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Chlorine dioxide; CASRN 10049-04-4 (10/12/2000)

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Chlorine dioxide

File First On-Line 11/01/90

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	10/12/2000
Inhalation RfC Assessment (I.B.)	on-line	10/12/2000
Carcinogenicity Assessment (II.)	on-line	10/12/2000

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Chlorine dioxide
CASRN — 10049-04-4
Last Revised — 10/12/2000

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an

estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

__I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Neurodevelopmental effects	NOAEL: 3 mg/kg-day (35 ppm sodium chlorite)	100	1	3×10^{-2} mg/kg-day
Two-generation rat drinking water study	LOAEL: 6 mg/kg-day (70 ppm sodium chlorite)			
CMA, 1996				

*Conversion Factors and Assumptions — MW of sodium chlorite = 90.5; MW of chlorite = 67.5. Doses (mg sodium chlorite/kg-day) were estimated by the study authors using measured water consumption and body weight data. To express doses as the chlorite ion, the estimated doses were multiplied by the molecular weight ratio of sodium chlorite to chlorite.

__I.A.2. Principal and Supporting Studies (Oral RfD)

Chlorine dioxide (ClO₂) in drinking water rapidly degrades to chlorite (ClO₂⁻), chlorate (ClO₃⁻), and chloride ion (Cl⁻). In an epidemiology study by Michael et al. (1981), chlorine dioxide rapidly disappeared from the stored water (within 2-4 hours) and water chlorite concentrations concomitantly increased. Once absorbed, chlorine dioxide and chlorite are cleared from the blood at similar rates and are similarly distributed throughout the body (Abdel-Rahman et al., 1979, 1982). Additionally, chloride is the major in vivo degradation product for chlorine dioxide, chlorite, and chlorate. The available data suggest that chlorine dioxide and chlorite have similar targets of toxicity and potencies. Therefore, the toxicity information for chlorite is relevant to deriving an RfD for chlorine dioxide. See also the oral RfD entry in the IRIS Summary for chlorite.

CMA (Chemical Manufacturers Association). (1996) Sodium chlorite: drinking water rat two-generation reproductive toxicity study. Quintiles Report Ref. CMA/17/96.

CMA (1996) conducted a two-generation study to examine reproductive, developmental neurotoxicity, and hematological endpoints in rats exposed to sodium chlorite. Thirty male and 30 female Sprague-Dawley rats (F₀) generation received drinking water containing 0, 35, 70, or 300 ppm sodium chlorite for 10 weeks and were then paired for mating. Males were exposed throughout mating and then were sacrificed. Exposure for the females continued through mating, pregnancy, and lactation until necropsy following weaning of their litters. Twenty-five males and females from each of the first 25 litters to be weaned in a treatment group were chosen to produce the F₁ generation. The F₁ pups were continued on the same treatment regimen as their parents. At approximately 14 weeks of age, they were mated to produce the F_{2a} generation. Owing to a reduced number of litters in the 70 ppm F₁-F_{2a} generation, the F₁ animals were remated following weaning of the F_{2a} to produce the F_{2b} generation. Pregnant F₁ females were allowed to litter and rear the F_{2a} and F_{2b} generations until weaning at postnatal day (PND) 21. Using water consumption and body weight data, the study authors calculated doses (adjusted for molecular weight) of 0, 3.0, 5.6, and 20.0 mg chlorite/kg-day for F₀ males; 0, 3.8, 7.5, and 28.6 mg chlorite/kg-day for F₀ females; 0, 2.9, 5.9, and 22.7 mg chlorite/kg-day for F₁ males; and 0, 3.8, 7.9, and 28.6 mg chlorite/kg-day for the F₁ females.

Numerous parameters were measured or calculated, including body weight, food and water consumption, estrus cycle in the F₀ and F₁, hematology and T₃ and T₄ levels in the F₁ (blood samples collected from 1 male and 1 female from the first 20 F₁ litters at age PND 25 and another group at 13 weeks). Additional parameters were reproductive/developmental toxicity parameters (i.e.,

gestation duration, litter size, pup body weight, pup developmental landmarks), total caudal sperm number and percent motile, sperm morphology in the F0 and F1, and organ weight and histopathological examination (brain, pituitary gland, liver, adrenal, spleen, thymus, kidneys, and reproductive organs) of all F0 and F1 controls and high-dose animals. An additional group of F1 pups was chosen for neurohistopathology on PND 11 (examination of the brain and spinal cord) or PND 60 (sensory ganglia, dorsal and ventral nerve roots, and several peripheral nerves and muscles).

Another group of F1 rats was examined for neurotoxicological endpoints (motor activity in a "Figure 8" Activity System and neuropathology on PND 60, auditory startle in the SR-Screening System, learning and memory retention in a water E-maze). A functional observational battery (FOB) was also conducted on the pups undergoing the auditory and learning assessments. This group was composed of 2 males and 2 females from 20 litters, and exposure was discontinued after weaning. Reevaluation of the auditory startle response was conducted in 20 males and 20 females in the F2a and F2b generations.

Reductions occurred in water consumption, food consumption, and body weight gain in both sexes in all generations at various times throughout the experiment, primarily in the 70 and 300 ppm groups. The authors attributed these reductions to lack of palatability of the drinking water solution, but did not show data to support this contention. Significant alterations related to treatment at 300 ppm include reductions in absolute and relative liver weight in F0 females and F1 males and females, reduced pup survival (increase in number of pups found dead and/or killed prematurely during lactation) and reduced body weight at birth and throughout lactation in F1 and F2, lower thymus and spleen weight in both generations, lowered incidence of pups exhibiting a normal righting reflex and with eyes open on PND 15, alteration in clinical condition in F2 animals chosen for neurotoxicity, decreases in absolute brain weight for F1 males and F2 females, delays in sexual development in males (preputial separation) and females (vaginal opening) in F1 and F2, and lower red blood cell parameters in F1. It is possible that the reported alterations in pup sexual maturation measures may be due to reduced pup body weight, but a definitive conclusion cannot be drawn. In the 70 ppm groups, reduced absolute and relative liver weight in F0 females and F1 males was observed. In addition, a significant decrease in maximum response to an auditory startle stimulus was noted in the 70 and 300 ppm groups on PND 24 but not on PND 60. Minor, statistically significant changes in hematological data at the 35 and 70 ppm concentrations (generally 1%-7%) in the F1 appear to be within normal ranges based on historical data and are, therefore, not considered clinically or biologically significant or adverse. The no-observed-adverse-effects level (NOAEL) for this study is 35 ppm (3 mg chlorite/kg-day) and the lowest-observed-adverse-effects level (LOAEL) is 70 ppm (6 mg chlorite/kg-day), based on lowered auditory startle amplitude and altered liver weights in two generations.

___I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 100.

The composite uncertainty factor (UF) of 100 includes a factor of 10 to account for uncertainties associated with interspecies extrapolation and a factor of 10 for intrahuman variability. Because the critical effect is developmental toxicity in a database that includes chronic studies, it is not necessary to use an uncertainty factor to account for use of a less-than-lifetime study.

MF = 1.

___I.A.4. Additional Studies/Comments (Oral RfD)

The short-term toxicity of chlorine dioxide was assessed in two human studies conducted by Lubbers and associates (Lubbers et al., 1981, 1982, 1984; Bianchine et al., 1981). These studies found no alterations in hematological or urine chemistry or in physical symptoms in human volunteers administered up to 0.34 mg/kg chlorine dioxide in drinking water for 1 day or administered 0.036 mg/kg-day of chlorine dioxide or chlorite in drinking water for 84 days.

Michael et al. (1981), Tuthill et al. (1982), and Kanitz et al. (1996) have examined communities with chlorine dioxide-disinfected water. In an epidemiological study of a community using chlorite as a

drinking water disinfectant, adult exposures ranged from 0 to 39.4 mg/day for chlorite for 10 weeks, and no consistent alterations in hematological parameters were reported (Michael et al., 1981). Tuthill et al. (1982) retrospectively compared morbidity and mortality data for a community that had utilized high levels of chlorine dioxide as a drinking water disinfectant with data from a neighboring community and found a greater postnatal weight loss in infants from the exposed community and no increase in the proportion of premature births when the age of the mother was controlled. The authors reported average monthly levels of 0.32 ppm of sodium chlorite added post-treatment, but did not report total chlorine dioxide levels in the treated water. Kanitz et al. (1996) followed 598 births to women who lived in a community with filtered water disinfected with chlorine dioxide, sodium hypochlorite, or both, and 128 births to women living in a community with well water that did not undergo disinfection treatment. Levels of chlorine dioxide in the water immediately after treatment were less than 0.3 mg/L, while chlorine residue was less than 0.4 mg/L. The authors concluded that infants of women who consumed drinking water treated with chlorine compounds during pregnancy were at higher risk for neonatal jaundice, cranial circumference \leq 35 cm, and body length \leq 49.5 cm. However, the epidemiological studies were limited by methodological problems such as lack of characterization of exposure to other agents in the drinking water, lack of drinking water consumption data, atypical baseline comparison data (in the Kanitz et al. study), and lack of control of potential confounding factors (such as nutritional and smoking habits, and age distribution).

Subchronic/chronic toxicity of chlorine dioxide in animals was investigated by Daniel et al. (1990) and Haag (1949). In the Daniel et al. (1990) study, groups of Sprague-Dawley rats (10/sex) were administered chlorine dioxide in drinking water for 90 days at concentrations of 0, 25, 50, 100, or 200 mg/L (0, 2, 4, 6, or 12 mg/kg-day for males and 0, 2, 5, 8, and 15 mg/kg-day for females). Significant increases in incidence of nasal lesions (goblet cell hyperplasia and inflammation of nasal turbinates) were found in the exposed animals. However, the study authors postulated that these lesions were most likely from inhalation of chlorine dioxide vapors at the drinking water sipper tube or from off-gassing of the vapors after drinking rather than ingestion of the drinking water. Thus, the 2 mg/kg-day dose group could be described as a LOAEL, but the toxicological significance of the findings was inconclusive because the lesions were not reported in any other studies and may possibly be an artifact of treatment.

Haag (1949) exposed groups of seven male and seven female rats to 0, 0.5, 1, 5, 10, or 100 mg/L chlorine dioxide in drinking water (0.07, 0.13, 0.7, 1.3, or 13 mg/kg-day) for 2 years. Survival in the 100 mg/L group was significantly decreased. No chlorine dioxide-related alterations were observed in the histopathological examination of representative animals from each group. Thus, a NOAEL of 10 mg/L (1.3 mg/kg-day) and a Frank Effect Level (FEL) (based on decreased survival) of 100 mg/L (13 mg/kg-day) can be identified from this study. Renal pathology, characterized by distention of the glomerular capsule and appearance of a pinkish staining material in the renal tubules, was observed in rats exposed to 100 or 1,000 mg/L chlorite in drinking water for 2 years (9.3 or 81 mg/kg-day).

Numerous animal studies have examined neurodevelopmental toxicity of chlorine dioxide and chlorite. These studies consistently show a LOAEL of 14 mg/kg-day and NOAEL of 3 mg/kg-day for multiple neurodevelopmental endpoints. Decreases in locomotor activity on PND 18-19, but not on days 15-17 or day 20, were observed in Sprague-Dawley rat pups administered gavage doses of 14 mg/kg-day chlorine dioxide on PND 5-20 (Orme et al., 1985). In in utero-exposed pups (dams exposed to 100 mg/L chlorine dioxide in drinking water [14 mg/kg-day] for 2 weeks prior to mating and throughout gestation and lactation), there was a consistent decrease in locomotor activity, but the activity was not statistically significantly lower than controls. Triiodothyronine (T3) and thyroxine (T4) were significantly decreased in the in utero-exposed pups and T4 levels were decreased in the postnatally exposed pups. No significant alterations in locomotor activity or T3 or T4 levels were observed in the offspring of rats exposed to 2 or 20 mg/L (1 or 3 mg/kg-day; exposure protocol the same as 100 mg/L group). However, there was a significant correlation between T4 levels and locomotor activity in all groups. Thus, this study identifies a NOAEL of 3 mg/kg-day and a LOAEL of 14 mg/kg-day.

Mobley et al. (1990) found decreases in exploratory activity on postconception days 36-39, but not on days 39-41 in offspring of Sprague-Dawley rats exposed to 100 ppm chlorine dioxide in the drinking water (14 mg/kg-day) for 10 days prior to mating with unexposed males and during the gestation and lactation periods. A significant decrease in litter weight was also observed. Mobley et al. also found significant decreases in exploratory activity on PND 36-39, but not on days 39-41, in the

offspring of Sprague-Dawley rats exposed to 40 ppm chlorine dioxide in the drinking water (6 mg/kg-day) for 10 days prior to mating and during gestation and lactation. T3 and T4 levels were not significantly altered. A slight decrease in activity was also observed in the offspring of rats exposed to 20 ppm (3 mg/kg-day). This study identifies a NOAEL of 3 mg/kg-day and a LOAEL of 14 mg/kg-day.

Decreases in exploratory activity (PND 60) were also observed by Taylor and Pfohl (1985) in offspring of Sprague-Dawley rats exposed to 100 ppm chlorine dioxide in the drinking water (14 mg/kg-day) for 14 days prior to breeding and throughout gestation and lactation. A nonsignificant decrease in locomotor activity was noted in PND 10-20. Decreases in home cage or wheel running activity occurred on PND 10 and 18-19 in pups (not exposed in utero) administered gavage doses of 14 mg/kg-day on PND 5-20. In addition to the decreases in motor activity, decreases in brain weight (primarily due to a decrease in cerebellar weight) and total cell numbers in the cerebellum were observed in the in utero-exposed pups. A LOAEL of 14 mg/kg-day was identified in this study; a NOAEL was not identified.

Toth et al. (1990) found decreases in forebrain weight, accompanied by decreases in protein content, on PND 21 and 35 in Long-Evans hooded rat pups receiving gavage doses of 14 mg/kg-day on PND 1-20. Dendritic spine counts in Krieg's area 18 (a visual association region of the cortex) were also significantly decreased. No gross lesions, loss of myelin, or changes in cells staining positive for Nissl substance in the forebrain, cerebellum, or brainstem were observed. T3, T4, and free T4 index were not significantly altered on PND 11, 21, and 35. The 14 mg/kg-day dose is a LOAEL for neurodevelopmental effects.

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).

___I.A.5. Confidence in the Oral RfD

Study — Medium

Database — High

RfD — Medium-to-High

The overall confidence in this RfD assessment is medium-to-high. Confidence in the CMA (1996) principal study is medium. Although the study design and analytical approaches are consistent with EPA testing guidelines, some limitations in the design and conduct of the study exist. These limitations include: (1) lack of pair-watered and -fed controls, which confounds the results and precludes definitive conclusions on whether the alterations in food and water consumption and body weight are related to water palatability or to a direct toxic effect of the agent; (2) developmental landmarks (e.g., vaginal opening in F2a group) were not reported for all groups; (3) grip strength and landing foot splay were not included in the FOB; and (4) discontinuation of exposure for the animals undergoing neurotoxicity testing minimizes the likelihood of finding a positive effect and precludes comparison of the data with those of other rats with continued exposure. Discontinuation of exposure after weaning reduces the opportunity to detect neurological effects from continuous or lifetime exposures similar to those expected from lifetime drinking water exposure in humans. Confidence in the database is high, because there are studies in multiple species, chronic duration studies in males and females, reproductive/developmental toxicity studies, and a multigenerational study. The threshold for adverse effects is consistently defined among the animal studies.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).

___I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is presented in the Toxicological Review of Chlorine Dioxide and Chlorite (CAS No. 10049-04-4 and 7758-19-2) (U.S. EPA, 2000).

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to U.S. EPA, 2000. ***To review this appendix, exit to [the toxicological](#)***

Agency Consensus Date - 9/20/2000

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Chlorine dioxide conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

__I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (Internet address).

__I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Chlorine dioxide
CASRN — 10049-04-4
Last Revised — 10/12/2000

The inhalation reference concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for the respiratory system (portal-of-entry) and effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/m³. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

__I.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	MF	RfC
Vascular congestion and peribronchial edema	NOAEL: None LOAEL: 2.76 mg/m ³ (1 ppm)	3,000	1	2 x 10 ⁻⁴ mg/m ³
60-day rat inhalation study	LOAEL _{ADJ} : 0.41 mg/m ³ LOAEL _{HEC} : 0.64 mg/m ³			
Paulet and Desbrousses, 1972				

Hemorrhagic alveoli and congested capillaries the lungs	NOAEL: None LOAEL: 6.9 mg/m ³ (2.5 ppm)			
45-day rabbit inhalation study	LOAEL _{ADJ} : 0.82 mg/m ³ LOAEL _{HEC} : 0.49 mg/m ³			

*Conversion Factors and Assumptions — MW = 67.46.

Paulet and Desbrousses, 1972: Assuming 25° C and 760 mm Hg, LOAEL (mg/m³) = 1.0 ppm x 67.46/24.45 = 2.76 mg/m³. LOAEL_{ADJ} = 2.76 mg/m³ x 5 hours/24 hours x 5 days/7 days = 0.41 mg/m³. The LOAEL_{HEC} was calculated for a gas:respiratory effect in the thoracic region. MV_a = 0.17 m³, MV_h = 20 m³, Sa_{TH} = 3,461.6 cm², Sh_{TH} = 640,581 cm². RGDR_{TH} = (MV_a/Sa_{TH}) / (MV_h/Sh_{TH}) = 1.57. LOAEL_{HEC} = LOAEL_{ADJ} x RGDR = 0.64 mg/m³.

Paulet and Desbrousses, 1970: Assuming 25° C and 760 mm Hg, LOAEL (mg/m³) = 2.5 ppm x 67.46/24.45 = 6.9 mg/m³. LOAEL_{ADJ} = 6.9 mg/m³ x 4 hours/24 hours x 5 days/7 days = 0.82 mg/m³. The LOAEL_{HEC} was calculated for a gas:respiratory effect in the thoracic region. MV_a = 1.10 m³, Sa_{TH} = 59,100 cm². RGDR_{TH} = (MV_a/Sa_{TH}) / (MV_h/Sh_{TH}) = 0.596. LOAEL_{HEC} = LOAEL_{ADJ} x RGDR = 0.49 mg/m³.

___I.B.2. Principal and Supporting Studies (Inhalation RfC)

Paulet, G; Desbrousses, S. (1970) On the action of ClO₂ at low concentrations on laboratory animals. Arch Mal Prof Med Trav Secur Soc 31(3):97-106.

Paulet, G; Desbrousses, S. (1972) On the toxicology of chlorine dioxide. Arch Mal Prof Med Trav Secur Soc 33(1-2):59-61.

Paulet and Desbrousses (1970) conducted 4 studies to investigate the toxicity of inhaled chlorine dioxide in rats and rabbits (strains not specified): (a) 5 male and 5 female rats were exposed to 10 ppm (28 mg/m³) 2 hours/day for 30 days; (b) 10 male rats, 10 female rats, and 5 rabbits were exposed to 5 ppm chlorine dioxide (14 mg/m³) 2 hours/day for 30 days; (c) 10 male and 10 female rats were exposed to 2.5 ppm (6.9 mg/m³) 7 hours/day for 30 days; and (d) 8 rabbits were exposed to 2.5 ppm chlorine dioxide (6.9 mg/m³) 4 hours/day for 45 days. The weekly exposure frequency was not reported; presumably it was 5 days/week. Control groups with equal numbers of animals were used for each study. The following adverse effects were observed at 10 ppm: nasal discharge and red eyes, localized bronchopneumonia with desquamation of the alveolar epithelium, and significantly increased blood erythrocyte and leukocyte levels. Similar, but less severe, respiratory tract effects were observed at 5 ppm; there were no alterations in erythrocyte or leukocyte levels at this concentration. Lymphocytic infiltration of the alveolar spaces, alveolar vascular congestion, hemorrhagic alveoli, epithelial erosions, and inflammatory infiltrations of the bronchi were observed in the rats exposed to 2.5 ppm. The study authors noted that body weight gain was "slightly slowed" (data not presented), and the erythrocyte and leukocyte levels were 85% and 116% of controls, respectively (statistical analysis not reported), in the rats exposed to 2.5 ppm. In rabbits exposed to 2.5 ppm chlorine dioxide, hemorrhagic alveoli and congested capillaries were observed in the lungs. Body weight gain was not adversely affected and erythrocyte and leukocyte levels were 80% and 116% of control (statistical analysis not reported, study authors state that the cell counts "changed very little"). Another group of rats and rabbits was sacrificed 15 days after termination of the 2.5 ppm exposure regimens. Recovery from the pulmonary lesions was evident in these animals. The liver was not adversely affected in the rats or rabbits following exposure to 2.5, 5, or 10 ppm chlorine dioxide. This study identifies a LOAEL of 2.5 ppm (6.9 mg/m³) for thoracic effects (alveolar congestion and hemorrhage and bronchial inflammation) in rats (7 hours/day for 30 days) and pulmonary effects (alveolar hemorrhage and capillary congestion) in rabbits (4 hours/day for 45 days).

In a followup study by Paulet and Desbrousses (1972), groups of eight Wistar rats (sex not reported)

were exposed to 1 ppm chlorine dioxide (2.8 mg/m³) 5 hours/day, 5 days/week, for 2 months. The study authors noted that weight gain and erythrocyte and leukocyte levels were not affected, but did not present concurrent control data. Vascular congestion and peribronchiolar edema were observed in the lungs of chlorine dioxide-exposed rats; no alterations in the epithelium or parenchyma were observed. This subchronic study identifies a LOAEL of 1 ppm (2.8 mg/m³) for respiratory effects in rats.

__I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 3,000.

MF = 1.

The uncertainty factor of 3,000 comprises a factor of 10 to account for extrapolation of a chronic RfC from a subchronic study, 3 for interspecies extrapolation using dosimetric adjustments, 10 for intrahuman variability, and 10 to account for extrapolation from a LOAEL for mild effects and for the lack of inhalation developmental and reproductive toxicity studies. EPA's policy is to limit the size of the composite UF to 3,000 in recognition of the lack of independence of these factors. (U.S. EPA, 1994). The LOAEL-to-NOAEL and database uncertainties are therefore coalesced into one UF of 10. The composite UF for this RfC is therefore 3,000.

__I.B.4. Additional Studies/Comments (Inhalation RfC)

Several case reports of accidental inhalation exposure to chlorine dioxide have been reported in the literature. Elkins (1959) described the case of a bleach tank worker who died after being exposed to 19 ppm chlorine dioxide (52 mg/m³) for an unspecified amount of time; another worker who was exposed at the same time survived. Elkins also stated that 5 ppm (14 mg/m³) was definitely irritating to humans. In a case reported by Exner-Freisfeld et al. (1986), a woman experienced coughing, pharyngeal irritation, and headache after inhaling an unknown amount of chlorine dioxide inadvertently generated while bleaching flowers. Seven hours after exposure, the woman was hospitalized with cough, dyspnea, tachypnea, tachycardia, rales on auscultation, and marked leukocytosis; a decrease in lung function (reduced vital capacity and 1-second forced expiratory volume) was also reported. Most of these symptoms were alleviated with corticosteroid treatment.

Meggs et al. (1996) examined 13 individuals (1 man and 12 women) 5 years after they were occupationally exposed to chlorine dioxide from a leak in a water purification system pipe. The long-term effects of the accident included development of sensitivity to respiratory irritants (13 subjects), disability with loss of employment (11 subjects), and chronic fatigue (11 subjects). Nasal abnormalities (including injection, telangectasia, paleness, cobblestoning, edema, and thick mucus) were found in all 13 individuals. Nasal biopsies taken from the subjects revealed chronic inflammation, with lymphocytes and plasma cells present within the lamina propria in 11 of the 13 subjects; the inflammation was graded as mild in 2 subjects, moderate in 8 subjects, and severe in 1 subject. Nasal biopsies from three control individuals showed chronic inflammation in one person. The average inflammation grading was statistically higher in the exposed subjects as compared with the controls. The number of nerve fibers in the biopsies was higher in the subjects (rare fibers in three subjects, moderate fibers in two subjects, and many fibers in three subjects) than controls, but the difference was not statistically significant.

Gloemme and Lundgren (1957), Ferris et al. (1967), and Kennedy et al. (1991) examined male workers occasionally exposed to high concentrations of chlorine dioxide that resulted from equipment failure. Concurrent exposure to chlorine gas and, in some cases, sulfur dioxide confounds interpretation of the results of these studies. Gloemme and Lundgren examined the respiratory health of 12 workers employed at a sulfite-cellulose production facility. Under normal working conditions, the atmospheric chlorine content was less than 0.1 ppm (chlorine dioxide levels were not measured); however, occasional equipment leakages would result in high levels of chlorine dioxide, chlorine, and/or sulfur dioxide. The workers reported respiratory (breathlessness, wheezing, irritant cough) and ocular (conjunctivitis and "halo phenomena") discomfort in connection with these leakage exposures. A slight, nonspecific chronic bronchitis was diagnosed in 7 of the 12 men.

In the Ferris et al. (1967) study, no significant alterations in pulmonary function (forced vital capacity, maximum expiratory flow, forced expiratory flow, and forced expiratory volume) were observed in 147 men employed at a pulp mill (length of employment not reported), compared with 124 men employed at a paper mill. The pulp mill workers were exposed to sulfur dioxide or chlorine dioxide and chlorine; the chlorine dioxide concentrations ranged from trace amounts to 2.0 ppm (average concentrations ranged from trace amounts to 0.25 ppm) and chlorine concentrations ranged from trace amounts to 64 ppm (average concentrations ranged from trace amounts to 7.4 ppm). When the pulp mill workers were divided into those exposed to sulfur dioxide and those exposed to chlorine or chlorine dioxide, significantly higher incidences of shortness of breath and excess phlegm were found in the chlorine/chlorine dioxide workers.

In the Kennedy et al. (1991) study of 321 kraft pulp mill workers exposed to chlorine and chlorine dioxide, significant increases in the incidence of wheezing, wheezing accompanied by breathlessness, and work-related wheezing were observed, compared with 37 workers at a rail maintenance yard. Personal time-weighted average (TWA) exposure concentration for chlorine at the pulp mill ranged from 5 to 14 ppm, whereas TWA for chlorine dioxide was below 0.1 ppm. However, 60% of the pulp mill workers reported one or more chlorine or chlorine dioxide "gassing" incidents. No significant differences in tests of pulmonary function were observed between the two groups. The pulp mill workers were divided into two groups based on self-reported accidental exposures to high levels of chlorine/chlorine dioxide gas ("gassing"). In the workers reporting one or more incidents of gassing, prevalence of wheezing and missed work because of chest illness was higher than in the pulp mill workers not reporting gassing incidents. Additionally, incidence of airflow obstruction (measured by a decrease in midmaximal flow rate and the ratio of 1-second forced expiratory volume to forced vital capacity) was higher in nonsmokers and former smokers reporting gassing incidents compared with smokers also reporting gassing incidents.

In a second series of animal studies conducted by Paulet and Desbrousses (1974), groups of 10-15 rats (sex and strain not reported) were exposed to 5, 10, or 15 ppm chlorine dioxide (41, 28, or 14 mg/m³) for 15-minute periods 2 or 4 times/day for 1 month. Control groups were similarly exposed to room air. At 15 ppm, 1/10 and 1/15 rats exposed for 2 or 4 times/day, respectively, died; body weight loss was observed in both groups. Histological alterations observed at this exposure level included nasal and ocular inflammation and discharge, bronchitis, catarrhus lesions of the alveoli with peribronchiolar infiltrations (more pronounced in the four times/day group). The alveolar lesions were reversible; 15 days after exposure termination, the lung histology was similar to controls. No histological alterations were observed in the liver. At 10 ppm, alveolar irritation and decreases in body weight gain were observed. No adverse effects on clinical signs, body weight gain, or histopathology of the lungs were observed at 5 ppm. Exposure to chlorine dioxide did not adversely affect hematological parameters. This study identified a NOAEL of 5 ppm (6.9 mg/m³) and LOAEL of 10 ppm (28 mg/m³) for lung damage following intermittent exposure for 15-minute periods, 2 or 4 times/day for 4 weeks.

Dalhamn (1957) conducted a series of inhalation studies to assess the toxicity of chlorine dioxide in the rat (sex and strain not reported). In the first study, a group of three rats was exposed once a week for 3 minutes to decreasing concentrations of chlorine dioxide (3,400 ppm [9,400 mg/m³] in week 1, 1,100 ppm [3,000 mg/m³] in week 2, and 800 ppm [2,200 mg/m³] in week 3); a second group of three rats served as controls. Respiratory distress and decreased body weight were observed in the chlorine dioxide-exposed rats. Bronchopneumonia and hyperemia of the renal corticomedullary junction were observed in two out of three rats; the renal hyperemia was also observed in the control group (2/3). In the second study, exposure to 260 ppm (720 mg/m³) chlorine dioxide for 2 hours resulted in ocular discharge, epistaxis, death (1/4 rats), pulmonary edema, and circulatory engorgement. In the third study, groups of five rats were exposed to 0 or approximately 10 ppm chlorine dioxide (28 mg/m³) 4 hours/day for 9 days in a 13-day period. Death (3/5 rats), rhinorrhea, "embarrassed respiration," and weight loss were observed in the chlorine dioxide-exposed rats. Respiratory infection with acute renal and hepatic congestion was also observed. The fourth study involved exposure of groups of 5 rats to 0 or approximately 0.1 ppm chlorine dioxide (0.28 mg/m³) 5 hours/day for 10 weeks (the number of exposure days per week was not reported). No effects on body weight gain were observed and no histological alterations were observed in the lungs, kidneys,

or liver. The Dalhamn (1957) studies identified a NOAEL of 0.1 ppm (0.28 mg/m³) in rats exposed 5 hours/day for 10 weeks and a LOAEL of 10 ppm (28 mg/m³) for respiratory tract irritation in rats exposed 4 hours/day for approximately 2 weeks. Note that the RfC value is the same as previously available on IRIS.

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).

__I.B.5. Confidence in the Inhalation RfC

Study — Low
Database — Low
RfC -- Low

The overall confidence in this RfC assessment is low. Confidence in the coprincipal studies by Paulet and Desbrousses (1970, 1972) is low. These studies identified only a LOAEL in rats and rabbits for adverse lung effects in 60- and 45-day studies and are lacking in experimental detail. Confidence in the database is also low. There were no adequate subchronic or chronic inhalation studies that examined nonlung effects and no acceptable developmental or reproductive studies for inhaled chlorine dioxide.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).

__I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is presented in the Toxicological Review of Chlorine Dioxide and Chlorite (CAS No. 10049-04-4 and 7758-19-2) (U.S. EPA, 2000)

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to U.S. EPA (2000). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF).***

Agency Consensus Date — 9/20/2000

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Chlorine dioxide conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

__I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

_II. Carcinogenicity Assessment for Lifetime Exposure

Chlorine dioxide
CASRN — 10049-04-4
Last Revised — 10/12/2000

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the

quantitative estimate in terms of either risk per µg/L drinking water or risk per µg/m³ air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in the Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Under the current guidelines (U.S. EPA, 1986), chlorine dioxide is classified as Group D; not classifiable as to human carcinogenicity because of inadequate data in humans and animals. Under the draft Carcinogen Assessment Guidelines (U.S. EPA, 1996), the human carcinogenicity of chlorine dioxide cannot be determined because no satisfactory human or animal studies assessing the chronic carcinogenic potential of chlorine dioxide have been located. Concentrates prepared from drinking water treated with chlorine dioxide did not increase the incidence of lung adenomas in Strain A mice, the skin tumor frequency in mice, or the incidence of gamma-glutamyl transpeptidase positive foci (a measure of preneoplastic changes) in rat livers (Miller et al., 1986). However, chlorine dioxide did induce a hyperplastic response in the mouse skin (Robinson et al., 1986). Both positive and negative results have been found in genotoxicity studies.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).

II.A.2. Human Carcinogenicity Data

None

II.A.3. Animal Carcinogenicity Data

None

II.A.4. Supporting Data for Carcinogenicity

Miller et al. (1986), using three short-term assays, tested the carcinogenic potential of drinking water disinfected with chlorine dioxide. Following disinfection with chlorine dioxide, the water samples (containing 0.5 mg/L chlorine dioxide residue) were concentrated 2,000 or 4,000 x with a macroreticular resin process. In a mouse initiation-promotion assay, groups of 14-34 SENCAR mice (sex not specified) were orally administered 0.5 mL of the 4,000 x concentrate in 2% emulphor 3 times/week for 2 weeks followed by topical exposure to 1.0 µg 12-tetradecanylphorbol-13-acetate (TPA) in acetone applied to the dorsal skin 3 times/week for 20 weeks, and were then sacrificed. No significant increases, compared with vehicle controls, in the number of skin tumors or the number of tumors per animal were observed.

In a lung adenoma assay (Miller et al., 1986), groups of 20 male and 20 female Strain A mice received 0.25 mL gavage doses of 2,000 x or 4,000 x concentrates in 2% emulphor 3 times/week for 8 weeks followed by a 16-week observation period. The number of animals with lung adenomas and the number of adenomas per animal were not significantly altered compared with vehicle controls.

Miller et al. (1986) also examined the development of liver foci in rats in a short-term assay. In this study, groups of partially hepatectomized rats received a single dose of concentrated water (chlorine dioxide concentration not reported) in 2% emulphor followed (1 week later) by administration of 500

ppm sodium phenobarbital in drinking water for 56 days; animals were sacrificed on day 70. A control group received nondisinfected water. No significant increases in the incidence of g-glutamyltranspeptidase foci were observed.

The potential for chlorine dioxide to induce proliferative epidermal hyperplasia was examined by Robinson et al. (1986). Groups of five dorsally shaved female SENCAR mice were placed in chambers filled with 0, 1, 10, 100, 300, or 1,000 ppm liquid chlorine dioxide; the chambers were designed to prevent the head from getting wet and to prevent inhalation of vapors. The animals were exposed 10 minutes/day for 4 days. A significant increase in interfollicular epidermal thickness was observed in the 1,000-ppm group but not at the lower concentrations. Increases in total cell numbers and basal cell numbers in skin sections were observed in both the 300 and the 1,000 ppm groups. In a second study, groups of 40 mice were immersed in 0 or 1,000 ppm chlorine dioxide for 10 minutes; animals (5/group) were killed 1, 2, 3, 4, 5, 8, 10, or 12 days post-exposure. A significant increase in interfollicular epidermis thickness was observed at all time periods, with the highest values at 10 and 12 days post-exposure. The authors concluded that even short-term dermal exposure to high concentrations of chlorine dioxide is capable of inducing hyperplastic responses in the mouse skin.

Both positive and negative results have been found in in vitro genotoxicity studies. Chlorine dioxide did not increase occurrence of chromosome aberrations in Chinese hamster fibroblast cells (Ishidate et al., 1984) but did increase occurrence of reverse mutation in *Salmonella typhimurium* (with activation) (Ishidate et al., 1984). However, water samples disinfected with chlorine dioxide did not induce reverse mutations in *S. typhimurium* with or without activation (Miller et al., 1986). In vivo micronucleus and bone marrow chromosomal aberration assays in Swiss CD-1 mice administered 0.1-0.4 mg via gavage for 5 consecutive days and sperm-head abnormality assay in B6C3F1 mice administered 0.1-0.4 mg via gavage for 5 consecutive days (0, 3.2, 8, and 16 mg/kg-day) were negative (Meier et al., 1985). Hayashi et al. (1988) reported positive results in the micronucleus assay in ddY mice following a single intraperitoneal injection of 3.2-25 mg/kg.

__II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

None

__II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

None

__II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

__II.D.1. EPA Documentation

Source Document — This assessment is presented in the Toxicological Review of Chlorine Dioxide and Chlorite (CAS No. 10049-04-4 and 7758-19-2) (U.S. EPA, 2000).

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to U.S. EPA, 2000. **To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF).**

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 9/20/2000

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Chlorine dioxide conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or

__II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address)

_III. [reserved]

_IV. [reserved]

_V. [reserved]

_VI. Bibliography

Chlorine dioxide

CASRN — 10049-04-4

Last Revised - 10/12/2000

_VI.A. Oral RfD References

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_VII. Revision History

Chlorine dioxide

CASRN — 10049-04-4

Date	Section	Description
11/01/1990	I.B	Inhalation RfC summary on-line
11/01/1990	VI.	Bibliography on-line
01/01/1992	IV.	Regulatory Action section on-line
09/01/1992	I.A	Oral RfD now under review
05/01/1993	I.A	Work group review date added
05/01/1993	II.	Carcinogenicity assessment now under review

12/01/1993	I.A.	Work group review date added
01/01/1994	I.A.	Work group review date added
08/01/1995	I.A., II.	EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September, 1995.
11/01/1995	II.	Carcinogenicity assessment on-line
11/01/1995	VI.C	Carcinogenicity references on-line
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and V. Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
10/12/2000	I., II., VI.	Oral RfD on-line, revised RfC and carcinogenicity assessment on-line
10/28/2003	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

_VIII. Synonyms

Chlorine dioxide

CASRN — 10049-04-4

Last Revised — 10/12/2000

- 10049-04-4
- Chlorine oxide
- Alcide
- Anthium Dioxide
- Caswell No. 179A
- Chlorine dioxide
- Chlorine peroxide
- CHLORINE (IV) OXIDE
- Chloroperoxyl
- CHLORYL RADICAL
- Dioxide de cloro [Spanish]
- Dioxide de chlore [French]
- Doxcide 50
- EPA Pesticide Chemical Code 020503
- HSDB 517

IRIS Home

Chronic Health Hazards for Non-Carcinogenic Effects

Reference Dose for Chronic Oral Exposure (RfD)

- Oral RfD Summary
- Principal and Supporting Studies
- Uncertainty and Modifying Factors
- Additional Studies/Comments
- Confidence in the Oral RfD
- EPA Documentation and Review

**Reference
Concentration for
Chronic Inhalation
Exposure (RfC)**

- Inhalation RfC Summary
- Principal and Supporting Studies
- Uncertainty and Modifying Factors
- Additional Studies/Comments
- Confidence in the Inhalation RfC
- EPA Documentation and Review

**Carcinogenicity
Assessment for
Lifetime Exposure**

**Evidence for Human
Carcinogenicity**

- Weight-of-Evidence Characterization
- Human Carcinogenicity Data
- Animal Carcinogenicity Data
- Supporting Data for Carcinogenicity

**Quantitative
Estimate of
Carcinogenic Risk
from Oral Exposure**

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

**Quantitative
Estimate of
Carcinogenic Risk
from Inhalation
Exposure**

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence
- EPA Documentation, Review and, Contacts

Bibliography

Revision History

Synonyms