Chlorine; CASRN 7782-50-5

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

STATUS OF DATA FOR Chlorine

File First On-Line 06/01/1994

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<th>Category (section)</th>
<th>Assessment Available?</th>
<th>Last Revised</th>
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I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Chlorine
CASRN — 7782-50-5
Last Revised — 06/01/1994

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of
information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this
substance for potential human carcinogenicity, a summary of that evaluation will be contained in
Section II of this file.

I.A.1. Oral RfD Summary

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<td>LOAEL: None</td>
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<td>Rat Chronic Drinking Water Study</td>
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*Conversion Factors and Assumptions: Doses determined based on body weight and water
consumption values from the study.

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

NTP (National Toxicology Program). 1992. NTP Technical Report on the Toxicology and
Carcinogenesis Studies of Chlorinated and Chloraminated Water in F344/N Rats and B6C3F1

In a 2-year study (NTP, 1992) Fischer 344/N rats and B6C3F1 mice (70/sex/group) were
administered chlorinated drinking water containing 0, 70, 140 or 275 ppm of available chlorine
(based on IR measurements of available atomic chlorine) for up to 104 weeks. Based on body
weights and water consumption values reported in the study, these doses correspond to doses of
4.2, 7.3 and 13.6 mg/kg-day for male rats; 4.2, 7.8 and 14.4 mg/kg-day for female rats; 7.4, 14.0
and 24 mg/kg-day for male mice; and 7.6, 14.2 and 24.2 mg/kg-day for female mice. Interim
sacrifices of 10 animals/sex/dose were performed at 15 and 66 weeks. A complete necropsy and
hematologic examination was performed on all animals at these times; additionally, a complete
histopathologic examination was conducted for all animals in the control and high-dose groups.
Results from these evaluations were unremarkable for both rats and mice. All animals were
subjected to complete necropsy and a histopathologic examination at completion of the study.
Survival among treated rats and mice was similar to controls. A decrease in water consumption
noted in both rats and mice apparently was dose-related. Mean body weights of all dosed male
rat groups, high-dose female rats, high-dose male mice and all dosed female mice groups appeared decreased compared with controls; these decreases never exceeded 10%.

In rats, water consumption was decreased 21% for males and 23% for females at the highest dose from weeks 53-104. No decreases were reported in food consumption and survival rates were similar for all groups of animals (treated and controls). At interim sacrifices (14 and 66 weeks) no significant differences in body weight, organ weights or body-to-organ weight ratios were reported. No differences were reported in blood chemistry or gross or microscopic histologic parameters. In the second year of the study, body weights were slightly reduced; however, the reduction in body weights was <10%. No other nonneoplastic lesions or effects were seen at 104 weeks in any treated animals.

In mice, body weights were decreased 5-8% for males and 5-7% for females, and water consumption was reduced 31% for males and 26% for females. Survival rates were similar for all groups. Significant decreases were noted in brain weights at 15 weeks and liver weights at 66 weeks for the high-dose males. These effects were not reported at 104 weeks and may be attributed to lower body weights and reduced water consumption. No alterations were reported in hematologic or histologic parameters.

The NOAEL of 275 ppm (13.6 or 14.4 mg/kg-day for male and female rats, respectively) is chosen as the basis for the chronic oral RfD. Mice received a higher dose on a weight basis (24 mg/kg) but effects, although equivocal, were observed. Doses between 14.0 and 24.0 mg/kg were not tested in rats. In addition, this NOAEL is supported by NOAELs from other chronic and subchronic rat studies. Therefore the 14.4 mg chlorine/kg in females is selected as the basis of the RfD.

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

UF — The uncertainty factor of 100 reflects 10 for interspecies extrapolation and 10 for the protection of sensitive human subpopulations. An additional factor to account for the lack of reproductive and developmental toxicity data is not considered necessary because these data are available from existing studies conducted with the related compounds monochloramine and chlorine.

MF — None

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

NOTE: In pure water, chlorine forms elemental chlorine (Cl2), chloride ion (Cl-) and hypochlorous acid (HOCl). As pH increases, hypochlorous acid dissociates to hypochlorite ion
(OCl-). The term "free chlorine" (free available chlorine, free residual chlorine) refers to the concentrations of elemental chlorine, hypochlorous acid and hypochlorite ion that collectively occur in water. Several factors, including chlorine concentration, pH, temperature, exposure to light and the presence of catalysts or organic material, affect the stability of free chlorine in aqueous solution. When free chlorine is added to water containing ammonia, chloramines are formed. For more information about the chemistry of chlorines, see U.S. EPA, 1992.

Other chronic oral studies as well as subchronic studies evaluating additional toxicologic parameters (hematology, serum chemistry and histopathology) support the NOAEL selected for deriving the RfD. These studies reported NOAEL values ranging from 10-24 mg/kg-day.

Hasegawa et al. (1986) studied the potential adverse effects in rats of long-term exposure to sodium hypochlorite in drinking water. Sodium hypochlorite (14% effective chlorine, purity not specified) was evaluated in F344 rats (50/sex/group) in a 2-year study at levels of 0.05% or 0.1% (approximately 13.5 and 27.7 mg/kg-day) in males and 0.01% or 0.2% (approximately 34.3 and 63.2 mg/kg-day) in females. Doses were estimated based on the authors' data. No difference in water consumption was observed during the experiment (104 weeks), except in the last 20 weeks when intake was higher in treated animals (10-20%).

High mortality was reported in all groups; 62 rats died during the experimental period and an additional 49 rats died during the 8-week recovery period. Survival rates were similar in all groups and for both sexes. In treated males, body weights were decreased <10% compared with controls; decreased weights were 96 and 93% of controls for low- and high-dose groups, respectively. For females, body weights were decreased 11% in the low-dose group and 20% in the high-dose group relative to controls. However, weight gains of 1-9% were reported for all treated animals during an 8-week recovery period. In males, absolute liver and brain weights were decreased as well as absolute and relative heart weight at the high dose only. In females, absolute and relative salivary gland weights were decreased at the low dose but not at the high dose. Additionally, in females absolute kidney weights were decreased at the high dose. No dose-related changes in hematologic or histologic parameters were observed. It should be noted that the extremely high water consumption rates reported in this study appear to be inconsistent with those reported by other investigators who have reported marked reductions in water consumption at similar or lower chlorine concentrations. This inconsistency precludes use of this study as the principal study.

F344 rats (50/sex) received sodium hypochlorite in drinking water for 104 weeks at doses of 0, 500 or 1000 ppm in males and 0, 1000 or 2000 ppm in females (Kurokawa et al., 1986). These doses correspond to 0, 70 and 140 mg/kg-day for males and 0, 95 and 190 mg/kg-day for females based on reference body weight and water consumption values (U.S. EPA, 1986). Following exposure, survival, clinical signs, water consumption and body weights were monitored.
Hematologic parameters and serum biochemical analyses were evaluated, and gross necropsy and histopathologic examinations were performed. In female rats a dose-related decrease in body weight relative to controls, approximately 10% in those exposed to 95 mg/kg-day and approximately 20% in those exposed to 105 mg/kg-day, was observed. No other dose-related effects were noted. A LOAEL of 95 mg/kg-day, based on weight loss, is indicated.

Abdel-Rahman et al. (1984) investigated the toxicity of hypochlorous acid in male rats (4/dose) that received dose levels of 0, 1, 10 or 100 mg/L in drinking water for up to 12 months. These doses correspond to approximately 0, 0.14, 1.4 and 14 mg/kg-day (based on assumed daily water consumption of 0.14 L/kg-day [U.S. EPA, 1986]). Although significant increases in blood glutathione levels and decreases in osmotic fragility were reported at various intervals in the study, these changes were inconsistent and did not indicate a dose-response pattern. A NOAEL of 14 mg/kg-day is identified for this study.

Groups of B6C3F1 mice (50/sex) received sodium hypochlorite in drinking water for 103 weeks at dose levels of 0, 500 or 1000 ppm (approximately 84 and 140 mg/kg-day, based on data provided in the study) (Kurokawa et al., 1986). No statistically significant effects on survival, clinical signs, water consumption, hematologic parameters or serum chemistry were noted. However, body weight gain was reduced as compared with controls in animals receiving sodium hypochlorite.

Male and female Sprague-Dawley rats (10/sex/dose) received chlorine in drinking water at dose levels of 0, 25, 100, 175 and 250 mg/L for 90 days (Daniel et al., 1990). Calculated dose levels were 0, 2, 7.5, 12.8 and 16.7 mg/kg-day for males and 0, 3.5, 12.6, 19.5 and 24.9 mg/kg-day for females (conversion provided by the author). Food and water consumption and body weight gain were monitored and hematologic and serum chemistry examinations were conducted. Organ weights were measured and tissues examined from the high-dose group. No consistent effects were observed on any of the parameters tested up to 250 mg/L of chlorine.

Groups of B6C3F1 mice (10/sex) were administered chlorine in drinking water at 0, 12.5, 25, 50, 100 and 200 mg/L for 90 days (Daniel et al., 1991). These doses correspond to 0, 2.7, 5.1, 10.3, 19.8 and 34.4 mg/kg-day for males and 0, 2.8, 5.8, 11.7, 21.2 and 39.2 mg/kg-day for females (conversions provided by authors). Clinical signs, survival, body weight, and food and water consumption were monitored. Hematologic and clinical chemistry parameters were evaluated, and gross and histopathologic examinations were performed. A concentration-related decrease in average water consumption was observed in both males and females with statistically significant decrease in females at the two highest doses. Decreased body weight gain, compared with controls, was observed in males and females with significant reduction (>10%) in males at the two highest doses; however, no other effects were observed in any of the other parameters measured. A NOAEL of 10 mg/kg-day is identified for this study.
In general, animal studies have demonstrated no evidence of reproductive or teratogenic effects of chlorine.

Druckrey (1986) studied the effects of highly chlorinated drinking water (100 mg/L) given daily to seven consecutive generations of BD II rats. Solutions were prepared weekly by bubbling chlorine gas through tap water. To insure a stable total dietary chlorine concentration, dry rat chow was cooked with chlorinated water prior to distribution to the parental generation. Subsequent generations received chlorine only in the water and ate a standard diet, resulting in an average daily dose of approximately 10 mg/kg-day chlorine.

Parental animals began treatment at 100 days of age. Rats were repeatedly mated and remained on treatment during pregnancy and lactation. Selected progeny were separated from their dams at 30-40 days and were designated the subsequent generation. Animals of the F3 and F4 generations consumed chlorinated water only until the birth of progeny. Subsequent generations remained on chlorinated water for their entire life span. Two groups of animals served as controls at the beginning and ending of the experimental period.

Weight gain among neonates was somewhat depressed during the first few days of life. By maturity the average body weight for all generations of test animals was about 5-10% greater than that of the untreated rats. Of 236 rats observed, no treatment-related effects were noted on the life span, fertility, growth, hematologic measurements or histology of liver, spleen, kidney and other organs. The incidence of malignant tumors in the treated rats was not found to differ from that of control group rats. A NOAEL of 10 mg chlorine/kg could be identified from this study.

In a reproductive study by Carlton et al. (1986), chlorine was administered by gavage in deionized water at doses of 1.0, 2.0 and 5.0 mg chlorine/kg-day to male (12/dose group) and female (24/dose group) Long Evans rats for 66-76 days. Males were treated for 56 days and females for 14 days prior to mating. Dosing continued during the 10-day mating period and afterwards females were dosed with chlorine daily during gestation and lactation. Males were necropsied at the end of the mating period. Dams and some offspring were necropsied at 21 days after birth. Other offspring were dosed with chlorine after weaning until they were 28-40 days old. No statistical differences were observed between the control and dose group in litter survival, litter size and pup weight. Developmental landmarks such as the mean day of eye opening and the average day of observed vaginal patency also were comparable across groups. Adult male rats exposed up to 5.0 mg/kg-day showed no adverse reproductive effects. A NOAEL of 5 mg/kg-day for maternal, fetal and neonatal effects can be defined from this study.

C3H/HEJ and C57Bl/6J mice were administered drinking water that had been treated with sodium hypochlorite and hydrochloric acid (10-13 ppm) to maintain the water at pH 2.5 over a 6-
month trial period (Les, 1968). Control animals received tap water, which varied in pH from 9.2-9.8, but was usually 9.6. In the treated animals, the number of mice born and the number weaned/dam were greater than in the control (p<0.01). The authors concluded that the treatment of C3H/HEJ and C57Bl/6J mice with chlorine and hydrochloric acid had no adverse effects on their reproductive performance.

McKinney et al. (1976) noted a periodic increase in reproductive failure among CD-1 mice. Mating, number of embryos per fertile female and embryonic development were affected. The effect was seasonal and was most severe in the winter. In the absence of any other observed variations in the animal husbandry, the authors attributed the reproductive deficiencies to the heavily chlorinated Durham, NC, city water consumed by the mice.

Two attempts were made to repeat the observations reported by McKinney et al. (1976). Chernoff et al. (1979) found no significant difference in the reproductive parameters of CD-1 mice consuming Durham, NC, drinking water as compared with the control group maintained on distilled water. The animals were maintained on the test or control water for a 2-week period after which mating was begun. Dams were sacrificed on day 18 of gestation. Exposure was continued throughout the course of the study (December-September). Dams were analyzed for differences in numbers inseminated, number pregnant, weight gain during gestation, organ weight and percent resorption. Fetuses were examined for skeletal and visceral anomalies as well as mortality and body weight. No statistically significant maternal or fetal effects were noted, except for a 28.1% incidence of supernumerary ribs in the group consuming tap water compared with 21.1% in the control group consuming distilled water (p<0.05).

In a second study, Staples et al. (1979) reported no significant overall influence on the incidence of malformed fetuses (skeletal or visceral malformations) that could be attributed to the chlorination of drinking water. The incidence of malformations in the controls was 8.1% compared with 7.8% in treated animals. Differences pointed in the opposite direction of the finding of McKinney et al. (1976). Two significant effects occurred in the month of January, and one occurred in the month of February. In January, a lower number of mated females CD-1 became pregnant, and the average number of implants/pregnant females was lower in the group consuming purified water. In February, the average fetal weight was lower in the purified-water group than in the tap-water group. Indeed, the presence of chlorine in the water seemed to confer a beneficial effect. The authors concluded that the results of their study did not support the findings of McKinney et al. (1976), although there were complicating factors in the Staples et al. (1979) study. There appears to be no evidence that would link chlorination at levels consistent with current practice to any adverse reproductive effects in the species so far examined.

Hulan and Proudfoot (1982) studied the effects of sodium hypochlorite in drinking water on Shaver broiler chickens. Sodium hypochlorite was added to the drinking water of chicks
(240/sex) at doses of 0, 300, 600 and 1200 ppm. A significant (p<0.01) reduction was found in the weight of chick, testes at dose levels of 600 and 1200 ppm of available chlorine. At these higher concentrations, however, there was also a decrease in total body weight, food and water consumption and an increase in mortality.

Meier et al. (1985) demonstrated that oral administration of a sodium hypochlorite solution, but not hypochlorous acid, resulted in dose-related increases in the amount of sperm-head abnormalities in male B6C3F1 mice. Ten animals/group were given 1 mL of a residual chorine solution daily for 5 days. Test solutions were prepared by bubbling Cl2 into a 1M solution of NaOH and adjusting the pH to either pH 8.5 (predominant species OCl-) or pH 6.5 (predominant species HOCl). The solutions were diluted with distilled water to 200 mg/L, 100 mg/L and 40 mg/L chlorine equivalents (8.0, 4.0 or 1.6 mg/kg-day, respectively). The mice were then sacrificed at 1, 3 or 5 weeks after the last dose was administered. In mice given OCl-, significant increases in sperm-head abnormalities were observed only at the 3-week interval at doses of 1.6 and 4.0 mg/kg-day. These results were reproduced in retrials of the experiment. HOCl administration at any dose was not associated with increases in sperm-head abnormalities.

Six virgin Sprague-Dawley rats were administered 0, 1, 10 or 100 mg HOCl/L in drinking water for 2.5 months prior to mating. Animals were maintained on the treated water after pregnancy was confirmed (day 0) and killed on day 20. Maternal weight at time of death was not reported. The incidence of fetal anomalies associated with exposure to hypochlorous acid solutions was not found to be statistically significant. Mean fetal weights from the 10 and 100 mg/L groups were less than the control, but this decrease was not statistically significant. Neither was there a significant difference in numbers of resorptions between control and treated groups. Examination of general trends in the study indicated an increase (not significant) in skeletal anomalies in animals treated with 10 mg HOCl/L. Soft tissue anomalies for the 100 mg HOCl/L treatment group were increased significantly by comparison with the control. The findings of these experiments were limited by the small number of study animals. Some of the calculations of anomaly percentages reported in the paper were incorrect. Furthermore, the rate of both skeletal and soft tissue anomalies appeared to be higher in the control group than in the low-dose treatment groups (Abdel-Rahman et al., 1982).

Exon et al. (1987) reported immunotoxic effects when sodium hypochlorite (5, 15 and 30 ppm) was administered in drinking water to Sprague-Dawley rats (12/sex/dose group) from weaning to 12 weeks of age. Based on reference body weight and water consumption values for subchronic exposure (U.S. EPA, 1986) the corresponding intake of chlorine was 0.7, 2.1 and 4.2 mg/kg-day. Parameters monitored were body weight, spleen and thymus weight, antibody production, delayed-type hypersensitivity (DTH) reactions, natural killer cell (NKC) cytotoxicity, oxidative metabolism response, phagocytosis by macrophages and production of interleukin 2 (IL2). The effects attributed to sodium hypochlorite treatment (at only the high dose) were reductions of
spleen weight, DTH reactions, oxidative metabolism by macrophages and elevated prostaglandin E2 production. The toxicological significance of these effects is not clear. A NOAEL and/or LOAEL were not defined in this study.

I.A.5. Confidence in the Oral RfD

Study — High
Database — Medium
RfD — Medium

Confidence in the principal study (NTP, 1992) is high to medium. Relevant endpoints in two animal species were examined after prolonged exposure by an appropriate route. An effect level was not achieved in the study, however, and higher levels may not be practicable due to taste aversion (and therefore reduced water consumption). Confidence in the database is medium. Information is available for mice and rats on the noncancerous toxicity of oral exposure to chlorine for subchronic periods. Developmental and reproductive toxicity of chlorine have been examined in mice and rats, but with suboptimal studies. Due to the chemical relationship between chlorine and monochloramine, reproductive and developmental studies for monochloramine may be used to satisfy data gaps for chlorine. Confidence in the RfD is medium.

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


The Drinking Water Criteria Document for Chlorine/Hypochlorous Acid/Hypochlorite Ion has undergone limited Agency Review.

Other EPA Documentation — None


Verification Date — 12/15/1993

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Chlorine conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.
I.A.7. EPA Contacts (Oral RfD)

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

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

Substance Name — Chlorine
CASRN — 7782-50-5

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Chlorine
CASRN — 7782-50-5

Not available at this time.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Chlorine
CASRN — 7782-50-5
VI.A. Oral RfD References


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VI.B. Inhalation RfC References

None

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VI.C. Carcinogenicity Assessment References

None
VII. Revision History

Substance Name — Chlorine
CASRN — 7782-50-5

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VIII. Synonyms

Substance Name — Chlorine
CASRN — 7782-50-5
Last Revised — 06/01/1994

- 7782-50-5
- 7681-52-9
- 7790-92-3
- Bertholite
- Caswell No. 179
- Chloor [Dutch]
- Chlore [French]
- CHLOR [German]
- Chlorine
- CLORO [Italian]
- Cloro [Spanish]
- EPA Pesticide Chemical Code 020501
- HSDB 206
- Hypochlorite (sodium)
- Hypochlorous acid
- MOLECULAR CHLORINE
- UN 1017