

## **PUBLIC NOTICE**

### **Initiation of Risk Assessments for Chemicals in Drinking Water**

**July 2004**

#### **A. Requirements**

The Calderon-Sher California Safe Drinking Water Act of 1996 (Health and Safety Code Sections 116270 et seq.) requires the Office of Environmental Health Hazard Assessment (OEHHA) to post notices on its Web site of water contaminants for which it is initiating work to develop public health goals (PHGs) for chemicals in drinking water. These are chemicals with existing state Maximum Contaminant Levels (MCLs), or those subject to new regulation. The law also describes the intent and general context of the PHGs (Health and Safety Code Section 116365). PHGs are concentrations of chemicals in drinking water that are not anticipated to produce adverse health effects following long-term exposures. These goals are advisory but must be used as the health basis to update the state's primary drinking water standards (MCLs) by the California Department of Health Services (DHS) (Health and Safety Code Section 116365(b)(1)).

There are approximately 85 chemicals for which state MCLs are presently available, and the Act requires review and update of the risk assessments at least every five years (Health and Safety Code Section 116365(e)(1)). Chemicals may also be reviewed by OEHHA if requested by DHS or required by legislative mandate. Opportunities for public comment and peer review are provided as required by statute.

#### **B. Implementation**

OEHHA has published 71 PHGs as of July 2004, although one of these evaluations, that for total chromium, has been rescinded. The technical support documents for the published PHGs are posted on the OEHHA Web site at [www.oehha.ca.gov](http://www.oehha.ca.gov).

PHGs for all the other chemicals that have state MCLs are currently in preparation, and the final group of PHGs with existing MCLs is planned to be released for public review this year. A 45-day public comment period will be provided after posting, followed by a public workshop. Scientific peer reviews are arranged through the University of California. The overall PHG process includes time for OEHHA to prepare revisions, for further public comment, and for OEHHA to prepare responses to comments. The final group of PHGs are planned for publication in 2005.

OEHHA has also prepared scientific memoranda for DHS on the MCLs for "Gross alpha" and "Gross beta." These MCLs are screening levels for radionuclides in drinking water, rather than regulatory standards for specific chemical entities. The memoranda discuss the relative risk from exposure to radioactivity derived from the various isotopes in the above categories. These documents are also posted on our Web site.

OEHHA is initiating evaluation for several chemicals for which new MCLs have been promulgated by U.S. EPA, which triggers a requirement that OEHHA prepare a PHG. In addition, re-review, as required by Health and Safety Code Section 116365(e)(1), is being initiated for chemicals for which initial PHGs were published in 1997 and 1999, as described in section C below.

### **C. Initiation of risk assessments**

Risk assessments are being initiated for the chemicals listed below, which are newly regulated:

- Bromate
- Chlorite
- Haloacetic acids
- Nitrosodimethylamine (NDMA)

Of the chemicals above, NDMA is being evaluated at the request of DHS, because of a pattern of increasing detections in California groundwater. The other three chemicals or chemical classes are the subject of new MCLs promulgated by the U.S. EPA, therefore requiring development of a PHG.

In addition, reviews are being updated for chemicals for which PHGs were prepared in the first years of our program, prioritized on the basis of availability of new data and significance as a drinking water contaminant. Chemicals that have currently been assigned for review include:

- Cadmium
- Copper
- Glyphosate
- Lindane
- Mercury
- Methoxychlor
- Oxamyl
- Pentachlorophenol
- Thallium
- Trichloroethylene

A brief description of these chemicals is provided below. OEHHA requests the submission of pertinent information on these contaminants that could assist our office in preparing or updating the risk assessment and deriving a PHG.

Generally, information submitted to OEHHA in response to this request should not be proprietary in nature, because all information submitted is a matter of public record. In the event that proprietary information is to be submitted, please contact OEHHA general counsel, Carol

Monahan at (916) 322-0493 or [cmonahan@oehha.ca.gov](mailto:cmonahan@oehha.ca.gov) in advance of the submission. Information must be submitted no later than **August 31, 2004** to:

Catherine Caraway  
Pesticide and Environmental Toxicology Section  
Office of Environmental Health Hazard Assessment  
P.O. Box 4010  
Sacramento, California 95812-4010  
Attn: PHG Project

All data timely submitted will be considered in the development of the PHG for these chemicals. The draft documents will be available for discussion at a public workshop and public comments will be solicited as described above in Section B. The final risk assessments will be utilized by DHS in potential revisions to the MCLs for the chemical in drinking water, as described in more detail on the DHS Web site at <http://www.dhs.ca.gov/ps/ddwem/chemicals/chemindex.htm>.

#### **E. Descriptions of chemicals or substances for review initiation**

##### **BROMATE**

Bromate is the  $\text{BrO}_3^-$  ion, a combination of bromine and oxygen. Bromate is listed as a B2 probable human carcinogen by the U.S. EPA (IRIS, 2004). The U.S. EPA oral reference dose (RfD) for noncancer effects is 0.004 mg/kg-day of bromate, based on kidney effects in rats in the chronic study of DeAngelo *et al.* (1998). In 1998, the U.S. EPA promulgated an MCL of 0.010 mg/L (10 ppb), and an MCLG of zero for bromate in drinking water, based on a weight of evidence evaluation of both cancer (multiple sites, both sexes, rats) and noncancer effects. Bromate, as the potassium salt, is listed as a group 2b possible human carcinogen by the International Agency for Research on Cancer (IARC, 1999). Bromate has been shown to be mutagenic via *in vitro* and *in vivo* scientific studies. In rats, long-term exposure to bromate in drinking water yielded adverse effects on liver and kidney and inhibited body weight gain. Multiple toxic effects have also been observed in humans. The principal concern for human exposure to bromate appears to be as a drinking water contaminant, formed as a byproduct from the ozonation disinfection process. Exposure may also occur from some commercially bottled drinking water. In the past, bromate was sometimes used as a food additive for beer, cheese, and bread.

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## **CADMIUM**

The PHG of 0.07 ppb for cadmium was published by OEHHA in 1999. Cadmium is a natural element in the earth's crust, and is usually found as a mineral combined with other elements such as oxygen (cadmium oxide), chlorine (cadmium chloride), or sulfur (cadmium sulfate, cadmium sulfide). All soils and rocks contain some cadmium, which may leach into groundwater. Cadmium has many uses, including batteries, pigments, metal coatings, and plastics. It enters water from waste disposal and spills or leaks at hazardous waste sites.

Exposure to high levels of cadmium severely damages the lungs and can cause death. Eating food or drinking water with very high levels severely irritates the digestive tract, and can cause kidney disease. Animals given cadmium in drinking water had high blood pressure, iron-poor blood, liver disease, and nerve or brain damage (ATSDR, 1999). IARC concluded that, based on

inhalation data, there is sufficient evidence in humans for the carcinogenicity of cadmium and cadmium compounds. However, the PHG is based on nephrotoxicity derived from an epidemiological study of a cross-sectional sample of the adult Belgian population. The U.S. EPA MCL for cadmium in drinking water is 5 ppb; the California MCL is also 5 ppb. The World Health Organization set a provisional tolerable daily intake of 60-70 µg of cadmium per day. DHS reported 570/11,736 detections of cadmium in drinking water in 1984-2001 (above the DLR of 1 ppb), and 119 MCL exceedances in 1984-2000. DHS has reviewed the cadmium MCL to determine whether it is feasible to lower the MCL substantially closer to the PHG value, and decided that this is not feasible, based on the relatively high DLR (DHS, 2004).

### **Pertinent findings since PHG development**

Dozens of new studies may be relevant to various aspects of the PHG document, including exposure, *in vitro* toxic effects on a variety of tissues and endpoints, and epidemiological investigations. However, no new cancer studies were found. The reports on associations of cadmium with various effects in humans and in animals should at least reinforce the prior assessment and assumptions. The study in rats of nerve changes after pre- and postnatal cadmium exposures (Yargicoglu *et al.*, 2000) may provide a more sensitive endpoint than used earlier. The study of cadmium effects on the rat prostate (Martin *et al.*, 2001) may be relevant to mechanisms of human prostate carcinogenesis, and evaluation of cadmium effects on mouse heart (Skowerski *et al.*, 2000) may be relevant to human cardiovascular effects. It is not clear whether any of the new studies might lead to a change in the PHG, but the large number of studies and variety of endpoints warrant further examination.

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## **CHLORITE**

Chlorite is a byproduct formed when drinking water is disinfected with chlorine dioxide gas. Drinking water treated in this manner constitutes the primary human exposure source for chlorite. In water, chlorite is a colorless anion with strong oxidizing properties and has a bitter, unpleasant taste at high levels.

The U.S. EPA and DHS have established an MCL of 1.0 mg/L for chlorite (DHS, 2003). The federal standard became effective nationwide on January 1, 2002 for any drinking water system serving 10,000 or more people. All drinking water systems must comply with this MCL beginning January 1, 2004 (U.S. EPA, 2002).

The federal MCL is based on neurodevelopmental delays and altered liver weights reported in two generations of rats exposed to chlorite *in utero*, via lactation and in drinking water (CMA, 1996). ATSDR used the same toxicological endpoints for their proposed intermediate-exposure maximum residue level (MRL) of 0.1 mg/kg-day for chlorite ingestion (ATSDR, 2002). Sodium chlorite - the compound used in toxicological studies on chlorite - currently is not considered to be a potential carcinogen. The U.S. EPA has classified sodium chlorite as a Group D compound, and IARC lists it as Group 3 (U.S. EPA, 2000a, b; IARC, 1997).

Pharmacokinetics studies conducted on Sprague-Dawley rats indicate that chlorite is rapidly absorbed from the gastrointestinal tract (Abdel-Rahman *et al.*, 1984). Once absorbed, it is widely distributed throughout the body with the highest concentrations being detected in the blood, stomach, testes, skin, lung, kidneys, small intestine, spleen, brain, bone marrow and liver. Elimination occurs relatively slowly via urinary excretion, with a half-life of over 35 hours (Abdel-Rahman *et al.*, 1982, 1984).

Toxicological studies reveal that oral exposure to chlorite can result in significant reproductive, hematological, endocrine and gastrointestinal effects. Reproductive effects include altered sperm morphology and decreased progressive movement (Carlton and Smith, 1985; Carlton *et al.*, 1987). Hematological effects reported are significant decreases in hematocrit and hemoglobin levels, increases in methemoglobin and neutrophil levels, decreases in mean erythrocyte counts, morphological changes in erythrocytes (Harrington *et al.*, 1995) and osmotic fragility (Couri and Abdel-Rahman, 1980) in rats; and decreases in erythrocyte levels and cell indices, decreases in hemoglobin levels, increases in reticulocyte count and methemoglobin levels in monkeys (Bercz *et al.*, 1982).

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## **COPPER**

The PHG of 170 ppb for copper was published by OEHHA in 1997. Copper is a reddish metal that occurs naturally in rocks, soil, water, and air. It also occurs naturally in plants and animals, and is a required mineral for human nutrition. Copper is found as a salt in combination with other compounds. Metallic copper can be found in the U.S. penny, electrical wiring, and some water pipes. Copper compounds are commonly used in agriculture to treat plant diseases like mildew, for water treatment, and as preservatives for wood, leather, and fabrics. Exposure to copper results mostly from the ingestion of food and water. High concentrations of this metal in drinking water may occur if the water is corrosive and there are copper plumbing and brass water fixtures in the home. Drinking or swimming in lakes or reservoirs recently treated with copper to control algae or that receive cooling water from a power plant may lead to high copper exposures. Home garden products that contain copper (e.g. fungicides) to control plant diseases are another potential source of exposure to copper.

Long-term exposure to copper dust can irritate the nose, mouth, and eyes, and cause headaches, dizziness, nausea, and diarrhea. Drinking water with higher than normal levels of copper may cause vomiting, diarrhea, stomach cramps, and nausea. High doses of copper, sometimes taken intentionally, can cause liver and kidney damage, and even death. Data are considered inadequate to establish a recommended dietary allowance of copper, but “safe and adequate levels” were estimated by the NRC as 0.5 to 1 mg/day for infants, and 2 to 3 mg/day for adults and adolescents. Average dietary intakes are about 1 to 2 mg/day; infant formula contains about 0.5 mg/L copper when reconstituted with water. The U.S. EPA has determined that copper is not classifiable as to carcinogenicity (IRIS, 2004); epidemiological studies of potential carcinogenic effects in humans are inconclusive. The PHG is based on a case report of gastrointestinal effects

in children, the sensitive group for stomach irritation (Spitalny *et al.*, 1984). U.S. EPA has adopted an Action Level and MCLG of 1.3 mg/L for copper in drinking water, and a secondary maximum contaminant level (SMCL) of 1.0 mg/L. The California Action Level is also 1.3 mg/L, with a secondary MCL of 1.0 mg/L. Copper was detected 1044 times out of 11,645 analyses in public drinking water supplies in the DHS reports for 1984-2001, and found 8 times above the Action Level in sampling from 1994-2001. DHS has not scheduled copper for possible reevaluation despite the fairly large difference between the PHG and the Action Level (DHS, 2004).

### **Pertinent findings since PHG development**

A drinking water study in rats (250 mg/L copper for 9 wks) finds that copper causes changes in both the protein content of the erythrocyte membrane and heme synthesis (Ozcelik *et al.*, 2002). There appears to be only one study (in animals) in the PHG pertaining to reproductive effects following exposure to copper. A study in rats reports that exposure to the salt copper chloride has adverse effects on sexual behavior, territorial aggression, fertility and the reproductive system of the adult male rat (Bataneh *et al.*, 1998).

Since the publication of the PHG, a number of studies using human subjects have reported LOAELs and/or NOAELs that are lower than the one used to derive the PHG. One study in adult humans (n=45) reported gastrointestinal effects associated with drinking tap water containing 5 mg/L copper or soluble copper (Pizarro *et al.*, 2001). In another study using human subjects, the acute NOAEL for copper in drinking water was determined to be 4 mg Cu/L (Araya *et al.*, 2001). Olivares *et al.* (2001) have identified the lowest thresholds for GI effects (nausea, vomiting, diarrhea, abdominal pain) in healthy adult human volunteers to date; the NOEL is 2 mg Cu/L and the LOAEL is 4 mg Cu/L. Children have been shown to be more susceptible than adults to copper, so one may presume the LOAEL in children may be even lower. However, Pizarro *et al.* (1999) report that a concentration of 2 mg Cu/L of potable water does not produce an increase in GI symptoms in infants, and that only concentrations greater than 3 mg Cu/L increase the number of episodes of nausea, vomiting and abdominal pain in women. Stenhammar (1999) provides a case report in children with symptoms similar to those in the study used to derive the PHG, with exposure to copper via drinking water. An examination of the science behind the EU and U.S. EPA guidelines concluded that these public-health protective values (2.0 and 1.3 mg/L, respectively) do not have “a firm scientific basis” and that “this is worrying in both health and public policy terms” (Fewtrell *et al.*, 2001). The new studies appear credible and compelling. The PHG must be re-evaluated and perhaps recalculated to reflect the new information. This is a difficult issue because of balancing nutritional requirements versus acute toxic effects at moderately higher exposures, the use of copper in household plumbing, and the complicated regulatory status of copper (an Action Level, not an MCL).

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## **GLYPHOSATE**

The PHG of 1000 ppb for glyphosate (Roundup) was published by OEHHA in 1997. Glyphosate is a widely used nonselective herbicide with agricultural and nonagricultural uses. It has relatively low toxicity in experimental animals and in humans. The PHG is based on a NOAEL of 175 mg/kg-day derived from a rabbit teratology study, where the critical effect observed was maternal mortality and diarrhea. The heavy use of glyphosate has resulted in the evaluation of its association with acute or chronic illnesses in a relatively large number of studies since the development of the PHG.

The PHG differs from the U.S. EPA's MCL of 700 ppb, developed in 1991, because it is based on a different study and uses different assumptions. The California MCL is also 700 ppb,

established in September 1994. No detections of glyphosate were reported by DHS in the recent analyses (1984-01) of public drinking water supplies.

### **Pertinent findings since PHG development**

New toxicity information is available on glyphosate since the publication of the PHG, which could have some impact on the existing toxicology and risk assessment sections of the PHG. Since glyphosate is a very heavily used pesticide, it represents a potential human exposure concern. Therefore the PHG update should be given priority, although there is no indication that the new information will change the PHG value.

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## **HALOACETIC ACIDS**

Haloacetic acids (HAAs) are a group of chemicals that are formed along with other drinking water disinfection byproducts (DBPs) when chlorine or other disinfectants used to control microbial contaminants in the water react with naturally occurring organic and inorganic matter in water, e.g., fulvates from decaying vegetation. HAAs are one of four regulated DBPs under the federal Safe Drinking Water Act. Among the major families of the DBPs, HAAs represent the second largest group detected, on a weight basis, next to the most prevalent group of trihalomethanes (THMs). The water solubility of HAAs is in general much higher than THMs (U.S. EPA, 1994).

Depending on the amount of bromide in the source water as well as the amount of chlorinated disinfectants added, varying amounts of chlorinated, brominated, and mixed bromochloro haloacetic acids are produced. The nine HAAs that have been identified in drinking water include monochloroacetic acid (MCA or  $\text{CH}_2\text{ClCOOH}$ ), dichloroacetic acid (DCA or  $\text{CHCl}_2\text{COOH}$ ), trichloroacetic acid (TCA or  $\text{CCl}_3\text{COOH}$ ), monobromoacetic acid (MBA or  $\text{CH}_2\text{BrCOOH}$ ), dibromoacetic acid (DBA or  $\text{CHBr}_2\text{COOH}$ ), bromochloroacetic acid (BCA or  $\text{CHBrClCOOH}$ ), bromodichloroacetic acid (BDCA or  $\text{CBrCl}_2\text{COOH}$ ), dibromochloroacetic acid (DBCA or  $\text{CBr}_2\text{ClCOOH}$ ), and tribromoacetic acid (TBA or  $\text{CBr}_3\text{COOH}$ ). Among the nine HAAs, five chemicals, which are known as HAA5, including MCA, DCA, TCA, MBA, and DBA, have been regulated by the U.S. EPA (U.S. EPA, 1998a). HAA5 is the sum of measured concentrations of MCA, DCA, TCA, MBA, and DBA. HAA6 refers to the sum of HAA5 and BCA concentrations. HAAs are solids or liquids at room temperature and are soluble in water. Unlike the volatile THMs, these halogenated organic chemicals have relatively low vapor pressure and are not expected to volatilize from drinking water or contaminated environmental media to any appreciable extent.

Human consumption of chlorinated drinking water has been epidemiologically linked to bladder, kidney, and rectal cancers (Bull and Kopfler, 1991; IARC, 1991). The U.S. EPA (1998b) has published the Stage 1 Disinfectants/Disinfection Byproducts Rule to regulate HAA5 at a MCL of 0.06 mg/L or 60 ppb annual average. This MCL standard became effective for large surface water public water systems in December 2001 and for small surface water and all ground water

public water systems in December 2003. In addition, the U.S. EPA has established an MCLG of zero for DCA based on sufficient evidence of carcinogenicity in animals, and a MCLG of 0.3 mg/L for TCA based on developmental toxicity and possible carcinogenicity (U.S. EPA, 1998b).

### **Monochloroacetic acid (MCA)**

U.S. EPA (1998b) has determined that MCA is a Group D chemical, not classifiable as to human carcinogenicity. In a NTP (1992) study, no statistically significant increases in tumor incidences were reported in rats and mice exposed to MCA via gavage.

### **Dichloroacetic acid (DCA)**

U.S. EPA has classified DCA as a probable human carcinogen, Group B2, and derived an oral slope factor of  $0.05 \text{ (mg/kg-d)}^{-1}$  based on liver adenoma and carcinomas in male B6C3F1 mice (Bull and Stauber, 1999; Daniel *et al.*, 1992; U.S. EPA, 2003, 2004a). DCA is a hepatocarcinogen in Fischer 344 rats and B6C3F1 mice (Bull and Stauber, 1999; DeAngelo *et al.*, 1999; Nelson *et al.*, 1990; Sanchez and Bull, 1990). DCA is also known as a peroxisome proliferator and produces tumors at doses less than required for peroxisome proliferation (DeAngelo *et al.*, 1989; Xu *et al.*, 1995). Genotoxicity, reproductive toxicity, embryotoxicity, neurotoxicity, and immunotoxicity of DCA have also been reported (Chang *et al.*, 1992). U.S. EPA has derived a drinking water concentration of 0.0007 mg/L at the one in 1,000,000 risk level for DCA (U.S. EPA, 2004a). U.S. EPA has derived an oral RfD of 0.0004 mg/kg-d for DCA based on lesions observed in the testes, cerebrum, cerebellum and liver in a subchronic dog oral bioassay (Cicmanec *et al.*, 1991; U.S. EPA, 2004a). U.S. EPA (1998b) has also promulgated an MCLG of zero for DCA in drinking water based on carcinogenicity. IARC (1995) concluded that there was inadequate evidence for the carcinogenicity of DCA in humans and limited evidence for its carcinogenicity in experimental animals, and gave DCA an overall classification of Group 3, not classifiable as to its carcinogenicity to humans. DCA is listed as a chemical known to the State to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).

### **Trichloroacetic acid (TCA)**

U.S. EPA has classified TCA as a possible human carcinogen, Group C, based on a lack of human carcinogenicity data and limited evidence of an increased incidence of liver neoplasms in both sexes of one strain of mice (Bull *et al.*, 1990; Bull and Stauber, 1999; DeAngelo, 1991; DeAngelo and Daniel, 1990; Herren-Freund *et al.*, 1987; Pereira, 1996; Pereira and Phelps, 1996; Sanchez and Bull, 1990). No evidence of carcinogenicity was found in rats (DeAngelo, 1991; DeAngelo and Daniel, 1992; DeAngelo *et al.*, 1997). TCA has been observed to act as a liver tumor promoter in rats or mice treated with an initiating dose of a carcinogen followed by chronic exposure to TCA in the drinking water (Herren-Freund *et al.*, 1987; Latendresse and Pereira, 1997; Parnell *et al.*, 1988; Pereira and Phelps, 1996; Pereira *et al.*, 1997). TCA is also known as a peroxisome proliferator (DeAngelo *et al.*, 1989; Xu *et al.*, 1995). Results from genotoxicity studies are mixed; TCA does not appear to be a point mutagen (OEHHA, 1999; U.S. EPA, 2004b). Developmental, reproductive, and systemic toxicity of TCA have also been

reported (Smith *et al.*, 1989). U.S. EPA (1998b) has promulgated an MCLG of 0.3 mg/L for TCA in drinking water based on developmental toxicity and possible carcinogenicity. IARC (1995) concluded that there was inadequate evidence for the carcinogenicity of TCA in humans and limited evidence for its carcinogenicity in experimental animals, and gave TCA an overall classification of Group 3, not classifiable as to its carcinogenicity to humans. TCA has been evaluated, and was not listed as a chemical known to the State to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) (OEHHA, 1999, 2003).

#### **Monobromoacetic acid (MBA)**

Limited acute spermatotoxicity of MBA has been reported in adult male rats (Linder *et al.*, 1994).

#### **Dibromoacetic acid (DBA)**

DBA has been reported to cause testicular damages in adult male rats (Klinefelter *et al.*, 2002; Linder *et al.*, 1994). In rats dosed with DBA, serum testosterone and sperm motion decreased, degenerative flagellar changes in cauda sperm and abnormal sperm head shapes were present. It has been shown to impair sexual function and fertility in male rabbits exposed to DBA in drinking water in a 25-week lifetime study (Veeramachaneni *et al.*, 2000). The results of both *in vivo* and *in vitro* exposure studies indicate that DBA is capable of altering spermatogenesis in adult male rats directly (Holmes *et al.*, 2001). DBA in the drinking water altered intestinal metabolism in Fischer 344 rats, which could influence bioactivation of promutagens and procarcinogens in the drinking water. Limited information on genotoxicity, reproductive toxicity, neurotoxicity, and immunotoxicity of DBA has also been reported. Some studies have indicated that acute doses of the brominated acetic acids are more potent inducers of oxidative stress and increase the 8-hydroxydeoxyguanosine (8-OH-dG) content of the nuclear DNA in the liver. The findings by Parrish *et al.* (1996) suggest that oxidative damage to DNA may play a more important role in the chronic toxicology of brominated compared to the chlorinated acetic acids.

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## **LINDANE**

The PHG of  $3.2 \times 10^{-5}$  mg/L (0.032 ppb) for lindane was published by OEHHA in February 1999. Lindane, the gamma isomer of hexachlorocyclohexane, has been used as an insecticide and as a therapeutic scabicide, pediculicide, and ectoparasiticide for humans and animals. Most pesticide uses have been cancelled, and lindane was not detected in any of the Department of Health Services drinking water sample reports from 1984-2001. Lindane is semivolatile and lipophilic, and has been found in human tissues and breast milk. The PHG is based on liver tumors in mice, with a human equivalent potency value of  $1.1 \text{ (mg/kg-day)}^{-1}$  calculated from a 1973 study. The U.S. EPA MCL is 0.0002 mg/L (0.2 ppb), established in 1991, and the California MCL is the same, established in 1994.

### **Pertinent findings since PHG development**

Additional data are available on mechanism of endocrinological effects of lindane, including potentially relevant basic toxicity studies and some largely negative epidemiology evaluations. Also, several recent publications are available on the (declining) levels of lindane in tissues and environmental media. However, no new cancer bioassays were found. Although most uses of lindane have been cancelled, it can still be used in humans for treatment of head lice. Therefore a health risk reassessment is relevant despite the lack of lindane detections in drinking water. Both cancer and non-cancer endpoints are appropriate to review.

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## **MERCURY**

The PHG of 1.2 ppb for inorganic mercury was published by OEHHA in December 1999. Mercury is an element and a component of many items (e.g., thermometers and other monitoring equipment; dental amalgams, batteries, switches). It was reported as found in 150/11,736 drinking water analyses in the DHS survey results for 1984-2001. Various effects have been reported in humans and animals following exposure to mercury-containing compounds. The predominant effect for inorganic mercury compounds is toxicity to the kidney. Chronic toxicity data was found inadequate in the 1999 PHG review and a six-month oral toxicity study was used to calculate the PHG. Based on the kidney toxicity reported, a No-Observable-Adverse-Effect-Level of 0.23 mg/kg-day was used to derive the PHG. The U.S. EPA MCL of 2 ppb (effective 6/24/77) is still in effect, and is consistent with the U.S. EPA RfD developed in 1995; the

California MCL is 2 ppb, also established in 1977. Fifty-seven exceedances of the MCL were noted in the DHS overview of monitoring results for 1984-2000. It should be noted that the MCL and PHG focus on inorganic mercury, rather than on the more toxic organic form, methylmercury, since the inorganic form predominates in drinking water.

### **Pertinent findings since PHG development**

Several potentially relevant new studies were identified. The key articles include several toxicological reviews on mercury published in 2002 regarding exposure to mercury from fish; several epidemiological studies regarding possible neurotoxic, cardiac or other effects associated with exposure to mercury from amalgam, dietary, or household sources; and studies on the potential neurotoxicity of mercury in mice following in utero exposure and exposure through breast feeding. However, these reports may not affect the PHG level since several of these studies refer mainly to methylmercury, and where inorganic mercury is involved, the doses are greater than the one used in the PHG calculation.

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## **METHOXYCHLOR**

The PHG of 30 ppb for methoxychlor was published by OEHHA in December 1999. Methoxychlor is an organochlorine pesticide similar in insecticidal action to DDT. Due to concern over its toxicity, methoxychlor registration was suspended in California in 1995. Methoxychlor has a variety of effects, some associated with its mild estrogenic activity. It has not been found to be carcinogenic. The PHG is based on a LOAEL of five mg/kg-day associated with effects on the female reproductive system. The U.S. EPA's MCL for methoxychlor is 40 ppb. The California MCL is also 40 ppb, established in September 1994. Methoxychlor was not detected in the public drinking water supply analyses reported by DHS from 1984-01.

### **Pertinent findings since PHG development**

Many additional studies relating to the effects of methoxychlor have been published since the development of the PHG. These data, including new information on the endocrine disruption potential of methoxychlor, could possibly lead to a revision of the PHG value. The Integrated Risk Assessment Section of OEHHA reviewed the risks of methoxychlor for the *Development of Health Criteria for School Site Risk Assessment Pursuant to Health and Safety Code Section 901g): Proposed RfDs for School Site Risk Assessment Draft Report* and derived a child-based risk value on the basis of new information which differs from the equivalent risk-based estimate in the PHG document. Since the pesticidal uses of methoxychlor have been banned, there would be a diminishing concern over human exposure, although some residues are expected to persist.

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## **NITROSODIMETHYLAMINE (NDMA)**

N-nitrosodimethylamine (NDMA) is a nitrosamine formed in many industrial and natural processes. It occurs in various foods and alcoholic beverages, is created from nitrates and nitrites in the human gut, and is also detected in cigarette smoke. The nitrosamines are considered as classic carcinogens, and a large amount of basic research on cancer mechanisms has been carried out on them (IARC, 1978; Preussmann and Stewart, 1984; Archer *et al.*, 1994, ATSDR, 1989; NTP, 2000; IRIS, 2004). Formation of DNA and RNA adducts of NDMA has been correlated with incidence of tumors (Belinsky *et al.*, 1989; Chhabra *et al.*, 1995; Souliotis *et al.*, 1995, 2002; Anderson *et al.*, 1996). Because of similarities among animals and humans in its metabolism to reactive intermediates (Herron and Shank, 1980; Yoo *et al.*, 1991; Yamazaki *et al.*, 1992), NDMA is considered to be a probable human carcinogen (IRIS, 2004).

NDMA has become more important in California because of its increasing detection in drinking water. It has been associated with the chloramine drinking water disinfection process, and may be formed from the nitrogen species added for chloramination (CDHS, 2003, 2004). Because of concern over the exposures and the carcinogenic properties of NDMA, California DHS requested that OEHHA develop a PHG for NDMA, to support the development of a California MCL. There is no federal Maximum Contaminant Level (MCL) for NDMA, but there is a California Action Level for NDMA of 0.01 g/L. NDMA is listed as a chemical known to the State of California to cause cancer under Proposition 65 (OEHHA, 2004).

Significant increases in tumors have been observed in numerous species of animals administered NDMA by oral, inhalation, and other routes of exposure. Evidence that specifically links exposure to NDMA to increased incidence of cancer in humans is generally lacking, but the available studies are suggestive (Delzell *et al.*, 1981; Sorahan *et al.*, 1989; Gonzalez *et al.*, 1994; Mirvish, 1995; Pobel *et al.*, 1995; Rogers *et al.*, 1995; De Stefani *et al.*, 1996; Knekt *et al.*, 1999; Straif *et al.*, 2000). Studies on other nitrosamines support the presumption of potential human carcinogenicity of NDMA (Bartsch and Montesano, 1984). The dose-response relationship derived by Peto and associates from the occurrence of liver tumors in female rats appears to be an appropriate study for cancer risk assessment (Peto *et al.*, 1991a,b).

Given the low volatility and skin permeability of NDMA, neither inhalation nor dermal exposure routes are expected to contribute significant amounts of exposure relative to the oral route. However, NDMA contributions from food sources are probably a relevant fraction of total exposure.

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## **OXAMYL**

The PHG of 50 ppb for oxamyl was published by OEHHA in December 1997. Oxamyl is a carbamate insecticide/acaricide and nematicide, and a growth plant regulator. The chief effect of oxamyl in animals is cholinesterase inhibition. The PHG is based on a NOAEL of 2.5 mg/kg-day where the critical effect is decreased body weight gain in rats. The PHG is different than the U.S. EPA's MCL of 200 ppb developed in 1991 because it is based on a different study and uses different assumptions. The California MCL is also 200 ppb, established in September 1994. No detections of oxamyl were reported in the recent surveys of public drinking water supplies (1984-01) reported by DHS.

### **Pertinent findings since PHG development**

Very few new studies relating to the effects of oxamyl have been found since the publication of the PHG. Although the information presented by the new studies doesn't appear likely to lead to a revision of the PHG value, the document deserves revision because it does not meet our current PHG document standards.

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## **PENTACHLOROPHENOL**

The PHG of 0.4 ppb for pentachlorophenol was published by OEHHA in December 1997. Pentachlorophenol is a wood-preserving insecticide and disinfectant. Generally considered a

very toxic substance, current pentachlorophenol uses are confined to specific outdoor applications such as utility poles. Pentachlorophenol has various noncarcinogenic effects and is considered to be a probable human carcinogen. The PHG is based a human equivalent slope factor of  $8.11 \times 10^{-2} \text{ (mg/kg-day)}^{-1}$  calculated based on tumors in a chronic mouse study. The PHG is different than the U.S. EPA's MCL of 1 ppb developed in 1991 because it is based on a different subset of information from the same mouse study and uses different assumptions. The California MCL is also 1 ppb, established in September 1994. Pentachlorophenol was detected once in 6,350 measurements of public drinking water supplies in analyses reported by the DHS for the period of 1984-01.

### **Pertinent findings since PHG development**

A large number of new studies relating to the toxic effects of pentachlorophenol were found. These studies cover a wide range of effects, and might lead to a revision of the PHG value. Revision of this PHG document should be made a high priority, because pentachlorophenol is an important environmental pollutant and there is a significant amount of new data available.

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## **THALLIUM**

The PHG of 0.1 ppb for thallium was published by OEHHA in 1999. Thallium is a bluish-white metal that is found in trace amounts in the earth's crust. Thallium has been obtained as a by-product from smelting other metals, but has not been produced in the U.S. since 1984. Currently, all the thallium is obtained from imports and from thallium reserves. Thallium is used mostly in manufacturing electronic devices, switches, and closures, primarily for the semiconductor industry. It also has limited use in the manufacture of special glass and for certain medical procedures. At one time, thallium sulfate was used in medicine as a depilatory agent. Thallium and various thallium compounds were also once used as pesticides, but their use was banned in the U.S. in 1972. Thallium enters the environment primarily from coal-burning and smelting, in which it is a trace contaminant of the raw materials.

Exposure to high levels of thallium can result in harmful effects on the nervous system (numbness in fingers/toes). Studies in people who ingested large amounts of thallium over a short time have reported vomiting, diarrhea, temporary hair loss, and effects on the nervous system, lungs, heart, liver, and kidneys. It has caused death. Studies in rats exposed to high levels of thallium showed adverse reproductive and developmental effects. Animal data suggest that the male reproductive system may be susceptible to damage by low levels of thallium. Thallium has not been classified by any authoritative body as to its human carcinogenicity. No studies are available in people or animals on the carcinogenic effects of breathing, ingesting, or touching thallium. The PHG is based on a noncancer endpoint, alopecia (hair loss) derived from a subchronic gavage study in rats. The U.S. EPA and California MCLs for thallium in drinking water are 2 ppb, which is constrained by the detection limit of 1 ppb. DHS reported 118 detections of thallium in 9689 analyses of drinking water from 1984-2001, and 47 MCL exceedances from 1984-2000. DHS also reports that a method development study is underway, and any considerations about decreasing the California MCL toward the PHG value are being deferred until this is completed (DHS, 2003).

### **Pertinent findings since PHG development**

Little is known about the precise mechanism by which thallium causes neurological manifestations in humans (e.g. ataxia, paralysis). A recent subchronic study in rats (Galvan-Arzate *et al.*, 2000), in which significant changes in lipid peroxidation were noted in both the

corpus striatum and cerebellum, suggests an active role of free radicals and oxidative events in the regional susceptibility of the brain to this metal. Male rats exhibited a dose-dependent increase in serum levels of aspartate aminotransferase, alanine transferase, and creatinine, hepatocyte necrosis and vacuolation in the liver and pathological changes in the renal tubules after i.p injection of thallium (Leung and Ooi, 2000). Though published *prior* to the development of the PHG, a developmental study of the toxicity of thallium in prenatal and postnatal rats on vasomotor activity (Rossi *et al.*, 1988) which was not included in the original PHG should be included because the route of exposure is via drinking water and this endpoint (the developing rat's vascular autonomic nervous system) may be the most sensitive indicator of developmental toxicity of thallium by the oral route in animals. The study may provide new information about the teratogenic/developmental effects of thallium. Also, the male reproductive system has been shown to be a susceptible target site to the toxic effects of thallium (Formigli *et al.*, 1986).

Several mechanistic studies may provide further perspective on thallium actions and effect. Studies exploring the mechanism of thallium-induced nephrotoxicity found no relation between toxicity in this target organ and riboflavin and/or GSH concentration (Appenroth and Winnefeld, 1999a,b), but may reveal a connection with effects on potassium transport (Zierold, 2000; Appenroth *et al.*, 2001).

Overall, the priority should be relatively high because this chemical has historically been detected in California drinking water at levels well above the current PHG, and the current MCL is 20 times the PHG.

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## **TRICHLOROETHYLENE**

The PHG of 0.8 ppb for trichloroethylene (TCE) was published by OEHHA in February 1999. TCE is primarily used as an industrial solvent for the vapor degreasing and cold cleaning of fabricated metal parts. It is also used in textile cleaning and solvent extraction processes. The current PHG is based on hepatocellular carcinomas and adenocarcinomas observed in two chronic bioassays on mice, in both sexes, by inhalation and oral routes of exposure. It is classified by IARC as a 2A carcinogen, indicating that it is a probable human carcinogen. The U.S. EPA MCL for TCE of 5 ppb was established in 1987 and the California MCL of 5 ppb was established in 1989. DHS reports that between 1984 and 2001, trichloroethylene has been detected 859 times out of 15,447 water samples taken. Between 1984 and 2000, the MCL for TCE was exceeded 332 times; between 1994 and mid-2002, it was exceeded 259 times. TCE has the most frequently exceeded California MCL for an organic chemical.

### **Pertinent findings since PHG development**

A large number of new animal and epidemiology studies were identified, as well as nearly two dozen reviews of the carcinogenicity and toxicity of TCE. The animal and epidemiological studies include new data on the carcinogenicity, ototoxicity, neurotoxicity, reproductive and developmental toxicity, immunotoxicity, nephrotoxicity, and other toxicological effects associated with TCE exposure. The reviews analyze the toxicological and epidemiological data, and discuss methodologies associated with classification of TCE as a carcinogen. One paper sharply questions IARC's dismissal of cancer data as irrelevant, citing that the carcinogenic mechanism is purportedly an animal-specific mechanism and not transferable to humans (Huff, 2002). The author contends that TCE data was "down-graded" or "under-graded." These new studies and analyses may have an effect on the methodology used and the value derived in the TCE document dated February 1999. The U.S. EPA has updated its TCE health risk assessment (U.S. EPA, 2001) since the PHG was published and has also upgraded its toxicity guidance for

effects on pregnant women and other potentially sensitive populations. Given that TCE is the most frequently exceeded organic MCL in the State, and that there are significant new data, the OEHHA re-review of this compound should be a high priority.

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