

**DRAFT**  
**For Review Only**

**Public Health Goal for**  
**Chlorite**  
**in Drinking Water**

**Prepared by**

**Pesticide and Environmental Toxicology Branch**  
**Office of Environmental Health Hazard Assessment**  
**California Environmental Protection Agency**

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**LIST OF CONTRIBUTORS**

To be added later

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## PREFACE

**Drinking Water Public Health Goal  
Pesticide and Environmental Toxicology Branch  
Office of Environmental Health Hazard Assessment  
California Environmental Protection Agency**

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances that may cause chronic disease shall be based solely on health effects and shall be set at levels that OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider potential adverse effects on members of subgroups that comprise a meaningful proportion of the population, including but not limited to infants, children, pregnant women, the elderly, and individuals with a history of serious illness.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. OEHHA shall consider additive effects of exposure to contaminants in media other than drinking water, including food and air, and the resulting body burden.
7. In risk assessments that involve infants and children, OEHHA shall specifically assess exposure patterns, special susceptibility, multiple contaminants with toxic mechanisms in common, and the interactions of such contaminants.

8. In cases of insufficient data for OEHHA to determine a level that creates no significant risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
9. In cases where scientific evidence demonstrates that a safe dose response threshold for a contaminant exists, then the PHG should be set at that threshold.
10. The PHG may be set at zero if necessary to satisfy the requirements listed above in items seven and eight.
11. PHGs adopted by OEHHA shall be reviewed at least once every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations or technical feasibility, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each primary drinking water standard adopted by DHS shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By state and federal law, MCLs established by DHS must be at least as stringent as the federal MCL, if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not intended to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at [www.oehha.ca.gov](http://www.oehha.ca.gov).

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## PUBLIC HEALTH GOAL FOR CHLORITE IN DRINKING WATER

### SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a proposed Public Health Goal (PHG) of 0.01 mg/L (10 µg/L, or 10 parts per billion [ppb]) for chlorite in drinking water. The proposed PHG is based on the sensitive endpoint of reversible, but significant, developmental delays in locomotor activity in newborn rats (Mobley *et al.*, 1990).

Chlorite is a disinfection byproduct produced in the treatment of drinking water with chlorine dioxide. Several studies (subchronic, chronic, and developmental) reveal that oral exposure to chlorite can result in significant hematological, endocrine, reproductive, and gastrointestinal effects as well as changes in neurobehavioral development. Reported effects include changes in methemoglobin; erythrocyte levels and morphology; serum thyroid levels; sperm morphology; sexual development; stomach ulceration; alterations in liver, brain, adrenal, kidney, spleen, and thymus weights; and decrements in auditory response and exploratory behavior. There are no acceptable carcinogenicity studies on chlorite; however, the existing lower-quality cancer studies and the limited positive genotoxicity data suggest that chlorite may be a weak carcinogen or have carcinogenic potential.

In the development of the proposed PHG, an acceptable daily dose (ADD) of chlorite was first calculated. The ADD represents an estimate of the maximum daily dose which can be consumed by humans for an entire lifetime without toxic effects, and includes the critical toxic dose from the most sensitive study divided by uncertainty factors to account for sensitive populations and a lifetime of exposure. For chlorite, the proposed ADD is 0.003 mg/kg-day, based on developmental delays in the study of Mobley *et al.* (1990) with a lowest observed adverse effect level (LOAEL) of 3 mg/kg-day in rats and a combined uncertainty factor of 1,000. The proposed PHG further calculates the health protective level of chlorite in drinking water based on exposure to neonates, the particular population of concern. Other potential exposure sources are considered, but are judged to be minimal.

The U.S. Environmental Protection Agency (U.S. EPA) Maximum Contaminant Level Goal (MCLG) for chlorite is 0.8 mg/L (800 ppb), set in 1998. This value is based on a Chemical Manufacturer's Association study (CMA, 1996) with a no observed adverse effect level (NOAEL) of 3 mg/kg-day based on a reduced response to auditory stimuli and a calculated reference dose (RfD) of 0.03 mg/kg-day, using a combined uncertainty factor of 100 (U.S. EPA 1998a,b, 2000). The current U.S. EPA Maximum Contaminant Level (MCL) for chlorite in drinking water is 1.0 mg/L (1,000 ppb), which became effective for large water systems on January 1, 2002. A California MCL has not yet been established; the Detection Limit for the Purposes of reporting (DLR) is 20 ppb.

## INTRODUCTION

The purpose of this document is to propose a Public Health Goal (PHG) for chlorite in drinking water. Chlorite is formed as a byproduct when drinking water is treated and disinfected with chlorine dioxide, a potent oxidizing agent.

Because chlorine dioxide rapidly degrades to chlorite in drinking water (Michael *et al.*, 1981) and rapidly converts to chlorite in laboratory animals (Abdel-Rahman *et al.*, 1980a), the pertinent scientific literature on chlorine dioxide as well as chlorite was evaluated to determine the most appropriate study and toxic endpoint for calculating a health-protective level. Most of the chlorite toxicological studies have utilized the sodium chlorite salt.

Chlorite, a strong oxidizing agent, is regulated as a drinking water contaminant by the U.S. EPA, with an MCL of 1.0 mg/L. Corresponding regulations for chlorite were finalized by the California Department of Health Services for an MCL of 1.0 mg/L on June 17, 2006. Both agencies categorize chlorite as a “disinfection byproduct” instead of an “inorganic” compound. The federal MCL was promulgated effective January 1, 2002 for drinking water systems serving 10,000 or more people. All drinking water systems were required to comply with this MCL beginning January 1, 2004.

The U.S. EPA Integrated Risk Information System (IRIS) reference dose (RfD) for chronic oral exposure to chlorite is 0.03 mg/kg-day, based upon neurodevelopmental effects in rats exposed to sodium chlorite in drinking water over the course of a two-generation study (CMA, 1996; U.S. EPA, 1998a,b, 2005). The Agency for Toxic Substances and Disease Registry (ATSDR) has proposed an oral intermediate-exposure Minimal Risk Level of 0.1 mg/kg-day for chlorite based on the CMA (1996) study as described by Gill *et al.* (2000) (ATSDR, 2004).

## CHEMICAL PROFILE

### *Chemical Identity*

Chlorite is an inorganic anion with strong oxidizing properties. Toxicological and chemical investigations typically are conducted using sodium chlorite. To generate chlorine dioxide for disinfection purposes, sodium chlorite or sodium chlorate are combined with strong acids. The chemical formula, synonyms and CAS number are listed in Table 1, which is adapted from the ATSDR toxicological profile on sodium chlorite (ATSDR, 2004).

**Table 1. Chemical Identity of Sodium Chlorite**

Chemical Name	Sodium Chlorite
Synonyms	Chlorous acid, sodium salt; Textone
Chemical Formula	NaClO <sub>2</sub>
Chemical Structure	Na <sup>+</sup> <sup>-</sup> O-Cl=O
CAS Registry Number	7758-19-2

***Physical and Chemical Properties***

Sodium chlorite is a strong oxidizer that is a solid white salt at room temperature. Technical grade sodium chlorite is approximately 80 percent pure and contains other salts (primarily sodium chloride and sodium chlorate) as impurities (Vulcan Chemicals, 2003). The following physical and chemical properties in Table 2 are adapted from ATSDR's toxicological profile on sodium chlorite (ATSDR, 2004).

**Table 2. Physical and Chemical Properties of Sodium Chlorite**

Property	Value or Information
Molecular weight (g/mol)	90.45
Color	White
Physical state	Solid
Melting point	180-200° C (decomposes)
Boiling point	Decomposes
Density	2.468 g/mL
Solubility Water Organic solvents	390 g/L at 30° C No data
Incompatibilities	Organic matter, sulfur, powdered coal; a powerful oxidizer

***Production and Uses***

Sodium chlorite is manufactured by reducing chlorine dioxide gas with a solution of sodium hydroxide. The solution is refined and converted to a dry solid. Technical grade sodium chlorite is approximately 80 percent pure sodium chlorite with sodium chloride and sodium chlorate salts as its primary impurities (Vulcan Chemicals, 2003). These act

as diluents for increased safety in storage and in handling, given the strong oxidizing properties associated with pure sodium chlorite (Kaczur and Cawfield, 1993; Vogt *et al.*, 1986).

More than 80 percent of all sodium chlorite produced is used for the generation of chlorine dioxide, which is generated when sodium chlorite is mixed with strong acid solutions. Because chlorine dioxide is so unstable, it is always generated onsite just prior to use (ATSDR, 2004).

Sodium chlorite is also used in disinfectant formulations and sterilization and must be registered with the U.S. EPA for each type of application as a disinfection product. Sodium chlorite is used in other industrial settings in NO<sub>x</sub> and SO<sub>x</sub> combustion flue gas scrubber systems; in the treatment and removal of toxic and odorous gases such as hydrogen sulfide and mercaptans; and as a solution formulation to oxidize copper surfaces in multilayer circuit boards (Kaczur and Cawfield, 1993). It is also used to bleach wood pulp in the manufacture of paper products (U.S. Department of the Interior, 2003). Currently, the use of sodium chlorite as a food sanitizer, as a dip or spray for meats and vegetables is being investigated (Gonzalez *et al.*, 2004; Oyarzabal *et al.*, 2004; Lim and Mustapha, 2004). However, no approved use of chlorite for this purpose has been found in the literature. Sodium chlorite is used in California for sterilization of bottling, food, milk and meat processing plants, as well as sanitizing hospitals and veterinarian clinics (CDPR, 2005).

In 1991, the production capacity of sodium chlorite was 7,700 metric tons (Kaczur and Cawfield, 1993). However, demand for sodium chlorite is anticipated to increase as water treatment facilities switch to the use of chlorine dioxide disinfection processes. For water treatment facilities there are a number of advantages for using chlorine dioxide rather than chlorine or ozone. It is more effective than chlorine as a biocide over a wide pH range; it is less corrosive and more compatible with some construction materials; it eliminates taste and odor problems from drinking water; and it does not react with organic matter to form trihalomethanes (THMs) like chloroform (ATSDR, 2004).

In the United States, sodium chlorite is produced by International Dioxide, Inc. and Vulcan Materials Company (SRI, 2001).

## ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

### *Air*

The available scientific literature contains no information about the levels of chlorite ions or sodium chlorite salt in the air. Air concentrations are expected to be very low because the anion and the salt are non-volatile.

### *Soil*

The available scientific literature contains no information on the levels of chlorite ions or sodium chlorite salts in soils. ATSDR reports that chlorite ions have not been identified

in any of the 1,613 hazardous waste sites proposed for inclusion on the U.S. EPA's National Priority List, but nonetheless notes that chlorite anions are anticipated to be mobile, and capable of leaching into groundwater. Chlorite can undergo oxidation-reduction reactions with components in the soil and sediments that could reduce its accumulation in groundwater (ATSDR, 2004).

It should be noted that chlorite discussed in this document is a chemical contaminant, and should not be confused with the silicate mineral complex known as chlorite (Lee *et al.*, 2003). The latter is a common component of clays, while the former is a disinfection byproduct.

## ***Water***

Chlorite ions are disinfection by-products (DBPs) formed when water is treated with chlorine dioxide. This treatment process is the primary source of chlorite in drinking water. Up to 70 percent of the chlorine dioxide added in the disinfection process is converted to chlorite ions in water, with the remaining portion converted to chlorate and chloride ions (Department of the Interior, 2003).

Sampling from four treatment plants in the United States using chlorine dioxide showed that treated water had chlorite concentrations ranging from 15 to 740 µg/L (Bolyard *et al.*, 1993). Drinking water treated with chlorine dioxide is anticipated to be the primary source of environmental exposure to chlorite. Chlorite is not typically derived from natural sources.

In California, the Detection Limit for the Purpose of Reporting is 0.02 mg/L (20 ppb) for chlorite (DHS, 2005b). Since chlorite is not yet regulated in California, no monitoring results are currently posted on the Department of Health Services Website.

## ***Food***

The available scientific literature contains no information on the levels of chlorite ions or sodium chlorite salt in food. There are a number of recent or ongoing investigations into the efficacy of sodium chlorite as an antimicrobial and sanitizing agent on food products (Gonzalez *et al.*, 2004; Oyarzabal *et al.*, 2004; Lim and Mustapha, 2004). No products are currently listed as approved for use in sanitizing food for human or animal consumption in the California pesticide registration database (CDPR, 2005). However, the Food and Drug Administration (FDA) permits the use of chlorite as a direct food additive, as an antimicrobial agent in food for human consumption, at levels of 50 to 1,500 parts per million (ppm) (ATSDR, 2004, citing 21CFR178.1010). Residual levels were not mentioned, although they would be expected to be lower, due to the reactive nature of this chemical.

## ***Other Sources***

The available scientific literature contains no information on the levels of chlorite ions or sodium chlorite salt from other sources of exposure.

**METABOLISM AND PHARMACOKINETICS*****Absorption***

A study conducted on Sprague-Dawley rats indicates that chlorite is rapidly absorbed from the gastrointestinal tract. Within two hours of a single oral gavage administration of 3 mL of 10 mg/L of radiolabeled chlorite ( $^{36}\text{ClO}_2^-$ ), peak plasma levels of  $^{36}\text{Cl}$  were reached. This concentration equates to an approximate dose of 0.13 mg/kg chlorite. Using the 72-hour excretion data, it can be calculated that at least 35 percent of the radiolabel was absorbed. The authors concluded that the absorption rate constant and half-time were 0.198/hour and 3.5 hours, respectively (Abdel-Rahman *et al.*, 1984a).

Dermal absorption of  $^{36}\text{Cl}$  was measured in Sprague-Dawley rats which had been administered ten daily applications of Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid that produce chlorine dioxide when mixed (Scatina *et al.*, 1983). As part of the Alcide, 0.6 g of  $^{36}\text{Cl}$ -labeled sodium chlorite was used to monitor absorption from the shaved backs of treated animals. Maximal levels of plasma  $^{36}\text{Cl}$  were reached after 72 hours. The authors concluded that the absorption rate constant and half-life were 0.0314/hour and 22.1 hours, respectively.

Because of its strong oxidizing properties, chlorite absorption is expected to occur via passive diffusion rather than active transport (ATSDR, 2004).

***Distribution***

Sprague-Dawley rats given a single oral gavage of 10 mg/L of radiolabeled chlorite ( $^{36}\text{ClO}_2^-$ ) show that elimination of chlorite from the blood is slow. The elimination half-life was 35.2 hours from the blood and the rate constant was 0.0197/hour. Chlorite was widely distributed throughout the body with the highest concentrations of the  $^{36}\text{Cl}$  being found in the blood, stomach, testes, skin lung, kidneys, small intestine, spleen, brain, bone marrow and liver (Abdel-Rahman *et al.*, 1982, 1984a).

***Metabolism***

Abdel-Rahman *et al.* (1980b) showed that chlorite is metabolized to a chloride ion. Sprague-Dawley rats were treated with a single oral gavage of 10 mg/L radiolabeled chlorite ( $^{36}\text{ClO}_2^-$ ) and monitored for 72 hours. By that time, approximately 87 percent of the radioactivity that was collected from the urine and 80 percent of the radioactivity in a plasma sample was chloride ion. This ultimate transformation to chloride ions is likely achieved via redox reactions with a variety of substances in biological systems that are readily oxidized.

***Excretion***

The primary route of excretion of orally administered chlorite is in the urine. Sprague-Dawley rats given radiolabeled chlorite ( $^{36}\text{ClO}_2^-$ ) and followed for 72 hours following a

single oral gavage administration of 10 mg/L excreted 35 and 5 percent of the radiolabel in the urine and feces, respectively. Nearly 90 percent of the urinary label was in the form of chloride ion (Abdel-Rahman *et al.*, 1984a).

Similarly, urinary excretion of  $^{36}\text{Cl}$  was observed in rats that had been dermally administered Alcide, an antimicrobial compound consisting of sodium chlorite and lactic acid that form chlorine dioxide when mixed (Scatina *et al.*, 1984). The rats had received ten daily applications, followed by an application of radiolabeled Alcide that contained 0.6 g of  $^{36}\text{Cl}$ -labeled sodium chlorite. Urinary excretion of  $^{36}\text{Cl}$  was greatest in the first 24 hours post application; the half-life of urinary elimination was 64 hours. The excreted radioactivity consisted of approximately equal portions of chloride ion and chlorite. No radioactivity was detected in feces or expired air.

## TOXICOLOGY

### *Toxicological Effects in Animals and Plants*

#### **Acute Toxicity**

Reported values for the LD<sub>50</sub> for sodium chlorite in rats range from 105 to 177 mg/kg. This is equivalent to 79-133 mg/kg of chlorite (Musil *et al.*, 1964; Seta *et al.*, 1991).

One exposure-related death per sex was observed during a 14-day range-finding study of rats administered gavage doses of sodium chlorite in the range of 25-200 mg/kg-day, which equates to 18.6-149.2 mg/kg-day of chlorite (Harrington *et al.*, 1995a). The deaths occurred on treatment days two and three. However, all four pregnant rats died that were gavaged on gestation days 8-10 with a dose of 200 mg/kg-day sodium chlorite, which is approximately 150 mg/kg-day of chlorite (Couri *et al.*, 1982a).

Cats given a single oral dose of chlorite in suspension developed significant methemoglobinemia within one to two hours after receiving a dose of 20 or 64 mg/kg (Heffernan *et al.*, 1979b).

#### **Subchronic Toxicity**

A number of hematological effects were reported by Harrington *et al.* (1995a). Rats were treated with sodium chlorite via gavage at doses that equaled 7.4, 19, or 60 mg/kg-day of chlorite for 13 weeks. High dose males had statistically significant decreases in their hematocrit and hemoglobin levels, increases in methemoglobin neutrophil levels, decreases in mean erythrocyte counts, morphological changes in erythrocytes and increased relative spleen and adrenal weights. Similarly mid-dose males had statistically significant increases in methemoglobin and neutrophil levels, decreases in lymphocyte count and increased relative spleen weights. In the high-dose group, females had significant decreases in mean erythrocyte counts, morphological changes in erythrocytes and increased relative and absolute adrenal weight, and relative spleen and kidney weights. At the mid-dose level, females had increased spleen weights. Body weight and

food consumption were not affected by treatment. Histopathological alterations in the high-dose group included squamous epithelial hyperplasia, hyperkeratosis, ulceration, chronic inflammation and edema in the stomach of seven males and eight females. The NOAEL in this study is set at 7.4 mg/kg-day and the LOAEL is 19 mg/kg-day for stomach lesions and increases in spleen and adrenal weights.

Bercz *et al.* (1982) examined the hematological and serum clinical chemistry effects of subchronic exposure to sodium chlorite in drinking water on adult African green monkeys. Five males and seven females per dose group were exposed to 0, 25, 50, 100, 200 or 400 mg/L chlorite in drinking water for four to six weeks. The authors reported statistically-significant, dose-related changes in hematological and serum chemistry parameters including decreases in erythrocyte levels and cell indices, subclinical increases in aspartate aminotransferase, slight decreases in hemoglobin levels, and slight increases in reticulocyte count and methemoglobin levels. Serum levels of the T4 thyroid hormone also were significantly reduced in the 400 mg/L group. The authors estimated that the dose this group received was 58.4 mg/kg-day. However, the data were not presented in a manner that would allow identification of threshold doses for these effects.

Moore and Calabrese (1982) found no significant alterations in body weight gain, absolute or relative kidney weights, water consumption, or kidney histology in mice exposed to sodium chlorite in drinking water for 30 or 90 days. Groups of 55-60 male C57L/J mice were exposed to 0, 4, 20 or 100 ppm sodium chlorite (0, 3, 15 or 75 ppm chlorite) in this study to assess renal toxicity.

No signs of methemoglobinemia were reported in rats exposed to sodium chlorite in the drinking water for 30-90 days (Heffernan *et al.*, 1979b). Chlorite concentrations were estimated to result in doses up to 50 mg/kg-day. At 30 days of exposure, slight anemia was reported in animals given above 10 mg/kg-day, returning to normal at 60 and 90 days of exposure.

## Genetic Toxicity

Sodium chlorite induced reverse mutations in *S. typhimurium* (with activation) and chromosomal aberrations in Chinese hamster fibroblast cells suggesting chlorite exposure can cause genotoxic effects (Ishidate *et al.*, 1984). Negative results were obtained from *in vivo* assays for micronuclei and bone marrow chromosomal aberrations in Swiss CD-1 mice, as well as sperm-head abnormalities in B6C3F<sub>1</sub> mice, following gavage administration of sodium chlorite at doses ranging from 0.25 to 1 mg/mouse/day for five consecutive days (Meier *et al.*, 1985). Hayashi *et al.* (1988) reported negative results for induction of micronuclei in mice that were administered sodium chlorite in single oral gavage doses ranging from 37.5 to 300 mg/kg, but positive results were obtained in mice subjected to single or multiple intraperitoneal injection of 7.5 to 60 mg sodium chlorite/kg. While the micronuclei tests appear to be negative, there is some data to suggest that chlorite may be genotoxic.

**Developmental and Reproductive Toxicity**

Mobley *et al.* (1990) investigated the hormonal and behavioral effects of sodium chlorite in drinking water on rats in a one-generation reproduction study funded by U.S. EPA. Groups of 12 female Sprague-Dawley rats were exposed to 0, 20, or 40 ppm chlorite in the drinking water. Control animals were given distilled water. Purity of the test ingredient was classified as “practical grade flakes,” which was confirmed to be equivalent to technical grade material (about 80 percent sodium chlorite) by a representative of the primary U.S. manufacturer of sodium chlorite (Vulcan Chemicals, 2005). Concentrations given to dams resulted in estimated chlorite doses of 0, 3 or 6 mg/kg-day, as reported by U.S. EPA (1994, 2000). ATSDR (2004) estimated the chlorite doses in this study as 2.6 and 5.2 mg/kg-day, possibly involving a different estimate for water consumption or a purity correction factor.

Dams were exposed for 10 days prior to mating and throughout gestation and lactation, until postconception day 42. Males were exposed only during the 5-day cohabitation period. The authors reported that there were no significant differences between treatment and control groups for litter size, gender composition, weight and weight gain, or day of eye opening. Six litters/group were housed continuously on postconception days 31 to 42 in a two-compartment home cage/activity cage apparatus to measure pup exploratory behavior. Measured activity consisted of counts of pup entries into the exploratory box, recorded as daily mean counts/ten minutes for each litter on days 36-40. Exploratory behavior increased rapidly in all groups from days 36 through day 40, as shown below in Table 3. Activity in the 20 ppm group was significantly decreased on days 36 and 37, but was comparable to controls thereafter. The 40 ppm group had significantly decreased exploratory activity compared to the control group on days 36-39, a duration that is double that of the 20 ppm group. Activity of the higher dose group was not significantly different from control on day 40, the last reported measurement.

**Table 3. Rat Pup Exploratory Activity After Exposure of Dams to Sodium Chlorite in Drinking Water During Gestation and Lactation (Mobley *et al.*, 1990)**

Group	Postconception Day				
	36	37	38	39	40
Controls	0.4	1.3	2.4	3.5	5.3
20 ppm	0.2*	0.9*	2.1	3.8	5.7
40 ppm	0.2*	0.7*	1.3*	3.2*	5.0

Estimated from the figure, to nearest 0.1 counts/10 minutes; \* p <0.05

Hormonal effects were assessed by conducting blood serum analysis on pups (only males) sacrificed on postconception days 37, 38 or 42, and on dams sacrificed on postconception day 42. Collections of day 37 and 38 were pooled for analysis. The authors reported that there were no significant differences in serum T3 (triiodothyronine) or T4 (thyroxine) levels observed in the 37-38 or the 42-day postconception pups. The

dams of these pups showed no significant differences between the control group for TT4 (total T4), TT3 (total T3) or FT3 (free T3) levels on day 42 postconception. However, a significant increase in free T4 was reported for pups in the 40 ppm group on postconception day 42. The authors noted the T3 uptake (an immunoglobulin binding assay) in treated pups was lower than controls (though not significantly) on the days pup activity was decreased; when uptake was similar in all groups, activity rates for all groups were virtually the same.

Whatever the underlying cause, the apparent delay in development of exploratory activity in this study suggests that neurodevelopment is a key endpoint, as expressed by behavior patterns, with a LOAEL for the dams of 20 ppm (3 mg/kg-day) chlorite in drinking water. This study identifies the most sensitive endpoint at the lowest exposure and is the basis for the proposed PHG.

In another study that explored developmental effects, the Chemical Manufacturers Association (CMA, 1996) conducted a two-generation study to examine reproductive, developmental, neurological, and hematological endpoints in rats exposed to sodium chlorite (subsequently reported by Gill *et al.*, 2000). Groups of 30 male and female Sprague-Dawley rats (the F<sub>0</sub> generation) were exposed to sodium chlorite in drinking water at concentrations of 0, 35, 70 or 300 ppm, which resulted in estimated chlorite doses of 0, 3.0, 5.7, or 21.0 mg/kg-day for males and 0, 3.9, 7.5, and 28.9 mg/kg-day for females. Control animals were treated with purified water. Exposure lasted for 10 weeks prior to mating and throughout the mating period. After mating, males were sacrificed and examined while females continued to receive sodium chlorite throughout gestation and lactation. To ensure that the doses remained constant throughout lactation when water intake increases, concentrations of sodium chlorite were adjusted accordingly. The F<sub>1</sub> generation had 25 males and females per group and was continued on the same treatment as their parents (chlorite doses of 0, 2.9, 6.0, or 22.9 mg/kg-day and 0, 3.9, 8.0, or 28.9 mg/kg-day for F<sub>1</sub> males and females, respectively). Animals were mated at about 14 weeks of age to produce F<sub>2a</sub> rats that were maintained through weaning on postnatal day 21. Due to a reduced number of litters in the mid-dose F<sub>2a</sub> generation, the F<sub>1</sub> animals were remated following weaning of the F<sub>2a</sub> rats to produce an F<sub>2b</sub> generation.

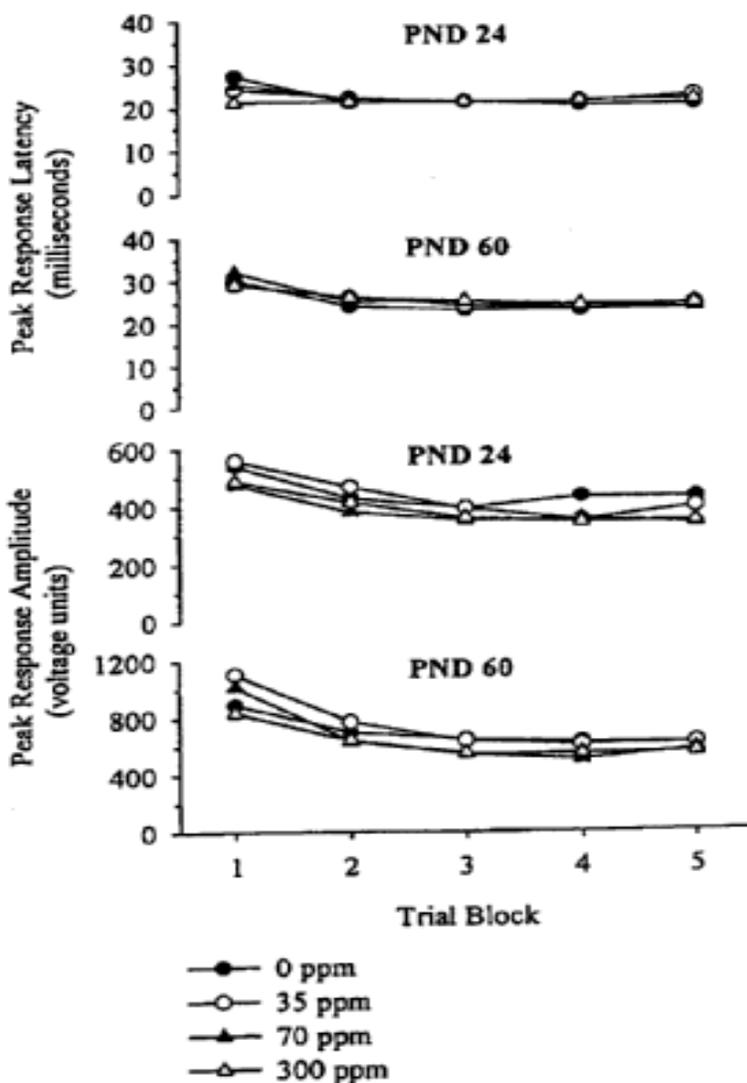
Several statistically significant effects were associated with exposure. At the highest dose, effects included reduced absolute and relative liver weight in the F<sub>0</sub> females and F<sub>1</sub> males and females, reduced pup survival and reduced body weight at birth and through lactation in F<sub>1</sub> and F<sub>2</sub> rats, lowered thymus and spleen weight in both generations, lowered incidence of pups exhibiting normal righting reflex and with eyes open on postnatal day 15, decreased absolute brain weight for F<sub>1</sub> males and F<sub>2</sub> females, delayed sexual development in F<sub>1</sub> and F<sub>2</sub> males (preputial separations) and females (vaginal opening), and lowered red blood cell parameters in F<sub>1</sub> rats. At the mid-dose, significantly reduced absolute and relative liver weight was observed in F<sub>0</sub> females and F<sub>1</sub> males.

In addition, a significant decrease in maximum response to an auditory startle stimulus was noted in two trial blocks at the mid- and high-dose neonatal groups on postnatal day 24, but not on day 60. Minor, statistically significant reductions in hematological parameters in F<sub>1</sub> pups were reported at the 35 and 70 ppm concentrations, although they appear to be within normal historical ranges. The authors considered these changes to be

biologically insignificant. However, they noted that these hematological parameters were significantly outside of the historical ranges in animals treated at the 300 ppm concentration; therefore, the effects seen at lower exposures may be related to treatment.

Other agencies reviewing the CMA study and the subsequent write-up by Gill *et al.*, 2000 have concluded that the auditory startle data as illustrated in Figure 1 represent a significant and relevant effect in weanling pups (U.S. EPA, 1998, 2000; ATSDR, 2004). The “trial block” data represent the results of five time trials, each comprised of ten acoustic trials per trial period for a total of 50 measurements.

Figure 1. Auditory Startle Response Data (from Gill *et al.*, 2000)



For the data described in Figure 1, test groups included 20 animals of each gender per group from the F<sub>2b</sub> generation. The hypothesis is that exposure to chlorite during gestation and lactation can result in developmental delays that adversely affect neurobehavioral outcomes. Other study results lend credence to this hypothesis, such as reductions in neonatal exploratory behavior (Mobley *et al.*, 1990) and lowered pup righting reflexes (CMA, 1996).

Significantly reduced absolute and relative liver weights in both sexes over two generations at both the mid-dose (70 ppm) and high-dose (300 ppm) were reported. The CMA study concluded that the NOAEL for this hepatic effect was the lowest dose tested of 35 ppm (2.9 mg/kg-day male dose level) and the LOAEL was the mid-dose level of 70 ppm (5.7 mg/kg-day). U.S. EPA, however, did not cite this endpoint as part of the basis for their chlorite MCL but instead identified the neurodevelopmental endpoint discussed above. They concluded that auditory startle response effects, when coupled with changes in absolute brain weight at 300 ppm, help justify a conclusion of significant neurotoxicity and a NOAEL of 35 ppm (2.9 mg/kg-day) (U.S. EPA, 1998a,b).

OEHHA concurs with U.S. EPA that there is evidence of neurodevelopmental toxicity (as well as other critical toxicological effects) at the mid- and high-dose levels in the CMA study and that the study LOAEL is 70 ppm (5.7 mg/kg-day). However, after reviewing the available scientific literature we conclude that the Mobley 1990 study provides the most sensitive endpoint at the lowest dose tested. This study examined a key behavior and endpoint that was not studied in the CMA study, and it reports that significant effects at a lower dose than that of the CMA study. Therefore, the significant reduction in exploratory behavior exhibited in weanling rats at the LOAEL level of 20 ppm (3.0 mg/kg-day) in the Mobley study is the most sensitive endpoint identified in the available scientific literature and as such provides the basis for the proposed PHG.

OEHHA has also examined an external peer review of the CMA study that was commissioned by U.S. EPA (U.S. EPA, 1997). Of the five independent experts who evaluated the original report, four stated that the conclusions regarding the NOAELs and LOAELs for certain toxicological endpoints needed to be revised. Most notably, the majority of the reviewers stated that the NOAEL for hematological parameters needed to be lowered with two of the reviewers stating that the study may have no NOAEL for this endpoint. One reviewer suggested “because concentrations were cut in half when F<sub>0</sub> and F<sub>1</sub> dams were nursing their pups, the actual concentrations tested have to be considered to be 0, 17.5, 35 and 150 ppm” for risk assessment purposes. U.S. EPA did not provide a response to this comment (U.S. EPA, 1998a,b). OEHHA has evaluated this and the other reviewers’ comments and concludes that without the full original study data, or additional supporting documentation, concurrence on this point is not possible at this time.

The reproductive effects of chlorite exposure were studied by Carlton and coworkers (Carlton and Smith, 1985; Carlton *et al.*, 1987) in three drinking water experiments on rats. In the first study, groups of 12 male Long-Evans rats were exposed to 0, 1, 10, or 100 ppm sodium chlorite in the drinking water for 56 days prior to mating and throughout a 10-day mating period. Groups of 24 female rats received the same concentration of sodium chlorite in drinking water for 14 days prior to mating and throughout gestation

and lactation. Estimated chlorite doses were 0, 0.09, 0.9 or 9 mg/kg-day for males and 0, 0.1, 1, or 10 mg/kg-day for females.

At the end of the breeding period, F<sub>0</sub> males were sacrificed and sperm parameters and histopathological examinations of the reproductive tract were conducted. Females were allowed to continue to term and were observed for conception rate, length of gestation and body weight. Litters were evaluated for size, perinatal survival, day of eye opening, day of vaginal patency, body-weight gain, and gross external abnormalities. At necropsy on lactation day 21, the F<sub>0</sub> females' hematological parameters were measured and their reproductive tracts were examined. Ten F<sub>1</sub> pups/sex/group were also necropsied on lactation day 21 when complete hematological parameters were measured and their reproductive tracts were weighed. Selected F<sub>1</sub> pups were retained for further developmental and hormonal evaluation.

Sperm counts were not significantly affected in F<sub>0</sub> males, but there was an observed trend towards decreased sperm progressive movement in the high-dose group. Observed fertility rates varied between 67 and 96 percent, but did not differ in a dose-dependent manner. Perinatal survival was comparable for all groups as was median day of eye opening (day 16) and day of vaginal patency (day 32). Significant decreases in serum T3 and T4 levels were consistently observed in the high-dose groups of F<sub>1</sub> males and females at postnatal days 21 and 40. The study identified a NOAEL of 0.9 mg/kg-day and a LOAEL of 9 mg/kg-day for altered thyroid hormone levels in offspring of dams exposed to sodium chlorite in drinking water.

Two follow-up studies were conducted to examine sperm parameter effects associated with sodium chlorite exposure (Carlton and Smith, 1985; Carlton *et al.*, 1987). In the first follow-up study, groups of 12 male Long-Evans rats were given drinking water containing 0, 100, or 500 ppm sodium chlorite (0, 9, or 45 mg/kg-day of chlorite) for 72-76 days. At necropsy, animals were given complete blood counts and a methemoglobin determination. An analysis of sperm was conducted that included sperm count, percent motility, drive range and morphological abnormalities. The authors reported that in the high-dose group, water consumption was significantly reduced. The second follow-up experiment exposed groups of 12 male Long-Evans rats to water containing 0, 1, 10 or 100 ppm concentrations of sodium chlorite (0, 0.09, 0.9, or 9 mg/kg-day chlorite) for 72-76 days. The authors concluded that there were no significant alterations in sperm count, sperm mobility, or mean progressive movement when each study was evaluated separately. However when the study data were pooled, there was a statistically significant trend toward decreased progressive movement in the 100 and 500 ppm groups. A significant increase in abnormal sperm was observed in the 100 and 500 ppm groups with the most common morphological abnormalities being frayed tails, open hooks and amorphous sperm head. The authors identified a NOAEL of 10 ppm (0.9 mg/kg-day chlorite) and a LOAEL of 100 ppm (9 mg/kg-day) for reproductive effects in rats exposed to sodium chlorite in drinking water. However, the biological significance of the minor changes in mean progressive movement or sperm morphology is unclear.

In a developmental study, Couri *et al.* (1982b) exposed groups of 7-13 female Sprague-Dawley rats to sodium chlorite in the drinking water during gestational days 8-15. The concentrations provided resulted in estimated chlorite doses of 0, 70, 440 or 610 mg/kg-

day. Litters were either delivered at term or by cesarean section on gestational day 22. Significant decreases in crown-rump length were observed at all doses in term-delivered litters and in the 70 mg/kg-day group that was cesarean-delivered. Fetal weights were not adversely affected. An increase in the number of resorbed and dead fetuses was observed in cesarean-delivered litters of all exposure levels; two litters out of five were totally resorbed in the high-dose group. Postnatal growth and the incidences of soft tissue and skeletal malformations were not adversely affected. This study identifies a LOAEL of 70 mg/kg-day for resorbed and dead fetuses and decreases in crown-rump length in the offspring of rats.

Suh *et al.* (1983) evaluated the potential for developmental effects from exposure to chlorite in drinking water by administering chlorite in the drinking water to groups of six to nine female Sprague-Dawley rats. Animals were exposed to chlorite-treated water at concentrations of 0, 1 or 10 mg/L (equivalent to doses of 0, 0.1 or 1.0 mg/kg-day chlorite) for 2.5 months prior to mating and during gestational days 0-20. Male rats in this study were not exposed. On gestational day 20, dams were sacrificed and fetuses were examined for external, skeletal, and visceral malformations. Although there were increased incidences of resorptions, no statistically significant increase was found. In the high-dose group, slight, statistically significant increases in crown-rump length compared with controls were reported. Skeletal defects, such as incompletely ossified or missing sternebrae, rudimentary ribs and incompletely ossified skull bones were increased in all treatment groups, but none was significantly different from controls. A NOAEL of 1.0 mg/kg-day for developmental toxicity was identified by this study.

Moore and coworkers (Moore and Calabrese, 1982; Moore *et al.*, 1980) conducted a study to evaluate the effect of exposure to sodium chlorite on conception and litter rates in A/J mice. Groups of 10 pregnant mice were given sodium chlorite in the drinking water throughout gestation and lactation at a concentration of 0 or 100 ppm, an estimated chlorite dose of 23 mg/kg-day. While a decrease in the conception rate was reported in the chlorite group (39 vs. 56 percent in controls), the statistical significance was not reported. No significant alterations in gestation length, litter size, number of pups dead at birth, or number of pups alive at weaning were observed. Pup growth was adversely affected, as shown by significantly lower average pup weaning weight and birth-to-weaning growth rate. This study identifies a LOAEL of 23 mg/kg-day of chlorite for developmental effects in the offspring of mice exposed to chlorite in the drinking water.

Harrington *et al.* (1995b) treated groups of 16 New Zealand white rabbits with sodium chlorite via their drinking water on gestation days 7-20 at concentrations of 0, 200, 600 or 1,200 ppm, giving estimated chlorite doses of 0, 10, 26, or 40 mg/kg-day. Dams were sacrificed on gestation day 28. Although the number and mean percentage of major external and visceral and skeletal abnormalities were higher in the 26 and 40 mg/kg-day groups, the authors did not consider these to be treatment-related adverse effects. Mean fetal weights in the 26 and 40 mg/kg-day groups were slightly lower (less than 9 percent, relative to controls). Also in the mid- and high-dose groups, the incidence of minor skeletal abnormalities and skeletal variants related to incomplete fetal bone ossification was higher than for controls. The authors state in their discussion that these alterations in fetal body weight and delayed ossification indicate embryonic growth retardation. However, it was noted that lower maternal food and water consumption and body weight

gain may be responsible, at least in part, for some of the fetal effects. The NOAEL for this study is set at 200 ppm (10 mg/kg-day) and the LOAEL is 600 ppm (26 mg/kg-day) based on lower fetal weight and delayed skeletal ossification.

## **Immunotoxicity**

Immunotoxicity data in animals is limited to accounts of treatment-related alterations in thymus and spleen weights. Harrington *et al.* (1995a) found significantly increased spleen weights in male rats administered sodium chlorite by gavage at a dose level of 80 mg/kg-day (60 mg chlorite/kg-day) for 13 weeks and in female rats similarly treated with 10 or 60 mg/kg-day of chlorite. In this study, increased spleen weights were attributed to morphological changes in erythrocytes. Several treatment-related deaths were reported at this dose.

In the CMA (1996) study, significantly lower spleen and thymus weights were seen in F<sub>1</sub> and F<sub>2</sub> rats that had been exposed to sodium chlorite via their mothers during gestation and lactation and via the drinking water after weaning at a dose level of 21.0 mg chlorite/kg-day.

## **Neurotoxicity**

No scientific reports were found that examined neurotoxicity parameters in animals after direct (postnatal) sodium chlorite exposures. However, neurodevelopmental effects were associated with chlorite exposure *in utero* as discussed in the reproductive and developmental section of this report. Specifically, behavioral effects included decreased exploratory activity (Mobley *et al.*, 1990) and reduced response to auditory stimuli (CMA, 1996; Gill *et al.*, 2000). CMA (1996) also reported significantly decreased absolute brain weights in two generations.

## **Chronic Toxicity**

In a chronic study by Haag (1949), groups of rats (seven/sex/group) were exposed to 0, 1, 2, 4, 6, 100 or 1,000 mg/L chlorite in drinking water for two years. These concentrations equate to approximate doses of 0, 0.09, 0.18, 0.35, 0.7, 9.3 or 81 mg/kg-day. Animals exposed to chlorite concentrations of 100 or 1,000 mg/L exhibited treatment-related renal pathology characterized by distention of the glomerular capsule and appearance of a pale pinkish staining material in the renal tubules. Based on renal effects, this study identifies a NOAEL of 6 mg/L (0.7 mg/kg-day) and a LOAEL of 100 mg/L (9.3 mg/kg-day). Interpretation of the study is limited by the unknown purity of the test compound.

Abdel-Rahman *et al.* (1984b) tested the hematotoxicity and other endpoints resulting from chronic ingestion of chlorite in drinking water. Groups of male Sprague-Dawley rats were exposed to 0, 10 or 100 mg/L chlorite in drinking water for 20 hours/day, 7 days/week for one year. These concentrations, adjusted for intermittent exposure, approximate doses of 0, 1 or 10 mg/kg-day. After 2, 5, 10 and 11 months of exposure there were significant decreases in body weight gain in the 100 mg/L group; body weight gain was also decreased in the 10 mg/L group (up to 18 percent lower than controls) at 10

and 11 months. Although this effect appeared earlier at the highest concentration, mean terminal body weight after 11 months of exposure was lower in low-dose rats than in high-dose rats. Osmotic fragility of erythrocytes was tested to determine if chlorite exposure could affect the cellular structure of red blood cells. While an increase in osmotic fragility means the erythrocytes more readily split apart, a decrease in osmotic fragility signifies that the membrane of the red blood cells has changed and is less permeable to normal biological processes. In this test, osmotic fragility was significantly decreased at 100 mg/L after two months of exposure to chlorite and continued to be so throughout the experiment. For the 10 mg/L group, significant decreases were seen after seven and nine months of exposure. By the ninth month of exposure, osmotic fragility was decreased by 58 and 75 percent for the low- and high-dose group, respectively. The study authors suggested that the decreased osmotic fragility might have been related to the disulfide bond between hemoglobin and the cell membrane as the result of oxidative stress. Other hematological effects include significantly decreased mean corpuscular hemoglobin concentrations for both groups at seven months; reduced erythrocyte counts in the 10 mg/kg-day group at nine months; and decreased hemoglobin concentrations in the 1 mg/kg-day group after nine months. Blood glutathione levels were also significantly decreased in both groups after two months, and in the high-dose group at four, seven and nine months. The study authors also studied the effect of exposure to chlorite on DNA synthesis (as measured by <sup>3</sup>H-thymidine) in various organs and tissues. After three months of exposure, DNA synthesis was decreased in the liver and testes at 1 and 10 mg/kg-day, increased in the intestinal mucosa at 1 mg/kg-day, and decreased in the intestinal mucosa at 10 mg/kg-day.

Couri and Abdel-Rahman (1980) evaluated hematological endpoints resulting from chronic exposure to chlorite in drinking water. In this study, groups of male Sprague-Dawley rats were exposed to 0, 10 or 100 mg/L chlorite in drinking water for 20 hours per day, seven days a week for one year. The concentrations, adjusted for intermittent exposure, approximate doses of 0, 1 or 10 mg/kg-day. After six months of exposures, both exposure groups had significantly increased blood glutathione reductase levels, and significantly decreased blood catalase and glutathione peroxidase levels. Blood glutathione levels were also significantly decreased in both groups. At 12 months of exposure, the 1 mg/kg-day group had significant changes in levels of blood glutathione reductase (decreased), glutathione peroxidase (decreased), catalase (increased) and blood glutathione (increased). The 10 mg/kg-day group had significantly reduced levels of blood peroxidase and blood glutathione.

Moore and Calabrese (1982) exposed groups of 55-60 male C57L/J mice to 0, 4, 20 or 100 ppm sodium chlorite (0, 3, 15 or 75 ppm chlorite) in the drinking water for up to 190 days to assess the renal toxicity of sodium chlorite exposure. No significant alterations in body weight gain, absolute or relative kidney weights, water consumption, or kidney histology were observed.

## **Carcinogenicity**

In an oral carcinogenicity study, Kurokawa *et al.* (1986) exposed rats and mice to sodium chlorite in drinking water. In the rat portion of the study, groups of 50 male and 50

female F344 rats were exposed to 0, 300 or 600 ppm of sodium chlorite in drinking water, which resulted in estimated chlorite doses of 0, 13.5 or 24 mg/kg-day for males and 0, 21 or 31 mg/kg-day for females. During the course of the experiment, all test animals became infected with the Sendai virus. As a result, the study was halted prematurely after 85 weeks of exposure. A slight dose-related decrease in body weight gain was observed. There were nonsignificant increased incidences of tumors in several organs, including the thyroid, pituitary, testis, adrenal glands and uterus.

In the mouse portion of the Kurokawa *et al.* (1986) study, groups of 50 male and 50 female B6C3F<sub>1</sub> mice were exposed for 85 weeks to 0, 250 or 500 ppm of sodium chlorite in drinking water, resulting in estimated chlorite doses of 0, 36 or 71 mg/kg-day. In high-dose males, significant increases in lung tumors were reported. The incidence of lung adenoma and the combined incidence of lung adenoma and adenocarcinoma were significantly increased compared with controls. High-dose males also had significantly increased incidences of hepatocellular carcinoma. Low-dose males had significant increases in liver tumors as well, which included an increased incidence of hyperplastic nodules and hepatocellular carcinoma. In the female mice, the only significant change in tumor incidence was an apparent dose-related decrease in malignant lymphoma/leukemia, which was significantly lower in the high-dose group. Chlorite exposure did not alter survival or body weight gain.

The study authors reported that severe fighting in the control males reduced the number of animals in this group by 30 percent. When the cancer incidence rates were compared with their historical controls in the National Toxicology Program (NTP) laboratories, they were within normal ranges. However, it is uncertain whether the authors were comparing full-term study results (104 weeks) to their abbreviated-term study results of 85 weeks. Since the incidence of tumors increases with age, the age at which tumors are assessed matters. Also the relevance of the NTP program historical control data to the results in this Japanese laboratory is unclear. Nonetheless, the authors reported that the results of these rat and mouse bioassays were inconclusive. Complicating the interpretation of these studies is the fact that the exposure durations for these species were considerably less than the lifetime exposure guidelines for adequate carcinogenicity studies.

Yokose *et al.* (1987) published a report on the mouse data presented in Kurokawa *et al.* (1986). The two accounts vary on a number of study factors, including the age of mice at the initiation of the experiment, the source from which the animals were obtained, the purity of the test substance, the number of tumor-bearing mice at the study end, and the duration of treatment. Yokose *et al.* (1987) indicated that exposure of mice was terminated at 80 weeks according to a guideline for carcinogenicity studies from the Ministry of Health and Welfare of Japan. However, a review of both studies and their similarities strongly indicates the data is from the same mouse study. Specifically, both studies report identical doses, identical numbers of surviving animals, identical survival curves and body weight curves, nearly exact numbers of tumors at each specific tissue site for each sex, and each study includes a discussion on the loss of control males due to excessive fighting early in the experiment. The authors of Yokose *et al.*, 1987 concluded that there was no clear evidence of a carcinogenic effect associated with sodium chlorite in drinking water on mice just as had Kurokawa *et al.*, 1986.

Kurokawa *et al.* (1984) tested sodium chlorite to determine if it can promote or cause cancer in Sencar mice. In the tumor-promoting experiment, the shaved backs of 20 female mice were treated with a single application of 20 nmol of dimethylbenzanthracene (DMBA). After one week, animals were dermally treated twice a week for 51 weeks with 0.2 mL of 20 mg/mL sodium chlorite diluted in acetone. In the complete carcinogen experiment only the sodium chlorite solution was applied dermally twice weekly for 51 weeks. None of the mice in the complete carcinogen experiment developed any skin tumors. However, six mice in the promotion study developed skin tumors, five of which had squamous cell carcinoma. The authors concluded that sodium chlorite could potentially promote cancer, although the tumor incidence was not statistically significant.

The cancer studies, though flawed, do suggest that chlorite exposure may be associated with an increased number of malignancies. It appears from the limited data available that chlorite may be a weak carcinogen or possibly a promoter; however, this inference cannot be confirmed at this point due to the inadequacies in the data.

## ***Toxicological Effects in Humans***

### **Acute Toxicity**

A 25-year old Chinese male who consumed 10 g of sodium chlorite dissolved in 100 mL of water in an apparent suicide attempt experienced abdominal cramps, nausea, and vomiting within a few minutes after ingesting the solution. He was diagnosed with profound methemoglobinemia. Respiratory distress and intravascular coagulation, likely secondary to the methemoglobinemia, persisted despite treatment with methylene blue. Acute renal failure followed a few days later (Lin and Lim, 1993).

No indication of any adverse physiological or hematological parameters were seen in 10 healthy adult male subjects who participated in an acute rising dose experiment on chlorite in drinking water. During the first treatment sequence, each man consumed two 500 mL solutions (separated by four hours) containing 0.01 mg/L chlorite. Subsequent treatments of 0.1, 0.5, 1.0, 1.8 and 2.4 mg/L were administered three days apart, with biological monitoring occurring between each treatment. Total cumulative dose was 0.083 mg/kg based on a body weight of 70 kg (Lubbers *et al.*, 1981, 1982).

### **Subchronic Toxicity**

In a 12-week study, investigators gave groups of 10 healthy adult males 500 mL solutions of 0 or 5 mg/L chlorite (0.04 mg/kg-day). General health parameters were unchanged as observed from clinical observations, physical examination, and measurement of vital signs. Serum clinical chemistry was normal for glucose, electrolytes, calcium, urea nitrogen, enzyme levels, and cholesterol. Hematological parameters were within the normal range for erythrocytes and total and differential leukocyte counts, hemoglobin, hematocrit, and methemoglobin, and serum T3 and T4 levels were stable (Lubbers *et al.*, 1984a).

A companion study by this group of authors was conducted to investigate chlorite for adverse effects in three healthy glucose-6-phosphate dehydrogenase (G6PD) deficient male subjects (Lubbers *et al.*, 1984b). Each subject was given a solution containing 5 mg/L chlorite (0.04 mg/kg-day) for 12 weeks. The subjects were given the same physical and clinical examinations as those from Lubbers *et al.* (1984a) and compared to the control group from that study. There were no significant differences in any of the parameters measured.

No adverse hematological or serum chemistry effects were found in an epidemiological study of inhabitants in a rural village who were exposed for 12 weeks to chlorine dioxide treated water. One week prior to the commencement of chlorine dioxide treatment by the water treatment facility and ten weeks after treatment began, 198 individuals from the community had their hematological and serum chemistry parameters evaluated. Blood samples from a control group of 118 people who were not exposed to chlorine dioxide treated water were taken at the same time. Hematological parameters included erythrocytes, leukocyte counts and reticulocyte counts, hemoglobin, hematocrit, methemoglobin, mean corpuscular volume and osmotic fragility. For the serum chemistry, blood urea nitrogen and total bilirubin levels were included. Weekly measured concentrations for chlorite ranged from 3.19 to 6.96 mg/L, from which the authors estimated daily chlorite intakes ranged from 0 to 39.4 mg/day. Assuming a 70 kg person, this equates to a dose of 0.56 mg/kg-day (Michael *et al.*, 1981).

## Genetic Toxicity

The available scientific literature contains no information on the genotoxicity of chlorite in humans.

## Developmental and Reproductive Toxicity

There are three epidemiological studies that examine developmental toxicity from chlorine dioxide-treated water. These studies have drawbacks that make interpretation equivocal.

Aggazzotti *et al.* (2004) conducted a case-control study to evaluate adverse pregnancy outcomes in nine Italian towns between October 1999 and September 2000, in which the drinking water contained chlorination byproducts. A total of 1194 subjects were enrolled, with 612 people serving as controls for 343 preterm births (defined as babies born on or after gestation week 26 and prior to the end of week 37) and 239 low-birth babies (defined as babies born post-gestation week 37 but who weighed less than the lowest 10<sup>th</sup> percentile). Exposure was assessed by surveying the mothers via a questionnaire about their water usage and personal habits during pregnancy. Water samples were also analyzed for concentrations of trihalomethanes, chlorite and chlorate. Sampling results indicated that median concentrations of trihalomethanes (THMs) were 1.10 µg/L, while the median concentration for chlorite was 216.5 µg/L and for chlorate was 76.5 µg/L. The study concluded that preterm births showed no association with any of the measured chlorination byproducts. Low birth weight, however, was associated with chlorite when inhalation exposure to chlorinated byproducts was taken into account,

when the chlorite concentration in drinking water was equal to or greater than 200 µg/L. The effect seen was reported to suggest a dose-response relationship. The authors also reported that a weak association was found with high THM exposures, greater than 30 µg/L, or when chlorite or chlorate was greater than 200 µg/L. Complicating the interpretation of this study is the lack of discussion of a number of critical components, including but not limited to nutritional factors, exposure to other chemicals, and precise quantities of tap water consumed.

Infant morbidity and mortality data was examined by Tuthill *et al.* (1982) from a community in which water had been disinfected with chlorine dioxide for over forty years. The data from this community was compared with another in which the water supply was treated by chlorination over the same time period. Exposure to chlorine dioxide-treated water was not linked to any adverse affect including fetal or perinatal mortality, birth weight, maximum weight loss, sex ratio or birth condition. The authors reported a significantly greater proportion of premature births in the community using chlorine dioxide as judged by physician assessment. However, other measures of premature birth, such as birth weight and gestational age were not considered. Infants from the community using chlorine dioxide exhibited statistically significant greater maximum weight loss after birth and smaller weight gain in 6 days, although these effects appeared to be partially linked to the mode of feeding practiced by the mother.

Births from two cities in Italy were evaluated by Kanitz *et al.* (1996). This team of investigators evaluated 548 births from the Galliera Hospital in Genoa, Italy and 128 births from the Chiavari hospital in Chiavari, Italy. The study focused on births from 1988 to 1989. Women who resided in Genoa had been exposed to drinking water that had been disinfected with chlorine dioxide, sodium hypochlorite, or both during their pregnancies. Women from Chiavari were exposed to well water that had not been treated with any disinfectants, and were considered the control group for this study. Hospital data on infant birth weight, body length, cranial circumference, neonatal jaundice, maternal age, smoking, alcohol consumption, education, and preterm delivery were analyzed. After adjusting for maternal education level, income, age, smoking, and sex of the child, the authors concluded that several effects seen in infants were linked with their mother's exposure to treated drinking water. These were an increase in neonatal jaundice, a reduction in cranial circumference, and smaller body lengths. Lower birth weights and a higher rate of preterm deliveries were also reported, but were not statistically significant. Interpretation of this study is complicated by the fact that a number of critical parameters (including exposure data, quantity of water consumed, exposure to other chemicals, nutritional habits, and other confounding variables) were not evaluated. As such, it is difficult to draw firm conclusions from this study.

## **Immunotoxicity**

The available scientific literature contains no information on the immunotoxicity of chlorite in humans.

## Neurotoxicity

The available scientific literature contains no information on the neurotoxicity of chlorite in humans.

## Chronic Toxicity

The available scientific literature contains no information on the chronic toxicity of chlorite in humans.

## Carcinogenicity

No reports were located in which cancer could be associated with exposure to chlorite in humans.

## DOSE-RESPONSE ASSESSMENT

### *Noncarcinogenic Effects*

A LOAEL of 20 ppm chlorite (a 3 mg/kg-day dose to the dam) was identified for neurodevelopmental effects as shown by significantly reduced exploratory behavior in rat pups on postconception days 36 and 37. At the next higher exposure concentration of 40 ppm (6 mg/kg-day), significantly reduced exploratory behavior was observed for four days (postconception days 36, 37, 38 and 39), suggesting a dose-response relationship for neonates exposed to chlorite during gestation and lactation (Mobley *et al.*, 1990).

ATSDR and the U.S. EPA both cited the Mobley *et al.*, 1990 study in their more recent risk assessments on chlorite, and stated that the delayed mobility effect seen at the lowest dose was statistically significant. However, they both labeled it as a NOAEL (ATSDR, 2004; U.S. EPA, 2000). These agencies did not explain their rationale for discounting the effects at the lowest dose. OEHHA acknowledges the difficulty in judging, for the purposes of risk assessment, when a statistically significant effect becomes biologically significant – i.e., can be considered to represent an adverse effect. However, the delay in development of exploratory behavior in this case appears to us to represent a true developmental toxic effect. Although the effect appeared to be reversible in this case, neonatal neurodevelopment delays can disrupt cortical neuronal migration and maturation and therefore may have long-term adverse consequences (which were not evaluated in this study). Because the neonatal developmental effect appears to be a reproducible, dose-dependent, and relevant endpoint, OEHHA has concluded that these statistically significant data should not be discounted.

Additional studies indicate that chlorite may affect neonatal development. In the two-generation rat study (CMA, 1996), pups born to mothers exposed to chlorite in drinking water may have had reduced auditory startle responses, which might represent learning problems. Other significant neonatal effects in this study included reductions in liver and brain weight, in pup survival, and body weight at birth, lowered pup righting reflexes,

and delayed sexual development. The study has been interpreted as having a NOAEL of 3 mg/kg-day (U.S. EPA, 1998a,b). Other drinking water studies have reported significant changes in serum thyroid hormone levels in pups exposed to chlorite during pre- and postpartum development (Carlton and Smith, 1985; Carlton *et al.*, 1987) at about the same effect levels (a LOAEL of 9 mg/kg-day and a NOAEL of 0.9 mg/kg-day).

Therefore OEHHA has chosen the one-generation study of Mobley *et al.* (1990) as the basis for the proposed PHG. Our evaluation uses the most sensitive endpoint for chlorite exposure of significant, but reversible, developmental delays in locomotor activity in rats, at the LOAEL concentration of 20 ppm chlorite in drinking water, which resulted in significantly decreased exploratory behavior on postconception days 36 and 37. The chlorite dose was estimated by U.S. EPA as 3.0 mg/kg-day, based on the dose to the dams.

## CALCULATION OF PHG

Calculation of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, for preparing foods, beverages and infant formulas. It is also used for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures.

### *Noncarcinogenic Effects*

For estimation of a health-protective concentration of a chemical in drinking water, an acceptable daily dose of the chemical from all sources will first be calculated. This involves incorporation of appropriate estimates of uncertainty in the extrapolation of the critical toxic dose from human or animal studies to the estimation of a lifetime daily dose for that is unlikely to result in any toxic effects. For this purpose, the following equation will be used:

$$\text{ADD} = \frac{\text{NOAEL/LOAEL in mg/kg-day}}{\text{UF}}$$

where,

ADD = an estimate of the maximum daily dose which can be consumed by humans for an entire lifetime without toxic effects;

NOAEL/LOAEL = no-observed-adverse-effect level or lowest-observed-adverse-effect level in the critical study;

UF = uncertainty factor.

Calculation of a public health-protective concentration (C, in mg/L) for a chemical in drinking water uses the following equation for noncarcinogenic endpoints:

$$C = \frac{\text{ADD mg/kg-day} \times \text{RSC}}{\text{L/kg-day}}$$

where,

RSC = relative source contribution (usually 20 to 80 percent, expressed as 0.20 to 0.80);

L/kg-day = daily water consumption for an infant, the critical population in this case.

The most sensitive endpoint for chlorite risk assessment is significant, but reversible, development delays in locomotor activity, as reported by Mobley *et al.*, 1990, from a one-generation study in rats. A LOAEL concentration of 20 ppm chlorite in drinking water was identified for significantly decreased exploratory behavior on postconception days 36 and 37. The chlorite dose was estimated by U.S. EPA as 3.0 mg/kg-day, based on the weights of the dams whose pups were exposed during gestation and lactation. A total uncertainty factor of 1,000 was used (10 for LOAEL to NOAEL extrapolation, 10 for interspecies extrapolation and 10 for intraspecies variability). Therefore, the acceptable daily dose is calculated as follows:

$$\text{ADD} = \frac{3 \text{ mg/kg-day}}{1,000} = 0.003 \text{ mg/kg-day}$$

Because neonates have been identified as the most susceptible population, a specific exposure calculation was used, based on neonatal drinking water rates. A recent rigorous analysis of drinking water consumption in the United States indicates that neonates (babies zero to six months of age) ingest 0.221 L/kg-day at the 95<sup>th</sup> percentile drinking water intake rate (U.S. EPA, 2004). This value is exclusive to tap water ingestion, and represents intake levels of just the infant population who received tap water during the course of the day. No other sources of water (i.e., bottled or commercial water) were included in this value, and data from infants who did not ingest tap water were not included in the derivation of this intake rate. To calculate the proposed PHG, the 95<sup>th</sup> percentile intake rate is used in conjunction with a relative source contribution of 100 percent to represent the fact that the sole source of chlorite exposure for this group is expected to be from drinking water used to reconstitute infant formula. Therefore:

$$C = 0.003 \text{ mg/kg-day} / 0.221 \text{ L/kg-day} \times 1.0 = 0.014 \text{ mg/L} = 10 \text{ ppb (rounded)}$$

In order to protect the identified sensitive subpopulation, the above estimated health-protective concentration for neonates of 0.014 mg/L, rounded to 10 ppb (one significant figure), is proposed as the public health goal for chlorite in drinking water.

## RISK CHARACTERIZATION

The proposed PHG of 10 ppb for chlorite is based on the premise that exposure to chlorite may result in neurodevelopmental effects. A one-generation study on test animals reported that neonatal rat pups born to mothers given drinking water containing chlorite had significant reductions in exploratory behavior (Mobley *et al.*, 1990). Pups born to mothers who received the lowest concentration of chlorite (20 ppm) displayed reversible, but significant, delays in locomotor activity on postconception days 36 and 37. At the next higher concentration (40 ppm), significant reductions in exploratory activity were extended over four consecutive days, postconception days 36, 37, 38 and 39, suggesting a dose-response trend for chlorite. Doses delivered to the offspring in utero and through mother's milk are unknown, but are likely to be lower than the dose given to the mother because of the reactivity of chlorite. Alternatively, the effects observed in offspring may be secondary to an unidentified maternal effect, such as a hormonal change or a change in nutrient delivery to the growing fetus.

The proposed PHG is intended to afford protection to neonates (infants ages zero to six months) who are undergoing rapid development and ingest large quantities of liquids. Therefore the PHG is calculated based on an infant's liquid consumption rate. However, the intake rate used in the PHG calculation is specific to community (tap) water and excludes all other water sources including bottled water or water contained in premade commercial products. Intake rates for this population were further refined by using "consumers only" data since a significant portion of babies under six months of age receive no tap water whatsoever, and the inclusion of these "zero consumers" would significantly skew the intake rates of those who do. Finally, both direct and indirect water consumption was considered since tap water can be ingested directly as a liquid, or indirectly when it is used to reconstitute powdered infant formula. Since neonates ingest the highest daily volume of water on a weight basis of any age group (U.S. EPA, 2004), it is anticipated that the proposed PHG is protective of other population categories.

U.S. EPA (1994) in their drinking water criteria document cited the 20 ppm concentration in the Mobley *et al.* (1990) study as a LOAEL, and derived an RfD of 0.003 mg/kg for chlorite. This was used in the document to derive a drinking water equivalent level of 0.11 mg/L and a proposed MCLG of 0.08 mg/L. The risk assessment for chlorite was revised in 1998 (U.S. EPA, 1998a,b) based on the two-generation rat reproductive study on sodium chlorite (CMA, 1996; Gill *et al.*, 2000). The U.S. EPA's revised risk assessment utilized a NOAEL of 3 mg/kg-day and a combined UF of 100. The rationale for this change was stated as follows (U.S. EPA, 1998b):

"The MCLG for chlorite was increased from the proposed value of 0.08 mg/L to 0.8 mg/L based on a weight-of-evidence evaluation of all health data on chlorite including a recent two-generation reproductive study sponsored by the Chemical Manufacturer's Association (CMA, 1996)."

OEHHA believes that the earlier study of Mobley *et al.*, with a LOAEL of 3 mg/kg-day, provides the most sensitive endpoint at the lowest dose tested from the available scientific literature. We do not concur with the decision made by U.S. EPA in their selection of the CMA study over this one. Since the Mobley study identified a key effect

in an endpoint not examined by CMA, there is no basis to determine that the effect identified by Mobley is any less significant. As such, OEHHA concludes that the significant reduction in exploratory behavior in rat pups as reported in the Mobley 1990 study should be the basis for the proposed chlorite PHG.

U.S. EPA (1998b) also considered the issue of a susceptible population, and concluded:

“Finally, EPA disagrees that an additional safety factor should be applied to provide additional protection for children or that drinking water consumption relative to the body weight of children should be used in developing the MCLG. The MCLG and MRDLG presented for chlorite and chlorine dioxide are considered to be protective of susceptible groups, including children, given that the RfD is based on a NOAEL derived from developmental testing, which includes a two-generation reproductive study. A two-generation reproductive study evaluates the effects of chemicals on the entire developmental and reproductive life of the organism. Additionally, current methods for developing RfDs are designed to be protective for sensitive populations. In the case of chlorite and chlorine dioxide a factor of 10 was used to account for variability between the average human response and the response of more sensitive individuals. In addition, the important exposure is that of the pregnant and lactating female and the nursing pup. The 2 liter per day water consumption and the 70 kg body weight assumptions are viewed as adequately protective of all groups.”

However, other recent evaluations of drinking water consumption by U.S. EPA do not support this stance (U.S. EPA 2004, 2005b). The recent U.S. EPA review of drinking water consumption rates (U.S. EPA, 2004) shows 90<sup>th</sup> and 95<sup>th</sup> percentile water consumption rates for various population groups, including pregnant women and infants, to be much larger than the defaults discussed above. For example, the total direct and indirect community water consumption rates (for consumers only) for infants less than 0.5 years of age are estimated as 181 and 221 mL/kg-day for the 90<sup>th</sup> and 95<sup>th</sup> percentile, respectively (versus 28.6 mL/kg-day for adults given above). These infant consumption estimates are 6.3 and 7.7 times the default consumption value. Because neuronal maturation is considerably prolonged in humans, and formula-fed neonates may clearly be exposed to tap water, we do not agree that basing the consumption value on the adult male body weight and a 2 L/day consumption value is health-protective. We therefore have utilized an infant drinking water consumption value in the PHG calculation.

OEHHA has also concluded that the available data do justify a combined uncertainty factor greater than 100, as in the original U.S. EPA risk assessment (U.S. EPA, 1994). The use of 10-fold factors for LOAEL-to-NOAEL, intraspecies, and interspecies extrapolations represents standard risk assessment practice of both U.S. EPA and OEHHA. We agree with U.S. EPA (1998b) as expressed in the quotation above that a separate susceptibility factor for children should not be necessary, but base our conclusion on the use of water consumption levels of neonates. Further discussion of the range of toxic effects and rationale for protection of infants follows.

Distribution data show that the liver is a key target organ of ingested chlorite (Abdel-Rahman *et al.*, 1982, 1984a). Hepatotoxic effects associated with chlorite exposure include significantly decreased absolute and relative liver weight as well as biochemical changes indicative of adverse liver effects. Other adverse effects associated with chlorite

exposure are reproductive, hematological, endocrine and gastrointestinal effects. Reproductive effects include altered sperm morphology and decreased progressive movement (Carlton and Smith, 1985; Carlton *et al.*, 1987). Some data also suggest that that chlorite may be a weak carcinogen or possibly a promoter; however, the carcinogen studies have flaws that make these data inconclusive.

Hematological effects reported in the literature 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.*, 1995a) and osmotic fragility (Abdel-Rahman *et al.*, 1984b; 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).

As discussed above, endocrine effects of chlorite include significant alterations in serum thyroid hormone levels in rat pups exposed *in utero* and via lactation (Carlton and Smith, 1985; Carlton *et al.*, 1987; Mobley *et al.*, 1990) and in adult monkeys given chlorite-containing drinking water (Harrington *et al.*, 1995a). Other endocrine-related effects include significantly increased adrenal gland weights associated with chlorite treatment (Harrington *et al.*, 1995a).

Gastrointestinal effects include involuntary salivation, squamous epithelial hyperplasia, hyperkeratosis, ulceration, chronic inflammation, and edema in the stomach (Harrington *et al.*, 1995a).

Populations that appear to be particularly susceptible include developing fetuses, neonates, infants and young children. The data suggest that chlorite may cross the placenta and cause neurological effects, as evidenced statistically significant neurodevelopmental effects in pups exposed to chlorite during gestation and lactation. However, these effects may also be due to hormonal or other biochemical effects in the mothers. In either case, the fetal or neonatal development appears to be most affected, since toxicological effects in the mothers were identified only at higher doses. Neonates, infants and young children may be particularly vulnerable to chlorite effects since neurological development continues after birth and gastrointestinal uptake of many nutrients and chemicals is greater in the neonate than in the adult.

Infants may also exhibit a greater degree of methemoglobinemia than adults following oral exposure to chlorite because infants form methemoglobin more readily than adults. This is due at least in part to the presence of hemoglobin F at birth, which is readily oxidized to methemoglobin. Additionally, infants may have an increased susceptibility to the hematological effects of chlorite exposure due to a lower capacity to enzymatically reduce methemoglobin coupled with a lower level of vitamin E (an important antioxidant), which is characteristic at birth.

Another potentially susceptible population is those who have glucose-6-phosphate dehydrogenase (G6PD) deficiency (Michael *et al.*, 1981). This results in a reduced capacity for maintaining adequate levels of glutathione, which can lead to enhanced destruction of red blood cells and hemolytic anemia. Approximately 10 percent of the African American population expresses G6PD deficiency. Moore and Calabrese (1980a)

demonstrated that G6PD-deficient human red blood cells exposed to chlorite exhibited markedly greater decreased glutathione and G6PD activity and increased methemoglobin levels than red blood cells from humans with normal G6PD activity. Abdel-Rahman and coworkers (Abdel-Rahman *et al.*, 1984b; Couri and Abdel-Rahman, 1980) noted decreased glutathione levels in rats chronically exposed to chlorite in the drinking water. Individuals who are deficient in NADH-dependent methemoglobin reductase, the principal means by which methemoglobin is reduced to hemoglobin, may exhibit a decreased ability to reduce methemoglobin. However, a quantitative estimate of the potential enhanced sensitivity of this population is not yet possible.

OEHHA concludes that the use of a combined uncertainty factor of 1,000 based on a sensitive neurodevelopmental endpoint in the PHG calculation should be protective for all sensitive subpopulations from adverse effects of chlorite in drinking water. The proposed PHG of 10 ppb is therefore judged to be adequately protective of pregnant women, neonates, infants, children, the elderly, persons with G6PD deficiency, and other potentially sensitive subgroups.

## OTHER REGULATORY STANDARDS

ATSDR (2004) has derived an intermediate-duration oral minimum risk level (MRL) of 0.1 mg/kg-day for chlorite based on a NOAEL of 2.9 mg chlorite/kg-day and a LOAEL of 5.7 mg chlorite/kg-day for neurodevelopmental effects (lowered auditory startle amplitude) in rat pups that had been exposed throughout gestation and lactation via their mothers (CMA, 1996; Gill *et al.*, 2000). The male parents were also treated. The estimated NOAEL of 2.9 mg chlorite/kg-day was divided by an uncertainty factor of 30 (10 for interspecies extrapolation and 3 to account for sensitive populations). In calculating this oral intermediate-duration MRL, the dose administered to the males was used.

U.S. EPA (2000) derived an RfD of 0.03 mg/kg-day for chlorite based on their estimated NOAEL of 3 mg/kg-day for neurodevelopmental effects in rat pups that had been exposed throughout gestation and lactation via their mother, based on the same study as described above (CMA, 1996; Gill *et al.*, 2000). The NOAEL of 3 mg chlorite/kg-day for the male parents was divided by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 to account for human variability). U.S. EPA derived an MCLG of 0.8 mg/L (800 ppb) from this value (U.S. EPA, 1994, 1998a,b, 2002). The current U.S. EPA Maximum Contaminant Level (MCL) for chlorite in drinking water is 1.0 mg/L (1000 ppb), which also became effective in California regulations on June 17, 2006.

U.S. EPA has classified sodium chlorite as Group D for carcinogenicity, signifying that it is not classifiable as a human carcinogen because of inadequate data in humans and animals (U.S. EPA, 2000, 2005). Similarly, the International Agency for Research on Cancer has identified sodium chlorite as Group 3 (IARC, 1997), which is defined as “not classifiable as to carcinogenicity to humans.”

The state of Maine has established a drinking water guideline for chlorite of 7 ppb (ATSDR, 2004).

Italian law, which will be in effect beginning December 2006, will require that chlorite levels in drinking water not exceed a limit of 200 ppb (Aggazzotti *et al.*, 2004).

In May 2005, Health Canada proposed a Maximum Acceptable Concentration (MAC) of 1,000 ppb for chlorite in drinking water during their public comment period (Health Canada, 2005a). Their proposed MAC is based on the CMA study discussed above; but in their analysis Health Canada acknowledged and discounted the significant neurobehavioral effects reported in Mobley as “small.” The proposed chlorite MAC is based on a 1.5 L/day drinking water ingestion rate and includes a total uncertainty factor of 100 for inter- and intraspecies variation. Health Canada currently notes that their chlorite MAC document is “in preparation” and gives no specific date for its finalization (Health Canada, 2005b).

**REFERENCES**

- Abdel-Rahman MS, Couri D, Bull RJ (1980a). Kinetics of ClO<sub>2</sub> and effects of ClO<sub>2</sub>, ClO<sub>2</sub><sup>-</sup>, and ClO<sub>3</sub><sup>-</sup> in drinking water on blood glutathione and hemolysis in rat and chicken. *J Environ Pathol Toxicol* 3:431-449.
- Abdel-Rahman MS, Couri D, Jones JD (1980b). Chlorine dioxide metabolism in rat. *J Environ Pathol Toxicol* 3:421-430.
- Abdel-Rahman MS, Couri D, Bull RJ (1982). Metabolism and pharmacokinetics of alternate drinking water disinfectants. *Environ Health Perspect* 46:19-23.
- Abdel-Rahman MS, Couri D, Bull RJ (1984a). The kinetics of chlorite and chlorate in the rat. *J Am Coll Toxicol* 3:261-267.
- Abdel-Rahman MS, Couri D, Bull RJ (1984b). Toxicity of chlorine dioxide in drinking water. *J Am Coll Toxicol* 3:277-284.
- Aggazzotti G, Righi E, Fantuzzi G, Biasotti B, Ravera G *et al.* (2004). Chlorination by-products (CBPs) in drinking water and adverse pregnancy outcomes in Italy. *J Water Health* 2:233-247.
- ATSDR (2004). Toxicological Profile for Chlorine Dioxide and Chlorite. Agency for Toxic Substances and Disease Registry, Department of Health and Human Services. September, 2004.
- Bercz JP, Jones LL, Garner L, *et al.* (1982). Subchronic toxicity of chlorine dioxide and related compounds in drinking water in the nonhuman primate. *Environ Health Perspect* 46:47-55.
- Bercz JP, Jones LL, Harrington RM, *et al.* (1986). Mechanistic aspects of ingested chlorine dioxide on thyroid function: impact of oxidants on iodide metabolism. *Environ Health Perspect* 69:249-255.
- Bolyard M, Fair PS, Hautman DP (1993). Sources of chlorate ion in US drinking water. *J Am Water Works Assoc* 85(9):81-88.
- Carlton BD, Smith MK (1985). Reproductive effects of alternate disinfectants and their byproducts. In: Jolley RL, *et al.*, eds. *Water chlorination: environmental impact and health effects*, vol. 5. Lewis Publications, Chelsea, MI, pp. 295-305.
- Carlton BD, Habash DL, Barsaran AH, *et al.* (1987). Sodium chlorite administration in Long-Evans rats: reproductive and endocrine effects. *Environ Res* 42:238-245.
- Carlton BD, Basaran AH, Mezza LE, *et al.* (1991). Reproductive effects in Long-Evans rats exposed to chlorine dioxide. *Environ Res* 56:170-177.
- CDPR (2005). Registered Pesticide Database Search - Sodium Chlorite. California Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. Accessed at: [www.cdpr.ca.gov/cgi-bin/label/labrep.pl](http://www.cdpr.ca.gov/cgi-bin/label/labrep.pl).
- CMA (1996). Chemical Manufacturers Association. Sodium chlorite: drinking water rat two-generation reproductive toxicity study. Quintiles Report Ref. CMA/17/96.

- Couri D, Abdel-Rahman MS (1980). Effect of chlorine dioxide and metabolites on glutathione dependent system in rat, mouse and chicken blood. *J Environ Pathol Toxicol* 3:451-460.
- Couri D, Abdel-Rahman MS, Bull RJ (1982a). Toxicological effects of chlorine dioxide, chlorite and chlorate. *Environ Health Perspect* 46:13-17.
- Couri D, Miller CH, Bull RJ, *et al.* (1982b). Assessment of maternal toxicity, embryotoxicity and teratogenic potential of sodium chlorite in Sprague-Dawley rats. *Environ Health Perspect* 46:25-29.
- Daniel FB, Condie LW, Robinson M, *et al.* (1990). Comparative subchronic toxicity studies of three disinfectants. *J Am Water Works Assoc* 82:61-69.
- DHS (2003). California Department of Health Services. Comparison of Federal and State MCLs: Maximum Contaminant Levels and Regulation Dates for Drinking Water Contaminants. U.S. EPA vs. CDHS. September 2003. Accessed at: <http://www.dhs.ca.gov/ps/ddwem/chemicals/mcl/mclindex.htm>
- DHS (2005a). Proposed Drinking Water Regulations. Disinfection and Disinfection Byproducts (R-62-00) (update of April 13, 2005). Accessed at: <http://www.dhs.ca.gov/ps/ddwem/publications/regulations/proposedregulations.htm>.
- DHS (2005b). Chemicals and Parameters in California Drinking Water Quality Database. Accessed at: [www.dhs.ca.gov/ps/ddwem/publications/download/storlist.xls](http://www.dhs.ca.gov/ps/ddwem/publications/download/storlist.xls).
- Gill MW, Swanson MS, Murphy SR, *et al.* (2000). Two-generation reproduction and developmental neurotoxicity study with sodium chlorite in the rat. *J Appl Toxicol* 20:291-303.
- Gonzalez RJ, Luo Y, Ruiz-Cruz S, McEvoy JL (2004). Efficacy of sanitizers to inactivate *Escherichia coli* O157:H7 on fresh-cut carrot shreds under simulated process water conditions. *J Food Prot* 67(11):2375-2380.
- Haag HB (1949). The effect on rats of chronic administration of sodium chlorite and chlorine dioxide in the drinking water. Report to the Mathieson Alkali Works from HB Haag of the Medical College of Virginia. February 7, 1949.
- Harrington RM, Shertzer HG, Bercz JP (1986). Effects of chlorine dioxide on thyroid function in the African green monkey and the rat. *J Toxicol Environ Health* 19:235-242.
- Harrington RM, Romano RR, Gates D, *et al.* (1995a). Subchronic toxicity of sodium chlorite in the rat. *J Am Coll Toxicol* 14:21-33.
- Harrington RM, Romano RR, Irvine L (1995b). Developmental toxicity of sodium chlorite in the rabbit. *J Am Coll Toxicol* 14:109-118.
- Hayashi M, Kishi M, Sofuni T, *et al.* (1988). Micronucleus test in mice on 39 food additives and eight miscellaneous chemicals. *Food Chem Toxicol* 26:487-500.
- Health Canada (2005a). Chlorite and Chlorate in Drinking Water. Document for public comment. Federal-Provincial-Territorial Committee on Drinking Water. May, 2005. Accessed at: [http://www.hc-sc.gc.ca/ewh-semt/alt\\_formats/hecs-sesc/pdf/pubs/water-eau/doc-sup-appui/chlorite-chlorate/chlorite-chlorate\\_e.pdf](http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/water-eau/doc-sup-appui/chlorite-chlorate/chlorite-chlorate_e.pdf).

- Health Canada (2005b). Guidelines for Canadian Drinking Water Quality - Supporting Documents. Accessed at: [http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/doc\\_sup-appui/index\\_e.html](http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/doc_sup-appui/index_e.html).
- Heffernan WP, Guion C, Bull RJ (1979a). Oxidative damage to the erythrocyte induced by sodium chlorite, *in vivo*. J Environ Pathol Toxicol 2(6):1478-1499.
- Heffernan WO, Guion C, Bull RJ (1979b). Oxidative damage to the erythrocyte induced by sodium chlorite, *in vitro*. J Environ Pathol Toxicol 2(6):1501-1510.
- IARC (1997). Sodium Chlorite (Group 3). Vol 52. International Agency for Research on Cancer, Lyon, France. Last update: November 1997. Accessed at: <http://www-cie.iarc.fr/htdocs/monographs/vol52/02-sodium%20chlorite.htm>.
- Ishidate M, Sofuni T, Yoshikawa K, *et al.* (1984). Primary mutagenicity screening of food additives currently used in Japan. Food Chem Toxicol 22:623-636.
- Kaczur JJ, Cawfield DW (1993). Chlorine oxygen acids and salts (ClO<sub>2</sub>, HClO<sub>2</sub>). In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol 5. Kroschwitz JI, ed. John Wiley and Sons, Inc., New York, NY, pp. 969-991.
- Kanitz S, Franco Y, Patrone V, *et al.* (1996). Associations between drinking water disinfection and somatic parameters at birth. Environ Health Perspect 104:516-520.
- Kurokawa Y, Takamura N, *et al.* (1984). Studies on the promoting and complete carcinogenic activities of some oxidizing chemicals in skin carcinogenesis. Cancer Lett 24:299-304.
- Kurokawa Y, Takamura S, Konishi Y, *et al.* (1986). Long-term *in vivo* carcinogenicity tests of potassium bromate, sodium hypochlorite, and sodium chlorite conducted in Japan. Environ Health Perspect 69:221-235.
- Lee BD, Sears SK, Graham RC, Amrhein C, Vali H (2003). Secondary mineral genesis from chlorite and serpentine in an ultramafic soil toposequence. Soil Sci Soc Am J 67:1309-1317.
- Lim K, Mustapha A (2004). Effects of cetylpyridinium chloride, acidified sodium chlorite, and potassium sorbate on populations of Escherichia coli O157:H7, Listeria monocytogenes, and Staphylococcus aureus on fresh beef. J Food Prot 67(2):310-315.
- Lim JL, Lin PS (1993). Acute sodium chlorite poisoning associated with renal failure. Ren Fail 15(4):645-648.
- Lubbers JR, Chauhan S, Bianchine JR (1981). Controlled clinical evaluations of chlorine dioxide, chlorite and chlorate in man. Fundam Appl Toxicol 1:334-338.
- Lubbers JR, Chauhan S, Bianchine JR (1982). Controlled clinical evaluations of chlorine dioxide, chlorite and chlorate in man. Environ Health Perspect 46:57-62.
- Lubbers JR, Chauhan S, Miller JK, *et al.* (1984a). The effects of chronic administration of chlorine dioxide, chlorite and chlorate to normal healthy adult male volunteers. J Environ Pathol Toxicol Oncol 5:229-238.

Lubbers JR, Chauhan S, Miller JK, *et al.* (1984b). The effects of chronic administration of chlorite to glucose-6-phosphate dehydrogenase deficient healthy adult male volunteers. *J Environ Pathol Toxicol Oncol* 5:239-242.

Meier JR, Bull RJ, Stober JA, *et al.* (1985). Evaluation of chemicals used for drinking water disinfection for production of chromosomal damage and sperm-head abnormalities in mice. *Environ Mutagen* 7:201-211.

Michael GE, Miday RK, Bercz JP, *et al.* (1981). Chlorine dioxide water disinfection: a prospective epidemiology study. *Arch Environ Health* 36:20-27.

Mobley SA, Taylor DH, Laurie RD, Pfohl RJ (1990). Chlorine dioxide depresses T3 uptake and delays development of locomotor activity in young rats. In: *Water Chlorination: Chemistry, Environmental Impact and Health Effects*, Vol. 6. Jolley RL, *et al.*, eds. Lewis Publications, Chelsea, MI, pp. 347-358.

Moore GS, Calabrese EJ (1980a). G6PD: A potential high-risk group to copper and chlorite ingestion. *Environ Pathol Toxicol* 4:271-279.

Moore GS, Calabrese EJ (1980b). The effects of chlorine dioxide and sodium chlorite on erythrocytes of A/J and C57L/J mice. *Environ Pathol Toxicol* 4(2-3):513-524.

Moore GS, Calabrese EJ (1982). Toxicological effects of chlorite in the mouse. *Environ Health Perspect* 46:31-37.

Moore GS, Calabrese EJ, Leonard DA (1980). Effects of chlorite exposure on conception rate and litters of A/J strain mice. *Bull Environ Contam Toxicol* 25:689-696.

Musil J, Knotek Z, Chalupa J, *et al.* (1964). Toxicological aspects of chlorine dioxide application for the treatment of water containing phenols. *SbVys Sk Chem Technol Prazd Oddil Fak Technol Pavil Vody* 8:327-345.

Orme J, Taylor DH, Laurie RD, *et al.* (1985). Effects of chlorine dioxide on thyroid function in neonatal rats. *J Toxicol Environ Health* 15:315-322.

Oyarzabal OA, Hawk C, Bilgili SF, *et al.* (2004). Effects of postchill application of acidified sodium chlorite to control *Campylobacter* spp. and *Escherichia coli* on commercial broiler carcasses. *J Food Prot* 67(10):2288-2291.

Scatina J, Abdel-Rahman MS, Gerges SE, *et al.* (1984). Pharmacodynamics of Alcide, a new antimicrobial compound, in rat and rabbit. *Fundam Appl Toxicol* 4:479-484.

Seta S, Miyake B, Sato H, *et al.* (1991). Acute oral toxicity and acute irritation test to skin and eye of sodium chlorite. *Kagaku Keisatsu Kenkyusho Hokogaku Hen* 44(1):7-22. (Japanese).

Suh DH, Abdel-Rahman MS, Bull RJ (1983). Effect of chlorine dioxide and its metabolites in drinking water on fetal development in rats. *J Appl Toxicol* 3:75-79.

SRI (2001). 2001 Directory of Chemical Producers, United States. SRI International, Menlo Park, CA, pp. 874-875.

Tuthill RW, Giusti RA, Moore GS, *et al.* (1982). Health effects among newborns after prenatal exposure to ClO<sub>2</sub>-disinfected drinking water. *Environ Health Perspect* 46:39-45.

- U.S. EPA (1981). Study of chlorine dioxide and its metabolites in man. Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC. EPA-600/1-81-068.
- U.S. EPA (1994). Final draft of the drinking water criteria document on chlorine dioxide, chlorite, and chlorate. Office of Science and Technology, Office of Water, U.S. Environmental Protection Agency, Washington, DC.
- U.S. EPA (1997). External Peer Review of CMA Study – 2-Generation, EPA Contract No. 68-C7-0002, Work Assignment B-14. Task 2 – Summary of Peer Review Comments and Transmittal of Original Comments Received from Peer Reviewers. The Cadmus Group, Inc., October 9, 1997.
- U.S. EPA (1998a). National Primary Drinking Water Regulations. Disinfectants and Disinfection Byproducts Notice of Data Availability. U.S. Environmental Protection Agency. Code of Federal Regulations 40CFR 141.63, pp. 15674-15692. Mar 31, 1998.
- U.S. EPA (1998b). National Primary Drinking Water Regulations. Disinfectants and Disinfection Byproducts. Final Rule. U.S. Environmental Protection Agency. Code of Federal Regulations 40CFR 141.63, pp. 69390-69476. Dec 16, 1998.
- U.S. EPA (2000). Toxicological review of chlorine dioxide and chlorite, in support of summary information on the Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Washington, DC.
- U.S. EPA (2002). National Primary Drinking Water Regulations. Maximum Contaminant Levels for Disinfection Byproducts. U.S. Environmental Protection Agency. Code of Federal Regulations 40CFR 141.64. April 24, 2002.
- U.S. EPA (2004). Estimated per capita water ingestion and body weight in the United States – an update. EPA/822/R-00/001. October, 2004. Accessed at: <http://www.epa.gov/waterscience/drinking/percapita/2004.pdf>
- U.S. EPA (2005a). Chlorite (sodium salt) (CASRN 77758-19-2). Integrated Risk Information System, U.S. Environmental Protection Agency. Updated last on October 12, 2000. Accessed at: <http://www.epa.gov/iris/subst/0648.htm>
- U.S. EPA (2005b). Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants. U.S. Environmental Protection Agency, Washington, D.C. EPA/630/P-03/003F.
- U.S. Department of the Interior (2003). DBP: Chlorite Fact Sheet. Revision date 4/4/03. Bureau of Reclamation, Water Treatment Engineering and Research Group. Accessed at: <http://www.usbr.gov/pmts/water/media/pdfs/DBP%20Chlorite.pdf>.
- Vogt H, Balej J, Bennett JE, *et al.* (1986). Chlorine oxides and chlorine oxygen acids. In: Ullmann's Encyclopedia of Industrial Chemistry, 5<sup>th</sup> edition, Vol A6. Gerhartz W, Yamamoto YS, Campbell FT, *et al.*, eds. VCH, New York, NY, pp. 493-500.
- Vulcan Chemicals (2005). Personal communication with Roger Etherington, Vulcan Chemicals, Birmingham, Alabama, February 17, 2005.

Vulcan Chemicals (2003). Product Specification for Sodium Chlorite (NaClO<sub>2</sub>).  
Technical Sodium Chlorite (80% Active Sodium Chlorite). Form No.: 6-1-0.  
Birmingham, AL. Accessed at:

[http://www.vul.com/vulchemicals/products/pdf/specifications/sodiumch/Sodium%20Chlorite%20Technical%20Specification%20\(3-02\).pdf](http://www.vul.com/vulchemicals/products/pdf/specifications/sodiumch/Sodium%20Chlorite%20Technical%20Specification%20(3-02).pdf).

Yokose Y, Uchida K, Nakae D, *et al.* (1987). Studies of carcinogenicity of sodium chlorite in B6C3F<sub>1</sub> mice. *Environ Health Perspect* 76:205-210.