Health Consultation

NITRATE CONTAMINATION AND METHEMOGLOBINEMIA IN THE STATE OF CALIFONIA

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry
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HEALTH CONSULTATION

NITRATE CONTAMINATION AND METHEMOGLOBINEMIA IN THE STATE OF CALIFORNIA

Prepared by:

California Department of Health Services
Under Cooperative Agreement with the
Agency for Toxic Substances and Disease Registry

BACKGROUND AND STATEMENT OF ISSUES

Rationale and purpose

The Environmental Health Investigations Branch of the California Department of Health Services (CDHS) received a call from a Regional Water Quality Control Board. The agency requested information on the occurrence of infant methemoglobinemia cases statewide, because it was studying the potential health effects of nitrate contamination of water sources. This report addresses the issue of methemoglobinemia cases. The original work for this topic was conducted as part of an investigation of whether there were methemoglobinemia cases in the vicinity of the Laboratory for Energy-Related Health Research (LEHR) site in Davis, California (Cerclis # CA289019000).

In California, nitrate and nitrite contamination of groundwater is a statewide problem resulting from agricultural practices. Over 464,000 persons statewide rely on individual well water for their drinking water (1). This is particularly true in unincorporated areas not serviced by municipal water supplies. If these wells contain elevated levels of nitrate, a health problem could result. The primary concern is about infants who drink formula mixed with well water. This could result in "blue baby syndrome," or methemoglobinemia, a potentially life-threatening condition in which the blood is unable to transport oxygen normally. Unlike other environmentally related illnesses that may develop after long term, chronic exposures, methemoglobinemia from nitrate-contaminated water is an acute and potentially fatal illness that poses its threat only during a very narrow window of time in a person's life. The fact that it is entirely preventable with very simple prevention measures makes it an especially worthwhile focus of health education efforts.

This health consultation investigates the occurrence of hospitalized cases of infant methemoglobinemia in an attempt to determine whether any could be nitrate-related from contaminated drinking water. This investigation is limited because other substances and conditions are capable of causing methemoglobinemia, and methemoglobinemia is not subject to mandatory physician reporting. This consultation reviews hospitalization data for the state of California for a 13-year period (1983-1995). Additionally, demographic and geographical information available about these cases is summarized, and relevant background information on nitrate and methemoglobinemia is provided.

Scope of report and exclusions

This report focuses on infant methemoglobinemia. Other hypothesized adverse health effects of nitrate in drinking water, such as cancer, miscarriages, diabetes, or birth defects, are not considered. Similarly, whether exposure to nitrate-contaminated water would be harmful to newborns and young infants at levels below those causing acute clinical methemoglobinemia is not addressed.

Sources of nitrates in the environment

Higher than typical levels of nitrate and nitrite can occur in several ways. Fertilizers containing nitrogen can be converted to nitrate in the soil (2). Water from irrigation or heavy rainfall, particularly following drought, can create runoff containing chemical fertilizers from nearby farm fields, which can then contaminate well water, especially in more shallow wells. Human and animal waste from livestock operations and septic tanks also create nitrate and nitrite when ammonia present in the waste is oxidized (2).

Nitrate and nitrite also occur naturally in the environment, and, in small amounts, are normal components of the human diet. Most of our daily nitrate intake comes from certain vegetables, and drinking water is generally only a small percentage of the total (2).

California CERCLIS sites with nitrate contamination

A number of the sites for which CDHS, in cooperation with the Agency for Toxic Substances and Disease Registry (ATSDR), has conducted a health assessment or other review have a nitrate contamination problem, either from site-related contamination or area-wide agricultural contamination (Table 1). The Laboratory for Energy-Related Health Research, in the Sacramento area, has nitrate contamination above the Maximum Contaminant Level (MCL) (3). The average concentrations in wells sampled near LEHR were above the MCL (3). Also in the Sacramento area, at least one private well near the Aerojet site had a nitrate reading above the MCL (4). At El Toro Marine Corps Air Station, nitrate was found in groundwater at concentrations 14 times the MCL (5). Several sites with nitrate contamination were identified in Fresno county, a heavily agricultural county: Industrial Waste Processing, where a municipal well was closed because of nitrate contamination exceeding the MCL (6), and at T.H. Agriculture and Nutrition, where nitrate contamination was found in private well samples above the MCL (7). Nitrates also are a contaminant in San Gabriel groundwater, another agricultural area; water suppliers relying on this groundwater have been dealing with these levels exceeding the MCL by blending the water they deliver to customers (8). However, because in California nitrate contamination generally results from agricultural practices, it is not considered a contaminant release under CERCLA ("Superfund") law, and thus may not be a focus of hazardous waste site investigations conducted by the US Environmental Protection Agency (USEPA) (8).

Maximum contaminant levels for nitrate/nitrite

Nitrate and nitrite are sometimes expressed in different ways, so the unit of measurement requires explanation. The level of nitrate or nitrite in water can be given as milligrams of nitrate per liter of water (mg/L) or parts of nitrate per million parts of water (ppm). Also, another way nitrate or nitrite can be reported is as mg/L (or ppm) of the nitrogen part of nitrate or nitrite. This is referred to as "nitrate (or nitrite) as nitrogen." The current MCL for nitrate in drinking water is 10 mg/L (nitrate as nitrogen) or 45 mg/L (nitrate). Table 2 shows the different ways MCLs are reported.

Nitrate as a cause of methemoglobinemia

The primary health concern due to nitrate or nitrite exposure is methemoglobinemia. Nitrate itself is relatively non-toxic, but it can cause methemoglobinemia after it is converted to nitrite by bacteria which are normally present in the gastrointestinal tract (9). Nitrite then enters the bloodstream, where it reacts with hemoglobin to form methemoglobin (9). Unlike hemoglobin, methemoglobin cannot transport oxygen. Low concentrations of methemoglobin occur in normal people, and methemoglobinemia concentrations of up to 10% may occur without clinical signs (2). This lack of oxygen in concentrations above 10% can produce cyanosis, characterized by bluish lips and skin color. Higher concentrations (25% and above) are associated with hypotension, rapid pulse, and rapid breathing; above 50% can be fatal (2). The level of toxicity of nitrate depends on how much of it is converted to nitrite, which depends on the concentration and type of bacteria present.

The risk of methemoglobinemia is most acute in infants in the first 6 months of life (10). The infant stomach has low acidity, which allows for the growth of bacteria that can convert nitrate to nitrite (9). Also, the type of hemoglobin in the infant's blood is more easily changed to methemoglobin than in an adult (9), and the enzyme systems that change methemoglobin back to hemoglobin are not developed properly yet, either (11). Once the intestinal tract is fully developed and other physiological changes have occurred, methemoglobinemia from nitrate in drinking water is no longer a risk.

Infants are at risk if they are fed nitrate- or nitrite-contaminated water, most likely mixed with powdered formula. This risk is increased if the water is boiled, as the nitrate becomes more concentrated. Bacterial count may contribute to toxicity by reducing nitrate to nitrite (9). Unfortunately, high bacterial content is often found in water with high nitrate levels (9). A deficiency of Vitamin C may also contribute to toxicity; on the other hand, supplements may be used in treatment of mild cases.

Potential for failure to recognize methemoglobinemia

It is possible the true incidence is underestimated, as morbidity and mortality among infants from nitrate-induced methemoglobinemia may be misdiagnosed, perhaps as sudden infant death syndrome (12). Because the onset of illness may be difficult to distinguish from other conditions, there is a danger of the exposure continuing, with possible severe consequences. One case history documents a baby girl born in 1986, who was initially breast-fed but later received formula mixed with well water (12). At her 1-month check-up, her mother reported episodes of blueness around her mouth, hands, and feet, which started when she was about two weeks old. The mother also reported the infant had some trouble breathing and had experienced episodes of diarrhea and vomiting. At the time, the physician attributed the blueness to the room temperature. At 7 weeks a pharmacist noted the child appeared not to be receiving enough oxygen, and she continued to receive formula prepared with well water. At 8 weeks, she began vomiting, had diarrhea, and became cyanotic. She was immediately taken to a doctor, who referred her to a hospital 33 miles away. Her respiration ceased en route. It was later determined that the well water was contaminated with 150 mg/L nitrate as nitrogen (12).

Although this fatality involved quite high levels of nitrate, it is easy to see how it could be difficult to recognize the condition in a timely manner.

Sensitive subpopulations and contributing conditions

Sensitive subpopulations have been identified for methemoglobinemia. These include African Americans, Alaskan Eskimos, and Native Americans, some of whom lack a hereditary enzyme that helps reduce methemoglobin levels in the blood (13). Also, dialysis patients are uniquely susceptible to methemoglobinemia, and it has been recommended that water for dialysis treatments not exceed 2 mg/L nitrate as nitrogen (10).

Infections and inflammatory conditions increase the process of methemoglobinemia production (2). Infants experiencing illnesses of this sort are thus at greater risk for developing methemoglobinemia when exposed to nitrate sources. Any individuals who suffer from stomach conditions such as gastric ulcers, pernicious anemia, adrenal insufficiency, gastritis, or gastric carcinoma are likewise at risk because these conditions reduce stomach acidity and cause more nitrate to be converted to hazardous nitrite (11).

ATSDR Child Health Initiative

ATSDR recognizes that infants and children, in general, may be more sensitive to exposures than adults who encounter contamination of their water, air, or food. Because children depend completely on adults for risk identification and management decisions, ATSDR is committed to evaluating their special interests at all sites, as part of the ATSDR Child Health Initiative.

In the case of nitrate and methemoglobinemia, as the health consultation discusses, infants under 1 year of age represent a special population that is more sensitive to nitrates. According to the 1990 census, over 424,000 infants under the age of 1 reside in California (14). As this health consultation primarily addresses this sensitive population, their special conditions and needs will not be additionally discussed in this section.

External causes of methemoglobinemia other than nitrate-contaminated well water

Although nitrate is one of the most commonly reported causes of methemoglobinemia, other substances and products are also capable of causing this condition, including: certain pharmaceutical agents, sulfonamides, topical and injected anesthetics (e.g. benzocaine and lidocaine), anti-malarial drugs, industrial solvents containing nitrobenzene, room deodorizer propellants, aniline dyes (which may be used in diapers), wax crayons, laundry ink, mothballs, and fungicides (9,15,16).

Exposure to nitrate in combination with other chemicals

It is also possible that simultaneous exposure to nitrate in combination with another substance could produce methemoglobinemia. A recent well-water methemoglobinemia case in Wisconsin was documented in which a 6 week-old infant consumed formula mixed with well water (17). Well water used for drinking and food preparation was filtered through a reverse osmosis unit.

A water sample from this source found nitrate at a level near the MCL (9.9 mg/L nitrate as nitrogen), and copper dissolved from pipes at levels above the copper MCL of 1.3 ppm (17). Copper is an emetic and gastrointestinal irritant, and the child's methemoglobinemia was thought to have been induced by the combined exposure to nitrate and copper (17).

DISCUSSION

Search for cases of methemoglobinemia

We sought to identify any cases of methemoglobinemia requiring hospitalization in infants that could have been caused by nitrate exposure via drinking water. To do this, we searched hospital discharge records available through the Office of Statewide Health Planning and Development (OSHPD). OSHPD data contain a record for every hospital discharge in the state of California, with the exception of federal hospitals. Data tapes from the 13 years 1983 through 1995 were searched for any hospital discharges which contained the diagnosis code for methemoglobinemia (289.7), based on the International Classification of diseases, 9th Revision (ICD-9). Records include codes for the principal diagnosis (the main reason for hospitalization) and up to 24 additional diagnoses; all were searched.

In addition to diagnosis codes, data on age, race, sex, year of diagnosis, zip code, county of hospital, and county (this was only available for years 1994 and later) were retrieved. Also, supplementary classification information of external causes of injury and poisoning, called e-codes in the ICD-9 system, were searched as to clues to the origin of the methemoglobinemia condition. Unfortunately, there is not a code specific enough to identify ingestion of nitrate-contaminated water as a cause of methemoglobinemia. The code e-866 may be the most likely code to be chosen: accidental poisoning by other and unspecified solid and liquid substances.

The OSHPD system instituted several changes to protect confidentiality more securely; these have affected the data that are available. First, as of 1990, the data were split into two tapes. The user had a choice of either receiving information on: 1) complete zip code and age by category, or 2) first three digits of zip code and exact age. For most of this analysis, we chose the full zip code, and used the age category of infants less than 1 year.

Characteristics of infants with methemoglobinemia

Total cases of hospitalizations for methemoglobinemia cases in infants under 1 year of age was 97 during the 13 years studied (Table 3). The distribution by race and sex is also reported. The 1990 California population distribution is also presented as a reference (18). Blacks have about 4.7 times the risk of whites, and Hispanic and Asians have about 1.4 times the risk. Among infants, the proportion of males was nearly 60%.

For the time period when age by week was available (1983-89), most infant cases (88%) occur in children under 6 months of age. We would have no reason to think that this proportion would be substantially different in the years 1990-95. This is consistent with what has been stated in scientific literature regarding a vulnerable window of time for infants. By year, the number of cases of methemoglobinemia in infants ranged between 1 and 14, with the average 7.5 per year (Table 4).

Geographically, because of the rarity of this illness, few zip codes contained more than one case. Although for confidentiality reasons the exact zip codes are not given, the cities containing zip codes with three or more cases are given in Table 4.

Methemoglobinemia was the principal diagnosis in 43% of cases, and it occurred within the first three diagnoses 87% of the time (Table 4). The other most frequent principal diagnoses pointed to areas of fluid, electrolyte, or acid-base balance disorders; various noninfectious gastroenteritis; and acidosis. Only two of the codes designating an external cause of injury (e-codes) were used. Neither suggested nitrate poisoning. The code for external cause of injury (accidental poisoning by other and unspecified solid and liquid substance) was not selected in any of the cases. However, it is quite likely that the cause of methemoglobinemia would not be known at the time of hospitalization; only later might well water be suspected and then tested. Thus we must rely on other information to assess what might have been a nitrate-related case.

Case-by-case analysis of methemoglobinemia hospitalizations most likely to be nitrate-related

In an attempt to identify the methemoglobinemia records that were most likely to be related to nitrate, the records were further grouped by specific diagnoses. The group was limited to methemoglobinemia as a primary diagnosis, which reduced the total from 97 to 42 records. Of these, a number had additional diagnosis codes that suggested other factors could be involved, such as anomaly of pulmonary valve; sickle cell trait; volume depletion; codes suggesting other infection; codes suggesting other drugs or treatments; and codes suggesting the problem was specific to the perinatal period. Some of these conditions may have either caused methemoglobinemia directly, or may have made the infant more vulnerable to methemoglobinemia when exposed to nitrate. Still, excluding those left 16. Diarrhea with acidosis is another cause of methemoglobinemia, and some cases have this code. Although children with diarrhea and acidosis would be more susceptible to the effects of nitrate, if we eliminate these cases also, 10 cases remain.

Ten cases with no alternative diagnosis code

Ten infant methemoglobinemia cases have no alternative diagnoses that suggest other causes of the condition. The records are not specific enough to indicate if the cause was nitrate-contaminated water without a specific investigation or possibly chart review. Of the types of admission codes possible (e.g. elective, urgent, emergency, etc.), 5 were emergency and 5 urgent. This is consistent with case histories noted in the literature.

The locations of the 10 varied. However, a total of 4 of these 10 cases were in unincorporated areas, which are more likely to have water supplied by private wells (Table 5).

Drinking water sources in 10 areas containing a case with no alternative diagnosis code

Although information on water source for each individual methemoglobinemia case is not available, the 1990 US census does contain information on well water usage by zip code (1). These categories are: 1) public system or private company water systems; 2) individual wells that are drilled; 3) individual wells that are dug (generally hand dug), and; 4) other water sources (such as from springs, creeks, rivers, lakes, cisterns, etc.) (1).

Table 5 provides the number of persons in each of these 10 zip codes using various sources of water. Each of the 10 zip codes had at least some persons receiving water from individual wells rather than a water system. The two areas in which a very large percentage of persons rely on well water were areas that included unincorporated lands. One of these was an unincorporated area in San Joaquin Valley, and the other an unincorporated area near Fresno (Clovis). Both are agricultural areas, which are thus likely to have nitrate contamination. The Clovis area contains a site formerly on the National Priorities List ("Superfund"), around which a number of private wells had a prior history of nitrate contamination levels exceeding the MCL. Still, we cannot know for certain if the methemoglobinemia cases in any of these areas were caused by nitrate contamination of well water.

Well water standards

Although the Safe Drinking Water Act as amended in 1986 mandates testing of public water systems for nitrate and other contaminants, water systems (including private wells) with fewer than 15 connections are not subject to this requirement (2). Thus, private well water users are at risk if they do not test their water for nitrates.

MCL safety factor

It appears that most cases of infant methemoglobinemia have involved water nitrate concentrations over twice the MCL. This is based on several reviews that found most cases in which the levels were known have occurred at levels greater than 100 mg/L, which is equivalent to 22.2 mg/L nitrate as nitrogen (10). This is slightly over twice the MCL of 10 mg/L. However, often the exposure levels are not known.

The lowest level for which no effect has been observed (NOAEL) is considered to be 10 mg/L (equivalent to the MCL) (11). This figure is based on data reviews in 1950-1951, although the standard has been reviewed since then (11). However, additional data suggest that a small percentage of methemoglobinemia cases may occur at levels closer to, or even below, the MCL (10). One review in 1971 of cases from 14 countries found that 3% occurred at concentrations of less than 8.9 mg/L nitrate as nitrogen, vs. MCL=10 mg/L (10). Also, the case in Wisconsin described earlier in this document is a more recent example of a case occurring at a level below what is considered to be the no adverse effect level. The LOAEL (the lowest level at which an effect has been observed) is set at 11-20 mg/L (11). Even without considering these exceptions, these values result in a very minimal safety margin, in contrast to other MCLs, which often have a built-in 10 to 1000-fold safety factor.

CONCLUSIONS

Many private well users are theoretically vulnerable to nitrate contamination and toxicity. Our examination of hospitalized methemoglobinemia cases was not definitive. Statewide over a 13-year period, 97 cases of infant methemoglobinemia were identified; in 42 of these cases methemoglobinemia was the principal diagnosis. Although the coding in the hospital discharge system is not specific enough to conclusively identify cases caused by nitrate contaminated well water, 10 of these cases lacked explanatory codes that could suggest an alternative cause for methemoglobinemia. Additionally, several cases occurred in agricultural, unincorporated areas of the state in which a relatively large proportion of residents rely on well water. Thus it is possible that some of the cases in the hospital discharge database were caused by nitrate-contaminated well water.

In spite of the insensitivity of the hospital discharge data, exposure to nitrate, either alone, or in combination with other contaminants, could cause health effects. Elevated levels of nitrate in private drinking wells pose a health hazard to infants under 6 months of age who ingest this water. The lack of a substantial margin of safety between the MCL and the level where health effects can be found, the fact that contaminants in well water may be concentrated by boiling, and that certain illnesses could increase an infant's susceptibility, further increase the chances this could occur. Also, possibly non-specific symptoms of nitrate poisoning may go undiagnosed.

Health education should include warnings to pregnant women about the risk of giving water contaminated with nitrates to young infants. CDHS has recently developed a fact sheet on nitrates for use statewide. Areas of the state in which a large number of persons use well water should be a priority. Additionally, more information on Californians' testing of individual wells is needed.

While there is no doubt that much of the nitrate contamination in California is agriculturally related, the health implications are significant enough that NPL site evaluation should routinely include consideration of nitrates, and testing should occur if there is a possibility of contamination, site-related or not.

PUBLIC HEALTH RECOMMENDATIONS AND ACTIONS

Actions Completed

Develop fact sheet for statewide use regarding risks of nitrates/nitrites (completed by CDHS).

Actions Planned

1. Distribute fact sheet to county environmental health officers and California Office of Drinking Water to give to private well water users to inform them of the risk of nitrate/nitrite, and what health protection steps they should take (CDHS, by end of 1999; fact sheet is currently under review by the directors of county environmental health programs).

Recommendations for Further Action

1. Contact appropriate professional organizations and agencies to suggest incorporation of nitrate warning messages into material given to women receiving prenatal counseling (such as the American College of Obstetricians and Gynecologists or American Academy of Pediatrics) (action to be undertaken by CDHS).

2. Consider ways to assess whether users of well water test their wells, and whether they are aware of the risk. For example, CDHS may be able to ask about private well use by adding pertinent questions to an on-going telephone survey of health and behavior factors for Californians.

3. Evaluate the need for nitrate testing as a part of routine site characterization.

Note: The interpretation and recommendations provided are based on the data in the information referenced. Additional data could alter the advice presented. Conclusions and recommendations are situation-specific, and should not be considered applicable to other situations. ATSDR/CDHS is committed to review or respond to additional requests if received.

Table 1. Selected National Priorities List ("Superfund") sites with documented nitrate well water contamination, California.

Superfund site, location	CERCLA number
Laboratory for Energy-Related Health Research, Davis	CA2890190000
Aerojet General Corporation, Rancho Cordova	CAD980358832
El Toro Marine Corps Air Station, Santa Ana	CAD6170023208
Industrial Waste Processing, Pinedale, Fresno County	CAD980736284
San Gabriel Valley (Areas 1-4), San Gabriel	CAD980677355, CAD980818512, CAD980818579, CAD980817985
T.H. Agriculture and Nutrition Company, Fresno	CAD009106220

Table 2. Different ways nitrate and nitrite MCLs are reported.

	Nitrate MCL	Nitrite MCL
mg/L	45	10
ppm	45	10
as nitrogen (mg/L)	10	1
as nitrogen (ppm)	10	1

Table 3: Race and sex of persons hospitalized for methemoglobinemia among infants under 1 year of age, California, 1983-1995; vs. California 1990 population (18,1).

Descriptive characteristic	Persons with methemoglobinemia under age 1 (%; n=97)	California 1990 population age under age 1 (%)
Race		
White	29.9	44.3
Black	25.8	8.2
Hispanic	35.1	38.1
Asian / other/ Unknown	9.3	9.4
Sex		
Male	58.8	51.0
Female	41.2	49.0

Table 4: Descriptive information about persons hospitalized for methemoglobinemia under 1 year of age; California, 1983-1995.

Descriptive variable	Methemoglobinemia cases in infants under 1 year of age (n=97)
Year	
1983	9
1984	3
1985	6
1986	7
1987	9
1988	6
1989	1
1990	14
1991	9
1992	8
1993	11
1994	5
1995	9
Cities containing the specific zip codes with greatest numbers of cases (zip codes not given for confidentiality reasons)	Pasadena; 5 San Francisco; 4 San Fernando (town); 4 La Puente; 3 Colton; 3
Methemoglobinemia as principal diagnosis	43%
Other most frequent Principal diagnoses (ICD-9 code)	• 276.5 (disorders of fluid, electrolyte, and acid-base balance; volume depletion; 10%) • 558.9 (other and unspecified non-infectious gastroenteritis and colitis; 9%) • v300 (live newborn; 6%) • 276.2 (acidosis; 5%)
E-codes used (n=4; 4%)	• Drugs, medicinal and biological substances causing adverse effects in therapeutic use (n=3). • e-924.8: accident caused by hot substance or object, caustic or corrosive material, and steam; other; (n=1).

Table 5: Drinking water sources in 10 areas containing a case of infant methemoglobinemia with no alternative diagnosis code[1,2,3]; numbers of persons served by different sources[4].

Location of zip code in which methemoglobinemia case occurred	Public system or private company	Individual well, drilled	Individual well, dug	Some other source
Hayward	21,132	122	43	0
Santa Ana	19,471	91	4	12
Simi Valley	18,200	16	0	5
San Pablo and unincorporated area	18,001	9	0	5
South Los Angeles	18,743	38	9	18
San Francisco	12,613	13	0	0
Unincorporated San Joaquin Valley	1,083	1,154	32	5
Clovis and unincorporated area	18,180	3,721	205	29
Stockton and unincorporated area	10,123	34	3	0
El Cajon	21,216	8	0	9

[1] infants under one year of age only.

[2] hospitalized cases of methemoglobinemia as principal diagnosis, 1983-1995.

[3] excluding cases with additional diagnosis codes that would suggest reasons other than nitrate-related methemoglobinemia from well water, although this does not mean these cases necessarily are nitrate-related.

[4] per 1990 US Census (1).

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CERTIFICATION

This Health Consultation for the Nitrate Contamination and Methemoglobinemia in the State of California was prepared by the California Department of Health Services under a cooperative agreement with the Agency for Toxic Substances and Disease Registry (ATSDR). It is in accordance with approved methodology and procedures existing at the time the Health Consultation was initiated.

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The Division of Health Assessment and Consultation (DHAC), ATSDR, has reviewed this Health Consultation and concurs with its findings.

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