U.S. EPA. IRIS Toxicological Review of Benzo[A]Pyrene (Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-17/003F, 2017.

Susceptible Populations and Lifestages (p. xxxi–xxxii)

Benzo[a]pyrene has been determined to be carcinogenic by a mutagenic mode of action in this assessment. According to the *Supplemental Guidance for Assessing Susceptibility from Early Life Exposure to Carcinogens* (U.S. EPA, 2005b), individuals exposed during early life to carcinogens with a mutagenic mode of action are assumed to have an increased risk for cancer. The oral slope factor of 1 per mg/kg-day and inhalation unit risk of 0.0006 per µg/m3, calculated from data applicable to adult exposures, do not reflect presumed early life susceptibility to this chemical. Although some chemical-specific data exist for benzo[a]pyrene that demonstrate increased early life susceptibility to cancer, these data were not considered sufficient to develop separate risk estimates for childhood exposure. In the absence of adequate chemical-specific data to evaluate differences in age-specific susceptibility, the *Supplemental Guidance* (U.S. EPA, 2005b) recommends that age-dependent adjustment factors (ADAFs) be applied in estimating cancer risk. The ADAFs are 10- and 3-fold adjustments that are combined with age specific exposure estimates when estimating cancer risks from early life (<16 years of age) exposures to benzo[a]pyrene.

Regarding effects other than cancer, there are epidemiological studies that report associations between developmental effects (decreased postnatal growth, decreased head circumference, and neurodevelopmental delays), reproductive effects, and internal biomarkers of exposure to benzo[a]pyrene. Studies in animals also indicate alterations in neurological development and heightened susceptibility to reproductive effects following gestational or early postnatal exposure to benzo[a]pyrene. More preliminary data suggest that effects on cardiovascular, kidney, pulmonary, and immune system development may result from early life exposures, although few in vivo developmental studies exist to confirm these findings.

Key Issues Addressed in Assessment (p. xxxii)

The overall RfD and RfC were developed based on effects observed following exposure to benzo[a]pyrene during a critical window of development. The derivation of a general population toxicity value based on exposure during development has implications regarding the evaluation of populations exposed outside of the developmental period and the averaging of exposure to durations outside of the critical window of susceptibility. Discussion of these considerations is provided in Sections 2.1.5 and 2.2.5.

***Populations or Lifestages Particularly Susceptible to the Hypothesized Mode of Action* (p. 1-99)**

A mutagenic mode of action for benzo[a]pyrene-induced carcinogenicity is considered relevant to all populations and lifestages. The current understanding of biology of cancer indicates that mutagenic chemicals, such as benzo[a]pyrene, are expected to exhibit a greater effect in early life exposure versus later life exposure (U.S. EPA, 2005b; Vesselinovitch et al., 1979). The EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b) recommends the application of age-dependent adjustment factors (ADAFs) for carcinogens that act through a mutagenic mode of action. Since a determination that benzo[a]pyrene acts through a mutagenic mode of carcinogenic action has been made, ADAFs should be applied along with exposure information to estimate cancer risks for early-life exposure.

Toxicokinetic information suggest early lifestages may have lower levels of some CYP enzymes than adults (Ginsberg et al., 2004; Cresteil, 1998); thus, lower levels of mutagenic metabolites may be formed in early lifestages. Though expression of bioactivating enzymes is believed to be lower in the developing fetus and children, metabolism of benzo[a]pyrene still occurs, as indicated by the detection of

benzo[a]pyrene-DNA or protein adducts or urinary metabolites (Naufal et al., 2010; Ruchirawat et al., 2010; Suter et al., 2010; Mielzyńska et al., 2006; Perera et al., 2005a; Tang et al., 1999; Whyatt et al., 1998). While expression of CYP enzymes is lower in fetuses and infants, the greater liver to body mass ratio and increased blood flow to liver in fetuses and infants may compensate for the decreased expression of CYP enzymes (Ginsberg et al., 2004). Activity of Phase II detoxifying enzymes in neonates and children is adequate for sulfation but decreased for glucuronidation and glutathione conjugation (Ginsberg et al., 2004). The conjugation of benzo[a]pyrene-4,5-oxide with glutathione was approximately one-third less in human fetal liver cytosol compared to adult liver cytosol (Pacifici et al., 1988).

In addition, newborn or infant mice develop liver and lung tumors more readily than young adult mice following acute i.p. exposures to benzo[a]pyrene (Vesselinovitch et al., 1975). These results indicate that exposure to benzo[a]pyrene during early lifestages presents additional risk for cancer, compared with exposure during adulthood, despite lower metabolic activity in early lifestages. Population variability in metabolism and detoxification of benzo[a]pyrene, in addition to DNA repair capability, may affect cancer risk. Polymorphic variations in the human population in CYP1A1, CYP1B1, and other CYP enzymes have been implicated as determinants of increased individual cancer risk in some studies (Ickstadt et al., 2008; Aklillu et al., 2005; Alexandrov et al., 2002; Perera and Weinstein, 2000). Some evidence suggests that humans lacking a functional GSTM1 gene have higher BPDE-DNA adduct levels and are thus at greater risk for cancer (Binkova et al., 2007; Vineis et al., 2007; Pavanello et al., 2005; Pavanello et al., 2004; Alexandrov et al., 2002; Perera and Weinstein, 2000). In addition, acquired deficiencies or inherited gene polymorphisms that affect the efficiency or fidelity of DNA repair may also influence individual susceptibility to cancer from environmental mutagens (Wang et al., 2010; Ickstadt et al., 2008; Binkova et al., 2007; Matullo et al., 2003; Shen et al., 2003; Cheng et al., 2000; Perera and Weinstein, 2000; Wei et al., 2000; Amos et al., 1999). In general, however, available support for the role of single polymorphisms in significantly modulating human PAH cancer risk from benzo[a]pyrene or other PAHs is relatively weak or inconsistent. Combinations of polymorphisms, on the other hand, may be critical determinants of a cumulative DNA-damaging dose, and thus indicate greater susceptibility to cancer from benzo[a]pyrene exposure (Vineis et al., 2007).

2.3.3. Derivation of the Oral Slope Factor (p. 2-36)

Another consideration in developing a human-equivalent slope factor is that slope factors are intended to provide an upper bound on the cancer risk of a randomly selected individual (U.S. EPA, 2005a), yet EPA's approach to quantifying low-dose cancer risk relies on a 95% upper bound on the cancer risk that typically only addresses experimental variability in homogeneous laboratory animals. The NRC (2009) observed that when cancer risk is expected to be linear at low exposures, as with benzo[a]pyrene, EPA's cancer risk values tend not to address human variability and susceptibility adequately. Concern for sensitive populations (separate from the consideration of increased sensitivity at early lifestages; see Section 2.5, Application of Age-Dependent Adjustment Factors [ADAFs]) suggests interpreting the near-continuous range of risk-estimate confidence intervals (CIs) from the three data sets (see CIs in Tables E-27 and E-28), of 0−1.4 per mg/kg-day, to represent a more heterogeneous population and supports use of the high value as a plausible upper bound.

The oral slope factor for benzo[a]pyrene is derived with the intention that it will be paired with EPA's relative potency factors for the assessment of the carcinogenicity of PAH mixtures. In addition, regarding the assessment of early life exposures, because cancer risk values calculated for benzo[a]pyrene were derived from adult animal exposures, and because benzo[a]pyrene carcinogenicity occurs via a mutagenic mode of action, exposures that occur during development should include the application of ADAFs (see Section 2.5).

Table 2-8. Summary of uncertainties in the derivation of benzo[a]pyrene oral slope factor (p. 2-39)

Consideration and impact on cancer risk value	Decision	Justification and discussion
Sensitive subpopulations ↑ oral slope factor to unknown extent	ADAFs are recommended for early life exposures	No chemical-specific data are available to determine the range of human toxicodynamic variability or sensitivity.

2.4.3. Inhalation Unit Risk Derivation (p. 2-43)

The inhalation unit risk for benzo[a]pyrene is derived with the intention that it will be paired with EPA's relative potency factors for the assessment of the carcinogenicity of PAH mixtures. In addition, regarding the assessment of early life exposures, because cancer risk values calculated for benzo[a]pyrene were derived from adult animal exposures, and because benzo[a]pyrene carcinogenicity occurs via a mutagenic mode of action, exposures that occur during development should include the application of ADAFs (see Section 2.5).

Table 2-10. Summary of uncertainties in the derivation of cancer risk values for benzo[a]pyrene (inhalation unit risk) (p. 2-46)

Consideration and impact on cancer risk value	Decision	Justification and discussion
Sensitive subpopulations ↑ inhalation unit risk to unknown extent	ADAFs are recommended for early life exposures	No chemical-specific data are available to determine the range of human toxicodynamic variability or sensitivity.

2.5. APPLICATION OF AGE-DEPENDENT ADJUSTMENT FACTORS (ADAFs) (p. 2-47–2-48)

Based on sufficient support in laboratory animals and relevance to humans, benzo[a]pyrene is determined to be carcinogenic by a mutagenic mode of action. According to the *Supplemental Guidance for Assessing Susceptibility from Early Life Exposure to Carcinogens* ("*Supplemental Guidance*") (U.S. EPA, 2005b), individuals exposed during early life to carcinogens with a mutagenic mode of action are assumed to have increased risk for cancer. The oral slope factor of 1 per mg/kg-day, and inhalation unit risk of 0.6 per mg/m3 for benzo[a]pyrene, calculated from data applicable to adult exposures, do not reflect presumed early life susceptibility to this chemical. Although chemical-specific data exist for benzo[a]pyrene that quantitatively demonstrate increased early life susceptibility to cancer (Vesselinovitch et al., 1975), these data were not considered sufficient to develop separate risk estimates for childhood exposure, as they used acute i.p. exposures (U.S. EPA, 2005b). In the absence of adequate chemical-specific data to evaluate differences in age-specific susceptibility, the *Supplemental Guidance* (U.S. EPA, 2005b) recommends that ADAFs be applied in estimating cancer risk.

The *Supplemental Guidance* (U.S. EPA, 2005b) establishes ADAFs for three specific age groups. These ADAFs and their corresponding age groupings are: 10 for individuals exposed at <2 years of age, 3 for exposed individuals at 2–<16 years of age, and 1 for exposed individuals ≥16 years of age. The 10- and 3-fold adjustments are combined with age-specific exposure estimates when estimating cancer risks from early life (<16 years of age) exposures to benzo[a]pyrene. To illustrate the use of the ADAFs established in the *Supplemental Guidance* (U.S. EPA, 2005b), sample calculations are presented for three exposure duration scenarios, including full lifetime, assuming a constant benzo[a]pyrene exposure of 0.001 mg/kg-day (Table 2-11).

Table 2-11. Sample application of ADAFs for the estimation of benzo[a]pyrene cancer risk following lifetime (70-year) oral exposure (p. 2-48)

Age group	ADAF	Unit risk (per mg/kg-d)	Sample exposure concentration (mg/kg-d)	Duration adjustment	Cancer risk for age-specific exposure period
0–<2 yrs	10	1	0.001	2 yrs/70 yrs	0.0003
2–<16 yrs	3	1	0.001	14 yrs/70	0.0006
≥16 yrs	1	1	0.001	54 yrs/70	0.0008
Total risk					0.002

The example exposure duration scenarios include full lifetime exposure (assuming a 70-year lifespan). Table 2-11 lists the four factors (ADAFs, cancer risk estimate, assumed exposure, and duration adjustment) that are needed to calculate the age-specific cancer risk based on the early age-specific group. The cancer risk for each age group is the product of the four factors in columns 2−5. Therefore, the cancer risk following daily benzo[a]pyrene oral exposure in the age group 0−<2 years is the product of the values in columns 2−5 or $10 \times 1 \times 0.001 \times 2/70 = 3 \times 10{-}4$. The cancer risk for specific exposure duration scenarios that are listed in the last column are added together to get the total risk. Thus, a 70-year (lifetime) risk estimate for continuous exposure to 0.001 mg/kg-day benzo[a]pyrene is $2 \times 10{-}3$, which is adjusted for early-life susceptibility and assumes a 70-year lifetime and constant exposure across age groups.

In calculating the cancer risk for a 30-year constant exposure to benzo[a]pyrene at an exposure level of 0.001 mg/kg-day for ages 0−30 years, the duration adjustments would be 2/70, 14/70, and 54/70, and the age-specific risks for the three age groups would be $3 \times 10{-}4$, $6 \times 10{-}4$, and $2 \times 10{-}4$, which would result in a total risk estimate of $1 \times 10{-}3$.

In calculating the cancer risk for a 30-year constant exposure to benzo[a]pyrene at an exposure level of 0.001 mg/kg-day for ages 20−50 years, the duration adjustments would be 0/70, 0/70, and 30/70. The age-specific risks for the three groups are 0, 0, and $4 \times 10{-}4$, which would result in a total risk estimate of $4 \times 10{-}4$.

Consistent with the approaches for the oral route of exposure (Table 2-11), the ADAFs should also be applied when assessing cancer risks for subpopulations with early life exposures to benzo[a]pyrene via the inhalation route (presented in Table 2-12).

Table 2-12. Sample application of ADAFs for the estimation of benzo[a]pyrene cancer risk following lifetime (70-year) inhalation exposure (p. 2-49)

Age group	ADAF	Unit risk (per (mg/m^3)	Sample exposure concentration (mg/m^3)	Duration adjustment	Cancer risk for age-specific exposure period
0–<2 yrs	10	6×10^{-4}	0.1	2 yrs/70 yrs	0.00002
2–<16 yrs	3	6×10^{-4}	0.1	14 yrs/70 yrs	0.00004
≥16 yrs	1	6×10^{-4}	0.1	54 yrs/70 yrs	0.00005
Total risk					0.00010