EPA/635/R-00/007

TOXICOLOGICAL REVIEW

OF

CHLORINE DIOXIDE

AND

CHLORITE

(CAS Nos. 10049-04-4 and 7758-19-2)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

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U.S. Environmental Protection Agency
Washington, DC

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FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to chronic exposure to chlorine dioxide and chlorite. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of chlorine dioxide and chlorite.

In Section 6, EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose response. Matters considered in this characterization include knowledge gaps, uncertainties, quality of data, and scientific controversies. This characterization is presented in an effort to make apparent the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's Risk Information Hotline at 513-569-7254.

AUTHORS, CONTRIBUTORS, AND REVIEWERS

Chemical Managers/Authors

Yogendra Patel, Ph.D.
OST/HECD
Office of Water
U.S. Environmental Protection Agency
Washington, DC

Diana Wong, Ph.D., D.A.B.T.
OST/HECD
Office of Water
U.S. Environmental Protection Agency
Washington, DC

Contributing Authors

Lisa Ingerman, Ph.D., D.A.B.T.
Senior Scientist
Syracuse Research Corporation
Portland, OR

Patricia McGinnis, Ph.D., D.A.B.T.
Senior Scientist
Syracuse Research Corporation
Philadelphia, PA

Mark Osier, Ph.D.
Senior Scientist
Syracuse Research Corporation
North Syracuse, NY

Reviewers

This document and summary information on IRIS have received peer review both by EPA scientists and by independent scientists external to EPA. Subsequent to external review and incorporation of comments, this assessment has undergone an Agencywide review process whereby the IRIS Program Manager has achieved a consensus approval among the Office of Research and Development; Office of Air and Radiation; Office of Prevention, Pesticides, and Toxic Substances; Office of Solid Waste and Emergency Response; Office of Water; Office of Policy, Planning, and Evaluation; and the Regional Offices.

AUTHORS, CONTRIBUTORS, AND REVIEWERS (continued)

Internal EPA Reviewers

Annie J. Jarabek
ORD / NCEA
Research Triangle Park, NC

Ginger Moser, Ph.D., D.A.B.T.
ORD / NTD/NHEERL
Research Triangle Park, NC

External Peer Reviewers

Paul E. Brubaker, Ph.D.
Consultant
Brubaker and Associates

James Edward Klaunig, Ph.D.
Division of Toxicology, Department of Pharmacology and Toxicology
Indiana University School of Medicine

June Dunnick, Ph.D.
Scientist
National Institute of Environmental Health Sciences

Calvin C. Willhite, Ph.D.
State of California, Department of Toxic Substances Control

Summaries of the external peer reviewers' comments and the disposition of their recommendations are in the Appendix.

1. INTRODUCTION

This document presents background and justification for the hazard and dose-response assessment summaries in the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS). IRIS summaries may include an oral reference dose (RfD), inhalation reference concentration (RfC), and a carcinogenicity assessment.

The RfD and RfC provide quantitative information for noncancer dose-response assessments. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis but may not exist for other toxic effects such as some carcinogenic responses. 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 noncancer effects during a lifetime. The inhalation RfC is analogous to the oral RfD, but it provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extra respiratory or systemic effects). It is generally expressed in units of mg/m^3.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral exposure and inhalation exposure. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. 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 $\mu g/m^3$ air breathed. Another form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

Development of these hazard identification and dose-response assessments for chlorine dioxide and chlorite has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA guidelines that were used in the development of this assessment may include the following: *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a); *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b); *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986c); *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991); *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998a); *Proposed Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1996a); *Reproductive Toxicity Risk Assessment Guidelines* (U.S. EPA, 1996b); *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988); (proposed) *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a); *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b); *Peer Review and Peer Involvement at the U.S. Environmental Protection Agency* (U.S. EPA, 1994c); *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995); *Science Policy Council Handbook: Peer Review* (U.S.

EPA, 1998b); and a memorandum from EPA Administrator, Carol Browner, dated March 21, 1995, Subject: Guidance on Risk Characterization.

Literature search strategies employed for these compounds were based on the CASRN and at least one common name. At a minimum, the following databases were searched: RTECS, HSDB, TSCATS, CCRIS, GENETOX, EMIC, EMICBACK, DART, ETICBACK, TOXLINE, CANCERLINE, MEDLINE, and MEDLINE backfiles. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document.

2. CHEMICAL AND PHYSICAL INFORMATION RELEVANT TO ASSESSMENTS

Chlorine dioxide (ClO_2; CASRN 10049-04-4) is a yellow to reddish-yellow gas at room temperature that is stable in the dark but is unstable in light. It is a strong oxidizing agent that under oxidant demand conditions is readily reduced to chlorite (ClO_2^-; CASRN 7758-19-2), another strong oxidizing agent. The *Drinking Water Criteria Document on Chlorine Dioxide, Chlorite, and Chlorate* (U.S. EPA, 1994d) provides the relevant information concerning dissociation byproducts of chlorine dioxide in water. The strong oxidizing ability of chlorine dioxide makes it useful as a drinking water disinfectant. Other uses of chlorine dioxide include bleaching textiles and wood pulp for paper manufacturing, antimicrobial applications, and reducing loads of adsorbable organic halogenated compounds in industrial effluents. Chlorite is also used for etching printed circuit boards. The physical and chemical properties of chlorine dioxide and chlorite are presented in Table 1.

Chlorine dioxide and chlorite are characterized together in this report because studies conducted with chlorite, the predominant degradation product of chlorine dioxide, are likely relevant to characterizing the toxicity of chlorine dioxide. In addition, studies conducted with chlorine dioxide may be relevant to characterizing the toxicity of chlorite. Chlorine dioxide is fairly unstable and rapidly dissociates, predominantly into chlorite and chloride, and to a lesser extent, chlorate. There is a ready interconversion among these species in water (before administration to animals) and in the gut (after ingestion) (U.S. EPA, 1994d). Therefore, what exists in water or the stomach is a mixture of these chemical species (i.e., chlorine dioxide, chlorite, chlorate) and possibly their reaction products with the gastrointestinal contents.

Table 1. Physical and chemical properties of chlorine dioxide and chlorite

Properties	Chlorine dioxide	Chlorite (sodium salt)
CAS registry number	10049-04-4	7758-19-2
Molecular formula	ClO_2	$NaClO_2$
Molecular weight	67.46	90.45
Melting point, °C	-59	decomposes at 180–200
Boiling point, °C	11	no data
Water solubility, g/L	3.0 at 25°C and 34 mmHg	39 at 30°C
Specific gravity	1.642 at 0°C	no data

Source: Budavari et al., 1989.

3. TOXICOKINETICS RELEVANT TO ASSESSMENTS

3.1. ABSORPTION

3.1.1. Gastrointestinal Absorption

3.1.1.1. *Chlorine Dioxide*

After ingestion, chlorine dioxide is rapidly absorbed from the gastrointestinal tract. Levels of radioactive chlorine in plasma peaked 1 hour after Sprague-Dawley rats were administered a single gavage dose of 100 mg/L $^{36}ClO_2$ (approximately 1.4 mg/kg) (Abdel-Rahman et al., 1979a). Peak plasma levels were achieved 2 hours after Sprague-Dawley rats received a gavage dose of 300 mg/L $^{36}ClO_2$ after a 15-day exposure to 100 mg/L chlorine dioxide in drinking water (Abdel-Rahman et al., 1979a). Approximately 30% of the 100 mg/L single gavage dose was excreted in the urine after 72 hours, indicating that at least 30% of the dose was absorbed (Abdel-Rahman et al., 1979a); the absorption rate constant and half time were 3.77/hour and 0.18 hours, respectively (Abdel-Rahman et al., 1982). Since total radioactivity was measured rather than identification of individual chemical entities, it was not clear from these reports whether the parent chlorine dioxide itself or the chlorite, chlorate, or chloride ion degradation products were absorbed.

3.1.1.2. *Chlorite*

Chlorite is also rapidly absorbed from the gastrointestinal tract. Peak plasma levels of radiolabeled chlorine were reached 2 hours after administration of a single gavage dose of 10 mg/L $^{36}ClO_2^-$ (approximately 0.13 mg/kg) to Sprague-Dawley rats. Using 72-hour urinary

excretion data, it can be assumed that at least 35% of the initial dose was absorbed (Abdel-Rahman et al., 1984a). The absorption rate constant and half-time were 0.198/hour and 3.5 hours, respectively (Abdel-Rahman et al., 1982). Since total radioactivity was measured rather than identification of individual chemical entities, it was not clear from these reports whether the parent chlorine dioxide itself or the chlorite, chlorate, or chloride ion degradation products were absorbed.

3.1.2. Respiratory Tract Absorption

No data were located on respiratory tract absorption of chlorine dioxide or chlorite.

3.1.3. Dermal Absorption

Scatina et al. (1984) reported on the dermal absorption of Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid, which when mixed immediately before use result in the formation of chlorine dioxide. 0.6 g ^{36}Cl-labeled sodium chlorite as part of the Alcide was used to monitor absorption following application to the shaved backs of 10 female Sprague-Dawley rats. Maximum absorption of ^{36}Cl into plasma was observed after 72 hours, where a plasma concentration of 69.4 µg% ^{36}Cl was reached. The absorption half-life was calculated to be 22.1 hours, which corresponds to a rate constant of 0.0314 hr^{-1}.

3.2. DISTRIBUTION

3.2.1. Chlorine Dioxide

Following a single 100 mg/L gavage dose of $^{36}ClO_2$, the ^{36}Cl was slowly cleared from the blood; the rate constant and half-time for elimination from blood were 0.0156/hour and 43.9 hours, respectively (Abdel-Rahman et al., 1982). Elimination from blood was shortened in Sprague-Dawley rats exposed to chlorine dioxide in drinking water for 2 weeks prior to receiving the 300 mg/L gavage dose of $^{36}ClO_2$; the rate constant and half time were 0.022/hour and 31.0 hours, respectively (Abdel-Rahman et al., 1979a). After removal from the blood, the radiolabel appeared to be widely distributed throughout the body, although the highest concentrations were found in the blood, stomach, and small intestines. The lung, kidney, liver, testes (assessed only in the 300 mg/L group), spleen, thymus, and bone marrow also had high concentrations of radiolabel 72 hours after dosing with 100 mg/L (single dose) or 300 mg/L (with 2-week drinking water exposure to 100 mg/L) (Abdel-Rahman et al., 1979a). Seventy-two hours after a single gavage dose of 100 mg/L $^{36}ClO_2$, most of the ^{36}Cl label in the plasma was in the form of chloride ion (Cl^-) and chlorite; the ratio of chloride to chlorite was 4 to 1 (Abdel-Rahman et al., 1979b).

3.2.2. Chlorite

Removal of chlorite from the blood is slow; the rate constant and half-time for elimination of ^{36}Cl from the blood were 0.0197/hour and 35.2 hours in Sprague-Dawley rats receiving a single gavage dose of 10 mg/L $^{36}ClO_2^-$ (Abdel-Rahman et al., 1982). Seventy-two hours after dosing, the highest concentrations of radiolabel were found in the blood, stomach,

testes, skin, lung, kidneys, small intestine, carcass, spleen, brain, bone marrow, and liver (Abdel-Rahman et al., 1982, 1984a).

3.3. METABOLISM

3.3.1. Chlorine Dioxide

Chloride ion is the ultimate metabolite of chlorine dioxide. Approximately 87% and 80% of radiolabeled chlorine in the urine (collected 0–72 hours after administration) and plasma (collected 72 hours after administration), respectively, are in the form of chloride ion following administration of a single gavage dose of 100 mg/L $^{36}ClO_2$ in rats (Abdel-Rahman et al., 1979b). Chlorite was a major metabolite, accounting for approximately 11% and 21% of urine and plasma ^{36}Cl, respectively; approximately 2% of the urinary ^{36}Cl was in the form of chlorate. An in vivo recovery study by Bercz et al. (1982) suggests that ingested chlorine dioxide is rapidly reduced in the stomach to nonoxidizing species (presumably chloride). Five minutes after chlorine dioxide was instilled into the stomach of a monkey, only 8% of the total oxidizing capacity equivalents of chlorine dioxide was recovered. Bercz et al. (1982) also reported that in vitro chlorine dioxide was rapidly reduced to chloride ion by saliva obtained from anesthetized monkeys.

3.3.2. Chlorite

Although fewer data are available on metabolism of chlorite, it is likely that metabolism of chlorite is similar to that of chlorine dioxide. Approximately 85% of the ^{36}Cl recovered in the urine of Sprague-Dawley rats 0–72 hours after administration of a single gavage of 10 mg/L $^{36}ClO_2^-$ was in the form of chloride; the remaining 15% was present as chlorite (Abdel-Rahman et al., 1984a).

3.4. ELIMINATION

3.4.1. Chlorine Dioxide

The radioactive chlorine label was primarily excreted in the urine of rats administered a single gavage dose of 100 mg/L $^{36}ClO_2$ (Abdel-Rahman et al., 1979a). During the first 24 hours after dosing, 18% of the label was excreted in the urine and 4.5% in the feces. Seventy-two hours after dosing, 31% and 10% of the label were excreted in the urine and feces, respectively; the label was not detected in expired air. The parent compound was not detected in the urine; most of the label was in the form of chloride, with smaller amounts as chlorite. The ratio of $^{36}Cl^-$ to $^{36}ClO_2^-$ was 5 to 1 during the first 24 hours and 4 to 1 during the first 72 hours (Abdel-Rahman et al., 1979b).

3.4.2. Chlorite

Urine was the primary route of excretion in rats administered a single gavage dose of 10 mg/L $^{36}ClO_2^-$. Twenty-four hours after dosing, 14% of the label was excreted in the urine and

0.9% in the feces; 35% and 5% of the label were excreted in the urine and feces, respectively, 72 hours after dosing (Abdel-Rahman et al., 1984a). Approximately 90% of the excreted label was in the form of chloride.

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS

4.1.1. Oral Exposure

4.1.1.1. *Chlorine Dioxide*

The short-term toxicity of chlorine dioxide was assessed in two human studies conducted by Lubbers and associates (Lubbers et al., 1981, 1982, 1984a; Bianchine et al., 1981). In the first study (Lubbers et al., 1981; also published as Lubbers et al., 1982), a group of 10 healthy male adults drank 1,000 mL (divided into two 500 mL portions, separated by 4 hours) of a 0 or 24 mg/L chlorine dioxide solution (0.34 mg/kg, assuming a 70 kg reference body weight). In the second study (Lubbers et al., 1984a), groups of 10 adult males were given 500 mL distilled water containing 0 or 5 mg/L chlorine dioxide (0.04 mg/kg-day assuming a reference body weight of 70 kg) for 12 weeks. Neither study found any physiologically relevant alterations in general health (observations and physical examination), vital signs (blood pressure, pulse rate, respiration rate, and body temperature), serum clinical chemistry parameters (including glucose, urea nitrogen, phosphorus, alkaline phosphatase, and aspartate and alanine aminotransferases), serum triiodothyronine (T3) and thyroxine (T4) levels, or hematologic parameters.

4.1.1.2. *Chlorite*

Lubbers et al. (1981, 1982, 1984a) also examined the toxicity of chlorite in normal healthy adults in studies that were run concurrently with the chlorine dioxide studies. In the single exposure study (Lubbers et al., 1981, 1982), 10 male adults consumed two 500 mL (separated by 4 hours) solutions containing 2.4 mg/L chlorite (0.034 mg/kg assuming a reference body weight of 70 kg). In a 12-week study (Lubbers et al., 1984a), groups of 10 men drank 500 mL solutions of 0 or 5 mg/L chlorite (0.04 mg/kg-day assuming a 70 kg body weight). No physiologically relevant alterations in general health (observations and physical examination), vital signs, hematologic (including erythrocyte and total and differential leukocyte counts, hemoglobin, hematocrit, and methemoglobin) or serum clinical chemistry (including glucose, electrolytes, calcium, urea nitrogen, enzyme levels, and cholesterol) parameters, or serum T3 or T4 levels were found in either study.

In a companion study, three healthy glucose-6-phosphate dehydrogenase deficient male subjects were given deionized water containing 5 mg/L chlorite (0.04 mg/kg-day assuming a reference body weight of 70 kg) for 12 weeks (Lubbers et al., 1984b). Compared with the

control group in Lubbers et al. (1984a), the chlorite exposure did not alter general health, vital signs, hematologic parameters (including erythrocyte and total and differential leukocyte counts, hemoglobin, hematocrit, and methemoglobin) or serum clinical chemistry (including glucose, electrolytes, calcium, urea nitrogen, enzyme levels, and cholesterol) parameters.

4.1.1.3. *Chlorine Dioxide–Disinfected Water*

Michael et al. (1981), Tuthill et al. (1982), and Kanitz et al. (1996) have examined communities with chlorine dioxide disinfected water. The focus of the Tuthill et al. (1982) and Kanitz et al. (1996) studies was developmental toxicity. Michael et al. (1981) measured hematologic (erythrocyte, leukocyte, and reticulocyte counts, hemoglobin and methemoglobin levels, hematocrit, mean corpuscular volume, and osmotic fragility) and serum chemistry (blood urea nitrogen and total bilirubin levels) parameters in 198 individuals 1 week before the community initiated the chlorine dioxide water treatment program and 10 weeks after initiation. Blood samples were collected at the same times from a control group of 118 individuals not exposed to chlorine dioxide–treated drinking water. The water treatment facility operated only 8 hours/day; water was drawn from storage tanks for the rest of the day. Chlorine dioxide rapidly disappeared from the stored water (within 2–4 hours), and chlorite levels concomitantly increased. Weekly average concentrations (presumably measured during plant operation hours) of chlorine dioxide ranged from 0.25 to 1.11 ppm, and chlorite concentrations ranged from 3.19 to 6.96 ppm (daily mean chlorite concentration was 5.21 ppm). Using measured water consumption rates (1.98 L/day), the study authors estimated that daily chlorite intakes ranged from 0 to 39.4 mg/day (0–0.56 mg/kg-day assuming a 70 kg reference body weight); the mean intake was 10.3 mg/day (0.15 mg/kg-day). The difference between pre- and posttreatment blood urea nitrogen levels was lower in the community with chlorine dioxide–disinfected water than in the control community. However, the study authors noted that this difference was probably because mild dehydration had occurred in the control community, the postinitiation sample was taken during extremely hot weather, and more individuals in the control group had active, outdoor jobs. No other hematologic or serum chemistry alterations were found.

Tuthill et al. (1982) retrospectively compared infant morbidity and mortality data for a community that had utilized "high" levels of chlorine dioxide as a drinking water disinfectant in the 1940s with data of a neighboring community using conventional drinking water chlorination practices. The authors reported average monthly levels of 0.32 ppm of sodium chlorite added post-treatment, but they did not report chlorine dioxide levels in the treated water. Exposure to chlorine dioxide–treated water did not adversely affect fetal, neonatal, postneonatal, or infant mortality, nor did it affect birthweight, sex ratio, or birth condition. Incidence of newborns judged premature by physician assessment was significantly higher in the community with chlorine dioxide–treated water. In reviewing this study, EPA (1994d) concluded there was no increase in the proportion of premature infants when the age of the mother was controlled and that there was a greater postnatal weight loss in infants from the exposed community.

Kanitz et al. (1996) followed 548 births at Galliera Hospital, Genoa, and 128 births at Chiavari Hospital, Chiavari, Italy, during 1988–1989. Data on infant birthweight, body length, cranial circumference, and neonatal jaundice and on maternal age, smoking, alcohol

consumption, education, and preterm delivery were collected from hospital records. Women in Genoa were exposed to filtered water disinfected with chlorine dioxide, sodium hypochlorite, or both; trihalomethane levels varied from 8 to 16 ppb in sodium hypochlorite-treated water and 1 to 3 ppb in chlorine dioxide–disinfected water. 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. Women residing in Chiavari used water pumped from wells, without any disinfection treatment, and served as the comparison group (controls). Odds ratios were determined for the somatic parameters by comparison of groups exposed to chlorine dioxide, sodium hypochlorite, or both with controls and adjusted for maternal education level, income, age, and smoking and for sex of the child. Neonatal jaundice occurred more frequently (odds ratio [OR] = 1.7; 95% confidence interval [CI] = 1.1–3.1) in infants whose mothers resided in the area where surface water was disinfected with chlorine dioxide, when compared with infants with mothers using nondisinfected well water. Infants born to mothers residing in areas where surface water was disinfected had smaller cranial circumference (# 35 cm) (OR = 2.2, 95% CI = 1.4–3.9 for chlorine dioxide; OR = 3.5, 95% CI = 2.1–8.5 for sodium hypochlorite vs. untreated well water; OR = 2.4, 95% CI = 1.6–5.3 for both vs. untreated well water). In addition, these infants had a smaller body length (# 49.5 cm) (OR = 2.0, 95% CI = 1.2–3.3 for chlorine dioxide vs. untreated well water; OR = 2.3, 95% CI = 1.3–4.2 for sodium hypochlorite vs. untreated well water). Risks for low-birthweight infants (# 2,500 g) were reported to be increased in mothers residing in areas using water disinfected with chlorite and chlorine dioxide, but these associations were not statistically significant. For preterm delivery (# 37 weeks), small but not statistically significant increased risks were found among mothers residing in the area using chlorine dioxide. The study 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 # 35 cm, and body length # 49.5 cm.

Interpretability of the results of Kanitz et al. (1996) is limited by lack of consideration of exposure and potential confounding variables such as quantity of water consumed during pregnancy, lack of quantitative exposure information, exposure to other chemicals in the water, and nutritional and smoking habits and age distribution of the women. In addition, baseline values for the infant sex ratio and percentage of low-weight births for the comparison group deviate from values presented by the World Health Organization for Italy. For example, the sex ratio (male/female live births * 100) used in the study for the comparison group was 86, but most recent data (for 1996, as cited in WHO, 2000) for Italy indicate a sex ratio value of 113. Although the percentage of low-weight births in the control group for the Kanitz et al. (1996) study was 0.8%, the percentage of low-weight births (< 2,500 g) in Italy for 1994 is 6%. The quality of the untreated well water is not known (i.e., whether it contained any chemical or biological contaminants). The atypical baseline data raise concerns about the control population selected for this study and render any comparison to them by the exposed group difficult to interpret, thereby precluding the ability to draw conclusions (Selevan, 1997).

4.1.2. Inhalation Exposure

4.1.2.1. *Chlorine Dioxide*

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/m^3) for an unspecified amount of time; another worker exposed at the same time survived. Elkins also stated that 5 ppm (14 mg/m^3) 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 subjects showed chronic inflammation in one subject. The average inflammation grading was statistically higher in the subjects 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 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 (1957) 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 discomfort (breathlessness, wheezing, irritant cough) and ocular discomfort (conjunctivitis and “halo phenomena”) connected with these leakage exposures. A slight, nonspecific chronic bronchitis was diagnosed in 7 of the 12 men. An earlier-observed bronchitis disappeared in one case, suggesting to the study authors that improved working conditions might entail reversal of this disorder.

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 (length of employment not reported) at a pulp mill, 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 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 workers 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 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 237 workers at a rail maintenance yard. Personal time-weighed 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, the prevalence of wheezing and missed work because of chest illness was higher than in the pulp mill workers not reporting gassing incidents. Additionally, the incidence of airflow obstruction (as 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.

4.1.2.2. *Chlorite*

No human inhalation exposure data for chlorite were located.

4.2. PRECHRONIC AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

4.2.1. Oral Exposure

4.2.1.1. *Chlorine Dioxide*

Although the subchronic/chronic toxicity of chlorine dioxide has been investigated in a number of studies, only Daniel et al. (1990) and Haag (1949) examined a wide range of endpoints. The other studies (Bercz et al., 1982; Abdel-Rahman et al., 1984b; Couri and Abdel-Rahman, 1980; Moore and Calabrese, 1982) focused on the hematologic system. To date, no studies have examined the carcinogenic potential of chlorine dioxide.

Daniel et al. (1990) exposed groups of 10 male and 10 female Sprague-Dawley rats to chlorine dioxide in drinking water for 90 days at concentrations of 0, 25, 50, 100, or 200 mg/L. These concentrations correspond to administered doses of 0, 2, 4, 6, or 12 mg/kg-day chlorine dioxide for males and 0, 2, 5, 8, or 15 mg/kg-day chlorine dioxide for females (calculated by the study authors using water consumption and body weight data). No exposure-related deaths were reported. Exposure to 200 mg/L resulted in significant reductions in terminal body weights and body weight gain (26%–29% lower than controls). Significant reductions in water consumption were observed in the males exposed to $ 50 mg/L and in females exposed to $ 25 mg/L; decreases in food consumption were also observed in the 200 mg/L males. Absolute liver weights were decreased in males at $ 50 mg/L, and absolute spleen weights were decreased in females at $ 25 mg/L. No consistent alterations in hematologic parameters (erythrocyte and total and differential leukocyte counts, hemoglobin levels, hematocrit, and mean corpuscular volume measured) were observed. Serum lactate dehydrogenase and aspartate aminotransferase levels were decreased and serum creatinine levels were increased in the males exposed to 100 or 200 mg/L; no other alterations in serum chemistry parameters were consistently found. A significant increase in incidence of nasal lesions (goblet cell hyperplasia and inflammation of nasal turbinates) was found in males exposed to $ 25 mg/L and in females at $100 mg/L. The study authors postulated that these lesions were likely caused by 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, 25 mg/L (2 mg/kg-day) can be described as a lowest-observed-adverse-effect level (LOAEL), but the toxicological significance of the nasal lesions is not known. Respiratory tract pathologies have not been reported in other oral studies and the effect may possibly be an artifact of treatment.

In a chronic toxicity study by Haag (1949), groups of seven male and seven female rats were exposed 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 as calculated by U.S. EPA, 1994d) for 2 years. Survival in the 100 mg/L group was significantly decreased. No chlorine dioxide-related alterations were observed in the histopathologic examination of representative animals (2–6/sex) from each group. Thus, a no-observed-adverse-effect level (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.

The Bercz et al. (1982) study used a rising-dose design in which each animal served as its own control. Five male and seven female adult African green monkeys (*Cercopithecus aethiops*) were exposed to 0, 30, 100, and 200 mg/L chlorine dioxide for 4–6 weeks. The study authors estimated chlorine dioxide administered doses to be 3.5 and 9.5 mg/kg-day in the 30 and 100 mg/L groups, respectively. Exposure to 200 mg/L resulted in erythema and ulceration of the oral mucosa, mucous nasal discharge, and avoidance of drinking water; exposure to 200 mg/L was terminated after 1 week because some of the animals showed signs of dehydration. No significant alterations in hematologic clinical chemistry (erythrocyte, total and differential leukocyte, and reticulocyte counts, hemoglobin levels, hematocrit, osmotic fragility, and methemoglobin levels) or serum clinical chemistry (creatinine, blood urea nitrogen [BUN], alkaline phosphatase, lactate dehydrogenase, and alanine and aspartate aminotransferase) parameters or body weight gain were observed. Serum T4 levels were significantly decreased in

the 100 mg/L chlorine dioxide-exposed monkeys after 6 weeks of exposure. Thus, this study identifies a NOAEL of 30 mg/L (3.5 mg/kg-day) and a LOAEL of 100 mg/L (9.5 mg/kg-day) for alterations in thyroid hormone levels in monkeys exposed to chlorine dioxide in the drinking water for 4–6 weeks.

Abdel-Rahman et al. (1984b) exposed groups of four male Sprague-Dawley rats to 0, 1, 10, 100, or 1,000 mg/L chlorine dioxide in the drinking water 20 hours/day for 11 months (doses of 0.10, 1, 10, and 100 mg/kg-day are estimated using a reference body weight of 0.523 kg and reference water intake of 0.062 L/day and adjusting for intermittent exposure). Significant reductions in body weight gain were observed in the 1,000 mg/L group at 2, 5, 7, 10, and 11 months and in all groups during months 10 and 11. A number of statistically significant hematologic alterations were observed; however, the magnitude of the alterations does not appear to be dose related. Osmotic fragility was decreased in the 100 and 1,000 mg/L groups after 2, 4, 7, or 9 months of exposure and in the 10 mg/L group only after 9 months of exposure. Erythrocyte counts were decreased in the 1 and 1,000 mg/L groups after 9 months of exposure, but not after 7 months. Reduced hematocrit and hemoglobin levels were observed in all groups at 9 months; hematocrit levels were significantly increased the 100 and 1,000 mg/L groups at 7 months. Mean corpuscular hemoglobin concentrations were increased in the 100 and 1,000 mg/L groups after 9 months. Blood glutathione levels were significantly reduced in the 1, 10, and 1,000 mg/L groups at 2 months; the 1 and 10 mg/L groups after 4 months; the 1 mg/L group after 7 months; and the 100 mg/L group after 9 months. DNA synthesis (assessed using ^{3}H-thymidine incorporation) was significantly reduced in the kidneys of rats exposed to 100 mg/L, decreased in the testes of rats in the 10 and 100 mg/L groups, and increased in the intestinal mucosa of rats exposed to 10 or 100 mg/L chlorine dioxide; thymidine incorporation was not significantly altered in the liver. The lack of a consistent relationship between dose and hematologic alterations and the small number of animals (four males/group) confound interpretation of the study.

Couri and Abdel-Rahman (1980) found significant increases in blood glutathione reductase levels in Sprague-Dawley rats (four males/group) exposed to 10, 100, or 1,000 mg/L chlorine dioxide in drinking water 20 hours/day, 7 days/week for up to 1 year (0, 0.1, 1, 10, or 100 mg/kg-day using reference body weights and drinking water intakes of 0.523 kg and 0.062 L/day, respectively, and adjusting for intermittent exposure). After 12 months of exposure, the erythrocyte glutathione reductase levels in rats exposed to 1, 10, 100, or 1,000 mg/L were similar to those of controls, but the levels of erythrocyte glutathione peroxidase were significantly increased at 100 and 1,000 mg/L. Erythrocyte glutathione concentrations were significantly decreased at 1, 10, and 100 mg/L after 6 months and at 1,000 mg/L after 12 months of exposure. Erythrocyte catalase levels were increased in the 1,000 mg/L group after 6 and 12 months of exposure and decreased in the 1 and 10 mg/L groups after 6 months of exposure.

In similarly exposed Swiss Webster mice (six males/group) (estimated doses of 0.18, 1.8, 18, and 180 mg/kg-day [as calculated by U.S. EPA, 1994d] for 1, 10, 100, and 1,000 mg/L chlorine dioxide, respectively, drinking water concentrations), glutathione peroxidase levels were decreased at 100 mg/L and increased at 1,000 mg/L after 12 months of exposure, and glutathione levels were decreased at 10 and 100 mg/L after 12 months (Couri and Abdel-Rahman, 1980).

Catalase levels were increased in the 10, 100, and 1,000 mg/L groups after 12 months of exposure. As with the Abdel-Rahman et al. (1984b) study, the inconsistent relationship between the dose and the magnitude of the alterations in the glutathione-dependent system makes interpretation of the results of this study difficult; additionally, it is not clear if these effects are biologically significant, precluding determination of a NOAEL and LOAEL for these studies.

Moore and Calabrese (1982) exposed groups of 10 A/J or C57L/J mice (sex not specified) to 0 or 100 ppm chlorine dioxide in drinking water for 30 days (0 or 19 mg/kg-day using a reference body weight of 0.0316 kg and water intake of 0.0078 L/day). No significant alterations in hematologic parameters (complete blood count, reticulocyte count, glucose-6-phosphate activity, and osmotic fragility) were observed in either mouse strain.

4.2.1.2. *Chlorite*

The database for chlorite subchronic/chronic systemic toxicity consists of the Harrington et al. (1995a) subchronic study, the Haag (1949) chronic study, and the Bercz et al. (1982), Abdel-Rahman et al. (1984b), Couri and Abdel-Rahman (1980), and Moore and Calabrese (1982) studies, which examined a limited number of endpoints. Kurokawa et al. (1986) is the only study that examined the carcinogenic potential of ingested chlorite.

Harrington et al. (1995a) administered doses of 0, 10, 25, or 80 mg/kg-day sodium chlorite (equivalent to 0, 7.4, 19, or 60 mg chlorite/kg-day, respectively) via gavage to Crl:CD (SD) BR rats (15/sex/group) for 13 weeks. In the 60 mg/kg-day group, four animals died during treatment and both sexes exhibited salivation, significantly decreased erythrocyte counts, and decreased total serum protein levels. The males receiving 60 mg/kg-day exhibited significantly decreased hematocrit and hemoglobin levels and increased methemoglobin and neutrophil levels, whereas in the females, methemoglobin levels were significantly decreased. Possible reasons for the decrease in methemoglobin in females, which is unexpected considering the known oxidative effects of sodium chlorite, were not discussed by the study authors. The following observations were also noted in the 60 mg/kg-day group: morphological changes in erythrocytes in some animals of both sexes, significant increases in relative adrenal and spleen weights in the males, increases in absolute and relative spleen and adrenal weight in females, and increases in relative liver and kidney weights in the females. Body weight and food consumption were not affected by treatment. Histopathologic alterations in the 60 mg/kg-day group included squamous epithelial hyperplasia, hyperkeratosis, ulceration, chronic inflammation, and edema in the stomachs of seven males and eight females. At 19 mg/kg-day, the following alterations were reported: occasional salivation in two males, hematologic alterations in males (increased methemoglobin levels and neutrophil count, decreased lymphocyte count), increases in absolute and relative spleen and adrenal weights in females, and histologic alterations in the stomach of two males, similar to those seen in the high-dose group. The increase in absolute splenic weight was attributed to morphological alterations in erythrocytes, but no explanation was provided for alterations in absolute adrenal weight. The NOAEL in this study is determined to be 7.4 mg/kg-day, and the LOAEL is 19 mg/kg-day for stomach lesions and increases in spleen and adrenal weights in rats subchronically treated with sodium chlorite.

In a chronic study by Haag (1949), groups of rats (seven/sex/group) were exposed to 0, 1, 2, 4, 8, 100, or 1,000 mg/L chlorite in the drinking water (0, 0.09, 0.18, 0.35, 0.7, 9.3, or 81 mg/kg-day, as calculated by U.S. EPA, 1994d) for 2 years. 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. These effects were also observed in a group of animals administered sodium chloride at a concentration equimolar to 1,000 mg sodium chlorite/L. The study author concluded that the renal pathology was a nonspecific salt effect, but this observation does not alter the observation that concentrations of 100 mg/L or higher led to adverse effects. Based on renal effects, this study identifies a NOAEL of 8 mg/L (0.7 mg/kg-day) and a LOAEL of 100 mg/L (9.3 mg/kg-day). The study was limited because an insufficient number of animals were tested per group, pathology was conducted on a small number of animals, and it did not provide adequate evaluations of more sensitive parameters, which would have been more useful in the overall assessment of chronic toxicity.

Two similarly designed studies, by Abdel-Rahman et al. (1984b) and Couri and Abdel-Rahman (1980), tested the hematotoxicity of chlorite in rats. Groups of four male Sprague-Dawley rats were exposed to 0, 10, or 100 mg/L chlorite in drinking water 20 hours/day, 7 days/week for up to 1 year (0, 1, or 10 mg/kg-day using a reference body weight of 0.523 kg and water intake rate of 0.062 L/day) and adjusting for intermittent exposure. At all measuring periods (after 2, 5, 7, 10, and 11 months of exposure), there were significant decreases in body weight gain in the 100 mg/L group; body weight gain also was decreased in the 10 mg/L group at 10 and 11 months. The study authors do not note whether water consumption was affected. No consistent alterations in erythrocyte count, hematocrit, or hemoglobin levels were observed. Mean corpuscular hemoglobin concentration was increased at both exposure levels after 7 months of exposure, but not after 9 months. Osmotic fragility was significantly decreased at 10 and 100 mg/L after 7 and 9 months of exposure. DNA synthesis (as measured by ^{3}H-thymidine incorporation) was decreased in the liver and testes at 10 and 100 mg/L, decreased in the intestinal mucosa at 100 mg/L, and increased in the intestinal mucosa at 10 mg/L. Blood glutathione reductase activity was significantly increased at 10 and 100 mg/L after 6 months of exposure and decreased at 10 mg/L after 12 months. Blood glutathione peroxidase was not altered after 6 months of exposure, but after 12 months it was decreased in both groups. Significant decreases in blood glutathione levels were observed in both groups. Blood catalase activity was decreased after 6 months of exposure in the 10 and 100 mg/L groups and increased in the 10 mg/L groups after 12 months. The lack of a consistent dose-effect relationship, small numbers of animals, and small magnitude of effects complicate interpretation of the results.

Moore and Calabrese (1982) also examined the hematotoxicity of chlorite. In this study, groups of 11–23 A/J or C57L/J mice (sex not specified) were exposed to 0, 1, 10, or 100 ppm sodium chlorite (0, 0.75, 7.5, or 75 ppm chlorite) in drinking water for 30 days. Significant increases in mean corpuscular volume, osmotic fragility, and glucose-6-phosphate activity were observed in both strains of mice exposed to 100 ppm; no other alterations in hematologic parameters were observed. This study identifies a NOAEL of 10 ppm sodium chlorite (1.9 mg/kg-day chlorite using a reference body weight of 0.0316 kg and water intake of 0.0078 L/day)

and a LOAEL of 100 ppm sodium chlorite (19 mg/kg-day) for hematologic effects in mice exposed to chlorite in drinking water for 30 days.

Using a rising-dose study protocol, Bercz et al. (1982) examined the effects of subchronic exposure to sodium chlorite in drinking water on hematologic and serum clinical chemistry parameters. Five male and seven female adult African green monkeys (*C. aethiops*) were exposed to 0, 25, 50, 100, 200, or 400 mg/L chlorite in drinking water for 4–6 weeks; the study authors estimated the dose for the 400 mg/L group to be 58.4 mg/kg-day. Each animal served as its own control. A number of statistically significant, dose-related alterations in hematologic and serum clinical chemistry parameters were observed. These included decreases in erythrocyte levels and cell indices, increases in aspartate aminotransferase (increases were subclinical), slight decreases in hemoglobin levels, and slight increases in reticulocyte count and methemoglobin levels. The data were not presented in a manner that would allow identification of threshold doses for the hematologic alterations. Other hematologic and clinical chemistry parameters and body weight were not affected. Serum T4 levels were significantly reduced in the 400 mg/L group.

To assess the renal toxicity of sodium chlorite, 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 30, 90, or 190 days. No significant alterations in body weight gain, absolute or relative kidney weights, water consumption, or kidney histology were observed.

In an oral carcinogenicity study conducted by Kurokawa et al. (1986) (mouse data were also presented in Yokose et al., 1987), groups of male and female F344 rats and B6C3F1 mice (50/sex/species/group) were exposed to sodium chlorite in the drinking water for 85 or 80 weeks (with a 5-week recovery period) (Yokose et al., 1987). The sodium chlorite concentrations were 0, 300, or 600 ppm for rats and 0, 250, or 500 ppm for mice. Using water consumption and body weight data, the study authors estimated the doses to be 18 and 32 mg/kg-day in male rats and 28 and 41 mg/kg-day in female rats. All groups of rats were infected with the Sendai virus. No adverse effect on survival was observed in the rats. A slight dose-related decrease in body weight gain was observed (body weight gain in the high-dose group was within 10% of controls). No chlorite-related increases in tumor incidence were observed in the rats.

For mice, daily doses of 0, 48, and 95 mg sodium chlorite/kg-day (0, 36, and 71 mg chlorite/kg-day) were calculated by EPA (1994d). In the mice, there were no significant chlorite-related alterations in survival or body weight gain; increased mortality was observed in the male control group, which was attributed to severe fighting. Significant increases in liver and lung tumors were observed in the male mice. Incidence of hyperplastic nodules in the liver was significantly increased in the low- and high-dose groups relative to controls (3/35 [reported as 6/35 in Yokose et al., 1987], 14/47, 11/43, in the control, low-, and high-dose groups, respectively) and combined incidence of liver hyperplastic nodules and hepatocellular carcinoma was increased in the low-dose group (7/35, 22/47, and 17/43, respectively). Incidence of lung adenoma (0/35, 2/47, and 5/43, respectively) and combined incidence for lung adenoma and adenocarcinoma (0/35, 3/47, and 7/43, respectively) were significantly increased in the high-dose group compared with controls. The study authors noted that incidences of liver hyperplastic

nodules and lung adenomas in the treated animals were within the range of historical controls in their laboratory and in the National Toxicology Program laboratories. The high mortality in the control males because of fighting may have contributed to the low tumor incidence in the concurrent control group, making statistical comparisons between concurrent controls and treated animals difficult to interpret. In the female mice, the only significant alteration in tumor incidence was a significantly lower incidence of malignant lymphoma/leukemia in the high-dose group (7/47, 5/50, 1/50, respectively). This study is considered inadequate for assessing carcinogenicity because of the relatively short exposure duration (80 weeks) and the high incidence of early mortality in the concurrent control males from excessive fighting.

4.2.2. Inhalation Exposure

4.2.2.1. *Chlorine Dioxide*

Paulet and Desbrousses (1970) conducted four studies to investigate toxicity of inhaled chlorine dioxide in rats and rabbits (strains not specified): (1) 5 male and 5 female rats were exposed to 10 ppm chlorine dioxide (28 mg/m^3) 2 hours/day for 30 days; (2) 10 male rats, 10 female rats, and 4 rabbits were exposed to 5 ppm chlorine dioxide (14 mg/m^3) 2 hours/day for 30 days; (3) 10 male and 10 female rats were exposed to 2.5 ppm chlorine dioxide (6.9 mg/m^3) 7 hours/day for 30 days; and (4) 8 rabbits were exposed to 2.5 ppm chlorine dioxide (6.9 mg/m^3) 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 controls (statistical analysis not reported; the study authors state that the cell counts "changed very little"). Another group of rats and rabbits were 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/m^3) 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 follow-up study by Paulet and Desbrousses (1972), groups of eight Wistar rats (sex not reported) were exposed to 1 ppm chlorine dioxide (2.8 mg/m^3) 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 they 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/m^3) for respiratory effects in rats.

In a second series of 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 (14, 28, or 41 mg/m^3) for 15-minute periods two or four times/day for 1 month. Control groups were similarly exposed to room air. At 15 ppm, 1/10 and 1/15 rats exposed two or four times/day, respectively, died; body weight loss was observed in both groups. Histologic alterations observed at this exposure level included nasal and ocular inflammation and discharge, bronchitis, and catarrhous 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 that of controls. No histologic 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 hematologic parameters. This study identifies a NOAEL of 5 ppm (14 mg/m^3) and LOAEL of 10 ppm (28 mg/m^3) for lung damage following intermittent exposure for 15-minute periods, two or four times/day for 4 weeks.

Dalhamn (1957) conducted a series of inhalation studies to assess 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 [9,500 mg/m^3] in week 1, 1,100 ppm [3,000 mg/m^3] in week 2, and 800 ppm [2,200 mg/m^3] 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 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/m^3) 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/m^3) 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 also were observed. The fourth study involved exposure of groups of five rats to 0 or approximately 0.1 ppm chlorine dioxide (0.28 mg/m^3) 5 hours/day for 10 weeks (frequency of exposure not reported). No effects on body weight gain were observed and no histologic alterations were observed in the lungs, kidneys, or liver. The Dalhamn studies identified a NOAEL of 0.1 ppm (0.28 mg/m^3) in rats exposed 5 hours/day for 10 weeks and a LOAEL of 10 ppm (28 mg/m^3) for respiratory tract irritation in rats exposed 4 hours/day for approximately 2 weeks.

4.2.2.2. *Chlorite*

No animal inhalation or intratracheal installation data were located for chlorite.

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES—ORAL AND INHALATION

4.3.1. Chlorine Dioxide

Carlton et al. (1991) administered daily gavage doses of 0, 2.5, 5, or 10 mg/kg chlorine dioxide in deionized water to groups of 12 male Long-Evans rats for 56 days prior to mating and throughout the 10-day mating period. Groups of 24 female rats received the same gavage doses for 14 days prior to mating, during the mating period, and throughout gestation and lactation. No significant alterations in mortality, clinical signs, fertility rates, sperm parameters, length of gestation, prenatal deaths, mean litter size, or mean pup weights were observed. A statistically significant delay in the day of eye opening was observed in pups from the 10 mg/kg-day group, but the study authors did not consider this effect to be biologically significant because it was not dose related (16.70, 15.59, 16.26, and 15.95 days in the 0, 2.5, 5, and 10 mg/kg-day groups, respectively). No significant alterations in reproductive tract organ weights were observed in the F1 male rats. In the F1 female rats, there were statistically significant decreases in absolute and relative vagina weights in the 10 mg/kg-day group, but no differences in terminal body weights or uterine and ovarian weights. No consistent chlorine dioxide-related alterations in T3 or T4 levels were measured in the F0 male and female rats and F1 male rats (hormone levels measured on postnatal days 17, 28, and 40). This study identifies a NOAEL of 10 mg/kg-day for reproductive effects in rats receiving gavage doses of chlorine dioxide.

In a developmental toxicity study by Suh et al. (1983), groups of six to eight female Sprague-Dawley rats were administered 0, 1, 10, or 100 mg/L chlorine dioxide in the drinking water (0, 0.1, 1, and 10 mg/kg-day using a reference body weight of 0.35 kg and water intake of 0.046 L/day) for 2.5 months prior to mating with unexposed males and during gestational days 0–20; the dams were killed on gestational day 20. A slight, nonsignificant decrease in maternal body weight gain was observed in the 10 and 100 mg/L groups. There was a statistically significant trend for decreasing number of implants per litter and number of live fetuses per dam. Total fetal weights and male fetal weights were significantly increased in the 100 mg/L group compared with controls; crown-rump length was not significantly affected. Incidences of skeletal anomalies did not significantly differ between groups. This study identifies a NOAEL of 10 mg/L (1 mg/kg-day) and LOAEL of 100 ppm (10 mg/kg-day) for developmental effects in the offspring of rats exposed to chlorine dioxide in the drinking water.

Toth et al. (1990) examined the neurodevelopmental toxicity of chlorine dioxide in the postnatally exposed Long-Evans hooded rats. Groups of four male and four female pups per litter received daily gavage doses of 0 or 14 mg/kg chlorine dioxide on postnatal days 1–20. The chlorine dioxide pups weighed significantly less than controls at ages 11, 21, and 35 days. No significant alterations in cerebellum or olfactory bulb weights were observed on postnatal days 11, 21, or 35. Forebrain weights were significantly lower in the chlorine dioxide-exposed pups on postnatal days 21 and 35. This reduction in forebrain weight was accompanied by reductions

in protein content on postnatal days 21 and 35 and reduced DNA content on postnatal day 35. The ratio of protein content to forebrain weight was decreased on postnatal days 11, 21, and 35; the protein content to cerebellum weight was increased on postnatal day 35. The ratio of DNA content to brain part weight was not significantly affected in the chlorine dioxide-exposed pups. No alterations in counts of branches of apical dendrites of cerebral cortical layer 5 pyramidal cells were observed, but dendritic spine counts in the Krieg's area 18 (a visual association region of the cortex) were 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 in the brains of chlorine dioxide-exposed pups. No significant alterations in T3 or T4 levels or free T4 index were observed on postnatal days 11, 21, and 35. This study identifies a LOAEL of 14 mg/kg-day for altered brain development (decreased forebrain weight and protein content) in postnatally exposed rats.

Mobley et al. (1990) exposed groups of 12 female Sprague-Dawley rats to 0 or 100 ppm chlorine dioxide in the drinking water (0 or 14 mg/kg-day using a reference body weight of 0.35 kg and water intake of 0.046 L/day) for 10 days prior to mating with unexposed males and during the gestation and lactation periods (until postconception days 35–42). No significant alterations in litter size were observed. At birth, the litter weight of the chlorine dioxide-exposed group was significantly lower than that of controls. Chlorine dioxide exposure significantly decreased exploratory activity on postconception days 36–39, but not on days 39–41. Although serum T3 and T4 levels were not significantly altered in the chlorine dioxide-exposed pups (assessed on postconception days 37 and 38), a significant decrease in T3 uptake was observed. Free T3 and T4 levels were lower in the chlorine dioxide group, but the difference was not statistically significant. On postconception day 42, there were no significant alterations in total T3 or T4, free T4, or T3 uptake. The day of eye opening was not significantly affected by chlorine dioxide exposure. Thus, 100 ppm (14 mg/kg-day) is a LOAEL for decreased litter weight and exploratory activity.

In a study conducted by Orme et al. (1985) designed to assess toxicity of chlorine dioxide on the thyroid, groups of female Sprague-Dawley rats were exposed to 0, 2, 20, or 100 mg/L in the drinking water (doses of 0, 1, 3, and 14 mg/kg-day were estimated by U.S. EPA, 1994d) for 2 weeks prior to mating and throughout gestation and lactation. In a companion study, groups of 5-day-old Sprague-Dawley pups (dams were not exposed) received gavage doses of 0 or 14 mg/kg-day chlorine dioxide on postnatal days 5–20. No significant alterations in pup weight were observed in the pups exposed in utero; the postnatally exposed pups weighed significantly less than controls on postnatal days 14–21. Age of eye opening was not affected by chlorine dioxide exposure. Locomotor activity was consistently decreased in the 100 mg/L group, but the decrease was not statistically significant. In the 14 mg/kg-day gavaged group, activity was significantly decreased on postnatal days 18–19; on days 15–17 and 20, activity levels were similar to controls. In the 100 mg/L group, there was a significant decrease in T3 and T4 levels; T4 levels were also significantly decreased in the 14 mg/kg-day group. In all groups, there was a significant correlation between T4 levels and locomotor activity. T4 levels were not significantly altered in the chlorine dioxide–exposed dams. This study identifies a NOAEL of 20 mg/L (3 mg/kg-day) and a LOAEL of 100 mg/L (14 mg/kg-day) for neurobehavioral effects (decreased

T3 and T4 levels and delayed development) in the offspring of rats exposed to chlorine dioxide in drinking water.

Taylor and Pfohl (1985) exposed groups of 13–16 female Sprague-Dawley rats to 0 or 100 ppm chlorine dioxide in drinking water (0 or 14 mg/kg-day calculated using a reference body weight of 0.35 kg and water intake of 0.046 L/day) for 14 days prior to breeding and throughout gestation and lactation. Groups of male pups from unexposed dams were administered 0 or 14 mg/kg chlorine dioxide via gavage from postnatal days 5 to 20. No significant alterations in maternal or pup body weights were observed in the group receiving 100 ppm in the drinking water. A significant decrease in whole brain weight, primarily because of a decrease in cerebellar weight, was observed in the 21-day-old offspring of dams receiving 100 ppm in the drinking water. A decrease in cerebellar total DNA content also was observed; the difference was caused by a decrease in total number of cells rather than in cell density. A nonsignificant decrease in locomotor activity (assessed at 10–20 days of age) was observed in the 100 ppm offspring. A significant decrease in exploratory behavior was observed in the 100 ppm offspring at 60 days of age. In the pups receiving gavage doses of chlorine dioxide, significant decreases in body weight, absolute and relative whole brain and forebrain weights, and forebrain DNA content and total cell number were observed in the 21-day-old pups; cerebellum and forebrain DNA content and total cell number were also significantly decreased in the 11-day-old pups. Significant decreases in home cage and wheel-running activity at ages 18–19 and 10 days, respectively, also were observed in the pups receiving gavage doses of chlorine dioxide. Thus, the LOAEL for neurobehavioral effects, decreased brain weight, and cell number in the offspring of rats exposed to chlorine dioxide in drinking water and in rats postnatally exposed to chlorine dioxide via gavage is 14 mg/kg-day.

4.3.2. Chlorite

The Chemical Manufacturers Association (CMA) conducted a two-generation study to examine reproductive, developmental neurotoxicity, and hematologic endpoints in rats exposed to sodium chlorite (CMA, 1996). Thirty male and 30 female Sprague-Dawley rats of the OFA(SD)IOPS-Caw strain (F0) generation received drinking water containing 35, 70, or 300 ppm sodium chlorite (concentrations of sodium chlorite in the drinking water were apparently adjusted to compensate for the 81.4% purity of the test material) for 10 weeks and were then paired (1M:1F) for mating. A similar group received purified water and served as controls. 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. Sodium chlorite concentrations were adjusted downward during lactation to offset increases in the volume of water consumed so that a constant intake (mg/kg-day) could be maintained. 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 F2a generation. Because of a reduced number of litters in the 70 ppm F1-F2a generation, the F1 animals were remated following weaning of the F2a to produce the F2b generation. Pregnant F1 females were allowed to litter and rear the F2a and F2b generations until weaning at postnatal day 21. Based on sodium chlorite intake (in mg/kg-day) calculated by

the study authors from measured water consumption and body weight, and adjusting for the molecular weight of sodium in sodium chlorite, doses for the F0 animals were 0, 3, 5.6, and 20 and 0, 3.8, 7.5, and 28.6 mg/kg-day chlorite for males and females, respectively. For the F1 animals, doses were 0, 2.9, 5.9, and 22.7 mg/kg-day chlorite for the males and 0, 3.8, 7.9, and 28.6 mg/kg-day chlorite for the females. Numerous parameters were measured or calculated, including body weight, food and water consumption, estrus cycle in the F0 and F1 rats, and hematology and T3 and T4 levels in the F1 rats (blood samples collected from 1 male and 1 female from the first 20 F1 litters at age 25 days and another group at 13 weeks). Other parameters measured were gestation duration, litter size, pup sex, pup body weight, pup developmental landmarks, number alive/dead pups in the F1 and F2 generations, total caudal sperm number and percent motile, morphology by computer-assisted sperm motility analysis in the F0 and F1 rats, and organ weight and histopathologic examination of the brain, pituitary gland, liver, adrenal gland, 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 postnatal day 11 (examination of the brain and spinal cord) or postnatal day 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 postnatal day 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 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.

There were reductions in water consumption, food consumption, and body weight gain in both sexes in all generations at various times throughout the experiment (e.g., during premating, pregnancy, gestation, postweaning), 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 reduced 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 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, alteration in clinical condition in F2 animals chosen for neurotoxicity, decrease in absolute brain weight for F1 males and F2 females, delay in sexual development in males (preputial separation) and females (vaginal opening) in F1 and F2 rats, and lower red blood cell parameters in F1 rats. The reported alterations in pup sexual maturation measures might 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. Minor, statistically significant changes in hematologic data at the 35 and 70 ppm concentrations (generally 1%–7%) in the F1 rats appear to be within normal ranges based on historical data and are therefore not considered clinically or biologically significant or adverse. In addition, a significant decrease in maximum response to an auditory startle stimulus was noted in the 70 and 300 ppm groups on postnatal day 24, but not on postnatal day 60. Analysis of the

E-maze data by EPA personnel indicated possible alterations in learning behavior in the 70 ppm group, but the differences from the conclusions of the report could not be resolved.

The CMA (1996) study is adequate in that it was conducted with sufficient numbers of animals of both sexes and examined numerous endpoints. The study is acceptable and consistent with EPA testing guidelines that were in effect at the time of the study (U.S. EPA, 1991). However, there are several limitations to this study. Lack of pair-watered and pair-fed control animals confounds the results and precludes definitive conclusions as to whether the alterations in food and water consumption and body weight are related to water palatability or a direct toxic effect of the agent. Developmental landmarks (e.g., vaginal opening in F2a group) were not reported for all groups. Grip strength and landing foot splay were not included in the FOB. 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. Although the study employed an exposure regimen consistent with testing guidelines and should potentially detect adverse effects on the developing nervous system, 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.

Interpretation of the neurobehavioral tests is limited. The report lacks detailed descriptions of experimental methods (e.g., size of the arena, length of observations) and positive control data (including estimates of variability) for the FOB. Positive control studies for the motor activity and E-maze studies used high doses of the validation chemicals, were not adequate to show the sensitivity of the methods, and showed only that effects of the chemicals at maximally toxic doses could be recognized. Variability in the startle response data was high. The high variability and problems in calibrating and operating the automated startle apparatus (as presented in the report) would tend to decrease the sensitivity of the test to detect a difference between control and treated groups, because differences in startle amplitude would have to be larger to attain statistical significance. In some cases, inappropriate statistical analyses were applied. For example, repeated-measures techniques were apparently not used to account for the fact that the rats were tested repeatedly, and it is not clear how nonparametric rank data were analyzed or why a log transformation was applied to the learning data. The NOAEL for this study is 35 ppm (2.9 mg/kg-day chlorite) and the LOAEL is 70 ppm (5.9 mg/kg-day chlorite) based on lowered auditory startle amplitude and altered liver weights in two generations.

Groups of 12 male Long-Evans rats were exposed to 0, 1, 10, or 100 ppm sodium chlorite (0, 0.7, 7, and 70 ppm chlorite) in the drinking water for 56 days prior to mating and throughout a 10-day mating period (Carlton and Smith, 1985; Carlton et al., 1985, 1987). Groups of 24 female rats were exposed to the same sodium chlorite drinking water concentrations for 14 days prior to mating, during the mating period, and throughout gestation and lactation. Doses of 0, 0.075, 0.75, and 7.5 mg/kg-day were estimated by EPA (1994d). No significant alterations in body weight gain or water consumption were observed. There was a wide degree of variability among fertility rates for the different groups (67%–96%), but no dose-related alterations in fertility rates were observed. No significant alterations in litter survival rates, median day of eye opening, or median day of observed vaginal patency were observed. Additionally, no alterations

were observed in gross and histopathologic examination of reproductive tract tissues, hematologic parameters, or testis, epididymis, and caudal epididymis weights. No significant alterations in sperm count or percentage of sperm mobility were observed. A trend toward decreased sperm mean progressive movement was observed in the 100 ppm group, but the velocity was not significantly different from controls. The percentage of abnormal sperm in sodium chlorite-exposed rats did not differ from controls. No significant alterations in T3 and T4 hormone levels were observed in the F0 males or females. T3 and T4 levels were measured in the F1 males and females on postnatal days 17 (males only), 21, and 40; significant decreases in hormone levels were consistently observed at 100 ppm at days 21 and 40. This study identifies a NOAEL of 10 ppm (0.75 mg/kg-day) and a LOAEL of 100 ppm (7.5 mg/kg-day) for altered thyroid hormone levels in the offspring of rats exposed to sodium chlorite in drinking water.

Carlton and Smith (1985) and Carlton et al. (1985, 1987) conducted two follow-up studies to further investigate the effect of sodium chlorite on sperm parameters. In these studies, groups of 12 male rats received drinking water containing 0, 100, or 500 ppm sodium chlorite (0, 70, and 370 ppm chlorite) or 0, 1, 10, or 100 ppm sodium chlorite (0, 0.7, 7, and 70 ppm chlorite) for 72–76 days. Water consumption was significantly decreased (28%) in the 500 ppm group; in other groups, water consumption was similar to that of controls. Estimated doses of 0.075, 0.75, 7.5, and 27 mg/kg-day were calculated for the 1, 10, 100, and 500 ppm groups, respectively. No significant alterations in body weight gain were observed in the sodium chlorite-exposed rats. As in the first experiment, there were no significant alterations in sperm count, percentage of sperm mobility, or mean progressive movement. However, there was a trend toward decreased progressive movement in the 100 and 500 ppm groups. When the three experiments were combined, there was a statistically significant reduction of direct progressive movement at 100 and 500 ppm. A significant increase in abnormal sperm was observed in the 100 and 500 ppm groups; the most common morphological abnormalities were frayed tails, open hooks, and amorphous sperm heads. Collectively, these studies identify a NOAEL of 10 ppm (0.75 mg/kg-day) and LOAEL of 100 ppm (7.5 mg/kg-day) for reproductive effects in rats exposed to sodium chlorite in drinking water.

Couri et al. (1982) exposed groups of 7–13 pregnant Sprague-Dawley rats to 0%, 0.1%, 0.5%, or 2% sodium chlorite (0%, 0.07%, 0.4%, and 1.5% chlorite) in the drinking water during gestational days 8–15. The litters were either delivered at term or by cesarean section on gestational day 22. Using the daily doses of 0, 34, 163, and 212 mg sodium chlorite/rat/day calculated by the study authors and an estimated body weight (midpoint of gestation day 1 body weights [0.280 kg] plus one-half of the body weight gain), doses of 0, 95, 590, and 820 mg/kg-day sodium chlorite (0, 70, 440, and 610 mg/kg-day chlorite) were calculated. Another group of four pregnant rats received daily gavage doses of 200 mg/kg sodium chlorite on gestational days 8–15. Profuse vaginal and urethral bleeding and 100% mortality were observed in the rats receiving 200 mg/kg gavage doses. No deaths were observed in the rats receiving sodium chlorite via drinking water. Weight loss and decreases in food and water consumption were observed at the 0.5% and 2% concentrations; decreased water consumption was also observed in the 0.1% group. Irregular blood cells, ruptured cells, and hemolysis were observed in the 2% and 200 mg/kg-day groups. Significant decreases in crown-rump length were observed in litters

term-delivered in the 0.1%, 0.5%, and 2% groups and in the 0.5% group cesarean-delivered on gestational day 22. Fetal weights were not adversely affected. An increase in the number of resorbed and dead fetuses was observed in litters delivered on gestational day 22 in the 0.1%, 0.5%, and 2% groups; two litters out of five were totally resorbed in the 2% group. Postnatal growth and the incidences of soft tissue and skeletal malformations were not adversely affected by in utero exposure to sodium chlorite. This study identifies a FEL of 0.1% for resorbed and dead fetuses and decreases in crown–rump length in the offspring of rats exposed to 0.1% sodium chlorite (70 mg/kg-day chlorite) in drinking water.

Groups of six to nine female Sprague-Dawley rats were administered 0, 1, or 10 mg/L chlorite in the drinking water (0, 0.1, or 1 mg/kg-day calculated using a reference body weight of 0.35 kg and water intake of 0.046 L/day) for 2.5 months prior to mating with unexposed males and during gestational days 0–20; the dams were killed on gestational day 20 (Suh et al., 1983). No significant alterations in general appearance or maternal body weight gain were observed. No significant alterations in number of implants (total and per dam), resorptions, or dead fetuses were observed. No difference in fetal body weights was observed. Crown-rump length was significantly higher in the 10 mg/L group compared with controls, but the difference was very small and is probably not biologically significant. Chlorite exposure did not significantly alter incidence of skeletal anomalies. This study identifies a NOAEL of 10 mg/L (1 mg/kg-day) for developmental toxicity in the offspring of rats exposed to chlorite in the drinking water.

Mobley et al. (1990) exposed groups of 12 female Sprague-Dawley rats to 0, 20, or 40 ppm chlorite in the drinking water (doses of 0, 3, and 6 mg/kg-day were estimated by U.S. EPA, 1994d) for 10 days prior to mating with unexposed males and during gestation and lactation until postnatal days 42–53. Chlorite exposure did not adversely affect litter size or pup weight gain. Significant, consistent decreases in exploratory activity were observed in the 40 ppm group on postnatal days 36–39, but not on days 39–41. In the 20 ppm group, there were significant decreases in activity on days 36 and 37, but not on days 38–40. No significant alterations in serum T3 or T4 levels were observed in the 37–38- or 42-day-old postconception pups. However, the free T4 levels were significantly increased in the 40 ppm group. The day of eye opening in the 20 and 40 ppm groups was similar to that of controls. A review of the results of this study relative to the findings of the newer developmental studies in the database suggests that the NOAEL for neurodevelopmental behavioral effects in rats exposed to chlorite in drinking water for this study is 20 ppm (3 mg/kg-day) and the LOAEL is 40 ppm (6 mg/kg-day).

Moore et al. (1980) (data also presented in Moore and Calabrese, 1982) exposed groups of pregnant female A/J mice to 0 or 100 ppm sodium chlorite in drinking water throughout gestation and lactation; 21 control and 12 exposed dams had litters. EPA (1994d) estimated that the 100 ppm sodium chlorite (75 ppm chlorite) concentration corresponds to a dose of 22 mg/kg-day. A decrease in the conception rate (number of females positive for vaginal plug/number of females producing litters) was observed in the chlorite group (39% vs. 56% in controls); the statistical significance was not reported. No statistically significant alterations in gestation length, litter size, number of pups dead at birth, and number of pups alive at weaning were observed. Pup growth was adversely affected, as shown by significant decreases in average pup weaning weight and birth to weaning growth rate. This study identifies a LOAEL of 100 ppm

(22 mg/kg-day) for developmental effects in the offspring of mice exposed to chlorite in the drinking water.

Harrington et al. (1995b) treated groups of 16 female New Zealand white rabbits with technical-grade sodium chlorite (80.6% purity) via their drinking water at levels of 0, 200, 600, or 1,200 ppm from gestation days 7–20, followed by terminal sacrifice at day 28. Water concentrations were maintained at the same levels throughout pregnancy and were not adjusted for changes in volume of water consumed. Based on measured water consumption, the study authors calculated a mean daily intake of approximately 0, 10, 26, or 40 mg/kg-day chlorite (corrected for purity and adjusted by the weight of the salt). Clinical condition, maternal body weight, and food and water consumption were measured daily. At necropsy, gravid uterine weights, number of corpora lutea, number of implantation sites, and live and dead fetuses were recorded. Live fetuses were weighed, examined for external abnormalities, sexed, and dissected, and a gross visceral examination was performed. Skeletal examinations were also performed. Abnormalities were categorized as minor or major, and the latter were thought to impair survival or fitness. Commonly observed variations were also recorded. The study authors did not state which malformations fell into each of these categories. There was no mortality, although two rabbits (one from each of the control and 26 mg/kg-day groups) were sacrificed in extremis because of a clinical condition unrelated to treatment. A significant decrease in water consumption during the treatment period was observed in the 26 and 40 mg/kg-day groups, and a decrease during treatment days 16–20 of pregnancy was observed in the 10 mg/kg-day group. The study authors attributed the decreases in consumption to lack of palatability of the drinking water solution, although no supporting data were presented. Food consumption was decreased in the 26 and 40 mg/kg-day groups during days 7–11 of pregnancy. Body weight gain of treated animals was decreased on days 7–19, although by day 26 these groups showed no differences from controls in body weight gain.

The authors concluded there were no treatment-related effects on pregnancy incidence, number of implantations, number of preimplantation losses, fetal sex ratio, number of live fetuses, or fetal visceral or structural abnormalities. Data for specific malformations and variations were not shown; instead, data were presented as the number or mean percentage of fetuses with major or minor external and visceral or skeletal abnormalities. The number and mean percentage of major external and visceral and skeletal abnormalities were increased in the 26 and 40 mg/kg-day groups (external/visceral: 6.6% and 2.9%, respectively, vs. 1.5% in controls; skeletal: 5.4% and 0%, respectively, vs. 0% in controls). Mean fetal weights in the 26 and 40 mg/kg-day groups were slightly decreased (< 9% relative to controls). In the 26 and 40 mg/kg-day groups, the incidence of minor skeletal abnormalities (13.9 and 14.2 for the 26 and 40 mg/kg-day groups, respectively, vs. 7.7% in controls) and skeletal variants related to incomplete fetal bone ossification (such as of the pubis and sternebrae) 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. The NOAEL for this study is 200 ppm (10 mg/kg-day chlorite) and the LOAEL is 600 ppm (26 mg/kg-day chlorite) based on decreased fetal weight and delayed skeletal ossification, decreased food and water consumption in the dams, and decreased body weight gain in the dams. Although this study employed sufficient numbers of animals and administered chlorite by a route relevant to human exposure, uncertainties exist in

interpretation of the results because of inadequate reporting of the number and types of specific abnormalities and variations. There is additional uncertainty as to whether the decreases in food and water consumption and body weight gain in the dams are caused by unpalatability or a direct toxic effect of the chlorite.

4.4. OTHER STUDIES

4.4.1. Other Carcinogenicity Studies

4.4.1.1. *Chlorine Dioxide*

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 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 postexposure. A significant increase in interfollicular epidermis thickness was observed at all time periods, with the highest values at 10 and 12 days postexposure. 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.

Miller et al. (1986) tested the carcinogenic potential of drinking water disinfected with chlorine dioxide using three short-term assays. Following disinfection with chlorine dioxide, the water samples (containing 0.5 mg/L chlorine dioxide residue) were concentrated 2,000× or 4,000× using 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 4000× concentrate in 2% emulphor 3 times/week for 2 weeks followed by topical exposure to 1.0 μg 12-tetradecanylphorbal-13-acetate (TPA) in acetone applied to the dorsal skin 3 times/week for 20 weeks and 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 2000× or 4000× 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 incidence of (-glutamyltranspeptidase foci were observed.

4.4.1.2. *Chlorite*

Kurokawa et al. (1984) also conducted dermal carcinogenicity studies. In a study to assess the ability of chlorite to act as a complete carcinogen, groups of 20 female SENCAR mice were exposed twice weekly for 51 weeks to 20 mg/mL sodium chlorite in acetone. The solution (0.2 mL; 100 mg/kg sodium chlorite per application) was applied to the shaved backs of the mice. The sodium chlorite exposure did not result in increased tumor incidence. To test the ability of chlorite to act as a tumor promoter, a single initiating dose of 20 :mol of dimethylbenzanthracene (DMBA) was applied to the skin of 20 SENCAR mice. The DMBA application was followed by a 51-week exposure to sodium chlorite (as described for the complete carcinogen study). Tumor incidence was 6/20 (30%) compared with 0/20 in mice that received DMBA followed by acetone treatments for 51 weeks. Squamous cell carcinomas were observed in 5/20 animals in the chlorite group. However, the results were not statistically significant.

4.4.2. Genotoxicity Studies

4.4.2.1. *Chlorine Dioxide*

Both positive and negative results have been found in in vitro genotoxicity studies. Chlorine dioxide did not increase chromosome aberrations in Chinese hamster fibroblast cells but did increase 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 chlorine dioxide via gavage for 5 consecutive days were negative, as was a 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) (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 chlorine dioxide.

4.4.2.2. *Chlorite*

Genotoxicity of chlorite was assessed in several in vitro and in vivo assays. In in vitro assays, chlorite induced reverse mutations in *S. typhimurium* (with activation) and chromosome aberrations in Chinese hamster fibroblast cells (Ishidate et al., 1984). In general, the results of the in vivo assays were negative. In the micronucleus assays, negative results were found in ddY mice following an oral gavage dose of 37.5–300 mg/kg chlorite single injection (Hayashi et al., 1988) and in Swiss CD-1 mice administered 0.25–1 mg chlorite via gavage for 5 consecutive days (0, 8, 20, and 40 mg/kg-day) (Meier et al., 1985). Using the same dosages, Meier et al. also reported negative results in the bone marrow chromosomal aberration assay in Swiss CD-1 mice and in the sperm-head abnormality assay in B6C3F1 mice. Positive results were found in the

micronucleus assay in ddY mice when the chlorite was administered via intraperitoneal injection (7.5–60 mg/kg) (Hayashi et al., 1988).

4.4.3. Mechanistic Studies

EPA (1994d) has extensively discussed the mechanism of action whereby chlorine dioxide and chlorite produce hematologic and systemic effects. The mechanisms are still incompletely understood. Oxidative damage to the erythrocyte and production of methemoglobin are most likely related to their properties as oxidants (U.S. EPA, 1994d). Chlorite is thought to be the intermediate species responsible in many of the hematologic effects of chlorine dioxide because of its more efficient production of methemoglobin, depletion of red blood cell (RBC) glutathione, and alteration of erythrocyte fragility.

In a series of experiments, Bercz and co-workers (1982, 1986); and Harrington et al. (1986) suggested that chlorine dioxide increases binding of dietary iodide to gastrointestinal tissue and contents, producing a functional iodide deficiency. Bercz et al. (1982) found decreased levels of circulating thyroxine in monkeys drinking water containing > 9.5 mg/kg-day chlorine dioxide, but not 44 mg/kg-day chlorite, for 4–6 weeks. In a follow-up study, Harrington et al. (1986) demonstrated increases in thyroid iodide uptake and a rebound in thyroxine levels in monkeys 1 year after an 8-week exposure to approximately 5 mg/kg-day chlorine dioxide in drinking water. Unlike monkeys, rats showed dose-related declines in thyroxine levels and no alteration in thyroid iodide uptake following an 8-week exposure to 10 mg/kg-day chlorine dioxide in drinking water.

Whether either or both of these mechanisms are operable in inducing reproductive, developmental, and neurodevelopmental effects is not known. One could also speculate that hypothyroidism, induced by chlorine dioxide alteration of iodide uptake in the gastrointestinal tract, might contribute to alterations in maternal or neonatal behavior. Alternative, as yet unknown mechanisms are also plausible because few definitive mechanistic data are available. Additional research is needed to understand whether the parent chlorine dioxide and/or its oxychlorine degradation products induce delays and alterations in fetal/neonatal neurodevelopment and behavior through disturbance in maternal thyroid function or directly within the embryo itself.

4.5. SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS AND MODE OF ACTION (IF KNOWN)—ORAL AND INHALATION

4.5.1. Oral Exposure

4.5.1.1. *Chlorine Dioxide*

The subchronic/chronic toxicity of chlorine dioxide has not been adequately assessed. The Haag (1949) chronic drinking water study reported decreases in survival in rats exposed to 13 mg/kg-day chlorine dioxide for 2 years, but the cause of death was not reported and no effects were observed at lower concentrations. The small number of animals tested and the limited

number and lack of sensitive endpoints examined make interpretation of this study difficult. Daniel et al. (1990) found increases in incidence of nasal lesions in rats exposed to $ 25 mg/L chlorine dioxide (2 mg/kg-day) in drinking water for 90 days; no other adverse effects were observed. However, it is not known if the nasal lesions resulted from inhaling chlorine dioxide vapors at the drinking water sipper tube or from off-gassing of the vapors after drinking. No other studies have reported similar effects. Other subchronic/chronic studies primarily examined hematologic parameters. Bercz et al. (1982) found significant decreases in serum T4 levels in monkeys exposed to 9.5 mg/kg-day chlorine dioxide in the drinking water for 4–6 weeks. Adverse hematologic effects could not be discerned in Abdel-Rahman et al. (1984b) because there was no consistent dose-effect relationship. Additionally, Daniel et al. (1990), Bercz et al. (1982), and Moore and Calabrese (1982) did not find hematologic alterations in rats, monkeys, or mice, respectively. Abdel-Rahman et al. (1984b) and Couri and Abdel-Rahman (1980) reported alterations in the glutathione-dependent system, in particular, decreases in erythrocyte glutathione levels, increases in glutathione peroxidase activity, and increases in erythrocyte catalase levels. However, as with the hematologic effects this group found, consistent relationships between dose and magnitude of the alterations were lacking.

A number of studies have consistently found developmental effects following in utero exposure or postnatal gavage administration of 14 mg/kg-day chlorine dioxide. The effects include altered brain development (decreases in forebrain and/or cerebellum DNA content, ratio of protein content to forebrain weight, and dendritic spine counts in a visual association area of the cerebral cortex) (Toth et al., 1990; Taylor and Pfohl, 1985), decreased locomotor or exploratory activity (Orme et al., 1985; Taylor and Pfohl, 1985), and increased T3 uptake (Mobley et al., 1990). Orme et al. (1985) found decreases in T3 and T4 levels in in utero and postnatally exposed pups; however, other studies did not find alterations in T3 and T4 levels in similarly exposed animals (Toth et al., 1990; Carlton et al., 1991).

The available data indicate that the critical effect of chlorine dioxide is neurodevelopmental toxicity.

4.5.1.2. *Chlorite*

A number of studies have examined the subchronic/chronic toxicity of chlorite; however, only the Harrington et al. (1995a) study examined a wide range of endpoints. This study identified a NOAEL and LOAEL of 7.4 and 19 mg/kg-day, respectively, for stomach lesions and alterations in spleen and adrenal weights in rats receiving gavage doses of sodium chlorite. The bolus administration of sodium chlorite might have contributed to the stomach lesions; these effects might not have been observed if the sodium chlorite had been administered in the drinking water. Haag (1949) found renal effects in rats drinking 9.3 mg/kg-day chlorite (NOAEL of 0.7 mg/kg-day); interpretation of the results of this study is limited by the small numbers of animals that underwent pathological examination and the limited number of endpoints examined. Abdel-Rahman et al. (1984b) and Couri and Abdel-Rahman (1980) found decreases in osmotic fragility, blood glutathione levels, and blood catalase activity in rats exposed to 1 and 10 mg/kg-day chlorite in drinking water. It is unclear, however, if these effects are statistically or biologically significant. In contrast, Moore et al. (1980) and Moore and Calabrese (1982) found

increases in osmotic fragility in mice exposed to 22 mg/kg-day chlorite in drinking water. Bercz et al. (1982) found decreases in erythrocyte and hemoglobin levels and decreases in T4 levels in monkeys exposed to 58.4 mg/kg-day chlorite.

As with chlorine dioxide, developmental toxicity appears to be the most sensitive effect of oral chlorite exposure. At exposure levels of 3 mg/kg-day and 6 mg/kg-day, Mobley et al. (1990) found significant decreases in exploratory activity in rat pups exposed to chlorite in utero. The changes at 3 mg/kg-day were small, whereas changes observed at 6 mg/kg-day were more consistent with findings from several other studies. Similarly, lowered auditory startle response and reduced liver weight were observed at 6 mg/kg-day, but not at 3 mg/kg-day, in rats in a two-generation study (CMA, 1996). At higher concentrations (19–28 mg/kg-day), decreases in fetal/pup body weight have been observed in mice and rabbits (Moore et al., 1980; Moore and Calabrese, 1982; Harrington et al., 1995b). Data from Carlton and Smith (1985) and Carlton et al. (1987) suggest that sperm may be a sensitive target of toxicity. Reductions in sperm progressive movement and increases in abnormal sperm have been observed in rats exposed to 7.5 mg/kg-day chlorite in drinking water for 72–76 days. However, the CMA (1996) two-generation study did not find any alterations in reproductive performance in rats exposed to 22.7 mg/kg-day chlorite in drinking water.

4.5.2. Inhalation Exposure

4.5.2.1. *Chlorine Dioxide*

Several human studies have examined the toxicity of inhaled chlorine dioxide (Gloemme and Lundgren, 1957; Elkins, 1959; Ferris et al., 1967; Exner-Freisfeld et al., 1986; Kennedy et al., 1991; Meggs et al., 1996). Despite the limitations of these studies (including poor exposure assessment, small number of subjects, and concomitant exposure to chlorine and/or sulfur dioxide), they consistently demonstrate that the respiratory tract is a very sensitive target of toxicity.

A series of studies by Paulet and Desbrousses (1970, 1972, 1974) and Dalhamn (1957) examined the acute and subchronic toxicity of chlorine dioxide in rats and rabbits. As with the human studies, the respiratory tract is the most sensitive target of toxicity. The effects include alveolar congestion and hemorrhage, bronchial inflammation, and peribronchiolar edema. A NOAEL for these effects has not been identified; the lowest LOAEL is 1 ppm (2.8 mg/m^3) in rats exposed to chlorine dioxide 5 hours/day, 5 days/week for 2 months (Paulet and Desbrousses, 1972).

4.5.2.2. *Chlorite*

No data are available on the toxicity of inhaled chlorite.

4.6. WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION—SYNTHESIS OF HUMAN, ANIMAL, AND OTHER SUPPORTING EVIDENCE, CONCLUSIONS ABOUT HUMAN CARCINOGENICITY, AND LIKELY MODE OF ACTION

4.6.1. Chlorine Dioxide

Under the current guidelines (U.S. EPA, 1986a), 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, 1996a), the human carcinogenicity of chlorine dioxide cannot be determined because no satisfactory human or animal studies assessing the chronic carcinogenic potential of chlorine dioxide were located.

No human or animal studies assessing the carcinogenic potential of chlorine dioxide were located. The carcinogenic potential of concentrates prepared from drinking water treated with chlorine dioxide was tested by Miller et al. (1986). The concentrates did not increase incidence of lung adenomas in Strain A mice, skin tumor frequency in mice, or incidence of gamma-glutamyl transpeptidase positive foci (a measure of preneoplastic changes) in rat livers. Robinson et al. (1986) found significant increases in skin thickness in SENCAR mice immersed in chlorine dioxide, suggesting that high concentrations of chlorine dioxide are capable of inducing hyperplastic responses in the mouse skin.

Both positive and negative results have been found in genotoxicity studies of chlorine dioxide. Exposure to chlorine dioxide did not induce chromosomal aberrations in vitro, but it did increase occurrence of reverse mutations (Ishidate et al., 1984). In vivo assays did not find increases in micronucleus induction, chromosomal aberrations, or sperm-head abnormalities following oral exposure (Meier et al., 1985), but they did find increases in micronuclei induction after intraperitoneal injection (Hayashi et al., 1988).

4.6.2. Chlorite

Under the current guidelines (U.S. EPA, 1986a), chlorite 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, 1996a), the human carcinogenicity of chlorite cannot be determined because of a lack of human data and limitations in animal studies.

No human studies assessing the carcinogenic potential of chlorite were located. Chlorite was tested for potential carcinogenicity in rat and mouse drinking water studies (Kurokawa et al., 1986; Yokose et al., 1987). These studies do not provide sufficient evidence to draw conclusions as to the carcinogenic potential of chlorite in humans. In the rat study (Kurokawa et al., 1986), exposure to sodium chlorite did not significantly increase the incidence of tumors. The short exposure duration (85 weeks) and high incidence of Sendai viral infection in control and exposed rats limit the use of this study to assess carcinogenicity.

In the mouse drinking water study (Kurokawa et al., 1986; Yokose et al., 1987), significant increases in liver and lung tumors were observed in male mice. Combined incidence of hepatocellular nodules and hepatocellular carcinomas was increased in the low-dose group, and combined incidence of lung adenomas and adenocarcinomas was elevated in the high-dose group relative to concurrent controls. However, these tumor incidences were within the range of values of historical controls in the study laboratory and in the National Toxicology Program laboratories (Kurokawa et al., 1986). This study is considered inadequate for assessing carcinogenicity because of the relatively short exposure duration (80 weeks) and the high incidence of early mortality in the concurrent control males from excessive fighting, making statistical comparisons between concurrent controls and treated animals difficult to interpret. No increases in tumor incidence were seen in female mice in this study.

Chlorite has been shown to be mutagenic in in vitro assays for reverse mutations and chromosome aberrations (Ishidate et al., 1984) and in an in vivo assay of micronucleus induction in which mice received an intraperitoneal injection of sodium chlorite (Hayashi et al., 1988). In vivo assays for micronucleus induction, chromosome aberrations, and sperm-head abnormalities were negative in mice receiving gavage doses of chlorite for 5 days (Meier et al., 1985; Hayashi et al., 1988).

4.7. SUSCEPTIBLE POPULATIONS

4.7.1. Possible Childhood Susceptibility

4.7.1.1. *Chlorine Dioxide and Chlorite*

Developmental delays have been observed in animal studies following in utero and postnatal exposure to ingested chlorine dioxide or chlorite, suggesting that infants and children may be more likely than adults to experience adverse effects following exposure to these chemicals, although the reasons for this increased sensitivity are not fully understood. It is well recognized that neurological development continues after birth and that gastrointestinal uptake of many nutrients and chemicals is greater in the neonate than the adult.

4.7.2. Possible Gender Differences

4.7.1.2. *Chlorine Dioxide and Chlorite*

No data are available to suggest there are gender differences in the toxicity of chlorine dioxide or chlorite.

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE (RfD)

5.1.1. Choice of Principal Study and Critical Effect—With Rationale and Justification

In general, human studies have not found adverse effects in individuals consuming low concentrations (0.04–0.15 mg/kg-day) of chlorine dioxide or chlorite in experimental studies (Lubbers et al., 1981, 1982, 1984a) or consuming drinking water disinfected with chlorine dioxide (Michael et al., 1981; Tuthill et al., 1982). An epidemiology study by Kanitz et al. (1996) found increases in the risk of several developmental effects (neonatal jaundice, small cranial circumference, and shorter body length) in a community with chlorine dioxide-disinfected drinking water. However, the Kanitz et al. (1996) study has numerous limitations (including multiple chemical exposures; lack of exposure data; lack of control for smoking, age, and nutritional habits; and atypical control data), making it difficult to interpret the study findings.

In animals, the most sensitive effect following oral exposure to chlorine dioxide or chlorite is neurodevelopmental delay. In utero exposure to chlorine dioxide or postnatal gavage administration of chlorine dioxide has resulted in altered brain development (decreases in brain weight, protein content, and cell number) (Taylor and Pfohl, 1985; Toth et al., 1990) and decreased locomotor or exploratory activity (Orme et al., 1985; Taylor and Pfohl, 1985; Mobley et al., 1990). The LOAEL for these effects is 14 mg/kg-day chlorine dioxide (Orme et al., 1985; Taylor and Pfohl, 1985; Mobley et al., 1990; Toth et al., 1980); Orme et al. (1985) identified a NOAEL of 3 mg/kg-day.

Neurobehavioral effects (lowered auditory startle amplitude, decreased brain weight, and decreased exploratory activity) are also the most sensitive endpoints following oral exposure to chlorite (Mobley et al., 1990; CMA, 1996). The LOAEL identified in the Mobley et al. (1990) developmental toxicity study and the CMA (1996) two-generation developmental toxicity study is 6 mg/kg-day chlorite; Mobley et al. (1990) also found significant decreases in exploratory activity at 3 mg/kg-day, but the difference between activity in this group and the controls was small. Thus, the NOAEL for neurobehavioral effects is 3 mg/kg-day chlorite. At higher concentrations (22–28 mg/kg-day chlorite), decreases in fetal/pup body weight have also been observed in mice and rabbits (Moore and Calabrese, 1982; Moore et al., 1980; Harrington et al., 1995b).

Chlorine dioxide in drinking water rapidly degrades to chlorite; in the Michael et al. (1981) study, chlorine dioxide rapidly disappeared from the stored water (within 2–4 hours) and chlorite levels 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., 1979b, 1982). Additionally, chloride is the major in vivo degradation product of both chlorine dioxide and chlorite. 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.

The CMA (1996) two-generation study was selected as the critical study for the development of an RfD for both chlorine dioxide and chlorite. Both in its study report (CMA 1996) and in a later journal article (Gill et al., 2000), CMA reported that the study defined a NOAEL of 70 ppm (6 mg/kg-day chlorite) and a LOAEL of 300 ppm (28.6 mg/kg-day chlorite) based on hematologic toxicity. For the reasons outlined below, EPA disagrees with CMA's choice of NOAEL and LOAEL values. Alterations in multiple endpoints define the LOAEL-NOAEL boundary in the CMA study. Effects observed included statistically significant decreases in pup body weight, absolute brain weight, liver weight, and lowered startle amplitude at the 28.6 mg/kg-day dose. Statistically significant decreases in auditory startle amplitude (F1 and F2 generations) and absolute and relative liver weights (F0 and F1) occurred at 6 mg/kg-day. Although different responses were found for auditory startle (as indicated by measures of amplitude, latency, and habituation), this is not unexpected given that these measures examine different aspects of nervous system function and thus can be differently affected. Transient alterations in neurofunctional (or neurochemical) measures, such as in the auditory startle response, can occur without neuropathological changes and are considered of neurotoxic concern (U.S. EPA, 1998a). Some of effects observed at 6 mg/kg-day and 28.6 mg/kg-day occurred in both sexes and in more than one generation. These effects are considered toxicologically significant, which is consistent with EPA guidelines for reproductive, developmental, and neurotoxicity risk assessment (U.S. EPA, 1991, 1996b, 1998a). The NOAEL for this study is 3 mg/kg-day chlorite and the LOAEL is 6 mg/kg-day chlorite based on lowered auditory startle amplitude and decreased liver weight.

Although the CMA (1996) study is adequate, having been conducted with sufficient numbers of animals of both sexes at multiple dose levels showing a range of effects, and having examined numerous endpoints, there are several limitations. Lack of pair-watered and pair-fed control animals confounds the results and precludes making definitive conclusions as to whether the alterations in food and water consumption and body weight are related to water palatability or a direct toxic effect of the agent. Discontinuation of exposure for the animals undergoing neurotoxicity testing limits the likelihood of finding a positive effect, precludes comparison of the data with those of other rats with continued exposure, and does not reflect the expected lifetime exposure by humans to these chemicals in drinking water. In addition, a lack of detailed description of experimental methods and positive control data (including estimates of variability), and in some cases inappropriate statistical analysis, limits interpretation of the neurobehavioral tests.

The principal study is supported by the developmental studies by Orme et al. (1985), Taylor and Pfohl (1985), Mobley et al. (1990), and Toth et al. (1990), wherein rats administered chlorite or chlorine dioxide at similar dosages in drinking water also showed alterations in exploratory and locomotor behavior and reduced brain weights (NOAELs of 3 mg/kg-day; LOAELs of 14 mg/kg-day).

5.1.2. Methods of Analysis—Including Models (PBPK, BMD, etc.)

The NOAEL/LOAEL approach was used to derive RfDs for chlorine dioxide and chlorite. The RfD was derived using the NOAEL of 3 mg/kg-day identified in the CMA (1996)

study. This dose was determined from the nominal water concentration based on measured water consumption and adjusted for the molecular weight of the salt, so that doses are expressed as the chlorite ion. (For example, males administered 35 ppm had intakes of sodium chlorite equivalent to 3.9 mg/kg-day. Adjusting for the molecular weight of sodium chlorite [MW = 90.5] relative to the chlorite ion [MW = 67.5] gives the NOAEL dose of 3 mg/kg-day chlorite.)

5.1.3. RfD Derivation—Including Application of Uncertainty Factors and Modifying Factors

The RfDs for chlorine dioxide and chlorite were derived by dividing the NOAEL of 3 mg/kg-day by an uncertainty factor of 100. This composite factor 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 a developmental effect 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. A default modifying factor of 1 is applied. The resultant RfD is 3×10^{-2} mg/kg-day:

$$\text{RfD} = 3 \text{ mg/kg-day} \div 100 = 3 \times 10^{-2} \text{ mg/kg-day}.$$

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

5.2.1. Choice of Principal Study and Critical Effect—With Rationale and Justification

5.2.1.1. *Chlorine Dioxide*

Human studies examining toxicity of inhaled chlorine dioxide are limited to several case reports (Elkins, 1959; Exner-Freisfeld et al., 1986; Meggs et al., 1996) and occupational exposure studies (Gloemme and Lundgren, 1957; Ferris et al., 1967; Kennedy et al., 1991) that involved concurrent exposure to chlorine and possibly sulfur dioxide. Although these studies cannot be used to establish risk assessment values, the results of these studies consistently demonstrate that the respiratory tract is a very sensitive target of chlorine dioxide toxicity.

A series of studies by Paulet and Desbrousses (1970, 1972, 1974) and Dalhamn (1957) examined the acute and subchronic toxicity of chlorine dioxide in rats and rabbits. The earliest Paulet and Desbrousses (1970) study identified a LOAEL of 2.5 ppm chlorine dioxide (6.9 mg/m^3) for thoracic effects (alveolar congestion and hemorrhage; bronchial inflammation) in rats exposed 7 hours/day (presumably 5 days/week) for 30 days and pulmonary effects (alveolar hemorrhage and capillary congestion) in rabbits exposed 4 hours/day (presumably 5 days/week) for 45 days; a NOAEL was not identified. A follow-up study by this group attempted to identify a threshold for respiratory effects (Paulet and Desbrousses, 1972). This study identified a LOAEL of 1 ppm (2.8 mg/m^3) for pulmonary effects (vascular congestion and peribronchiolar edema) in rats exposed 5 hours/day, 5 days/week for 2 months; a NOAEL was not identified. The Dalhamn (1957) study identified a NOAEL of 0.1 ppm chlorine dioxide (0.28 mg/m^3) for lung damage in rats exposed 5 hours/day (frequency of weekly exposure not reported) for 10

weeks; a LOAEL of 10 ppm (28 mg/m^3) for respiratory tract irritation was identified in rats exposed 4 hours/day for 9 days in a 13-day period.

Collectively, the results of the human and animal studies suggest that the respiratory tract is the critical target. The Paulet and Desbrousses (1970, 1972) studies were selected as cocritical studies. The 1972 study identified the lowest LOAEL for a sensitive endpoint (respiratory tract effects); however, the study duration (2 months) is shorter than the typical subchronic study (approximately 90 days) and only one exposure concentration was tested. The 1970 study is used to support the identification of the critical effect and critical concentrations; this study tested several concentrations in two species for durations of 30 or 45 days.

5.2.1.2. *Chlorite*

An RfC for chlorite is not recommended at this time. No human or animal studies examining the toxicity of inhaled chlorite were located. Although the available human and animal data on inhaled chlorine dioxide support the derivation of an RfC for this chemical, these data cannot be used to derive an RfC for chlorite. Under ambient conditions, airborne chlorite is likely to exist as a particulate, whereas inhalation exposure to chlorine dioxide is as a gas. Based on their physical and chemical properties, it is anticipated that inhaled chlorine dioxide and chlorite would have very different modes of exposure. Therefore, the potential hazards associated with exposure to these two chemicals are also very different. In the absence of data demonstrating parallels in pharmacokinetic behavior following inhalation exposure—as are available following oral exposure—derivation of an RfC for chlorite from the available data for chlorine dioxide is not recommended.

5.2.2. Methods of Analysis—NOAEL/LOAEL

5.2.2.1. *Chlorine Dioxide*

The NOAEL/LOAEL approach was used to calculate the RfC for chlorine dioxide. A benchmark concentration (BMC) analysis could not be conducted because the report of the Paulet and Desbrousses (1970, 1972) studies did not include incidence data.

The RfC was derived using the Paulet and Desbrousses (1970, 1972) studies as co-critical studies. From the LOAEL of 1 ppm for pulmonary effects in rats identified in the Paulet and Desbrousses (1972) study, concentration in mg/m^3 was calculated using a molecular weight of 67.46 and the assumption of 25°C and 760 mmHg:

$$\text{LOAEL} = 1 \text{ ppm} \times 67.46/24.45 = 2.8 \text{ mg/m}^3 \text{ (Paulet and Desbrousses, 1972 - rats).}$$

The duration-adjusted LOAEL ($\text{LOAEL}_{\text{ADJ}}$) was calculated by multiplying the LOAEL by the daily exposure duration (5 hours/day) and the weekly exposure frequency (5 days/week):

$$\text{LOAEL}_{\text{ADJ}} = 2.8 \text{ mg/m}^3 \times 5 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 0.41 \text{ mg/m}^3 \text{ (rat).}$$

The human equivalent concentration (HEC) for the LOAEL ($LOAEL_{HEC}$) was calculated by multiplying the $LOAEL_{ADJ}$ by the regional gas dose ratio for the thoracic region of the respiratory tract ($RGDR_{TH}$). The $RGDR_{TH}$ was calculated using the following equation:

$$RGDR_{TH} = \frac{\left[\frac{MV}{SA}\right]_A}{\left[\frac{MV}{SA}\right]_H}$$

where MV is the minute volume in rats (0.118 m^3/min; 0.17 m^3/day) and humans (13.8 m^3/min; 20 m^3/day) and SA is the surface area of the thoracic region in rats (3461.6 cm^2) and humans (640,581 cm^2).

$LOAEL_{HEC}$ = 0.41 mg/m^3 × [(0.118 m^3/min / 3461.6 cm^2) / (13.8 m^3/min / 640,581 cm^2);

$LOAEL_{HEC}$ = 0.41 mg/m^3 × 1.57 = 0.64 mg/m^3.

Similarly, for the Paulet and Desbrousses (1970) study, using values of 1.10 m^3/min for the minute volume and 59,100 cm^2 for the surface area of the thoracic region of rabbits, the calculation of the $LOAEL_{HEC}$ is as follows:

LOAEL = 2.5 ppm × 67.46/24.45 = 6.9 mg/m^3.

$LOAEL_{ADJ}$ = 6.9 mg/m^3 × 4 hours/24 hours × 5 days/7 days = 0.82 mg/m^3.

$LOAEL_{HEC}$ = 0.82 mg/m^3 × [(1.10 m^3/min / 59,100 cm^2) / (13.8 m^3/min / 640,581 cm^2);

$LOAEL_{HEC}$ = 0.82 mg/m^3 × 0.596 = 0.49 mg/m^3.

5.2.3. RfC Derivation—Including Application of Uncertainty Factors and Modifying Factors

5.2.3.1. *Chlorine Dioxide*

The RfC for chlorine dioxide is derived by dividing the $LOAEL_{HEC}$ thoracic effects by an uncertainty factor of 3,000. This uncertainty factor 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 uncertainty factor to 3,000 in recognition of the lack of independence of these factors (U.S. EPA, 1994b). The LOAEL to NOAEL and database uncertainties are therefore coalesced into one uncertainty factor of 10. The composite uncertainty factor for this RfC is therefore 3,000. No modifying factor is used for this assessment.

$$RfC = 0.64 \text{ mg/m}^3 \div 3{,}000 = 2 \times 10^{-4} \text{ mg/m}^3.$$

or

$$RfC = 0.49 \text{ mg/m}^3 \div 3{,}000 = 2 \times 10^{-4} \text{ mg/m}^3.$$

As can be seen, the same value for the RfC can be calculated using the LOAEL from either of the key studies. Note that this is the same value as was verified by the RfC workgroup in 1990, as no new data were available.

5.3. CANCER ASSESSMENT

5.3.1. Chlorine Dioxide

The oral and inhalation databases are inadequate to assess the carcinogenicity of chlorine dioxide in humans or animals; thus, derivation of an oral slope factor and inhalation unit risk level is precluded.

5.3.2. Chlorite

The oral and inhalation databases are inadequate to assess the carcinogenicity of chlorite in humans or animals; thus, derivation of an oral slope factor and inhalation unit risk level is precluded.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

6.1. HUMAN HAZARD POTENTIAL

Chlorine dioxide and chlorite are strong oxidizing agents used as drinking water disinfectants and to bleach textile and wood pulp for paper manufacturing. Chlorine dioxide and chlorite are rapidly absorbed from the gastrointestinal tract and slowly cleared from the blood. Chlorine dioxide and chlorite, primarily in the form of chloride, are widely distributed throughout the body and predominantly excreted in the urine. Chloride is the major urinary "metabolite" for both chlorine dioxide and chlorite. No data are available on the pharmacokinetics of inhaled or dermally applied chlorine dioxide or chlorite.

In general, human ingestion studies have found no adverse effects in adults and neonates living in areas with chlorine dioxide-disinfected water. However, these studies are fraught with methodological problems, such as lack of characterization of exposure to other agents in the drinking water and control of potential confounding factors. These studies do little to confirm a possible association between exposure to chlorine dioxide and chlorite and adverse reproductive or developmental outcome in humans. Inhalation exposure to chlorine dioxide results in

respiratory irritation in humans. However, these studies also poorly characterize exposure, and the occupational exposure studies involve concomitant exposure to chlorine and/or sulfur dioxide.

Animal toxicity databases for chlorine dioxide and chlorite is fairly comprehensive, composed of subchronic and chronic studies, reproductive and developmental studies, and toxicokinetic and mechanistic information. Multiple animal studies have shown similar alterations in neurodevelopmental endpoints, such as brain weight and behavioral measures. The majority of these studies have used sufficient numbers of animals and employed routes of exposure (gavage and drinking water) relevant to human exposure. The majority of the developmental studies have utilized rats and have shown a fairly consistent definition of the NOAEL/LOAEL.

Reproductive studies in male animals are not consistent in demonstrating alterations in spermatogenic indices, that is, abnormal morphology or motility; however, reported effects seem to appear at doses higher than the adverse developmental effects. Similarly, clinically or toxicologically significant alterations in hematologic parameters occur at higher doses.

The mode of action for induction of adverse neurodevelopmental effects is not known. It is also not known whether the rat is an adequate model for toxicity of chlorine dioxide and chlorite in humans. However, this species is widely used to characterize reproductive and developmental effects in humans.

Animal studies have demonstrated that the respiratory tract is the most sensitive target of toxicity following inhalation exposure to chlorine dioxide. No animal inhalation studies are available for chlorite.

No human studies assessing the carcinogenic potential of chlorine dioxide or chlorite were located. Chlorine dioxide carcinogenicity has not been tested in animal bioassays. Chlorite was not shown to increase tumor incidences in rats and mice; these studies are considered inadequate for assessing human carcinogenicity because the exposure was for less than a lifetime, a high incidence of Sendai virus was found in the rats, and mortality was high in the mouse control group because of excessive fighting.

Areas of scientific uncertainty in this assessment include the mode of action of chlorine dioxide and chlorite in producing adverse effects on multiple organ systems, including reproductive, developmental, and hematologic effects. Inherent in the uncertainty over the mode of action is identification of the susceptible populations or subgroups, and additional research in this area would help to better quantify the additional risk to these groups. Well-designed and conducted epidemiologic studies in communities with drinking water disinfected with these chemicals would decrease uncertainty in the utilization of animal models for determination of human health effects.

6.2. DOSE RESPONSE

Quantitative estimates of human risk as a result of low-level chronic chlorine dioxide or chlorite oral exposure are based on animal experiments, because no adequate human exposure data are available. Neurodevelopmental toxicity is the primary effect in offspring of rats exposed to chlorine dioxide or chlorite in drinking water. Quantitative estimates of human risk as a result of low-level chronic chlorine dioxide inhalation exposure are based on animal experiments, because no adequate human inhalation data are available. The respiratory tract appears to be the primary target of toxicity in human and animal studies.

The oral RfD for chlorine dioxide or chlorite is 3×10^{-2} mg/kg-day. This is 1/100 of the NOAEL, using neurodevelopmental toxicity in a two-generation rat study as the indicator of adverse effects. 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. 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.

The inhalation RfC for chlorine dioxide is 2×10^{-4} mg/m^3. This concentration is 1/3,000 of the HEC for thoracic effects in rats (Paulet and Desbrousses, 1970, 1972). No human or animal data were located for chlorite that could be used to derive an RfC. Overall confidence in the RfC for chlorine dioxide is low. The studies by Paulet and Desbrousses (1970, 1972) identify only a LOAEL in rats and rabbits for adverse lung effects in 60- and 45-day studies and lack experimental detail. There were no adequate subchronic or chronic inhalation studies that examined extrarespiratory effects, and no acceptable developmental or reproductive studies on inhaled chlorine dioxide.

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APPENDIX A. EXTERNAL PEER REVIEW— SUMMARY OF COMMENTS AND DISPOSITION

The support document and IRIS summary for chlorine dioxide and chlorite have undergone both internal peer review performed by scientists within EPA and a more formal external review performed by scientists in accordance with EPA guidance on peer review (U.S. EPA, 1994c). Comments made by the internal reviewers were addressed prior to submitting the documents for external peer review and are not part of this appendix. The external peer reviewers were tasked with providing written answers to general questions on the overall assessment and on chemical-specific questions in areas of scientific controversy or uncertainty. A summary of significant comments made by the external reviewers and EPA's response to these comments follows.

Question 1. Are you aware of any other data/studies that are relevant (i.e., useful for hazard identification or dose-response assessment) for the assessment of the adverse health effects, both cancer and noncancer, of this chemical?

Comments: Two reviewers did not find any new relevant studies that would have any impact on the conclusions of this document. Four additional references were mentioned by the two other reviewers. One reviewer concurred that the results of the EPA evaluation agree with IARC (vol. 52, 1991), and there is inadequate evidence for the carcinogenicity of sodium chlorite in experimental animals. One reviewer commented on sensitive subgroups of the population and potential effects on blood chemistry parameters in renal dialysis patients when chlorine dioxide was used as a disinfectant. Also, one reviewer suggested a statement should be made on whether chlorite can be designated as a tumor promoter based on an initiation/promotion study on mouse skin (Kurokawa et al., 1984) and if the promoting activity is related to epidermal hyperplasia induction after topical exposure to sodium chlorite.

Response to Comments: The effects of chlorine dioxide and chlorite on human subjects and blood chemistry are described in the *Drinking Water Criteria Document on Chlorine Dioxide, Chlorite, and Chlorate* (U.S. EPA, 1994d) and in this Toxicological Review. All relevant ingestion studies, including the additional studies mentioned by the reviewers, have been evaluated in the drinking water criteria document, which was used in preparing this Toxicological Review. Changes seen in the tumor promoter study on mouse skin were not statistically significant.

Question 2. For RfD, RfC, and cancer, where applicable, have the most appropriate critical effects been chosen? For the cancer assessment, are the tumors observed biologically significant?

Comments: Two reviewers reiterated that it would appear that NOAELs around 3 mg/kg-day for the neurodevelopmental and behavioral effects are the most appropriate to develop the RfD for the oral exposure route, that the selection of the Paulet and Desbrousses (1972) study

for developing the RfC for chlorine dioxide is appropriate, and also that there is still no adequate evidence for the carcinogenicity of chlorine dioxide or chlorite. Other reviewers also stated that there are inadequate cancer data for risk assessment. One reviewer commented that an independent pathology group should review the histopathology diagnoses in the CMA (1996) study.

Response to Comments: The CMA (1996) study was vigorously subjected to independent peer review at EPA and by external reviewers. It was also reviewed by the stakeholders. Additional review of the histopathology diagnoses was not performed because the most sensitive endpoints (neurofunctional effects) were not histologic in nature.

Question 3. For RfD and RfC and cancer, have the appropriate studies been chosen as principal?

Comments: The external reviewers reiterated that appropriate studies were chosen for chlorine dioxide and chlorite. One reviewer stated that actual study reports cited were not available for review; the reviewer also suggested review of additional studies for irritating effects of chlorine dioxide in humans and questioned whether humans were more sensitive than rodents to chlorine dioxide.

Response to Comments: EPA cited the suggested studies as appropriate within the text. Studies describing irritating effects of chlorine dioxide in humans are described in the text. Data on the comparative sensitivity of rodents and humans to chlorine dioxide are not available. The 10-fold uncertainty factor for animal to human extrapolation was deemed an appropriate adjustment for this data gap.

Question 4. Studies included in the RfD and RfC and cancer under the heading "Supporting/Additional Studies" are meant to lend scientific justification for the designation of critical effect by including any relevant pathogenesis in humans, any applicable mechanistic information, any evidence corroborative of the critical effects, or to establish the comprehensiveness of the data base with respect to various endpoints. Should some studies be removed?

Comments: Reviewers indicated that additional and supporting studies cited for the RfD, RfC, and cancer assessments are appropriate and that no studies should be removed. One reviewer commented that he would question the quality and utility of studies that were conducted 50 years ago when quality assurance procedures and chemical production procedures and specifications were not what they are today. One reviewer asked whether any attempts were made to obtain histopathology slides from the unpublished Haag et al. (1949) studies.

Response to Comments: EPA agrees that no additional and supporting studies should be removed from this document. EPA did not attempt to acquire the histopathology slides from the unpublished Haag et al. (1949) chronic studies of chlorine dioxide in rats since they are older studies.

Question 5. Are there other data that should be considered in developing the uncertainty factors or the modifying factor? Do you consider that the data support use of different (default) values than those proposed?

Comments: One reviewer was unaware of any additional or other data that should be considered in developing the uncertainty factors for chlorine dioxide or chlorite. One reviewer questioned whether it would be useful to review/discuss the risk analysis that supports the use of chlorine dioxide and sodium chlorite as indirect food additives or as components of consumer products such as mouthwash or toothpaste. A comment was made that the report should compare lifetime animal and human oral exposures to chlorine dioxide or chlorite on the basis of mg/kg body weight and mg/mL body surface. One reviewer commented that patients on extracorporeal hemodialysis using home equipment may be potentially exposed to 70–90 times the residues exposed by adults who merely consume the water. A question was raised on the data available to support selection of an uncertainty factor that takes into account for those individuals with deficient glucose-6-phosphate dehydrogenase activity and neonates with sluggish methemoglobin reductase activity.

Response to Comments: EPA agrees with a reviewer that additional or other data are not warranted for this risk assessment. EPA followed the customary guideline for risk assessment for development of an RfD derivation. EPA did not examine chlorine dioxide or chlorite as indirect food additives or as components of consumer products such as mouthwash or toothpaste. EPA discussed individuals with deficiency in glucose-6-phosphate dehydrogenase and methemoglobin reductase as a potential susceptible subpopulation in the drinking water criteria document (U.S. EPA, 1994d). EPA thinks that an uncertainty factor of 100 is adequate to protect this group as well as the 80,000 Americans on renal dialysis.

Question 6. Do the confidence statements and weight-of-evidence statements present a clear rationale and accurately reflect the utility of the principal study and the comprehensiveness of the data? Do these statements make sufficiently apparent all the underlying assumptions and limitations of these assessments? If not, what needs to be added?

Comments: External reviewers indicated that the confidence and weight-of-evidence statements were clearly and rationally presented. One reviewer indicated that the comprehensiveness of the data was adequately presented and the underlying assumptions and limitations of the assessments were sufficently presented. One reviewer mentioned that the confidence statements for the RfC for chlorine dioxide should indicate whether humans are more susceptible to chlorine dioxide.

Response to Comments: Adequate information is not available to determine if humans are more susceptible. EPA has applied a 10-fold uncertainty factor for extrapolation from animals to humans to address this area of uncertainty.

Question 7. Is the weight of evidence for cancer assigned at the appropriate level (where applicable)?

Comments: External reviewers indicated that cancer assessment was not applicable for chlorine dioxide and chlorite, as the data are inadequate. One reviewer commented that a statement should be made concerning the designation of sodium chlorite as a tumor promoter in mouse skin under the conditions examined in the Kurokawa et al. (1984) study.

Response to Comments: The reviewers agreed that the cancer assessment was assigned at the appropriate level. EPA does not agree that such a statement should be made as the increased tumor incidence did not attain statistical significance.