

## 2. RELEVANCE TO PUBLIC HEALTH

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CHLORINE DIOXIDE AND CHLORITE IN THE UNITED STATES

Chlorine dioxide is a yellow to reddish-yellow gas that can decompose rapidly in air if it is present at high concentrations. Because it is a hazardous gas, chlorine dioxide is always made at the place where it is used. Chlorine dioxide is used as a bleach at pulp mills to make paper and paper products, and in publicly-owned treatment works (POTW) as a disinfectant for drinking water. In 2001, chlorine dioxide was used to decontaminate a number of public buildings following the release of anthrax spores in the United States. Chlorine dioxide is a very reactive compound and will not exist in the environment for long periods of time. In air, chlorine dioxide will dissociate in sunlight into chlorine gas and oxygen. Chlorine dioxide, a strong oxidizer, will react quickly in water to form by-products such as chlorite ions.

EPA has set the maximum concentration of chlorine dioxide and chlorite ion for drinking waters at 0.8 and 1.0 mg/L, respectively. However, the concentrations of chlorine dioxide and chlorite ion in drinking water may be higher or lower than these levels.

Human exposure to chlorine dioxide and its by-products (e.g., chlorite ion) occurs primarily by ingestion of drinking water. People who live in communities where chlorine dioxide is used in drinking water treatment have a greater probability of exposure to chlorine dioxide and chlorite ions than individuals who do not. About 5% of the water treatment facilities serving more than 100,000 people in the United States use chlorine dioxide to treat drinking water. This would translate to about 12 million people who may be exposed to chlorine dioxide and chlorite ions in the United States. However, the total number people exposed will be higher if smaller facilities (i.e., those serving less than 50,000 people) are also included in this value.

### 2.2 SUMMARY OF HEALTH EFFECTS

Available human and animal data indicate that airborne chlorine dioxide ( $\text{ClO}_2$ ) primarily acts as a respiratory tract and ocular irritant. Chlorite ( $\text{ClO}_2^-$ ) does not persist in the atmosphere either in ionic form or as chlorite salt, and is not likely to be inhaled. Potential for human exposure to chlorine dioxide or chlorite may be greatest via the oral exposure route because chlorine dioxide is sometimes used as a

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disinfectant for drinking water. Available human and animal data indicate that oral exposure to relatively large amounts of chlorine dioxide or chlorite may result in irritation of the digestive tract, the severity of which is likely to be dose-dependent. In addition, high-level oral exposure results in increased levels of methemoglobin in the blood, which reduces the ability of oxygen to bind with hemoglobin.

Other hematological changes have been observed in animals exposed to chlorine dioxide and chlorite. However, the degree of reported changes does not appear to be dependent upon the amount of exposure, and the toxicological significance of such changes is not clear. Nor has the toxicological significance of changes in thyroid hormone levels in the blood been established.

Both chlorine dioxide and chlorite appear to induce delays in neurodevelopment, as evidenced by delayed brain growth, decreased locomotor and exploratory behavior, and altered auditory startle response in animals exposed during critical periods of neurodevelopment. It is not known whether similar chlorine dioxide- or chlorite-induced neurodevelopmental effects might occur in humans.

Limited carcinogenicity data for chlorine dioxide and chlorite do not indicate a particular cancer concern, but adequate animal cancer bioassays have not been performed. Genotoxicity testing has produced mixed results. Chlorine dioxide and chlorite do not appear to be reproductive toxicants.

Neurodevelopmental effects appear to be of greatest toxicological concern, particularly in light of the fact that chlorine dioxide and chlorite may be used as disinfectants for drinking water. Therefore, the following brief discussion includes only developmental effects. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information regarding the potential for other chlorine dioxide- or chlorite-induced health effects.

**Developmental Effects.** Neurodevelopmental effects, such as decreases in brain weight, brain cell number, exploratory behavior, and locomotor activity, have been observed in rat pups whose mothers were exposed to chlorine dioxide before mating and during gestation and lactation and other rat pups that were directly exposed via oral gavage only during postnatal development. Decreases in exploratory behavior and amplitude of auditory startle response have been reported in rat pups whose mothers were orally exposed to chlorite during gestation and lactation. Perinatal exposure to chlorine dioxide or chlorite has also resulted in altered serum thyroid hormone levels or activity. Although mechanisms of action responsible for mediating these chlorine dioxide- and chlorite-mediated thyroid hormone effects

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have not been identified, it is widely understood that the thyroid hormone, T3, is essential for normal development of the nervous system, and that T3 is synthesized from the deiodination of T4.

### 2.3 MINIMAL RISK LEVELS (MRLs)

#### *Inhalation MRLs*

An acute-duration inhalation MRL was not derived for chlorine dioxide because adequate human or animal data are not available.

No inhalation MRLs were derived for chlorite. The only available information regarding health effects following inhalation exposure to chlorite was limited to a single study of lethality in rats exposed to aerosols of sodium chlorite, an exposure scenario not likely to be encountered in environmental or occupational settings. Furthermore, lethality is a serious effect, and therefore cannot be used as the basis for deriving an MRL.

- C An MRL of 0.001 ppm (0.003 mg/m<sup>3</sup>) has been derived for intermediate-duration inhalation exposure (15–365 days) to chlorine dioxide.

This MRL is based on a lowest-observed-adverse-effect-level (LOAEL) of 1 ppm for respiratory effects in rats. Paulet and Desbrousses (1970) exposed groups of 10 rats/sex (strain not specified) to chlorine dioxide vapors at concentrations of 0 or 2.5 ppm, 7 hours/day for 30 days. The weekly exposure frequency was not reported. Chlorine dioxide-exposed rats exhibited respiratory effects that included lymphocytic infiltration of the alveolar spaces, alveolar vascular congestion, hemorrhagic alveoli, epithelial erosions, and inflammatory infiltrations of the bronchi. The study authors also reported slightly decreased body weight gain, decreased erythrocyte levels, and increased leukocyte levels, relative to controls. Recovery from the pulmonary lesions was apparent in rats examined after a 15-day recovery period. In a follow-up study designed to examine a lower exposure level (Paulet and Desbrousses 1972), eight Wistar rats (sex not reported) were exposed to chlorine dioxide vapors at a concentration of 1 ppm, 5 hours/day, 5 days/week for 2 months. The authors stated that weight gain and erythrocyte and leukocyte levels were not affected, but concurrent control data were not presented. Chlorine dioxide-induced respiratory effects included peribronchiolar edema and vascular congestion in the lungs. No alterations in epithelium or parenchyma were seen.

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Collectively, these studies adequately identify a LOAEL for respiratory effects associated with intermediate-duration inhalation exposure to chlorine dioxide. The intermediate-duration inhalation MRL for chlorine dioxide was based on the LOAEL of 1 ppm identified in the Paulet and Desbrousses (1972) study, which was adjusted to 0.15 ppm (LOAEL<sub>ADJ</sub>) to compensate for intermittent exposure, converted to the human equivalent concentration (LOAEL<sub>HEC</sub>) of 0.3 ppm, and then divided by an uncertainty factor of 300 (3 for interspecies extrapolation using dosimetric adjustments, 10 for the use of a LOAEL, and 10 to account for sensitive populations).

A chronic-duration inhalation MRL was not derived for chlorine dioxide because chronic inhalation exposure studies in humans or animals are not available. An approach using an uncertainty factor for extrapolating from intermediate- to chronic-duration exposure was not used because it is not known whether respiratory irritation, observed during intermediate-duration inhalation exposure to chlorine dioxide, might result in more persistent effects in cases of chronic-duration exposure. Furthermore, it is not likely that humans would be chronically exposed to significant concentrations of chlorine dioxide vapors in environmental or occupational settings.

***Oral MRLs***

Acute-duration oral MRLs were not derived for chlorine dioxide or chlorite because adequate human or animal data are not available.

- C An MRL of 0.1 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to chlorite.

This MRL is based on a no-observed-adverse-effect-level (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 (Gill et al. 2000). Groups of 30 male and 30 female Sprague-Dawley rats (F<sub>0</sub>) received sodium chlorite in the drinking water at concentrations of 35, 70, or 300 mg/L (approximate chlorite doses of 3, 5.7, and 21 mg/kg/day for males and 3.9, 7.6, and 29 mg/kg/day for females) for 10 weeks prior to mating and during mating, after which exposure of females continued throughout gestation and lactation. Groups of F<sub>1</sub> pups were continued on the same treatment regimen as their parents (chlorite doses of 2.9, 6, and 23 mg/kg/day and 3.9, 7.6, and 29 mg/kg/day for F<sub>1</sub> males and females, respectively). Low-dose female pups exhibited slight, but statistically significant differences in some hematological parameters, relative to controls. No

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other effects were seen in pups of this exposure level, and the hematological effects were not considered to be adverse. A significant decrease in maximum response to an auditory startle stimulus was noted in mid-dose pups on postnatal day 24, but not on postnatal day 60. Mid-dose F<sub>1</sub> pups also exhibited reduced liver weight. Significant effects at high dose included reduced absolute and relative liver weight in F<sub>1</sub> males and females, reduced pup survival, reduced body weight at birth and throughout lactation in F<sub>1</sub> and F<sub>2</sub> rats, lower thymus and spleen weight in both generations, lowered incidence of pups exhibiting normal righting reflex and with eyes open on postnatal day 15, decreased in 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 separation) and F<sub>1</sub> and F<sub>2</sub> females (vaginal opening), and lowered red blood cell parameters in F<sub>1</sub> rats. The NOAEL of 2.9 mg/kg/day was divided by an uncertainty factor of 30 (10 for interspecies extrapolation and 3 to account for sensitive populations). An uncertainty factor of 3 rather than 10 was used for sensitive populations because the critical effect (neurodevelopmental delay) occurred in a sensitive population (perinatal rat pups).

Chlorine dioxide in drinking water rapidly degrades to chlorite (Michael et al. 1981). In laboratory animals, orally administered chlorine dioxide is rapidly converted to chlorite and chloride ion (Abdel-Rahman et al. 1980b). Being both a strong oxidizer and water soluble, chlorine dioxide is not likely absorbed in the gastrointestinal tract to any great extent. Chlorite is the most likely source of systemic toxicity resulting from oral exposure to either chlorine dioxide or chlorite. Therefore, the intermediate-duration oral MRL derived for chlorite should also be applicable to chlorine dioxide.

Chronic-duration oral MRLs were not derived for chlorine dioxide or chlorite. No human studies were available in which chronic oral exposure to chlorine dioxide or chlorite were evaluated, and available chronic-duration oral studies in animals identified LOAELs that were higher than those observed for developmental effects following exposures of significantly shorter duration.

