the safety and effectiveness of the product?
MR. HONG: Object to form.
A. EPA would rely upon information provided by Syngenta and other Paraquat registrants as well.
BY MR. DICKENS:
Q. And for a period of time, Syngenta was the only registrant of Paraquat products?
A. I believe that's an accurate statement.
Q. And that was certainly true at the time that Paraquat was initially registered, correct?
MR. HONG: Object to form. Lacks foundation.
A. Given the time frame being in the '60s, that's well before my time. I'm not aware of another registrant, I certainly know Syngenta didn't exist in the '60s.

BY MR. DICKENS:
Q. During -- and understanding that Syngenta didn't -- well, Syngenta and its legacy companies, correct; you understand there were companies that preceded Syngenta?
A. Yes, sir.
Q. How about during your time, was there a period of time where Syngenta was the only registrant of pesticide-containing products?
A. In my entire career or --
Q. Correct.
A. -- when I was regulatory --
Q. With the company?
A. I believe in the '90s we were the only -- to the best of my recollection, I believe we were the only registrant in the '90s and I think that's correct.
Q. Only in the '90s?
A. I believe there was a registrant in the very early 2000s and then around 2005 and '06 other registrants started entering into the marketplace.

MR. HONG: And Counsel, is this with respect to Paraquat or pesticide-containing products? I just want to make sure that that's clear.
BY MR. DICKENS:
Q. Did I say pesticide-containing products?
MR. HONG: Yes, you did.
BY MR. DICKENS:
Q. I meant Paraquat-containing products. And that's what you answered; is that right?
A. That's what I was -- sorry, I misinterpreted the question to be Paraquat-containing products.
Q. The record that's done by the registrant to the EPA, that would come under Section 682 of FIFRA?
A. That is correct.
Q. And you'd agree that if Syngenta does not follow the requirements of FIFRA 682 it would be a criminal violation, right?
A. Syngenta is obligated to follow the requirements of FIFRA 682. I'm not exactly aware

of the penalties for that, but as a company, we are required and we do comply with the requirements of FIFRA 682.
Q. Did you know at some point in time whether or not it would be a criminal violation for not filing FIFRA 682?
A. Again, I'm not sure -- my assumption is if you violate FIFRA, then you would be in violation of also if it is a criminal violation, yes, but Syngenta complies with 682, so I'm not familiar with us not complying with 682.
Q. Do you recall testifying in June 24, 2020 that, I agree that if you do not follow the requirements of FIFRA 682 that it would be a criminal violation?
A. I believe that was what was in my testimony.
Q. And prior to this deposition, did you go back and review your prior testimony from those earlier depositions?
A. I did not. To answer your question, sir, I did not.

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Q. Now, there are various committees within Syngenta responsible for submitting safety information to the EPA, right?
A. Various committees within the company --
Q. Responsible for determining whether or not safety information --
A. We have an established process that involves committees, yes, sir.
Q. And one of those committees is the PRF or Potentially Referable Findings committee?
A. That is correct.
Q. And there was also a 682 committee within the United States?
A. That is correct.
Q. Can you just explain briefly what the interaction between the PRF and the 682 committee was?
A. Briefly. When a potential finding that is being questioned is identified or given or referred to the PRF committee, the PRF committee consist of different subject matter experts who would evaluate it and make a determination whether

or not it needed to be forwarded to the relevant regional country team. In our case in the U.S. it would be the 682 committee.
Q. And then the 682 committee would make a determination as to whether or not it would be submitted to the EPA, right?
A. They would receive the information from the PRF committee and do their analysis and make that determination.
Q. And you served on the 682 committee during your tenure with Syngenta and its predecessor?
A. Not as a standing member but on a add need basis. So the way our 682 committee works is there are standing members and then when you're representative or manager for a particular active ingredient that is having a 682 question, often you're brought in to be part of that discussion, but in general, I didn't sit as a permanent member of the 682 committee.
Q. But you would be aware of information submitted and determinations made by the 682 committee as you were one of the individuals who

would then forward that onto the EPA?
A. That is correct.
Q. And you're familiar with the 682 requirements under federal statute FIFRA, right?
A. Correct.
Q. Are you familiar with EPA guidance on the type of information to be submitted under 682?
A. Generally so, yes, sir.
Q. Is there ever a time with respect to Paraquat or the 682 committee did not submit information to the EPA when the PRF committee recommended that it was indeed reportable?
MR. HONG: Object to form.
A. I cannot recall a specific time.
By MR. DICKENS:
Q. So as far as you recall, the 682 committee always followed the recommendations with respect to Paraquat by the PRF committee, correct?
MR. HONG: Same objection.
A. I can only speak to the time in which I was the Paraquat regulatory manager, and it is my best recollection that the 682 made the

determination based upon the members of the committee and what they believed the correct approach was.
I don't remember a distinct time they would have come to a different conclusion from the PRF committee.
MR. DICKENS: I'm going to hand you what we'll mark as Exhibit 16 to the record.
(Exhibit 16 was marked.)
THE WITNESS: Yes, sir.
I have scanned this quickly sir.
BY MR. DICKENS:
Q. And I hand you Exhibit 16 dated April 3rd, 1998. It's a notice to manufacturers, formulators producers, distributors, registrants of the pesticide products guidance on final FIFRA 6(a)(2) regulations.
Do you see that?
A. I do.
Q. And this is an EPA document, correct?
A. It is.
Q. And it's a document that you would have

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seen and reviewed during your time with the regulatory department at Syngenta?
A. Correct.
Q. And it's your understanding that this is the guidance that was in place throughout your entire tenure with the regulatory department between 2006 and 2022, right?
A. I would agree this is guidance. I don't believe it's the only guidance. There is also the actual statute 6(a)(2) which provides more specific -- more specific requirements.
Q. And that's fair. So there is a statute FIFRA 6(a)(2), right?
A. Yes, sir.
Q. And then this document was put out by the EPA providing additional guidance beyond what's included in 6(a)(2), right?
A. Yes, sir.
Q. And are you aware of any other guidance documents, such as this, that were put in place after 1998, between 1998 and 2022?
A. Put in place by the...

Q. EPA.
A. I don't recall any off the top of my head.
Q. And under background on the first page, [As read] "The purpose of this -- the rule is to clarify what information to submit, how and when to submit it, as well as which failures to report information, or delays in reporting, will be regarded by EPA as violations of Section 6(a)(2), and actionable under other FIFRA sections." Correct?
A. Correct.
Q. The purpose of this document is to provide registrants comprehensive guidance on implementing new regulations related to 6(a)(2) of FIFRA, correct?
A. I don't know if I would characterize it as new regulations. I think it's interpretation of the current regulations.
Q. And the EPA itself says [As read] "Guidance on implementing new regulations" on Page 1, right?
A. I stand corrected then.

Q. But certainly this guidance and the regulations, they would have been the same between the time you were involved in regulatory between 2006 and 2022, right?
A. That would be my understanding.
Q. I'm going to turn your attention to Page 7, there's a section Causation and Delayed Effects.
Do you see that?
A. I see that.
Q. Under this section it notes that [As read] "In the past, an incident was reportable if the registrant inferred that a link existed between the effect and the exposure or if similar incidents occurred three or more times. Under the new regulations, neither an inference nor a pattern needs to be established before reporting an incident."
Now, that was your understanding of the guidance and regulations related to causation and effects of pesticide products, right?
A. This is the guidance as stated in the

document, yes, sir.
Q. It was your understanding that Syngenta would need to report an incident regardless of whether or not the company made an inference or determined there was a pattern of incidents in order to have that reported to the EPA?
MR. HONG: Object to form.
A. I wouldn't want to speak on specifically there.
BY MR. DICKENS:
Q. Well, certainly you were involved in making decisions and determinations as to whether or not adverse effects would be reported to the EPA, correct?
A. As part of -- as a participating member in those discussions relevant questions on my AIs, I would have been part of the team that would evaluate that.
Q. Would the team that would investigate that and making determinations as to whether or not to report it first make an inference as to whether or not there was causation before an adverse effect

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was submitted to the EPA?
MR. HONG: Object to form.
A. So the team would take due diligence with subject matter experts to understand the question at hand and follow the established processes of the team.
BY MR. DICKENS:
Q. For example, if -- well, you've stated before, Syngenta's position is that Paraquat does not cause Parkinson's Disease, correct?
A. That is our position.
Q. Would you report incidents where an individual or Syngenta becomes aware of an individual's allegation that their Paraquat exposure caused Parkinson's Disease?
MR. HONG: Objection. Incomplete calls -- hypothetical. You can answer the question.
A. We have reported when we have received litigation notices of such allegations.
BY MR. DICKENS:
Q. Have you reported incidents alleging Parkinson's Disease from Paraquat exposure outside

of litigation events?
MR. HONG: Object to form.
A. Myself or the 6(a)(2) teams?
MR. DICKENS: The 6(a)(2) teams.
MR. HONG: Same objection.
A. When you say incidents, are we talking human incidents, sir?
BY MR. DICKENS:
Q. Correct?
A. I'm not aware. I can't speak with authority on the entirety of the 6(a)(2) team submissions in my time. Other than what I mentioned about references to litigation, I cannot specifically recall reporting anything from the 6(a)(2) team of a human incident.
Q. Are you aware of human incidents outside of litigation events where an individual has reported Parkinson's Disease after Paraquat exposure?
MR. HONG: Object to the form.
A. I'm aware of the allegations in the different literature.

BY MR. DICKENS:
Q. How about outside the literature?
MR. HONG: Same objection.
A. Within the scope of the litigation notices that would be the extent.
BY MR. DICKENS:
Q. Turning your attention to Page 8?
A. Yes, sir.
Q. In the very bottom section on expert opinion information.
Do you see that?
A. Yes, sir.
Q. It says [As read] "Conclusions or opinions of experts must be submitted under FIFRA 6(a)(2) if the registrant possess the information and either, the information is otherwise reportable under one of the substantive provisions of the rule, or the registrant knows or should reasonably know that the information alone or in conjunction with other information might raise concerns about the continued registration of a pesticide, or about the appropriate terms and conditions of

registration of a pesticide."
First of all, did I read that correctly?
A. Yes, sir.
Q. Is that your understanding as to the reporting requirements of Syngenta for expert opinion information?
MR. HONG: Object to form.
A. The document says what it says. Here, I agree with how you read it. It's my understanding based upon 6(a)(2) that if the information is already available in the public record, then we have a -- do not have an obligation to make an additional report.
BY MR. DICKENS:
Q. And when you -- what's your understanding with respect to when you say public record? What does that mean?
A. Scientific publications, or presentations at say public meetings such as science and toxicology meetings and other venues where the public is aware where EPA may or may not be in attendance.

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Q. Expert information or expert opinions that includes opinions of individuals within the company; you would agree with that?
A. Yes. We have experts within our organization, yes, sir.
Q. And if those experts provided opinions that were otherwise reportable or the company knew might raise concerns about the continued registration of one of Syngenta's pesticides, that would be reportable, right?
MR. HONG: Objection. Incomplete hypothetical. You can answer the question.
A. If an expert within the company raised it, it would go through the appropriate 6(a)(2) process and the determination would be made based upon the guidance and policies of that committee.
BY MR. DICKENS:
Q. The policies of that committee would they follow the guidance provided by the EPA with respect to what's reportable?
A. The policies of the 6(a)(2) committee are crafted to ensure we were compliant with the

requirements of 6(a)(2).
Q. So if an expert within the company provided an opinion that was reportable under 6(a)(2), it would be reported, right?
MR. HONG: Objection. Incomplete hypothetical.
A. And I would assume in that hypothetical situation it would go through the processes of the 6(a)(2) committee and be determined whether or not it's reportable.
BY MR. DICKENS:
Q. And the 6(a)(2) committee, that consisted only of members of Syngenta, right?
A. To the best of my understanding, yes.
Q. So the expert opinion of someone within Syngenta would then go to others within Syngenta to make determination as to whether or not it's reportable to the EPA?
MR. HONG: Object to form.
A. If it went through the PRF 6(a)(2) committee, those would be Syngenta subject matter experts evaluating.

BY MR. DICKENS:
Q. The expert opinions on the next page, Page 9?
A. Yes, sir.
Q. "They play an important role in agency decision-making," that's what the EPA instructs registrants, right?
A. Let's see here, where are we on this, sir.
Q. Very first full sentence on that page.
A. I see that. I'm sorry. I was in the next paragraph. Okay.
Q. That's what the EPA's instructing registrants, right?
A. That is what they are instructing.
Q. And then the EPA gives some specific examples of reportable expert opinions, right?
A. Correct.
Q. One, [As read] "Investigator opinions concluding exposure may have caused the particular adverse effect." Right?
A. I see that.
Q. They specifically say may there, right?

A. I see that.
Q. It doesn't need to be a definitive conclusion that it absolutely caused it, but if an investigator concludes it may have caused it, that would be reportable, right?
MR. HONG: Object to form.
A. That is how it's stated.
BY MR. DICKENS:
Q. And that would be what the 6(a)(2) committee would have implemented during their review of particular investigator opinions?
MR. HONG: Object to form.
A. I'm sure it would have been factored into their deliberations.
BY MR. DICKENS:
Q. So are you saying it only factored in or would -- they would actually follow this guidance that that would be reportable.
MR. HONG: Objection. Incomplete hypothetical.
A. I cannot speak definitively to each of the meetings of the 6(a)(2) committee, but the way it

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is structured they're supposed to follow all the policies to ensure regulatory compliance, and this being in there, I'm sure that would have been part of the considerations.

BY MR. DICKENS:

Q. Do you know whether it would have been part of the considerations?

A. I can't speak to any meetings I wasn't a part, of sir.

Q. Well speak to the ones you are a part of.

A. I believe we followed all of the guidance and guidelines and that everything we did was in compliance.

Q. Another example of reportable expert opinions by the EPA, [As read] "Scientific opinions that test data demonstrate that a pesticide causes a particular adverse effect."

Do you see that?

A. I see that.

Q. That's a specific reportable expert opinion that the EPA is saying should be reported, right?

A. So as I read through this, this gives specific examples or are you asking more broadly than that?

Q. I'm saying the EPA would consider scientific opinion testing -- that the test data demonstrates pesticide causes a particular adverse effect as reportable, right?

A. Within the confines or the guidance of the 6(a)(2) policy, it may or may not be reportable.

Q. Goes to say [As read] "Expert opinions reflecting aggregate risks posed by a pesticide may be higher than previously believed."

That's another one of the examples EPA gives as a reportable expert opinion, right?

A. That is correct, sir.

Q. EPA instructs [As read] "In any particular case if a registrant has questions concerning whether the agency considers an expert opinion reportable under 6(a)(2), they're encouraged to reach out and contact an officer in the Office of Pesticide Programs."

Do you see that?

A. Yes.

Q. As far as you know in your involvement with the 6(a)(2) committees, has Syngenta ever reached out to an officer in the Office of Pesticide Programs to make a determination as to whether or not an expert opinion was reportable?

A. I'm not aware of any such communications.

Q. Turn to Page 13.

A. Yes, sir.

Q. Section Extra Territorial Adverse Effect.

Do you see that?

A. Yes, sir.

Q. We discussed information from outside the United States earlier with respect to that Findlay study. Do you recall that?

A. I do.

Q. That would have been considered extraterritorial under your understanding?

A. I understand that to be outside of the United States.

Q. And that's what your understanding of what EPA means by extraterritorial?

A. That is my understanding.

Q. EPA says, [As read] "Information derived from studies or incidents occurring outside the United States is reportable if the information is relevant to a pesticide registration held by the registrant possessing the information, and the information is otherwise reportable."

Do you see that?

A. I do.

Q. And then the second paragraph goes on to say [As read] "The Agency will consider all such information reportable unless an expert concludes that differences between the formulation of product involved and the foreign information and product registered in the United States make the information irrelevant to the product registered in the United States."

Do you see that?

A. I do, sir.

Q. There's a lot of words in that sentence but your understanding that the EPA would consider information reportable unless some expert

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concludes there's differences between the two formulations that would otherwise make it not reportable, right?

A. That is what's stated, yes, sir.

Q. We can put this aside. When we looked at the comments to the EPA and specifically with respect to the biological monitoring studies we discussed the Findlay, a 1998 report, right?

A. Correct.

Q. And that report provides data demonstrating low systemic exposure of Paraquat from all routes of exposure, right?

A. I believe that's what the summary of the report says.

Q. And we discussed the fact that Syngenta had conducted additional biomonitoring studies?

A. Correct.

Q. And some of those studies may or may not have been submitted to the EPA for consideration, right?

A. Yes, sir.

MR. DICKENS: I'm going to go ahead and

hand you what we'll mark as Exhibit 17.

(Exhibit 17 was marked.)

THE WITNESS: Okay. Sir.

BY MR. DICKENS:

Q. Exhibit 17 is an e-mail with an attachment e-mail from you to Chris Howard, March 7, 2007.

Do you see that?

A. Yes.

Q. Deemed important high, sensitivity confidential.

Do you see it?

A. I do.

Q. Who is Chris Howard?

A. He would have been an attorney at the time, sir.

Q. And you're attaching a PRF file used to draft my letter. Do you know what you're referring to as my letter?

A. Yes, we would have made, based upon this, a 6(a)(2) -- we were considering making a 6(a)(2) submission to EPA. That would have been referring to a draft letter.

Q. So a draft letter for a 6(a)(2) whereby information on what's included in the attachment would be submitted to the EPA, right?

A. Correct.

Q. And what would be the purpose of that 6(a)(2) letter?

A. When we received this information as summarized in the PRF report, the committee did an analysis and were trying to determine the best way to report this information.

Q. Do you know what the PRF committee concluded?

A. I believe the ultimate conclusion was to include this under our HE category. So I believe it was part of the periodic reporting that comes under the HE.

Q. So the letter that you initially prepared, that would have not have been under the HE submission category, correct, it would have been a stand-alone submission to the EPA?

A. It would have --

MR. HONG: Object to form.

A. Yes, if I was drafting a letter, it would have been for a stand-alone submission.

BY MR. DICKENS:

Q. So there was a consideration within the company as to submitting the results of the particular study titled biomonitoring study in vines, repeat application; France as a stand-alone, right?

A. There was some consideration of that, yes, sir.

Q. And you were working on the letter that would be used to go ahead and submit that information?

A. Correct.

Q. And the attachment, can you identify what the attachment is?

A. The attachment is the summary of the PRF team and then also has further information from the 6(a)(2) discussion.

Q. And this is a standard form that would have been used within Syngenta for referable findings in 6(a)(2)?

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A. For evaluation of those, yes, sir.
Q. And who would have completed say Section 1(a) in the brief description of the findings?
MR. HONG: Object to form.
BY MR. DICKENS:
Q. If you know?
A. I don't believe I know actually.
Q. The name of study director/originator that's a BM Elliot, a Syngenta product toxicologist.
Do you see that?
A. Yes, sir.
Q. What is your understanding of BM Elliot as a study director/originator?
A. I knew Barry Elliot. He was one of our toxicologists and study director could mean the person who actually monitored or directed the study, but the originator could be whoever is making a referable finding. So they may be the same person but not necessarily.
Q. In this particular study, was a monitoring study conducted by TNO on behalf of Syngenta in

France, right?
A. That's my understanding of this.
Q. It's a Syngenta commission study?
A. It is.
Q. Two of the 15 workers in this study had urine levels that resulted in estimated basis in excess of the AOEL; is that right?
A. I believe that's correct. I'm looking through it now but that's my recollection.
Q. The AOEL, that's Acceptable Operator Exposure Level?
A. Yes, sir, that's the European approach to occupational risk assessment, a little different than what's done in the U.S.
Q. But that's defined as the maximum active -- amount of active substance to which operator may be exposed without an adverse health effect, right?
A. I'm trying to remember what that acronym is, I think it's adverse observable effect level. I was never a European risk assessor. I just remember the acronym.

Q. So it's a maximum amount someone can be exposed to a particular product without being at risk for a health effect?
A. Based upon the European approach.
Q. Okay. And two of the individuals in this study exceeded that level by 116 and 780 percent, right?
A. Yes, sir, I see that on the top of Page 2.
Q. And it would be based on that information that you were putting the letter for a stand-alone submission to the EPA, right?
A. Correct.
Q. And this was actually application by knapsack sprayers, right?
A. I believe that's correct.
Q. Knapsack spraying at this time was permitted in the United States?
A. It would have been -- we call it backpack, a little different phraseology.
Q. Same thing though, right.
A. Essentially the same thing.
Q. So backpack spraying at this time was

still going on in the United States but now there's been a restriction, right?
A. As part of the human health mitigation decision there was, yes, sir.
Q. And on behalf of the proposal from the EPA to restrict that, right?
A. Correct.
Q. The information from this study was never submitted as a stand alone, right?
A. No, sir.
Q. So the EPA made its proposal to restrict knapsack brain without the benefit of having this information as to two workers exceeding the --
MR. HONG: Object to form.
A. EPA's position on backpack was related more to the concerns about transfer and potential for the leaking. This particular study, if you take a look at the specifics of it and one of the reasons why EPA would struggle to find relevant information in this case study is you have a non-U.S. formulation and you also have workers that were engaged in activities that involve not

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wearing PPE, which may be different.
So under that relevant clause that we looked in the previous document, those type of data would not inform EPA to do a risk assessment.
MR. DICKENS: Move to strike.
BY MR. DICKENS:
Q. Sir, the question was, the EPA made its proposal to restrict knapsack spraying without the benefit of having the information in this study, that's correct, right?
MR. HONG: Object to form.
A. EPA would have had the report and the aggregate from the study, but they would not have had the specific study itself.
BY MR. DICKENS:
Q. You mentioned differences with the formulation. What was the difference between the formulation in the United States and that used in France?
A. My recollection of the Arabics is that's a Paraquat Diquat, if I'm remembering correctly --
THE COURT REPORTER: Paraquat what? I'm

sorry.
A. Paraquat and Diquat combination formulation. We have never registered a Paraquat Diquat premix in the United States, if I'm remembering the correct formulation. In the U.S., we have only had either or at least at this time frame, and I don't think we ever have done a premix with Paraquat and Diquat.
BY MR. DICKENS:
Q. Okay. Turn your attention to the first page that we were looking at of the PRF?
A. Of this page? Yes, sir.
Q. And in that Section 1(a), it references [As read] "A group of 15 workers was monitored, two consecutive daily applications of Paraquat Inteon 49409AL." Is it your understanding that that Paraquat Inteon was a Paraquat and Diquat combination?
A. No, sir, not with that clarification. The Arabics, if it's 89409AL, that is 100 gram per liter Inteon formulation based on this. In the U.S. our Inteon formulation was 240 grams per

liter.
Q. So this Paraquat Inteon being used by these squares was 100 grams per liter, right?
A. Yes.
Q. The amount of the Inteon, Paraquat Inteon in the United States was 240 grams per liter?
A. That is correct, sir.
Q. So the only difference between what's being sprayed in France and the United States is the product in France had less Paraquat?
A. No, sir.
MR. HONG: Object to form.
A. That's not correct. If you take a look at the code there, the way our formulation codes are designated, A is the initial code, then there's a number and you see two letters afterwards.
In the U.S. the Inteon formulation was A7813, so that defines the composition of the U.S. formulation. The fact that this has an A9409, that would indicate a different composition, so while it would have had similar components, the compositions would be different.

BY MR. DICKENS:
Q. What was different between the compositions?
A. I would have to take a look at them and map them out side by side, but I can say with confidence when the formulation code has a different number, it indicates there's different constituents in there.
Q. So is it Syngenta's position that if the composition of the formulation was different in the slightest respect it wouldn't be reportable because it was different formulations?
MR. HONG: Object --
BY MR. DICKENS:
Q. Is that Syngenta's position?
MR. HONG: Object to form.
A. When you say, different in the slightest, you would have to do an analysis of the formulations to determine what the difference is. I do know, for example, our U.S. formulation hit the maximum level of a medic that we could put in 1.5 grams per liter. I do not believe the global

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formulations had the maximum --
BY MR. DICKENS:
Q. You agree that Syngenta did submit under 6(a)(2) information from products and formulations that were not registered in the United States in the past?
A. I think that certainly is possible.
Q. Not possible, that happened, right; you recall that?
A. I -- well, just the fact that we submitted here that would confirm that.
Q. When you say, "submitted here," though, you didn't submit any details of that, right?
A. I believe this was just submitted in the aggregate reporting.
Q. And that aggregate reporting, all that does is list a check box, right?
MR. HONG: Object to form.
A. Yes, sir. It provides a much higher level of detail or a much -- it's a very brief. It's not a letter, per se.
BY MR. DICKENS:

Q. Not a letter, per se, it includes no information about the nature of the study or the findings or anything about those workers, right?
MR. HONG: Object to form.
A. It's a very brief summary that there was an incident, but I don't believe there's significant detail associated with it.
BY MR. DICKENS:
Q. Doesn't even identify what that incident was?
A. I would have to look at it but I agree.
Q. Now, if we can turn to the next page, PRF approach committee, and they recommend to refer based on exceedance of the EU regulatory operator exposure level, right?
A. Yes, sir.
Q. And then this went over to the 6(a)(2) committee for determination of how it should be submitted?
A. First off, if it is reportable and then how it would have been reported.
Q. Eventually 6(a)(2) committee did make a

determination to submit this in tabular form, right?
MR. HONG: Object to form.
A. I believe that's how it was submitted, sir.
MR. DICKENS: You can put that aside. Hand you what we'll mark as Exhibit 18.
(Exhibit 18 was marked.)
THE WITNESS: Okay, sir, I have scanned through this.
BY MR. DICKENS:
Q. So this is another submission and I'm going to ask you questions regarding a second study, biomonitoring study, but this is a document dated February 27, 2008.
Do you see that?
A. Yes, sir.
Q. This is submission of aggregate 6(A)(2) incident report?
A. Yes.
Q. So this would include, kind of, HE reporting that you referred to earlier, right?

A. Yes, sir.
Q. And this is where the company would report incidence in an aggregate report without details, correct?
A. That looks correct.
Q. On this cover letter from Sharon Waynick there's enclosures and then there's a five next to that, right?
A. I see that.
Q. And then the next five pages include, kind of, the aggregate incident report information, right?
A. I see that, yes, sir.
Q. And this is typically how those aggregate reporting would be done, right?
A. It appears consistent with that.
Q. And you were and during your time had submitted aggregate reporting as well as Ms. Waynick, correct?
A. I don't recall myself submitting aggregate reporting. I believe typically what I would have done would be letters specifically.

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Q. And that's for the specific individual reporting outside of aggregate?
A. Yes, sir.
Q. Now, before we get there, there's information here -- I'll refer to the second page where there's some BCCs or blind copies?
A. Yes.
Q. Those blind copies include all enclosures, right?
A. It does say with all enclosures, so I would assume, yes.
Q. And so the information that's attached as supporting correspondence here that wouldn't actually be submitted to the EPA, right, after the first five pages?
A. Yes, I do not believe this would have been submitted to EPA.
Q. So under the submission to the EPA there's -- sorry on Page 3 there's Paraquat, dichloride. There's a section that says Paraquat nonspecification and then it has a one in the HE column.

Do you see that?
A. I see that.
Q. And this is how that type of information from the biomonitoring studies would have been reported to the EPA, right?
A. I believe that's how this information was reported. I didn't put this together but that's my understanding.
Q. So the only information the EPA would have got with respect to that study that found two workers exceeding the AOEL was the number one within HE, right?
A. To the best of my understanding, yes.
Q. Turning your attention to the Bates number ending 5618-R2?
A. Okay. This right here, sir. Okay.
Q. So this adverse event incident form -- once again this wouldn't be submitted to the EPA, right?
A. I do not believe this form would have been submitted to EPA, sir.
Q. It specifically says HE report as HE,

right?
A. Correct. And Dennis Hackett was the head of our 6(a)(2) committee, so that would be who indicated that.
Q. This is another monitoring study conducted on behalf of Syngenta in Martinique, correct?
A. That appears to be correct, sir.
Q. This study two workers had measured exposures exceeding the European AOEL once again, right?
A. That is correct.
Q. So we have a study, biomonitoring study in France where workers exceeded AOEL and now we have one in Martinique where the workers exceeded AOEL, right?
A. That's what is stated, yes, sir.
Q. The information with respect to the fact that now there's two studies conducted by Syngenta where workers exceeded the AOEL, that was never submitted to the EPA, right?
MR. HONG: Object to form. Lacks foundation.

A. If you could please restate.
BY MR. DICKENS:
Q. At no point did anyone at Syngenta inform the EPA that two biomonitoring studies conducted by Syngenta had workers exceeding the acceptable operator exposure level?
MR. HONG: Same objection.
A. Other than what I see here, I have no knowledge of any additional communication on that.
BY MR. DICKENS:
Q. The only information submitted with respect to these two biomonitoring studies were the ones that were listed in the HE correct?
MR. HONG: Object to form. Assumes fact not in evidence. You can answer the question.
A. The only information that I'm aware of is what's been presented here.
BY MR. DICKENS:
Q. The Martinique biomonitoring study itself was not submitted to the EPA, correct?
MR. HONG: Object to form.
A. I do not believe it was.

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BY MR. DICKENS:
Q. And the French biomonitoring study itself was never submitted to the EPA?
A. To the best of my understanding, it has not been.
Q. Findlay the Spain study, biomonitoring study, that was submitted to the EPA?
MR. HONG: Object to form.
A. Certainly we reference it in that communication. As far as it being specifically submitted, I believe it was. I can't say definitively but I believe it was.
BY MR. DICKENS:
Q. Would Syngenta typically cite to studies that EPA had no idea about?
A. We would reference -- I've seen where we have referenced a study and EPA sometimes will request it, sometimes not. So, for example, if we make a reference to a study, there's been times we've offered to provide and EPA has not requested it.
Q. We can agree that the formulation approved

for use in Spain was not the same formulation registered in the United States at the time of Findlay study, right?
MR. HONG: Object to form. Lacks foundation.
A. I would have to look at it to be 100 percent sure, but historic in the U.S. had different formulations than the rest of the world.
MR. DICKENS: Hand you what we'll mark as Exhibit 19.
(Exhibit 19 was marked.)
THE WITNESS: Counsel, after this can we take a brief break?
MR. HONG: We've been going about an hour.
MR. DICKENS: Yeah, after this brief document.
THE WITNESS: Thank you.
BY MR. DICKENS:
Q. Exhibit 19 is an e-mail chain in which you're involved in September of 2007; is that correct?
A. Correct, sir.

Q. And it begins, I'll start on the initial e-mail, you received an e-mail from a Roland Dieterle to you September 10, 2007, right?
A. That is correct.
Q. And he received a call from John Miranda from Dole on Paraquat; is that right?
A. That's what he had communicated, yes.
Q. And you recall this conversation or issue?
A. Very vaguely, but yes.
Q. At this point in time, you were in the regulatory department for Paraquat?
A. Yes, sir.
Q. Roland is asking you to confirm a statement on Paraquat and Parkinson's Disease in RED, right?
A. Correct.
Q. And he forwards you an e-mail from David Scott summarizing his call with John Miranda at Dole, right?
A. He did.
Q. And the information that David Scott forwarded indicates that John Miranda at Dole had

concerns on the Paraquat CFI decision.
Do you see that?
A. That is correct.
Q. Dole had done a lot of research on the internet on the issue and found the Rochester papers and the Paraquat thread which does not mention Parkinson's.
Do you see that?
A. I do.
Q. At this point in time, the Paraquat -- and do you know what they're referring to by RED?
A. Yes, sir.
Q. What is that?
A. That's the Registration Eligibility Decision document which was published in 1997, if I remember correctly.
Q. So that 1997 published by the EPA?
A. That is correct.
Q. So that 1997 EPA document doesn't mention Parkinson's Disease, right?
A. I do not believe it does.
Q. And you'd agree by that point in 1997,

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Syngenta had not submitted any neurotoxicity studies to the EPA for consideration?

MR. HONG: Object to form. Lacks foundation. Go ahead and answer.

A. Yes, that predates my time, so I don't think I can confirm that.

BY MR. DICKENS:

Q. Do you know when the fist neurotoxicity study was submitted to the EPA?

MR. HONG: Same objection.

A. I do know toxicity neurotox studies that I submitted once I came into this role.

Q. And when was that?

A. 2006, around that time frame, 2006 or '07.

Q. Do you know whether or not studies had been submitted prior to that?

A. From my memory, no, sir.

Q. No, you can't recall or no, they were not?

MR. HONG: Object to form.

A. I cannot recall at this point.

BY MR. DICKENS:

Q. John Miranda of Dole goes on to say, [As

read] "The issue was a rising cake, prompted high level discussions with senior VPs of legal and marketing at their company." Right?

A. Yes, sir.

Q. And "they had a concern of Parkinson's health liability that may accrue with the Dole use of Paraquat." Right?

A. That is what the concerns expressed, yes, sir.

Q. And that's being expressed by Dole to members of Syngenta specifically, right?

A. Appears it was sent to David Scott, yes, sir.

Q. The statement, [As read] "Removal of Paraquat would be a major blow to the current business, particularly Pineapple which is an overriding concern."

Do you see that?

A. I see that.

Q. Dole did go on to stop using Paraquat, right?

MR. HONG: Object to form. Lacks

foundation.

A. I believe that to be the case.

BY MR. DICKENS:

Q. And Dole did that even though they recognized it would be a major blow to their business, right?

MR. HONG: Object to form.

A. I can't speak to Dole's motivation.

BY MR. DICKENS:

Q. Well, Dole tells you their motivation here in this e-mail, right; they're concerned about the Parkinson's issue?

MR. HONG: Same objection.

A. Yes, sir, but I don't want to speak for Dole.

BY MR. DICKENS:

Q. Do you know or based on your understanding of this time in 2007 moving forward whether or not Dole expressed any other concerns with respect to their Paraquat use on pineapples or in their business generally?

MR. HONG: Object to form.

A. I have no specific recollection of that.

BY MR. DICKENS:

Q. The only recollection you have is concerns over Parkinson's?

MR. HONG: Object to form.

A. This document is the only information I have any recollection of, sir.

BY MR. DICKENS:

Q. Go back to what's the second page of the document. In your e-mail to John Abbott, September 13, 2007 copying Roland Dieterle. Now John Abbott in September of 2007, was he your supervisor at that time?

A. Yes, sir.

Q. What was his role specifically, if you know?

A. He was the head of the herbicide regulatory team and I reported to him. He may have been the head of the whole regulatory department at that point, but certainly he lead the herbicide team.

Q. And you provide your thoughts on Roland's

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question and say, [As read] "We should perhaps instead of mentioning Parkinson's directly, say something to the effect that registrants have a statutory responsibility to notify the EPA of any information they come into possession of that would be relevant to the evaluation of the safety of registered products." Right?

A. Yes, sir.

Q. And that was your recommendation with respect to a statement on Paraquat and Parkinson's Disease to Dole specifically?

MR. HONG: Object to form.

A. I was reaching out to John because I was relatively new in the role and wanted to make sure that my response was something that he thought was appropriate.

BY MR. DICKENS:

Q. And appropriate to responding to Dole's concerns of Parkinson's Disease?

A. Yes.

Q. And that statement or the response is that or indicating that Syngenta has a duty and

responsibility to notify the EPA of information that would come into their possession with respect to adverse effects such as Parkinson's Disease, right?

MR. HONG: Object to form.

A. Correct.

BY MR. DICKENS:

Q. And the suggestion then to Dole would be that the EPA made its determination but we're keeping them informed as to everything we know about Paraquat and Parkinson's Disease; is that right?

MR. HONG: Same objection.

A. Could you please restate that, sir. Sorry. I was reading the next page.

BY MR. DICKENS:

Q. Yeah, the statement to Dole indicates that Syngenta is providing the EPA everything they know about the issue of Parkinson's and Paraquat?

MR. HONG: Object to form. Mischaracterizes the document.

A. My proposed statement that I wanted John

to help was to make sure I was conveying to Dole that we were -- that Syngenta would take its reporting obligations for any adverse effects to any particular adverse effect, not one particular. And John helped me to come up with a better comment and trying to see what John's comment was but I was seeking his guidance on that.

BY MR. DICKENS:

Q. And John's comment on the bottom of Page 1?

A. Yes, sir.

Q. [As read] "Registrants are required to submit to EPA any information they obtain that is relevant to the safety of their registered products."

Do you see that?

A. I see that.

Q. And you agree with that statement?

MR. HONG: Object to form.

A. I agree with that.

BY MR. DICKENS:

Q. Following this requirement, [As read]

"Syngenta's provided results from studies conducted by researchers outside Syngenta that's alleged a connection between Paraquat and Parkinson's Disease."

Do you see that?

A. I see that.

Q. So this is telling Dole that Syngenta has provided results from studies conducted by people outside Syngenta alleging connection between Paraquat and Parkinson's Disease, right?

A. That's what the sentence states, yes, sir.

Q. And specifically you're telling Dole that in response to their concern as to continuing to use Paraquat in light of that Parkinson's risk?

A. This was the statement that we provided.

Q. Do you agree with the statement that Syngenta has provided any information that they obtain relevant to the Parkinson's Disease issue on their registered product Paraquat?

MR. HONG: Object to form.

A. As asked, any information is so broad I can't speak to any information. I think Syngenta

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has gone through a systematic process of keeping EPA informed on its understandings and the information it gets.

BY MR. DICKENS:

Q. Do you believe Syngenta at this point in time in 2007 had provided results from all studies on neurotoxicity and Parkinson's Disease that they had in their possession?

MR. HONG: Object to form.

A. I was very new in the role at that time, so I don't have awareness prior to that. I can talk about what we've provided since I've been in the role.

MR. DICKENS: Why don't we go ahead and take our break.

THE VIDEOGRAPHER: The time is 2:19 p.m. We are now off the record.

(A break was taken from 2:19 p.m. to 2:32 p.m.)

THE VIDEOGRAPHER: This is the beginning of media unit No. 6 in the video-recorded deposition of Mr. Montague Dixon. The time is 2:32 p.m. Eastern. We are going back on the

record.

Counsel, you may proceed.

BY MR. DICKENS:

Q. Mr. Dixon, we were talking about the Dole e-mail in September of 2007?

A. Yes, sir.

Q. And Dole's manufacturer, not manufacturer, their company involved in a business that includes fruits, such as pineapples, bananas, correct?

A. Yes, sir.

Q. I want to look back at Exhibit 18, which is that TNO Martinique study?

A. This one, sir.

Q. That's correct. And specifically Bates number ending 5618-R2?

A. Okay. I'm here.

Q. Martinique, this is the second of the two studies that we had looked at with respect to biomonitoring; the first in France and this was the Martinique one, correct?

A. Correct.

Q. There's an incident date here of September

24, 2007?

A. I see that, yes, sir.

Q. And that's just literally a week after the correspondence with Dole, correct?

A. That appears correct, yes, sir.

Q. And this study is specific to knapsack spraying on banana plantations, right?

A. Correct.

Q. Did you ever inform Dole of the findings in the knapsack spraying of banana plantations on this biomonitoring study?

A. I'm not aware of any such communication.

Q. Was there ever any communications to Dole instructing them to provide additional PPE or safety information to reduce the amount of exposure to Paraquat?

A. I'm not aware of such communications.

Q. Now, with respect to the Dole e-mail, we were talking about the statement of Syngenta providing results from studies conducted by researchers outside Syngenta that's alleged connection between Paraquat and Parkinson's

Disease, right?

A. Yes, sir.

Q. And that's specific to providing those results to the EPA, correct?

A. Based on how it's written, Syngenta's provided results from studies contacted that appears to be consistent with the statement before about EPA.

Q. So you're informing Dole that you've submitted and provided results from studies Paraquat Parkinson's Disease to the EPA, correct?

A. That's what the statement says.

MR. DICKENS: Go ahead and mark Exhibit 20.

(Exhibit 20 was marked.)

THE WITNESS: Okay, sir.

BY MR. DICKENS:

Q. So Exhibit 20 is e-mail correspondence with an attachment once again, and this is e-mail correspondence beginning with you to Alan Nadel May 22nd, 2008 with respect to PRFs on Paraquat and Parkinson's Disease, right?

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A. I see that. Yes, sir.
Q. And you write to Roland Dieterle on that same day and say [As read] "Only two incidences were identified and have been captured on your template."
Do you see that?
A. I see that.
Q. So you went and actually reviewed all of the PRF's to determine what was submitted to the EPA on Paraquat Parkinson's Disease, correct?
A. I would -- I can't say just looking at this document what the scope of the review is. I would like to know specifically what Roland was asking ahead of time.
Q. It appears from the subject line PRF's Paraquat Parkinson's Disease USA EU, right; that's the subject line on this particular e-mail?
A. That is correct, sir.
Q. The attachment includes indeed two PRF's that were submitted to the EPA, correct?
A. Yes, sir.
Q. This is consistent with your earlier

e-mail that only two incidences were identified right?
MR. HONG: Object to form.
A. The earlier e-mail being in this one here, sir?
BY MR. DICKENS:
Q. Correct.
A. Yes.
Q. It's your understanding up to this point in May of 2008 only two incidences of 6(a)(2) reports were submitted to the EPA involving Paraquat and Parkinson's Disease?
A. I'm not sure based upon not having the context of Roland's inquiry prior to this of whether or not there was something that would have limited it to just those two, so I don't know how broad his initial request was. I don't recall.
MR. DICKENS: Let's go ahead and mark Exhibit 21 for the record.
(Exhibit 21 was marked.)
THE WITNESS: Are we keeping 20, too?
MR. DICKENS: You can keep it close.

THE WITNESS: Okay, sir.
MR. DICKENS: So this is an e-mail from Dennis Hackett who we talked about earlier to you and others, June 20, 2012, right?
A. That is correct.
Q. This is attaching a list of PRFs Syngenta reviewed for reporting under FIFRA 6(a)(2), right?
A. That appears to be the list, yes, sir.
Q. And up through the 2012 time frame, right?
A. It indicates through 2012 for Syngenta. Dennis does indicate he does not have the similar log from the Zeneca time frame.
Q. If you turn to the attachment, there are 6(a)(2)s for Paraquat beginning with the info received in 2001 all the way through 2011, right?
A. Yes, sir.
Q. And if we compared this to the prior to exhibit in 2006, we see the time course and reversibility?
A. Yes.
Q. Is that right?
A. Yes.

Q. And then in 2007, we see the information for publication on Paraquat toxicity data?
A. Correct.
Q. You'd agree that there's no other information that is deemed reportable on Paraquat Parkinson's Disease?
A. Within the context of this table or the previous document?
Q. Within the context of this table.
A. That's 2006, appears in 2011 there may be one.
Q. And which one?
A. Talking about multiple interperitoneal administration.
Q. Okay. But we can agree then at least up and through May of 2008 when you sent your e-mail to Roland Dieterle indicating only two incidences were identified, that that appears correct, right?
A. The fact that his e-mail indicates PQPD and those two are listed there, that would seem to be correct, sir.
Q. So your e-mail of 2008 are what we can now

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agree two incidences of 6(a)(2) reporting to the EPA. This was approximately eight months after your statement to Dole with respect to submitting information on Paraquat and Parkinson's Disease to the EPA, right?

MR. HONG: Object to form.

A. Time frame seems about right.

BY MR. DICKENS:

Q. So that information on Paraquat and Parkinson's Disease submitted to the EPA, that really consists of the two documents submitted that are contained in the exhibits that we looked at in your e-mail to Roland Dieterle?

MR. HONG: Object to form.

A. Those are those two studies, yes, sir.

BY MR. DICKENS:

Q. I want to -- in the 2012 --

A. If I may, one is a study and one's a publication.

Q. That's fair. Going back to the 2012 document. I want to ask you a question, number 832 in that attached spreadsheet.

A. Number 832. Okay.

Q. It's reportable no and it's listed there Korean formulation, not USA.

Do you see that?

A. I do.

Q. It appears that wasn't submitted because it's not a U.S. formulation. Do you agree with that?

A. Certainly that's the implication of that statement.

Q. You can put that aside I'll hand you what we'll mark as Exhibit 22?

(Exhibit 22 was marked.)

THE WITNESS: Okay.

BY MR. DICKENS:

Q. This is a letter from you to the EPA dated April 27, 2011, right?

A. That is correct.

Q. And it is submission under 6(a)(2), correct?

A. Correct.

Q. And this is the type of individual letter

that you would have drafted and sent in for a 6(a)(2) report that you discussed earlier; is that correct?

A. Yes.

Q. And so while you weren't involved in aggregate reporting, you would put together the individual submissions, right?

A. Correct.

Q. And this particular submission involves the product Gramoxone Inteon, right?

A. Yes, sir.

Q. And formulation -- you discussed that a little earlier A7813K, right?

A. Yes, sir.

Q. And that's the Inteon that was registered in the United States?

A. Correct.

Q. And that formulation consisted of Paraquat?

A. Paraquat with the active ingredient.

Q. And this study involved four male beagle dogs dosed once with 8, 128, and 256 milligrams of

Paraquat.

Do you see that?

A. I do.

Q. There's supporting correspondence behind that.

Do you see that?

A. I do.

Q. Now, the supporting correspondence, once again, that would not been included or submitted to the EPA?

A. I do not believe it typically is included.

Q. The only thing that would be included is the cover letter that you signed off on, right?

A. Not always. Sometimes, for example, if it's referencing an article or some other type of information that would be included. For studies such as this, once it's provided to the Agency, if the Agency were to request additional information, it would be provided.

Q. In this study, if we can turn to the PRF report for it?

A. Yes, sir.

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Q. It appears the study was part of a program designed to influence new formulation of Paraquat. Do you see that?
A. Yes, sir. We were, as part of this research program, trying to prove that Inteon was a safer formulation than other formulations available in the market place.
Q. And you conducted some animal testing in order to show or prove that, right?
A. Correct.
Q. And the EPA never asked you to conduct all of those testing or studies, right?
A. That is correct.
Q. But the company chose to do any way?
A. Correct.
Q. Now, it mentions three doses of male beagle bulldogs, undiluted formulations and it lists what those formulations were.
Do you see that?
A. Yes.
Q. Findings, [As read] "Most animals fully recovered with body weight and food consumption

values achieving near normal levels by the study termination." Right?
A. Correct.
Q. Then in 1(c), there's comments from the project leader. No dog administered the Paraquat Inteon previously been euthanized, but only one of the four animals administered this dose with euthanized, remaining three survived, right?
A. Correct.
Q. But as indicated in the earlier letter, that was submitted due to the death of the one animal?
A. Correct.
Q. Is that your understanding?
A. Yes, sir. It was a new finding at that dose level for that formulation.
Q. And as you see in 2(a) for the PRF approach committee, nevertheless in view of past representations to US EPA, this is the first animal requiring euthanasia after administration at dos level, it was considered appropriate to refer that death to the EPA, correct?

A. Yes, sir.
MR. DICKENS: I want to hand you Exhibit 23.
(Exhibit 23 was marked.)
THE WITNESS: Okay, sir.
BY MR. DICKENS:
Q. I'm going to direct your attention first, to the very last page of this document. An e-mail from Dennis Hackett to multiple individuals including you, May 6, 2011.
Do you see that?
A. I see that.
Q. Dennis Hackett states, [As read] "The attached PRF concerns an acute oral study conducting a dog with a Paraquat formulation not registered in the U.S. I do not feel this is reportable in the U.S." Right?
A. Yes, sir.
Q. And the basis for that is this is not a formulation registered in the United States, correct?
A. Correct.

Q. Let's look at this actual study. This is once again part of a program designed to introduce new formulation of Paraquat, right?
A. Correct.
Q. And so that was part of a program designed to introduce new formulations of Paraquat in the United States and elsewhere, right?
A. Yes, sir.
Q. And it involves four beagle dogs, correct?
A. Correct.
Q. And they were dosed with doses equivalent to what was used in the U.S. study that we just looked at, right?
A. Correct.
Q. So the dosing was the same. The only difference was the formulation that was used?
A. That appears to be the case, yes, sir.
Q. And in this study, there weren't just one death of the beagle dogs, correct; there were three of four dogs that died?
A. That appears to be correct, yes, sir.
Q. So it's the same study, same type of

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doings, same dosage, the only difference being the formulation, right?

A. Let me -- let me for just a moment just confirm the does of which the dogs died, sir. Okay. Thank you.

THE VIDEOGRAPHER: Counsel, before we continue, Mr. Dixon, would you mind raising your microphone please?

THE WITNESS: Yes, sir. Is that okay?

THE VIDEOGRAPHER: Yes.

BY MR. DICKENS:

Q. So can you confirm that it is the same dosage, same type of animal that's being used?

A. Correct.

Q. And the only difference being the formulation?

A. Correct.

Q. And in this study, there's three of four deaths instead of one of four deaths?

A. Correct.

Q. But the study that actually showed 75 percent the of animals dying was not reported to

the U.S. EPA, right?

A. Correct.

MR. HONG: Object to form.

BY MR. DICKENS:

Q. If we can turn to page PRF approach committee comments.

Do you see that?

A. I do.

Q. They confirm the need to euthanize two animals at 128 milligrams of Paraquat was unexpected, right?

A. Correct.

Q. Overall committee concluded this study meets the technical criteria for referral based on the two dogs requiring euthanasia after administration of the Korean formulation at a dose equivalent to 128 milligrams, right?

A. Correct.

Q. So the PRF committee recommends that this would be referable, right?

A. The last sentence states that, yes, sir.

Q. But ultimately the 6(a)(2) committee

determines, well, its not registered in NAFTA, that includes the United States, right?

A. Yes, sir, specific to the U.S. for the 6(a)(2) committee.

Q. So we're not going to report it to the U.S. EPA?

A. That was the determination, yes, sir.

Q. We will report the study that showed on the one of four deaths but not the one that showed the three of four deaths?

A. Yes, sir, because they were different formulations as such; one was not registered in the U.S. not considered relevant.

Q. What is the difference between the Korean Inteon formulation and the US formulation?

A. Going from memory, I would not be able to be specific. I could certainly give you broad characterizations in that the Korean formulation had a different dosing load and probably given the fact its got a different root number, they had different overall composition.

MR. DICKENS: I'm going to hand you what

we'll mark as Exhibit 24.

(Exhibit 24 was marked.)

A. Okay. Sir.

BY MR. DICKENS:

Q. Exhibit 24 is e-mail chain which includes you following PRF approach committee and the Korean Inteon formulation, right?

A. I see that.

Q. And on the second page, one of the e-mails that was forwarded to you is an e-mail from Andy Cook April 8, 2011, right?

A. I see that.

Q. And Andy Cook lays out differences between the --

A. Yeah, just so -- I'm in the e-mail chain but this was not to me.

Q. Understood. But it's fair to say that that e-mail from Andy Cook to Fernando Suarez was indeed forwarded to you?

A. It did come to me, yes, sir.

Q. So this would something you would have reviewed back in 2011?

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A. I would have been aware of it, yes, sir.
Q. And this is specific with respect to the PRF approach on the Korean Inteon formulation, right?
A. Yes.
Q. And that's the Korean formulation that was used in the dog study we just looked at, right?
A. A 3879 EX. Yes.
Q. And so specifically --
THE COURT REPORTER: I'm sorry. It was 8-3.
THE WITNESS: I'm sorry. A 3879 E as in Edward, X as in X-ray.
BY MR. DICKENS:
Q. So Andy Cook lays out the differences between the Inteon formulations, right?
A. Yes, sir.
Q. U.S. Inteon A7813 K, that is the formulation that was used in the dog study that was reported to the EPA, right?
A. Correct.
Q. And that contains 240 grams of Paraquat

Ion per liter no surfactant, right?
A. Yes.
Q. And it lists the Korean Inteon and that's the one that was used in the Korean formulation dog study, right?
A. Correct.
Q. And that is 200 grams per Paraquat ion per liter and that's actually less Paraquat than any U.S. Inteon formulation, right?
A. Yes.
Q. But that includes a trace of surfactant, right?
A. That's what's indicated, yes.
Q. That's the only difference between the Korean formulation and the U.S. Inteon formulation is it's less Paraquat that has a trace of surfactant, right?
MR. HONG: Object to form.
A. Yeah, I don't think we can say that's the only difference, those are the only differences that Andy identified in that e-mail, there could be others.

Q. And Andy Cook was specifically differentiating the Inteon formulations for the purpose of determining whether or not the PRF committee should report the findings to the EPA, right?
MR. HONG: Object to form.
A. Let me take a second just to read. All I can go by is what he states here and he's talking about the compositions and the formulations strength, sir.
BY MR. DICKENS:
Q. And he says [As read] "The formulation strength isn't terribly relevant." Right?
A. That's what he states, yes, sir.
Q. And in fact, in comparing the two, the only difference he actually states is that trace of surfactant?
A. That appears to be what he identifies, yes, sir.
Q. We talked about the surfactant earlier and you couldn't recall whether or not the labeling in the U.S. required addition of a surfactant?

A. Not off the top of my head.
MR. DICKENS: I'll hand you what we'll mark as Exhibit 25.
(Exhibit 25 was marked.)
BY MR. DICKENS:
Q. Exhibit 25 is a letter November 24, 2015 including a labeling for Gramoxone SL 2.0 from 2015?
A. Correct.
Q. This is a time frame in which you were still working in the regulatory department?
A. Yes, sir.
Q. And this letter actually came to you, correct?
A. It did, yes, sir.
Q. Turn your attention to Page 12 of the label. Page 12 is Use of Nonionic Surfactant Or Crop Oil Concentrate Methylated Seed Oil.
Do you see that?
A. Yes, sir.
Q. And it states [As read] "Always add one of the following (failure to use one of the following

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recommended rates will result in reduced performance of Gramoxone SL 2.0." Right?

A. I see that, yes, sir.

Q. One of those is a nonionic surfactant?

A. Correct.

THE COURT REPORTER: I'm sorry. You're trailing off at the end.

BY MR. DICKENS:

Q. I'm sorry. One of those is a nonionic surfactant, correct?

A. Yes, sir.

Q. And the label instructs users to [As read] "Add nonionic surfactant containing 80 percent or more surface-active agent at a minimum of .25 percent." Right?

A. Correct.

Q. Now, this is what users were instructed to do in 2015. Does this refresh your recollection as to whether or not the labeling in 2006, for example, instructed users to use a nonionic --

MR. HONG: Object to form.

A. I would have to look at that specific

label, but this is a relatively common recommendation for herbicides that when you're preparing the tank after you put the formulated product in to add additional components and in this case a nonionic surfactant.

BY MR. DICKENS:

Q. So the users of Gramoxone, the ones who actually out there spraying, aren't spraying just Paraquat, they're also spraying Paraquat with the nonionic surfactant, correct?

MR. HONG: Object to form.

A. They would be spraying -- they would never be spraying -- let me rephrase that. Following the label directions, you would never directly apply the formulation; you would dilute it into the -- you wold put it into a mix tank, dilute it and add other things. So the application spray would be whatever was mixed in the mix tank.

BY MR. DICKENS:

Q. And that, based on what Syngenta is recommending to its consumers in the labeling would include nonionic surfactant?

A. That is correct.

Q. And that nonionic surfactant would be in the final mixture of what's out there being sprayed on crops and on the -- used in agriculture?

A. Once it's put into the tank, it would be part of the spray.

Q. And yet, Syngenta determined that a Gramoxone product with a trace of surfactant wouldn't be relevant because the formulation was different than what is used in the United States?

MR. HONG: Object to form. Lacks foundation.

A. I'm not an expert to speak on that. I will say there were formulation differences.

BY MR. DICKENS:

Q. That formulation difference, the only one we know of, as we sit here today, is that there was a trace of surfactant from the Korean formulation, right?

MR. HONG: Same objection.

A. That in the case of trace we don't know

what the surfactant is, we don't know if it's a nonionic surfactant. The term surfactant is a very broad statement, so with specificity, it would be hard to know exactly which surfactant he's referring to.

BY MR. DICKENS:

Q. So we looked at the guidance from the EPA with respect to reporting. Do you recall that?

A. Yes, sir.

Q. And with respect to the exterritorial reporting requirements, it said it would be considered relevant unless an expert determined the formulation differences mattered, right?

MR. HONG: Object to form.

BY MR. DICKENS:

Q. Summarizing?

A. That sounds correct to what we read before.

Q. And so then who was the expert at Syngenta that determined that the Korean Inteon formulation was so different that it didn't need to be reported?

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A. I believe that was handled in the 6(a)(2) committee so it would have been the committee. I don't know the particular individual that would have made the determination. It would have been a committee determination.

Q. Didn't you vote specifically on referring or whether or not to refer that report to the EPA under 6(a)(2)?

A. That was --

MR. HONG: Object to form.

A. That was so long ago. I don't recall exactly what my vote would have been. I believe that was 2011, if I'm correct.

BY MR. DICKENS:

Q. If an expert within Syngenta did determine that the Korean Inteon formulation was substantially different that it didn't need to be reported, would that be noted somewhere in PRF minutes or anywhere else?

MR. HONG: Object to form.

A. The PRF committee did take minutes.

BY MR. DICKENS:

Q. Would that also note who voted in what way as to whether or not something should be referred to the EPA?

A. I would have to review those particular minutes to know whether or not they reported who voted for what.

Q. And just generally, and not with respect to this particular incident, but generally would the minutes include information on each individual's vote?

A. I don't specifically recall.

Q. I'm going to bring back up the guidance, EPA guidance.

MR. HONG: What exhibit number?

MR. DICKENS: I do not know. 16.

THE WITNESS: 16.

BY MR. DICKENS:

Q. Thank you. Turn to Page 13.

A. Yes, sir. Okay.

Q. This is the Extraterritorial Adverse Effect Information, right?

A. Yes, sir.

Q. And the section we looked at in the second paragraph [As read] "Agency will consider all such information to be reportable unless an expert concludes that differences between the formulation of product involved in the foreign information and product registered in the United States make the information irrelevant to the product registered in the United States."

Do you see that?

A. Yes, sir.

Q. So is it your understanding that the PRF or 6(a)(2) committee found that the Korean Inteon formulation was irrelevant to the U.S. formulation?

MR. HONG: Object to form.

A. The statement I believe I saw that Dennis Hackett indicated it was not a U.S. formulation, so not considered reportable.

BY MR. DICKENS:

Q. So there was a blanket determination that any nonU.S. formulation would not be reportable in the United States; is that fair?

MR. HONG: Object to form.

A. I would not agree that was fair. I think it was -- he was speaking specifically in this particular case, sir.

BY MR. DICKENS:

Q. Going back to the Korean Inteon PRF that was deemed not reportable?

A. Which document, sir?

Q. I should be keeping a better track. Next one. Right after -- one more. That exhibit right there. 23, I believe.

A. Okay. Sir.

Q. Turn to the last page once again?

A. Yes, sir.

Q. In the e-mail from Dennis Hackett, he specifically instructs those on the e-mail chain, right, to [As read] "Please review and vote in lieu of having a meeting." Right?

A. Correct.

Q. So the individuals included in this e-mail would cast a vote as to whether or not this Korean Inteon formulation would be reported to the EPA?

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A. That's what indicated, yes.
Q. You're one of those individual?
A. Yes, sir.
Q. So you may not recall here today, but you would have casted a vote one way or the other?
A. Given this document, yes, I would have.
Q. And the ultimate vote was don't report, right?
A. Do not report.
Q. Did anyone reach out to the 6(a)(2) officer with the EPA to determine whether or not it should be reported?
A. Not that I'm aware of.
Q. I mean, that was within Syngenta's right, right, to reach out to an officer to -- if there was any questions as to whether or not something should be reported?
A. Certainly we can always reach out to EPA if we have questions.
Q. And ask specifically, hey, do you think this should be reported, right?
A. If we believe there was uncertainty, they

could do that.
Q. And that wasn't done in this case, right?
A. Not to my recollection or not to my awareness.
Q. And as far as you know, it was never done in any case related to Paraquat, right?
MR. HONG: Object to form.
A. I have no immediate recollection of any such reaching out to EPA on any case with Paraquat.
BY MR. DICKENS:
Q. Now, as more information became known with respect to Paraquat, certainly you could have submitted the Korean Inteon formulation study later on down the road, correct?
MR. HONG: Object to form. Calls for speculation.
A. Yes. I don't know under what circumstances we would have made a decision to submit that formula, sir.
BY MR. DICKENS:
Q. Well, you did it with the Marks study,

right?
A. The Marks studies, sir, in 2019?
Q. Yes.
A. Yes.
Q. So there's nothing that prevented you from submitting something later on down the road should you determine it might be relevant, correct?
A. If a determination were made that a study was relevant, we could submit.
Q. And you did learn personally after 2011 that surfactants increase absorption and toxicity of Paraquat,right?
MR. HONG: Object to form.
A. I have no -- no understanding of that. I have no awareness of that, sir; not that I recall or can think of.
MR. DICKENS: I'm going to hand you Exhibit 26.
(Exhibit 26 was marked.)
BY MR. DICKENS:
Q. Exhibit 26 is a chain of various e-mails. I'm going to only refer to the chain of e-mails

beginning Bates number ending in 9300?
A. Okay. I'm here.
Q. This e-mail begins with -- on the top e-mail from Brian Reeve to you and Dan Campbell November 15, 2012.
Do you see that?
A. Yes.
Q. It's a little over a year after the Korean Inteon formulation vote on the 6(a)(2) committee, right?
A. That appears chronologically, correct.
Q. And Brian Reeve, he was on the 6(a)(2) committee, right?
A. I believe he was at that time.
Q. And he forwards you an e-mail, [As read] "FYI-confidential and privileged. Do not forward or distribute." Right?
A. I see that. Yes, sir.
Q. And forwarding you e-mails regarding Paraquat formulation issues?
A. Yes, sir.
Q. And specifically an e-mail from a Phil

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Botham?
A. That is correct.
Q. And you're familiar with Phil Botham?
A. I am.
Q. And who is he?
A. He is one of our scientists in the EU.
Q. A scientist in the EU working on Paraquat at this time?
A. Yes, sir. Apparently at this time and he has worked a lot on Paraquat.
Q. What you're told based on Phil Botham's e-mail on November of 2012 in number one, [As read] "Some surfactants can improve the absorption of Paraquat across the GI tract of rabbits by up to three orders of magnitude by mucosa of the tract."
Do you see that?
A. I do see that.
Q. Then on the next page he gives overall conclusions, right?
A. Yes, sir.
Q. [As read] "Overall conclusion is the

addition of surfactants will normally increase the absorption of Paraquat and hence, increase the toxicity." Right?
A. That's what is stated here.
Q. And that's the overall conclusion by a science who worked a lot of Paraquat, right?
A. Sir, I didn't recall this e-mail, but now that I'm reading it, I certainly see what it said here. Yes, sir.
Q. So the addition of surfactant to Paraquat is going to increase the toxicity, that's what it's saying, right?
MR. HONG: Object to form.
A. That's Dr. Botham's statement, yes, sir.
BY MR. DICKENS:
Q. And he's a scientist working on Paraquat within the company?
A. That is correct, sir.
Q. So certainly the death of additional dogs within the Inteon studies could be explained by the trace of surfactant within the Korean Inteon formulation; you would agree with that?

MR. HONG: Object to form. Lacks foundation. Calls for expert testimony, but you can answer the question.
A. As a nontoxicologist, I wouldn't want to hazard a guess if that's the cause.
BY MR. DICKENS:
Q. But we can agree that the users in the United States would be spraying or adding surfactants to their Paraquat before spraying?
MR. HONG: Object to form.
A. In accordance with the label recommendation, yes.
BY MR. DICKENS:
Q. So the absorption and the toxicity of the Paraquat with the surfactants would be higher than Paraquat alone?
MR. HONG: Same objection.
A. I don't know that I have the expertise to answer that.
BY MR. DICKENS:
Q. But Dr. Botham also tells you that [As read] "I would finally like to stress that product

safety's advice continues to be that when surfactants are added to a Paraquat formulation, it is not possible to claim safety equivalence to surfactant-free formulation without conducting confirmatory testing." Right?
A. In the context of what's being stated there, I think it's a little different than the tank. Basically he's talking about direct addition to the formulations versus after the fact.
So I think what he's saying there is a comparison of formulation to formulation, not formulation to spray mix.
Q. And that's fair, but what we do know is whether it's added before or after, Paraquat with surfactants increase absorption and toxicity, right?
MR. HONG: Object to form. Calls for expert --
A. I can't answer that, sir.
BY MR. DICKENS:
Q. Well, you're aware that Syngenta attempted

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to or did run tests on with surfactants and showed an increase toxicity, right?

MR. HONG: Object to form.

A. Are you referring to this document, sir?

BY MR. DICKENS:

Q. I'm referring generally. Are you aware that Syngenta conducted tests of Paraquat with surfactant that showed increased toxicity?

MR. HONG: Object to form.

A. I think given how broadly the question is asked I'm not sure that I can answer directly, sir.

BY MR. DICKENS:

Q. Well, Phil Botham actually indicates in the first part we looked at about surfactant's increasing the absorption of Paraquat across the GI tract of rabbits; he's not just guessing that that's the case, right?

A. Yes, sir, but -- and he's talking here a technical evaluation and your question was did Syngenta win the studies. I don't know if he's referring to Syngenta studies or literature

publications.

Q. If --

MR. HONG: Counsel, we're running up on an hour, maybe a break in the next 5 minutes or so.

BY MR. DICKENS:

Q. Sure. If Syngenta attempted to register a product that included Paraquat with surfactants, they'd have to run additional safety testing, correct?

MR. HONG: Object to form.

A. Syngenta when it registers a formulation including the Paraquat formulation, part of the regulatory requirements are to do acute toxicity testing on the formulations. Those would involve traditionally the -- your dermal absorption study, inhalation.

However, when we went to get Gramoxone 3 registered, which is our current offering, we agreed to take the maximum PPE category of category one in order to avoid unnecessary animal testing because we knew no matter what, we would still be in the maximum PPE category.

So therefore, we would not have run the acute tox test on that formulation because we already were taking the maximum PPE required by law on that.

BY MR. DICKENS:

Q. That formulation, that doesn't involve a surfactant, right?

A. Our current formulation I believe does have trace amounts of surfactant in it.

Q. And is that included on the labeling?

A. No. The listing of the labeling only in the U.S. for all pesticides traditionally is just the active ingredient and other components, other I believe (inaudible).

Q. Has Syngenta instructed farmers and other users of Paraquat that by mixing surfactants with the Paraquat increases toxicity?

MR. HONG: Object to form.

A. I'm not aware of such communication.

BY MR. DICKENS:

Q. Did you -- Syngenta ever attempt to amend its labeling to warn consumers that the addition

of surfactants would increase absorption or toxicity?

MR. HONG: Object to form.

A. I'm not aware of any such communication.

BY MR. DICKENS:

Q. Was there ever any communication to the EPA while you were involved from 2006 to 2022 informing them of Syngenta's opinion and conclusion that the addition of surfactant would increase absorption and toxicity of a product?

MR. HONG: Object to form. Assumes fact not in evidence.

A. I'm not aware of any such communication.

MR. DICKENS: We can take a break.

THE VIDEOGRAPHER: The time is 3:22. We are now off the record.

(A break was taken from 3:22 p.m. to 3:32 p.m.)

THE VIDEOGRAPHER: This is the beginning of media unit 6 of the video-recorded deposition of Mr. Montague Dixon. The time is 3:32 p.m. Eastern. We are now back on the record.

Counsel, you may proceed.

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BY MR. DICKENS:
Q. Mr. Dixon, before we took our break, you mentioned that the current formulation includes surfactant, right?
A. I believe that to be the case, sir.
Q. Did anyone at Syngenta go back and submit studies conducted by Syngenta which involved Paraquat and a built-in surfactant?
MR. HONG: Object to form.
A. What type of study, sir?
BY MR. DICKENS:
Q. Toxicity study specifically.
MR. HONG: Object to form.
A. Not that I'm aware of.
BY MR. DICKENS:
Q. You would agree that toxicity studies on Paraquat with a built-in surfactant is now certainly relevant if the current product has a surfactant built in, right?
MR. HONG: Object to form.
A. Our product that we currently have now, sir, I would not agree with that.

BY MR. DICKENS:
Q. You wouldn't agree that those toxicity studies are relevant?
MR. HONG: Object to form.
A. Not necessarily, sir.
BY MR. DICKENS:
Q. On what basis would toxicity studies not be relevant if they include Paraquat with a built-in nonionic surfactant?
A. I didn't necessarily indicate that the product itself has a built-in nonionic surfactant. If it has a surfactant characteristic of it, I'm not sure. There's multiple possible surfactants, so from my recollection, there would be. I believe there is a surfactant. I don't know if it's a nonionic surfactant, and I believe you still have the recommendation on the label for the addition of surfactant.
Q. So not only does it have some surfactant in it, but you add more to it, right?
MR. HONG: Object to form.
A. Yes, the purpose of the surfactant in the

formulation would be different potentially than the surfactant (inaudible).
And the reason I made the comment about the study, sir, is the Paraquat formulation that we currently are using has followed all of the EPA testing guidelines.
BY MR. DICKENS:
Q. As far as you know, Syngenta hasn't ever submitted any studies involving the toxicity of a Paraquat -- of Paraquat with a built-in surfactant, right?
MR. HONG: Object to form. For all time?
BY MR. DICKENS:
Q. For all time.
MR. HONG: Object to form. Lacks foundation.
A. I would not agree with that conclusion. I believe some of the dogs study work that was done would have made reference to X U.S. formulations as well.
BY MR. DICKENS:
Q. You said X U.S. formulations?

A. The formulations not registered in the U.S. I'm going off my memory but we were doing comparisons across different formulations, so there's certainly a possibility that some of those formulations may have had it and then historically, given the entirety is if we're including the all time period.
I don't know the composition of formulations that would have been involved in any testing in the 80s or 90s.
Q. Now, the PRF committee, we looked at the document where Dennis Hackett was asking for a vote, right?
A. Yes, sir.
Q. And how did that work on the 6(a)(2) committee with respect to whether or not something would be referred to the EPA, was it majority rules?
A. I do not remember the exact determining criteria there. My assumption would be it would be majority rules, but I would have to look and see what the criteria are.

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Q. For the Korean formulation, you indicated that you're not an expert in formulation issues or differences between surfactants and how that affects toxicity, right?
A. Correct.
Q. And you agree that not everyone on the 6(a)(2) committee had that toxicology experience, right?
MR. HONG: Object to form.
BY MR. DICKENS:
Q. There's individuals in there who are attorneys, for example, right?
A. Correct.
Q. And yet it's -- well, why don't I bring that document up one more time.
MR. HONG: What exhibit, Counsel? I believe it's Exhibit 23, for the record.
MR. DICKENS: Thank you, Don. 23.
THE WITNESS: I have it, sir.
BY MR. DICKENS:
Q. So, for example, in the Korean formulation, these are the individuals who would

be voting as to whether or not to submit something to the EPA, right?
A. Yes.
Q. And as you indicated, you don't have the toxicology experience with respect to make determinations as to effects of surfactants, for example?
A. No, sir. There are certainly a significant number of toxicologists on this e-mail.
Q. So with respect to the individuals on this e-mail, though, we don't know once again if it's majority rules? Do the toxicologist have a bigger say? Did their vote count more?
A. I cannot speak to that. I just don't recall how that final decision was made.
Q. Was there a policy and procedure in place for the 6(a)(2) committee with respect to reporting?
A. We certainly do have a policy and procedures as far as 6(a)(2) committee.
Q. Would that include how votes would be

counted and determined?
A. I certainly believe it would outline how those decisions are made.
Q. And that would have been outlined throughout the entire period that you were involved in 6(a)(2) determinations while at Syngenta?
A. I certainly believe that to be the case.
Q. It's fair to say that certain individuals voting on whether or not 6(a)(2) should -- whether 6(a)(2) reports should be made on particular toxicity studies don't have toxicology experience; we can agree on that?
A. Not everyone making a vote would, no, sir.
Q. With respect to the U.S. or the Korean formulation of Inteon, you don't know once again how each individual voted?
A. I do not, no, sir.
Q. What would be the purpose of you voting if you didn't have experience as to developments of the different formulations?
MR. HONG: Object to form.

A. We would have presentations and discussion with the subject matter experts and from that we would form our understanding of what we believe the appropriate sets to be. We're not relied on to be the experts, but we would learn from the experts.
BY MR. DICKENS:
Q. And that would happen at some type of meeting?
A. Yes. So, for example, like, in this particular document here where it talks about the comments, it goes through that type of information that we might be presented such as this information is consistent with what's already known about this.
So it's, you know, the experts are in there to help inform people who don't have the expertise or the relevance of the findings.
Q. Okay. And in this particular instance, Exhibit 23, Dennis Hackett's e-mail, he says [As read] "Please review and vote in lieu of having a meeting." Right?

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A. Correct.
Q. And so a meeting would not have occurred with respect to this particular incident?
A. At least based upon this e-mail it appears there was not a meeting. It appears that what he was asking us to do was to review the information.
Q. And so the only thing you would have had before making your vote was what we have right here in front of us, right?
A. That appears consistent with the e-mail, sir.
Q. And as you indicated, you have no knowledge as to what the differences between the Korean formulation and the U.S. formulation were?
A. As I'm sitting here today, I do not. I certainly could go back and take a look at the formulation comparisons but just having memorized it, no, sir, I don't.
Q. Did you do that? Would you have gone back and actually done that evaluation as to what are the differences?
A. I probably did not do a systemic

evaluation of the differences as part of this process.
Q. So you voted without having a knowledge as to whether or not the formulations were different or how?
MR. HONG: Object to form.
A. I certainly knew the formulations were different because of the work that we had been doing, and I know the only formulation registered in the U.S. at that particular time was a 7813K which was a Gramoxone Inteon. Having a different route, it would be just obvious the other formulation was different.
BY MR. DICKENS:
Q. So you knew the formulations were different but you don't know how?
A. I knew they were different. I can't speak to how much detail I looked at at the time, but certainly they would have been clearly different just having the different formulation routes, and throughout that time period, when we were doing these Inteon studies, certainly would have had

multiple situations where I would have seen the different formulation comparisons or different formulation compositions of multiple formulations, not just these two, probably a half dozen.
Q. But you wouldn't have known the toxicology differences between the two formulations to be able to say whether or not the Korean Inteon formulation was irrelevant to the product registered in the United States, right?
A. I'm certainly not a tox expert, so I would not be able to give an expert tox opinion on that.
Q. And the guidance from the EPA specifically says the information's reportable unless an expert, right, concludes that the differences between the products are such that one, the foreign would be irrelevant to the U.S. product, right?
A. In the document you shared with me, that is stated.
Q. It's fair to say that nonexperts were certainly involved in the 6(a)(2) determinations for Syngenta?

MR. HONG: Object to form.
A. With respect to toxicity, not everyone listed here is a tox expert.
MR. DICKENS: Go ahead and mark Exhibit 27 for the record.
(Exhibit 27 was marked.)
BY MR. DICKENS:
Q. Exhibit 27 is excerpts from a notebook which was produced in your custodial file?
A. Yes, sir.
Q. The excerpt from these handwritten notes -- first of all, do you recognize the notebook?
A. I do, sir.
Q. Is this your handwriting?
A. It is, sir.
Q. And would you keep and maintain notes during your involvement with Paraquat?
A. I did. Yes, sir.
Q. And you kept those notebooks?
A. I did.
Q. And this appears to be excerpts from one

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of those notebooks?
A. That is correct.
MR. HONG: Just so the record is clear, Exhibit 27 appears to be Mr. Dixon's notebook but only excerpts of Mr. Dixon's notebook and not a complete copy of Mr. Dixon's notebook.
MR. DICKENS: I'll go ahead and mark as 28 a complete copy.
(Exhibit 28 was marked.)
BY MR. DICKENS:
Q. I'll be asking about the excerpt marked as Exhibit 27 but the full notebook being 28.
MR. HONG: And you're welcome, Mr. Dixon, to look at the full notebook if you need more context in the answer that counsel will provide you.
A. We'll wait for the answer or the question.
BY MR. DICKENS:
Q. So this section of your notebook is with respect to Paraquat dermal exposure.
Do you see that?
A. Yes, sir.

Q. And its comparing toxicity of Inteon with nonInteon, right?
A. Yes, that's what it states.
Q. It includes dermal, oral, right?
A. Correct.
Q. It states [As read] "Old formulation if not off skin irritates and -- do you know if that says creates partial --
A. That would be portal.
Q. Okay. [As read] "Creates portal of entry for Paraquat." Right?
A. Yes, sir.
Q. So you'd agree Paraquat and the formulations on the market in the United States are skin irritants, right?
A. Yes, sir.
Q. And those skin irritants can irritate the skin, and when that happens, it increases dermal absorption?
A. That's one of the critical reasons why we emphasize the importance of washing your skin where there can be any dermal exposure immediately

which is clearly stated in the labels.
MR. DICKENS: I'll move to strike.
BY MR. DICKENS:
Q. You agree that skin irritants can irritate the skin and when that happens, it increases dermal absorption, correct?
MR. HONG: Objection. Asked and answered. You can answer the question again.
A. Certainly material left on the skin over a long period of time can damage the skin and that can have impact.
BY MR. DICKENS:
Q. And you agree surfactants also are skin irritants?
MR. HONG: Object to form.
A. I'm not an expert on surfactant s. I don't know if they're skin irritants or not, sir.
BY MR. DICKENS:
Q. And once the skin's irritated, that would create a portal of entry for Paraquat. Those are your words, right?
A. Yes.

MR. HONG: Object to form.
BY MR. DICKENS:
Q. And that means, once a skin is irritated, Paraquat can get through easily?
MR. HONG: Object to form.
A. My document -- or the document says that at that time I indicated it would create a portal of entry.
BY MR. DICKENS:
Q. And that's true even if it's not Paraquat that's irritating the skin, but if Paraquat comes into contact with previously-irritated skin, that would also serve as a portal of entry for Paraquat, correct?
MR. HONG: Objection. Calls for expert opinion. You can answer the question.
A. I would certainly not want to speculate on the toxin pact of that, sir, whether or not it would do that.
BY MR. DICKENS:
Q. So do you believe there's a difference between Paraquat's irritation of the skin and just

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irritated skin generally with respect to absorption of Paraquat?

MR. HONG: Same objection. Calls for expert opinion.

A. I'm not sure that all irritation is the same, sir.

BY MR. DICKENS:

Q. You say, [As read] "Must get irritation, first; once skin damaged, goes through, right?

MR. HONG: Objection.

A. Please restate, sir.

BY MR. DICKENS:

Q. Your words written down in your own handwriting [As read] "Must get irritation first; once skin damaged, goes through?

A. That is stated there.

Q. And goes through, that's Paraquat, right?

A. In that case, I don't know if I'm looking at -- looks like there's Diquat above, Paraquat, so I believe that's in reference to Paraquat.

Q. So once the skin is damaged, Paraquat goes through, correct?

MR. HONG: Objection. Form.

A. That's what the note says.

BY MR. DICKENS:

Q. And that was known by you during the time you were involved in regulatory determinations involving Paraquat?

MR. HONG: Objection.

A. Those were my notes at the time based on what I was either learning or having heard at that time.

BY MR. DICKENS:

Q. And you mentioned there was times where you would meet specifically with the EPA with respect to Paraquat, right?

A. That's correct.

Q. And that involved various issues associated with Paraquat over the course you were involved in the regulatory department from 2006 to 2022?

A. Yes, sir.

Q. And that included conversations specific to Paraquat and Parkinson's Disease, right?

A. Presentations we made, yes, sir.

Q. Presentations -- when you say "we," the company, you meant?

A. Correct.

Q. And you were involved in those presentations?

A. I was, sir.

MR. DICKENS: Go ahead and mark Exhibit 29 for the record.

(Exhibit 29 was marked.)

THE WITNESS: Okay, sir. I've done a quick review.

BY MR. DICKENS:

Q. This involves a February 6 meeting with EPA. Do you recall that?

A. February 6, 2017, yes, sir.

Q. And the attachments include draft notes, as well as presentation materials or slides from that particular meeting, right?

A. That appears to be correct, sir.

Q. And you did, in fact, attend that meeting?

A. Yes, sir.

Q. And do you recall that meeting as you sit here today?

A. Yes, sir.

Q. Turn to page 2.

A. Yes.

Q. Which is -- appears to be PowerPoint slides and Paraquat research program?

A. Yes, sir.

Q. February 6, 2017 you're listed, correct?

A. Yes, sir.

Q. And then there's agenda items and who was presenting on those, right?

A. Correct.

Q. With you, was a Nick Sturgess and Charles Breckenridge, right?

A. That is correct, sir.

Q. And who is Nick Sturgess?

A. Nick Sturgess would have been one of our scientists from the UK.

Q. And Charles Breckenridge; who is he?

A. A U.S. scientist.

Q. So Nick Sturgess toxicologist, what is

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Charles Breckenridge's background?
A. Toxicologist as well, sir.
Q. And the three of you presented to the EPA with respect to Paraquat, right?
A. That is correct.
Q. And anything in particular with respect to Paraquat?
A. Well, what is laid out in the agenda there, sir.
Q. Part of this conversation included information with respect to Paraquat and Parkinson's Disease, correct?
A. That is correct, about our research program. That is and looks like the entire scope of the presentation.
Q. Turn to Bates ending in 9857?
A. Okay, sir.
Q. And you have a slide with respect to Considerations By Other Regulatory Agencies.
Do you see that?
A. That is correct.
Q. And this is actually part of your slides,

correct?
A. That is correct.
Q. And so you put these together to present to the EPA?
A. I did.
Q. And you note that Australia, Brazil and U.S. have been regularly updated on the topic by Syngenta in face-to-face meetings, right?
A. Yes, sir.
Q. And that topic being Parkinson's Disease?
A. Our research program on Parkinson's Disease.
Q. And with respect to Brazil, you note and inform the EPA [As read] "Paraquat remains under evaluation by the ANVISA board." Is that right?
A. That is correct, yes.
Q. One of the unstated objectives of the EPA meeting was to understand to what extent ANVISA had approached the U.S. EPA regarding Paraquat and Parkinson's Disease, right?
MR. HONG: Object to form.
A. We did acquire as to any communications

that they had had.
BY MR. DICKENS:
Q. And at this time, you're informing the EPA Paraquat remains under evaluation, right?
A. That is correct.
Q. Did you provide any additional information to EPA during this meeting with respect to ANVISA's findings or determinations with respect to Paraquat and Parkinson's Disease?
A. No, sir. To my recollection, this is all we presented. For clarity, I would not have had any direct communications with APVMA or ANVISA, so I would relay any information from our global regulatory manager who would be Andy Cook, and these bullet points would be summarizing the information as he would have given to me.
MR. DICKENS: I'll move to strike everything after or beginning with for clarity.
BY MR. DICKENS:
Q. Did you do anything -- strike that. You were the individual informing the EPA specifically with respect to these other regulatory agencies,

right?
A. Correct.
Q. And so to obtain this information, you would have had discussions with Andy Cook and others?
A. Andy Cook primarily, sir.
Q. Do you recall what Andy Cook told you with respect to the status of these other regulatory agencies review on Paraquat and Parkinson's Disease?
A. The best of my recollection, I've summarized the key points in the slide here to communicate to the Agency.
Q. And those are the key points relayed to you by others within Syngenta?
A. To the best of my recollection, they would have primarily been communicated by Mr. Cook.
Q. He told you nothing else with respect to Brazil's review, for example?
A. I don't think that would be a fair characterization. I certainly was aware that there was work going on in Brazil. I believe that

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what's presented here is what we had discussed would be important to present to EPA.
Q. So what's important is presented here in this slide?
A. This is the information we wish to convey.
Q. Turn your attention to Bates number ending 9930, it's towards the end?
A. Yes, sir. 930?
Q. 9930?
A. Okay. Okay, I see that, sir.
Q. This is from the presentation of Charles Breckenridge?
A. That is correct, sir.
Q. And he provides a Weight of Evidence Assessment of Causality, and that's causality for Paraquat use and Parkinson's Disease?
A. This -- unfortunately, I'm not very skilled in epidemiology, so I wouldn't want to speak too much to what Charles said, but this is the document that he presented, sir.
Q. There's information on Paraquat use and then there's Bradford Hill viewpoints listed on

the left-hand corner side, right?
A. I see that, yes, sir.
Q. And includes the strength of association of .9, right?
A. Strength of association to .9, is that a particular slide spot, sir? I'm trying to find --
Q. Sorry. On the right-hand side under Paraquat use --
A. Yes, sir --
Q. Just in the chart?
A. I see that. Okay.
Q. And then the next down on the left biological gradient and it says no. High use tier one studies.
Do you see that?
A. I see that.
Q. Temporality not established, correct?
A. That's what stated.
Q. Consistency, inconsistent?
A. Yes.
Q. Specificity, highly specific?
A. I see that.

Q. Plausibility, uncertain, right?
A. Yes.
Q. Coherence, no?
A. Yes.
Q. Experimental evidence, no studies?
A. Yes.
Q. And analogies exist, right?
A. That's what's stated.
Q. And this is what Charles Breckenridge presented to the EPA with respect to causality based on Bradford Hill viewpoints, right?
A. That appears to be the point of the slide, yes, sir.
Q. And you were there when he was presenting this, right?
A. I was, yes, sir.
Q. And at the end, two pages later, there's some conclusions, right?
A. I see that, yes, sir.
THE COURT REPORTER: Some what?
BY MR. DICKENS:
Q. Some conclusions, correct?

A. Correct, sir?
Q. And those conclusions, first one, these ones again are conclusions that Syngenta is making to the EPA based on the science and the evidence, right?
A. These would be the conclusions we presented at the meeting, yes, sir.
Q. Number one, [As read] "Paraquat has no effect on neurochemical stereological or neuropathological endpoints in the SNpc or striatum of a sensitive strain of mouse given maximum tolerated doses." That's what you presented, right?
MR. HONG: Object to form. Mischaracterizes the document.
A. I believe Charles presented that, sir.
BY MR. DICKENS:
Q. So Charles presented that. Now, at this point in time in 2016, once again we've established the Marks studies, for example, have been submitted to the EPA for their consideration?
MR. HONG: Object to form. I believe you

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mean 2017, right, Counsel?
BY MR. DICKENS:
Q. I do. February 6, 2017, the Marks studies hadn't been submitted for their determination or review?
A. Correct.
Q. Charles Breckenridge relies on various studies Tomenson & Campbell, that's a Syngenta study, right?
A. I'm not sure if those were Syngenta studies or not.
Q. It was done in production workers; do you recall that?
A. Yes. That reminds me yes, the Widnes study. Okay. Yes, sir.
Q. And the Widnes study then, that was the witness facility in which Paraquat was manufactured at a old Syngenta legacy company?
A. If my memory serves correct, in the UK, sir.
Q. And there's a Brent & Schaeffer study?
Do you see that?

A. I do.
Q. That's another Syngenta study, do you know that?
A. I'm not sure if Brent & Schaeffer were Syngenta, but I recognize the study.
Q. You can say that Breckenridge 2016, that's a Syngenta study?
A. That is a Syngenta study, yes, sir.
Q. The findings that Breckenridge studies causal relationship between Paraquat and Parkinson's is not supported, right?
A. That is what he states, sir.
Q. Turn to the next page and there's some meeting notes here, from February 6, 2017.
A. I see that, yes, sir.
Q. At the bottom last sentence or last two sentences on this page, [As read] "Syngenta inquired of Brazilian statement that they have been in contact with EPA."
Do you see that?
A. I do.
Q. [As read] "EPA indicated there has not

been an ongoing dialogue and that they were contacted to answer general questions." Right?
A. I see that.
Q. [As read] "Any interaction was not indicated to be significant or ongoing." Right?
A. Correct.
Q. So the take away was that EPA wasn't aware of where the Brazilian regulatory agency was with respect to their findings on Paraquat and Parkinson's, correct?
MR. HONG: Object to form. Mischaracterizes document.
A. No, sir, I can't speak to EPA's knowledge, sir.
BY MR. DICKENS:
Q. Well, it's fair to say that any conversations or interaction that they had with the Brazilian regulatory agencies was not significant or ongoing, correct?
A. And that's -- that's what's stated, yes.
Q. And you specifically went with an objective of asking EPA what those conversations

were?
A. Correct.
Q. And they didn't tell you we know whether or not or where they are with their regulatory review, did they?
A. All I can recall is what's stated here that they have indicated their not been an ongoing dialogue, but I can't speak to what EPA has done before or after.
Q. Considering that was one of the objectives of going, you would expect that if they did say we're fully aware of where the Brazilian regulatory agency was with respect to their evaluation, that that would be included here in the minutes, right?
MR. HONG: Object to form.
A. Can you please restate that, sir.
BY MR. DICKENS:
Q. Yeah, you'd fully expect that considering it was one of the objectives to find out where EPA and Brazilian communications were on Paraquat and Parkinson's Disease, that if EPA was fully aware

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of what they were doing it would be noted here in the minutes?
A. Certainly would have included in the minutes what EPA had shared with me and that's what's present, sir.
Q. Turn to the last page.
A. When I say shared with me, shared with us during the meeting, just for clarity.
Q. Very last sentence here [As read] "Syngenta commented EFSA also did meta-analysis, however, they missed some studies, double counted. Syngenta does not agree with EFSA conclusion there's a possible link associated with Parkinson's Disease and Paraquat." Right?
A. That's what stated.
Q. So Syngenta didn't agree -- and what's EFSA?
A. I believe that's the European Food Safety Administration.
Q. The regulatory agency in Europe?
A. I believe so, sir.
Q. And that European regulatory agency

believed there was a possible link with Parkinson's Disease and Paraquat?
MR. HONG: Objection. Lacks foundation.
BY MR. DICKENS:
Q. That's what you noted here in these notes, right?
MR. HONG: Same objection.
A. I don't know that I noted that; that may have been a note from one of the other attendees at the meeting.
BY MR. DICKENS:
Q. One of those other attendees at the meeting, this EPA meeting noted that EFSA's conclusion was there's a possible link with Parkinson's Disease and Paraquat, right?
MR. HONG: Same objection.
A. Yeah, the document states that Syngenta does not agree with the EFSA conclusion, so I cannot contradict that statement.
BY MR. DICKENS:
Q. Well, Paraquat is banned in Europe, right?
MR. HONG: Object to form.

A. I think that's a mischaracterization -- mischaracterizations of the status of Paraquat in Europe.
BY MR. DICKENS:
Q. You agree it has been banned in Europe, right?
MR. HONG: Object to form.
A. Again, I disagree with that characterization. Syngenta chose not to reregister it in Europe and so it's no longer sold in Europe, but I do not believe it's correct to characterize that the European union has banned Paraquat.
BY MR. DICKENS:
Q. You can agree Syngenta didn't just decide to stop selling Paraquat in Europe without any concerns being raised by EFSA or the European regulatory agencies, right?
MR. HONG: Object to form.
A. My recollection of that, sir, was around 2006 or '07. There was some communication from something called the Court of First Instance, and

Syngenta was going to be required to do additional studies to support a reregistration, and given the limited market size in Europe, Syngenta didn't feel that the cost of doing the studies justified doing it for such a limited use in Europe.
BY MR. DICKENS:
Q. And that was all based on concerns raised by the European regulatory agencies of toxicity of Paraquat, correct?
MR. HONG: Object to form.
A. Yeah, I would have to go back and refresh my memory on the specifications. I just know that general -- my memory is that the general recollection that we were not willing to do the additional studies because we did not feel that it was justified for the limited use of Paraquat in Europe.
BY MR. DICKENS:
Q. You don't recall why the European regulatory agencies wanted additional studies?
A. I would certainly need to go back and refresh my memory. I believe that was 2006 or

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'07, maybe '08, but it was quite a long time ago, sir.

Q. So generally you remember the company didn't want to do studies but you can't recall why?

A. I can recall why we did not want to do the studies. I believe the determination was that it was such a limited use pattern in Europe that the cost of doing additional studies would not offset the potential limited term for keeping the product registered in Europe.

Q. You can't recall a single instance of the European regulatory agencies raising toxicity concerns about Paraquat?

MR. HONG: Objection. Asked and answered for the third time. You can answer.

A. I've given you my best recollection of what happened during that time frame, sir.

BY MR. DICKENS:

Q. As you sit here today, can you recall any regulatory agencies other than the United States raising concerns of toxicity in Paraquat?

A. My primary focus is the U.S., so that's really what I'm able to speak most definitively on.

Q. Can you speak of any outside researchers or scientists expressing concerns of toxicity of Paraquat?

A. I'm certainly aware of, for example, the literature that we've discussed here. I'm also aware of concerns that have happened in other parts of the world around, for example, suicide activities around Paraquat. So certainly aware of some of that.

Q. Is Paraquat sold in Brazil?

A. I do not believe it is sold in Brazil any longer.

Q. And what do you recall about why it's no longer sold in Brazil?

A. I believe the Brazilian authorities basically indicated it could no longer be sold in Brazil. I would need to refresh my memory; that would have been Andy Cook's regulatory domain.

MR. DICKENS: I'll go ahead and hand you

what we'll mark as Exhibits 30 and 31.

(Exhibits 30-31 were marked.)

BY MR. DICKENS:

Q. Exhibit 30 is an e-mail from Andy Cook to you, October 20, 2016.

Do you see that?

A. I do, sir.

THE COURT REPORTER: I'm sorry. What was the date.

MR. DICKENS: October 20, 2026.

MR. HONG: And for the record, Exhibit 31 is an English translated copy of the National Health Surveillance Agency's Typical Reassessment Opinion by ANVISA dated June 13, 2016. This is not the original but please proceed.

BY MR. DICKENS:

Q. Okay. The attachment that was sent to you, sir, that was in English, correct?

A. I believe so.

Q. And you would have reviewed the document in English, right?

A. Yes, sir.

Q. So it would have been a translation of the Brazilian document that was sent over but you received the English version from Andy Cook?

A. Correct.

Q. Now, this in October 20, 2016, this was before your February 2017 meeting with the EPA, correct?

A. Correct.

Q. So you would have received this copy of Exhibit 31 prior to going in and presenting on the regulatory status in Brazil with respect to Paraquat and Parkinson's Disease, right?

A. Right.

Q. Exhibit 31 is a technical reassessment opinion dated June 13, 2016.

Do you see that?

A. I do see that, sir.

Q. And this is a technical report that was prepared by the Brazilian Regulatory Agency?

MR. HONG: Object to form.

A. That appears to be the case.

BY MR. DICKENS:

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Q. And specifically toxicologist within the Brazilian Regulatory Agency, right?
A. Let's see here. It's indicated coming from the General Toxicology Office, so I would assume that to be the case.
Q. We can agree this June 13, 2016 report was never submitted to the EPA, right?
A. I do not believe it has ever been submitted to the EPA.
Q. Do you believe that the individuals who prepared this report would not be considered as an expert under the guidance for FIFRA 6(a)(2) regulations?
MR. HONG: Object to form.
A. I don't know the individual, so I can't speak on their qualifications, sir.
BY MR. DICKENS:
Q. But a determination was made not to submit this to the EPA for their consideration or review, right?
MR. HONG: Object to form.
A. I'm not aware of a specific consideration

or determination of that, sir.
BY MR. DICKENS:
Q. And not only was it not submitted, but during your February 2017, meeting it wasn't even mentioned that this report existed, right?
MR. HONG: Object to form.
A. I don't believe it was. I'm going to look back at what it said, but I don't believe it was, sir. Actually, let's see here, public 2716 in which they refer to Paraquat re-evaluation and consider results, so there's references to work and Brazil. I don't see a specific reference to this document.
BY MR. DICKENS:
Q. And as you said, that slide you reported all that you thought was relevant for EPA at that point in time, right?
MR. HONG: Object to form. Mischaracterizes prior testimony.
A. I presented in that form what was agreed upon from the team as important to communicate.
BY MR. DICKENS:

Q. Now, this report we'll turn to the third page, Brazilian Regulatory Agency, toxicology team determined [As read] "Based on the currently-available evidence their strong weight of evidence (animal studies and epidemiological studies) indicating that Paraquat is associated to the triggering of Parkinson's Disease in humans." Correct?
A. I see that.
Q. And once again, this wasn't reported to the EPA in any way?
A. Not that I'm aware of.
Q. Deemed by the team presenting as not relevant to the EPA's determination on the question of Paraquat and Parkinson's Disease?
MR. HONG: Object to form.
A. Take a flip back to make sure what was being said at that meeting, sir. I don't see conclusions here nor for the Australian, so it looks like we just made them aware these analysis were going on, but looks like we did not communicate specific conclusions from the

different regulatory bodies.
BY MR. DICKENS:
Q. So the report to the EPA that their evaluation -- that Paraquat remained under evaluation, right?
A. In Brazil?
Q. Correct.
A. Yes, sir.
Q. And nothing as to the actual final conclusions made in this June 13, 2016?
MR. HONG: Object to form.
A. I believe all we presented is what's in this line text, sir.
BY MR. DICKENS:
Q. Brazilian Regulatory Agency goes on, [As read] "Considering the current scientific knowledge, it is concluded Paraquat is mutagenic and is a risk factor in Parkinson's Disease with evidence of causality between exposure and the disease." Right?
A. I believe that's what stated in the document, sir.

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Q. And you knew this going into that February 2017 meeting with the EPA?
MR. HONG: Object to form.
A. Knew that this document existed?
BY MR. DICKENS:
Q. Correct?
A. Yes.
Q. And you knew that conclusion by the Brazilian Regulatory Agency as well?
A. It was in the documents, sir.
Q. Turn to page 46?
A. 46 of 78, sir?
Q. Yes. Begins on the top, [As read] "Task force argues no robust assessment of the exposure for most epidemiological studies."
Now, with respect to Brazil and this finding and this determination, Syngenta actually was able to participate in presenting information and data to Brazil.
Do you have an understanding of that?
MR. HONG: Object to form. Lacks foundation.

A. I would have not been involved in that, so that would have been something Andy Cook would have been involved in, sir.
Q. And Brazil specifically identifies Brent & Schaeffer?
A. It is indicated in the document here, yes.
Q. As well as Tomenson & Campbell?
A. I see that, yes, sir.
Q. And these were two of the studies that were specifically referenced to the EPA during Charles Breckenridge's presentation, right?
A. That is correct.
Q. They note that in Brent & Schaeffer they assessed Parkinson's Disease recovered or lived for up to 30 days after intoxication of Paraquat. Is that your understanding of the Brent & Schaeffer study?
MR. HONG: Objection. Lacks foundation.
A. Broadly, yes.
BY MR. DICKENS:
Q. Considering Parkinson's is neurodegenerative with slow and progressive

evolution, it cannot be expected that a study with such experimental design would provide any signs of relation between Paraquat and Parkinson's Disease, right?
A. That is what's stated, but I'm not an expert in that field, so I can't speak to the validity of that statement.
Q. You've heard that criticism of Brent & Schaeffer in the past, haven't you?
MR. HONG: Object to form.
A. I have heard that criticism, yes.
BY MR. DICKENS:
Q. And that criticism by numerous individuals including the EPA, right?
MR. HONG: Object to form.
A. I don't recall a specific criticism from EPA, but I have heard that criticism.
BY MR. DICKENS:
Q. And you heard that criticism before your meeting with the EPA in February 2017?
A. I cannot recall when I would have heard that criticism but I have heard it.

Q. Well, you certainly heard it from this Brazilian document prior to that February 2017 meeting, right?
A. Correct.
Q. Tomenson & Campbell that's the mortality of workers in the Paraquat factor, right?
A. That's my understanding of that study.
Q. And that was the Widnes study you referenced?
A. I believe, yes, sir.
Q. They specifically referred to Tomenson & Campbell; they being the Brazilian Regulatory Agency, as extremely fragile and was not considered relevant to assess the role of Paraquat in the Parkinson's pathogenesis.
Now, you've heard criticisms of the weight of Tomenson & Campbell for Parkinson's Disease, right?
A. I may have. I don't recall a specific time other than what's in the document here.
Q. Turn to page 47 of 78, the last full paragraph beginning thus?

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A. Yes.
Q. [As read] "Thus it can be observed that Paraquat had been associated with Parkinson's Disease and epidemiological studies developed by different research groups and in different populations."
Do you see that?
A. I see that.
Q. It lists a number of studies after that, right?
A. I see that.
Q. And it lists some metaanalysis, correct?
A. I see that.
Q. Now, first document we looked at, Exhibit 1 here today, was the talking points which suggested that there is no credible evidence linking Paraquat and Parkinson's Disease.
Do you recall that?
A. I recall looking at the document, sir.
Q. And that no scientific study had concluded that Paraquat causes Parkinson's Disease, right?
A. I believe that was in the talking points.

Q. At any point in time --
A. I would like to go back and take a look at that, if I may, just to make sure that my recollection is not off on that. That was number one, sir?
Q. Exhibit 1.
A. Okay. Just for clarity, can you restate those two just so I can make sure I understood correctly.
Q. Talking points suggested there's no credible evidence linking Paraquat and Parkinson's Disease?
A. I see that statement, yes, sir.
Q. And this statement is in 2021, right?
A. I'm sorry. In 2021, this would be in 2021.
Q. So once again, this Brazilian statement from 2016?
A. That is 2016 this document.
Q. Did Syngenta make a determination that the Brazilian Regulatory Agency is not a credible organization?

MR. HONG: Objection. Lacks foundation.
A. I wouldn't want to speak on behalf of Syngenta on that, sir.
BY MR. DICKENS:
Q. Talking points also say no peer reviewed study, including the larger study which involved 38 thousand farmers, has ever concluded Paraquat causes Parkinson's Disease, right?
A. I see that statement, yes, sir.
Q. But you can agree that in fact there are numerous epidemiological studies that do find statistically-significant increased risk of Parkinson's Disease following Paraquat exposure, right?
MR. HONG: Objection. Lacks foundation. Calls for expert testimony. You can answer if you can.
A. I'm not an epidemiological expert, so I can only go by what I read, sir.
BY MR. DICKENS:
Q. You are involved in determining what information is going to be presented to the EPA in

your role between 2006 and 2022, correct?
A. As part of a larger team.
Q. And there were discussions within that larger team that you participated in as to how to present that epidemiological information, right?
A. That would be correct.
Q. And so you participated and determined exactly what we're going to tell the EPA with respect to epidemiology?
A. I did not make those determinations on my own, sir. It would have been involved as a team effort with subject matter experts who could speak to the strength or weakness of particular studies.
Q. But you did participate. You put in your viewpoint as to what should be submitted, right?
A. I was certainly part of the team.
Q. And you agree -- or do you know that Tanner 2011 is part of the AHS letter?
MR. HONG: Objection. Lacks foundation. Calls for expert testimony.
You can answer if you can.
A. That's the type of information I would

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have relied on someone like a Charles Breckenridge to help me understand, sir.
BY MR. DICKENS:
Q. Would you turn to page 49.
A. Yes, sir.
Q. Brazilian Regulatory Agency did their own Bradford Hill analysis. Do you see that?
A. I see that.
Q. And it's actually comparing their analysis to Breckenridge 2016, right?
A. I see that, yes, sir.
Q. Breckenridge 2016 is what was relied on in your presentation to the EPA in 2017, right?
A. I believe that is correct, sir.
Q. Just like we saw in the presentation slides, the strength of RR.9, that's what was submitted to the EPA, right?
A. That is correct.
Q. Now, none of the information based on ANVISA's Bradford Hill analysis was presented to the EPA in any way, right?
MR. HONG: Object to form. Lacks

foundation.
A. I have no recollection of that information being presented to EPA.
BY MR. DICKENS:
Q. Do you know whether or not the scientists at the Brazilian Regulatory Agency have a financial incentive in Paraquat one way or the other?
MR. HONG: Objection. Calls for speculation.
A. I -- I can't speak for the people of Brazil, sir.
BY MR. DICKENS:
Q. What you can say is that this Brazilian analysis of the Bradford Hill was not submitted to the EPA in 2017 or ever, to your knowledge, right?
MR. HONG: Objection. Lacks foundation. Go ahead.
A. I have no recollection of the study ever having been submitted to the EPA.
BY MR. DICKENS:
Q. Was there a (6)(a)(2) committee meeting as

to whether or not to submit this information to the EPA?
A. Not that I recall, sir.
Q. You'd agree that this would constitute as an expert opinion under the guidance of FIFRA (6)(a)(2), right?
MR. HONG: Object to form.
A. I can't --
MR. HONG: Calls for a legal conclusion.
A. I can't speak to the expertise of the Brazilian analysis, sir.
BY MR. DICKENS:
Q. Well, you can speak to the expertise of a (6)(a)(2) analysis with respect to whether or not something should be submitted. You voted on stuff like that, right?
A. I was part of the team that would have voted. But specifically with the Brazilian analysis, I don't know who did the analysis. I don't know the qualifications. So I would be purely speculating on whether or not it was a valid analysis and whether they were experts.

BY MR. DICKENS:
Q. Do you believe, having reviewed this actual document, that it should be submitted under (6)(a)(2)?
MR. HONG: Object to form.
A. Yeah. I cannot speculate on that, sir.
BY MR. DICKENS:
Q. Well, if you were asked to vote right now, you would certainly do it, right, in lieu of a meeting?
MR. HONG: Object to form. Incomplete hypothetical.
A. Yeah. No, sir, I can't indicate what I would do in that situation.
BY MR. DICKENS:
Q. You'd agree you got more information in this report than you did in the Korean Inteon formulation that wasn't submitted, right?
MR. HONG: Same objection.
A. I can't speculate what I would do if there was a vote on this report, sir.
BY MR. DICKENS:

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Q. Did you ask about the qualifications of authors of this report to determine whether or not they were truly experts?
A. No, sir.
MR. HONG: Do you want to take a break in five minutes. We've been going about an hour.
MR. DICKENS: If we can go --
MR. HONG: Are you almost done?
MR. DICKENS: Not completely --
MR. HONG: Okay.
MR. DICKENS: -- but to the 30(b)(6) portion. Why don't we do it now. That way I can make sure we get everything together. I want take a 10-minute break.
MR. HONG: Okay.
THE VIDEOGRAPHER: The time is 4:29. We are now off the record.
(Brief recess.)
THE VIDEOGRAPHER: This is the beginning of media unit number 7 of the video-recorded deposition of Mr. Montague Dixon. The time is 4:43 p.m. Eastern. We are now back on the record.

Counsel, you may proceed.
BY MR. DICKENS:
Q. Mr. Dixon, at some point in time, you learned of a Syngenta worker in Mexico who developed Parkinson's disease; is that correct?
A. I don't recall that particularly, sir. I'm sorry.
MR. DICKENS: Go ahead and mark Exhibit 32 and 33 for the record.
(Exhibits 32 and 33 were marked.)
THE WITNESS: I don't recall this document, but I do recognize that Alan provided it to me.
BY MR. DICKENS:
Q. Okay. So Exhibit Number 32 is an e-mail from Alan Nadel to you, May 29, 2013.
Do you see that?
A. Yes, sir.
Q. And then the next exhibit is the attachment, which is the English version or translation.
Do you see that?

A. I see that.
Q. The heading of this document is [As read] "Parkinson's Disease By Occupational Exposition to Paraquat," right?
A. I see that.
Q. And the third page begins [As read] "Work medical history."
A. I see this.
Q. There's a 43-year-old man with no genetic load for Parkinson's disease or relevant history for the condition described here. Later on, he had to monitor pesticide spills. If this happened, he had to open the door -- and then it explains that. Do you recall this particular incident or case?
A. Until you presented me this document, I have -- I had not remembered this document.
Q. Do you remember this document now?
A. It's not ringing a bell, but as I'm reading through it to try to make sure I comprehend what's in it, sir.
Q. Do you recall the name Grimaldo in any

way?
A. Was that a potential Paraquat formulation?
Q. No. It is the individual, the name of the man who was injured.
A. I'm sorry. I did not.
Q. I made it very vague for you.
A. Okay.
Q. Do you recall attending any meetings where this particular case was discussed?
A. I honestly do not.
Q. Based on your understanding of the review of this document, the individual being referenced here went on to develop Parkinson's disease; is that correct?
MR. HONG: Objection.
A. I'm going to read the discussion real quick just to make sure.
I see on page 863, it appears to make that statement, sir.
BY MR. DICKENS:
Q. And the conclusion on page 865 was that it was established exposure to Paraquat-generated

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Parkinson's disease. Do you see that?
A. That is what the document states, sir.
MR. DICKENS: I'm going to hand you Exhibit 34, for the record.
(Exhibit 34 was marked.)
THE WITNESS: I recognize the document, sir.
BY MR. DICKENS:
Q. Okay. And this is minutes from a Paraquat issues leadership team meeting, July 9, 2013, right?
A. I -- I believe so, yes.
Q. And you were in attendance by telephone for minutes 1 and 2, right?
A. Correct.
Q. Okay. Turn to page 2. Under issue 1, the last paragraph of that issue, Mr. Sullivan said that [As read] "an agreement with Syngenta's in-house counsel in Mexico, instead of challenging directly an article which appeared in a journal published by Mexico -- in Mexico by the IMSS publications assembled by Andy Cook, as well as a

Syngenta position statement on the alleged link between Paraquat and Parkinson's disease, will be filed in the pending court proceedings."
Do you recall this discussion at -- during this meeting?
A. Only by being reminded by the document here.
Q. And there was a discussion with respect to what Syngenta's response would be in light of a publication on an incident in Mexico, right?
A. To the extent it's recorded here, that's what I can recall.
Q. And it specifically references that IMSS ruling in the Grimaldo case as well as the underlying medical opinion. Do you see that?
A. I see that.
Q. And do you have an understanding that the Grimaldo case is what's being referenced in the earlier Exhibit 33 that we looked at?
A. Yes, sir.
Q. And do you have an understanding that the Grimaldo case that we looked at in 33 is a former

Syngenta employee?
MR. HONG: Object to form. Lacks foundation.
A. I did not know or recall that Mr. Grimaldo was a former Syngenta employee.
BY MR. DICKENS:
Q. Did you know that before you sat here today?
A. I did not recall that. If I did, I didn't remember anything till -- on this until I saw this document.
Q. Can you tell us whether or not Exhibit 33 was submitted to the EPA.
MR. HONG: Objection.
A. I have no recollection that Exhibit 33 was submitted to EPA.
BY MR. DICKENS:
Q. You were the main liaison in 2013 between the EPA and Syngenta, right?
A. Yes.
Q. Do you -- did you ever tell them in that time frame that there was a Syngenta employee who

has alleged Parkinson's disease after exposure to Paraquat?
A. I don't recall having any conversation like that, sir.
Q. Ever at any point when you were involved in regulatory?
MR. HONG: Object to form.
A. I cannot recall a conversation like that.
BY MR. DICKENS:
Q. But you can recall conversations where you talked about the Widnes study of formulation workers and no increased risk of Parkinson's disease, right?
A. In what context, sir?
Q. In any context.
A. I was aware generally of the Widnes study, but I don't remember details of specification conversations about it.
Q. Do you recall whether or not the Grimaldo case was submitted to a (6)(a)(2) committee meeting to determine whether it should be submitted to the EPA?

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MR. HONG: Objection to form.
A. Sitting here today, I do not recall that happening.
BY MR. DICKENS:
Q. And you don't recall the fact that it was submitted to the EPA one way or the other, right?
A. I do not believe it was submitted. I do not recall.
Q. Why would this not, a Grimaldo case of a former employee alleging Parkinson's disease after Paraquat exposure, not be submitted to the EPA?
MR. HONG: Object to form. Calls for speculation.
A. I can't speculate on that, sir.
BY MR. DICKENS:
Q. You were involved in (6)(a)(2) determinations in this time frame, were you not?
A. I was.
Q. You were voting on (6)(a)(2) determinations and whether or not they should be submitted to the EPA, right?
A. I was.

Q. So you can't speculate as to why an adverse effect of Parkinson's disease in one of your own employees would not be submitted to the EPA?
MR. HONG: Object to form.
A. I don't have a recollection of the discussions around this particular case, sir.
BY MR. DICKENS:
Q. Why would the medical opinion not be submitted?
MR. HONG: Object to form. Calls for speculation.
A. I -- I don't have any recollection of -- of this particular incident, sir.
BY MR. DICKENS:
Q. A medical opinion would be an expert opinion, right?
A. It could be considered an expert opinion.
Q. And it'd be an expert opinion that exposure to a pesticide may have caused a particular adverse effect, right?
A. In -- I have no recollection on this

particular case, so if you're reading from the (6)(a)(2) guidance, that's what's stated there.
Q. But you would agree that a finding from a medical doctor that exposure to a pesticide may have caused Parkinson's disease would be considered an expert opinion deemed reportable under the (6)(a)(2) guidance?
MR. HONG: Objection. Calls for a legal conclusion.
A. I -- I would not make that conclusion on that, sir. It would need to go through the appropriate process.
BY MR. DICKENS:
Q. Sir, did you consider your (6)(a)(2) votes as legal conclusions when you were making them?
MR. HONG: Object to form.
A. Yeah. The (6)(a)(2) votes was participating in the team decision, sir.
BY MR. DICKENS:
Q. But you'd make your own individual vote, would you not?
A. As a member of the team making that

decision, sir.
Q. And that vote would be a legal conclusion?
A. I would not be able to make a legal conclusion. I'm not a lawyer, sir.
Q. But you could make a conclusion as to whether or not an expert opinion about an exposure to pesticide may have caused a particular adverse effect, because you would have voted on that?
MR. HONG: Objection to form.
A. I would have expressed an opinion or indicated a vote if I was asked a question on that. I don't recall ever being asked to vote on that, sir.
BY MR. DICKENS:
Q. Do you recall ever, any instance, come to the (6)(a)(2) committee between exposure to Paraquat and an adverse effect?
A. Exposure to Paraquat and an adverse effect. I recall the Thiruchelvam study in 2008. That would be the only one I can think of that was directly related to Parkinson's disease.
Q. You've had reports of individuals who

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ingested Paraquat who died that were submitted to the EPA, right?

A. That is correct, sir.

Q. And there were medical opinions that associated that exposure to Paraquat with the deaths of those individuals, correct?

A. In some cases, yes. In some cases, the conclusion was the person died after ingestion, so there was an inference it was a direct relationship.

Q. And in those instances where someone died after ingestion, if there was a medical opinion, those would have been reported to the EPA during a (6)(a)(2) committee?

MR. HONG: Object to form.

A. Yes, sir.

And just for clarity, when I'm saying "medical conclusions," often in the (6)(a)(2) process around these unfortunate and tragic accidental ingestions, our contact with the hospital or the operating facility would -- would be terminated because of HIPAA concerns. So there

was not always a definitive conclusion.

However, under FIFRA (6)(a)(2), if there was a death associated with a product, you have 15 days to make that report, and we always tried to honor that 15-day period.

BY MR. DICKENS:

Q. Okay. There were instances where individuals would ingest Paraquat and survive?

A. There have been those cases, yes, sir.

Q. And they had adverse health effects as a result of ingesting the Paraquat?

MR. HONG: Object to form.

A. I believe that's a reasonable statement, yes.

BY MR. DICKENS:

Q. And there are times when those medical doctors at the hospitals or the physicians would communicate with Syngenta or report that information, right?

A. The way that information would be received would be communications through PROSAR, which is a third-party contractor would have had those

communications. So they would follow up with the particular reporting, either hospital, nurse or whoever, capture as much information as possible, and then we would process that.

Q. Okay. So the PROSAR reports would come from not just physicians, but anyone can report an adverse effect associated with Paraquat, right?

A. We have on our labels a contact number and that would be -- have that information to give to ProPharma. It was ProPharma, then PROSAR.

Q. And then what would Syngenta from a (6)(a)(2) standpoint do with that information reported to PROSAR?

A. It depends on the nature of the information, sir.

Q. If it was a report of an adverse effect alleged to have been caused by Paraquat?

MR. HONG: Object to form.

A. Yes, sir. And that depends on the nature of the effect. If -- if it was something that would be deemed, for example, a moderate or severe, there's different categories within the

reporting, HA being the tragic situations or fatalities, down to the HE, which are no observed effects.

Q. Okay. But under any of those scenarios, it would be reported to the EPA under either HA all the way down to HE, right?

A. Correct.

Q. So had Mr. Grimaldo called PROSAR and reported it, would you have reported it to the EPA in that instance?

MR. HONG: Object to form. Incomplete hypothetical.

A. I would not want to speculate without having all the information at the time.

BY MR. DICKENS:

Q. Had he called up and -- and reported that exposure to Paraquat caused a severe skin rash, is that something that would be reported?

MR. HONG: Objection. Incomplete hypothetical.

A. It would involve a process of analysis within the group. One of the key elements is that

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this particular individual's outside of the country, so that would weigh into the fact -- was it a U.S. formulation? We do not sell U.S. formulations in Mexico. Therefore, that would have been part of consideration. Is a -- for example, a skin burn for a non-U.S. formulation relevant for a U.S. formulation report?

BY MR. DICKENS:

Q. It's fair to say you knew at this time of this report in 2013 that the EPA was considering Paraquat and Parkinson's disease specifically, right?

MR. HONG: Object to form.

A. I certainly would not conclude that EPA was expressing concerns about Parkinson's disease or -- EPA, from the work we were doing in that time frame with the human health mitigation, it was purely -- shouldn't say "purely" -- it was primarily to address accidental ingestions and potentials for spills and splashes to either get in the eyes or on the skin, sir.

BY MR. DICKENS:

Q. Do you believe the EPA ever had any concerns between Parkinson's disease and Paraquat exposure?

MR. HONG: Objection. Calls for speculation.

A. I can't speak on behalf of EPA, sir.

BY MR. DICKENS:

Q. And you agree that the EPA relies on Syngenta, as one of the registrants for Paraquat, to provide information with respect to adverse effects and Paraquat, correct?

MR. HONG: Object to form.

A. EPA relies upon as, one of it's sources, registrants. They certainly rely on other sources as well.

MR. DICKENS: And we will mark as Exhibit 35.

(Exhibit 35 was marked.)

BY MR. DICKENS:

Q. Exhibit 35 begins with an e-mail from an Ana Pinto to you, May 21, 2021. Do you see that?

A. Yes, sir.

Q. And it's a question regarding Paraquat documents, right?

A. That is correct, sir.

Q. [As read] "We were recently contacted by a law firm involved in the Parkinson's disease litigation, and they referenced some documents the agency has supposedly never seen."

Now, this is similar to what occurred in 2019; is that right?

MR. HONG: Object to form.

A. Yes, sir. I can just go by what's saying -- what they're -- she's saying there, which is a law firm indicated there were documents that they had not received.

BY MR. DICKENS:

Q. And we talked about when the Marks studies, for example, were submitted in December of 2019, that was in response to an attorney reaching out and indicating there were additional documents to be submitted, right?

MR. HONG: Object to form.

A. Correct.

BY MR. DICKENS:

Q. She says, [As read] "I assume Syngenta has submitted any and all relevant studies and/or reports under FIFRA section (6)(a)(2), but I just wanted to check in with you to see if there's anything that we don't already have and you think we should take a look at."

Do you see that?

A. I do see that, sir.

Q. And that's on a Friday, right?

A. Yes, sir.

Q. Sorry. She goes on -- I might as well finish it. [As read] "We want to make sure we're not missing anything as we get ready to complete the Paraquat ID," right?

A. Yes, sir.

Q. And then you respond on Tuesday, May 25th, to Ana Pinto, right?

A. Yes, sir, that appears to be the time.

Q. You say, [As read] "Thanks for your time today. It was good speaking with you."

Do you recall a telephone conversation

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with Ana Pinto?
A. Not -- not the specifics, but based upon the comment here and -- it appears that I did have a conversation with her.
Q. [As read] "And following up on that conversation to confirm what is required under FIFRA section (6)(a)(2) and in connection with EPA's registration review of Paraquat, Syngenta Crop Protection LLC" -- Syngenta, that's your employer, right?
A. That's correct, sir.
Q. -- "has submitted all relevant Paraquat studies, reports and/or information to the EPA," right?
A. Yes, sir.
Q. That's what you reported to the EPA in May of 2021, that the -- Syngenta submitted all relevant studies reports and information related to Paraquat and Parkinson's disease?
A. Correct.
Q. What did you do prior to reporting back to Ana Pinto to confirm whether or not all relevant

Paraquat studies or reports had been submitted?
A. I'm trying to remember back to that time frame. I would have most likely spoken with our tox team, taken notes, also spoken with my managers just to make sure that we had done an evaluation to confirm that we'd submitted everything that should have been submitted.
I don't remember the specific sequence, but that is how I would go about trying to analyze a question like that, sir.
Q. Did you go back and look as to what had when submitted under FIFRA (6)(a)(2) previously?
A. Certainly, I would have likely taken a look at something called NPIRS -- NPIRS, National Pesticide Information Registry (sic) System -- and that's where, when documents and studies are submitted to EPA, they're recorded -- and would have certainly checked base with the different team members just to make sure that we were confident in that statement.
Q. What team members would you have checked in with?

A. Likely would have spoken with Andy Cook. Likely would have spoken with certainly, probably, Brian Reeve and other people within the organization.
I don't remember the specific folks, being four years ago, but those are who I anticipate I would have touched base with.
Q. Would you have asked to see all of the neurotoxicity information with respect to Paraquat and Parkinson's disease to make a determination as to whether or not it was relevant and should be submitted?
MR. HONG: Object to form.
A. Yeah. I don't recall making any such ask.
BY MR. DICKENS:
Q. Did you go back and review the prior toxicity studies conducted on Paraquat internally to determine whether or not it should be submitted to the EPA?
A. All toxicity studies, sir.
Q. On Paraquat.
A. On Paraquat. But all toxicity studies on

Paraquat?
Q. Correct.
A. I certainly don't think I would have done that. I would have relied on our subject matter experts to do tox evaluations. But it would be, I would say, impractical to look at every tox study ever done on Paraquat. But I certainly stand by this statement that I believe we had submitted everything that was required.
Q. Now, Ana Pinto doesn't say everything that's required in her ask, does she?
A. Well, let me take a quick look.
No. She is asking for anything that they don't have and they think we should take a look at.
Q. So Syngenta determined that there's nothing else on the question of Paraquat and Parkinson's disease that should be submitted that the EPA may want to take a look at. That was the determination of you and Syngenta at that time, right?
MR. HONG: Object to form.

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A. That is consistent with the statement above, yes, sir.
BY MR. DICKENS:
Q. She wanted to make sure they're not missing anything as they complete their Paraquat ID. What is that referring to?
A. That, sir, that would be the interim decision.
Q. Interim decision on what?
A. That is a step in that reregistration review process that we discussed earlier.
Q. Was it specific to any particular issue?
A. No, sir. The way the reregistration review process works is they evaluate the existing database against potential changes in requirements in the guidelines to make sure the database is complete. They assess the use patterns, do risk assessment, confirm that the product as registered still meets the FIFRA risk benefit standard.
And if changes need to be made, those are communicated in the PID, and that would be where you will have potential modifications, for

example, to label use patterns per the requirements. So that's -- that's the purpose of the PID.
Q. So the purpose of it is to make sure that the necessary information is considered to assure that Paraquat can be used safely and effectively by consumers and users, right?
MR. HONG: Object to form.
A. Used safely and effectively as intended, by users.
BY MR. DICKENS:
Q. And that the labeling is sufficient in order to protect those who are indeed using Paraquat, right?
A. I think that's an accurate statement, yes, sir.
Q. And Ana Pinto and the EPA wanted to make sure they weren't missing anything to make sure that labeling was indeed sufficient to protect those users of Paraquat?
A. I wouldn't want to speak specifically on Ana other than just the request that was put

before us.
Q. So you needed to consider her request, and then get back to her, right? So you needed to make the determination as to exactly what she was asking, right?
A. Correct.
Q. And so you did that?
A. We did have a conversation that following Monday, I believe.
Q. When did you make the -- have these conversations with others within Syngenta as to whether or not any additional information was available to submit?
A. It would have had to be that Monday, sir.
Q. So you had it on that Monday, and then had an answer for Ana Pinto that next following day, right?
A. That appears to be the sequence, sir.
Q. Those conversations you had with the others in Syngenta, was that by phone?
A. Could have been by phone. Could have been walking down the hall talking to people.

Q. Someone like Andy Cook, that would have been by the phone?
A. Definitely by phone with Andy.
Q. Do you know how long that conversation would have been?
A. No, sir. I -- I couldn't -- couldn't recall from that long ago how long that conversation would have been.
Q. Now, sir, you understand that you have been designated to testify on behalf of Syngenta with respect to a particular topic. Is that your understanding?
A. Yes, sir.
MR. DICKENS: Handing you what we'll mark as Exhibit --
MR. HONG: Can we go off the record before you start with this --
MR. DICKENS: -- 36.
MR. HONG: -- segment.
MR. DICKENS: Yes, we can.
MR. HONG: All right. Thank you.
THE VIDEOGRAPHER: The time is 5:10. We

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are now off the record.
(Brief recess.)
THE VIDEOGRAPHER: This is the beginning of media unit number 8 in the video-recorded deposition of Mr. Montague Dixon. The time is 5:14 p.m. Eastern. We are now back on the record. Counsel, you may proceed.
MR. DICKENS: Mr. Dixon, I've handed you Exhibit 36, which is Plaintiff's notice of Rule 4007.1(e) Notice of Deposition of Syngenta Crop Protection LLC and Syngenta AG's Corporate Designee.
(Exhibit 36 was marked.)
BY MR. DICKENS:
Q. Do you see that?
A. Yes, sir.
Q. Have you seen this document before?
A. I have.
Q. Now, it's my understanding that you have been designated to speak on behalf of Syngenta with respect to topic number 84, which is on page 24.

A. Yes, sir.
Q. And that topic is specific to whether Syngenta submitted the following reports to the EPA and, if so, the form and date of submission.
Do you see that?
A. I do see that, sir.
Q. And there are a number of documents that are listed specifically under number 84, right?
A. Yes, sir.
Q. Did you undertake a review to determine whether or not those reports have been submitted to the EPA?
A. I did, sir.
Q. And when did you undertake that review?
A. Starting approximately a week ago.
Q. Okay. Have any of the documents listed in number 84 been submitted to the EPA?
A. Yes. One of them in particular, I identified, sir. It would be CTLHR2357. I believe that is -- let's see here -- summary... 200 grams spray... preliminary investigations, four-hour acute inhalation study.

MR. DICKENS: And you've been handed a document with some notes that I'm going to go ahead and mark as Exhibit 37.
THE WITNESS: Okay.
MR. DICKENS: You have one in front of you, I see.
THE WITNESS: Yes, sir.
(Exhibit 37 was marked.)
BY MR. DICKENS:
Q. Now, this document, is this something that you prepared?
A. It is, sir.
Q. And this document -- can you tell me what this document is meant to represent?
A. Yes, sir. So based upon the -- the titles listed here, I looked at the system I mentioned before, the national pesticide information registration system that's managed by Purdue. I also looked at our internal Syngenta database, which is -- and I did a search based on the search terms "Paraquat" and "Gramoxone," limiting the region to the U.S. to try to see whether or not I

could identify these studies.
The other thing is I actually had PDF copies provided to me of these studies, and then once I had those studies, I went through and tried to analyze them to understand the nature of the study and why or why it would not have been submitted to the U.S.
This document that you have here is the notes that I -- I took based upon that analysis of the documents from -- from opening up and reading them and trying to do the diligence to see whether or not it had been submitted, and if so, why not -- if or if not, why that would be the case.
Q. Did anyone assist you in the preparing this document marked as Exhibit 37?
A. No, sir.
Q. Did you speak with anyone to confirm any information with respect to what's included here in Exhibit 37?
A. No, sir.
Q. And so the one document that you identified -- well, identified as being reported,

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is that included here in this document?
A. Yes, sir. If you look at about three quarters of the way down, you'll see something called an MRID number, 48877203. That is the -- when you submit a document to the EPA, they assign a tracking number called a MRID number, and that's that document number there.
Q. Okay. And that document was submitted in June -- on 29, 2012?
A. That is correct, sir.
Q. And that is a report on Paraquat spray strength solution preliminary investigations four-hour acute inhalation toxicity in the rat, right?
A. Yes, sir.
Q. And was that submitted through the (6)(a)(2) process?
A. No, sir. That was submitted as part of the Paraquat registration review.
Q. So in addition to what could be submitted through (6)(a)(2), there were other mechanisms by which Syngenta can submit information to the EPA?

A. That is correct.
Q. And can you explain how that process would work?
A. Sure. There are several different avenues by which a registrant may submit information to EPA. If you're proposing a regulatory action, you would include the supporting studies and documents, so that would go in as part of either a -- CLIA (ph) action or perhaps a -- something called a fast-track notification.
When EPA opens up reevaluation, such as the case in the Paraquat registration reevaluation, you are -- there are certain comment periods that are open, but you're allowed to provide supporting information along the way.
One other area where you would see potential for documents being submitted is often during these reevaluation processes, there'll be something called a data call-in, and when there's a data call-in, then registrants are given a certain period of time to submit a study or a rationale why a study would not be needed.

Q. I want to look at some of these particular documents --
A. Okay.
Q. -- in light of the information you provide in the notes.
MR. DICKENS: Go ahead and mark Exhibit 38.
(Exhibit 38 was marked.)
BY MR. DICKENS:
Q. And Exhibit 38 is -- appears to be the last document on page 2 --
A. Yes, sir.
Q. -- of your notes. And this is a study report on [As read] "Paraquat Penetration Through Protective Clothing Materials in the Malaysian Gramoxone Formulation." Do you see that?
A. I do, sir.
Q. And the date of this is March of 1986, right?
A. Yes, sir.
Q. Now, the Malaysian formulation, Syngenta did rely on studies in Malaysia that were

submitted to the EPA with respect to the safety profile of Paraquat, right?
A. I'm trying to recall. Was there one of those being the biomonitoring study?
Q. As you recall here today.
A. As I recall here today, I can't -- I don't recall any specific Malaysian study supporting U.S. registration.
Q. With respect to -- and this has been deemed not reportable because it's a non-U.S. formulation, right?
A. We would not have submitted this type of study because it's a non- U.S. formulation.
Q. But I think we can establish that non-U.S. formulation studies and reports have been submitted with respect to Paraquat in the past, right?
MR. HONG: Object to form.
A. I think that has happened. It depends on the nature of the type of study. A study such as this would not necessarily provide useful information to EPA.

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BY MR. DICKENS:
Q. Did you ask the EPA whether or not it would be useful information?
MR. HONG: I'm just going to object to this being outside the scope of topic 84.
So, Mr. Dixon, you can testify in your personal capacity. This is not imputed to Syngenta the company.
Go ahead.
A. I certainly have not spoken with EPA on that.
BY MR. DICKENS:
Q. This particular study tested [As read] "the efficiency of protective clothing materials against Paraquat penetration from a Gramoxone formulation."
Do you see that?
A. Yes.
Q. And it was testing the penetration rates and breakthrough times of Paraquat?
A. That's, I believe, the study, the purpose of the study.

Q. On various type of PPE?
MR. HONG: And I'm just going to -- just one second, Mr. Dixon. I'm going to lodge an objection. All questions related to the substance of Exhibit 38 fall outside the scope of topic 84.
So to the extent you answer questions related to the substance of Exhibit 38, it will be in your personal capacity, sir.
BY MR. DICKENS:
Q. Is that right, sir?
A. I'm sorry, sir. Can you restate.
Q. Yeah. This particular study involved penetration of Gramoxone formulation through various types of protective clothing?
MR. HONG: Same objection.
THE COURT REPORTER: Various types of...
MR. DICKENS: Protective clothing.
MR. HONG: Counsel, can I get a standing objection to that.
MR. DICKENS: You can have a standing objection.
MR. HONG: Thank you.

A. That appears to be the stated purpose of the study.
BY MR. DICKENS:
Q. And that included unfinished cotton, correct?
A. I -- I did not read the study in detail for that, but as I open it up, I see unfinished cotton in section 2.3.2. So, yes, my analysis of these studies was just whether or not they had been submitted in the potential rationale but not any type of evaluation of the quality of the study, sir.
Q. Sir, when the EPA asked whether or not all information was submitted in 2011 to Ana Pinto, did you review this particular study to decide whether or not it was relevant for submission to the EPA?
MR. HONG: Same objection. Outside the scope.
You can answer in your personal capacity, sir.
A. No, sir.

BY MR. DICKENS:
Q. Were you aware of this study prior to reviewing in association with offering testimony on behalf of Syngenta for this deposition?
MR. HONG: Same objection. Outside the scope.
A. I do not believe I was aware of this particular study.
BY MR. DICKENS:
Q. And this particular study concluded that Tyvek, corovin, unfinished cotton, cannot be recommended for protective clothing for use during the application of Gramoxone, right?
A. That is what's stated in the document, sir.
Q. Was this type of test performed on the U.S. formulation, to your knowledge?
MR. HONG: Same objection. Outside the scope.
A. I have no knowledge it -- that it was done.
BY MR. DICKENS:

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Q. Do you believe the finding that application of a Gramoxone formulation -- strike that. Do you believe that a finding that Tyvek, corovin and unfinished cotton is not effective at preventing exposure to Paraquat relevant for the EPA's determination under the PI?

MR. HONG: Same objection.

A. Sir, given -- given my evaluation of this as to whether or not it's submitted, that goes into an area that I haven't worked in in a long time, so I wouldn't want to speculate without doing an in-depth analysis of this study.

BY MR. DICKENS:

Q. Sir, would you agree that in order to determine whether or not this was reportable to the EPA, you would have had to have some knowledge of the substance of this particular report?

MR. HONG: Same objection. Outside the scope.

A. I can't speak to that, sir.

BY MR. DICKENS:

Q. The U.S. labeling for Paraquat in the

United States does not recommend users wear polyurethane-coated Tyvek, right?

MR. HONG: Same objection.

A. I -- I would have to look at the label, but I do not believe it does.

BY MR. DICKENS:

Q. It recommends unfinished cotton?

MR. HONG: Same objection.

A. I need to look at the label. My recollection is it recommends coveralls.

BY MR. DICKENS:

Q. It previously recommended long sleeves, long pants, right?

MR. HONG: Same objection.

A. Right.

BY MR. DICKENS:

Q. Didn't differentiate between what type of clothing would be worn?

MR. HONG: Same objection.

A. Not to my knowledge. That -- that would be atypical for U.S. PPE requirements.

If I may expand, EPA has set PPE

requirements based upon certain toxicity categories and results, and so the registrants are required to use EPA-stated PPE recommendations. In the case of Paraquat, it was long-sleeve pants and long shirts.

BY MR. DICKENS:

Q. And that PPE specific on the U.S. label is meant to prevent the skin-to-skin -- skin contact with Paraquat, right?

A. The way the PPE levels are determined within the U.S. regulatory framework is something called an operational -- occupational risk assessment where you have to establish an MOE. That's the margin of exposure. And so the elite -- the tiered layer of personal protective equipment is geared to get to an acceptable MOE level.

Q. And the purpose being to prevent Paraquat from getting on the skin of the users, correct?

MR. HONG: Same objection.

A. I mean, the purpose of the PPE recommendations is to reduce exposure to an

acceptable level.

BY MR. DICKENS:

Q. And reduce exposure to Paraquat, right?

MR. HONG: Same objection.

A. The -- the framework is for whatever active ingredients you're working on. It's the same framework in the regulatory space.

BY MR. DICKENS:

Q. And the long sleeves, long pants, that's exposure to dermal exposure, right? It's nothing different?

MR. HONG: Same objection.

A. Yeah, long sleeve, long pants would be dermal exposure.

BY MR. DICKENS:

Q. Did you make a finding that a study indicating that unfinished cotton and Tyvek was not suitable to protect the users from dermal contact to Paraquat, was irrelevant for the EPA?

MR. HONG: Objection. Outside the scope.

A. Sir, I did no such -- excuse me -- no such analysis. When I was reviewing this document, it

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was to try to understand what amount had been submitted.

BY MR. DICKENS:

Q. Do you know whether or not any expert within Syngenta made a determination that the Malaysian formulation was so different from the U.S. formulation that the findings in this study were irrelevant?

MR. HONG: Objection. Outside the scope. Calls for speculation.

Answer in your personal capacity, sir.

A. I -- I'm not able to answer that. I have no views on that, sir.

BY MR. DICKENS:

Q. Now, with respect to submissions to the EPA, that doesn't end, right? I mean, in your regulatory capacity, you have a duty to submit information to the EPA even if it occurred years ago if it becomes relevant to a safety analysis, right?

MR. HONG: Same objection. Answer in your personal capacity, please.

A. I wouldn't want to speculate on that, sir.

BY MR. DICKENS:

Q. So you don't know whether or not there'd be any duty to submit past information to the EPA if it becomes relevant for an adverse health effect associated with the -- with Paraquat?

MR. HONG: Same objection.

A. I would be speculating without more information on the nature of the past -- past information you're referring to.

BY MR. DICKENS:

Q. So any (6)(a)(2) reviews with respect to studies and data and information, that would all be from the time you would have sat in 2006 moving forward?

MR. HONG: Same objection.

BY MR. DICKENS:

Q. You wouldn't have looked backward?

MR. HONG: Same objection. Incomplete hypothetical.

A. Yeah. I -- I can't answer without looking backwards. No, sir.

BY MR. DICKENS:

Q. Do you -- do you recall any instance where you submitted old information because you deemed it relevant to safety analysis or evaluations or questions asked by the EPA with respect to the safety of Paraquat?

MR. HONG: Object to outside the scope and to form.

A. I don't recall any pulling out things from the past to resubmit.

MR. DICKENS: Can we take a 10-minute break.

THE WITNESS: Yes, sir.

THE VIDEOGRAPHER: The time is 5:34. We're now off the record.

(Brief recess.)

THE VIDEOGRAPHER: The time is 5:41 p.m. Eastern. We are now back on the record. Counsel, you may proceed.

BY MR. DICKENS:

Q. Mr. Dixon, I want to look again at your notes with respect to the studies identified in

Number 84. And, specifically, you have the description of the study in the notes you prepared, right?

A. Yes, sir.

Q. And in those notes, specific on that last document we looked at, was the Malaysian Gramoxone formulation, and your note was it's a non-U.S. formulation, right?

A. Yes, sir.

Q. And by saying non-U.S. formulation, is that meant to mean it's not reportable because of that?

A. In general, when we submit information to EPA to support U.S. registrations, it's based on U.S. formulations due to the different compositions of formulations region to region.

Q. And specifically, the note section that you include for each of these particular studies, those notes are meant to represent the basis for why it wasn't reportable?

A. Based upon any analysis, that would be the first conclusion I'd come to as why it would not

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have been. You know, some of these studies go back into the '70s, so my analysis is seeing what the study said and trying to understand why it may or may not have been reported.

Q. Okay. Did you undertake for exhibit -- for example, Exhibit 38, a determination of the difference between the U.S. Gramoxone formulation and the Malaysian formulation for this particular study?

MR. HONG: Objection. Outside the scope.

A. To the extent I could determine that from the information in the document, yes.

BY MR. DICKENS:

Q. And did you do that for this particular document?

A. Yes, sir, to the extent possible. And I say that in a broad sense. Not having the specific statement of formula, I have to make inferences based upon the concentration, and these concentrations do not align with U.S. concentrations that were registered.

Q. And in order to complete this chart, you

made a determination that based on EPA statutes and regulations that, because it's a non-U.S. formulation, it would not be required to be reported by Syngenta, right?

MR. HONG: Same objection.

A. Certainly did not make that based upon specific EPA statutes. It's EPA and traditional practices within industry that if a formulation is not registered in the -- at the EPA, we would not typically send information for them to consider.

BY MR. DICKENS:

Q. Let me go back to -- once again, to Exhibit 23, the guidelines. And the guidelines, once again, for extraterritorial adverse effect information, right?

A. Uh-huh.

Q. We looked at the sentence before, [As read] "But the agency will consider all information to be reportable unless an expert concludes differences between the formulation of product involved and the foreign information of product registered in the United States make the

information irrelevant to the product registered in the United States," right?

MR. HONG: Objection. Outside the scope.

A. That's what's stated in the document, sir.

BY MR. DICKENS:

Q. And that's what EPA deems reportable with respect to foreign information on foreign products, right?

MR. HONG: Same objection.

A. That's what's stated in the document, sir.

BY MR. DICKENS:

Q. And in order to say in Exhibit 37, then, that it was not reportable because it was a non-U.S. formulation, did you undertake an analysis as to whether or not an expert concluded the difference between the Malaysian formulation and the U.S. formulation makes the information irrelevant?

MR. HONG: Same objection.

A. I did no such analysis, and that would be a very challenging analysis to do given the age of the study. I would have to have documents that I

do not necessarily have any access, so I don't know whether such an analysis was made at that time or not.

BY MR. DICKENS:

Q. It's fair to say you, then -- but you did not do that analysis for any of the studies included in this chart?

A. No, sir. My analysis, as I had indicated, was to look at the formulation and see whether or not it was equivalent to a U.S. formulation. And my basis for doing that was trying to determine, if a study wasn't submitted, was there a logical reason why it would not have been submitted. That's based on a cursory review, certainly not being able to go back and do an in-depth analysis of all the historical records that may or may not have occurred on that document.

Q. But you can't reasonably say the study's not reportable without undertaking that analysis the EPA tells you to do, that an expert concludes the differences make the information irrelevant, right?

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MR. HONG: Same objection.
A. Well, I -- when I went to do this, I -- do this analysis, that was not the charge I was given. It was whether or not it was submitted and what format. So what I did here was determined it wasn't submitted, tried to understand why, but did not feel I was charged with going in and trying to piece together the history of the decision on why I was not informed.
BY MR. DICKENS:
Q. But you did go in and give your note and opinion on whether or not the study was reportable or not, right?
MR. HONG: Same objection.
A. Yes. I certainly wanted to take a look at it so I could have some idea of the nature of study and why it may or may not have been.
BY MR. DICKENS:
Q. Okay. But you agree, then, that you didn't follow the EPA guidelines for (6)(a)(2) reporting in doing so for these particular studies?

MR. HONG: Same objection.
A. That wasn't the task I was given, sir.
BY MR. DICKENS:
Q. But the task, in your opinion, was to make an opinion as to whether or not they were reportable, and I'm assuming that's reportable under (6)(a)(2)?
A. No, sir.
Q. Okay. Reportable to the EPA at all?
A. Whether or not it would be likely a study would be submitted for EPA to use. EPA, when it received studies, typically only wants to receive study if there's a purpose for it. They need to know that the data is applicable for a regulatory decision.
Q. So EPA would only -- when you say they only want to receive a study if there's a purpose for it, what do you mean by purpose for it?
MR. HONG: Same objection.
A. In a broad sense, as a regulatory manager, my experience with EPA, it would be absolutely impractical for EPA to receive every study ever

conducted by a registrant everywhere in the world. There's just no way they could go -- it would be tens of thousands if not hundreds of thousands of studies they would be presented with. So it's my understanding EPA, when it receives studies, it's necessary for them to -- they receive studies to inform them on regulatory decisions.
BY MR. DICKENS:
Q. Regulatory decisions that include safety decisions?
MR. HONG: Same objection.
A. Regulatory decisions including all regulatory decisions.
BY MR. DICKENS:
Q. That includes safety decisions?
MR. HONG: Same objection.
A. Yes, sir.
BY MR. DICKENS:
Q. And that includes information relevant to the labeling for the product?
MR. HONG: Same objection.
A. Correct.

BY MR. DICKENS:
Q. And the sufficiency of the label of the product?
A. Yes --
MR. HONG: Same objection.
A. And EPA labels are based upon formulation-specific criteria, so that's why the acute tox testing is done for each formulation and why you don't have a general set of PPE that crosses all formulations. You have to submit the acute tox testing for your formulation in order for EPA to be able to include the acute tox safety warnings, first aid statements and things such as that.
BY MR. DICKENS:
Q. On page 2, there's the Brazilian assessments. Do you see that?
A. Page 2 --
Q. Of your notes --
A. Oh, I'm sorry, sir.
Q. -- Exhibit 37. Yeah, I completely changed that on you. Exhibit 37, your notes.

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A. Yes, sir. Let me go to them. Page 2. Okay.
Q. There's three Brazilian studies listed there, correct?
A. Let's see here. I see one, two and three, yes, sir.
Q. And none of those were reported to the EPA, correct?
A. I do not believe Syngenta directly reported those studies, no, sir.
Q. And based on your review and evidence and everything you did to be able to speak on Syngenta's behalf, you concluded they didn't submit those, right?
A. I didn't find evidence that we submitted those. And these would be studies and information that are in the public domain. EPA would have access to them.
Q. So you found that these Brazilian studies are in the public domain?
A. In general, any regulatory decision from either ANVISA or APVMA, once they make these

decisions, they are published.
Q. Do you know when they were published?
MR. HONG: Object to scope.
A. I can't give you a specific date, sir.
BY MR. DICKENS:
Q. Okay. Do you know where they're published?
MR. HONG: Same objection.
A. That would be from our Brazilian regulatory person to actually give that definitive on that.
BY MR. DICKENS:
Q. So as you sit here today, you can't even say whether or not they're publically available. You just expect that they would be?
MR. HONG: Same objection.
A. It would be shocking for them not to be.
BY MR. DICKENS:
Q. Did you do a review to confirm whether or not they're publically available.
MR. HONG: Same objection.
A. Not for the scope of this.

BY MR. DICKENS:
Q. So for the scope of this -- but you did just testify that they were publically available, right?
MR. HONG: Same objection.
A. Yes, I believe they are publically available.
BY MR. DICKENS:
Q. Based on what?
A. Based upon the fact that regulatory agencies such as EPA, APVMA, ANVISA, when they make regulatory decisions, they are generally put out for public notice.
Q. Did you yourself go online to see if they were published?
A. I did not, sir.
Q. Did you have anyone on your behalf go online to see if they were, in fact, published?
MR. HONG: Same objection.
A. Not for this exercise, sir.
BY MR. DICKENS:
Q. Do you know if the English translations of

these documents are published?
MR. HONG: Same objection.
A. I do not know. Obviously, we had one copy of it, but I don't know if that was a translated copy that we had done or if that was public from the earlier exhibit that you showed me.
BY MR. DICKENS:
Q. The second document identified here --
A. On the same page, the second --
Q. The Page 1. I'm sorry.
A. Okay. Sorry. Yes, sir.
Q. Your notes include [As read] "published academic journal article, foreign language." Do you see that?
A. I do see that, sir.
Q. Do you know whether or not that article was available in English?
MR. HONG: Object to form. Outside the scope.
A. I do not.
BY MR. DICKENS:
Q. Did you check to see if it's available in

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English?
A. I --
MR. HONG: Same objection.
A. I did not, sir.
BY MR. DICKENS:
Q. If you submit foreign studies or information internally to the EPA, do you -- does the company registrant have a duty to translate those before doing so?
MR. HONG: Same objection.
A. Yes, sir. May I get you to restate that? I think you said if we submit it internally.
BY MR. DICKENS:
Q. Yeah, if you had an internal study, for example, that was in a foreign language, would the registrant have a duty to translate that for submission to the EPA?
MR. HONG: Same objection.
A. I certainly believe a registrant would do that.
BY MR. DICKENS:
Q. And why?

MR. HONG: Same objection.
A. For the ability of the agency to understand the information being provided.
BY MR. DICKENS:
Q. And so if the information -- for example, those ANVISA reports -- were not in English, do you have an understanding that the EPA would typically receive those and translate them on their own?
MR. HONG: Same objection. Calls for speculation.
A. Yeah. I cannot speak to how EPA handles communications. I certainly know EPA's involved with joint meetings with regulators, such as OECD meetings, the joint meetings, so EPA is frequently in conversations with other regulators that speak different languages. I don't know their specific practices for sharing documents with each other in different languages.
MR. DICKENS: Hand you what we'll mark as Exhibit 39.
THE WITNESS: Yes, sir.

Thank you, sir.
(Exhibit 39 was marked.)
BY MR. DICKENS:
Q. And what I've just handed you is actually the second to last document notation included in Exhibit 37, which are your notes, which is the Paraquat operator exposure. Do you see that?
A. I do see that, sir.
Q. And that's by Graham Chester and Andy Cook?
A. That is, yes, sir.
Q. And this document was not reported to the EPA, correct?
A. I do not -- it was not, no, sir.
Q. And you --
A. Although information within the document -- there are some studies within the document that were submitted to EPA, but the document itself, to my knowledge, was not.
Q. Okay. And not all of the information within the document was submitted to the EPA either, right?

A. No, I do not believe that to have been the case.
Q. And you deemed it not reportable for what reason?
A. I'm not sure if this is the same version I had. The version that I looked at, I believe, was marked as a draft. I don't see that on this. But having said that, assuming it's the same document, the studies that would have been applicable for U.S. agronomic practices, U.S. equipment, U.S. formulations, those were the Gramoxone Extra studies, and those were submitted.
Q. Now, you did submit Andy Cook's memo to the EPA citing the Findley study in the comments, right?
A. That is correct, sir.
Q. So you did submit some findings of Andy Cook with respect to operator exposure studies to the EPA, right?
MR. HONG: Counsel, can I have a standing objection to scope for this document -- the substance of this document?

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MR. DICKENS: I'm not sure there's a cutoff point for the independent -- the individual examination of him, but go ahead.

MR. HONG: Objection to scope.

A. Okay. And could you restate that, sir?

BY MR. DICKENS:

Q. Yeah. You did go ahead and submit findings of Andy Cook with respect to operator exposure studies to the EPA for their consideration?

MR. HONG: Same objection.

A. And that was the document we discussed earlier, yes, sir.

BY MR. DICKENS:

Q. And that cited the one study, the Findlay study, right?

MR. HONG: Same objection.

A. I believe that's the correct reference, yes.

BY MR. DICKENS:

Q. Turn your attention to Bates number ending 8774.

A. Okay.

Q. Right before tractor-mounted application studies, there's a notation there, [As read] "The French and Martinique studies are the most modern guidance compliance studies available and are the ones of choice for assessment of absorbed dose for risk assessment purposes under the specific conditions of habitual use."

Do you see that?

MR. HONG: Just so the -- before you answer, Mr. Dixon, just so the record is clear, I'm going to object to any questions related to the substance of Exhibit 39 as outside the scope of topic 84. So you can answer in your personal capacity. Go ahead.

A. I do see the sentence, sir.

BY MR. DICKENS:

Q. And those French and Martinique studies are the two studies we looked at earlier in the deposition, right?

MR. HONG: Same objection.

A. Without having specific study references, it is my assumption they are.

BY MR. DICKENS:

Q. And Andy Cook and Graham Chester make reference to the fact that those two studies were the most modern guidance compliance studies available, right?

MR. HONG: Same objection. Calls for speculation.

A. I'll confirm that's what stated in the document.

BY MR. DICKENS:

Q. And they are the ones for choice for assessment of absorbed dose for risk assessment purposes, right?

MR. HONG: Same objection.

A. Again, confirming that's what the document states.

BY MR. DICKENS:

Q. Now, that information and opinion was not included in the memo submitted to the EPA in the comments for their registration, right?

MR. HONG: Same objection.

A. I do not believe that statement was in that document, sir.

BY MR. DICKENS:

Q. And, in fact, the French -- the two studies that Andy Cook and Graham Chester determined were the ones for choice for assessment of absorbed dose, those have never been seen by the EPA, we already established, right?

MR. HONG: Same objection. Calls for speculation. Mischaracterize testimony on the record. Go ahead, sir.

A. I would not want to speculate whether or not the agency has seen those, sir.

BY MR. DICKENS:

Q. Well, we -- we looked at those two studies, right, and we've established they were only on the HE, right?

MR. HONG: Objection to form and outside the scope.

A. They were submitted as part -- the information in those studies was included as the HE, yes, sir.

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BY MR. DICKENS:
Q. And there wasn't any specific information with respect to the actual findings within those biomonitoring studies submitted to the EPA in those submissions, right?
MR. HONG: Object to form and scope.
A. All that I'm aware of is what we discussed.
BY MR. DICKENS:
Q. And what you had seen back at the time in the determination to submit them as HEs?
MR. HONG: Same objection.
A. They -- they were considered by the appropriate committee and team, and then the submission reflected the conclusion of the team.
BY MR. DICKENS:
Q. And, sir, you also met with the EPA in March of 2010 with respect to Paraquat. Do you recall that?
A. Yes, sir.
Q. And part of that meeting, there was a discussion of a DEFRA study?

MR. HONG: Same objection.
A. I would like -- I believe that to be the case, but I would need to go through the documents to confirm that.
MR. DICKENS: Go ahead and mark Exhibit 40 for the record.
MR. HONG: I'm going to state for the record that all questions related to Exhibit 40 fall outside the scope of topic 84 of the notice.
Mr. Dixon, all questions answered related to Exhibit 40 should be answered in your personal capacity, not the corporation's.
THE WITNESS: Thank you, sir.
(Exhibit 40 was marked.)
THE WITNESS: I see the document here, sir.
BY MR. DICKENS:
Q. And you did attend this meeting in March of 2010; is that right?
A. I did.
MR. HONG: Same objection.
For the record, Exhibit 40 appears to be a

draft of a presentation to the EPA in 2010 and not a final draft.
BY MR. DICKENS:
Q. Turn your attention to the Bates number ending 8507.
A. I'm there, sir.
Q. This slide's [As read] "Independent Support of Safe Use Risk Assessment for Operators." Do you see that?
A. I see that.
MR. HONG: Same objection.
BY MR. DICKENS:
Q. It was a McIntosh and Kedderis UK DEFRA-sponsored study. Right?
MR. HONG: Same objection.
MR. DICKENS: What's the objection?
MR. HONG: Outside the scope.
A. Yes, I see that listed there, sir.
MR. DICKENS: Outside the scope of the...
MR. HONG: Topic 84, sir.
BY MR. DICKENS:
Q. And you're testifying here in your

individual capacity, correct?
A. For this topic.
Q. And you were at the meeting in March of 2010?
A. I was.
Q. And you were there when these slides were presented?
A. Correct.
Q. And you did, in fact, discuss at that meeting the McIntosh and Kedderis study, right?
A. That is listed here, yes, sir.
Q. And that's the DEFRA study that was ongoing, right?
A. That is a DEFRA study. I'm not sure if it's the same one as listed here, but that is a DEFRA study.
Q. And it's specifically referencing a poster at that point in time, right?
A. Correct.
Q. And it's respect -- references the type of study developed in mouse physiologically-based pharmacokinetic model for Paraquat, right?

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MR. HONG: Object to form.
A. Uh-huh.
BY MR. DICKENS:
Q. Is that a yes?
A. Yes. I'm sorry.
Q. And after this, the EPA did request that that poster be submitted. Do you recall that?
MR. HONG: Objection.
A. That sounds familiar. I believe so.
BY MR. DICKENS:
Q. Do you know whether or not you did, in fact, submit that poster to the EPA?
A. If requested, I'm confident we would have.
Q. And you do recall that that poster would have been requested, right?
MR. HONG: Object to form.
A. I don't specifically recall that.
Q. Do you recall receiving correspondence requesting that you submit that poster?
MR. HONG: Object to form.
A. Being 14 years ago, I don't specifically remember that correspondence. I will say as well

that it's certainly possible the EPA would have requested it, and it does look like this was a public presentation as well.
BY MR. DICKENS:
Q. Even as a public presentation or poster, EPA still could have requested it from Syngenta to submit, right?
MR. HONG: Object to form.
A. Correct.
BY MR. DICKENS:
Q. Now, the page 1 of Exhibit 37, your notes, refers to public studies sponsored by DEFRA. Do you see that?
A. Let's see here. Yes. I see that, yeah.
Q. Okay. And you deemed that as not reportable, right?
A. It was not a Syngenta study, sir.
Q. Okay. And you still deemed it not reportable, right?
A. Correct. Not -- not as a Syngenta study. It was a study conducted by DEFRA.
Q. And you have -- in fact, we looked at the

two incidences where, by 2008, information had been submitted on Paraquat and Parkinson's to the EPA, right?
A. Okay. Yes, sir.
MR. HONG: Let me get my objection in. Outside the scope.
Go ahead.
A. And I want to just ask, given that we're going on both topics, what topic am I? Am I back on 84 or am I back on --
BY MR. DICKENS:
Q. That's fine. No. You're still on the individual.
A. Okay.
Q. And I'm specifically asking you about the earlier exhibit we looked at from 2008 on the two incidences that were submitted on Paraquat and Parkinson's disease. Do you recall that?
A. Are you referring to the (6)(a)(2) report with Thiruchelvam and the other?
Q. That's right.
A. Yes, sir.

Q. And one of those was an outside study that was not a Syngenta study, right?
A. It was a publication, if I remember correctly.
Q. And that was deemed submittable and reportable by the (6)(a)(2) committee?
A. That is my recollection of that, yes, sir.
Q. Now, you deemed or determined that the last document on page 37, the exponent examination analysis of the role of Paraquat and maneb -- it goes on -- that was not reported to the EPA, first of all, right?
A. I have no information showing that it was reported to the EPA.
Q. And you understand that this is the final report of the poster that you discussed at the March 2010 meeting with the EPA?
MR. HONG: Objection to form.
A. Yes. I -- I would have to see the poster and compare it to the study. I don't recall the specifics of the poster other than what's summarized here and certainly do not see a

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reference to maneb in the documents -- or slide 6, in the document on 37 references maneb.

THE COURT REPORTER: Man...

THE WITNESS: Maneb, M-A-N-E-B.

MR. DICKENS: Go ahead and mark Exhibit 41 for the record.

(Exhibit 41 was marked.)

THE WITNESS: Okay, sir. I see this.

BY MR. DICKENS:

Q. Okay. And this the document you reviewed to determine whether or not it was reported to the EPA, correct?

A. Correct.

Q. And this document you reference is a public study, but we can confirm it wasn't published, right?

MR. HONG: Objection to form.

A. Actually, it -- as I look at it, it says [As read] "DEFRA intends to publish this form on its website unless there are strong reasons not to." So it appears that DEFRA's intention was to publish this.

Q. Do you know whether or not it was published on its website or not?

MR. HONG: Object to form. Outside the scope.

A. I cannot confirm that at this time.

BY MR. DICKENS:

Q. Did you attempt to confirm that?

MR. HONG: Same objection.

A. No, sir.

BY MR. DICKENS:

Q. Did you check to see if this was published in any way outside the website, in a peer-reviewed journal?

MR. HONG: Same objection.

A. I did not.

BY MR. DICKENS:

Q. Do you know if the EPA has this report?

A. I cannot --

MR. HONG: Same objection.

A. I cannot confirm or deny whether EPA has this. I don't know.

BY MR. DICKENS:

Q. Did you attempt to determine in any way whether or not EPA has this report?

A. I did not, sir.

Q. And so this particular document indicates it may be published on its website, right?

MR. HONG: Same objection.

A. Yes, sir.

BY MR. DICKENS:

Q. Did you confer with anyone in Syngenta to see if they were aware of whether or not it was ever published on their website?

MR. HONG: Same objection.

A. I did not.

BY MR. DICKENS:

Q. Other than the fact it's a public study, is there any other reason why you deemed this particular report not reportable?

MR. HONG: Same objection.

A. That was my analysis, is just that it was already a public -- it was a non-Syngenta study and it was -- based upon what I read, I believed it to be publically available.

BY MR. DICKENS:

Q. And your understanding of the -- publically available is just that it's out there somewhere in the public that the EPA could find it?

MR. HONG: Same objection.

BY MR. DICKENS:

Q. Is that your understanding?

A. My understanding is that if information is known in the public sphere, whether it's literature, professional society meetings or other reputable sources, then it's not considered a new finding; therefore, it's not reportable.

BY MR. DICKENS:

Q. How is the determination made as to whether it's known?

MR. HONG: Same objection.

A. I think on a case-by-case, there's an analysis of the information, and -- and the different subject matter experts would evaluate it to see whether or not it would be publically known.

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So if, for example, this poster that's mentioned here appears to have been presented at the 2008 Society of Toxicology meeting, that is certainly a very public forum and one heavily attended by EPA personnel.

BY MR. DICKENS:

Q. Turning your attention to Bates number ending 147.

A. Yes, sir.

Q. And there's information here on future work intranasal transport.

Do you see that?

A. I do see that.

Q. Now, this information wasn't included in the 2008 poster, was it?

MR. HONG: Objection. Outside the scope.

A. I would have to review the poster to determine that, and I -- I don't recall the contents of that poster.

BY MR. DICKENS:

Q. Do you recall any findings from DEFRA and its intranasal transport findings ever being

presented by Syngenta to the EPA?

MR. HONG: Same objection.

A. I have no recollection of that, sir.

BY MR. DICKENS:

Q. The DEFRA says, [As read] "However, of interest concerning this topic, intranasal dosing in the PBPK model portion of the study indicates fast and extensive circulation of Paraquat in the brain tissue. Paraquat detected in the brain after intranasal exposure was tenfold higher than the model predicted."

Do you see that?

MR. HONG: Objection.

A. I see that, sir.

BY MR. DICKENS:

Q. And you were aware by 2012, certainly, that the EPA had concerns of intranasal exposure to Paraquat, right?

MR. HONG: Same objection.

A. Based upon the work we talked about in 2000, yes, around nosebleeds.

BY MR. DICKENS:

Q. [As read] "The authors conclude the preliminary observation has implications for exposure to humans -- exposure of humans to any neuroactive or neurotoxic substances that deposit in the nasal cavity during inhalation," right?

A. That's what's stated, sir.

Q. And you're not aware of whether or not the EPA has ever seen this particular document, right?

MR. HONG: Same objection.

A. I cannot speak to EPA's knowledge on that, sir.

BY MR. DICKENS:

Q. Turn back to page 2 of Exhibit 37.

A. Okay, sir.

Q. Specifically, there's an exponent sensitivity analysis of the Tanner, et al. case control study. Do you see that?

A. I do, sir.

Q. And you reviewed that in order to determine whether or not it was reportable or not, right?

A. I did, sir.

Q. And --

A. Let me -- let me rephrase.

I reviewed it to see whether or not it had been reported within the context of -- of topic 84, and it had not been reported, and so I said -- I then tried to determine why it may not have been reported or submitted to the EPA.

Q. Your notes indicate it's not reported, right?

A. In the context of my notes, not -- not from a FIFRA or (6)(a)(2) perspective. I'm just saying, looking at this, we -- I couldn't find evidence it had been submitted, and in my read of it, I would say this was not something that would have likely been reported because it was publically -- public data.

Q. Okay. So you actually reviewed the document, though, in order to make that determination that it was not reportable?

A. I certainly scanned it to try to understand what it was.

Q. So you scanned it to determine what it was

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and determined it wasn't reportable, correct?
A. Based upon my quick review, I scanned it and determined it was unlikely to be something that would have been reported.
MR. DICKENS: Go ahead and mark this as Exhibit 42.
(Exhibit 42 was marked.)
THE WITNESS: Thank you.
Just for clarity, sir, I'm operating under topic 84?
BY MR. DICKENS:
Q. For now, yeah.
This is the document that you reviewed in order to make a determination as to whether or not the document was submitted to the EPA, correct?
A. This appears to be the same PDF document I look at, yes, sir.
Q. And this is as same document that you reviewed and deemed that this information would not be reportable to the EPA?
A. Based upon my review of it, yes, I determined this would be publically available, and

so not potentially reported.
Q. Okay. You deemed this document, Exhibit 42, as publically available?
A. When I looked at it. But now as I'm looking at, I see it says [As read] "confidential attorney-client work product," so my analysis of being publically available would not have been correct.
Q. Okay. And your -- and just to be fair, your actual notes here say it's a reanalysis of public study data, right?
A. Correct.
Q. Okay. So this -- were you saying that this, in fact, was publically available or is reanalyzing public study documents, specifically Tanner?
A. I believe when I looked at this, I did not pick up on the confidential attorney-client privilege, so I believe --
MR. HONG: Mr. Dixon, I think he's referring to the notes here.
THE WITNESS: Yes, yes.

A. But I think the reason I said that this was not reportable -- I don't think I had recognized the attorney-client privilege mark on the top of it.
BY MR. DICKENS:
Q. Okay. And would your analysis change with respect to whether or not this information would be reportable under the determination that it is not, in fact, publically available?
A. Based on the fact that it is an analysis of publically available data, reanalysis, I do not know that the determination would have been that it would be reportable. I would have had to rely on subject matter experts to really look at it and determine the impact of the reanalysis.
Q. Okay. And you didn't to do that?
A. No, sir.
Q. And in your review of this document, it was an analysis of the Tanner case control study, right?
A. That is correct.
Q. And from the Agricultural Health Study?

A. Correct.
Q. Now, the Tanner case control study, that was presented to the EPA in your meeting in 2017, right?
MR. HONG: Object to scope.
A. I would need to compare and make sure it's the same. I -- I don't know if that's the only Tanner study there is, so...
BY MR. DICKENS:
Q. Okay. And this Tanner study specifically is making findings with respect to incident and prevalent cases, right? That's the reanalysis being done?
MR. HONG: Object to scope.
A. I -- I did not go into an in-depth read of the document, so I don't know the specifics beyond just the nature of the overall assessment.
BY MR. DICKENS:
Q. Now, there were comments made to the initial Tanner study in the comments that you submitted to the EPA in 2019, right?
MR. HONG: Same objection.

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A. I -- I recall there were comments about the Tanner work in there, yes, sir.
BY MR. DICKENS:
Q. Okay. And specifically, there was comments on the limitation of Tanner because it didn't differentiate between incident and prevalent cases, right?
MR. HONG: Same objection.
A. I would have to go back and review that. I know that section of comments was put together by Dr. Breckenridge, who's more expert in that field. So I believe that is a statement that is in there, but I would need to look at it closely to confirm that's an exact statement.
BY MR. DICKENS:
Q. And those statements that -- were actually submitted to the EPA by you, though, right?
MR. HONG: Same objection.
A. Yes, sir. So how -- how the process works is, when we have these type of public comments, my job as the primary contact is to have the dialogue with the EPA but to rely on the expert analyses

from the subject matter experts, human health experts, E-FED experts.
In the case of something like this, I would have relied on someone like Charles, who is certainly an -- much more expert in this area than I am, and I would collate their comments into a final document to submit.
BY MR. DICKENS:
Q. And Dr. -- sorry. Back to Exhibit 42 on the reanalysis, and specifically page 9. And under number 1 on page 9 it states, [As read] "We tested a series of alternative models by using different subsets of the data or using alternative co-variants as follows."
A. Sir, I might be looking at a different -- I see number 1 being [As read] "separate -- separate analyses for the incident and prevalent PD cases."
Q. Yeah, that -- that's fair. I kind of jumped up one sentence to put it into context. But --
A. Okay.

Q. -- for this analysis, they tested a series of alternative models using different subsets, and one of them being separate analysis for incident and prevalent cases.
A. I see that.
MR. HONG: Same objection.
BY MR. DICKENS:
Q. And page 12, after undergoing the analysis, last full paragraph, [As read] "In summary, the extensive set of alternative analysis shows there is a degree of robustness in the association between Paraquat exposure and risk of Parkinson's disease in the FAME study," right?
MR. HONG: Same objection.
A. That's what stated.
BY MR. DICKENS:
Q. And so in the comments and in meetings with the EPA, Syngenta criticized Tanner for failing to differentiate between incident and prevalent cases, correct?
MR. HONG: Same objection.
A. I have no specific recollection of such

criticism, sir. If it's in that document there, I would need to look at and remind -- be reminded.
BY MR. DICKENS:
Q. We can look at the 2019 comments submitted to the EPA, I wish could identify the exhibit number for --
A. No. I can find it. I'm familiar with it. How about number 15?
Q. Number 15 it is, and specifically page 27.
A. Okay. Yeah, so these were the comments that would have been collated from Dr. Breckenridge.
MR. HONG: Mr. Dixon, your -- your testimony as it relates to Exhibit 15 during this portion of the examination is on your personal capacity because it falls well outside the scope of topic 84. But go ahead, sir.
THE WITNESS: Thank you.
BY MR. DICKENS:
Q. And there's weightings of specific studies. Do you see that?
A. Let's see here. The weightings.

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Weightings. Weightings.
Can you guide me to it on the page, sir.
Q. Under 2.2.
A. 2.2. Okay. I see that, yes.
Q. Okay. And in 2.2.1, they reference the FAME study.
A. I see that.
Q. It's being rated as high quality, the only study to receive that rating, and that's actually the rating by EPA itself. That's your understanding, right?
MR. HONG: Object to form.
A. I don't have the specific understanding on that. That's what -- I collated these comments but I did not specifically author these comments.
Q. The next sentence: [As read] "However, an important limitation of the study is that the investigators did not differentiate between incident and prevalent cases in their statistical analysis, right?
MR. HONG: Objection. Lacks foundation.
A. That is stated.

BY MR. DICKENS:
Q. And you reviewed this at the time you submitted it in 2019, right?
A. I would have reviewed it, yes.
Q. Yeah. And these are --
A. However, as -- not as an epidemiological or toxicological expert; as a regulatory person trying to make sure the sentences make sense.
Q. And as a regulatory person submitting comments on Syngenta's position with respect to EPA findings, right?
MR. HONG: Objection.
A. Correct.
BY MR. DICKENS:
Q. And One of the comments made by Syngenta and submitted by you was that a limitation of the Tanner study was they didn't differentiate between incident and prevalent. That's what will you told the EPA in 2019, right?
MR. HONG: Object to form.
A. That is the information contained in the document here, sir.

BY MR. DICKENS:
Q. What isn't mentioned in that document is that Syngenta had a reanalysis of the Tanner data from 2013 which showed there is no difference even under analysis of incident and prevalent cases, right?
MR. HONG: Object to scope. Lacks foundation. Calls for expert opinions.
A. Yes. I relied on the comments from our epidemiological experts to populate that section of the document. So I -- I tried to rely on the experts for those comments.
BY MR. DICKENS:
Q. And all I'm asking is, it's fair to say that nothing within the comments you submitted to the EPA in 2019 mentions the fact that there was a reanalysis and data from 2013 considering the incident and prevalent cases, right?
MR. HONG: Object to scope and lacks foundation.
A. I cannot recall a statement like that being in the comments.

BY MR. DICKENS:
Q. And based on your review and everything you looked at in preparation for today's deposition, in fact, this sensitivity analysis was never submitted to EPA at any point in time, right?
A. I have no recollection that it has been submitted.
Q. Not only no recollection; you actually undertook a search to figure out whether or not it had been submitted, right?
A. I did not find evidence in my search that it had been submitted.
MR. DICKENS: I have no further questions. Thank you.
MR. HONG: Mr. Dixon, I just have a few questions.
THE WITNESS: Okay.
EXAMINATION
BY MR. HONG:
Q. Why don't we start with your Exhibit 37, sir. Do you have that in front of you?

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A. I do, sir.
Q. My first question to you is, with respect to Exhibit 37, did you list all the reasons why each document that's enumerated here in Exhibit 37 was not submitted to the EPA?
A. No, sir.
Q. Is this an exhaustive list of all the possible reasons why Syngenta may or may not have submitted these studies to the EPA -- or these studies or documents enumerated here in topic 84, to the EPA?
A. No.
MR. DICKENS: Object to form.
A. No, sir.
BY MR. HONG:
Q. Okay. And, Mr. Dixon, do you recall being asked questions today by Counsel regarding why Syngenta submitted certain studies but not other studies?
A. I do.
Q. Does Syngenta have to submit all studies, reports or information in its possession to the

EPA?
A. That is not a requirement, sir.
Q. Why not?
A. Because of the sheer volume of information that would be presented to the EPA, it would be very impractical for the agency to process or handle. So the types of studies we submit -- so, for example, we wouldn't submit a range-finding study when we're testing multiple dose levels. We hone in on the appropriate dose level, then do the definitive study, and that would be the study that would be submitted.
Q. Is Syngenta obligated to submit all studies, reports or information in its possession to the EPA?
A. Not all studies or reports within its possession.
Q. And why not?
A. Just the sheer volume, and many of those studies or reports would not be deemed of -- to provide significant or helpful information to the agency.

Q. Sir, do you recall Counsel asking you questions about the (6)(a)(2) committee?
A. I do, sir.
Q. Were you ever a sitting member on the (6)(a)(2) committee?
A. Not a permanent sitting member.
Q. Were you ever an adjunct member?
A. On a -- whenever an issue came up that would be associated with a molecule that I was responsible for, yes.
Q. So, sir, is that your definition of an adjunct member?
A. Yes. We -- we had a standing process with the (6)(a)(2) committee. There are members that -- that -- that are consistently on there as the official committee. But then, depending on the topic, additional people are brought in as appropriate.
And in the case of a regulatory manager, if a product is being considered for (6)(a)(2), that regulatory manager with that product responsibility would often be included.

Q. As an adjunct member, do you get to decide on how the (6)(a)(2) committee should make certain determinations?
A. Not individually make the decision that drafts the committee, just contribute to the decisions.
Q. And just so the record is clear, sir, who or which committee is ultimately responsible for deciding whether a study or a finding should be reported to the EPA?
A. Within the United States, it would be the U.S. (6)(a)(2) committee.
Q. So you don't make those decision individually, correct?
A. Individually, no, sir.
Q. Sir, you were asked about information submitted to EPA, including (6)(a)(2) reporting in the aggregate. Do you recall that, sir?
THE COURT REPORTER: I'm sorry. Including...
MR. HONG: In the aggregate.
THE COURT REPORTER: No. Submitted to

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EPA, including...
MR. HONG: (6)(a)(2) reporting in the aggregate.
BY MR. HONG:
Q. Do you recall that, sir?
A. I do, sir.
Q. Can EPA request additional details or information about Syngenta's submissions, including those in the aggregate?
A. EPA can request information from Syngenta at any time for any reason, including if they were to receive a (6)(a)(2) report and wanted additional information.
Q. So if EPA had asked additional information regarding the Martinique study that Counsel examined you about or the French vine study that also Counsel asked you questions about, would Syngenta have provided that information?
A. Absolutely.
Q. And in fact, there have been instances and times when EPA has asked you or Syngenta for additional information, to which Syngenta then

provided that information, correct?
MR. DICKENS: Object to form.
A. Yes, that has occurred.
BY MR. HONG:
Q. Now, Mr. Dixon, you were also asked questions by Counsel about your non-U.S -- - about non-U.S. regulatory actions, correct?
A. Correct.
Q. Do you recall that testimony?
A. I do.
Q. What role, if any, did you have in non-U.S. regulatory activities on behalf of Syngenta?
A. The only real role I would have was to be informed and to certainly understand what was happening in the rest of world, but I never had any direct communications with any regulatory body outside of the U.S. that I can recall with respect to Paraquat.
Q. Okay. Now, Mr. Dixon, I'm going to ask you to pull up Exhibit 31.
A. This is the...

And I'll take one step back. I have had meetings. The only foreign country I've had meetings with is I do have meetings with PMR in Canada, but I do not recall if those -- Paraquat was the topic. But that's the only time I've ever had external interactions with a foreign regulatory body.
Q. And thank you for that clarification, sir.
Just so the record is clear, during your tenure as Syngenta's liaison for -- with the EPA, did you have any oversight whatsoever related to non-U.S. regulatory activities?
A. No, sir.
Q. Now, with respect to Exhibit 31, you have that in front you, right, sir?
A. I do have that, sir.
Q. Do you recall Counsel asking you questions about Exhibit 31?
A. I do.
Q. For the record, Exhibit 31 is the 2015 technical reassessment opinion by ANVISA?
A. That is correct, sir.

Q. Sir, is this a scientific study?
A. I would not classify this as a study. As more of -- instead, it appears to be more of a review of existing data and studies.
Q. Sir, to your knowledge, is Exhibit 31 a public document?
A. I certainly believe it is a public document.
Q. And if it's a public document, fair to say that the EPA would have had access to it, correct?
A. EPA should have access to it.
Q. And in fact, it's fair to say that at the time of Syngenta's 2017 presentation to the EPA on its Paraquat -- or on its Parkinson's disease research, EPA would have been aware of Exhibit 31. It's possible, right, sir?
MR. DICKENS: Object to form.
A. I would certainly say it is possible.
BY MR. HONG:
Q. Because it's a public document, right?
MR. DICKENS: Objection to form.
A. Yes, sir.

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BY MR. HONG:
Q. Now, Mr. Dixon, I would like to show you Exhibit 7. Could you pull that document back up.
A. Yes, sir. I hope to be able to.
Q. And I have a copy right here.
A. I have it right here. I have it right here, sir. This document, sir?
Q. Yes, sir.
A. Okay.
Q. Do you recall Counsel asking you questions about Exhibit 7?
A. I do.
Q. And Exhibit 7, Counsel had asked you questions about a January 6, 2016 meeting with the EPA. Do you recall that?
A. Yes, I do.
Q. As it relates to that January 6, 2016 meeting, sir, was that meeting at all related to Parkinson's disease?
A. No, sir.
Q. Okay. You can put that document down now. Mr. Dixon, do you recall Counsel asking

you questions about the EPA and its ability to analyze the science?
A. I do.
Q. The plaintiff's lawyers in this case have suggested that the EPA is unreliable and unable to understand the science surrounding Parkinson's disease. Do you agree with that statement?
MR. DICKENS: Object to form.
A. Could you restate it, please.
BY MR. HONG:
Q. Sure. The plaintiff's lawyer in this case have suggested that the EPA is unreliable and unable to understand the science surrounding Parkinson's disease. Do you agree with that statement?
MR. DICKENS: Object to form.
A. I do not.
BY MR. HONG:
Q. Why not?
A. I believe EPA has very competent technical experts and scientists. They not only rely on their internal reports, but they also on occasion

bring in external experts. They did, from my recollection, exhaustive examination of the literature, including all of the information we have provided, and concluded there was not a definitive relationship between Parkinson's and Paraquat.
MR. HONG: Thank you, sir. No further questions.
MR. DICKENS: I have some follow-up questions.

EXAMINATION

BY MR. DICKENS:
Q. Mr. Dixon, who is the neurologist at EPA who is evaluating Paraquat?
THE COURT REPORTER: I'm sorry. Can you say that again?
BY MR. DICKENS:
Q. Who is the neurologist at EPA evaluating Paraquat?
A. I don't have a specific name on that, sir.
Q. You've worked with the EPA up and through 2022. Who was the neurologist you were working

with at the EPA who was evaluating Paraquat then?
A. Sir, I -- I would have been working with the regulatory liaison, so I don't directly speak with the scientist.
Q. So you don't know whether or not there's any neurologist at the EPA evaluating Paraquat?
MR. HONG: Object to form.
A. From direct memory, I cannot tell you the titles or background of the people that would have been involved in the meeting other than to say that EPA has what are called the health effects division, and within there are experts that should be very qualified to look at all health-related -- human health-related issues.
BY MR. DICKENS:
Q. During your time when you were working in the regulatory department, you told others within Syngenta that EPA was underresourced and understaffed, right?
MR. HONG: Object to form.
A. I -- I have made that statement and I believe that to be the case, sir.

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BY MR. DICKENS:
Q. Now, with respect to the ANVISA report and whether or not that was publically available, you have no evidence to base a statement that the ANVISA report was publically available in 2017, do you?
A. I have no basis to confirm that was or was not, other than the traditional approach that when government regulatory agencies make regulatory decisions, they tend to make them available to the public.
Q. Now, during that meeting with the EPA in 2017, you didn't tell them ANVISA completed their report or review; you said it was ongoing, right?
MR. HONG: Object to form.
A. My understanding from what was in the slide is that it was ongoing.
BY MR. DICKENS:
Q. So there was no indication that this report was even finalized, existed, was out there, was publically available, right?
A. Based on what was presented, I can only

say what was presented in the meeting.
Q. And you don't know whether or not ANVISA held off on publishing that report at the time of your meeting that you had in hand from -- in February of 2017, correct?
MR. HONG: Object to form.
A. Yeah. I can't -- I can't speak to the actions of ANVISA, sir.
BY MR. DICKENS:
Q. And "the actions of ANVISA" meaning whether or not it was publically available, that the EPA could have it?
A. Correct. I can't speak to the actions of ANVISA.
Q. Did you ask EPA whether or not they had the ANVISA report during the meeting?
A. I do not recall asking that question, sir.
Q. You had a discussion, or Counsel asked you about, the Martinique and French vine study. Do you recall that?
A. Your question on that, sir?
Q. Do you recall counsel for Syngenta asking

you questions about that?
A. I don't recall the specific question either. It may have been just a minute ago.
Q. It's been a long day. And he asked you this. Yeah, he asked that whether or not EPA can request additional details on the study.
A. Oh, I do recall that, yes, sir.
Q. And what type of information is typically submitted to the EPA under HE reporting, aggregate reporting?
A. I believe it is just that. It's the type of information we looked at today.
Q. Okay. And what type of information? Is that moderate, severe injuries?
A. My understanding from the HE categorization is that those are reports of exposure, and if I remember the categorization breakdowns correctly, where there are -- were no observed effects.
Q. So all the EPA knew is that some people were exposed to Paraquat and had no adverse effect, right?

MR. HONG: Same objection -- or objection. Lacks foundation.
A. All I can indicate is that what we provided to the EPA was in that report, that -- that aggregate report.
BY MR. DICKENS:
Q. They had no information that those involved biomonitoring studies that were sponsored by Syngenta, right?
MR. HONG: Objection.
A. I can't speak to what EPA knew other than, yeah, I can speak to what we provided, which was the aggregate report.
BY MR. DICKENS:
Q. Those studies weren't published, were they?
A. Not in the U.S., that I'm aware of.
Q. The only ones who had the information from those studies was Syngenta?
MR. HONG: Same objection. Calls for speculation.
A. I can only speak to what I know in the

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U.S. I don't know if those studies were made available elsewhere in the world.
BY MR. DICKENS:
Q. And they Weren't made available to the EPA in the United States, were they?
A. I have --
MR. HONG: Objection to form.
A. I have not been able to determine if they were provided.
BY MR. DICKENS:
Q. And the EPA can't ask for additional details about specifics of a study that they have no idea even exists, can they?
MR. HONG: Objection. Form.
A. I can't speak to EPA. If they -- how they would go about if they saw a broad category, what would be their trigger to ask for more or not.
BY MR. DICKENS:
Q. Now, you say you can't speak about the EPA, but you said that they don't want every study because of the sheer volume of them, right?
A. Correct.

Q. Did EPA tell you that they don't want certain studies submitted because it's too much?
A. Not me directly but I am anecdotally aware of those comments.
Q. And that's why they, in fact, put out something like a guidance that tells you exactly what must be reported, right?
A. Correct.
Q. And that guidance is specific to guiding industry to say, we don't want every study, but if it meets these definitions, you must submit them, correct?
A. It provides that guidance. There are the guideline studies that are clearly required, those that are conditionally required and those that are voluntary studies. And then to your question, there's also the guidance that was put out in that document.
Q. And EPA expects that the registrants of pesticide products will follow that guidance, correct?
A. They do, and I believe we do.

MR. DICKENS: No further questions.
MR. HONG: Just a couple of questions, Mr. Dixon.

EXAMINATION

BY MR. HONG:
Q. Could you pull back up Exhibit 31.
A. May I add some context to one of my earlier answers?
Q. Sure, sir.
A. So just specifically on the meeting for the human health mitigation decision, we're trying to remember that was the 2016 meeting. I don't remember all the specific content that was presented, but the driver in that meeting was around trying to prevent the type of injuries that we talked about earlier, the spills, accidental ingestions. And so that was the meeting where we were discussing the mitigation options, including potentially going to closed systems and other things such as that.
So that was the context of that meeting. You know, I don't remember word for word

everything that happened, but I just wanted to make sure I put that into context.
And, sir, you were asking for 31. Is this the ANVISA document?
Q. Yes, sir.
A. Okay.
Q. Do you have it in front of you?
A. Yes, sir.
Q. Okay. With respect to Exhibit 31, do you see there at the top, it says, [As read] "Analysis of the contributions to the proposed reassessment of active ingredient Paraquat, supported by the technical reassessment opinion number 01 of 2015/GGTOX/ANVISA, object of the Public Consultation number 94 of October 8, 2015"?
Do you see that, sir?
A. I do see that.
THE COURT REPORTER: Of October...
MR. HONG: Say that again.
THE COURT REPORTER: Of October...
MR. HONG: Of October 8, 2015.
BY MR. HONG:

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Q. And then -- sir, do you see that?
A. I do see that.
Q. And then I'd like to direct your attention to the penultimate sentence in the first full paragraph there. Do you see where it starts "This analysis"?
A. Okay. Let's see. "This analysis." Yes.
Q. It reads, [As read] "This analysis supported the technical note of the national health surveillance agency, ANVISA, and the proposition of technical regulation indicating the prohibition of this active ingredient in Brazil, which was included in the public consultation, CP, in the end of 2015." Do you see that, sir?
A. I do see that.
Q. And if you look at the last paragraph -- second full paragraph that reads [As read] "The technical note" -- do you see that?
A. I see that.
Q. -- "with this understanding was included in the CP." Do you see that, sir?
A. Yes.

Q. And the CP, based on this document, is the public consultation, correct?
A. That -- that appears to be correct, yes, sir.
MR. HONG: No further questions.
THE VIDEOGRAPHER: If there are no more questions, this will conclude today's testimony as given by Mr. Montague Dixon. The time is 6:48 p.m. Eastern, and we are now off the record.
THE COURT REPORTER: Before you all go, can I just get the transcript orders on the record as far as delivery time.
MR. DICKENS: I don't care about delivery time.
You guys probably --
MR. HONG: We have a standing order --
MR. DICKENS: Yeah. We'll take the rough and then the final whenever.
(Whereupon, the deposition concluded at 6:48 p.m.)

CERTIFICATE

I, Okeemah S. Henderson, RPR, the officer before whom the foregoing deposition was taken, do hereby certify that the foregoing transcript is a true and correct record of the testimony given; that said testimony was taken by me stenographically and thereafter reduced to typewriting under my direction; that reading and signing was requested; and that I am neither counsel for, related to, nor employed by any of the parties to this case and have no interest, financial or otherwise, in its outcome.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed my notarial seal this 22nd day of July, 2024.

My commission expires:
August 31, 2024



Okeemah S. Henderson, RPR
Official Court Reporter

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ATTACHMENT F

National Health
Surveillance Agency

TECHNICAL REASSESSMENT OPINION NO. 08/GGTOX/Anvisa, of June 13, 2016

Analysis of the contributions to the proposed reassessment of the active ingredient Paraquat supported by the Technical Reassessment Opinion no. 01 of 2015/GGTOX/Anvisa, object of the Public Consultation no. 94 of October 8, 2015.

SUMMARY

The reassessment of the active ingredient Paraquat was determined by Resolution – RDC No. 10 dated February 22, 2008 due to the existence of studies showing the high acute and chronic toxicity of this active ingredient. The Oswaldo Cruz Foundation (Fiocruz) was hired to elaborate the technical note addressing all the relevant toxicological aspects of the active ingredient Paraquat. In 2015, the General Toxicology Office (GGTOX) analyzed the technical reassessment note of the active ingredient Paraquat elaborated by Fiocruz to evaluate the content and legal basis presented and conclude on which toxicological effects of Paraquat to humans were relevant from the regulatory point of view. This analysis supported the technical note of the National Health Surveillance Agency (Anvisa) and the proposition of technical regulation indicating the prohibition of this active ingredient in Brazil, which was included in the Public Consultation (CP) in the end of 2015. In 2016, GGTOX concluded the consolidation of the contributions of the CP and reviewed the contested toxicological aspects as well as analyzed new data and documents presented during this regulatory phase.

The technical note elaborated by Fiocruz concluded that Paraquat classified under all the prohibitive criteria for registration related to health established by Act no. 7.802 of June 1989 and by Decree no. 4.074 of January 4, 2002, because it considered the evidences in scientific literature related to acute intoxication, mutagenicity, endocrine deregulation, carcinogenesis, reproductive toxicity, teratogenesis and Parkinson's Disease to be sufficient. However, the conclusions made by Fiocruz were not necessarily based on an analysis with evaluation of the quality of the studies, according to regulatory criteria, or with correct interpretation regarding the suitability of the indication of the toxicological aspects as being prohibitive criteria for registration. Therefore, after analyzing the technical note of Fiocruz, Anvisa concluded that there was sufficient weight of evidence and legal basis for the prohibition of Paraquat in Brazil only for the following aspects: severity of the cases of occupational and accidental intoxications, due to the fact that the use of protection equipment (IPEs) does not guarantee full protection against intoxication by Paraquat, with the real level of exposure of workers exceeding the acceptable occupational exposure levels (AOELs); due to the existence of evidences of the triggering of Parkinson's Disease and evidences of its mutagenic potential. The technical note with this understanding was included in the CP, as well as the technical regulation proposal prohibiting Paraquat in Brazil.

Majority of the contributions received in the CP highlighted the impacts of the prohibition or severe restriction of Paraquat related to the agronomic aspects (lack of substitutes, problems with weed resistance, difficulty in pest control, increased use of other herbicides), economic aspects (loss of productivity, increased production cost, negative impacts on neighboring countries) and environmental aspects (impossibility of direct planting, increased soil degradation, increased emission of CO_2).

The analysis of the scientific literature studies showed that there are cases of severe acute intoxication of exposed workers but majority occurs from the incorrect use of Paraquat. Regarding the national scenario of Paraquat intoxication, it was observed that death is predominant in cases of suicidal and accidental intoxication. Therefore, considering the real possibility of intoxication by the product when used correctly in farming, severe acute intoxication is not common and the cases of acute occupational intoxication tends to be either moderate or mild, with effective antidotes and treatments

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able to revert the health damages resulting from occupational exposure to Paraquat-based products.

Therefore, it is concluded that Paraquat, in relation to acute intoxication, is not classified under any prohibitive criterion for pesticide registration in Brazil. However, it is worth emphasizing that occupational exposure to Paraquat is relevant, especially due to evidences of higher human sensitivity to dermal exposure to this pesticide, with possible systemic absorption by this route of exposure. Furthermore, the cases of severe acute intoxication by accidental ingestion of Paraquat or suicide attempt are disturbing. Soon, considering all these aspects related to acute intoxication by Paraquat, even if it is concluded that this active ingredient classifies under other criteria considered prohibitive for registration, very restrictive risk mitigating measures would be imperative for it to remain in the country.

Although it was concluded to not include Paraquat in prohibitive criteria for registration due to acute intoxications by this pesticide, the conclusions on mutagenicity and Parkinson's Disease were kept, even after in-depth analyses, because the conclusions presented initially by Anvisa were confirmed in the consolidation phase of the CP.

The scientific evidences currently available on the mutagenic potential of Paraquat show that there is sufficient weight of evidence to prove its potential of inducing chromosomal aberrations in somatic cells *in vitro* and *in vivo* in different species and by different exposure routes, including dermal. Considering that the effect observed in somatic cells is enough to characterize its mutagenic potential in germinative cells, because it was possible to prove the inexistence of mutation in germinative cells and, in these cases, this is the scientific and regulatory understanding currently being used. Furthermore, the exposure to Paraquat reaches the testicles, affecting the spermatozoids, causing more concern with the mutagenicity of Paraquat in germinative cells, and the dermal exposure of humans is relevant and more important than the exposure of animals, thus rural workers may be susceptible to the mutagenic effects of Paraquat.

Based on the currently available evidences, there is a strong weight of evidence (animal studies and epidemiological studies) indicating that Paraquat is associated to the triggering of Parkinson's Disease in humans. Considering that the consequences of human exposure to Paraquat is more relevant than animal exposure, because Parkinson is a serious progressive disease whose treatment only delays the symptoms but is not able to revert the condition, that is, there is no cure and, due to the known severity of this disease to humans, it is possible to concluded that Paraquat may prove to be more dangerous to humans than what is shown by tests with laboratory animals and there is no antidote and efficient treatment. Although monitoring studies do not show exposures above the AOEL, it is known that Paraquat can be absorbed through the dermal route and even low doses are a concern due to the evidences associating this active ingredient to parkinsonism. It is not possible to state that the currently accepted AOEL is a safe limit in relation to the effects of Paraquat on dopaminergic neurons resulting from long-term exposure of rural workers.

Considering the current scientific knowledge, it is concluded that Paraquat is mutagenic and is a risk factor in Parkinson's Disease, with evidence of causality between exposure and the disease, being classified under the following prohibitive criteria for registration: (a) Scientific evidences of mutagenicity according to the updated results of experiences of the scientific community (Section c, Paragraph 6, Article 3 of Act no. 7.802, of 1989); (b) Lack of antidote or efficient treatment (Item II of Article 31 of Decree no. 4.074 of 2002 and Section b, Paragraph 6, Article 3 of Act no. 7.802, of 1989); (c) Evidences that the active ingredient is more dangerous to humans than what is shown in laboratory tests with animals (Item VII of Article 31 of Decree no. 4.074 of 2002 and Section e, Paragraph 6, Article 3 of Act no. 7.802, of 1989).

Based on the scientific data currently available and due to the classification of the toxicological aspects of Paraquat under the prohibitive criteria for registration established in the Brazilian legislation, the prohibition of the production, export, import, marketing and use of products made with this active pesticide ingredient in the country is suggested.

I – REPORT

The Technical Reassessment Opinion no. 01 on the toxicological reassessment of the active ingredient Paraquat considered that this pesticide presents unacceptable acute

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toxicity, it has no antidote or efficient treatment, it is mutagenic and potentially capable of triggering parkinsonism in exposed workers, suggesting the cancellation of the registrations of the products made with this active ingredient.

During the public consultation (CP) no. 94 of 2015, referring to the Collegiate Board Resolution (RDC) proposal on the reassessment of the active ingredient Paraquat, a total of 2,879 contributions were received of which 39 were supported by files attached to the CP form (Table 1). Anvisa also received new documents filed by the Task Force referring to the CP that supported its argument and a document sent as an entity letter from abroad (Gremiagro), which was duly included electronically in the FormSUS. It was observed that 106 of these contributions agreed with the Resolution proposal, 57 partially agreed with the proposal and the other 2,716 contributions completely disagreed with the proposal or disagreed with the need for regulation.

Other contributions were received outside the deadline or mentioned in public consultations that occurred simultaneously with CP no. 94 of 2015. These contributions were not included in the CP results of Paraquat but their contents were addressed in this opinion since their arguments was very similar to that of the other contributions received.

Table 1. List of files attached to the contributions of the Public Consultation no. 94 dated October 8, 2015.

File	Topic
3655996_218117.pdf	Article on the appearance of glyphosate-resistant weeds.
3666610_218117.docx	Agronomic and economic importance - attached to the topics with the benefits of Paraquat.
3682503_218117.pdf	Agronomic and economic importance - attached to the topics with the benefits of Paraquat.
3688648_218117.pdf	Efficiency in the early harvest of corn.
3688648_218117.pdf	Letter to Anvisa from Fundação MS Para Pesquisa e Difusão de Tecnologias Agropecuárias [MS Foundation for Research and Diffusion of Agricultural Technology] – Technical arguments on the agricultural importance of Paraquat (weeds, handling of resistance, direct planting, harvest planning, environmental safety).
3688691_218117.pdf	Letter to Anvisa from Fundação MS Para Pesquisa e Difusão de Tecnologias Agropecuárias [MS Foundation for Research and Diffusion of Agricultural Technology] – Technical arguments on the agricultural importance of Paraquat (weeds, handling of resistance, direct planting, harvest planning, environmental safety).
3693722_218117.ods	Price of primary products – Out of scope.
3698496_218117.pdf	Agronomic and economic importance - attached to the topics with the benefits of Paraquat.
3700257_218117.pdf	Article on the impact of the prohibition of Paraquat in the suicide rates of South Korea.
3702195_218117.pdf	Agronomic and economic importance - attached to the topics with the benefits of Paraquat.
3703887_218117.docx	Toxicological aspects: Use of odorizing and emetic substances, herbicide applied in the direction of the soil, application only once or twice in the crop cycle, many times used in the mechanized form. The cases of death predominantly result from suicide and not related only to Paraquat. The distribution of Fuller's Earth and the training of medical doctors are important. Agronomic Aspects: Direct planting with reduced soil erosion, voluntary plants, lack of alternatives with similar characteristics.
3703923_218117.docx	Resistance and increased use of other herbicides.
3706548_218117.docx	Agronomic and economic importance - attached to the topics with the benefits of Paraquat.
3706762_218117.pdf	Agronomic and economic importance - attached to the topics with the benefits of Paraquat.
3709443_218117.pdf	Agronomic importance.

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3709559_218117.jpg	Photo of plant.
3711856_218117.docx	Importance of Paraquat in citrus crops.
3718279_218117.pdf	Direct planting, sustainable agriculture and use of Paraquat – masters thesis.
3721336_218117.pdf	Pack insert.
3724859_218117.pdf	Agronomic importance – Presentation, Fernando Adegas.
3726078_218117.docx	Data on medical care of cases of humans exposed to PARAQUAT PESTICIDE registered at the Toxicological Information Center of Santa Catarina (CIT/SC) in the period of 2003 to 2014.
3726398_218117.pdf	Document of the Brazilian Herbicide Resistance Action Committee (HRAC-BR) clarifying the importance of Paraquat in weed control, direct planting and resistance handling.
3726922_218117.docx	Agronomic and economic importance - attached to the topics with the benefits of Paraquat.
3727106_218117.docx	Agronomic and environmental importance.
3730205_218117.pdf	Minutes of the meeting of CONAPRE (Argentina) on the implications of the Rotterdam Convention on the use of Paraquat in Argentina.
3730600_218117.docx	Personal data – Out of scope.
3730672_218117.pdf	Document from Sungenta treatment of Paraquat intoxications. Main points addressed: lack of specific antidote, occupational exposure not resulting in systemic intoxication, medical treatment for acute intoxications is accepted by the medical community and is contained in the pack insert of the products, USEPA publications recognize this treatment.
3730840_218117.jpg	Personal photo – Out of scope.
3731564_218117.pdf	Agronomic importance, Ias [Healthy Eating Index] association.
3731608_218117.pdf	Out of scope – Article: Effect of the association of herbicide clomazone to chitosan-alginate nanospheres in the absorption in soils.
3731622_218117.xlsx	Intoxication data. Antonio Pedro University Hospital of the Fluminense Federal University.
3731739_218117.pdf	Document on behalf of the Brazilian Association of Toxicology Information Centers and Clinical Toxicologists (Abracit) presenting a summary of the major scientific evidences to support the removal of the Paraquat herbicide from the Brazilian market. Morbimortality data: Between the years 2007 and 2014, SUS [Unified Health System] registered 25,919 cases of intoxications by pesticides of agricultural use, of which 1283 of these cases resulted in the death of the intoxication victims. According to the data of the Brazilian Intoxication Registration System (Datatox), there were a total of 117 cases of Paraquat intoxication only in the year 2014 and 2015, of which 29 resulted in death. The document highlighted it as the potential chronic damage of the occupational exposure due to leading to the death of neurons through the induction of oxidative stress and reproduction of pathological characteristics of Parkinson's Disease in animal models. These damages would not be a real problem to farmers if the absorption of these agents in occupational circumstances were not plausible. However, there are references indicating high levels of Paraquat in exposed workers. It also highlights that a systematic review showed that the mortality of patients intoxicated by Paraquat was 85% and the use of cyclophosphamide reduced this mortality to 60%. In other words, even after receiving the best treatment, more than half of the people died from Paraquat intoxication. Reviews with positive results in the treatment of intoxications were cited but

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	the lethality still remains very high (higher than 50%). It is worth highlighting that the effectiveness of this treatment in real scenarios would be very low since cyclophosphamide is a high cost chemotherapy drug that requires manipulation by a pharmacist in controlled chemical safety environments (laminar flow hood, sterile manipulation room with suitable exhaust and particle count). It also made reference to a study indicating that the number of suicides in South Korea reduced after the removal of Paraquat from the market; this information was considered important because it debunks that the removal of Paraquat from the market will have no impact on health. It was emphasized that it was necessary to evaluate the economic impact not only in relation to the increase in cost and loss of productivity in agriculture but the expenses with health and productivity loss of the intoxicated people must also be considered, citing Sri Lanka and China as countries where the banishment of Paraquat did not cause significant economic loss, despite being countries with intensive use of this pesticide and the damages from the permanence of Paraquat in the market exceeded the burden from its banishment.
3733582_218117.pdf	Review of the factors that place pollinators and the European agriculture at risk - Out of scope.
3733957_218117.pdf	Comments on epidemiological studies relating Paraquat to Parkinson's disease.
3735272_218117.docx	Analytic opinion on the Regulatory Rules (Economic Monitoring Department of the Ministry of Finance) indicating the lack of competitive impact.
3735905_218117.pdf	Embrapa Soja opinion on direct planting and agronomic importance.
3736418_218117.pdf	Addresses the impacts of the use of pesticides to health, citing the pesticide intoxication data registered at the Toxicological Information Center of Santa Catarina between the years 2003 and 2009 (discussed in the opinion).
3737088_218117.pdf	Bibliographic review on intoxication by Paraquat, Efficacy of various treatments with different approaches. It did not specifically talk about the penta conjugate treatment but addressed the reduction of mortality in treatments that are included in some of the steps of the penta conjugate treatment protocol. It highlighted the best survival rates in the use of immunosuppressants, antioxidants, hemoperfusion, methylprednisolone, vitamins B and C, propfol, vitamin E.
3737168_218117.pdf	List of substitutes.

Among the contributions received that disagreed with the proposal or the need for regulation, majority presented arguments related to the agronomic, environmental and economic importance of this active ingredient and the losses of its removal from the market: lack of substitute, resistance, impossibility of direct planting, difficulty in pest control, economic loss to the country, productivity loss, increased production costs, increased use of other types of herbicides, difficulty in soil preservation, and negative impacts on neighboring countries. Some of these contributions suggest reconciliation between maintenance of the Paraquat-based products in the market and mitigation of the health risks, proposing some actions that can be used to achieve this objective:

a) Conduct risk assessment;
b) Assessment of the possibility of partial cancellation of the registration only for crops with higher risk of contamination of the applicator (for example, perennial crops and crops that require manual application);
c) Intensification of the inspection of the sale and use of the product;
d) Maintenance of the registration until the existence of substitutes;
e) Incentive to register substitutes;

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f) Assessment of the efficiency of possible substitutes;
g) Improvement in the monitoring of its use and residues;
h) Intensification of the training of manipulators of the products;
i) Accreditation of applicators;
j) Restriction of use (packaging, sites permitted for aerial application, back spraying, maintenance of only mechanized application);

The importance of conducting a more in-depth regulatory impact analysis was also mentioned in the CP. It is worth highlighting that few contributions presented arguments related to the analyses of the effects of Paraquat to health.

In addition to the CP, the good regulatory practices can contemplate additional steps like the complementary instruction in which, among other options, panels can be performed to allow the in-depth analysis with assessment of additional information that can support the final decision. In the reassessment of the active ingredient Paraquat, based on the importance of the RDC proposal resulting from the reassessment of this active ingredient, the need to expand the debate on the contributions received was observed and hence a Technical Panel with experts was organized after the CP.

The Technical Reassessment Panel of the active ingredient Paraquat was planned to deepen the discussions on occupational exposure, mutagenicity and parkinsonism, toxicological aspects prohibitive for registration considered relevant in the reassessment of Paraquat, with the main purpose of detailing the arguments presented in the CP to support the consolidation of the understanding of Anvisa and the elaboration of a final decision on the reassessment of Paraquat. Furthermore, the analysis of the contributions of the CP showed the need to expand the debate on the impacts of the results of the reassessment of Paraquat in agriculture, in the economy and in the environment.

The following experts in the areas of toxicology and agronomy affiliated with institutions of reference were invited to the panel to discuss all these aspects:

a) Estefânia Moreira, researcher of the Londrina State University;
b) Ligia Fruchtengarten, physician of the São Paulo Intoxication Control Center;
c) Fernando Adegas, researcher of Embrapa;
d) Hamilton Ramos, researcher of the Agronomic Institute of Campinas.

Representatives of the Paraquat Task Force and other bodies involved in the reassessment of pesticides (Ministry of Agriculture, Livestock and Supply (MAPA) and Brazilian Institute of Environment and Renewable Natural Resources (IBAMA)) were also invited.

After the analyses of the contributions and with the discussions in the panel of experts on the reassessment of Paraquat, some aspects of the Reassessment Opinion no. 1/GGTOX/Anvisa were reviewed and will be presented and discussed below.

1. International Status

After the CP, the table with the international status of the technical reassessment opinion was updated (table 1).

Table 1. International status of paraquat.

Country	Regulatory status
United States	Restricted use. The application should be monitored by a certified applicator. Application close to schools and homes, in parks, golf courses and playgrounds is prohibited. Re-entry interval of 12 to 24 hours. Aerial application allowed. In March 2, 2016, EPA initiated a public consultation on the proposal of even more restrictive measures after concluding that the intoxication data were disturbing. The measures proposed were: packaging in closed systems that allowed the direct transfer to the application equipment and that cannot be opened without destroying the packaging; special training for certified applicators, emphasizing that transfer of container and inappropriate storage cannot occur; changes in the label and distribution of supplementary material, with warnings to emphasize the

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	toxicity and associated risks of Paraquat-based products; prohibition of manual and back application; use restricted to certified applicators, that is, individual workers under the supervision of applicators will be prohibited.
Canada	Restricted use. Aerial application allowed. Reassessment concluded in December 2015. Restrictions adopted: classified in the restricted class, application only by certified or licensed applicators, addition of IPEs for back and tractor-driven application, inclusion of specifications for IPEs and tractor cabins, inclusion of warnings, medical cares and additional precautions in the pack insert, reduction of Paraquat concentration in the end-use product, use of the same mixing tank only for other pesticides specified in the pack insert, modification of the packaging to facilitate volume measurement without having to transfer the liquid to another container, implementation of handling program by the company.
Australia	Restricted use. Only terrestrial application. Under reassessment.
New Zealand	Restricted use. Only terrestrial application.
European Union	Prohibited since 2009, but the import of products with residues of this herbicide is allowed.
Switzerland	Prohibited since 1983.
Norway	Prohibited. Voluntary cancellation of the products.
Japan	Restriction in the concentration of the product.
Bosnia-Herzegovina	Prohibited.
Indonesia	Use for certain crops only by professionals with special permission.
Kuwait	Prohibited since 1985.
Cambodia	Prohibited since 2003.
Laos	Prohibited since 2010.
Arab Emirates	Prohibited since 2005.
Syria	Prohibited since 2005.
South Korea	Prohibited since 2012.
Philippines	Restricted use.
China	Prohibited. Cancelation of the registrations and production in 2014. Production allowed only for export. Use permitted until 2016.
Sri Lanka	Prohibited.
Columbia	Aerial application is prohibited.
Uruguay	Restricted use. Only products with packages of 1 to 30 liters and with dye are allowed.
Belize	Restricted use. Only terrestrial application.
Chile	Restricted use. Aerial application is prohibited.
Costa Rica	Restricted use. Aerial application is prohibited.
Jamaica	Restricted sale.
Ivory Coast	Prohibited since 2004.
Cape Verde	Prohibited since 2011.
Senegal	Prohibited since 2011.
Nigeria	Prohibited since 2011.
Mauritania	Prohibited since 2011.
Mali	Prohibited since 2011.
Republic of Chad	Prohibited since 2011.
Burkina Faso	Prohibited since 2007.
Guinea Bissau	Prohibited since 2011.
Gambia	Prohibited since 2011.
Malaysia	After the period of restricted use, there is currently registration only for formulations with concentrations of 100 g/L

Restricted use: use is allowed but with restrictions (limited concentration of the active ingredient, exclusively terrestrial application, application exclusively by accredited persons, among others).

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Paraquat was prohibited in the entire European Union (EU) after judicial determination that contested the decision of the reassessment by the European Commission in maintaining the use of this active ingredient (UE, 2007). The reasons that led the Court to remove Paraquat from the list of authorized products were:

1) Existence of studies in scientific literature relating Paraquat to Parkinson's disease that were not considered in the reassessment;
2) The reassessment concluded that there was no neurotoxicity but did not satisfy all the necessary process requirements;
3) There was no assessment of a French study on the occupational exposure considered relevant;
4) In a Guatemalan study, the exposure of one of the operators was 118% above the permitted level, although he was using the product in the appropriate conditions;
5) The French study used as basis to allow the use of Paraquat, in its conclusions, warnings about the use of back sprayers in the application of products, reinforcing the doubts regarding the conclusion of harmlessness of the use of Paraquat-based products.

Although the use of Paraquat is prohibited in the EU, the export of products to the EU with the same maximum levels of residues considered acceptable before the decision to not include this active ingredient in the list of authorized products.

According to the contributions from Syngenta, representative of the Paraquat Task Force, products made with this active ingredient are registered and sold in various developed and developing countries around the world, including in major agricultural markets under demanding regulatory systems like the USA, Canada, Australia, Japan and New Zealand.

According to Syngenta, Paraquat is currently registered and sold in the following countries: Angola, Honduras, Peru, Antigua and Barbuda, India, Philippines, Argentina, Indonesia, Rwanda, Australia, Iran, Samoa, Bahamas, Iraq, São Tomé e Principe, Bangladesh, Israel, Singapore, Barbados, Jamaica, Solomon Islands, Belize, Japan, South Africa, Bolivia, Kenya, Saint Christopher and Nevis, Brazil, Kiribati, Saint Lucia, Cameroon, Madagascar, Saint Vincent and the Grenadines, Canada, Malawi, Sudan, Chile, Malaysia, Suriname, Marshall Islands, Tahiti, Colombia, Mauritius, Taiwan, Cook Islands, Mexico, Tanzania, Costa Rica, Morocco, Thailand, Cuba, Myanmar, Tonga, Dominica, Namibia, Trinidad and Tobago, Dominican Republic, Nauru, Turkey, Ecuador, New Zealand, Tuvalu, El Salvador, Nicaragua, Uganda, Ethiopia, Nigeria, Uruguay, Fiji-Niue, USA, Grenada, Pakistan, Vanuatu, Guatemala, Panama, Venezuela, Guyana, Papua New Guinea, Vietnam, Haiti, Paraguay, Zambia.

2. National Status

According to the contributions made by the Ministry of Agriculture, Livestock and Supply (MAPA), Paraquat is registered for weed control in pineapple, cotton, rice, banana, potato, coffee, sugarcane, citrus, kale, beans, apple, corn, rubber tree, soybean and wheat crops and it is also authorized as a drying agent for cotton, rice, potato, sugarcane, corn and soybean. In addition to these crops, there is a monograph for avocado, asparagus, beet, cocoa, coconut, pasture, pear, peach, sorghum (post-emergency and drying agent). Fifteen Paraquat-based technical products and twelve formulated products are registered as observed in tables 2 and 3.

Table 2. List of Paraquat-based technical products registered in Brazil.

Trademark	Registration Owner	Registration
Alamos Paraquat Technical	ALAMOS DO BRASIL	8314
CHN Paraquat Technical	ALLIERBRASIL AGRO LTDA.	11312
Helm Paraquat Technical	HELM DO BRASIL MERCANTIL LTDA	3808
Rainbow Paraquat Technical	RAINBOW DEFENSIVOS AGRÍCOLAS LTDA.	2513
Sinon Paraquat Technical	SINON DO BRASIL LTDA.	07805
Zeneca Paraquat Technical	SYNGENTA PROTEÇÃO DE CULTIVOS LTDA.	0678498
Paraquat Technical 500	STOCKTON - AGRIMOR DO BRASIL LTDA.	2108
Paraquat Technical ZY	ALLIERBRASIL AGRO LTDA.	11712

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China Paraquat Technical	ALLIERBRASIL AGRO LTDA.	11212
Syngenta Paraquat Technical	SYNGENTA PROTEÇÃO DE CULTIVOS LTDA.	014507
Paraquat Technical Yn	ALLIERBRASIL AGRO LTDA.	11112
Ouro Fino Technical DCP	OUROFINO QUÍMICA LTDA	9814
Alta Paraquat Dichloride Technical	ALTA – AMÉRICA LATINA TECNOLOGIA AGRÍCOLA LTDA.	12414
Nufarm Paraquat Technical	NUFARM INDÚSTRIA QUÍMICA E FARMACÊUTICA S.A.	8914
Atanor Paraquat Technical	ATANOR DO BRASIL LTDA.	9214
CCAB II Paraquat Technical	CCAB AGRO S.A.	6916
CCAB Paraquat Technical	CCAB AGRO S.A.	13315

Table 3. List of Paraquat-based formulated products registered in Brazil.

Trademark	**Registration Owner**	**Registration**
Laredo	HELM DO BRASIL MERCANTIL LTDA	13309
Orbit	SINON DO BRASIL LTDA.	2010
Tocha	STOCKTON - AGRIMOR DO BRASIL LTDA.	13208
Gramocil	SYNGENTA PROTEÇÃO DE CULTIVOS LTDA.	1248498
Gramoxone 200	SYNGENTA PROTEÇÃO DE CULTIVOS LTDA.	1518498
Helmoxone	HELM DO BRASIL MERCANTIL LTDA	14908
Paradox	SINON DO BRASIL LTDA.	5006
Pramato	AGROLI INDÚSTRIA QUÍMICA LTDA.	396
Gramoking	RAINBOW DEFENSIVOS AGRÍCOLAS LTDA	6115
Quatdown	RAINBOW DEFENSIVOS AGRÍCOLAS LTDA	5815
Sprayquat	RAINBOW DEFENSIVOS AGRÍCOLAS LTDA	5915
Nuquat	NUFARM INDÚSTRIA QUÍMICA E FARMACÊUTICA S.A.	1216
Flak 200	CROPCHEM LTDA	11415

* Access to Agrofit (http://agrofit.agricultura.gov.br/agrofit/principal_agrofit) on 06/08/2016.

The contributions made by MAPA in the CP no. 94 of 2015 are presented below and allows a deepening of the discussion on the existence of substitutes and on the importance of Paraquat-based products in Brazil. These contributions were made based on the technical positions of Embrapa and other researchers that considered the resistance aspect of weeds and maintenance of direct planting as relevant to justify the maintenance of the Paraquat registration.

According to the Researcher Fernando Adegas (Embrapa Soja), Paraquat is important for the stability of the agricultural reproduction system, which may be put at risk with the banishment. The use of Paraquat-based products occurs mainly on soy crops, performed in eight Brazilian states by medium-sized and big farmers that use advanced production systems and with high technology. There are still no plants resistant to Paraquat in Brazil and this has allowed it use as an alternative to fighting against Glyphosate-resistant weeds. The Glyphosate-resistant weeds are present in over 15 million hectares of agricultural area and distributed among the main brazilian agricultural producing states: they have already reached the states in the South (RS, SC, PR), Southeast (SP, MG), Central West (MS, MT, GO, TO), Northeast (BA, PI) and North (MA), which is considered very disturbing to MAPA.

A registered company sent to MAPA a study conducted by Agricultural Engineer Prof. Dr. Alexandre Medonça de Barros (consultant of MB Agro and professor at the School of Economics of the Getúlio Vargas Foundation) in 2015 on the impact in the direct losses and in the production chain of soybean. This same study was sent to Anvisa during the Public Consultation made by the Paraquat Task Force. The major losses mentioned by this study were:

a) Deceleration of the productivity gains of soybean crop in Brazil.
b) Limitations to the use of transgenic crops tolerant to glyphosate (all the current varieties of transgenic soybean).
c) Limitations to the adoption of direct planting.
d) Increase in the use of herbicides and operating cost of its application.
e) Reduction of the production value and profitability of the farmer.
f) Negative effects on the socioeconomic conditions of the population.

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g) Reduction of tax collection.
h) Reduction of exports and lowest increase of the commercial balance of the country.
i) Increase in the environmental impact of soybean crop with the reduction of direct planting area and increased use of herbicides and machinery.
j) Low soil protection (increased erosion) and increased emission of carbon due to the reduced direct planting area.
k) Low planting speed, hindering the use of the best soybean sowing season and delaying the planting of second corn crop (associated to higher climatic risk).
l) Reduction of the competitiveness of the Brazilian soybean farmer in relation to farmers of other countries, with possible reduction of the Brazilian share in the global production.
m) Low food supply with increase in the production costs of meat and oils.

This same study showed that the potential impacts on the economy are significant, able to reach a reduction of about R$27 billion in Gross Value of Production (GVP), with loss of two million jobs and reductions of R$25 billion in labor income and R$4.7 billion in tax collection (Barros and Hausknecht, 2015).

The direct planting technique is considered fundamental by MAPA and the Task Force for the country's agriculture and an excellent substitute of the traditional farming system because it is based on the principles of sustainability with social, economic and environmental dimensions, integrating productivity increase, reduced use of fossil fuels, increased atmospheric carbon sequestration and reduced oil erosion (Freitas and Landers, 2014). Other advantages to farmers and to the environment were mentioned in the CP and were included in table 5.

Table 5. Advantages in the use of Paraquat to the environment and farmers presented by MAPA in the CP, according to the study of Barros and Hausknecht (2015).

Advantages to farmers	Advantages to the environment
Efficient control of weeds. Rapid action. Safe for use on registered crops. Allows more than one crop per crop season. Protects soil fertility. Increases productivity. Prevents workers from performing manual weeding. Higher quality of life to the worker.	Reduces soil erosion. Increases organic matter in the soil. Reduces the emission of carbon gas. Increases soil biodiversity. Aids in preserving the quality of the water. Avoids the use of harrowing and plowing.

MAPA and Task Force also mentioned the Program for Reduction of Greenhouse Gases in Agriculture (ABC Program) as the main strategy for the mitigation and adaptation to climate changes for the sustainable development in agriculture, whose work was coordinated by the Presidential Staff, by MAPA and by the Ministry of Agrarian Development (MDA), with active participation and representation of the civil society. The objectives are to reduce the emission of greenhouse gases originating from agricultural activities with the following actions: direct planting system; reduction of deforestation; increase of agricultural production on sustainable bases, crop-livestock-forest integration, animal waste treatment; adaptation of rural properties to environmental legislation; expansion of cultivated forest area; and stimulation to the recovery of degraded areas.

The ABC Program is funding the adoption of direct planting in 8 million hectares until 2020. Seventy percent of the grain production area (83 million hectares in 2030) should adopt the direct planting system and prioritize the use of varieties and crops that perform biological nitrogen fixation.

The Task Force also reported in its contributions some advantages of using Paraquat in direct planting:

a) Increase of the organic mater in soil, with consequent reduction of carbon in the atmosphere;
b) Reduction of carbon gas in the atmosphere (sequestration of 0.15 to 1.7 tons of carbon/ha/year);
c) Increase in productivity;

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d) Reduction of the use of diesel oil and consequent release of greenhouse gases;
e) Reduction of erosion with consequent reduction of the contamination of water bodies and silting;
f) Reduction of water loss in the soil;
g) Greater use of nutrients by plants.

MAPA emphasized that it, Anvisa and Ibama, as competent federal authorities in the assessment of pesticides and similar products, have the important role in the society of reaching a balanced decision that provides the farmer with tools to produce while seeking food safety and protecting human health and the environment, based on the best science available internationally and using the risk assessment considering the brazilian reality, always promoting good agricultural practices, as well as the responsible and safe use of these inputs. MAPA believes that Paraquat is a very important product to the Brazilian agriculture, not only in the control of infesting plants but for it being a tool with unique and fundamental characteristics for direct planting, aiming at environmental preservation with the control of soil erosion and avoiding loss of fertile soil and silting of lakes and rivers.

MAPA also clarified that the relevance of Paraquat to direct planting supported the commitments established by the Presidency at the United Nations Framework Convention on Climate Change (COP-21) with the commitment of greenhouse gas reduction. Among the proposed actions is the expansion of the use of Direct Planting System ratified in article 12 of Act 12.187 of October 2009, which establishes the National Policy on Climate Change.

In view of the importance of Paraquat to agriculture in Brazil, the suggestion made by MAPA in the CP was to proceed with the occupational risk assessment to identify the scenarios with unacceptable risks and apply the mitigation measures based on these results. This aspect will be discussed in the topics below because the relevance of this assessment should be made specifically for each toxicological aspect.

Like MAPA, the Brazilian Confederation of Agricultural and Livestock (CNA) recognizes the importance of Paraquat to the Brazilian agribusiness for being used on crops of high relevance to the Brazilian economy and for being responsible for the success of the Direct Planting System, a practice that reduces the emission of carbon in agriculture. As a total-action herbicide, it is one of the main options for handling the pre-seeding operation of plantations performed in direct planting, being an important product for the maintenance and expansion of this planting system in Brazil. Direct planting is a practice the revolutionized the Brazilian agriculture by proposing a more conservational farming that drastically reduces soil erosion compared to the conventional farming.

At the 15th Conference of the Parties, of the United Nations Framework Convention on Climate Change (UNFCCC), the Brazilian government disclosed the voluntary commitment to reduce the emissions of greenhouse gases by 2020. One of the proposed actions is the expansion of the use of direct planting in straw. Paraquat has a broad action spectrum and therefore acts rapidly and in different climate conditions as is the case of Brazil. In the contributions, the importance of this pesticide in locations with plenty of rain was highlighted. It also highlighted the need to not base the prohibition of this active ingredient on decisions made by other countries since Brazil has edaphoclimatic, soil and weed particularities, with the lack of alternatives as efficient as Paraquat to avoid losses. Brazil is a country with different climatic conditions and there is the need for a wider diversity of alternatives for pest control.

According to the report cited by MAPA and the Task Force in their contributions on the biological and economic aspects of the use of Paraquat in Brazil (Adegas and Osipe, 2015), the prohibition of this active ingredient in the utilization modalities will cause farmers to have an average annual increase of R$ 407,672,429.53, representing an expenditure of 129.25% higher than the annual cost with the use of Paraquat due to the need to use alternative herbicides for drying, perennial crops and direct planting (Carfentrazone, Chlorimuron, diquat, 2,4-D, flumioxazin, glyphosate, ammonium glufosinate, saflufenacil, ametryn, bromacil+diuron, flazasulfuron, among others). Regarding the number presented in the report, it is worth highlighting that there are some errors in the calculations made, where the expenditure increase would be about 100% of the current cost.

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Although the calculations overestimated the percentage increase of the average production cost with the use of other herbicides, the value of 100% continues to be high and represents almost double the exposure in the case of cancellation of the registration of Paraquat-based products. These values were obtained from the mean value of different substitute herbicides, thus the choice of cheaper products does not represent a very significant increase in costs. Furthermore, this study considered crops with permission in the monograph but for which the Task Force favorably manifested the cancelation in order to reduce the cases of acute intoxication. The Task Force represented by Syngenta emphasizes its contribution that, during the years, various crops were being removed to reduce the intoxications of small farmers. The Task Force also proposed the discontinuation of various crops to minimize the access to Paraquat and proposed maintaining the use of the herbicide only in cotton, rice, banana, potato, coffee, sugarcane, citrus, beans, corn, soybean and wheat crops and as a drying agent of sugarcane, soybean and potato. However, various crops removed by Syngenta still have established use in the monograph, requiring the review of their permanence since the Task Force warned about the need for their discontinuation.

Diverging from the proposal of the Task Force in the CP to withdraw the use for some crops, MAPA highlighted the importance of Paraquat to small farmers, stating that there was no alternative with the same efficiency and cost.

The Task Force also presented a study on the economic impact of the registration cancellation of Paraquat-based products in Australia, considering the different scenarios. This Australian study is more compete than the Brazilian report that was presented, but both studies have converging results and foresee an increase in production cost, increase in the resistance to Glyphosate, loss of productivity, reduction of production yield, unemployment, reduction in export, increase in expenditure with herbicides and manual labor and loss of soil structure.

The presentations of the Task Force, MAPA and the Embrapa researcher Dr. Fernando Adegas at the panel of experts observed all these arguments used in the contributions in CP no. 94 of 2015, reaffirming the agronomic and economic importance of Paraquat to Brazil and discussing some exposure mitigation measures. In the Panel, in addition to the previously presented measures, the Task Force only added the proposal of intensifying the training projects of the health professionals, the industry and the applicator.

MAPA also indicated that the removal of Paraquat from the market will compromise the competitiveness of the Brazilian agriculture. Among the main agricultural benefits of the use of paraquat, MAPA cited the following:

a) Conservation of soil humidity, erosion reduction and consequent improvement in its nutrition and structure;
b) Early harvest with better use of the land and greater yield to the farmer;
c) Use of the ideal planting window for the subsequent crops, resulting in greater productivity;
d) Sustainable handling of tolerant and resistant weeds;
e) Preservation of the direct planting system and low carbon agriculture, reduction of risks and increase in income to the farmer;
f) Competitiveness of the Brazilian agriculture and livestock production in the international market.

Dr. Fernando Adegas especially highlighted the importance of Paraquat due to the need for diversification of herbicides in chemical handling, concluding that:

a) Paraquat is an important alternative to the handling of weeds resistant to other herbicides, especially to Glyphosate;
b) As a total-action herbicide, Paraquat is one of the main options for handling the pre-seeding in direct planting, being important for the maintenance and expansion of this planting system in Brazil;
c) There is no specific substitute for Paraquat, which is why the handling of weeds will be compromised by the non-use of the product, with likely increase in the quantity of herbicides in the systems where it is currently being used;
d) The problems with voluntary plants should increase with the increase of crops resistant to herbicides. Even though Paraquat is registered for this purpose, it is one of the most promising products in the control of these infesting plants.

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It can be observed that the discussion on the prohibition of Paraquat is very complex and deserves attention, because many contributions highlighted the problems that would be faced with the cancellation of the registration of Paraquat-based problems related to the agronomic impacts (lack of substitutes, problems with weed resistance, difficulty in pest control, increased use of other herbicides), economic impacts (loss of productivity, increased production cost, negative impacts on neighboring countries) and environmental impacts (impossibility of direct planting, increased soil degradation, increased emission of CO_2). Furthermore, the need for reconciliation between the permanence of Paraquat-based products in the market and the mitigation of the health risks was constantly emphasized. The main measures proposed for this reconciliation to be possible were:

a) Risk assessment;
b) Intensification of the inspection of sales and use;
c) Monitoring the use;
d) Intensification of the monitoring of the wastes;
e) Maintenance of the registration until the existence of substitutes;
f) Incentive to register substitutes;
g) Sale with electronic agronomic prescription control linked to pre-application and post-application assessment reports;
h) Assessment of the efficiency of possible substitutes;
i) Training, qualification and orientation programs on the use;
j) Accreditation of applicators;
k) Prevention of the development of resistance with the implementation of alternative handling;
l) Restriction of the use (perennial crops, packages of 1L, aerial application, back spraying, maintenance of only mechanized application, maintenance only for pre-planting of annual crops, limitation of the quantity of product use to one or two crop seasons);
m) Review of the pack insert, with inclusion of relevant information;
n) Training of health professionals;
o) Restriction of the sale to rural farmers;
p) Monitoring of acute intoxications;
q) After sales follow-up by the company to monitor the handling;
r) In-depth analysis of the regulatory impact.

1. Acute Toxicity

In various contributions of CP no. 94 of 2015, a review of the cases of acute intoxication by Paraquat was requested, indicating the need for analysis of the relevance of uncommon accidental cases where Paraquat was used for a non-allowed purpose, such as to kill lice, or in cases of intoxication that occurred in unforeseen situations, such as a fallen airplane and the presence of fire during application of the product. Just like the cases of intoxication resulting from voluntary ingestion, these uncommon accidental cases occur from the incorrect use of the product or from unforeseen accidents and, therefore, cannot be determining factors for the banishment of the active ingredient, but should be the focus of preventive actions.

Besides pesticides, many other products can be used incorrectly and cause irreversible consequences to health, but this is not sufficient reason for them to be prohibited. Generally, many chemical products, when used incorrectly, enable the appearance of severe clinical manifestations different from the clinical effects expected from the suitable occupational use. Therefore, the concern should be on the need to prevent the accidental cases, voluntary ingestion and incorrect use.

When the occupational intoxications are analyzed, it is observed that there are cases of severe acute intoxication in exposed workers but they are mostly due to incorrect use: failure to use individual protection equipment, suction of the pesticide with the mouth, prolonged use of clothes with spilled Paraquat, failure to wash the body after dermal contact with the pesticide, use of the product even after the occurrence of dermal injury.

The issue to be raised is whether there are efficient ways of preventing acute intoxications resulting from misuse, since we know the Brazilian reality and know that the

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adhesion to the use of IPE is extremely low and that applicators in general have low instruction and knowledge. In view of the serious complications that the use of Paraquat represents both from occupational exposure and from accidents and voluntary ingestions, it would be essential, in case it is maintained, to elaborate an acute intoxication prevention plan with monitoring mechanisms that is able to confirm that this plan is successful.

The contributions received in the Public Consult no. 94 of 2015 allow the assessment of the national scenario in relation to intoxications by Paraquat in some locations in Brazil. According to the data of the Toxicology Information Center of Santa Catarina (CIT/SC), sent with the contribution in the CP and referenced in the works of the University of Santa Catarina (Santello, 2009), it was observed that the intoxication by pesticides from 2003 to 2014 corresponded to about 6% of the cases of intoxication at CIT/SC, of which only 3.9% of these occurred due to exposure to Paraquat. The number of cases of intoxication by Paraquat is relatively small; however, form the total number of deaths by pesticides, 29% occurred from intoxication by Paraquat. The lethality of Paraquat is high since 23% of the cases of intoxication resulted in death.

This condition is more disturbing when only cases of suicide attempts are considered. It is observed that between 2003 and 2014, a total of 111 cases of suicide attempts by Paraquat were attended to at CIT/SC, of which 48% resulted in death, that is, the lethality of Paraquat significantly increases when only the suicide data is used. From the total of 58 cases of death by Paraquat intoxication, 53 cases occurred from suicide attempts, one due to an abortion attempt, two cases were accidental and one case had its cause ignored. In other words, during this period there was no record of any clearly occupational case that resulted in death and, as explained by Santello (2009), all the occupational cases were cured.

In the Technical Reassessment Panel for Paraquat, Dr. Lígia Fruchtengarten presented important data from the Intoxication Control Center of São Paulo (CCI/SP) of 2015, showing that from the 7,273 registered cases of intoxication only 1.04% was related to the use of agricultural pesticide. From 2006 to 2015, the intoxications by Paraquat corresponded to about 5% of the total cases of intoxication by agricultural pesticides (65 cases). Among the intoxications by Paraquat, 43 cases were suicide attempts (65%), 11 cases were occupational exposure (16%) and 8 cases were accidental (14%). The other three cases were of unknown cause. From these 65 cases of intoxication by Paraquat, twelve resulted in death and three patients recovered completely. The other 50 cases had unknown prognostics. The CCI/SP data showed that there was a very similar standard in the cases of intoxication by Paraquat in all the CITs, of which lack of data and low notification is a general problem that significantly compromises this assessment.

Dr. Lígia Fruchtengarten also presented some data from DATATOX, which shows the occurrence of 50 cases of intoxication by Paraquat in 2014 and 83 cases in 2015. From the cases of 2015, eleven were accidental (13%), 23 were occupational (28%) and 49 were suicide attempts (59%). From these 83 cases, 16 resulted in death, all from suicide attempts. There was only one case of severe intoxication after occupational exposure. The other accidental and occupational cases resulted in mild to moderate intoxication.

The contribution received by the coordinator of the Intoxication control center of the Antônio Pedro University Hospital of the Fluminense Federal University also showed that the severe intoxication by Paraquat is more common in suicide cases. Between January 2009 and November 2015, ten cases of intoxication by Paraquat were notified out of a total of 7,065 cases (6.8%). Six cases were suicide attempts, two cases were accidents involving children and two were occupational accidents. Three of these cases resulted in death, all from suicide, but one was likely associated to cocaine overdose (patient presented sudden cardiac arrest in less than 24 hours after exposure). This contribution highlighted that the kerosene sold without any restriction also caused death by accidental ingestion of two children, Bupropion was responsible for three suicidal deaths and the number of deaths by other pesticides was five, all suicidal, including some with low toxicity. Furthermore, lead was responsible for eight deaths (one accidental case, one homicidal and six suicidal), in other words, despite the cancellation of the registration of Aldicarb-based products, other substances were incorporated in the lead, which continues to be the means of committing suicide.

As can be observed in the presented data and as discussed by Dr. Lígia Fruchtengarten in her contribution to CP no. 94 of 2015, and in her presentation at the

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Technical Reassessment Panel for Paraquat, the severe cases of intoxication by Paraquat notified and monitored at the intoxication centers generally result from the ingestion of Paraquat-based products in suicide attempts, for which there is really no specific antidote.

In view of the high number of suicidal deaths by Paraquat ingestion, various contributions received during CP no. 94 of 2015 considered it a priority to establish suitable strategies to avoid this type of death. The major strategy mentioned as efficient was the reduction of the access to this pesticide since changes in the concentration of addition of emetics has not proven to be efficient in reducing the deaths after ingestion. However, the intoxication data presented by the Intoxication Centers in CP no. 94 of 2015 showed how incoherent it would be to prohibit the sale of Paraquat exclusively due to the fact that it is associated to suicide attempts, because it is event that other pesticides or even other types of products are as important as it in the number of death cases and measures are not taken to prohibit their sale.

As explained by Dr. Lígia Fruchtengarten in her contribution to CP no. 94 of 2015 and in the Technical Reassessment Panel for Paraquat, the discussion on suicide should be addressed more comprehensively by the health system and should involve other aspects, including the social problems. It is also necessary to consider that the banishment may not improve the death rates by suicide, only force the use of another means. In other words, before making an extremely restrictive decision, it is necessary to create effective strategies in the prevention of cases of intoxication by Paraquat based on methodologies supported by internationally respected entities like the World Health Organization (WHO). The World Health Organization has a suicide prevention guide that indicates which alternatives should be adopted to reduce the cases of deaths. These alternatives will be discussed later in this opinion.

The participants of CP no. 94 of 2015 also showed concern with the lack of efficiency of the treatments for intoxications by Paraquat and with the lack of scientific background of the protocol proposed by the Task Force. Regarding the proposed protocol, it is worth highlighting that there is actually a scientific background but there is no consensus regarding its efficiency due to the shortage of data available. On the other hand, various contributions mentioned the need to standardize the treatment protocol in order to obtain greater efficiency with the use of measures that are newer and with greater treatment potential than some interventions currently performed, and also because a single guideline will allow the measurement of results in a more uniform way. The need for standardization and measurement of the efficacy of this protocol was addressed both in the CP and at the panel of experts.

With the contributions of the CP and with the discussion promoted at the Technical Reassessment Panel for Paraquat, it is observed that various isolated proposals have been made during the last decades for the treatment of intoxication by Paraquat, with the aim to reduce the absorption and impact of tissue lesion, especially the progressive pulmonary fibrosis. The elimination measure with extracorporeal removal by hemodialysis also proved to be efficient, but only if performed very early during the first hours after ingestion, which is not compatible with the reality of our health system. In general, there is a consensus on the great challenge of the treatment of severe intoxications by Paraquat and the need to try and improve the prognostics of the patients. Regarding this necessity, the reviews of the most recent literature indicate a possible treatment with positive results in the associated use of corticoids, immunosuppressants and N-acetylcysteine, but there is still the need for analysis of more results to conclude its efficiency. Protocol based on these evidences was proposed by the Task Force for Paraquat to be implemented as standard in the treatment of intoxications because it could be of greater contribution in the recovery attempt of patients than the practices adopted without any systematization.

In the Technical Reassessment Panel for Paraquat, Dr. Lígia and Dr. Sérgio Graff also highlighted the existence of few specific antidotes in the treatment of majority of the severe intoxications, such as the case of Paraquat. Even when available, the access in Brazil is difficult. The alternative in majority of the cases is a suitable support and decontamination treatment. Therefore, the penta-conjugate treatment protocol proposed by the Task Force may bring positive results, better than the current results, in the treatment of intoxicated patients. Furthermore, it was discussed that the local intervention for the treatment of workers and health professionals that treat these patients is of extreme importance to reduce the risk of exposure and improve the quality of the treatment.

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Regarding the problems faced in the treatment of severe intoxications by Paraquat, Dr. Lígia Fruchtengarten emphasized that there is considerable lack of knowledge by the health professionals regarding the severity of the intoxication and the need for early treatment in the intoxications by Paraquat, requiring the training of health professionals; there is also difficulty in the transfer of patients to hospitals of greater complexity and Specialized Dialysis Units. There is also low local availability of the qualitative test for confirmation of the diagnosis and the serum level for quantitative control of the intoxication cases, as well as lack of activated charcoal and medication suggested in the conjugate treatment at the health facilities (immunosuppressants, antioxidants and N-acetylcysteine). Other challenges for the assessment of the success of this protocol are the need to monitor the treatment until the final evolution of the cases of intoxication and the fact that there is still insufficient number of cases to assess the results of the proposed treatment.

The existence of an antidote or efficient treatment for acute intoxications by Paraquat is not considered. The clinical protocol presented by the Task Force cannot be considered efficient because it is not capable of reversing the intoxication condition of a patient to an acceptable healthy condition, and there is no reliable data on the reduction of the mortality of intoxicated patients. According to the report filed by the Task Force on June 29, 2015, the high mortality resulting from intoxications by Paraquat associated to the fact that there is no specific antidote or treatment is admitted, showing the need to seek for a more efficient treatment, which would be this proposed protocol. The treatment addressed in the report does not present any innovation in relation to what is already known in scientific literature, it only proposes a new approach, seeking to concomitantly treat or prevent the symptoms of various actions of Paraquat in the body. however, this protocol has not generated a treatment that can guarantee that the intoxicated patient will have real and great chances of recovery and, meanwhile, it is not considered an efficient treatment to revert the clinical condition of sever intoxication. If the broad action antidotes were sufficient to revert the severe intoxications by Paraquat it would have then been possible to consider that an efficient antidote or treatment existed.

In the contributions, many argued about the concept of antidote, but it would not be plausible for the entity responsible for the health of the population to accept such a broad concept of antidote for intoxications by pesticides because people's lives must be preserved an antidote or treatment can only be considered efficient when it is able to revert the prognostics of death for at least majority of the cases of intoxication. Efficient treatment is that which favorably influences in the recovery of the patient, producing desired effects and, in the case of a severe intoxication such as one resulting from Paraquat ingestion and that leads to death, the desired effect is for at least majority of the cases to be reverted and for patients to not die or have severe and disabling aftereffects, reducing the quality of life.

Despite the shortage of specific antidotes, in general, the prognostics of intoxications by Paraquat improved considerably with the advances in the other treatment phases. However, severe intoxication by Paraquat is highly lethal even when these treatments are used. In the contributions of the Task Force, this concern is clear when it is said that "the systemic symptoms, involving liver and kidney failure, are self-limited and reversible, with the pulmonary fibrosis phase, when installed, is considered irreversible and responsible for the lethality of the cases of intoxication by oral route". Therefore, despite the efforts to standardize a treatment protocol for those intoxicated with Paraquat, there is still no efficient antidote or treatment for severe acute intoxication by Paraquat generally resulting from suicide.

The treatment protocol proposed for severe intoxications cannot be considered efficient; however, the cases where the patients present severe symptoms or those that result in death are mostly related to intentional ingestion of the product to attempt suicide. Normally, the dermal, eye and inhalatory routes are unable to produce severe systemic conditions such as those observed by intentional ingestion and exposure should be avoided with the use of IPE. Should intoxication occur through these routes, it tends to be recoverable and develops towards being cured. Therefore, considering the real possibility of intoxication by the product when used for agricultural purposes, according to the established correct use, the severe acute intoxication is not common and the cases of acute occupational intoxication tends to be either moderate or mild, with efficient antidotes and

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treatment capable of reversing these types of damages to health resulting from occupational exposure to Paraquat-based products.

The contributions also highlighted the inclusion of warnings on labels and pack inserts warning about the danger, warnings against the transfer of the product to other packages and the inclusion of an indicative dye of substance improper for use as food or undesirable smell to warn the user, in addition to the inclusion of an emetic agent.

1.1. Prevention of cases of suicide by Paraquat

Some contributions received in the Public Consultation no. 94 of 2015 highlighted the importance of the prohibition of the product based on the cases of suicide. The suicide cases should a constant concern to the health system. As can be observed in the Mortality Information System of DATASUS, Brazil has a suicide rate of about 5 cases/100 thousand inhabitants, lower than the global rate (11.4/100 thousand inhabitants) and lower than the rate of South Korea (24.8/100 thousand inhabitants) or Japan (19 cases/100 thousand inhabitants); nevertheless, it continues being a high rate. The data in Brazil are very disturbing especially when the rates of the States are analyzed individually because it is observed that they are very high in some states like Santa Catarina (13.2/100 thousand inhabitants) and Rio Grande do Sul (19.5/100 thousand).

According to WHO, the countries should establish strategic suicide attempt prevention plans involving a number of coordinated measures to enable the reduction of the cases. Limiting the access to the means used to commit suicide attempt is only one of the various actions that should be taken (WHO, 2012).

WHO discusses that the restriction to access is a key element in the prevention but it emphasizes that the restriction policy, such as limitation of access to pesticides, requires a clear understanding of the method preferences among the various susceptible groups and the cooperation and collaboration between various public and private sectors of the society in an integrated and synergistic action (Who, 2012). It also reinforces that to take any measure in order to reduce the rate of suicides, it is necessary to have deep knowledge of the prevalence, characteristics and methods used because the suicidal behaviors are very different between the communities. Furthermore, the prevalent suicide method in a community may change rapidly and spread.

The access restriction is a key element in the prevention because it provides the individuals with the opportunity to reflect on their actions. However, restriction requires detailed understanding of the suicide methods used by the community. Among the actions cited by WHO as efficient is the limitation of the access to pesticides. It is worth highlighting that WHO does not recommend the banishment of the pesticides but the limitation of their use in order to hinder the obtainment of pesticides during the moment of despair (WHO, 2012).

Pesticides represent 30% of the deaths by suicide in the world and WHO defends that restriction measures would be very efficient for these cases, being easier to prevent this type of suicide with restrictive measures than the cases of hanging, for example.

According to WHO, the prevention of suicide requires many coordinated measures:

a) Mental health policy;
b) Policy for reduction of the excessive use of alcohol;
c) Suitable access to health facilities for the treatment of mental disorders and disorders resulting from drug abuse;
d) Restriction of the access to the methods used by the community for suicide attempt, editing of laws and national and local regulation.
e) Responsive reports in the media;
f) Increase in awareness campaigns on health disorders, drug abuse and suicide.

In the reassessment of a pesticide, Anvisa's role is to observe in which of these measures it should intervene in order to contribute in the reduction of the rates in Brazil. The restriction of the means used to commit suicide includes the reduction of availability, accessibility and attractiveness. Regarding the access to measures of restriction of the access to pesticides, WHO mentions the following measures as relevant:

a) Ratification, implementation and application of international conventions on chemical products and hazardous wastes;

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b) Legislation to remove locally problematic pesticides;
c) Compliance with the regulations on the sale of pesticides, reducing the access through safer storage and correct elimination, reduction of the toxicity and improvement of medical care.

Therefore, taking measures to limit the access to pesticides can help avoid more deaths by suicide. However, this action should be combined with other important measures.

A publication cited in the public consultation as relevant for showing reduction of the number of suicides in South Korea deserves a detailed discussion, considering the recommendations of WHO regarding how the prevention of suicide should be conducted (WHO, 2012; Myung et al., 2015).

According to Myung and collaborators, suicide is a very serious problem in South Korea, with the third highest rate in the world (24.8/100 thousand inhabitants). Paraquat was the most widely used pesticide for suicide in South Korea (35.5% of the deaths), causing strong concern in the country because it is a pesticide with high mortality rates. Myung and collaborators (2015) correlated the rate of suicide reduction to the prohibition of Paraquat in the country, because a significant reduction was observed in the suicides by intoxication with herbicides and fungicides soon after the prohibition. There was also significant reduction in the total suicide rate with the same standard. The reduction of these rates was explained by the fact that the use of Paraquat in suicide attempts resulted from impulsive acts; without the product available in the market, the person sought other ways that are generally less deadly.

The approach made by Myung and collaborators (2015) is relevant but some considerations should be classified because they highly weaken the association made in this publication. The reduction was observed immediately after the prohibition of Paraquat, during the period when its sale was still allowed. The author assumes that this occurred because the availability to consumers was reduced since farmers started storing Paraquat-based products. This hypothesis was raised by authors but there is not enough information to reach this conclusion. Furthermore, the study was conducted assessing the rates of suicide attempts by pesticides in a general manner and not the rates of specific suicides for Paraquat, which would have been essential to observe the sale soon after the prohibition. It is also necessary to consider that the prohibition of Paraquat is related to the change of the suicide prevention policy that occurred during that time, encouraging debates and prevention actions, which may have had a direct impact on this reduction in the rate of suicide attempt.

In addition to the considerations above, the analysis of these results should consider some other aspects because the authors themselves mentioned that other factors may have aided this reduction. Firstly, the authors discussed that the increased rate before the prohibition of Paraquat could have been associated to the concomitant financial crises in the country. Therefore, just like the increase in the rate of suicide attempt coincided with the emergence of the financial crisis, its reduction occurred concomitantly with the economic recovery of South Korea. In other words, it is plausible that these changes in the rate of suicide attempts had a higher correlation with the Korean financial crises than with the prohibition of Paraquat. The authors also mentioned various fragilities of this study: unknown factors were not accessed and considered in the statistical analysis, the time of analysis was too short, there was no investigation of the long-term effects of substitutes and it was not possible to access specific data on Paraquat.

In view of the above regarding suicide and the need for intervention through restrictive measures for access to Paraquat-based products, it is first necessary to assess the profile of suicides by Paraquat in Brazil and consider this data to propose regulatory measures. Damas and collaborators (2012) assessed the suicide attempt data in Santa Catarina, State with the second highest rate in Brazil. Between 1994 and 2006, it was observed that 55.7% of the suicide attempts occurred from the use of medication, 33.7% were pesticides, 5.2% were household cleaning and industrial chemical products and 3.5% were from drug abuse. It is worth highlighting that in 2006 it was already possible to observe a very different profile, with the use of medication in suicide attempts being more than twice the use of pesticides.

The epidemiological profile outlined by Schmitt and collaborators (2008) on the suicides in the extreme west of Santa Catarina showed a change of the means used, which

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fits in the manifestation of WHO that changes in the preference method are constant. In the study of Schmitt and collaborators (2008), hanging occurred in over 70% of the cases for both men and women, the use of fire arm occurred in 9% for women and 13% for men and the ingestion of chemical substances was used by 11% of the women and 5% of the men. For this analysis, the ingestion of any substance was included in the cases of intoxication (pesticides, drugs, household cleaning products, among others). This standard was discussed as being very curious by the authors of the study because predominant economic activity in the extreme west of SC is based on agriculture and the use of pesticides in suicide attempts was expected to be the predominant method, but this was low. Meneghel and collaborators (2004) also observed that hanging was the major method used in the suicide attempts in Rio Grande do Sul (state with the highest number of suicides) in the period between 1980 and 1990. Fire arm appeared in second place. Drugs and unspecified means appeared in third place and sharp instrument appeared in fourth place.

The proposition of restrictive measures should also consider the actions with this same objective proposed by other countries. With the aim to reduce the cases of intoxication by Paraquat, USEPA published on March 2, 2016 the Public Consultation on its proposal for mitigation of intoxications by Paraquat (USEPA, 2016a). USEPA discussed that paraquat is extremely dangerous, the corresponding ingestion of 1.5 teaspoons being fatal and without any known antidote. It also considered that Paraquat-based products are associated to a disproportionally high number of incidents of intoxication, including accidental ingestions, typically fatal, as well as severe or moderate occupational exposure (spilling, splashes and leaks) after skin or eye contact. All the information on incidents available since 2000 were reviewed, observing during this period 27 deaths (11 intentional, 8 accidental, 2 intentional/accidental, 2 resulting from drifts, 3 without information); 22 severe intoxications (4 accidental ingestions. 0 occupational, 1 suicide attempt, 1 drift, 7 without information); 181 moderate (mainly occupational) and 352 mild (USEPA, 2014). Based on the number of incidents and on the severity of the cases, USEPA believes that the mitigation measures proposed are necessary for the continued registration of Paraquat-based products (USEPA, 2016b). It is worth emphasizing that Paraquat is still being reassessed by USEPA and the draft should be published in 2017 for comments. According to USEPA, all the measures proposed were discussed with the registrants of the technical products. Among the measures proposed by USEPA are:

a) Changes in the labels emphasizing the toxicity of Paraquat and availability of additional warning leaflets.
b) Development of education and handling projects and training materials for users of Paraquat-based products.
c) Adoption of a closed system in the packaging.
d) Restriction of the use of Paraquat to certified applicators, prohibiting application by workers monitored by the certified applicator.

In order to propose these measures, USEPA conducted an economic impact analysis and observed that the changes on the labels should not cause any negative impact, but the change to the closed packaging system will cost about 500 to 700 dollars per user, which means a total of 12.5 to 17.5 million dollars. The prohibition of manual application was not estimated because it will not be accurate due to the non-availability of data. The restriction of use to certified people will increase the costs by 1.3 million dollars and the development of training material will involve costs of 3100 to 4700 per registrant (USEPA, 2016c).

The concentration reduction of the product to 5% was one of the measures suggested to USEPA (USEPA, 2014). Presently, the Paraquat-based products have a concentration of about 30% and the ingestion of only 15 mL is enough to kill an adult man of 70kg. If the products had a concentration of 5%, the ingestion of 30 mL can theoretically be considered non-lethal. The company argued that the production, storage, transport and application of the volume of product necessary to achieve same application dose used presently would be impossible. Besides the economic unfeasibility, the company argued that this measure may not represent an increase in the survival rates after intoxication due to the high toxicity of the product (Dixon and Wells, 2014).

Nagami and collaborators (2013) also concluded that the adoption of the concentration reduction of the products is not a very significant strategy because they discovered that, although Japan had reduced the concentration from 24% to 5% of Paraquat

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in the products, the mortality rate by suicide remained the same at about 80%. In view of these justifications, USEPA did not adopt this measure in its proposal. On the other hand, the Canadian regulatory agency PMRA (Health Canada's Pest Management Regulatory Agency) considered that the results in Japan showed an improvement in the death scenario by Paraquat intoxication and decided that in Canada the concentration of Paraquat in the final product will be reduced to a concentration lower than the lethal concentration or lower than the concentration that causes serious damages to the eyes or skin. The application rate will continue to be the same, thus there will be no increase in exposure (PMRA, 2015).

This measure adopted by PMRA is one of the various actions that determined by the Canadian agency after the reassessment of Paraquat in the country. In the reassessment conducted by PMRA, all the chronic risk information was reviewed and the points considered relevant were the potential risk of effects in health resulting from accidental exposure during occupational use and the occupational risk of back application. Among the measures proposed by PMRA are:

a) Inclusion of Paraquat in the restricted class: use exclusively by certified/licensed applicators;
b) Changes in the label including additional IPEs, warnings of danger and treatment;
c) Prohibition of mixing in tanks used for other pesticides;
d) Reduction of the concentration of Paraquat in the end-use product;
e) Change of the packaging with the addition of a mechanism to measure the volume required for application;
f) Education and handling program that includes information to vendors and users on the new risk mitigation measures and on the importance of complying with the recommendations of the label, as well as on the prevention of accidental exposure.

1.2 Occupational Exposure

Occupational exposure was discussed in the Technical Reassessment Panel for Paraquat and in some contributions of CP no. 94 of 2015, especially by health professionals and by the Task Force. In her contributions to the CP and panel, Dr. Lígia Fruchtengarten emphasized that in dermal or eye effects or lesions may occur in occupational exposure when the individual protection precautions appropriate for application of the product are not observed and that only skin lesion and significant increase of the absorption of Paraquat are expected when there is prolonged skin contact.

The Task Force and some other participants from CO also claimed that acute intoxication with Paraquat through dermal administration is not relevant and the cases are restricted to inadequate use of the products. However, it is important to point out that there is no consensus about the importance of cutaneous absorption during occupational exposure to Paraquat. Both USEPA and PMRA have already confirmed that although the studies in animals show low dermal absorption, the data in humans indicate that they are more sensitive to Paraquat in chronic exposure, resulting in bigger damage to skin and higher systemic absorption of this herbicide (PMRA, 2015; USEPA, 2016b). I.e., the studies of cutaneous absorption in animals do not characterize the toxic potential of Paraquat for human health adequately and thus, occupational exposure shall be a concern of the regulatory agencies. That is why, PMRA and USEPA have sought strategies to minimize the exposure of workers. PMRA, despite of reporting higher sensitivity of the humans, concluded that the daily exposure of the workers is minimum in Canada, because the use of IPE [*Individual Protection Equipment*] would be sufficient to protect them even during manual spraying for the treatment of oat (the only culture, for which use of Paraquat-based products in this modality is allowed). USEPA, as detailed above, intends to keep the product register, but has proposed quite restrictive measures.

Paraquat Technical Reassessment Opinion No. 1 dated 2014, supported by discussions either in the scientific literature or of other regulatory agencies, has already concluded the same about the intoxication of workers exposed to Paraquat, and even after the contributions received in CP No. 94, dated 2015, it is considered that occupational exposure cannot be based on damages to the skin or dermal absorption of Paraquat obtained from studies in animals. Thus, the discussion of the toxicological aspects and the proposals for mitigation measures shall take the evidences of higher human sensitivity to dermal exposure Paraquat with possibility of relevant systemic absorption through this administration route into consideration.

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Initially, the Task Force presented some proposals to mitigate the risk of occupational exposure to Paraquat, such as:

a) Intoxication monitoring program with expansion of the number of CITs;
b) Maintenance of the safety elements in the products (emetic, drying and odorizing agents);
c) Training of agricultural workers with emphasis on prevention from occupational exposure, storage and recommendations in case of ingestion;
d) Training of community agents for monitoring of psychiatric diseases;
e) Medical seminars prioritizing regions, where there are records of death due to intentional intoxication;
f) Distribution of activated charcoal, Dithionite test and treatment protocol folder kits in reference hospitals;
g) Educational programs in partnership with rural development program services;
h) Adoption of the Paraquat Safety Plan (detailed hereunder);
i) Use restrictions;
j) Using 0.5% of the funds for educational and handling programs.

Many of these measures can be efficient and necessary for the reduction of the cases of intoxication; however, it is essential to present more detailed planning containing clear indicators of effectiveness for the follow-up of such measures, in case it is concluded to keep the Paraquat-based products on the market.
One of the concerns regarding the occupational exposure pointed out in Technical Reassessment Report No. 01 was the results observed in the models for prediction of the exposure to the Paraquat-based products, because the exposure to this active substance would extrapolate the proposed AOELs (acceptable occupational exposure levels) (Pesticide Safety Directorate, 2002) and this would be unacceptable considering the severe toxic effects of Paraquat and the signs of induction of Parkinsonism, discussed in more details in item 3 herein. The Task Force presented some relevant arguments both in its contribution to CP and in the Technical Reassessment Panel and therefore, it was necessary to discuss this aspect more deeply.
During the reassessment of Paraquat in the EU, it was verified that there was AOEL extrapolation using several models of exposure prediction, as already discussed in Reassessment Opinion No. 01. However, EFSA committee responsible to reassess Paraquat concluded that the results of the field monitoring studies indicated that the prediction models overestimated the actual exposure of the workers exposed to Paraquat and that there was no significant risk to the workers´ health when the products were used as recommended and according to the good agricultural practices (Pesticide Safety Directorate, 2002).
After the EFSA decision to maintain the registers of Paraquat-based products, some countries from the EU protested against this opinion, indicating several studies, in which it would be possible to identify worrying exposure of works and confirming the results of the exposure prediction models. The discussion made by Sweden against the decision of the EFSA committee was considered relevant and was used as grounds for the position adopted in Paraquat Technical Reassessment Opinion No. 1; however, the Task Force presented contra-arguments and therefore, the monitoring studies were reviewed as it can be seen in chart 2 (EU, 2007).
During the reassessment of Paraquat in the EU, the disagreement of some countries in relation to the EFSA conclusion about the occupational exposure was based mainly on observation that the doses of Paraquat obtained in these monitoring studies exceeded the proposed AOEL. However, it was later verified, by conducting new studies, that the initially proposed value for AOEL could be increased based on the toxicological evidences. Thus, from the analysis of the monitoring studies, it can be concluded that they actually do not reveal exposure above the AOEL; however, it is evident that there is potentially relevant exposure to Paraquat, especially when the IPE is not used correctly.

Chart 2. Studies for monitoring exposure to Paraquat

SWAN, 1969 - Malaysia (1965) - Backpack application in rubber tree plantations. - Gowning: shirt or T-shirt, long trousers, socks and closed shoes. Washing of the body before and after application. - Period of exposure 12 weeks (6 times a week): approximately 2600 gallons. - Paraquat detected in all workers´ urine at least at some period along the exposure (78/134 urine samples). - Symptoms: testicle dermatitis, scaling on the hands and the ears, severe epistaxis. - The highest concentration of Paraquat detected was 0.32 ppm, but the bigger part was lower than 0.1 ppm.	- Detection of Paraquat in the urine of exposed workers, but not using IPE.

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SWAN, 1969 - Malaysia (1967) - Backpack application in rubber tree plantations. - Gowning: a group with common clothes (shirt or T-shirt, long trousers, socks and closed shoes, washing the body before and after application) and a group with IPE (boots, gloves and face mask). - Period of exposure 12 weeks (6 times a week): approximately 1800 gallons. - Paraquat detected in quite lower number of samples than in the study dated 1965 (53/394), but it was applied at lower quantity. - Symptoms: testicle dermatitis, scaling on the hands and the ears, nose bleeding. - The highest concentration of Paraquat detected was 0.15 ppm. - Higher percentage of the urine samples positive for Paraquat was found in the workers, who used common clothes (18 to 50%). The use of IPE reduced the percentage of positive samples to 7 to 14%. - Symptoms: dermal irritation, urticaria, genitals dermatitis, dermal lesion, epistaxis.	- It is possible to detect Paraquat in the exposed workers´ urine, even when they use IPE. - There is an expressive reduction of the detection of Paraquat in urine, when IPE is used.
STAIFF et al.; 1975 - USA - Spraying in orchards by tractor or backpack spraying in gardens. - Body exposure determined by means of absorbing paper and washing the hands after the application. - Inhalation measures by specific filters in the breathers. - Gowning: without IPE (tractor). - Urine samples taken during and after exposure. - Low dermal and respiratory exposure. - Higher exposure of the hands. - The dermal exposure varied from 0.01 to 3.4 mg/h for tractor application and from 0.01 to 0.57 mg/h for application in gardens. - No Paraquat was found in the urine samples. - Limit of detection 0.02 ppm.	- The assessed scenarios are not compatible to the backpack application in field culture, which enables detection of Paraquat in other studies; - Higher limit of detection than the limit of other studies, which verified Paraquat in the exposed workers´ urine. - Lack of sensitivity of the analytical method.
WOJECK et al., 1983 - USA - Tractor application of Paraquat in tomato and citrus cultures. - Gowning: long or short sleeved shirts, long trousers, socks, closed shoes or boots. Many workers used hats. - The use of closed cabin or high clearance tractor reduced the exposure by about 85%. - Paraquat was found in the urine of one worker only (0.033 ppm). - Limit of Detection: 0.012-0.041 ppm.	- Limit of detection higher than the limit in the studies, which verified Paraquat in the exposed workers´ urine. - Lack of sensitivity of the analytical method.
CHESTER et al. 1993 - Sri Lanka. - Broth preparation, tank supply, manual backpack sprayer application in tea plantation. - Paraquat quantification in urine at every 24 hours (broth preparation and spraying) by radioimmunoassay. - Gowning: short-sleeved shirt, pants or shorts, no socks and no closed shoes. Frequent washing habit. - Urine collected one day before the first application up to seven days after the last application (total of thirteen days). - Exposure quantification measured by the recovery of Paraquat in overalls with hood, gloves and socks. - Amount and concentration of Paraquat in spraying solution lower than usual backpack sprayer applications. - Paraquat detection limit in urine is 0.03 µg/ml. - Paraquat was not detected in any urine sample.	- Detection limit higher than the limit of studies, which found Paraquat in the urine of exposed workers. - Lack of sensitivity of the analytical method.
MEIER, 1995 - USA. - Application of Paraquat using an open cabin tractor in pecan orchards. - Gowning: Long clothes, boots and gloves. - Paraquat detected in the urine of 6/17 workers on the exposure day. - Paraquat excreted quickly (2 to 3 days). - Paraquat detected in urine at concentrations of 6 ng to 26 ng/mL. - The average exposure to Paraquat was 0.0002 mg/kg bw/day. - Limit of detection: 0.005 µg/mL. - Higher absorbed amount: 0.00044 mg/kg bw/day, in a worker who did not used the IPE properly.	- Nine operators did not use IPE or gloves. - Paraquat values in blood and in urine indicate doses with values between 0 and 60% of AOEL. - Average exposure corresponds to 28% of AOEL. - Only workers who did not use the IPE properly had values of Paraquat in urine close to AOEL.
BERNA et al., 1996 - Costa Rica - Backpack sprayer application in banana plantations. - Dermal exposure measured by means of absorbent papers, respiratory exposure by personal air samples and systemic exposure by urine samples - Gowning: some used long clothes and gloves. Everyone used boots. - Symptoms: bubbles on the skin; burns on the hands, thighs, back, testicles and legs; redness, irritation and burning sensation in the eyes, problems with nails and epistaxis. - Dermal exposure varied from 0.2 to 5.7 mg/h. - Areas with higher levels of dermal exposure: wrists, back and legs. - Inhalational exposure varied according to the day and dermal exposure varied according to the type of plantation.	Paraquat was detected in the urine of two out of the ten monitored employees, no use of IPE.

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- Paraquat limit of detection in urine is 0.03 µg / ml. - Paraquat detection only in two urine samples from two workers (higher level 0.24 µg / L)	
FINDLAY et al., 1998 - Spain (1997). - Backpack sprayer application in citrus orchards. - Broth preparation, supply and manual backpack sprayer application of 15L Paraquat during 6 hours (one day). - Broth preparation and supply gowning: long clothes, boots, rubber gloves and facial visor. - Broth and preparation supply gowning: simple long overall and boots. - Urine collected at every 24 hours for seven days, the collection started on the day before the first application. - Limit of detection: 0.00075 µg/mL - Paraquat detected in the urine of 18/20 of workers after application for 4 or 5 days. - The paraquat values in urine ranged from 7.90 µg/mL to 262 µg/ml. - Average absorbed dose: 0.00015 mg/kg bw/day. The highest dose absorbed was 0.00041 mg/kg bw/day - Total elimination of Paraquat within 72 hours maximum, only one worker showed Paraquat in urine until the 5th day.	- The use of gloves could reduce the number of samples with Paraquat as well as the detected levels. - Absorbed dose was lower than AOEL for all workers, even using less IPE than recommended. - The rate of dermal exposure was also similar to that found in other occupational studies. - The highest amount of Paraquat detected in urine corresponds to absorption of 56% of AOEL.
LEE at al., 2009 - Costa Rica (2001). - Urine was collected from 119 Paraquat handlers (backpack sprayer application) and 59 non-manipulators, who also worked on the cultures. - Coffee culture gowning: long clothes and boots, 50% were using overalls and aprons. - Gowning for the cultures banana and palm: overalls, gloves, respirator and apron. - Paraquat quantification limit in urine: 2 ng/mL. - For the manipulators, 83%, 47% and 64% of the urine samples were lower than the quantification limit before, during and after spraying, respectively. - The culture, for which workers had higher levels of Paraquat in urine samples was the banana, followed by coffee and finally, palm. - The average quantity of Paraquat in urine for exposed workers was 6.3 µg / 24 h. - There was no variation in the level of Paraquat regarding the type of activity performed (mixing, loading, application or maintenance of equipment).	Paraquat detection in urine, even when using IPE.

Based on the new AOEL, Syngenta presented risk assessment for the use of Paraquat-based products, using the American database – PHED (The Pesticide Handler Exposure Database) to estimate the exposure of the exposed workers. The scenarios were selected according to the Brazilian reality, seeking data in Brazil, which could also ground this risk assessment. The simulations were carried out using less IPE than the recommended on the package inserts of the products in Brazil. To determine the non-observed adverse effect level (NOAEL = 0.56 mg/kgbw/day), a 90-day study in dogs (more sensitive species) was selected, in which lesions in the lungs and the kidneys were observed. The company pointed out that this period can be considered conservative, because the time of exposure of the workers in field would be much shorter, because the Paraquat-based products are not applied continuously. As the oral absorption of Paraquat is lower than 80%, the company carried out a bioavailability study, in order to determine the oral absorption factor for the correction of the systemic NOAEL, resulting in NOAEL = 0.073 mg/kg bw/day. Thus, there was increase in the AOEL value to 0.00073 mg/kg bw/day. Using this AOEL for risk assessment, there was no extrapolation of the scenarios by the PHED prediction model as it can be noted in the chart below (chart 3). All exposure scenarios, according to a study presented by Syngenta, presented values below AOEL. It shall be pointed out that the simulation was made with less IPE than the recommended in a package insert in Brazil.

Chart 3. Percentage of daily dermal exposure to Paraquat in relation to AOEL for the PHED scenarios

PHED Scenario	IPE	% AOEL
Liquids, open system, broth preparation, tank supply, air application.	Simple clothing (long shirts, long pants made of simple cotton, socks and shoes) WITH gloves resistant to chemical products.	59.8
Liquids, open system, broth preparation and tank supply, application by closed cabin tractor with bar.	Simple clothing WITH gloves resistant to chemical products.	7.2
Liquids, open system, broth	Simple clothing WITH gloves	14.5

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preparation and tank supply, application by closed cabin tractor with bar.	resistant to chemical products.	
Liquids air application (fixed wing/closed cabin)	Simple clothing WITHOUT gloves resistant to chemical products.	13.0
Application by open cabin tractor with bar.	Simple clothing WITH gloves resistant to chemical products.	4.4
Application by closed cabin tractor with bar.	Simple clothing WITHOUT gloves resistant to chemical products.	3.1
Liquids, broth preparation and tank supply, application by backpack sprayer.	Simple clothing WITH gloves resistant to chemical products.	17.9

From the results from exposure prediction and the results from the monitoring studies, Syngenta concluded that the occupational exposure does not present unacceptable risk to the workers. However, the regulatory agencies have adopted measures to reduce exposure to Paraquat even more, because they do not consider that the initial register already contemplates all measures necessary for the mitigation of the risks of Paraquat to health. For example, USEPA and PMRA recently proposed the adoption of more restrictive measures to reduce exposure to Paraquat even more, because there are cases of occupational intoxication, which shall be mitigated and the exposure of human beings seems to be more relevant that that of animals used as models in the toxicological studies.
Furthermore, the monitoring studies reveal that Paraquat can be absorbed in doses, which, despite of not exceeding AOEL, are worrying due to the evidences associating this active substance to Parkinsonism, and it is difficult to affirm that the currently accepted AOEL is a safe limit in relation to the effects of Paraquat on the dopaminergic neurons pursuant to exposure along the workers´ life. This subject will be deeper discussed later in a specific topic.

In many monitoring studies, additional clinical exams were made, including hematological and biochemical exams, to assess the hepatic and the renal function, as well as pulmonary functional tests, concluding that the use of Paraquat under normal conditions (including without the use of IPE) does not represent a serious risk to the workers´ health in relation to these analyzed aspects. Therefore, it is not considered that Paraquat might cause severe intoxication in workers from the analysis of these monitoring studies, as well as from the case studies and the Brazilian data from the intoxication centers, as well as the data from Agrotoxline reported by the Task Force. However, it shall be pointed out that Parkinsonism will be further detailed and shall be assessed separately from the other toxic aspects of occupational exposure, because depending on the evidences, it might represent a higher risk to the workers´ health and, as precaution, it might need much more restrictive measures, although the studies currently demonstrate that exposure to Paraquat is below the level stipulated as safe.

1.3. Paraquat Product Safety Program (PPSP)

PPSP proposed by the Task Force includes different actions, which together could be used for the reduction of the cases of intoxication by Paraquat. For the execution of such actions, the Task Force proposed using 0.5% of the sales of the Paraquat-based products.
One of the proposed actions within this plan is monitoring of the intoxications, in order to determine measures to reduce the currently observed indexes. The proposal of the Task Force is to use Agrotoxline, an intoxication notification system exclusively for pesticides implemented by Toxiclin in July 2012 for monitoring of intoxications; five public toxicology centers are part of this system: Centro de Controle de Intoxicações de Londrina, Centro de Informações Toxicológicas do Rio Grande do Sul (Porto Alegre), Centro de Controle de Intoxicações de São Paulo (Jabaquara), Centro de Informações Anti-Veneno da Bahia – CIAVE (Salvador) and Centro de Informações e Assistência Toxicológica (Brasília).
In this system, the intoxication survey is done by the trade name and by the active substance of the herbicide. From June 2012 to May 2015, 46 out of the 2,285 cases of intoxication were results from intoxication by Paraquat. 21 of these 46 cases were pursuant to occupational exposure (45.65%), 18 to attempts of suicide (39.13%) and 4 to accidents (8.7%). All severe intoxications and deaths were suicide cases. The cases of occupational exposure included only the intoxications considered moderate or slight. It was also perceived that there is a delay in diagnosis, lack of basic resources in the health units, and little training of the health professionals.

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PPSP proposed by the Task Force is focused on monitoring (by means of the Agrotoxline notification system) and training as an attempt to unify the programs of the different manufacturers. Monitoring is essential to allow the determination of actions and training to be ministered to the users (focused on the correct and safe use, storage, recommendations not to transfer package, use of IPE and hygiene fundamentals), people who recommend (focused on the molecule characteristics, use indications and necessary protection measures) and physicians (focused on diagnosis and treatment).
The trainings proposed by the Task Force are divided in external and internal training. The internal training would be aimed at the people involved in production, commercialization, technical recommendation, marketing and regulatory areas. The external training would involve users, buyers and appliers by means of obligatory online training at the time of purchase and with validity period, as well as training in person, where necessary, in addition to training for the medical class.
The Task Force reports that other measures were taken to reduce the exposure of small producers to Paraquat, such as exclusion of the cultures avocado, asparagus, beetroot, cocoa, tea, coco, pear, peach, sorghum, grapes and pastures in November 2006. In July 2008, the exclusion of the herbicide for desiccation of rice and the dose reduction from 1.5-3.0 L/ha to 1.5-2.0 L/ha were approved, in addition to the exclusion of the application in desiccation of corn and cotton. However, these restrictions were made for the Syngenta products, and the other registering companies should become adequate and the monograph should be updated.
It shall be pointed out that according to contributions made in the documents delivered by the proper Task Force (represented by Syngenta), the Paraquat registration for tea and cotton would be essential. However, Syngenta reports that they excluded these cultures, because they considered that this action is a way to reduce the exposure of the small agricultural producers. According to the proposal of the Task Force, Paraquat will remain authorized only the cultures cotton, rice, banana, potato, coffee, sugarcane, citric fruits, beans, corn, soybean, wheat and as desiccant in the cultures sugarcane, soybean and potato. Furthermore, many contributions from professionals from the agronomy area pointed out the importance to use Paraquat in fallow land, pre-cultivation areas, between the culture rows, picking, track cleaning and desiccation, especially for control of weeds in cultures, such as banana and corn.
Syngenta, representing the Task Force, proposed other regulatory actions as well: exclusion of the application on the cultures pineapple, kale, apple, rubber tree and grapes and elimination of the 1 L package. In the CP contributions, elimination of the 1 L packages and exclusive use on grain and fiber were also suggested. Although the Task Force has proposed the exclusion of the application on apples, in the public consultation, it was mentioned that Paraquat is the only product registered for this culture.

1.4. Education and handling program: Center-South Project for Beans and Corn

g) Place: Paraná
h) Target population: 120 thousand small producers of corn and beans (culture rotation).
i) Period: from 1989 to the present date.
J) Periodicity: Annual
k) Diagnosis: low productivity and yield; soil degradation; inadequate handling of weeds, diseases and plague; low access and incorrect and unsafe use of the agricultural technologies, among which the pesticide.
l) Participants: Syngenta, Emater-PR, Embrapa Arroz e Feijão and Instituto Agronômico do Paraná (Iapar).
m) Participation: 3,000 producers participated in the administrative units and it is estimated that more than 10,000 visit at least one of the more than 200 events held during the year.
n) Description: The project guides the producers about the good practices in all cultivation stages, including about the correct and safe use of pesticides.
o) Results: The project helped increasing the production level of the region above the average for the State, improve the yield for the producer and promote higher quality of life in the region, in addition to reduction of the cases of intoxication by pesticides. Initially, the use of IPE was about 30% and increasing gradually to levels higher than 60%.

Education and handling programs, such as Center-South Project for Beans and Corn, are essential for training of workers involved in the use of pesticides and consequently, for the mitigation of the risks to health associated to the manipulation of these substances. Therefore, considering the high toxicity inherent to Paraquat, the maintenance of the register of this active substance shall be conditioned to expansion and better structuring of projects of this kind, with follow-up of their results by Anvisa.

2. Genotoxicity and mutagenicity of Paraquat

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During the consolidation of CP No. 94 dated 2015, the limitations pointed out in the contributions regarding the studies used in TECHNICAL REASSESSMENT OPINION No. 01 dated 2015/GGTOX/ANVISA were assessed and those considered relevant were included in chart 4 and used for the final assessment of the mutagenic potential of Paraquat.
It shall be pointed out that some of the assessed studies present limitations, which do not make them inconclusive, and it is possible to use their results. On the other hand, some assessed studies presented substantial limitations, which impeded the use of their results in the assessment of the weight of the evidence.
It was verified that *in vitro* study considered valid for point mutation in mammal's cell and the prompt genic mutation studies in bacteria strains are consistently negative, and there was only one positive result for *in vitro* tests in unicellular eukaryote cell. This single result *in vitro* in fungus is not sufficient to conclude on the induction of point mutation by Paraquat.
Four *in vivo* and *in vitro* results in mammal´s cells were negative; however, in fourteen tests, it was possible to see clearly occurrence of mutation of the chromosome aberration type. Some of the studies for assessment of chromosome aberrations in *Drosophila melanogaster in vivo* and in mammal´s cells *in vitro* (test with mouse lymphoma) could indicate occurrence of point mutations; however, they were not carried out in a way to differentiate the parameters, which determine the type of mutation and, as there are no other evidences of point mutation occurrence, they can be used only to give weight of evidence to the induction of chromosome aberration by Paraquat.
Studies in germinative cells were considered inconclusive due to their limitations. However, although currently, there is no evidence proving the potential of Paraquat to induce mutation in germinative cells, it was found that the exposure to Paraquat reaches the testicles affecting the spermatozoids (Rios et al., 1995; D´Souza et al.; 2006). Furthermore, all positive tests presented in chart 4 related to the assessment of genotoxicity grant strong weight of evidence to the observation of induction of chromosome aberrations in somatic cells by exposure to Paraquat.

Chart 4. Summary of the results from the mutagenicity studies for Paraquat.

PARAQUAT MUTAGENICITY					
Reference	Concentration	Type of test	Limitations	Assessed parameter	Result
Report No. CTL/P/243	99%	*In vitro* Ames	-	Point mutation	NEGATIVE
Report No. 20725-2002	45%	*In vitro* Ames	-	Point mutation	NEGATIVE
Benigni et al., 1979	NI	*In vitro* Ames	-	Point mutation	NEGATIVE
Speit et al., 1998	NI	*In vitro HPRT* in lung fibroblasts of Chinese hamster	High cytotoxicity in the higher doses.	Point mutation	NEGATIVE
Report No. CTL/P/442 - 1979	100%	*In vitro* Cytogenetic in rat cells	Paraquat associated to the Giensa stain provoked alterations in the morphological appearance of the chromosomes, which can be confused with chromosome aberrations. This artifact was prevented upon five washings in the cells. No mitotic index was determined.	Chromosome aberration	NEGATIVE
Tanaka and Amano 1989	NI	*In vitro* Chromosome aberration in lung cells of Chinese hamster	Cellular viability was not assessed, but the concentration used was compatible to that of other studies. Gaps were accounted for. Lack of positive control.	Chromosome aberration	NEGATIVE
Report No. CTL/P/442 - 1979	100%	*In vivo* Micro-nucleus in mice	Paraquat associated to the Giensa stain provoked alterations in the morphological appearance of the chromosomes, which can be confused with chromosome aberrations. This artifact was prevented upon five washings in the cells. No mitotic index was determined.	Chromosome aberration	NEGATIVE
Report No. CTL/P/1369	33.7% (ion)	*In vivo* Micro-nucleus in mice	The decrease of the PCE/NCE ratio was very small and it occurred only at the highest dose. I.e., it is not possible to be sure that the substance reached its target. Only two doses were used, and dose-response analysis	Chromosome aberration	NEGATIVE

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			was not possible. Lower doses would be perfect.		
Benigni et al., 1979	NI	*In vitro* Resistance to 8-azaguanine in *Salmonella typhimurium*	High toxicity in higher doses.	Point mutation	INCONCLUSIVE
Moody and Hassan, 1982	NI	*In vitro* Ames	Number of revertants expressed according to the survival (revertants/ 10^8 survivors); it does not enable assessing whether the increase is due to mutagenic action or cell death at higher concentration.	Point mutation	INCONCLUSIVE
Study RF-3252.401.182.04 - 2005	50%	*In vitro* Ames	The correct doses were not used, and there were number of doses with cytotoxicity lower than the recommended in the OECD guidelines.	Point mutation	INCONCLUSIVE
Osch et al., 2010	NI	*In vivo* Point mutation in *harlequin* mice	Increase considered small by the author himself, without dose-response assessment.	Point mutation	INCONCLUSIVE
Cantavenera et al., 2007	NI	*In vitro* Ames	Carried out only with one strain. Without dose-response curve.	Point mutation	INCONCLUSIVE
Report No. CTL/P/1560 - 1987	33.7% (ion)	*In vivo* Cytogenetic in rats Alpk: AP	Negative history unacceptable, because the reference is from a poster presented in a conference. The aberration count data per animal was not presented, but the average percentage of cells, without standard deviation. Not all doses were tested in 12 h, only the highest dose. All doses were tested only in 24 h. The highest dose was tested in 48 h. The number of metaphases analyzed per animal (50) was lower than the recommended (200).	Chromosome aberration	INCONCLUSIVE
Report No. CTL/P/367 - 1978	100%	*In vivo* Cytogenetic in rats	The mitotic index was not determined. Morphological alterations in the chromosomes make analysis of the chromosome aberrations difficult. The number of metaphases analyzed per animal (50) was lower than the recommended (200).	Chromosome aberration	INCONCLUSIVE
Ribas et al., 1997	99%	*In vivo* Micro-nucleus in human lymphocytes	The lymphocyte donors´ age is not described. The treatment period was 2 h, and the recommended period is from 3 to 6 h. Number of analyzed cells lower than the recommended.	Chromosome aberration	INCONCLUSIVE
Ribas et al., 1997	99%	*In vivo* Chromosome aberrations in human lymphocytes	The lymphocyte donors´ age is not described. The treatment period was 2 h, and the recommended period is from 3 to 6 h. Number of analyzed cells lower than the recommended.	Chromosome aberration	INCONCLUSIVE
Nicotera, 1985	NI	*In vivo* Chromosome aberrations in fibroblasts of Chinese hamster	Reduction of the mitotic index in the highest concentrations. Inclusion of gaps in the analysis.	Chromosome aberration	INCONCLUSIVE
Cantavenera et al., 2007	NI	*In vivo* Chromosome aberrations in V79 cells	Cytotoxicity was not described. Increase not statistically significant.	Chromosome aberration	INCONCLUSIVE
Anderson et al., 1976	NI	*In vivo* Dominant lethal in mice	Interval between doses longer than the recommended	Point mutation in germinative cells	INCONCLUSIVE
Pasi et al., 1974	NI	*In vivo* Dominant lethal in mice	The study was carried out at one dose only, it cannot be classified in the that suggested by the OECD protocol. In addition, the number of animals used was small.	Point mutation in germinative cells	INCONCLUSIVE
IRI Report No. 145	23.9%	*In vivo* Dominant lethal	Without increase in embryonic or fetal death in	Point mutation in germinative cells	INCONCLUSIVE

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		in mice	mating from 4 to 8 weeks and without significant difference in the embryonic or fetal death in mating in weeks 1 and 2, but there was a big variation between the groups in the first 3 weeks.		
Report No. CTL/P/1351 - 1985	99.6%	*In vivo* Cytogenetic in humans	Highest dose with 68% toxicity (perfect between 50 and 60%)	Chromosome aberration	POSITIVE
Report No. CTL/P/1398 - 1985	45.66%	*In vitro* Mice lymphoma cells L5178Y	High cytotoxicity doses (less than 20% viability), in which there was increase in the mutation frequency, with impaired interpretation of the data, because it was not possible to assess the mutagenic potential. In test, in which no increase of mutation frequency was observed, perfect cytotoxicity was not achieved as well (quite below the recommended). Shorter exposure (2 h) than the recommended.	Point mutation and/or chromosome aberration	POSITIVE
Gaivão et al., 1999	NI	*In vivo* Eye stain in *Drosophila melanogaster (SMART)*	High mortality in the last dose (40 to 80%). Without valid OECD guideline.	Point mutation and/or chromosome aberration	POSITIVE
Gaivão et al., 1996	NI	*In vivo* Eye stain in *Drosophila melanogaster (SMART)*	High mortality in the last dose (40 to 80%). Without valid OECD guideline.	Point mutation and/or chromosome aberration	POSITIVE
Jovtchev et al., 2010	NI	*In vitro* Chromosome aberration in human lymphocytes	Donors aged between 41 and 52 years. No positive control data was presented. Treatment period 1 h.	Chromosome aberration	POSITIVE
Sofuni and Ichiadte Jr., 1988	NI	*In vitro* Chromosome aberrations in fibroblasts of Chinese hamster	No cytotoxicity and use of positive control are reported. Number of analyzed cells below the recommended	Chromosome aberration	POSITIVE
Lin et al., 1987	45%	*In vitro* Chromosome aberrations in ovarian cells of Chinese hamster	-	Chromosome aberration	POSITIVE
McGregor et al., 1988	NI	*In vitro* Mice lymphoma assay (MLA)	There was no differentiation between small and big colonies, not allowing differentiation of the type of mutation.	Point mutation AND/OR chromosome aberration	POSITIVE
Benigni et al., 1979	NI	*In vitro* Genetic mutation in *Aspergillus nidulans*	Time of exposure inadequate. No use of positive control.	Point mutation	POSITIVE
Torres et al., 1992	99%	*In vivo* Wing stain in *Drosophila melanogaster (SMART)*	Without valid OECD guideline. There was no differentiation between types of stains.	Point mutation and/or chromosome aberration	POSITIVE
Ortiz et al., 2000	> 98%	*In vivo* Micro-nucleus in mice	Intraperitoneal administration. Assessment of a single dose. Number of PCE assessed lower than the recommended.	Chromosome aberration	POSITIVE
Speit et al., 1998	NI	*In vitro* Chromosome aberration in lung fibroblasts of Chinese hamster	High cytotoxicity at the highest doses.	Chromosome aberration	POSITIVE
Melchiorri et al., 1991	98%	*In vivo*	Intraperitoneal administration.	Chromosome aberration	POSITIVE
Melchiorri et al., 1998	98%	*In vivo* Micro-nucleus in mice	Intraperitoneal administration	Chromosome aberration	POSITIVE
D´Souza et al., 2005	~ 100%	*In vivo* Micro-nucleus in rat	Dermal administration. Number of PCE analyzed lower than the recommended. No use of positive control.	Chromosome aberration	POSITIVE
Report No. CTL/P/1339 - 1985	99.6%	*In vitro* Non-scheduled synthesis in rat hepatocytes	Without valid OECD guideline.	Genotoxicity	NEGATIVE

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Report No. CTL/P/1550 - 1987	33.7% (ion)	*In vivo* Non-scheduled synthesis of DNA in rat hepatocytes	Number of animals and cells analyzed per animal lower than the minimum recommended number.	Genotoxicity	NEGATIVE
Speit et al., 1998	NI	*In vitro* Comet in lung fibroblasts of Chinese hamster	High cytotoxicity at the highest doses.	Genotoxicity	NEGATIVE
Wang et al., 1987	45%	*In vitro* Exchange of sister chromatids in ovarian cells of hamsters	Only two concentrations used, and it was not possible to verity the dose-response relation. Without valid OECD guideline.	Genotoxicity	NEGATIVE
Report No. CTL/P/1392 - 1985	99.4%	*In vitro* Exchange of sister chromatids	-	Genotoxicity	POSITIVE
Yamamoto et al., 2001	NI	*In vitro* DNA break	The result does not show action in an intact cell.	Genotoxicity	POSITIVE
Ribas et al., 1995	98%	*In vitro* Comet in human lymphocytes	There is no description of the positive and the run controls.	Genotoxicity	POSITIVE
Dusinská et al., 1998	NI	*In vitro* Comet in lung macrophages and pneumocytes of the type II	Cellular viability was not assessed, but the concentration used was compatible to that in other studies.	Genotoxicity	POSITIVE
Ross et al., 1979	NI	*In vitro* Alkaline elution	-	Genotoxicity	POSITIVE
Tanaka, 2000	NI	*In vitro* Exchange of sister chromatids in lung cells of hamsters	Only two concentrations used, and it was not possible to verify the dose-response relation. Cytotoxicity was not reported, but the concentration used was compatible to that in other studies. Without valid OECD guideline.	Genotoxicity	POSITIVE
Wang et al., 1987	45%	*In vitro* Exchange of sister chromatids in trachea epithelial cells of rat	Only two concentrations used, and it was not possible to verify the dose-response relation. Without valid OECD guideline.	Genotoxicity	POSITIVE
Tanaka and Amano, 1989	NI	*In vitro* Exchange of sister chromatids in lung cells of Chinese hamster	Cellular viability was not assessed, but the concentration used was compatible to that in other studies.	Genotoxicity	POSITIVE
Ribas et al., 1997	99%	*In vitro* Exchange of sister chromatids in human lymphocytes	The age of the lymphocyte donors was not described.	Genotoxicity	POSITIVE
Benigni et al., 1979	NI	*In vitro* Non-scheduled synthesis of DNA in human cells similar to epithelial	-	Genotoxicity	POSITIVE
Petrovska, 1999	NI	*In vitro* Comet assay in HeLa and Hep G2 cells	-	Genotoxicity	POSITIVE
Parry, 1977	PF	*In vitro* Mitotic recombination in *Saccharomyces cerevisiae*	Without valid OECD guideline.	Genotoxicity	POSITIVE
D´Souza et al., 2006	~ 100%	*In vivo* Morphological alterations in germinative cells of rat	Selection of maturation stages did not comprehend all phases.	Induction of morphological alterations in spermatogenesis	POSITIVE
Rios et al., 1995	PF	*In vivo* Morphological alterations in the spermatogenesis in mice	No positive control was used in the assay.	Induction of morphological alterations in spermatogenesis	POSITIVE
Rios et al., 1995	PF	*In vivo* Chromosome aberration in bone medulla cells	No positive control was used in the assay. Inclusion of the number of gaps in the analysis.	Chromosome aberration	INCONCLUSIVE
Salam et al., 1993	PF	*In vitro* Genic mutation *Saccharomyces cerevisiae*	Very low purity. Lack of positive control. The induction of genic conversion, reverse mutation	Point mutation and chromosome aberration	INCONCLUSIVE

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			and mitotic recombination observed only at high concentrations, in which survival is very much reduced. Without valid OECD guideline.		
Nicotera, 1985	NI	*In vitro* Exchange of sister chromatids in fibroblasts of Chinese hamster	Reduction of the mitotic index at the highest concentrations, and only one analyzable concentration was left.	Genotoxicity	INCONCLUSIVE

Legend: PF: Formulated Product; NI: Not Informed; Blue: Negative results for mutagenesis; Red: Positive results for mutagenesis; Brown: Inconclusive results, which do not provide evidence for the mutagenicity classification of the active substance; Purple: genotoxicity tests and/or tests carried out with PF.

Thus, the results from the mutagenesis tests reveal that Paraquat is able to provoke chromosome aberrations either *in vitro* or *in vivo* in different species (*in vitro* in mammals´ and human cells; *in vivo* in drosophila and mammals) and by different exposure routes (intraperitoneal and dermal). This conclusion, although with some small differences, is according to the interpretations of the mutagenesis studies carried out by other international agencies, such as the Food and Agriculture Organization of the United Nations – FAO), the Joint FAO/WHO Meeting on Pesticide Residues – JMPR, USEPA and EFSA.

USEPA reported that Paraquat is weakly positive in a test of mouse lymphoma L5178Y with metabolic activation, inducing mutation in the cells exposed to Paraquat for two hours. Paraquat also presented a positive result with chromosomic damage in human cells in a cytogenetic test with and without metabolic activation and it was positive in the sister chromatid exchange test with and without metabolic activation. On the other hand, Paraquat was not mutagenic in the Ames tests and it was negative for chromosome aberrations in rat bone medulla. It also considered that there was no evidence of mutagenicity in mice in the lethal dominating test and there was no induction of unscheduled DNA synthesis in hepatocytes *in vitro* and *in vivo* (USEPA, 1997).

Regarding *in vitro* genotoxicity of Paraquat, the EFSA Reassessment Committee concluded that it has mutagenic potential in L5178Y cells with metabolic activation, it does not induce unscheduled DNA synthesis in hepatocytes, but it is clearly clastogenic in pulmonary cell of Chinese hamster with and without metabolic activation. Despite of these positive results, the European Union considered Paraquat non-genotoxic *in vivo*, because this substance did not present clastogenic effects in rat and mouse bone medulla cells in a micronucleus test, it did not induce unscheduled DNA synthesis in hepatocytes and there is no evidence of induction of effects in fertility or increase of the incidence of lethal dominating mutations in doses up to 4 mg/kg p. c./day in rats (Pesticide Safety Directorate, 2002). Therefore, EFSA concluded that Paraquat does not present genotoxic risk *in vivo*, despite of the positive results *in vitro*.

However, it shall be pointed out that the assessments made by USEPA and EFSA are old and thus, they do not consider more recent genotoxicity and mutagenicity studies available in the literature.

FAO reported positive results *in vivo* for genotoxicity in a cytogenetic study with human lymphocytes and a sister chromatid exchange test in lung fibroblasts of hamsters, both carried out according to the OECD protocols (FAO, 2003). In addition, JMPR reviewed a big part of the genotoxicity studies and reported that many consistent positive results were obtained in studies for damage to DNA in mammals´ cells (chromosome aberration, cytogenetic studies, chromosomic damages, sister chromatid exchange, unscheduled DNA synthesis and DNA break in comet tests) and concluded that these results indicate in vitro genotoxic potential of Paraquat (Marrs and Adjei, 2003). For JMPR, Paraquat is clastogenic in high concentrations in vitro. JMPR emphasizes that the action mechanism of paraquat includes the generation of free radicals and the oxidative stress and that the non-observation of genotoxic effects in some tests, especially those with low concentrations of the active ingredient, may result from the antioxidant defense mechanism of the body. However, in its report, JMPR makes an exception reinforcing that the *in vivo* tests for micronucleus formation has been positive in mice, one with oral administration and two with intraperitoneal administration and, although the dose used has been considered high, it is possible to conclude that Paraquat can also induce chromosomal damages *in vivo*; however, it has been considered unlikely for it to cause damages to human beings in dietetic concentrations (Marrs and Adjei, 2003).

JMPR is right when concluding that it is unlikely mutations to occur in humans in dietetic concentrations, because it is not expected that Paraquat will leave residues in the food (this discussion shall be approached more deeply later); however, occupational exposure is extremely relevant, because the workers are in direct contact with the product and, as discussed above, dermal exposure is considered a concern by the main international regulatory agencies (USEPA. 2016b and PMRA, 2015).

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The chromosome mutation observed for Paraquat would not be a concern if it occurred only in somatic cells, once the potential to provoke chromosome aberrations does not seem to be associated to any severe chronic event (the results from the carcinogenicity studies did not reveal any significant alteration). On the other hand, the only study available for assessment of the mutagenic potential in germinative cells was considered inconclusive given the low concentration of the active substance (use of commercial product) and the inconsistency of the results (significant difference among some groups, but with big variety of responses). There are also studies assessing the Paraquat action under the morphology of the spermatozoids with clearly positive results. Although the morphological alterations do not enable a definite conclusion about the genotoxic action of Paraquat on the germinative cells, they provide sufficient evidence that the substance reaches the testicles (Yauk et al. 2015).

When there is no conclusive data about the mutagenic potential of a substance, as for Paraquat, it is considered that the effect observed in somatic cells is sufficient to characterize the mutagenic potential of the substance in germinative cells (EU, 2013). IPCS - International Program on Chemical Safety also harmonized its understanding about mutagenicity this way, considering that the substances shall be considered mutagenic for germinative cells, when there are positive results for mutagenic effects in somatic cells *in vivo*, with potential to affect germinative cells confirmed by evidences, which show occurrence of exposure of the germinative cells to the mutagen. In these cases, it shall be assumed that the substance has mutagenic potential for the germinative cells and represents risks to the future generations (Eastmond et al., 2009).

This definition of mutagenicity reflects the current scientific understanding and its normative adoption has been proposed in RDC to replace Ordinance No. 03, dated January 16, 2002 (CP No. 87 dated October 02, 2015). Thus, based on this understanding, it can be concluded with the currently available evidences that Paraquat is mutagenic also for germinative cells, because there is a proof of somatic mutation *in vivo* and the Paraquat action on spermatozoids and there is no consistently negative study proving the lack of mutagenic effect on the germinative cells.

Although Decree No. 4.074 dated January 4, 2002 defines that a pesticide shall be forbidden in Brazil when it is considered mutagenic, able to induce mutation in at least two tests, one of them to detect genic mutations and the other to detect chromosomic mutations (Item V, Art. 31), Law No. 7.802 dated July 11, 1989 determines that it is forbidden to register pesticides, which reveal mutagenic characteristics, according to the results from **up-to-date experiences in the scientific community**. Currently, the concern regarding the mutagenicity of a substance is not restricted to assessment of occurrence of point or chromosomic mutations, because it is important to assess the consequence from the mutation in the somatic and the germinative cells, i.e., its potential effects on the exposed population´s health. In somatic cells, as explained above, there is no great concern about the mutagenic potential of Paraquat, once no important effects have been observed in the chronic carcinogenicity studies. However, it was not possible to discard the mutagenic potential of Paraquat in germinative cells based on the available studies. Thus, severe effects resulting from induction of mutation in germinative cells could place the exposed population´s health at risk. It shall be pointed out that the population considered exposed would be only the rural workers, because it is not expected for Paraquat to leave residues in food.

The relevance of the mutations in germinative cells is evident considering the number of cases of dominating, recessive autosomal genetic diseases related to sex. Many genetic disorders are caused by recessive mutations (cystic fibrosis, phenylketonuria, Tay-Sachs disease, among others). Most of these mutations are inherited and expressed when the recessive genes are received from both parents. New mutations have higher importance in incidence of dominating diseases rather than recessive, because a single mutation is sufficient to express the diseases already in the first generation. For dominating diseases with mild effect, reduced penetrance or manifestations at more advanced age, the contribution of the parental generation seems higher than for new mutations. In addition to the occurrence of inherited diseases, genic mutations in germinative cells contribute to alterations in fertility, including multi-factor disorders with delayed manifestation, such as heart disease, high blood pressure and diabetes. As a difference from point mutations, which are generally inherited from past generations, a big part of the chromosomic abnormalities looks like new mutations in the parents´ germinative cells (Cassarett and Doull´s, 2001). Unlike the somatic mutation, which is generally associated to carcinogenesis, a single mutation in a germinative cell may lead to a big variety of diseases, in addition to being the primary cause of embryonic and fetal death. It is recognized that new mutations in germinative cells contribute to neurological disorders, cancer and many other diseases (Yauk et al.; 2015).

Considering the expose de above, Paraquat shall be considered mutagenic although it induces only chromosomic mutation, because:

I – The analysis of the mutagenicity studies both in the scientific literature and in the tests carried out by the registering companies showed that there is sufficient

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evidence to prove the potential of Paraquat to induce chromosome aberrations in somatic cells *in vitro*, *in vivo*, in different species and by different exposure routes (including dermal).

II – When there is no conclusive data about the mutagenic potential of a substance in germinative cells, as for Paraquat, it shall be considered that the effect observed in somatic cells is sufficient to characterize the mutagenic potential in germinative cells.

III - It was not possible to prove the inexistence of mutation in germinative cells.

IV - Exposure to Paraquat reaches the testicles, affecting the spermatozoids, and provokes somatic mutation *in vivo*, therefore, it is considered that Paraquat is mutagenic for germinative cells.

V - Mutagenic effects in germinative cells lead to severe consequences (alterations in fertility, malformations, embryonic death, neurological disorders, congenital abnormalities, including multi-factor disorders with delayed manifestation, such as heart disease, cancer, high blood pressure and diabetes), representing high risk to the exposed population´s health.

VI - The main international regulatory agencies and the present opinion concluded that dermal exposure of human beings is relevant and most important than animal exposure, therefore, rural workers (exposed population) are susceptible to the mutagenic effects of Paraquat.

VII - Law 7.802 dated 1989 determines that it is forbidden to register pesticides, which reveal mutagenic characteristics, according to the results from **up-to-date experiences in the scientific community**.

It shall be pointed out that the potential to provoke somatic chromosome aberrations does not seem to be associated to any severe chronic event, because the results from the carcinogenicity studies do not reveal any significant alteration. However, as there is no evidence of lack of severe effects for chromosomal mutations in germinative cells, the only alternative not to propose prohibition of the active substance Paraquat, based on its mutagenic potential, would be obtaining of clearly negative results in tests for assessment of the mutagenic potential of Paraquat in germinative cells, carried out according accepted international protocols.

3. Neurotoxicity

TECHNICAL REASSESSMENT OPINION No. 01 DATED 2015/GGTOX/ANVISA concluded that the studies in animals reveal causality relation between the occurrence of effects typically associated to Parkinsonism and the exposure of laboratory animals to Paraquat based on the studies from the literature and the studies presented by the registering company.
However, the Task Force considers that there were no effects related to Parkinsonism after oral administration of Paraquat, even when using doses, which are significantly higher than the doses currently used to determine occupational and dietetic exposure. It also determined that Technical Reassessment Opinion No. 01 dated 2015/GGTOX/ANVISA emphasized a lot the loss of neuronal cells observed in one of the studies with stereological assessment and did not emphasize the other important toxicological parameters (neurochemical and neuropathological). Furthermore, the company argued that in order to be considered important, the loss of neurons should be reproducible. In relation to all these arguments of the Task Force, it shall be clarified that many studies were assessed either in the dossier or in the scientific literature and a big part of them showed clear effects in different parameters related to Parkinsonism and not only neuronal depletion as already discussed in TECHNICAL REASSESSMENT OPINION No. 01 DATED 2015/GGTOX/ANVISA.
The Task Force also argues that only results, which are statistically significant, shall be considered in the analysis, because the effect can only be considered when statistical difference is achieved. Regarding this aspect, it is important to highlight that the assessment of the result from the studies shall take all data available into consideration, in addition to the statistical differences: results from other studies, biological significance, response dose and reproducibility. Actually, the exclusive assessment of these studies would not clearly show a statistical difference and would not be sufficient to conclude about the relation between Paraquat and Parkinsonism. However, statistical trends were observed for some effects in the studies of the registering companies, which, when assessed together with the several results from studies in the scientific literature, provide sufficient evidence to conclude that exposure to Paraquat would lead to characteristic Parkinsonism effects in animal models.
The Task Force also discussed about other aspects they consider insufficient to conclude about the alterations provoked by Paraquat in the nervous system, such as irrelevant exposure route, time of

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exposure, sensitivity of the animal models, dopamine levels found, administered doses. All these aspects have already been assessed and deeply discussed in TECHNICAL REASSESSMENT OPINION No. 01 DATED 2015/GGTOX/ANVISA and therefore, none of the presented arguments change the initial conclusion of the assessment regarding the relation between Parkinsonism and Paraquat in the studies carried out in laboratory animals.

Unlike the affirmed by the Task Force, it cannot be considered that the animal models are poor, according to discussion made by Dr. Estefânia Moreira in the technical panel for assessment of Paraquat and already presented in Technical Reassessment Opinion No. 01 dated 2015/GGTOX/Anvisa, because different effects related to Parkinsonism have been observed by independent research groups.

Among the already observed effects, which relate Paraquat to Parkinsonism, the following can be mentioned: statistically significant decrease of neurons immune-marked for tyrosine hydroxylases (TH) in the substantia nigra (SN) and considerable loss of dopaminergic neurons (25-65%); statistically significant alterations of the motor function; significant induction of oxidizing stress in the brain (activation of microglia, decrease of anti-oxidizing agents, increase of pro-oxidizing markers); reduction of dopamine or alteration in its metabolism; neuronal accumulation of α-synuclein; decrease of proteasome activity (Brooks et al., 1999; Manning-Bog et al., 2002; McCormack et al., 2002; Manning-Bog et al., 2003, McCormack & Di Monte, 2003; McCormack et al., 2005; Ossowska et al., 2005a; Ossowska et al., 2005b; Ossowska et al., 2006; Choi et al., 2006; Fernagut et al., 2007; Purisai et al., 2007; Kang et al., 2009; Somayajulu-Nitu et al., 2009; Kang et al., 2010; Wills et al., 2012). Furthermore, several *in vivo* studies with non-mammals, such as nematodes, fish and drosophila (Jimenex-Del-Rio et al., 2008; Inamdar et al., 2012; Bortolotto et al., 2014; González-Hunt et al., 2014; Cassar et al., 2015) and *in vitro* and *in situ* studies (Choi et al., 2016) provided evidence of effects associated to Parkinsonism resulting from exposure to Paraquat observed in mammals *in vivo*.

It shall be pointed out that although the Task Force insists in arguing that the studies carried out by the group, which the researcher Mona Thiruchelvan took part in, shall be disregarded from the analysis as it has been proven that this researcher changed its test data about Parkinson´s with paraquat; all results of the other researchers from this research group cannot be invalidated. The data corrupted by Mona Thiruchelvan were identified and did not ground the conclusion of the reassessment opinion. It would not be correct to disregard the results of the other researchers for assuming that all of them had been falsified as well. In addition, it is necessary to point out that other independent research groups presented similar results.

From the observations of the experimental studies, it is possible to conclude that the evidenced effects are similar to the alterations observed in patients with Parkinson´s disease, which reinforced the idea that Paraquat is a risk factor for this disease. It shall be emphasized that the design of the experimental studies does not allow establishment of NOAEL for degeneration of dopaminergic neurons and that the brain elimination half-life of Paraquat makes its concentration higher in the brain after repeated administrations (even if in 1-week intervals). In addition, it was found that the brain concentrations achieved after oral and intraperitoneal administration are similar. However, the relevance of these experimental findings in the extrapolation for human beings depends on the analysis of several existing epidemiological studies.

According to the Task Force, the epidemiological studies do not allow concluding that studies with Parkinson´s and Paraquat reveal unacceptable risk to support the recommendation for register cancelation, because it considers that the epidemiological studies are inconclusive. It was argued that TECHNICAL ASSESSMENT OPINION No. 01 DATED 2015/GGTOX/ANVISA did not take important studies into consideration for epidemiological analysis, such as Brent and Schaeffe (2011) and Tomenson and Campbell (2011). It was also argued that the Mandiel´s and collaborators´ study (2012) indicating the faulty issues of the epidemiological studies FAME (Farming and Movement Evaluation Study) by Tanner and collaborators (2011) in relation to the methodological aspects, the different criteria of eligibility for selection of controls, the execution of controls for developing Parkinson´s, the low participation rate, the much higher proportion of interviewed people replaced among cases than in the controls, the substantial differences in the participation rates between cases and controls and the lack of estimations based only on exposure reported at the time of enrolment, has not been assessed.

The Task Force also argues that no robust assessment of the exposure for most epidemiological studies has not been made; however, it mentioned two quite limited studies to prove that there is no relation between exposure to Paraquat and the Parkinson´s disease (Brent and Chaeffer, 2011; Tomenson and Campbell, 2011).

Brent and Schaeffer (2011) assessed the occurrence of the Parkinson´s disease in patients, who recovered or lived for up to thirty days after intoxication by Paraquat. Considering that Parkinson´s is a neurodegenerative disease, with slow and progressive evolution, it cannot be expected that a study with such experimental design would provide any signs of relation between Paraquat and the Parkinson´s disease, therefore, this study has been considered inadequate for discussion of this toxicological aspect in the reassessment of the active substance Paraquat.

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Tomenson and Campbell (2011) carried a study out assessing the mortality of workers in a Paraquat factory by Parkinson´s and other causes; Although the Task Force argues that the authors clearly show that exposure to Paraquat did not cause Parkinson´s in the workers, this study is extremely fragile and was not considered relevant to assess the role of Paraquat in the Parkinson´s pathogenesis. This study included assessment of workers, who worked between 1961 and 1995, and workers, who were followed up until 2009. Different workers with different functions in the factory were included. The study itself mentions that there is limited data about the exposure of the workers, and it is not sufficient to make a quantitative or qualitative assessment of the exposure. The article also reveals that it is likely for the workers to have been exposed to medium or high levels of Paraquat after 1980. Furthermore, the time and the level of exposure are not known. The causes of death have been assessed by means of death certificates, in which it is not expected Parkinson´s to be indicated as cause of death, because the death, even when related to Parkinson´s, could not have been declared as complication of the disease. In addition, many workers might have not had diagnosis of Parkinson´s during their lives and obviously, this would not be reported in the death certificate, where the direct cause of death is stated.

In the contributions to CP, the need to include discussion about the Elbaz and collaborators (2009) study has also been argued; in this study, no association between the Parkinson´s disease and exposure to Paraquat has been found. The authors of the study explain that the observation of this results, which is in conflict with the other epidemiological studies, may have occurred because in France, Paraquat is used mainly as non-selective herbicide to kill weeds around the plantations, resulting in low levels of exposure. In addition, if there is gene-environment interaction, paraquat can be associated to the Parkinson´s disease only in more susceptible individuals. Opposite results have been found by Ntzani and collaborators (2013), who analyzed different epidemiological studies to assess the association of Paraquat to Parkinson´s, and observed that these epidemiological studies indicated such association. Of course, it is inherent to any epidemiological assessment to have some limitations in the assessment made by Ntzani and collaborators (2013), which, although do not invalidate the analysis carried out, impede assertive conclusion about the causality between exposure to Paraquat and Parkinson´s disease. Thus, it would be necessary to include carefully outlines epidemiological studies. For example, in the Ntzani study, it would be important to assess more complete epidemiological studies with detailed description of the use of IPE to assess the reduction of this association, the use of more grounded data than using of questionnaires and the reduction of confusion factors.

Recently, Furlong and collaborators (2015) assessed whether the use of gloves and hygiene habits modify the association between pesticides and the Parkinson´s disease. FAME (Farming and Movement Evaluation) is a case-control study within the Agricultural Health Study (AHS). The use of IPE and hygiene practices were determined by a questionnaire and the use of gloves below 50% of the time and in 50% of the time was separated. High association between the Parkinson´s disease and the use of globes for time below 50% was found out, and this association did not occur when gloves were used 50% of the time. The study did not determine consistent relation between the adoption of hygiene practices and the reduction of the association between Parkinson´s and exposure to Paraquat. The authors discussed that gloves are determining factor for dermal exposure, not using gloves exposes the worker at higher doses of the herbicide. Thus, it can be suggested that in the epidemiological studies, in which no association between Paraquat and the Parkinson´s disease has been found, the results may have been masked by the fact that using IPE is common in the assessed community. The authors also discuss that this results may not be directly pursuant to the use of gloves, but to the adoption of another behavior, because people, who use gloves, trend to handle pesticides in a safer way, reducing their exposure. It shall be pointed out that as any epidemiological study, this study presents relevant limitations, such as the use of a small number of cases (although bigger than that in many studies) and broad confidence interval, among others. Despite of such limitations, the study is considered relevant for analysis in the reassessment of Paraquat.

Regarding the epidemiological results from AHS, among them FAME (Tanner et al., 2011), USEPA clarified at the beginning of its reassessment of Paraquat that these findings will be considered in the reassessment, as well as those, which demonstrate potential relation between exposure to Paraquat and the Parkinson´s disease (USEPA, 2011). AHS is considered a high-quality prospective study with the following strong points: big sample, high response obtained and the fact of being prospective. Among its weak points, the following can be mentioned: very homogeneous sample (white men), lack of knowledge about the frequency of exposure or application, among others.

The results of Tanner and collaborators (2011) and Kamel and collaborators (2007), coming from AHS, reveal that there was an increase in the probability of occurrence of Parkinson´s disease among the workers, who used Paraquat, which supports the experimental toxicological findings (USEPA, 2012). This assessment is still in progress at USEPA and the final conclusion has not been disclosed yet. However, in the public consultation dated March 2, 2016 (USEPA, 2016b), USEPA clarified that for the time being, only cases related to incidents have been assessed. However,

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USEPA pointed out the results from the AHS studies again, explaining that a modest association in relation to asthma or chronic bronchitis had been verified in both AHS studies, considering that the data did not provide strong evidence of such relation; but in relation to Parkinson´s, the probability ratio had been considered high.

Thus, it can be observed that Paraquat has been associated to the Parkinson´s disease in epidemiological studies developed by different research groups and in different populations (Liou et al., 1997; Costello et al., 2009; Tanner, 2011; Kamel, 2007; Furlong et al., 2015) and in recent meta-analyses (Pezzoli and Cereda 2013; Ntzani et al., 2013), although some studies have observed lack of such association (Engel et al., 2001; Hertzman et al., 1994). A conclusive analysis about the causality of exposure to Paraquat in the pathogenesis of the Parkinson´s disease would be possible only by means of development of better outlined epidemiological studies, which may demand a long time. It is important reminding that the limitations of the epidemiological studies may make interpretation of the results difficult due to the possible effects of confusing factors related either to interest exposure or risk of disease, which limits the capacity of the epidemiological studies to provide convincing evidence of causality (USEPA, 1994).

It is considered that causality is suspected if different studies show consistent findings; if the association between the agent and the risk of disease is strong (i.e., there is high ratio of chances) and if the association is in accordance with the biological theory. Proving animal data helps defending causality, especially upon establishment of biological reasonability and potential mechanisms. However, failure to detect association in an epidemiological study is not sufficient to disregard it, especially if the studies have limited statistical power due to the reduced size of the sample or the reduced follow-up time. Thus, in assessment of the weight of the evidence of epidemiological studies related to exposure to a substance, it is necessary to make a subjective judgment of the weight of the data from several studies and their conflicting conclusions. For Paraquat, the results from the epidemiological studies are conflicting and there are confusion factors either in the studies showing causality or in those that don´t. However, there are several studies and meta-analyses, which demonstrate a relation between Paraquat and the Parkinson´s Disease and the assessment of the inconsistencies does not allow to disregard such association. The confidence in epidemiological studies, when there is no direct measurement of exposure, is challenging; however, when the fact that the studies carried out in animals by different research groups are consistently positive and the fact that there is a big number of publications about the Paraquat action mechanism in the Central Nervous System (Choi et al., 2016) are added, it can be considered that, based on the currently available data, there is bigger evidence of causality relation between Paraquat and the Parkinson´s Disease rather than evidence of lack of relation.
This conclusion can be proven by a study delivered to Anvisa by Syngenta (Breckenridge et al., 2016) with the purpose to assess the weight of the evidence of the association between the Parkinson´s Disease and different aspects related to life in field, including exposure to Paraquat. In the results from the meta-analysis, a positive relation of association between Parkinson´s and Paraquat was observed, with significant different in the risk ratio. The authors concluded that there might be a risk factor associated to the rural life style, the use of pesticides (Paraquat was one of the assessed) and the consumption of water from wells, but that the results until today have not identified such factors conclusively, proposing the development of more studies, in order to characterize such relations.
Breckenridge and collaborators (2016) observed risk ratios (RR) for the Parkinson´s Disease significantly higher than 1.0 for exposure to Paraquat when compared to lack of exposure (RR=1.69 and RR=1.47; IC=1.01-2.13; I^2-69.9%, p=0.0001 with fixed and random assessment of the effects, respectively). When in the assessment the high use of Paraquat was compared to lack of use, this ratio was even higher, 1.75 (IC=1,19-2.57, I2=78.9%, p=0.0026) and 1.99 (IC=0.84-4.71) for fixed and random effects, respectively. These results confirm the results from the meta-analyses, where relation between Parkinsonism and Paraquat was observed, so that the authors of this study did not affirm for sure that these results reveal non-association between Paraquat and Parkinson´s; they only conclude that it is not possible to observe the same consistently negative relation of the association between smoking and the Parkinson´s disease for Paraquat and other assessed factors.
In the assessment of the weight of the evidence, Breckenridge and collaborators (2016) used only one qualitative method (Bradford Hill), not considering all available literature about the subject, they did not use even the results from their own meta-analysis, because they considered a single study as relevant for the assessment of the evidence weight. In a meta-analysis, classification of the studies attributing different weights according to their quality is important. However, th e classification of the studies by Breckenridge and collaborators (2016) was made exclusively based on the way of diagnosis (clinical by a specialist) and the availability of individual exposure data. Thus, only one study was classified as level 1 and used to grant strength to the assessment of the evidence weight. As discussed above, the studies cannot be disregarded based on a few limitations. The restriction made by Breckenridge and collaborators (2016) was disproportional and good-

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quality and internationally recognized studies, such as the AHS, were disregarded in the attribute strength of assessment of the evidence weight. In chart 5, assessment of the evidence weight made by the authors of the study, using the same method, and the assessment made based on the discussions in this opinion and considering all results from the meta-analysis by Breckenridge and collaborators (2016), and not only a single epidemiological study, can be observed.

Chart 5. Comparison of the assessments of the evidence weight of the causality relation between the Parkinson´s Disease and the exposure to Paraquat, according to the Bradford Hill qualitative method.

Attribute	Concept	Breckenridge et al., 2016	Anvisa
Strength	The bigger the risk ratio, more probable the causality relation.	**RR = 0.90** **Without statistical difference**, because only one epidemiological study was used for the assessment of this attribute, disregarding relevant studies.	**RR = 1.69** (use of Paraquat) **RR = 1.75** (high use of Paraquat) **With statistical significance** obtained from the meta-analysis of Breckenridge et al., 2016.
Consistency	Consistency of the associations between exposure and disease observed in independent studies indicates causality.	**Inconsistent.** All epidemiological results with RR significantly higher than 1.0 were disregarded.	**Consistent.** (Costello et al., 2009; Liou et al., 1997, Tunner, 2011; Kamel, 2007; Furlong et al., 2015)
Specificity	A specific association for given group of individuals or for a disease.	**Highly specific.**	**Highly specific.**
Temporality	For a factor to be causal, it shall precede the disease. Single condition considered essential.	**Not established.** All results from studies from the literature were disregarded.	**Confirmed** by consistent studies in the literature, demonstrating that PQ promotes death of dopaminergic neurons (precursor effect of Parkinson's) *
Biological Gradient	If the risk to develop the disease increases with the dose (exposure), the association is more likely to be causal.	**Not existing.** There is no level 1 study with high use of Paraquat.	**Existing.** RR = 1.69 (use of Paraquat) RR = 1.75 (high use of Paraquat)
Reasonability	If it is reasonable that the agent causes the disease, based on the current knowledge, the association is more likely to be causal.	**Uncertain.** Arguments that there are results demonstrating that Paraquat has oxy-reduction potential and could provoke death of dopaminergic neurons, but that these are controversial.	**High.** Data from *in situ, in vitro* and *in vivo* studies of different research groups prove that Paraquat is able to provoke several effects related to parkinsonism with statistical significance. *
Coherence	Whether the data is consistent with other data, for example, the known distribution of the disease in the population.	**Not existing.**	**Unavailability of data for such comparison.**
Experimental evidence	Causal inference is more probable if it is supported by experimental data. For example, if the implementation of a preventive measure, such as the reduction of the exposure results in reduction of the risk.	**Inexistent studies.** The Furlong and collaborators (2015) study was disregarded.	**There is an experimental evidence.** Furlong and collaborators (2015) assessed whether the use of gloves and hygiene habits modified the association between pesticides and the Parkinson´s Disease, finding out high association when gloves were used for less than 50% of the time, but the association did not exist, when gloves were used 50% of the time.
Analogy	Analogy between the current association with other exposure-disease relation proves causality inference.	**Existing.**	**Existing.** MPTP is a substance, which is structurally similar to Paraquat and causes Parkinson´s.
CONCLUSION		No causality relation between the Parkinson´s Disease and exposure to Paraquat.	There is causality relation between the Parkinson´s Disease and exposure to Paraquat.

Legend: RR: Risk Ratio; PQ: Paraquat. In red: attributes associating PQ to the Parkinson´s Disease. In green: attributes that do not associate PQ to the Parkinson´s Disease. For RR, the data of the meta-analysis of Breckenridge et al., 2016 was used. Even higher values were found in the epidemiological studies and in other meta-analysis.
* Brooks et al., 1999; Manning-Bog et al., 2002; McCormack et al., 2002; Manning-Bog et al., 2003; McCormack & Di Monte, 2003; McCormack et al., 2005; Ossowska et al., 2005a; Ossowska et al., 2005b; Ossowska et al., 2006; Choi et al., 2006; Fernagut et al., 2007; Purisai et al., 2007; Kamel et al., 2009; Somayajulu-Nitu et al., 2009; Kang et al., 2010; Li et al., 2012; Wills et al., 2012.

It is possible to find out that the epidemiological studies provide strong sings of causality between the exposure to Paraquat and the Parkinson´s disease. Although one study indicates that the use of IPE can be sufficient to mitigate this risk (Furlong et al., 2016), this result is unique and there is no sufficient knowledge in the scientific literature about the Parkinson´s Disease and about the action mechanism of Paraquat in human beings to ground the determination of a safe level of exposure.

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Therefore, it is not possible to affirm that use restrictions would be sufficient to protect the health of rural workers, who handle Paraquat.

Based on the currently available evidences, there is a strong evidence weight (studies in animals and epidemiological studies) indicating that Paraquat is associated to the development of the Parkinson´s Disease in humans. Considering that the consequences from the exposure to Paraquat in human beings are more relevant than in animals, because Parkinson´s is a severe, progressive disease, whose treatment only retards the symptoms, but which is not able to revert the condition, i.e., there is no cure, and in face of the recognized severity of this disease for human beings, it is possible to conclude that Paraquat may reveal to be more hazardous for human beings than the tests with laboratory animals can demonstrate and there is no antidote or efficient treatment. Therefore, there is classification of Paraquat in the prohibitive criteria for registration determined by items "b" and "e", §6, article 3, Law 7.802, dated 1989.

It is expected that exposure to Paraquat would be restricted to workers, who manipulate this pesticide, and the population in general would not be susceptible to exposure upon consumption of food, because there is no evidence that the use of Paraquat leaves residues. Thus, due to the fact that the risk related to Paraquat is restricted to a part of the population, specific measures for mitigation of exposure could be determined as an alternative to the prohibition of this active substance. However, the proposal of measures to mitigate the risk to the workers is extremely difficult and cannot be grounded technically, because there is no scientific evidence about which level of exposure would be sufficient to assure the safe use of this pesticide. Therefore, even if some measures may result in lower exposure of workers to Paraquat, protection against possible development of the Parkinson's disease cannot be fully guaranteed. The clarification of these aspects also demands scientific progress, which demonstrates the exact action mechanism of Paraquat in humans and whether there are safe levels of exposure for protection against this effect.

In face of the exposed above, for adoption of any measure, either register cancelation or proposal of restrictions, it is necessary to consider that:

I. There is a strong evidence (studies in animals and epidemiological studies) indicating the causality relation between the Parkinson´s Disease and the exposure to Paraquat;
II. The Furlong and collaborators (2015) study indicates that the results, which do not show association between PD and Paraquat may have been masked by the use of IPE;
III. The Furlong and collaborators (2015) study indicates that the use of gloves impedes the association between the use of Paraquat and the Parkinson´s Disease observed initially;
IV. The only exposure considered worrying from the health point of view is the occupational, because there is no evidence that Paraquat leaves residues in food;
V. The development of the Parkinson´s Disease, according to the results from the studies in animals, probably demands continuous exposure and high doses. However, in the epidemiological studies, it is observed that the current exposure would already be sufficient, showing that the consequences for human beings may be more severe than the studies in animals can demonstrate;
VI. Recent assessment of the risk after occupational exposure to Paraquat using the American model PHED indicates that the exposure to Paraquat in the different assessed scenarios does not extrapolate AOEL;
VII. The main international regulating agencies and the present opinion concluded that dermal exposure of human beings to Paraquat is relevant and more important than exposure of animals, therefore, rural workers (exposed population) are susceptible to the mutagenic effects of Paraquat;
VIII. With the current scientific knowledge, it is not possible to determine AOEL for parkinsonism (and it is not expected that such knowledge will be available in short terms);
IX. Parkinsonism is classified in two prohibitive criteria for registration of pesticides in Brazil: lack of antidote and efficient treatment and more severe consequence for human beings than the tests in animals can demonstrate;
X. USEPA proposed adoption of extremely restrictive measures, such as use of closed-system and inviolable packages and exclusion of backpack spraying application, which may result in big reduction of the exposure of the users;
XI. There are no scientific grounds to propose restrictive measures for exposure to Paraquat, because there is a single study indicating that the reduction of the exposure seems to be sufficient to limit the development of the disease.

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III – CONCLUSION

1. Acute intoxication and exposure

The cases of acute severe occupational intoxication by agricultural use of Paraquat, as stipulated, are not predominating and trend to be moderate or slight, with antidotes and efficient treatment able to revert the damages to health pursuant to occupational exposure to products made based on this pesticide. Therefore, this toxicological aspect cannot be classified in any criteria for registration prohibition in Brazil. However, occupational exposure to Paraquat is relevant, mainly due to the evidences of higher human sensitivity to dermal exposure to this pesticide, with possibility for system absorption by this route of exposure. Furthermore, the cases of acute severe intoxication by accidental ingestion of Paraquat or attempt to suicide are worrying. Considering these facts, Canada and the United States proposed adoption of restrictive measures for reduction of the cases and the severity of the intoxications associated to Paraquat.

Considering all these aspects related to acute intoxication by Paraquat, even it was not concluded that this active substance was classified in the criteria considered prohibitive for registration, quite restrictive risk-mitigation measures would be indispensable.

2. Mutagenicity

With the currently available scientific evidences, it was verified that:

I – The analysis of the mutagenicity studies either in the scientific literature or in the tests carried out by the registering companies showed that there is sufficient evidence weight to prove the potential of Paraquat to induce chromosome aberrations in somatic cells *in vitro* and *in vivo* in different species and by different exposure routes (including dermal).

II – When there is no conclusive data about the mutagenic potential of a substance in germinative cells, as for Paraquat, it shall be considered that the effect observed in somatic cells is sufficient to characterize its mutagenic potential in germinative cells.

III – It was not possible to prove the inexistence of mutation in germinative cells.

IV – Exposure to Paraquat reaches the testicles, affecting the spermatozoids and provokes somatic mutation in vivo, therefore, it is considered that Paraquat is mutagenic for germinative cells.

V – Mutagenic effects in germinative cells lead to severe consequences (alterations in fertility, malformations, embryonic death, neurological disorders, congenital abnormalities, including multi-factor disorders with delayed manifestation, such as heart disease, cancer, high blood pressure and diabetes), representing high risk to the exposed population.

VI – The main international regulatory agencies and the present opinion concluded that dermal exposure of human beings is relevant and most important than animal exposure, therefore, rural workers (exposed population) are susceptible to the mutagenic effects of Paraquat.

VII - Law 7.802 dated 1989 determines that it is forbidden to register pesticides, which reveal mutagenic characteristics, according to the results from **up-to-date experiences in the scientific community**

Considering these aspects, despite that Decree 4.074 dated 2002 determines that a substance is mutagenic when there is a proof of point and chromosome mutation (Item V. Art. 31), it is possible to conclude that this scientific understanding is out-of-date and would allow pesticides with mutagenic potential in germinative cells, able to cause severe effects to health, to be kept on the market. Thus, according to the current scientific knowledge and Law No. 7.802 dated 1989, which prohibits registration of mutagenic pesticides (item c, §6, Art. 2), it shall be considered that Paraquat is mutagenic, representing risk to the population´s health.
It is important to point out that the potential to provoke somatic chromosome aberrations does not seem to be associated to any severe chronic event, because the results from the carcinogenicity studies do not reveal any significant alteration; however, there is no evidence of the absence of severe for the chromosome mutations in germinative cells. Thus, the only alternative not to propose prohibition of the active substance Paraquat, based on its mutagenic potential, would be obtaining of clearly negative results in mutagenicity tests with germinative cells, carried out according to internationally accepted protocols.

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3. Parkinsonism

Based on the currently available evidences, there is a strong evidence weight (studies in animals and epidemiological studies) indicating that Paraquat is associated to the development of the Parkinson´s Disease in humans. Considering that the consequences from the exposure to Paraquat in human beings are more relevant than in animals, because Parkinson´s is a severe, progressive disease, whose treatment only retards the symptoms, but which is not able to revert the condition, i.e., there is no cure, and in face of the recognized severity of this disease for human beings, it is possible to conclude that Paraquat may reveal to be more hazardous for human beings than the tests with laboratory animals can demonstrate and there is no antidote or efficient treatment. Therefore, there is classification of Paraquat in the prohibitive criteria for registration determined by items "b" and "e", §6, article 3, Law 7.802, dated 1989.

The monitoring studies actually do not reveal exposure above AOEL; however, it is observed that Paraquat can be absorbed in doses, which, despite of not exceeding AOEL, are worrying due to the evidences associating this active substance with parkinsonism, and it is difficult to affirm that the currently accepted AOEL is a safe limit in relation to the effects from Paraquat on the dopaminergic neurons pursuant to exposure along the rural workers´ life.

It is expected that exposure to Paraquat would be restricted to workers, who manipulate this pesticide, and the population in general would not be susceptible to exposure upon consumption of food, because there is no evidence that the use of Paraquat leaves residues. Thus, due to the fact that the risk related to Paraquat is restricted to a part of the population, specific measures for mitigation of exposure could be determined as an alternative to the prohibition of this active substance. However, the proposal of measures to mitigate the risk to the workers is extremely difficult and cannot be grounded technically, because there is no scientific evidence about which level of exposure would be sufficient to assure the safe use of this pesticide. Therefore, even if some measures may result in lower exposure of workers to Paraquat, protection against possible development of the Parkinson's disease cannot be fully guaranteed. The clarification of these aspects also demands scientific progress, which demonstrates the exact action mechanism of Paraquat in humans and whether there are safe levels of exposure for protection against this effect.

In face of the exposed above, for adoption of any measure, either register cancelation or proposal of restrictions, it is necessary to consider that:

I. There is a strong evidence (studies in animals and epidemiological studies) indicating the causality relation between the Parkinson´s Disease and the exposure to Paraquat;
II. The Furlong and collaborators (2015) study indicates that the results, which do not show association between PD and Paraquat may have been masked by the use of IPE;
III. The Furlong and collaborators (2015) study indicates that the use of gloves impedes the association between the use of Paraquat and the Parkinson´s Disease observed initially;
IV. The only exposure considered worrying from the health point of view is the occupational, because there is no evidence that Paraquat leaves residues in food;
V. The development of the Parkinson´s Disease, according to the results from the studies in animals, probably demands continuous exposure and high doses. However, in the epidemiological studies, it is observed that the current exposure would already be sufficient, showing that the consequences for human beings may be more severe than the studies in animals can demonstrate;
VI. Recent assessment of the risk after occupational exposure to Paraquat using the American model PHED indicates that the exposure to Paraquat in the different assessed scenarios does not extrapolate AOEL;
VII. The main international regulating agencies and the present opinion concluded that dermal exposure of human beings to Paraquat is relevant and more important than exposure of animals, therefore, rural workers (exposed population) are susceptible to the mutagenic effects of Paraquat;
VIII. With the current scientific knowledge, it is not possible to determine AOEL for parkinsonism (and it is not expected that such knowledge will be available in short terms);
IX. Parkinsonism is classified in two prohibitive criteria for registration of pesticides in Brazil: lack of antidote and efficient treatment and more severe consequence for human beings than the tests in animals can demonstrate;

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X. USEPA proposed adoption of extremely restrictive measures, such as use of closed-system and inviolable packages and exclusion of backpack spraying application, which may result in big reduction of the exposure of the users;
XI. There are no scientific grounds to propose restrictive measures for exposure to Paraquat, because there is a single study indicating that the reduction of the exposure seems to be sufficient to limit the development of the disease.

Considering the current scientific knowledge, it was concluded that Paraquat is mutagenic and that it is risk factor for Parkinson's Disease, with evidence of causality between exposure and the disease. Therefore, the active substance Paraquat is classified in the following criteria that prohibit registration:

a) Scientific evidences of mutagenicity according to the updated results from experiences in the scientific community (Item c, §6, Art. 3, Law No. 7.802 dated 1989).
b) Lack of antidote or efficient treatment (Item II, Art. 31, Decree No. 4.074 dated 2002 and Item b, §6, Art. 3, Law No. 7.802 dated 1989).
c) Evidences that the active substance is more hazardous for the man than demonstrated in laboratory tests with animals (Item VII, Art. 31, Decree No. 4.074 dated 2002 and Item e, §6, Art. 3, Law No. 7.802 dated 1989).

Despite of the classification of the active substance Paraquat in the criteria that prohibit registration, it is necessary to clarify some relevant aspects:

I – New studies about the mutagenic potential in germinative cells, carried out according to internationally accepted protocols and with consistently negative results may reveal the lack of mutagenicity of Paraquat, which would classify it in the register-prohibition criteria determined in Item c, §6, Art. 3, Law No. 7.802 dated 1989).

II. – Considering that Parkinson is a progressive disease and probably demands repeated exposure to Paraquat to be developed, knowing that exposure to Paraquat is possibly restricted to a part of the population (rural workers); and knowing that a recent epidemiological study has indicated that the limitation of the exposure, by means of gloves, showed to be sufficient to disassociate the exposure to Paraquat from the Parkinson´s Disease, the possibility to propose restrictive measures to mitigate exposure could be considered. However, it cannot be concluded that it is possible to prevent the development of the Parkinson´s Disease with reduction of the exposure to Paraquat based on one study only, because important aspects about Paraquat the action in human beings and the development of the Parkinson´s Disease have not yet been clarified. Therefore, with the currently available knowledge, it is not possible to propose scientifically grounded restrictive measures for the mitigation of the risk associated to exposure to Paraquat, because it is not yet possible to determine which the safe levels of exposure are.

Based on the currently available scientific data and considering the classification of the toxicological aspects of Paraquat in the prohibitive registration criteria provided in the Brazilian legislation, I suggest production, export, import, trade and use of all products made based on this pesticide active substance to be forbidden in the country.

This is the opinion for superior consideration.

Brasília, June 13th, 2016

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Juliana Machado Braz
Expert on Regulation and Health Surveillance

(x) Approved
( ) Not Approved, according to document:

Brasília, 06/14/2016.

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Camila Queiroz Moreira
Reassessment Coordinator

(x) Approved

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( ) Not Approved, according to document:

Brasília, 06/16/2016.

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Post-registration Manager

(x) Approved

( ) Not Approved, according to document:

Brasília, 08/26/2016

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