The following document is a report written by the Agency for Toxic Substances and Disease Registry in 2004. The report examines the adverse health impacts of exposure to drinking water in Pahokee and South Bay contaminated by trihalomethanes (THMs). THMs are a byproduct of the water treatment process which result when the intake water is high in dissolved organic compounds, such as backpumped water, and is treated with chlorine. THMs are known to be carcinogenic and may be linked to birth defects. The report concluded that the public faced an indeterminate health risk from exposure to THMs and recommended limiting the exposure of pregnant women to these dangerous chemicals. Importantly, the report noted that the public in Pahokee and South Bay may have been exposed to these dangerous chemicals for the past ten years, and that exposure to the chemical can occur through ingestion (such as drinking the water), inhalation (such as inhaling steam from cooking with the water), or dermal contact (such as bathing in the water).

Health Consultation

Public Comment Release

Total Trihalomethanes

PAHOKEE AND SOUTH BAY MUNICIPAL WATER SYSTEMS
(a/k/a PAHOKEE/SOUTH BAY)

WEST PALM BEACH/SOUTH BAY, PALM BEACH COUNTY, FLORIDA

MARCH 24, 2004

Comment Period End Date: May 21, 2004

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry
Division of Health Assessment and Consultation
Atlanta, Georgia 30333

Health Consultation: A Note of Explanation

An ATSDR health consultation is a verbal or written response from ATSDR to a specific request for information about health risks related to a specific site, a chemical release, or the presence of hazardous material. In order to prevent or mitigate exposures, a consultation may lead to specific actions, such as restricting use of or replacing water supplies; intensifying environmental sampling; restricting site access; or removing the contaminated material.

In addition, consultations may recommend additional public health actions, such as conducting health surveillance activities to evaluate exposure or trends in adverse health outcomes; conducting biological indicators of exposure studies to assess exposure; and providing health education for health care providers and community members. This concludes the health consultation process for this site, unless additional information is obtained by ATSDR which, in the Agency's opinion, indicates a need to revise or append the conclusions previously issued.

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HEALTH CONSULTATION

(PUBLIC COMMENT RELEASE)

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(a/k/a PAHOKEE/SOUTH BAY)

WEST PALM BEACH/SOUTH BAY, PALM BEACH COUNTY, FLORIDA

Prepared by:

Exposure Investigation and Consultation Branch
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Summary

In 2002, the Region 4 office of the United States Environmental Protection Agency (EPA) asked the Agency for Toxic Substances and Disease Registry (ATSDR) to determine whether the levels of the total trihalomethanes (THMs) detected in the Pahokee and South Bay Florida public water systems present a public health hazard to residents of these communities.

The use of chlorine disinfection in public water supplies is extremely effective in preventing exposure to harmful bacteria and viruses and subsequent disease. Trihalomethanes (THMs) are chemicals formed as by-products of chemical disinfection. THMs are one of many groups of disinfection by-products (DBPs) formed as a result of the chlorination of water containing organic material. Total THM concentrations consist of the sum of four specific chemicals: bromodichloromethane, dibromochloromethane, bromoform and chloroform. ATSDR was asked to focus on THMs because they are the most monitored of the DBPs and may serve as a surrogate for other DBPs.

For a two-year period starting in October of 2000, quarterly total THMs average in the Pahokee water system exceeded 0.26 milligrams per liter (mg/L), with peak levels exceeding 1.0 mg/L. Similar levels were observed in the South Bay water system from December 2000 through April 2002. Prior to 2000 sampling was less frequent but the total THM levels measured in Pahokee and South Bay water systems ranged from 0.29 to 0.45 mg/L. In 2001, Palm Beach County Health Department initiated public health actions to reduce total THM levels prior to the effective date of Environmental Protection Agency (EPA) regulations that restricted total THM levels for public water systems serving less than 10,000 persons.

In samples collected in August of 2003, the quarterly total THM average in the Pahokee water distribution system was 0.143 mg/L. The quarterly total THM average in the South Bay water distribution system was 0.072 mg/L (September 2003). For the third quarter of 2003, the annual running average of total THMs was 0.086 mg/L for Pahokee and 0.062 mg/L for South Bay.

A definitive conclusion regarding the potential public health hazard of THM exposure at Pahokee and South Bay cannot be determined for all populations due to limitations in appropriate data and uncertainties in exposure and effect levels. While laboratory animal studies do not indicate that adverse health effects would be expected at current or past THM levels at Pahokee and South Bay, some epidemiological studies suggest an association between adverse birth outcomes and chlorinated drinking water at quarterly average THM levels (<0.100 mg/L) lower than those reported for Pahokee and South Bay (0.290 to 0.450 mg/L).

While all of the THMs cause toxicity and are carcinogenic in laboratory animals at high doses, little is known about the dose response of bromoform, bromodichloromethane, and dibromochloromethane at low doses. However, much is known about chloroform and its mode of action. It is assumed that other THMs may act similarly. In laboratory animal studies, chloroform toxicity does not occur until a threshold is reached; carcinogenic effects are not observed until after toxicity and compensatory tissue regeneration begins; and developmental/reproductive toxicity does not occur below levels where maternal toxicity occurs. Animal data were derived using one route of exposure (ingestion, inhalation, or dermal) to one chemical, or using total THMs without knowing the individual chemical composition of THMs and other DBPs.

Several epidemiology studies suggest an association between adverse birth outcomes (developmental/reproductive) and exposure to total THMs at levels (<0.100 mg/L) well below those reported (approximately 0.400 mg/L) in Pahokee and South Bay water systems prior to 2002. Epidemiological studies were conducted in populations assuming multiple routes of exposure (ingestion, inhalation, and dermal), but relative proportions of individual routes were unknown. Also, exposure included other DBPs in addition to THMs, but the specific chemical composition was unknown. Specific exposure routes may be important in the secondary prenatal exposure from internal dose and pharmacokinetic considerations.

Historically, exposure levels in epidemiological studies have not been well characterized. The location of residence, distance from treatment plant, chlorination use, and public water source were often used as indicators of exposure in the early studies. However, studies of adverse pregnancy outcomes within the last 15 years have used quarterly average THM levels to estimate exposures during specific trimesters of pregnancy. Studies of adult cancers within the last 15 years have estimated exposures based on annual averages of total THM in the water system. Sampling may have been performed at locations not representative of worst-case exposure. Peak levels may not have been considered, but may occur during critical developmental periods that could result in adverse developmental outcomes. A well-conducted health study with an emphasis on exposure assessment may clarify the relationship between adverse health outcomes and low dose exposure.

The potential effect of chemical mixtures cannot be adequately addressed because there are hundreds of disinfection by-products in drinking water but only a few are routinely monitored. The scientific literature reports no clear conclusion from results of laboratory animal studies of THM mixtures, whereas epidemiological studies are suggestive of potential associations and reflect an exposure to chemical mixtures in chlorinated drinking water.

In conclusion, while the results of laboratory animal studies suggest that the levels of total THMs detected in Pahokee and South Bay would not result in adverse health effects, laboratory animal studies are conducted by only one route of exposure to usually only one chemical. Human exposure to DBPs, including THMs, occurs by multiple routes to more than one chemical. Therefore, animal and human studies do not have equivalent study designs in that chemical exposure and routes of exposure are not the same. Human studies are not conclusive but suggestive of a potential association between adverse birth outcomes (developmental /reproductive) and DBP levels below those reported to have been common in Pahokee and South Bay communities. Concern is greatest for the prenate, which may be exposed to peak levels during critical developmental periods. Because of the uncertainty surrounding chlorinated drinking water exposure and adverse birth outcomes, ATSDR recommends appropriate public health activities to reduce exposure to potentially susceptible populations if peak THM levels result in violations of the Environmental Protection Agency's Maximum Contaminant Level (MCL).

Background and Statement of Issues

In August 2002, the United States Environmental Protection Agency (USEPA) asked the Agency for Toxic Substances and Disease Registry (ATSDR) to determine whether the levels of the total trihalomethanes (TTHMs or total THMs) detected in the Pahokee and South Bay, Florida, public water systems presented a public health hazard to residents of these communities.

The Cities of Pahokee and South Bay are located in south central Florida's Palm Beach County—on the southeastern edge and southern edge of Lake Okeechobee, respectively. The populations of Pahokee and South Bay are approximately 6,500 and 4,000. The majority are African-American, Creole, or Latino. Appendix A contains maps of the area and the demographic descriptions of these communities.

Lake Okeechobee covers 730 square miles and is the source for both the Pahokee and the South Bay public water supplies. The Pahokee and South Bay public water systems are estimated to be 50 to 60 years old [1].

Trihalomethanes (THMs) are one group of chemicals formed as byproducts of chemical disinfection. In public water systems, chemical disinfection is used to prevent exposure to harmful microorganisms. Chlorine and chloramines are the most commonly used chemical disinfectants for public water supplies. Total THMs consist of bromodichloromethane, bromoform, chloroform, and dibromochloromethane. THMs are formed when the chlorine or bromine chemically bonds with naturally occurring organic material in the water supply. During disinfection, in addition to THMs, at least 10 other classes of disinfection byproducts (DBPs) are produced, including haloacetic acids [2].

In 1979, for community water systems serving more than 10,000 persons, USEPA established a maximum contaminant level (MCL), highest level of a contaminant allowed in public drinking water supplies, for total THMs of 0.1 milligrams per liter (mg/L). Compliance with the total THM MCL is determined by calculating the annual running average of the four most recent of quarterly averages of distribution system samples[3]**.** MCLs are legally enforceable standards established to protect against any illness that could result from exposure to drinking water contaminants. USEPA also established a total THM MCL to protect against possible cancer, liver and kidney effects associated with THM exposure [4].

Effective January 2002, USEPA lowered the total THM MCL to 0.080 mg/L to protect the public from the potential health effects from disinfection byproducts for surface water systems serving more than 10,000 persons [5]. However, this MCL did not apply to public water systems serving less than 10,000 persons—such as the Cities of Pahokee and South Bay until 2004. Beginning on January 1, 2004, small community water systems, (those serving less than 10,000 persons) must comply with the USEPA's MCL for total THM. Also by January 1, 2004, small systems must comply with the haloacetic acid MCL of 0.06 mg/L [4].

The Florida Department of Environmental Protection (DEP) has granted Palm Beach County Health Department the authority to enforce the Safe Drinking Water Act for the county's drinking water systems. Following detection of the elevated total THM levels in the Pahokee and South Bay water systems, in the winter of 2001 the Palm Beach County Health Department issued consent orders to the two cities [6, 7]. The consent orders required Pahokee and South Bay to lower total THMs to less than 0.10 mg/L.

After issuance of the consent orders, in 2002 Pahokee and South Bay took several steps to lower the THM levels in their public water supplies. Pahokee installed a pre-treatment chlorine dioxide system for the treatment of the raw water and installed a chloramine disinfection system for treatment of filtered water. South Bay established a chloramine disinfection system and, to lower the pH of the water, implemented carbonic acid addition. The South Bay water utility director also initiated a program to flush periodically the distribution lines, thus further reducing THM levels [1].

In October of 2001, the Secretary for the Florida Department of Health, Dr. John Agwunobi, wrote to USEPA Administrator Whitman requesting guidance on elevated levels of total THMs in the Pahokee and South Bay water systems. In a written response dated January 2002, USEPA indicated that additional rule making would address peak elevated levels of total THMs. USEPA added, however, that it will be several years before this rule making will affect small community systems like Pahokee and South Bay.

By written notification and by water customer mailings, Pahokee and South Bay water department managers have notified their customers (residents) of elevated levels of total THMs in the water supply [1]. The mailing content included standard EPA Safe Drinking Water Act language regarding possible liver, kidney, central nervous system and cancer effects from THM exposure, but did not include information about possible reproductive or developmental effects. As of January 2002, USEPA requires a discussion of possible reproductive or developmental effects in its THM notification requirements for affected public water systems serving greater than 10,000 persons. However, this notification requirement did not extend to systems with populations less than 10,000, such as Pahokee and South Bay, until January 2004.

Environmental Data

During the preparation of this health consultation, ATSDR reviewed water sampling results for total THM analyses provided by the Palm County Health Department and the Florida Department of Environmental Protection (FL DEP) [8, 9, 10]. ATSDR obtained these data from samples collected from 1994 to September 2003 by the city water departments and by the Palm Beach County Health Department.

In the late 1990s, the Florida Department of Health and Florida DEP required small community water systems showing evidence of elevated total THMs to initiate routine monitoring for total THMs. Beginning in 2000, the Palm Beach County Health Department required Pahokee and South Bay water systems and other small community systems in Palm Beach County to perform monitoring for total THMs.

Pahokee Total THM Levels

Figure 1 depicts the levels of total THMs collected from the Pahokee water samples at the point of entry (POE) into the distribution system, immediately following water treatment. Total THM levels ranged from a high of 0.92 mg/L in November of 2001 to a low of 0.022 mg/L in November of 2002. Samples collected in September of 1993 (0.425 mg/L) and April 1996 (0.413 mg/L) suggest that total THM levels have been elevated for several years or longer.

Figure 2 depicts total THM levels for the Pahokee distribution system samples together with the annual running average. The annual running average is based on the mean of the most recent four-quarter distribution system averages. Sampling of Pahokee's distribution system for THMs was initiated in October of 2000. Total THM levels in the distribution samples ranged from 0.98

mg/L in November of 2001 to 0.026 mg/L in November of 2002. The City of Pahokee implemented the use of ammonia to produce chloramine disinfection during the summer of 2002 and the elimination of "pre" chlorinating raw water in November of 2002. During June and August of 2003, quarterly total THM levels were 0.087 mg/L and 0.143 mg/L, respectively. The annual running average peaked in June 2002 (0.55 mg/L) and dropped to 0.086 mg/L in August 2003.

South Bay Total THM Levels

Figure 3 depicts the levels of total THMs for samples collected from the South Bay POE from November 1994 to September 2003. Total THM levels ranged from 1.1 mg/L (September of 2001) to 0.066 mg/L (November of 2002). Samples collected in November of 1994 (0.373 mg/L) and February 1996 (0.352 mg/L) suggest that total THM levels have been elevated for several years or longer.

Figure 4 depicts the total THM levels for the South Bay distribution system samples along with the annual running average, from December 2000 through September 2003. Total THM levels in the distribution samples ranged from a high of 1.1 mg/L in September of 2001 to a low of 0.046 mg/L in March of 2003. The decrease in total THM levels in the August through November 2002 samples is attributed to plant modifications which include the elimination of pre-chlorination and the use of the chloramine treatment. The annual running average fell from 0.73 mg/L in October 2001 to 0.062 mg/L in June of 2003.

Composition of Pahokee and South Bay Total THMs

Figures 5 and 6 depict the composition of total THMs in the point of entry and in four distribution samples collected from Pahokee and South Bay systems on August 19, 2002. Chloroform accounted for 80 to 84% and 53 to 67% of the total THMs in Pahokee and South Bay samples, respectively. Bromodichloromethane accounted for 13 to 17% and 21 to 29% of the total THMs in the Pahokee and South Bay samples, respectively. Dibromochloromethane accounted for 2 to 3% and 11 to 17% of the total THMs in the Pahokee and South Bay samples, respectively. Bromoform accounted for less than 2% of the total THMs in the Pahokee and South Bay samples.

Figures 5 and 6 also depict how the THM levels can vary within a water distribution system. Such variation is attributed to differences in raw water quality over time and differences in water residence time within the distribution system. Low water levels in Lake Okeechobee and drought conditions could have contributed to the peak total THMs in the Pahokee and South Bay systems during the fall of 2001. Distribution system dead-ends can allow water containing high levels of THMs to remain in the system after the levels have dropped both at the point of entry and at other areas of the distribution system with shorter residence times—increased distribution system residence time can result in increased THM concentrations.

Peak Levels in Summer and Fall of 2001

The intentional draw-down of Lake Okeechobee followed by drought conditions resulted in historically low water levels during the spring of 2001. Once the lake levels dropped, water from outlying canals was pumped back into the lake. Canal water can contain organic material from the runoff of agricultural lands, including pesticides and nutrients. This series of events likely resulted in the increased organic loading of the lake water and contributed to the peak total THM levels in the Pahokee and South Bay systems during the fall of 2001 [8].

Other Water Systems in Florida

ATSDR reviewed monitoring results from other water systems in Florida to

- determine whether these systems were also experiencing total THM levels exceeding the MCL, and
- gain perspective on the extent and potential source of the issue.

ATSDR found that several other public water systems in Florida have elevated levels of total THMs.

ATSDR reviewed the Florida Department of Environmental Protection's (DEP's) public water supply system water quality database [11]. During the period from 1999 through 2001, one or more samples from 30 additional community water systems equalled or exceeded 0.24 mg/L of total THMs. Samples from 14 of these systems exceeded 0.40 mg/L of total THMs.

Drinking Water Dispensing Stations

Palm Beach County Health Department, with financial assistance from USEPA Region 4, established drinking water dispensing stations in Pahokee and South Bay [7]. Water dispensed at these stations is free to the public and is treated with granular activated carbon (GAC), which reduces THM levels. In 2001, two stations were established in Pahokee: one at the St. Mary Roman Catholic Church at 1200 East Main Street and the other adjacent to the city hall. In 2002, a dispensing station was also established at the Miracle by Faith Christian Community School, at 1165 Martin Luther King Boulevard in South Bay.

Palm Beach County Health Department officials have reported that less than 100 gallons per day of water is drawn from these dispensing stations [7]. This low usage could be in part attributed to a lack of awareness of THM concern or the lack of awareness of the existence or location of the dispensing stations. Other barriers could include the inconvenience of traveling to the dispensing station or, in the alternative, of purchasing bottled water from retail stores.

Discussion

This discussion represents a summary of the site-specific environmental data and peer-reviewed toxicological and epidemiological information. More detailed toxicological and epidemiological information is presented with reference citations in Appendix D.

Exposure to THMs in drinking water can occur primarily by drinking the water (ingestion), breathing THMs volatilized during showering, bathing, or cooking (inhalation), and absorption through the skin and mucus membranes (dermal contact). Total THMs are composed of chloroform, bromodichloromethane, dibromochloromethane, and bromoform. Chloroform is the most prevalent THM at Pahokee and South Bay and has been the most scientifically-investigated THM. Because the THMs are structurally and chemically similar, it can be inferred in the absence of conflicting information that they will act through similar mechanisms and cause similar effects. Therefore, much of the toxicological discussion involves the use of chloroform as a surrogate for total THMs.

Conclusions drawn from reviews of toxicological data do not appear to agree with conclusions drawn from reviews of epidemiological data. Toxicological data indicate that adverse health effects would not be expected from exposure to THMs at levels reported currently or observed in the limited past sampling in Pahokee and South Bay. Epidemiological studies suggest a potential

public health concern for prenatal exposures to chlorinated drinking water at current and past levels. However, it is not appropriate to directly relate these toxicological and epidemiological studies. Toxicological data are derived largely from laboratory animal studies where exposure usually occurs by a single route, usually ingestion, to a single chemical. Epidemiological studies are based on studies of human exposures to drinking water, containing various THMs and other DBPs, by multiple routes of exposure. The maternal and prenatal pharmacokinetics of multiple chemical exposure by multiple exposure routes may add important information to toxicological studies when considering potential prenatal effects.

When THMs are ingested, first pass metabolism occurs in the liver before being distributed to the rest of the body through the circulatory system. When THMs are inhaled, the parent compound is distributed to the body by the circulation system before being metabolized by the liver. Thus, more parent compound THMs per dose would potentially be delivered across the placenta to the prenate by a maternal inhalation exposure than by a maternal ingestion exposure.

The exposure of most concern is a short-term maternal exposure resulting in a secondary exposure to the prenate during development. Limited laboratory animal reproductive or developmental data exist for THMs other than chloroform. Laboratory animal studies indicate that chloroform exposure during pregnancy can result in reproductive and developmental toxicity. But effects are reported at levels equal to or greater than levels which cause toxicity in the mother. Therefore, laboratory animal studies suggest that reproductive and developmental effects could be secondary to maternal toxicity. Thus, laboratory animal studies indicate that chloroform toxicity would not be expected at levels below those causing maternal toxicity. But the comparison of these findings in laboratory animal studies by a single exposure route is not equivalent to humans typically exposed by multiple routes to a mixture of DBPs, including THMs.

Adverse birth outcomes in several epidemiological studies have been associated with exposure to chlorinated drinking water. Accurate exposure data is a significant limitation in most epidemiological studies. The actual amount of THMs to which an individual might have been exposed (by inhalation, ingestion, and dermal exposures) has not been well characterized. In most studies that based exposure on THM sample data, positive associations with adverse birth outcomes have been reported and have occurred at THM levels lower than past exposure levels estimated at Pahokee and South Bay. In epidemiological studies of THMs and adverse birth outcomes reporting low but positive odds ratios, statistical significance has been variable. Lack of statistical significance could be due to such factors as chance, study design, insufficient power, low levels of THMs, or exposure misclassification.

The level of maternal exposure at which adverse developmental or reproductive effects will occur from multiple exposure routes to THMs and other DBPs is the principal knowledge gap limiting ATSDR's evaluation of the public health implications of the Pahokee and South Bay THM exposures. This effect level cannot be determined without additional health investigations that include accurate THM exposure data. For example, many epidemiological studies of chlorinated drinking water exposures have relied on periodic water system monitoring and residence location as an indicator of the level of THM exposure [2].

Some human epidemiological studies have reported associations between THMs in chlorinated drinking water and bladder cancer; other studies have linked THMs with colon and rectal cancers. These studies have shown weak but positive associations, but were limited by exposure uncertainties leading to the inability to establish a causal link between chlorinated drinking water

and cancer. Exposures in these epidemiological studies included exposure by inhalation, ingestion, and dermal contact to THMs and other DBPs. Thus, these exposures were somewhat different than exposures in laboratory animal studies.

While all THMs are presumed to be carcinogenic at some dose, cancer effects from chloroform exposure in animals are presumed to occur only after tissue damage and resulting tissue regeneration. If other THMs act by a similar mechanism, cancer effects would only occur at levels significantly greater than those observed at Pahokee and South Bay. Risk assessment of the cumulative cancer risks for total THM exposure estimates a slight increase in the risk for developing cancer, assuming no threshold for cancer-related toxicity. This is a conservative estimate of risk containing a high level of uncertainty as limited scientific information is available for THMs other than chloroform, which indicates a toxicity threshold.

Water distribution system THM concentrations can be quite variable, temporally and spatially. Environmental data from the Pahokee and South Bay water systems demonstrate peak concentrations that have been reported to be 2–3 times the annual average (Fig 1-4). Quarterly sampling, conducted from 2000 to present, may not capture peaks and may not represent actual exposure [2]. Prior to 2000, sampling was even less frequent. Also, sampling locations may not include potential worse-case scenarios such as dead end lines or areas of low water usage. These limitations could result in exposure misclassification and possibly lead to underestimates of risks and distortions of exposure-response relationships. A biologically relevant exposure period for possible effects on prenatal development could be a few weeks or months. Peak exposure during this period may not be measured by periodic monitoring. As a result, use of water utility sampling data is generally considered inadequate for reproductive or developmental epidemiology studies of THM exposure. Researchers continue to recommended methods of improving the exposure assessment aspect for future epidemiology studies of THM and of improving the determination of the reproductive and developmental effects of those studies [2].

The elevated total THM levels at Pahokee and South Bay, the epidemiological studies suggesting associations between THMs and adverse birth outcomes, and the uncertainties in the level of maternal exposure at which adverse developmental or reproductive effects will occur provide a basis for prudent public health intervention at this site. Additionally, health education activities should be performed to provide guidance to potentially susceptible populations to enable them to lower their individual exposure. Finally, to better characterize the potential health implications of multiple exposure routes to a mixture of DBPs, including THMs, epidemiological and pharmacokinetic investigations should be considered.

Child Health Considerations

In communities faced with air, water, or food contamination, the many physical differences between children and adults demand special emphasis. Children could be at greater risk than are adults from certain kinds of exposure to hazardous substances. Children play outdoors and sometimes engage in hand-to-mouth behaviors that increase their exposure potential. Children are shorter than adults are; this means they breathe dust, soil, and vapors close to the ground. A child's lower body weight and higher intake rate results in a greater dose of hazardous substance per unit of body weight. If toxic exposure levels are high enough during critical growth stages, the developing body systems of children can sustain permanent damage. Finally, children are dependent on adults for access to housing, for access to medical care, and for risk identification. Thus adults need as much information as possible to make informed decisions regarding their children's health.

Children in Pahokee and South Bay are exposed to THMs when public water is used for cooking, drinking water, and bathing. Although laboratory animal studies do not indicate the prenate is more susceptible to single-route exposures to individual THMs, evidence from epidemiological studies suggests the prenate could be affected by multi-route drinking water exposures to a mixture of DBPs. ATSDR has considered possible effects on the prenate and children in the toxicological evaluation of THM exposure and has made appropriate recommendations. Children were not identified as a susceptible population. However, prenatal exposure remains of concern because of epidemiological evidence suggesting an association between adverse birth outcomes and chlorinated drinking water exposure and the lack of an identified level of maternal exposure at which adverse developmental or reproductive effects will occur. Although uncertainties preclude a definitive conclusion of a health hazard, ATSDR recommends prudent public health actions to reduce secondary exposure to the prenate by reducing primary exposure to women of child-bearing age if peak THM levels result in MCL violations.

Conclusions

ATSDR formulates conclusions based on the strength of toxicological, epidemiological, and environmental information. Conclusions reflect site-specific exposure scenarios to address potential health concerns and may not be applicable to other exposure scenarios.

Municipal water users in Pahokee and South Bay could have been exposed to total THMs, through multiple routes of exposure that exceeded the MCL in drinking water for at least 10 years. Because of multiple chemical exposures (THMs and other DBPs), multiple routes of exposure (ingestion, dermal, and inhalation), infrequent sampling and analysis, and the spatial and temporal THM variation within the distribution system, the exposure dose is uncertain. Moreover, the level of maternal exposure to DBPs, including THMs, at which adverse developmental or reproductive effects will occur is unknown.

Current exposures (2002 and later).

1. Pending additional investigations to evaluate epidemiological evidence and develop additional exposure information, ATSDR considers current prenatal exposures as *an indeterminate public health hazard* (Appendix B defines ATSDR's public health hazard categories. Indeterminate indicates that a professional judgment on the level of health hazard cannot be made because information critical to such a decision is lacking). This conclusion is based on the following:

    - Toxicological studies and epidemiological studies may not render equivalent conclusions. Epidemiological studies of chlorinated drinking water exposures by multiple routes may not be equivalent to laboratory animal studies of exposure to one THM by a single exposure route. Laboratory animal studies indicate that exposure to current levels of THMs would not cause adverse health effects, but uncertainties in exposure route pharmacokinetics and the level of maternal exposure at which adverse developmental or reproductive effects will occur preclude characterization as no apparent public health hazard.
    - Epidemiological studies provide suggestive but not conclusive evidence of an association between multi-route chlorinated drinking water exposures containing DBPs, including THMs, and adverse birth outcomes. The epidemiological evidence is insufficient for characterization as a public health hazard. Moreover,

the epidemiological evidence for an association at exposures below the MCL is less suggestive than at exposures above the MCL.

- Peak THM and other DBP levels are unknown and could be of concern in short-term prenatal exposures.

2. Exposures occurring at current levels of total THMs (near the MCL) are not expected to result in adverse health effects in the general population.

Past exposures (before 2002).

1. ATSDR considers past prenatal exposure to elevated total THMs as *an indeterminate public health hazard* because:
    - Although THM levels were higher in the past, the uncertainties presented above under current exposures would also apply to past exposures.
    - Historical peak levels are unknown.
2. Exposures occurring at historical THM levels are not expected to result in adverse health effects in the general population.

Recommendations

While toxicological data do not support describing exposures as presenting a health hazard at estimated exposure levels, the uncertainty of accurate exposure dose and the suggestion of potential adverse birth outcomes in epidemiological studies indicate following a prudent course of public health action. Therefore, ATSDR recommends the following:

1. Conduct more frequent monitoring or other effective means to characterize the frequency, magnitude, and spatial distribution of peak total THM levels within the public water systems. In this effort ATSDR can provide assistance with GIS-based mapping.
2. Implement measures to reduce secondary THM exposure to the prenate (via maternal dermal, ingestion and inhalation exposure) if peak THM levels, as determined by frequent monitoring, result in Maximum Contaminant Level (MCL) violations.
3. Conduct health education and community involvement activities for the South Bay and Pahokee communities
4. Investigate the feasibility of performing additional health investigation activities to determine the occurrence of adverse birth outcomes associated with multi-route exposure to THMs and other DBPs.
5. Investigate the feasibility of using physiologically based pharmacokinetic (PBPK) models to evaluate multiple routes of exposure.

Public Health Action Plan

Actions Completed

The cities of Pahokee and South Bay have provided resources to upgrade water treatment facilities, personnel, and methods. They have also provided effective operation and maintenance of their respective water treatment plants in an effort to achieve and

maintain compliance with the MCL for total THMs of 0.08 mg/L. THMs were monitored on a monthly basis following the water plant improvements.

The Palm Beach County Health Department and the Region 4 U.S. Environmental Protection Agency funded and established public drinking water stations dispensing GAC-treated water.

ATSDR has developed electronic GIS-based mapping of the distribution systems of Pahokee and South Bay.

Actions Ongoing

To achieve and maintain compliance with the MCL for total THMs of 0.08 mg/L, the cities of Pahokee and South Bay are continuing to provide resources necessary for the effective operation and maintenance of their respective water plants.

Palm Beach County Health Department is continuing to operate and maintain drinking water dispensing stations until THM levels can be maintained below the MCL during periods of seasonal peaks, i.e., summer and fall months. To ensure proper operation dispensing stations are inspected and tested on a periodic (i.e., weekly) basis.

Cities of Pahokee and South Bay/Palm Beach County Health Departments are continuing to monitor THMs and other relevant DBPs.

Actions Planned

ATSDR will work with its local and state public health partners to develop a health education plan for the Pahokee and South Bay communities.

ATSDR's Division of Health Studies will investigate the feasibility of performing additional health investigation activities to determine the occurrence of adverse health outcomes in Pahokee and South Bay.

To better characterize multiple routes of exposure, ATSDR's Division of Toxicology will investigate the feasibility of using physiologically based pharmacokinetic (PBPK) modeling.

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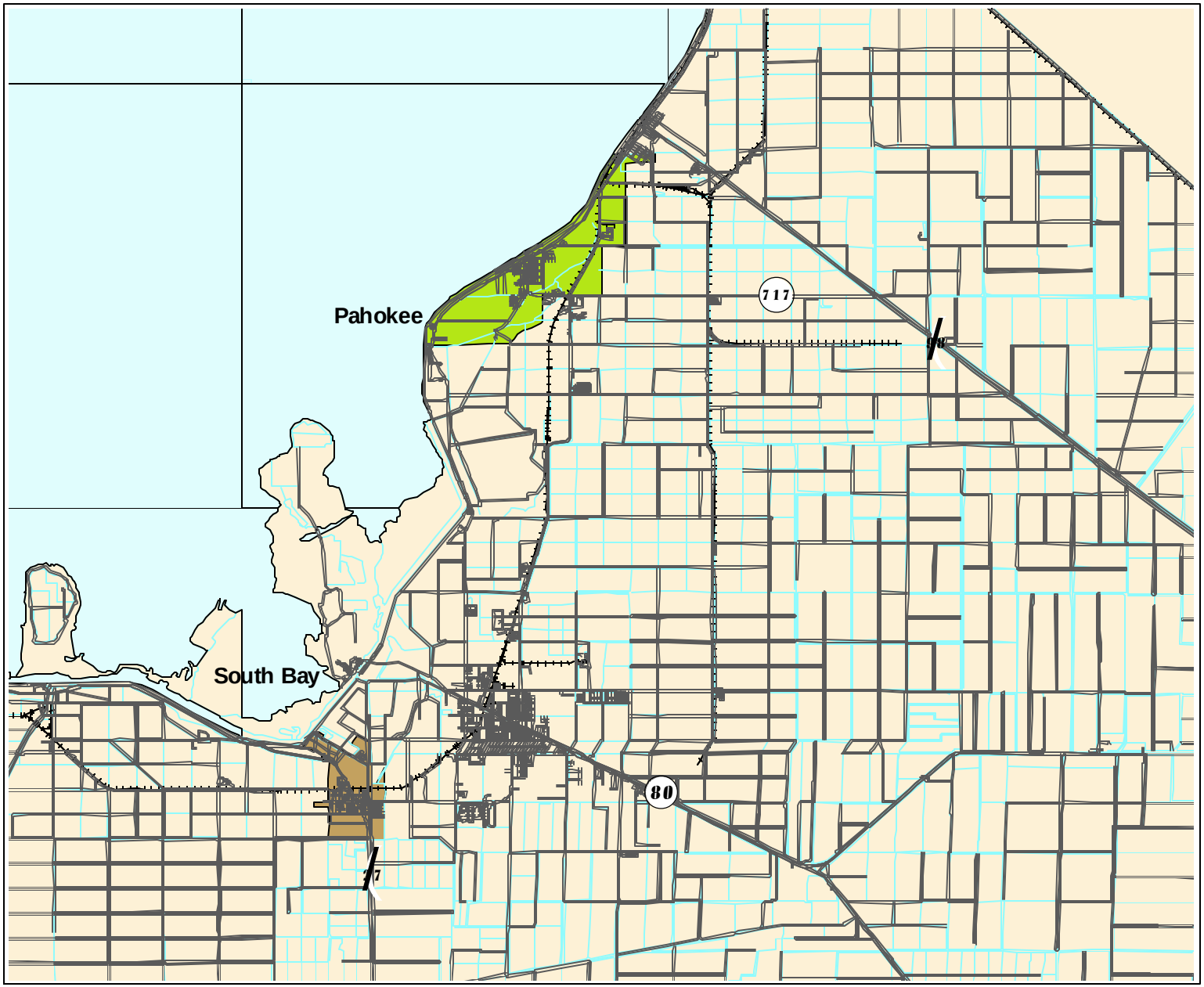
11 Florida Department of Environmental Protection. Chemical data for 1999, 2000, 2001. Tallahassee, FL: Drinking Water Section. Available at: http://www.dep.state.fl.us/water/drinkingwater/chemdata.htm. Last accessed 31 July 2003.

Appendices

Appendix A - GIS Intro Maps



Demographics

	Pahokee	South Bay
Total pop.	5,926	3,859
White	1,486	935
Black	3,319	2,583
Am. Indian	6	11
Asian	30	10
Pac.Islander	0	1
Other race	910	225
Two+ races	175	94
Hispanic	1,756	755
Age <=6	794	377
Age >=65	492	231
Females 15-44	1,190	572

Legend

- Streets and Roads
- City of Pahokee
- City of South Bay
- Lake Okeechobee
- Railroads
- Waterways

3 0 3 6 Miles

VICINITY MAP
Pahokee/South Bay Site Area
Palm Beach County, Florida

ATSDR GIS SAIDS

EWG10312002

Demographics of One-Mile Buffer

Total pop.	8910
White	1883
Black	5639
Am. Indian	9
Asian	36
Pacific Isl.	5
Other race	1105
Two+ races	234
Hispanic	2123
Ages <= 6	1265
Ages >= 65	686
Females 15-44	1916

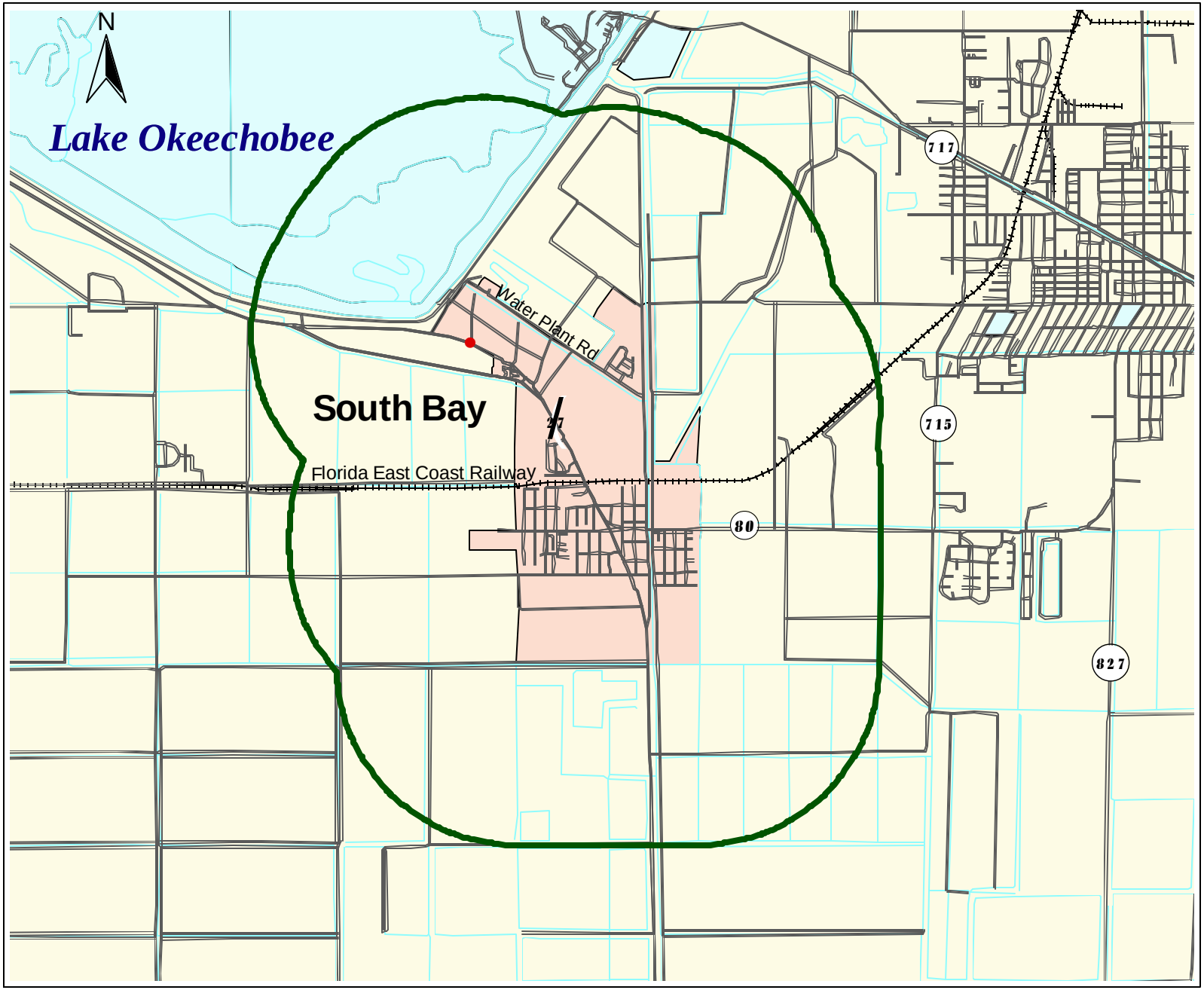
Legend

- 180 N. Lake St.
- Streets and Roads
- Railroads
- Waterways
- City of Pahokee
- One-Mile Buffer
- Lake Okeechobee

Pahokee/South Bay Site Area
City of Pahokee
Palm Beach County, Florida

ATSDR GIS SAIDS

EWG 11 052002



Demographics of One-Mile Buffer

Total pop.	**3896**
White	**962**
Black	**2583**
Am. Indian	**11**
Asian	**15**
Pacific Isl.	**1**
Other race	**230**
Two+ races	**94**
Hispanic	**772**
Ages <= 6	**379**
Ages >= 65	**237**
Females 15-44	**581**

Legend

- 1313 N. US Hwy. 27
- One-mile Buffer
- Roads
- Railroads
- Waterways
- City of South Bay
- Lake Okeechobee

1 0 1 2 Miles

Pahokee/South Bay Site Area
City of South Bay
Palm Beach County, Florida

EWG11052002

ATSDR GIS SAIDS

Appendix B - Interim Criteria of Actions for Levels of Public Health Hazard from ATSDR Public Health Assessment Guidance Manual, May 1, 1999

CATEGORY A: URGENT PUBLIC HEALTH HAZARD

This category is used for sites where short-term exposures (< 1 yr) to hazardous substances or conditions could result in adverse health effects that require rapid intervention.

This determination represents a professional judgment based on critical data which ATSDR has judged sufficient to support a decision. This does not necessarily imply that the available data are complete; in some cases additional data may be required to confirm or further support the decision made.

Criteria:

Evaluation of available relevant information* indicates that site-specific conditions or likely exposures have had, are having, or are likely to have in the future, an adverse impact on human health that requires immediate action or intervention. Such site-specific conditions or exposures may include the presence of serious physical or safety hazards, such as open mine shafts, poorly stored or maintained flammable/explosive substances, or medical devices which, upon rupture, could release radioactive materials.

**** Such as environmental and demographic data; health outcome data; exposure data; community health concerns information; toxicologic, medical, and epidemiologic data.***

ATSDR Actions:

ATSDR will expeditiously issue a health advisory that includes recommendations to mitigate the health risks posed by the site. The recommendations issued in the health advisory and/or health assessment should be consistent with the degree of hazard and temporal concerns posed by exposures to hazardous substances at the site. Based on the degree of hazard posed by the site and the presence of sufficiently defined current, past, or future completed exposure pathways, one or more of the following public health actions can be recommended:

- biologic indicators of exposure study
- biomedical testing
- case study
- disease and symptom prevalence study
- community health investigations
- registries
- site-specific surveillance
- voluntary residents tracking system
- cluster investigation
- health statistics review
- health professional education
- community health education
- substance-specific applied research

CATEGORY B: PUBLIC HEALTH HAZARD

This category is used for sites that pose a public health hazard due to the existence of long-term exposures (> 1 yr) to hazardous substance or conditions that could result in adverse health effects.

This determination represents a professional judgement based on critical data which ATSDR has judged sufficient to support a decision. This does not necessarily imply that the available data are complete; in some cases additional data may be required to confirm or further support the decision made.

Criteria:

Evaluation of available relevant information* suggests that, under site-specific conditions of exposure, long-term exposures to site-specific contaminants (including radionuclides) have had, are having, or are likely to have in the future, an adverse impact on human health that requires one or more public health interventions. Such site-specific exposures may include the presence of serious physical hazards, such as open mine shafts, poorly stored or maintained flammable/ explosive substances, or medical devices which, upon rupture, could release radioactive materials.

**Such as environmental and demographic data; health outcome data; exposure data; community health concerns information; toxicologic, medical, and epidemiologic data.*

ATSDR Actions:

ATSDR will make recommendations in the health assessment to mitigate the health risks posed by the site. The recommendations issued in the health assessment should be consistent with the degree of hazard and temporal concerns posed by exposures to hazardous substances at the site. Actions on the recommendations may have occurred before the actual completion of the public health assessment.

Based on the degree of hazard posed by the site and the presence of sufficiently defined current, past, or future completed exposure pathways, one or more of the following public health actions can be recommended:

- biologic indicators of exposure study
- biomedical testing
- case study
- disease and symptom prevalence study
- community health investigations
- registries
- site-specific surveillance
- voluntary residents tracking system
- cluster investigation
- health statistics review
- health professional education
- community health education
- substance-specific applied research

CATEGORY C: INDETERMINATE PUBLIC HEALTH HAZARD

This category is used for sites when a professional judgement on the level of health hazard cannot be made because information critical to such a decision is lacking.

Criteria:

This category is used for sites in which "*critical*" data are *insufficient* with regard to extent of exposure and/or toxicologic properties at estimated exposure levels. The health assessor must determine, using professional judgement, the "criticality" of such data and the likelihood that the data can be obtained and will be obtained in a timely manner. Where some data are available, even limited data, the health assessor is encouraged to the extent possible to select other hazard categories and to support their decision with clear narrative that explains the limits of the data and the rationale for the decision.

ATSDR Actions:

ATSDR will make recommendations in the health assessment to identify the data or information needed to adequately assess the public health risks posed by the site.

Public health actions recommended in this category will depend on the hazard potential of the site, specifically as it relates to the potential for human exposure of public health concern. Actions on the recommendations may have occurred before the actual completion of the public health assessment.

If the potential for exposure is high, initial health actions aimed at determining the population with the greatest risk of exposure can be recommended. Such health actions include:

- community health investigation
- health statistics review
- cluster investigation
- symptom and disease prevalence study

If the population of concern can be determined through these or other actions, any of the remaining follow-up health activities listed under categories A and B may be recommended.

In addition, if data become available suggesting that human exposure to hazardous substances at levels of public health concern is occurring or has occurred in the past, ATSDR will reevaluate the need for any follow-up.

CATEGORY D: NO APPARENT PUBLIC HEALTH HAZARD

This category is used for sites where human exposure to contaminated media may be occurring, may have occurred in the past, and/or may occur in the future, but the exposure is not expected to cause any adverse health effects.

This determination represents a professional judgement based on critical data which ATSDR considers sufficient to support a decision. This does not necessarily imply that the available data are complete, in some cases additional data may be required to confirm or further support the decision made.

Criteria:

Evaluation of available relevant information* indicates that, under site-specific conditions of exposure, exposures to site-specific contaminants in the past, present, or future are not likely to result in any adverse impact on human health.

****Such as environmental and demographic data; health outcome data; exposure data; community health concerns information; toxicologic, medical, and epidemiologic data; monitoring and management plans.***

ATSDR Actions:

If appropriate, ATSDR will make recommendations for monitoring or other removal and/or remedial actions needed to ensure that humans are not exposed to significant concentrations of hazardous substances in the future. Actions on the recommendations may have occurred before the actual completion of the public health assessment.

The following health actions, which may be recommended in this category, are based on information indicating that no human exposure is occurring or has occurred in the past to hazardous substances at levels of public health concern. One or more of the following health actions are recommended for sites in this category:

- community health education
- health professional education
- community health investigation
- voluntary residents tracking system

However, if data become available suggesting that human exposure to hazardous substances at levels of public health concern is occurring, or has occurred in the past, ATSDR will reevaluate the need for any follow-up.

CATEGORY E: NO PUBLIC HEALTH HAZARD

This category is used for sites that, because of the absence of exposure, do NOT pose a public health hazard.

Criteria:

Sufficient evidence indicates that no human exposures to contaminated media have occurred, none are now occurring, and none are likely to occur in the future.

ATSDR Actions:

No public health actions are recommended at this time because no human exposure is occurring, has occurred in the past, or is likely to occur in the future that may be of public health concern.

Appendix C - Estimating Exposure from Multiple Exposure Routes (Ingestion, Dermal Inhalation)

When showering in THM-contaminated water, a resident may be exposed from (1) breathing the portion of the contaminant that is released into the air and (2) absorbing the contaminant through the skin. A resident could inhale the vapor while showering and while standing in the bathroom immediately after showering.

One study in humans has demonstrated that the dermal absorption dose of chloroform is comparable to the shower inhalation dose [1].

ATSDR made the following assumptions to estimate chloroform exposure to residents who have used Pahokee and South Bay public water:

(1) a resident takes a 10 minute shower once per day, and

(2) a resident spends an additional 15 minutes in the bathroom after showering.

The maximum concentration of chloroform in the bathroom can be estimated by the following mathematical formula [2]:

$$C_a = \frac{C_w \times k \times F \times t}{V}$$

where:

C_a = air concentration in milligrams per liter (mg per cubic meters)

C_w= chloroform concentration in tap water in milligrams per liter (assumed to be 0.400 mg/L)

k = volatile mass transfer coefficient in liter per minute (conservatively assumed to be .9)

F= flow rate in liters per minute (L/min) (assumed to be 8 liters per minute)

t = shower time in minutes (10 minute shower)

V = bathroom volume in liters (assumed to be 10 cubic meters) (This is approximately the size of a small bathroom.)

If the concentration of chloroform in the shower water is 0.400 mg/liter (the estimated median exposure during the peak period of 2000), the maximum concentration of chloroform in the bathroom air is estimated to be 2.88 milligrams per cubic meter (mg/m^3) or 0.59 parts per million (ppm) (4.88 mg/m^3 = 1 ppm).

Assuming an adult breathes 1.0 cubic meter of air per hour and ingests two liters of water per day, the estimated exposure during showering and subsequent bathroom use and ingestion are as follows:

shower inhalation dose = (2.88 mg/m^3) x (1.0 m^3/hr) x (10/60 hr) = 0.48 mg/day

one shower/day

sink inhalation dose = (2.88 mg/m^3) x (1.0 m^3/hr) x (15/60 hr) = 0.72 mg/day

shower dermal dose = shower inhalation dose = 0.48 mg/day

ingestion dose = 0.400 mg/L x 2 L/day = 0.8 mg/day

total dose = $shower_{inh}$ + $sink_{inh}$ + $shower_{der}$ + ingestion = 2.48 mg/day

This model estimates a worst-case air concentration during showering and bathroom use since it does not take into account dilution from ventilation in the bathroom, and it assumes exposure at a maximum air concentration throughout duration of the bathroom use. The chloroform concentration will gradually increase to a maximum at the end of the shower then gradually decrease once the shower is turned off.

This model does not include THM exposure from cooking and laundering which is expected to be minimal.

References

1 Andelman JB. Total exposure to volatile organic compounds in potable water. In: Ram NM, editor. Significance and treatment of volatile organic compounds in water supplies. Boca Raton, FL: Lewis Publishers; 1990. p. 485–504.

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Appendix D - Toxicology of Trihalomethanes

General Toxicology

Trihalomethanes (THMs) are chemicals formed as by-products of chemical disinfection. THMs are one of many groups of disinfection by-products (DBPs) formed as a result of the chlorination of water containing organic material. Because of similar metabolism and toxicity, THMs are usually added together and addressed as total trihalomethanes. The U.S. Environmental Protection Agency's (USEPA's) maximum contaminant level (MCL) for drinking water is based on total THMs. Total THM concentrations consist of the sum of four specific chemicals: bromodichloromethane, dibromochloromethane, bromoform, and chloroform. Chloroform is the most studied of the THMs in terms of its metabolism and modes of action. Toxicological data for other THMs are more limited but indicate similar patterns of metabolism and toxicity. While toxicological studies usually address single compounds and routs of exposure, epidemiological studies have addressed exposure by total THMs and not by individual components. Laboratory animal studies indicate that chloroform and, presumably, other THMs exert toxic effects only after metabolic biotransformation to a reactive intermediate. While the following discussion focuses on chloroform toxicity, it should be noted that actual human exposures could consist of multiple routes of exposure to a complex mixture of disinfection byproducts (DBPs), including THMs, haloacetic acids, and others. Epidemiological studies of chlorinated drinking water exposures would necessarily include exposures to THMs and other DBPs.

Gastrointestinal absorption of chloroform by animals is rapid (peak blood levels at about 1 hour) and extensive (64–98%) [1, 2]. Limited data in humans indicate that gastrointestinal absorption is also rapid and extensive. While most laboratory animal studies of oral chloroform absorption have used oil-based vehicles and gavage dosing, most human exposure is via household use of drinking (potable) water which includes ingestion, inhalation, and dermal contact. The absorption following gavage administration of corn oil or water was similar. Time-to-peak blood concentration was similar for both, but chloroform concentrations were lower for corn oil gavage than aqueous gavage at all time points and the area under the curve was lower for chloroform in oil compared to chloroform in water [3]. These data indicate chloroform absorption was faster and greater from water than from corn oil, or first-pass metabolism in the liver might contribute to or explain the difference in blood concentrations [2,4]. During short-term exposures, mouse liver tumors were observed with gavage delivery of chloroform in oil but not with chloroform delivered *ad libitum* in drinking water [5].

Chloroform is also absorbed by both the dermal and inhalation routes of exposure [6]. Breath levels measured in human subjects after a normal shower were twice the breath levels measured after inhalation-only shower exposure, indicating an equivalent contribution from either inhalation or dermal routes of exposure. Breath levels measured after either exposure correlated with tap water levels of chloroform [7]. Other studies on human subjects observed blood levels of THMs higher after showering or bathing compared to ingestion, with chloroform levels higher than other THMs [8].

Chloroform, at concentrations similar to those reported in Pahokee and South Bay drinking water, is initially metabolized in animals and humans by the P450 enzymes, principally CYP2E1. While nearly all tissues are capable of metabolizing chloroform, the rate is greatest in liver, kidney, and nasal mucosa [9]. These tissues are also the principal sites of toxicity. The chief oxidative product is trichloromethanol, which rapidly and spontaneously dehydrochlorinates to form phosgene (CCl2OH), believed to be the oxidative metabolite responsible for much of

chloroforms toxicity. A free radical is formed upon reductive metabolism. At these concentrations, nearly all of a dose is metabolized; and as the concentration increases, increasing amounts are exhaled as the unmetabolized parent compound [10].

Excretion occurs primarily through the lungs, either as chloroform or carbon dioxide, with less than 0.01% excreted in the urine [4]. More than 90% of an oral dose was recovered in expired air within 8 hours [10].

Mode of Toxicity

The reactive metabolites formed during oxidative or reductive P450 metabolism are electrophilic and react with a wide variety of nucleophiles including enzymes, proteins, or the polar heads of phospholipids. Chloroform is metabolized to phosgene, which is highly reactive, and can bind with and inactivate cellular molecules. Phosgene is hypothesized to form covalent adducts with cellular macromolecules, affecting function and potentially leading to cell death. This mode of toxicity is supported by the finding in some reports that glutathione protects against the toxic effects of chloroform and that toxicity occurs only after glutathione levels have been depleted [9,11,12].

The toxicity of chloroform in the liver, kidney, and nasal mucosa is related to the metabolism of chloroform in these tissues. Nasal effects are the result of internal absorption and metabolism of chloroform as lesions also occur following oral exposure and the spatial patterns do not correlate with inhalation contact with surfaces [13,14]. Toxicity occurs in those tissues that have the highest ability to metabolize chloroform, and toxicity can be increased or decreased by agents increasing or decreasing the activity of the metabolic enzymes. In addition, differences in sex and species sensitivity to chloroform correlate with differences in metabolic capacity [15].

Non-cancer effects

Breathing air, eating food, or drinking water containing very high levels of chloroform for long periods can damage the liver and kidneys. Short-term exposure to very high concentrations of chloroform can cause neurological effects such as dizziness, fatigue, headache, loss of consciousness, and death [16]. These levels are much higher than those associated with drinking water exposures in Pahokee and South Bay and are not expected to occur in Pahokee or in South Bay.

Most of the metabolic activity at environmental exposure levels would be expected to occur by oxidative metabolism resulting in reactions with cellular enzymes, proteins, and the polar heads of phospholipids. Reactions with these macromolecules can have a variety of effects on viable cell function and cell wall integrity, depending on the particular macromolecules involved and extent of the reactions. The covalent binding of reactive intermediates to cellular molecules is highest in areas of the liver and kidney where cytotoxicity is greatest [17].

Reproductive and Developmental Effects

It is not known whether chloroform causes reproductive or developmental effects in people.

Laboratory animal studies have shown that miscarriages occurred in rats and mice that breathed air containing 30 to 300 ppm chloroform during pregnancy and in rats that orally ingested chloroform during pregnancy. Offspring of rats and mice that breathed chloroform during pregnancy had birth defects. Abnormal sperm were found in mice that breathed air containing 400-ppm chloroform for a few days. These levels are much higher (1000x) than exposure levels

associated with the use of drinking water. Oral laboratory animal studies indicate that effects occur at the same or higher doses as those that cause effects in the mother, suggesting that offspring effects could be secondary to maternal toxicity [18,19]. Inhalation laboratory animal studies are more limited than oral studies but suggest that prenatal toxicity may not be secondary to maternal inhalation toxicity [20,21].

Human epidemiological studies that estimated exposures during each trimester based on quarterly THM sample data have provided moderate evidence for associations with small for gestational age and neural tube defects. Neural tube defects are birth defects of the central nervous system evident at birth. These studies have also found suggestive evidence for associations with other birth defects, fetal deaths, spontaneous abortions, and miscarriages [22,23,24,25,26]. Studies have consistently suggested positive associations at levels of THMs considerably lower than the historical levels in Pahokee and South Bay. Most studies were performed at THM levels below comparison values for health concern—levels believed to be safe, and at which exposure would not be expected to result in adverse health effects even for sensitive populations. Statistical significance has been variable; whether the variability is from study design, insufficient numbers, or low THM levels which were insufficient for dose response characterization is unknown. Exposure characterization is another limitation of these epidemiological studies. In addition, most studies have used surrogates for exposure classification (such as residence location and THM sample data) instead of individual exposure information, such as the quantity of water actually consumed. Biological plausibility for developmental effects from exposure to chloroform has also been reported [27].

At Pahokee and South Bay, the THM levels measured during quarterly monitoring might not be indicative of actual exposures to the residents because of the spatial and temporal fluctuations in total THMs within the water systems and because peak levels might not be captured.

Cancer Health Effects

EPA describes the carcinogenic potential of THMs as follows: bromodichloromethane (probable carcinogen based on sufficient animal data and inadequate human data); dibromochloromethane (possible carcinogen based on limited animal and inadequate human data); bromoform (probable carcinogen based on sufficient animal and inadequate human data), and chloroform (probable carcinogen based on sufficient evidence in animals and likely to be carcinogenic to humans by all routes of exposure under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues. Chloroform is not likely to be carcinogenic to humans by any route of exposure under exposure conditions that do not cause cytotoxicity and cell regeneration.)[15]. While all THMs have carcinogenic potential at some dose, chloroform has been the most studied and is the most prevalent THM found in chlorinated drinking water. While mode of action for other THMs has not been investigated as much as chloroform, it is assumed in the absence of conflicting information that the chemical similarity may lead to similar metabolism and mode of action and effect [28, 29, 30]. Therefore, most of the discussion is centered around knowledge of chloroform.

There have been a number of epidemiological studies of cancer in humans exposed to chlorinated drinking water. Chlorinated drinking water typically contains chloroform, other trihalomethanes, and a variety of other disinfection byproducts and exposure occurs by multiple routes. Exposure to disinfection byproducts has been most consistently associated with bladder cancer in humans [31,32]. Current epidemiological data are insufficient to establish a causal relationship between exposure to THMs in drinking water and increased risk of cancer, but the evidence can be characterized as moderate for a cause-effect relationship with adult bladder and rectal cancers after a lifetime of exposure (i.e., >25 or >30 years).

Chloroform has been shown to cause increased incidence of liver and kidney tumors in several laboratory animal species by several exposure routes. This carcinogenic response in laboratory animals, however, occurs only at dose levels that result in cytotoxicity. The strength of evidence indicates that carcinogenic responses observed in animals are associated with regenerative hyperplasia that occurs in response to cytolethality [3,33]. Findings from laboratory animal studies include:

- liver tumors in both sexes of mice develop after daily doses by corn oil gavage [34],
- liver tumors in female mice are seen only after bolus corn oil dosing, but not found after administration by other routes (drinking water and inhalation) [5],
- kidney tumors are found in male mice exposed via inhalation, corn oil gavage, or in toothpaste preparations [35], and
- kidney tumors are found in male rats exposed via drinking water or corn oil gavage [36].

In numerous cases exposure relates to an increase in the Labeling Index without an increase in cancer incidence, indicating that exposures adequate to cause toxicity and regenerative cell proliferation do not always lead to cancer. Measuring the Labeling Index is a surrogate measure of increases in replication by measuring the proportion of cells in S phase and therefore indicates when cells divide and form new cells. Cell regeneration is detected in all cases of tumorigenicity in laboratory animals. There are no observed cases in laboratory animals of the presence of tumors where cell regeneration is not also present at the same or lower doses. Tumors only develop at doses causing persistent cytotoxicity and regenerative proliferation, regardless of route of exposure or dosing regime [15].

Available data on the mutagenic and genotoxic potential of chloroform are mixed, but the majority of tests are negative, and some of the positive results are observed only at extreme exposure conditions. Genotoxicity data on chloroform support a conclusion that chloroform is not strongly mutagenic and that genotoxicity is not likely to be the predominant mode of action underlying its carcinogenic potential. In initiation-promotion studies, chloroform does not promote development of hepatic lesions in rats or in two strains of mice, nor does it initiate or act as a co-carcinogen—although it was a promoter in rat liver when administered in oil.

The theory that sustained cell proliferation to replace cells killed by toxicity can be a significant risk factor for cancer is plausible and generally accepted [37]. Sustained cytotoxicity and regenerative cell proliferation can result in a greater likelihood of spontaneous mutations being perpetuated with the possibility of one or more of these resulting in uncontrolled growth. Continuous stimulus of proliferation by growth factors involved in inflammatory responses increases the probability that damaged cells can transverse cell cycle checkpoints carrying unrepaired DNA alterations. Chemicals that promote cell division can convey a selective growth advantage to preexisting initiated cells, with less time available to be repaired before mitosis. Cells undergoing cell division are inherently more susceptible to initiation than are slowly growing or nondividing cells. DNA undergoing replication is more exposed to nucleophilic attack than DNA covered with histones and arranged in nuceosomes [38,39].

Cumulative cancer risk assessment, assuming addition of risks is appropriate, indicates that risks from historical exposures are estimated to have been 2E-04 for the exposure routes of ingestion, inhalation, and dermal. Since alternate drinking water has been provided, estimated cumulative risks for inhalation and dermal exposures have been reduced to 1E-04. Bromodichloromethane

(6E-05, based on an Oral Slope Factor of 6.2E-2/mg/kg/day) and chlorodibromomethane (5E-05, based on an Oral Slope Factor of 8.4E-02/mg/kg/day) represented the highest risk. Assumptions include a drinking water concentration of 0.400 mg/L, consumption of 2 L/day, inhalation rate of 1 m^3/hour for 20 minutes/day, dermal exposure for 10 minutes/day, a body weight of 70 kg, and a duration of 10 years. To examine a worst-case scenario for each chemical, individual constituents of total THMs were assigned weights based on historical maximum quarterly values (e.g. bromodichloromethane represented <29%, chlorodibromomethane represented <17%, bromoform represented <2%, and chloroform represented <85%). These worst-case individual estimates of risk were summed to represent a worst-case cumulative risk scenario. For perspective, using the same assumptions, cumulative cancer risks at the total THM MCL of 0.080 mg/L are estimated to be 4E-05; whereas, lifetime exposure to total THM MCL levels are estimated to be 2E-04.

Comparison Values

Non-cancer, oral comparison values (Table 1) have been developed by ATSDR and EPA based on laboratory animal studies determining the lowest level where effects were observed (an oral dose of 15 mg/kg/day in dogs) or where no effects were observed (26 mg/kg/day in rodents) [40, 5]. Effects have been reported in humans medicinally exposed at an oral dose of 21 mg/kg/day [41]. At Pahokee and South Bay, oral exposure estimates for drinking water were about 0.01 mg/kg/day or about 1000 times below levels at which effects have been observed in laboratory animals or non-drinking water exposures in humans.

Table 1. Trihalomethane Comparison Values.

Trihalomethane	***Oral MRL (mg/kg/day)*** ***Inhalation MRL (ppb)***			***CREG (ppb)***
	Acute	Intermediate	Chronic	Oral/inhalation
chloroform	0.3 100	0.1 50	0.01 20	NA
bromodichloromethane	0.04 NA	NA	0.02 NA	0.6/NA
chlorodibromomethane	0.04 NA	NA	0.03 NA	0.4/NA
bromoform	0.6 NA	NA	0.2 NA	4/0.9

THM: Trihalomethane
MRL: Minimum Risk Level
CREG: Cancer Risk Evaluation Guide
NA: Not Available
mg: milligram
kg: kilogram
ppb: parts per billion

A chloroform inhalation concentration of greater than 2 ppm for exposure to both rodents and humans, resulting in a weekly human dose of 0.27 mg/kg/day, was used to develop inhalation comparison values [42, 43]. At Pahokee and South Bay, maximum airborne chloroform concentrations occur during showering and sink exposures for brief periods each day, resulting in a weekly inhalation dose from drinking water exposure estimated to have been 0.0006 mg/kg/day, or 400 times less than the inhalation comparison value for chloroform.

Chemical mixtures and multiple routes of exposure

Studies used to establish comparison values do not reflect actual drinking water exposure scenarios. Laboratory animal studies administered chloroform by gavage, water bottles, or toothpaste, appropriately limiting exposure to one route (ingestion). By the ingestion route of exposure, chemicals are first transported from the gut to the liver before distribution to the rest of the body. With chloroform, the metabolites of interest are too reactive to exit the liver before reacting with cellular constituents. By the inhalation route of exposure, chemicals are first distributed from the lungs throughout the body before being metabolized by the liver. The route of exposure is thus especially important when considering prenatal exposures. Human exposures to drinking water not only involve ingestion, but also inhalation and dermal exposure. Therefore, epidemiological studies could more accurately reflect actual exposure scenarios and could explain why some studies have suggested human health effects at levels at which adverse health effects would not be expected from laboratory animal studies.

Laboratory animal studies have not adequately addressed the potential health implications for chemical mixtures or multiple routes of exposure. Most human epidemiological studies have not quantitatively identified the chemicals in the drinking water mixtures to which exposure occurred. The distribution and quantity of chemicals can vary considerably. While chloroform and bromodichloromethane are the most prevalent THMs, other disinfection byproducts of health concern could be present in chlorinated drinking water, including haloacetic acids and 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX). There is evidence of the importance of consideration of chemical mixtures in drinking water as dichloroacetic acid and trichloroacetic acid, normal constituents of chlorinated drinking water, could potentiate chloroform-induced toxicity [44] while other studies have reported less than additive responses to mixtures of disinfection byproducts [45]. Chloroform has been included in laboratory animal studies of an artificial mixture of chemicals found at hazardous waste sites. While reproductive, immunological, and hematopoietic effects have been reported in these studies, it is not possible to discern the specificity of interactions [46,47,48,49].

Assuming that addition of the dose to which one might be exposed by each exposure route is appropriate, the cumulative daily dose would be 2.48 mg/day or 0.035 mg/kg/day (see Appendix C). Addressing multiple exposure routes requires the appropriate pharmacokinetic evaluation of the multiple exposures.

Strength of Evidence

ATSDR develops professional judgement conclusions based on the strength of all evidence. The main sources of evidence in this assessment are environmental, toxicological, and epidemiological. Following is a summary of the strengths and weaknesses of each.

Environmental

Environmental data describe THM levels at Pahokee and South Bay as exceeding MCL levels for at least 10 years. Data also indicate spikes that are at least 2-3 times the quarterly averages. Most historical data are quarterly averages which may not capture spikes or represent actual exposure conditions. The spatial and temporal variation in the distribution system has not been characterized and sampling locations may not reflect worse-case locations for THM exposure.

Toxicological

Laboratory animal studies indicate that THM exposure at levels found currently and in the past at Pahokee and South Bay would not be expected to result in adverse noncancer (including developmental/reproductive effects) or cancer health effects. Most studies were conducted with exposure by only one route (generally by gavage) to only one chemical (generally to chloroform). Developmental/reproductive studies involving inhalation exposure are limited.

Laboratory investigations of human exposures to drinking water indicates that inhalation, dermal, and ingestion are equivalent routes of exposure with showering or bathing activities resulting in higher THM blood levels than ingestion [8].

Epidemiological

Virtually all the studies *suggest* an association between adverse birth outcomes and THM levels in chlorinated drinking water. Most of the studies had statistically significant findings. Exposure characterization in these studies is was based on quarterly THM sample data so there is imprecision as to the exact levels of THMs a mother may have been exposed during pregnancy. Some of the studies also could not obtain the mother's water consumption information during her pregnancy. The routes of exposure include ingestion, inhalation, and dermal. The THM levels in the drinking water systems included in these studies were considerably lower than levels reported at Pahokee and South Bay.

In conclusion:

A maternal inhalation and dermal exposure during showering or bathing with chlorinated tap water could result in a prenatal exposure which may be simulated in epidemiological studies but may not be simulated in toxicological studies. Uncertainties in low dose exposures to THMs and other DBPs, maternal and prenatal pharmacokinetics, and the level of maternal exposure at which adverse developmental or reproductive effects will occur preclude a definitive public health hazard conclusion but indicates a need for additional information and suggests that exposure intervention would be a prudent public health activity.

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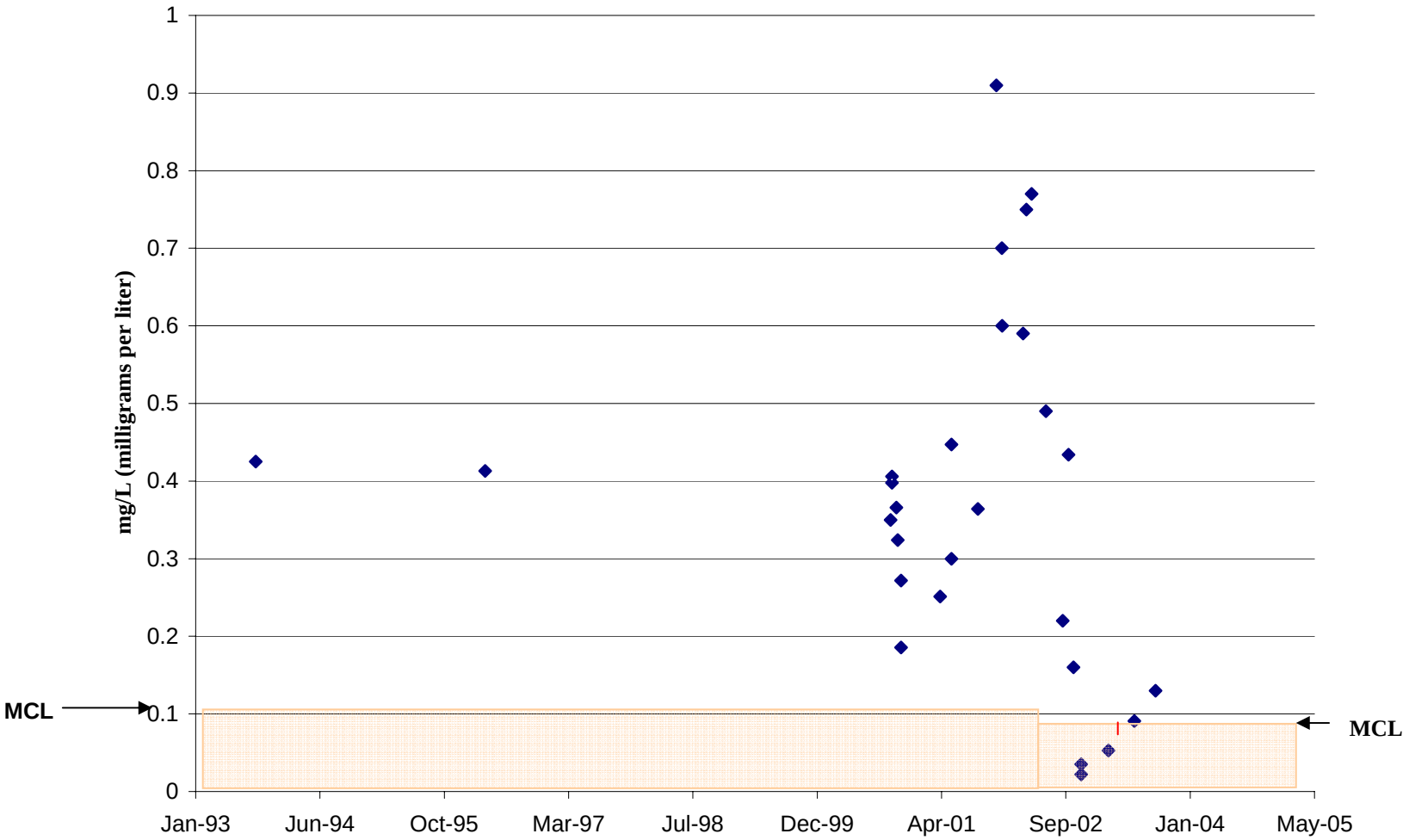
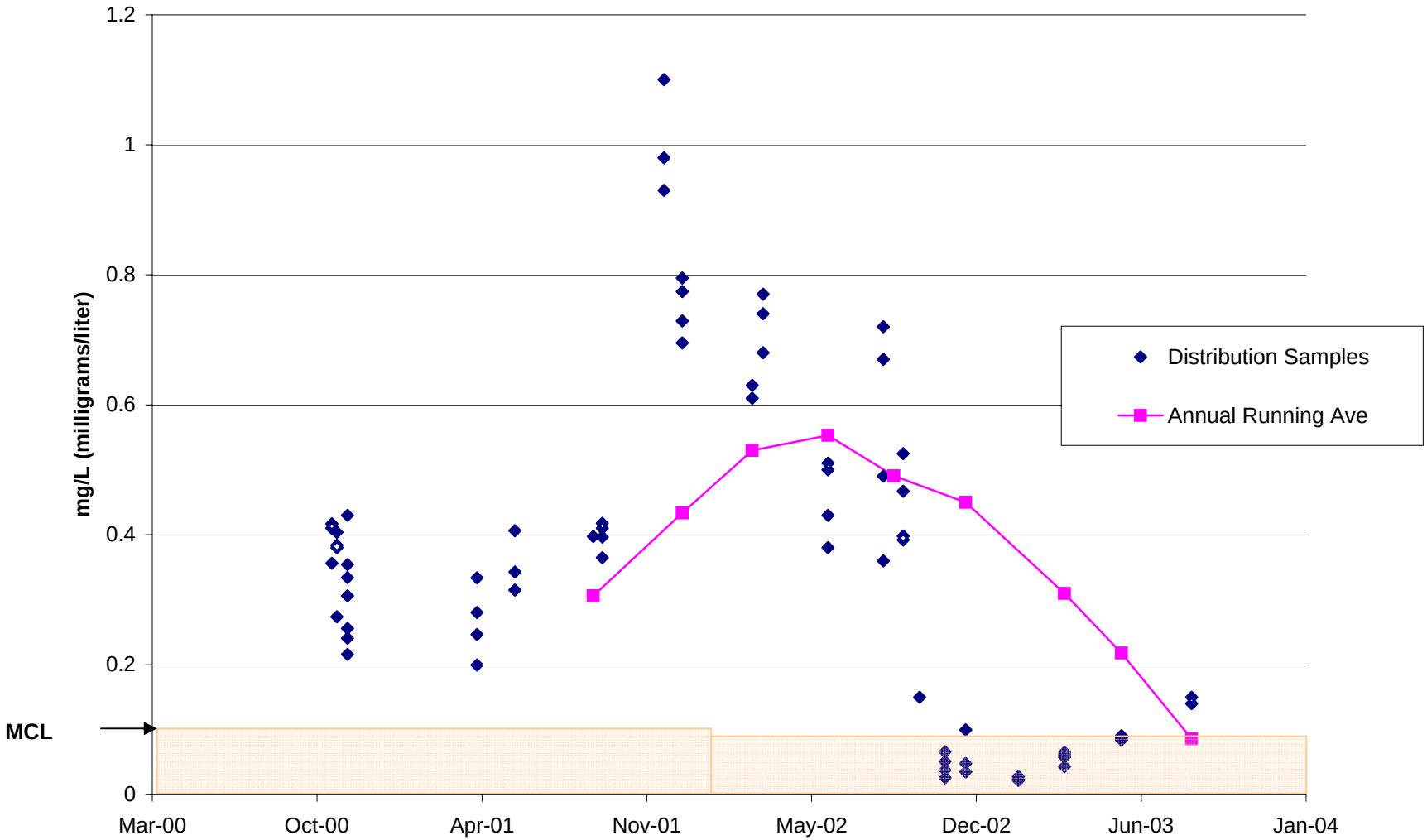
Appendix E – Figures

Figure 1 - Total Trihalomethane (THM) Levels in the Pahokee, Florida Municipal Water System - Point of Entry Samples



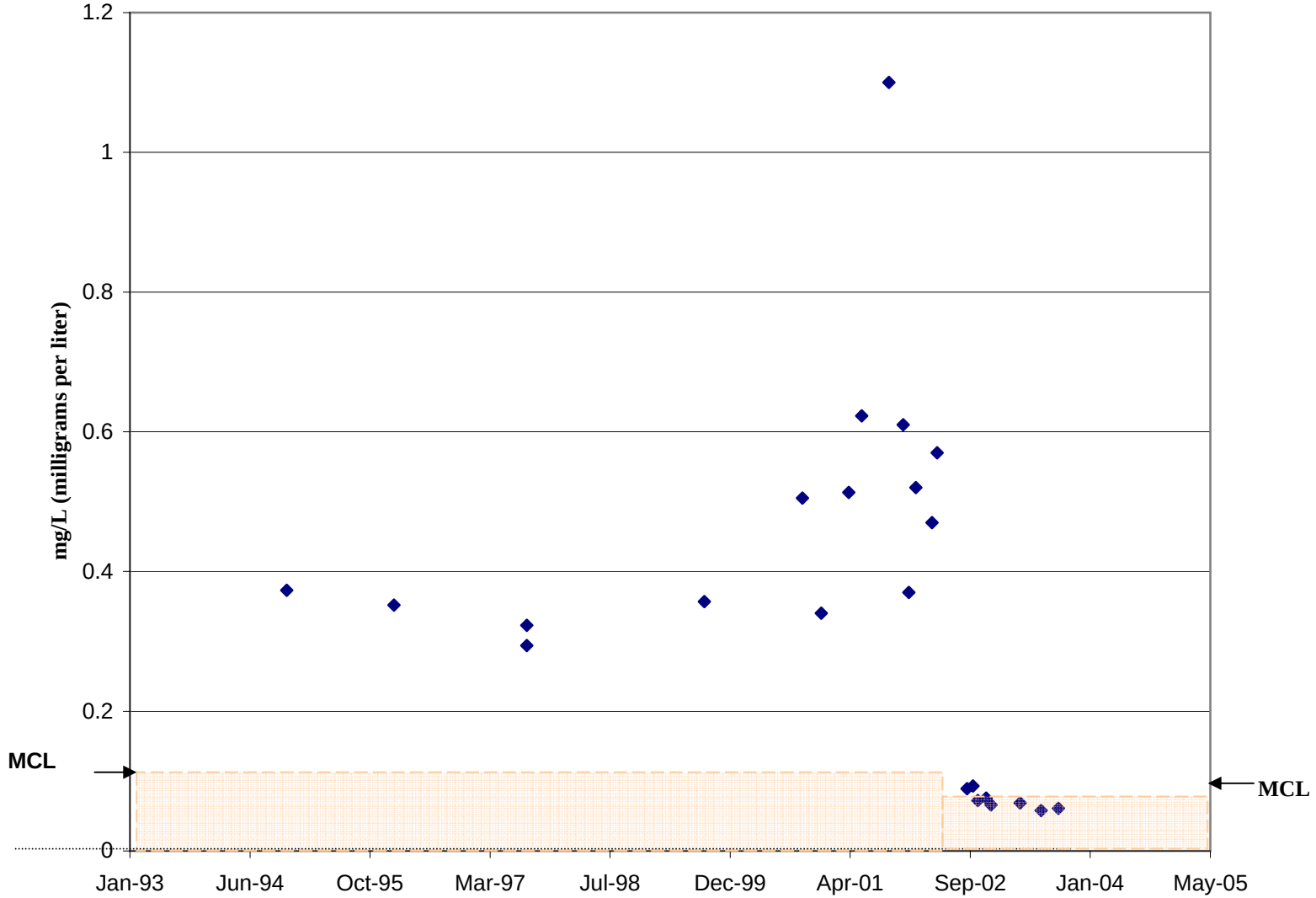
MCL = United States Environmental Protection Agency's Maximum Contaminant Level for Total Trihalomethanes for water systems serving more than 10,000 persons, and systems serving less than 10, 000 starting in January 2004

Figure 2 - Total Trihalomethane (THM) Levels in the Pahokee, Florida Municipal Water System - Distribution Samples



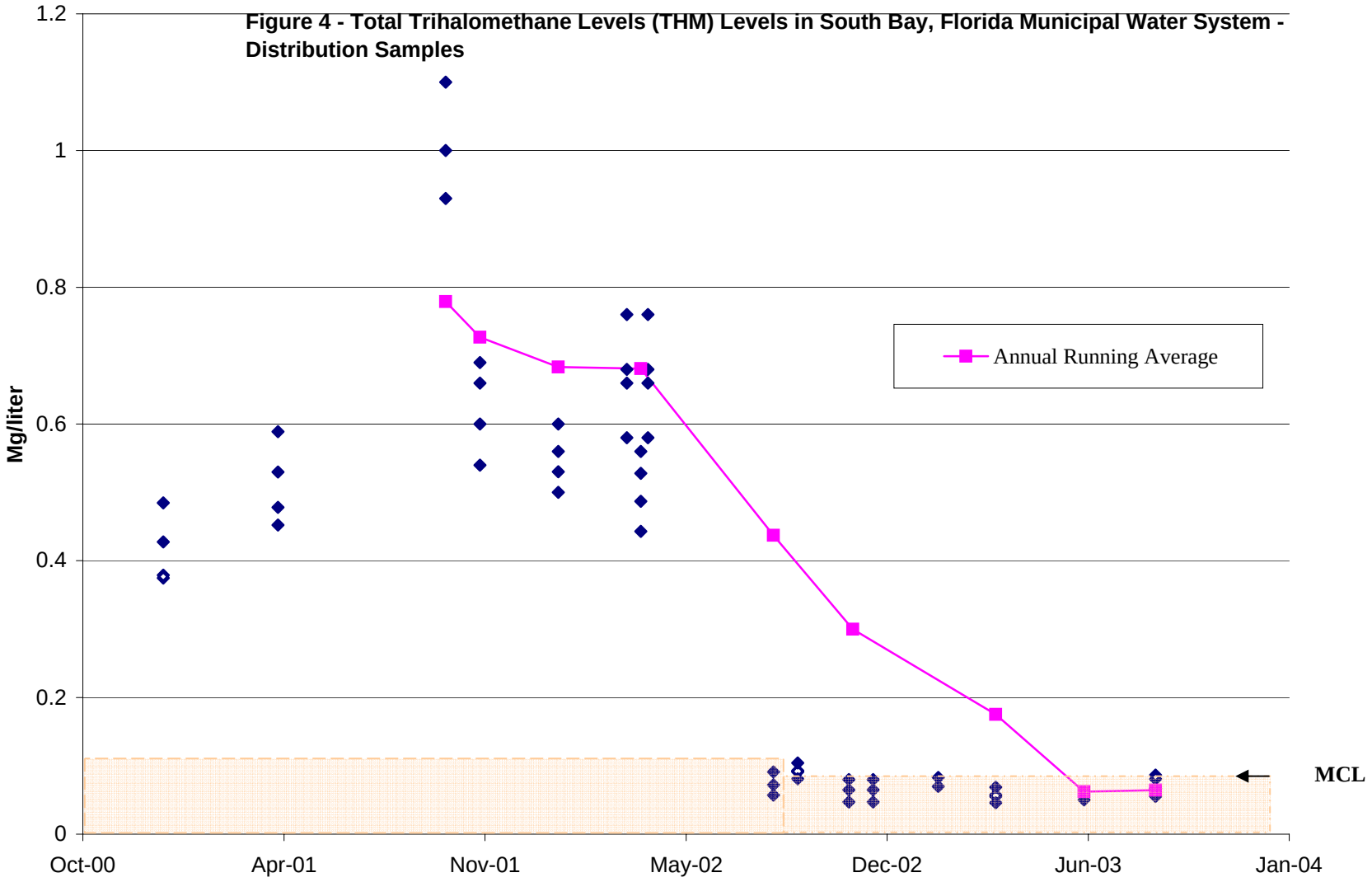
MCL = United States Environmental Protection Agency's Maximum Contaminant Level for Total Trihalomethanes for water systems serving more than 10,000 persons, and systems less than 10,000 starting in January 2004

Figure 3 - Total Trihalomethane Levels (THM) Levels in the South Bay, Florida Municipal Water System - Point of Entry Samples



MCL = United States Environmental Protection Agency's Maximum Contaminant Level for Total Trihalomethanes for water systems serving more than 10,000 persons, and systems serving less 10, 000 after January 2004

Figure 4 - Total Trihalomethane Levels (THM) Levels in South Bay, Florida Municipal Water System - Distribution Samples



MCL = United States Environmental Protection Agency's Maximum Contaminant Level for Total Trihalomethanes for water systems serving more than 10,000 persons, and systems serving less 10, 000 after January 2004

Figure 5 -The Composition of Total Trihalomethanes in the Pahokee Florida Municipal Water System - Water Samples - Aug 2002

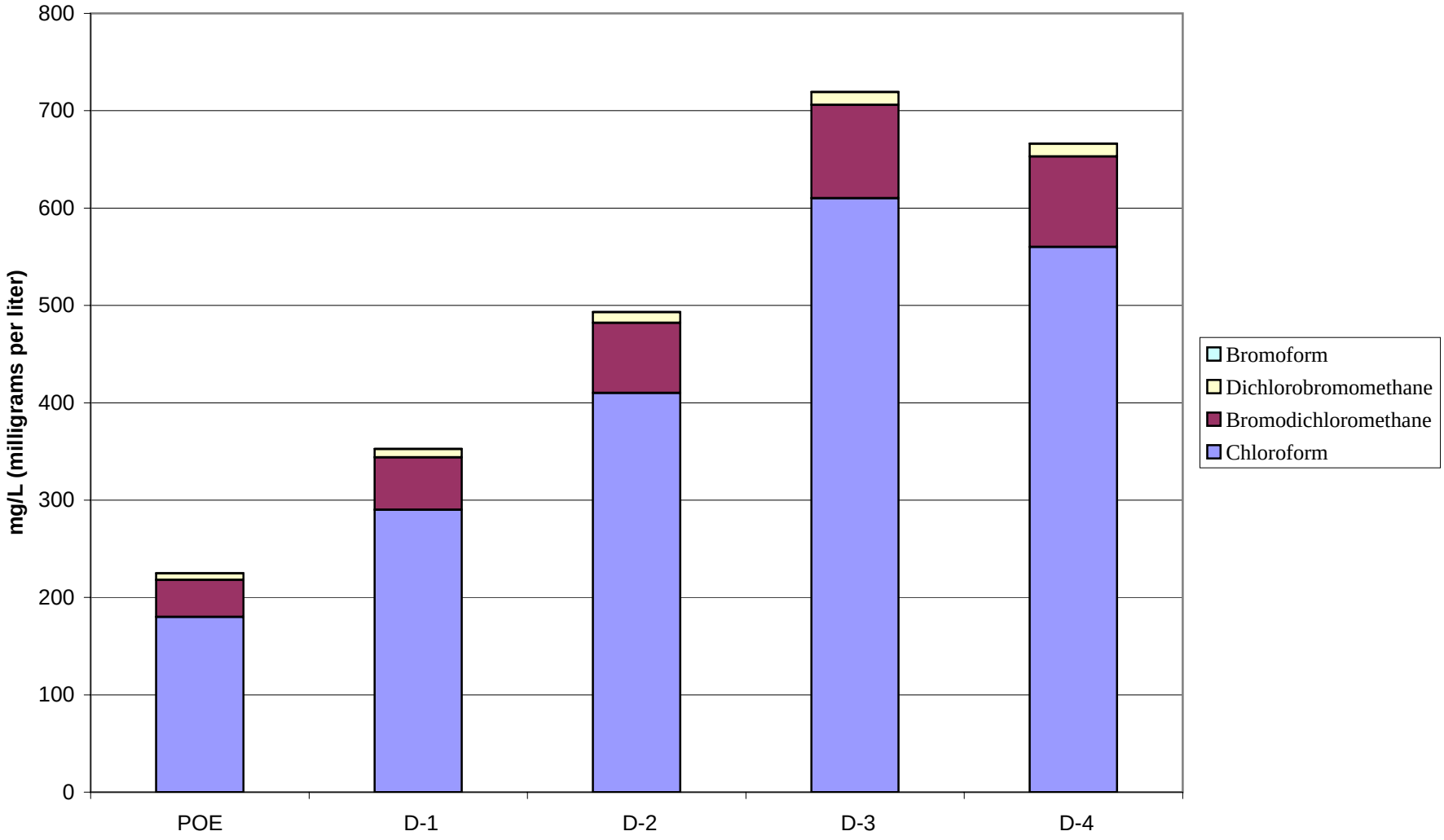


Figure 6 - The Composition of Total Trihalomethanes in the South Bay Florida Muncipal Water System Water Samples - August 2002