

Chlorine Dioxide, Chlorite and Chlorate in Drinking-water

Background document for development of
WHO Guidelines for Drinking-water Quality

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Preface

Access to safe drinking-water is essential to health, a basic human right and a component of effective policy for health protection. A major World Health Organization (WHO) function to support access to safe drinking-water is the responsibility “to propose ... regulations, and to make recommendations with respect to international health matters ...”, including those related to drinking-water safety and management.

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006 and the second addendum to the third edition was published in 2008. The fourth edition was published in 2011, and the first addendum to the fourth edition was published in 2017.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water was prepared. The draft health criteria document was submitted to a number of scientific institutions and selected experts for peer review. The draft document was also released to the public domain for comment. Comments were carefully considered and addressed as appropriate, taking into consideration the processes outlined in the *Policies and Procedures Used in Updating the WHO Guidelines for Drinking-water Quality* (http://apps.who.int/iris/bitstream/10665/70050/1/WHO_HSE_WSH_09.05_eng.pdf) and the *WHO Handbook for Guideline Development* (http://www.who.int/publications/guidelines/handbook_2nd_ed.pdf), and the revised draft was submitted for final evaluation at expert consultations.

During the preparation of background documents and at expert consultations, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Meeting on Pesticide Residues and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO website and in the current edition of the GDWQ.

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Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comments are greatly appreciated.

Abbreviations

ADI	acceptable daily intake
ASC	acidified sodium chlorite
BMD	benchmark dose
BMD ₁₀	benchmark dose for a 10% response
BMDL ₁₀	lower 95% confidence limit for the BMD ₁₀
bw	body weight
CAS	Chemical Abstracts Service
CT	concentration × time
DPD	<i>N,N</i> -diethyl-1,4-phenylenediamine sulfate
F ₀	parental generation
F ₁	first filial generation
FAO	Food and Agriculture Organization of the United Nations
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOAEL	lowest-observed-adverse-effect level
MDL	method detection limit
NOAEL	no-observed-adverse-effect level
ppm	part per million
PQL	practical quantification limit
USA	United States of America
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

Contents

1. GENERAL DESCRIPTION	1
1.1 Identity	1
1.2 Physicochemical properties	1
1.3 Organoleptic properties.....	1
1.4 Major uses and sources in drinking-water	2
1.5 Environmental fate.....	2
2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE.....	3
2.1 Air	3
2.2 Water.....	3
2.3 Food	3
2.4 Estimated total exposure and relative contribution of drinking-water.....	4
3. TOXICOLOGICAL SUMMARY	4
3.1 Chlorine dioxide.....	4
3.1.1 Kinetics and metabolism in laboratory animals and humans.....	4
3.1.2 Effects on laboratory animals and in vitro test systems.....	5
3.1.2.1 Short-term and long-term exposure	5
3.1.2.2 Carcinogenicity and mutagenicity	5
3.1.2.3 Reproductive and developmental toxicity	6
3.2 Chlorite and chlorate.....	6
3.2.1 Kinetics and metabolism in laboratory animals and humans.....	6
3.2.2 Effects on laboratory animals and in vitro test systems.....	6
3.2.2.1 Acute, short-term and long-term exposure	6
3.2.2.2 Carcinogenicity and mutagenicity	7
3.2.2.3 Reproductive and developmental toxicity	8
3.2.2.4 Other studies	8
3.2.3 Effects on humans.....	8
3.2.4 Mode of action for effects on thyroid	9
4. PRACTICAL ASPECTS	9
4.1 Analytical methods and analytical achievability	9
4.2 Treatment and control methods and performance	11
5. PROVISIONAL GUIDELINE VALUES.....	12
5.1 Chlorine dioxide.....	12
5.2 Chlorite	12
5.3 Chlorate.....	13
6. REFERENCES	13

1. GENERAL DESCRIPTION

Chlorate and chlorite arise from the use of chlorine dioxide and hypochlorite as disinfectants and oxidants.

1.1 Identity

The Chemical Abstracts Service (CAS) registry numbers and molecular formulas for chlorine dioxide, chlorate and chlorite are given in Table 1.

Table 1. CAS numbers and molecular formulas

Compound	CAS No.	Molecular formula
Chlorine dioxide	10049-04-4	ClO ₂
Chlorate (sodium salt)	7775-09-0	NaClO ₃
Chlorite (sodium salt)	7758-19-2	NaClO ₂

1.2 Physicochemical properties

The physicochemical properties of chlorine dioxide, chlorate and chlorite are given in Table 2.

Table 2. Physicochemical properties

Property	Chlorine dioxide ^a	Sodium chlorate	Sodium chlorite
Boiling point (°C)	11	>300 (decomposes)	–
Melting point (°C)	–59	248	180–200 (decomposes)
Density at 0 °C (g/cm ³)	1.64 (liquid)	2.5	2.5
Vapour pressure at 25 °C	–	Negligible	Negligible
Water solubility (g/L)	3.01 (25 °C)	101 (20 °C)	390 (17 °C)

^a Conversion factor in air: 1 part per million (ppm) = 2.8 mg/m³.

Sources: National Academy of Sciences (1987); Budavari, O'Neill & Smith (1989); Meister (1989)

1.3 Organoleptic properties

The taste and odour threshold for chlorine dioxide in water has been reported to be approximately 0.4 mg/L (National Academy of Sciences, 1987). Others have reported taste and odour thresholds as low as 0.2 mg/L (Roche & Benanou, 2007). Although chlorine dioxide can reduce odour from some water components, it has also been reported to have caused strong chlorinous odours in some residences during distribution (Dietrich & Hoehn, 1991). Chlorine dioxide's water solubility – and hence its odour threshold – is decreased with reduced pressure and increased temperature. The sudden evaporation of chlorine dioxide from cold water (<8–10 °C) released at the tap can lead to a chlorine dioxide odour, and this effect may be increased by heating the water to 40 °C (Suffet, Mallevalle & Kawczynski, 1995). Kerosene-like and cat urine-like odours were produced in some homes with new carpets when volatilizing chlorine dioxide reacted with airborne volatiles (Dietrich & Hoehn, 1991).

1.4 Major uses and sources in drinking-water

Chlorine dioxide is used as a disinfectant and for odour and taste control in water and in food sanitation. Dosages for taste and odour reduction or disinfection may be in the range of 0.07–2 mg/L. Example concentration × time (CT) disinfection values at 20 °C for 2 log and 4 log virus reductions are 2 and 12.5, respectively; and for *Giardia*, 10 and 15, respectively (USEPA, 1999 a). Acidified sodium chlorite (ASC) is also used in food sanitation.

Chlorine dioxide is explosive under pressure and is usually produced on site. Sodium chlorate and sodium chlorite are used in the production of chlorine dioxide. Sodium chlorate is also used in the production of paper; in the manufacture of dyes, matches and explosives; for tanning and finishing leather; and in herbicides and defoliants. Sodium chlorite is used in the production of paper, textiles and straw products and in the manufacture of waxes, shellacs and varnishes (National Academy of Sciences, 1987; Budavari, O'Neill & Smith, 1989; Meister, 1989).

Chlorine dioxide is stable in pure water in the absence of reducing agents and ultraviolet light; however, in normal water, its disproportionation to chlorite and chlorate is a function of basicity and is catalysed by transition metal ions such as iron and copper (Lee, Kim & Lee, 2004; G. Gordon, personal communication, 2015), as well as by hypobromite and hypochlorite ions (Gates, 1998; Wang & Margerum, 2002). Chlorine dioxide is also reduced to chlorite and chloride by reactions with total organic carbon components (Lee, Kim & Lee, 2004; G. Gordon, personal communication, 2015).

Chlorite is present at steady state in hypochlorite solutions and is an intermediate between hypochlorite and chlorate (AWWA, 2009) and, ultimately, perchlorate. Chlorite, chlorate and, ultimately, perchlorate ions are formed during the slow decomposition of hypochlorite solutions (Adam et al., 1992; Hutchison, Mole & Fielding, 1994; Stanford et al., 2011), especially at warm temperatures. As the solution ages and the available chlorine concentration decreases, it is necessary to dose more product to achieve the desired residual chlorine concentration, with a consequent increase in the amount of chlorate added to the treated water. The decomposition of solid calcium hypochlorite is much slower, and consequently contamination with chlorate is less likely to be significant. However, if calcium hypochlorite solutions are prepared and stored before use, then decomposition to form chlorate would also slowly occur. A predictive model for the formation of chlorate and perchlorate during storage of hypochlorite has been published (AWWA, 2009).

1.5 Environmental fate

Chlorine dioxide is stable in pure water in the dark, but it is photoreactive in sunlight (Lenntech, 2011), producing chlorate, chlorite and chloride, especially in alkaline solution (Cotton & Wilkinson, 1962). Chlorate is susceptible to biodegradation to chloride by reductive processes in the environment. Thus, pesticidal and industrial releases of chlorate may not entirely survive to reach drinking-water sources. Chlorite ions will be mobile in soils and may leach into groundwater; however, oxidation–reduction reactions may reduce the concentration of chlorite ions capable of leaching into groundwater (ATSDR, 2004).

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Air

Occupational exposure to chlorine dioxide gas may occur during its manufacture, in the paper and pulp bleaching industries, during charging of the aqueous solution into drums, and during its use as a sterilizing agent in hospitals, as a biocide in water treatment and as an improving agent in flour. During manufacture and subsequent captive use of the gas, good process plant control is essential because of the explosive nature of the gas (IPCS, 2002).

The occupational exposure limits for chlorine dioxide in the United States of America (USA) are 0.1 part per million (ppm) (0.3 mg/m³) (time-weighted average) and 0.3 ppm (0.9 mg/m³) (short-term exposure) (NIOSH & OSHA, 1978).

2.2 Water

Chlorite and chlorate occur in drinking-water as disinfection by-products when chlorine dioxide is used for disinfection. The total dosage of chlorine dioxide could be an indicator of the potential upper-bound concentrations of chlorate and chlorite. Gates, Ziglio & Ozekin (2009) suggest that chlorite levels can generally range from 30% to 70% of the chlorine dioxide dose and that chlorate levels are generally less than that, at about <20% of the dose. When chlorine dioxide is used as the final disinfectant at typical doses, the resulting chlorite concentration would normally be less than 0.2 mg/L, but could be somewhat higher (e.g. Health Canada, 2008). Chlorate is also present in water that has been disinfected with hypochlorite. A 1996 Information Collection Rule survey of chlorate in disinfected drinking-water in the USA reported that in water treatment plants using hypochlorite, the median chlorate concentration was 99 µg/L, the 90th percentile concentration was 239 µg/L and the maximum concentration was 502 µg/L (USEPA, 2006). Chlorate concentrations above 1 mg/L have been reported when hypochlorite was used (Stanford et al., 2011), but such high concentrations would be unusual unless hypochlorite is stored under adverse conditions (see Section 4.2 for more information). In water treatment plants using chlorine dioxide, the median chlorate concentration was 129 µg/L, the 90th percentile concentration was 264 µg/L and the maximum concentration was 691 µg/L (USEPA, 2006).

2.3 Food

Chlorite and chlorate may occur in foods as a result of the uses of chlorine dioxide, sodium chlorate or sodium chlorite in flour processing, as a decolorizing agent for carotenoids and other natural pigments (chlorine dioxide), as a bleaching agent in the preparation of modified food starch (sodium chlorite), as an indirect additive in paper and paperboard products used for food packaging (sodium chlorite) and as a defoliant, desiccant and fungicide in agriculture (sodium chlorate) (USEPA, 1983; CMA, 1989; USFDA, 1990). Foods prepared with water containing chlorate may also accumulate chlorate from the water used in cooking (Asami et al., 2013).

The data available to the sixty-eighth meeting of the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) (WHO, 2008) showed that residues of chlorite and chlorate in most foods treated with ASC declined to levels below the limits of detection with time (after treatment, rinsing and a holding period). The occurrence data used in the calculation of the dietary exposure estimates by

CHLORINE DIOXIDE, CHLORATE AND CHLORITE IN DRINKING-WATER

JECFA (see Section 2.4) were as follows: for meat and meat products, 0.1 mg/kg for both chlorite and chlorate; for seafood and freshwater fish, 0.01 mg/kg for chlorite and 0.1 mg/kg for chlorate; and for fruits and vegetables, 0.01 mg/kg for chlorite for all fruits and vegetables, except for leafy vegetables (0.23 mg/kg), and 0.01 mg/kg for chlorate.

2.4 Estimated total exposure and relative contribution of drinking-water

Where hypochlorite or chlorine dioxide is used as a disinfectant, the major route of environmental exposure to chlorite and chlorate is expected to be through drinking-water. There may be trace residues in some foods as a result of use as a disinfectant by the food industry, and food uptake of chlorate can occur from drinking-water used in cooking (Asami et al., 2013).

Foods such as rice that retain cooking water can provide an indirect dietary source of chlorate from drinking-water. In the study by Asami et al. (2013), the total tap water contribution to total daily intake ranged from 47% to 58% in that high rice consumption environment. Cooking of foods in water where water is not significantly retained probably reduces the exposures that might occur from agricultural residues.

The United States Environmental Protection Agency's (USEPA) Pesticide Program estimated intake of dietary chlorate from field trial data or from a film thickness model for fruits and vegetables, because dietary chlorate exposures from foods were not available from monitoring data (USEPA, 2006). Other assumptions were used for milk, meat and crop treatment values. The USEPA (2006) estimated diet-only exposure to be 2.7 µg/kg body weight (bw) per day for all populations, 4.5 µg/kg bw per day for infants aged less than 1 year and 8.4 µg/kg bw per day (the highest estimate) for those aged 1 to 2 years. It concluded that risk from exposure through food only was below the level of concern for the general population and various population subgroups (USEPA, 2006). Comparison of the 90th percentile drinking-water concentrations from the USEPA Information Collection Rule drinking-water survey with age-related dietary intake estimates for the general population yields calculated food intakes of less than 20% of intakes from food plus water, except for the group aged 1 to 2 years (USEPA, 2011).

International mean dietary exposures from ASC-treated food have been estimated to be 0.2–0.7 µg/kg bw per day for chlorite and 0.1–0.6 µg/kg bw per day for chlorate, whereas national estimates for European Union countries of mean to 95th percentile dietary exposures in the general population were 0.9–3 µg/kg bw per day for chlorite and 0.3–0.6 µg/kg bw per day for chlorate. JECFA noted that the estimates were highly conservative and based on worst-case assumptions, as it was assumed that all the treated foods would be consumed daily over a lifetime and that all treated foods consumed contained the maximum residual levels of chlorite and chlorate (WHO, 2008).

3. TOXICOLOGICAL SUMMARY

3.1 Chlorine dioxide

3.1.1 Kinetics and metabolism in laboratory animals and humans

Chlorine dioxide is chemically reactive when ingested. No particular organ appears to selectively concentrate the by-products following exposure (Abdel-Rahman, 1985).

CHLORINE DIOXIDE, CHLORATE AND CHLORITE IN DRINKING-WATER

Following oral ingestion by monkeys, chlorine dioxide was rapidly converted into chloride ion and, to a lesser extent, chlorite and chlorate (Bercz et al., 1982). In rats, excretion of chloride and, to a lesser extent, chlorite ion is mainly via the urine, smaller amounts being excreted in faeces (Abdel-Rahman, Couri & Bull, 1982). At typical low drinking-water levels, chlorine dioxide would be decomposed by oxidation–reduction reactions with saliva and stomach contents (Abdel-Rahman, Couri & Bull, 1984).

3.1.2 Effects on laboratory animals and in vitro test systems

3.1.2.1 Short-term and long-term exposure

Drinking-water containing chlorine dioxide at a concentration of 0, 10 or 100 mg/L (equivalent to approximately 0, 1.5 and 15 mg/kg bw per day) was administered to mice (10 per dose) for 30 days with no apparent effects on blood parameters. The no-observed-adverse-effect level (NOAEL) for this study was 15 mg/kg bw per day (Moore & Calabrese, 1982). Similar negative results were obtained in 60-day and 12-week studies with African green monkeys (Bercz et al., 1982; Harrington, Shertzer & Bercz, 1986). In a 90-day study with Sprague-Dawley rats at drinking-water concentrations ranging from 0 to 200 mg/L, enzymatic changes suggested liver toxicity; the principal effect was histopathology of nasal turbinates from inhalation of the gas (Daniel, Condie & Robinson, 1990). Although chlorine dioxide is water soluble, it is a gas at room temperature, so there can be difficulty in interpreting toxicity findings.

In a 2-year study in rats at drinking-water concentrations up to 100 mg/L, the NOAEL was 10 mg/L (1.3 mg/kg bw per day); there was no correlation between treatment and histopathological findings, and an increased incidence of tumours was not observed (Haag, 1949).

3.1.2.2 Carcinogenicity and mutagenicity

In the 2-year drinking-water study in rats described in the previous section, an increased incidence of tumours was not observed (Haag, 1949).

Chlorine dioxide was mutagenic in *Salmonella typhimurium* strain TA100 without metabolic activation (Ishidate et al., 1984). No sperm head abnormalities were observed in male mice following gavage administration of chlorine dioxide. No chromosomal abnormalities were seen in either the micronucleus test or a cytogenetic assay in mouse bone marrow cells (Meier et al., 1985).

In an in vitro cytogenetics assay with Chinese hamster ovary cells, there was activity without metabolic activation at 60 µg/mL, and there was an absence of mitotic cells at 30 µg/mL. At 2.5–15 µg/mL, there was a dose-related, statistically significant increase in the number of metaphases with chromosome aberrations. With metabolic activation, cell toxicity and an absence of mitotic cells were observed at 75 µg/mL. A statistically significant increase in the number of metaphases with chromosome aberrations was noted at 50 µg/mL (Ivett & Myhr, 1986).

In a mouse lymphoma forward mutation assay (using L5178Y TK^{+/-}), marked toxicity at 37 µg/mL and a dose-related increase in mutant frequency were observed without metabolic activation. With metabolic activation, marked toxicity was observed at 65 µg/mL, and there was also a dose-related increase in mutant frequency (Cifone & Myhr, 1986).

3.1.2.3 Reproductive and developmental toxicity

In a one-generation gavage study, chlorine dioxide was administered to Long-Evans rats at 0–10 mg/kg bw per day (Carlton et al., 1991). IPCS (2002) did not report any impairment of reproductive function or developmental effects.

In groups of female Sprague-Dawley rats exposed to chlorine dioxide at drinking-water concentrations ranging from 0 to 100 mg/L, significant depression of serum thyroxine and an increase in serum triiodothyronine were observed at 100 mg/L (14 mg/kg bw per day for the dams) in the pups at weaning, but not in the dams. The NOAEL for neurobehavioural exploratory and locomotor activities was 20 mg/L (3 mg/kg bw per day) (Orme et al., 1985). Another developmental neurotoxicity study in rat pups administered chlorine dioxide by oral intubation at 14 mg/kg bw per day did not reveal any changes in brain tissues (Toth et al., 1990). Groups of female Sprague-Dawley rats dosed with chlorine dioxide at 0–7 mg/kg bw per day for 10 weeks prior to mating showed no clinical signs of toxicity and no exposure-related mortalities among the dams, and there were no effects on litter anomalies (Suh, Abdel-Rahman & Bull, 1983).

3.2 Chlorite and chlorate

3.2.1 Kinetics and metabolism in laboratory animals and humans

Chlorite and chlorate are rapidly absorbed into the plasma and distributed throughout the body, with the highest concentrations in plasma. At typical low drinking-water levels, chlorite would be decomposed by oxidation–reduction reactions with saliva and stomach contents. The rate of reduction of chlorate is slower than that of chlorite, as indicated by its measured biphasic half-lives in the rat of 6 and 36.7 hours, respectively (Abdel-Rahman, Couri & Bull, 1984).

Chlorite and chlorate are excreted primarily in the urine, with lesser amounts excreted in faeces. Most of the chlorine label is in the form of chloride, with lesser amounts of chlorate; chlorite is rarely detected (Abdel-Rahman, Couri & Bull, 1982; Hakk, Smith & Shappell, 2007). Abdel-Rahman, Couri & Jones (1980) and Abdel-Rahman, Couri & Bull (1984) concluded that once chlorite and chlorate are ingested, they are rapidly degraded in the body to chloride and consequently are not considered to be of toxicological concern following chronic exposure in drinking-water.

3.2.2 Effects on laboratory animals and in vitro test systems

The text in this section has been taken primarily from WHO (2008), with some minor editing. The details and references for the studies cited in this section may be found in WHO (2008), which is available online at <http://www.inchem.org/documents/jecfa/jecmono/v59je01.pdf>. The citation of references in this section indicates that the text has not been taken directly from WHO (2008). The critical studies are identified here and in Section 5. The EFSA (2014) evaluation of perchlorate was also reviewed, and it was concluded that although it utilized a different risk assessment approach, the report included no significant additions to the studies evaluated by WHO (2008).

3.2.2.1 Acute, short-term and long-term exposure

ASC and chlorite are of moderate acute toxicity, but only limited acute toxicity data were available on chlorate. Studies conducted with sodium chlorite in a number of species

CHLORINE DIOXIDE, CHLORATE AND CHLORITE IN DRINKING-WATER

demonstrated that the most consistent finding is oxidative stress associated with changes in erythrocytes. This observation was also supported by a number of biochemical studies conducted *in vitro*. Some studies have indicated that the effect may be related to a reduction in serum glutathione levels, thus reducing the body's ability to protect the erythrocytes from the effects of sodium chlorite. Other studies have indicated that sodium chlorite may cause damage to the erythrocyte membrane. For effects on erythrocytes, the lowest lowest-observed-adverse-effect level (LOAEL) of 19 mg/kg bw per day, expressed as chlorite, was derived from a 13-week gavage study in rats in which the NOAEL was 7.4 mg/kg bw per day, expressed as chlorite. Studies on sodium chlorate in a number of species showed some effects on haematological parameters and on body weight gain.

Although sodium chlorate has also been reported to have effects on erythrocytes, changes in thyroid histology (e.g. colloid depletion, hypertrophy, incidence and severity of hyperplasia) and in thyroid hormones were the most sensitive effects observed in rats administered sodium chlorate in drinking-water for 21 or 90 days. Male rats were more sensitive than females, as is commonly seen with substances that affect thyroid function. In one of the two available 90-day studies, thyroid hypertrophy and decreased colloid were observed in male rats given sodium chlorate at drinking-water concentrations of 1 mg/L as chlorate (equivalent to about 0.1 mg/kg bw per day as chlorate) and above. In general, effects including incidence and severity of follicular cell hyperplasia were dose related and more consistently observed at chlorate doses of 75 mg/kg bw per day and above.

3.2.2.2 Carcinogenicity and mutagenicity

Sodium chlorite was not carcinogenic following a number of long-term studies, although these were not conducted to current standards. The International Agency for Research on Cancer concluded in 1991 that sodium chlorite was not classifiable with respect to carcinogenicity to humans. Sodium chlorite has given positive results in some, but not all, *in vitro* genotoxicity assays and in one of the two available *in vivo* mouse micronucleus assays involving intraperitoneal administration. Negative results were obtained in several *in vivo* assays, for induction of bone marrow micronuclei, chromosome aberrations and sperm head abnormalities, involving oral administration of sodium chlorite to mice.

Sodium chlorate has been tested for carcinogenicity in rats and mice under the United States National Toxicology Program. There was no evidence of carcinogenic activity in male B6C3F1 mice and equivocal evidence in female mice based on marginally increased incidences of pancreatic islet neoplasms. Sodium chlorate produced positive results in some *in vitro* assays, but not for induction of bone marrow micronuclei or chromosome aberrations following oral administration to mice. There was some evidence of carcinogenic activity in male and female F344/N rats based on increased incidences of thyroid gland neoplasms. The incidence of thyroid gland follicular hypertrophy was enhanced compared with control groups at doses lower than those resulting in increased tumour incidences and was significantly greater than the control incidence in the male rats at all tested doses. Therefore, the lowest dose, equivalent to approximately 5 mg/kg bw per day, expressed as chlorate, was the LOAEL. Because a NOAEL was not identified in the study, JECFA applied a benchmark dose (BMD) approach to derive a point of departure on the dose–response curve. The USEPA BMD software version 1.4.1 was used for modelling the rat thyroid gland follicular cell hypertrophy data. The calculated BMD values for a 10% increase in thyroid gland follicular cell hypertrophy in the male rats (BMD₁₀) ranged from 1.9 to 5.9 mg/kg bw per day,

CHLORINE DIOXIDE, CHLORATE AND CHLORITE IN DRINKING-WATER

expressed as chlorate. The values of the lower 95% confidence limit for the BMD₁₀ (BMDL₁₀) ranged from 1.1 to 4.4 mg/kg bw per day, expressed as chlorate. JECFA used the lowest BMDL₁₀ of 1.1 mg/kg bw per day, expressed as chlorate, which was derived from the model giving the best fit to the data, for its further evaluation of chlorate. For female rats, the BMD₁₀ values ranged from 4.7 to 12.6 mg/kg bw per day, and the BMDL₁₀ values ranged from 3.0 to 6.4 mg/kg bw per day.

3.2.2.3 Reproductive and developmental toxicity

Reproductive toxicity studies have shown no adverse effects of ASC or sodium chlorite on fertility. A multigeneration study of reproduction and developmental neurotoxicity was available in which sodium chlorite was administered to rats in drinking-water at a concentration of 35, 70 or 300 mg/L. Published information indicated that the highest dose tested resulted in effects on body weight in both sexes of the parental generation and a range of effects in the offspring, including decreased body weight, changes in haematological parameters and a decrease in maximum startle response amplitude at postnatal day 24, but not at postnatal day 60. A small but statistically significant decrease in maximum startle response amplitude was also reported at the middle dose at postnatal day 24. JECFA considered that this observation was attributable to perturbed habituation in the control animals. Other effects observed in the offspring of the high-dose group (i.e. reduced absolute brain weight and slight delays in attainment of sexual maturity) could be attributable to reduced body weight. Although the authors (Gill et al., 2000) concluded that the NOAEL for sodium chlorite was 70 mg/L (8 mg/kg bw per day for males and 10 mg/kg bw per day for females), JECFA concluded, based on data contained only in the unpublished original study report showing reduced absolute and relative liver weights in the F₀ females and F₁ males and females of the high-dose group and in the F₀ females and F₁ males of the mid-dose group, that the low dose in this study, equivalent to 3 mg/kg bw per day, expressed as chlorite, was the NOAEL.

Administration of sodium chlorate to pregnant rats resulted in no maternal or developmental effects at the highest dose tested, 1000 mg/kg bw per day. Neurodevelopmental end-points were not investigated in this study, and no multigeneration study was available. In a study in which female rats were exposed to chlorite or chlorate at 1 or 10 mg/L in their drinking-water for 10 weeks, fetuses taken on the 20th gestation day showed no external, visceral or skeletal malformations (Suh, Abdel-Rahman & Bull, 1983, 1984).

3.2.2.4 Other studies

Other *in vivo* studies on nephrotoxicity, immune function and sperm quality indicated that such effects would not be critical to the safety assessment.

3.2.3 Effects on humans

Studies in healthy adult male volunteers lasting up to 12 weeks showed no clear treatment-related effects on blood, urine analysis or physical examination at doses of sodium chlorite and sodium chlorate estimated to be in the region of 0.036 mg/kg bw per day, expressed as chlorite or chlorate. The authors concluded that the absence of detrimental physiological responses within the limits of the study demonstrated the relative safety of oral ingestion of chlorine dioxide, chlorate and chlorite (Lubbers, Chauhan & Bianchine, 1981, 1982; Lubbers & Bianchine, 1984; Lubbers et al., 1984a,b).

3.2.4 Mode of action for effects on thyroid

Based on the negative in vivo genotoxicity data and the nature of the histopathological observations, JECFA concluded that a non-genotoxic mode of action was likely for the induction of thyroid tumours by sodium chlorate. This mode of action is likely to be mediated via decreased serum thyroid hormones, leading to increased release of thyroid stimulating hormone and consequent stimulation of thyroid cell proliferation and thyroid gland growth, which can lead to thyroid tumours in rodents.

In addition to thyroid carcinogenesis, this mode of action raises concerns about possible neurodevelopmental effects, as thyroid hormone status is critical to normal brain development.

4. PRACTICAL ASPECTS

4.1 Analytical methods and analytical achievability

Methods are available for the determination of chlorine dioxide, chlorite and chlorate in water. Several of these methods are summarized in Table 3 (adapted from Health Canada, 2008); details on these analytical procedures can be found in the primary references cited in that table. The limits of detection for these methods are generally below 0.1 mg/L.

CHLORINE DIOXIDE, CHLORATE AND CHLORITE IN DRINKING-WATER

Table 3. Analytical methods for chlorine dioxide, chlorite and chlorate in drinking-water

Methodology	Reference method ^a	MDL ^b (µg/L)	PQL ^c (µg/L)	Interferences	Comments	Reference
Amperometric	Standard Method 4500-ClO ₂ -E	100 (ClO ₂ ⁻)	500 (ClO ₂ ⁻)	Manganese, copper, nitrate and other oxidants	Identify Cl ₂ , ClO ₂ , ClO ₂ ⁻ and ClO ₃ ⁻ ; adequate for utility use in daily testing	APHA, AWWA & WEF (1998)
Ion chromatograph/ conductivity	USEPA Method 300.0 (1993B Revision 2.2)	10 (ClO ₂ ⁻) 3 (ClO ₃ ⁻)	50 (ClO ₂ ⁻) 15 (ClO ₃ ⁻)	Chloramine, ClO ₂	Good sensitivity, high expertise required; cannot determine Cl ₂ or ClO ₂	USEPA (1999b)
Ion chromatograph/ conductivity	USEPA Method 300.1 (1997E Revision 1.0)	0.45 (ClO ₂ ⁻) 0.78 (ClO ₃ ⁻)	2.2 (ClO ₂ ⁻) 3.9 (ClO ₃ ⁻)	Chloramine, ClO ₂	Good sensitivity, high expertise required; cannot determine Cl ₂ or ClO ₂	USEPA (1998)
Ion chromatograph/ conductivity and ultraviolet/visible detectors	USEPA Method 317.0 (Revision 2.0*)	1.6 (ClO ₂ ⁻) 0.24 (BrO ₃ ⁻)	8.0 (ClO ₂ ⁻) 1.2 (BrO ₃ ⁻)	ClO ₂	Similar to 300.1; post-column reactor with o-dianisidine dihydrochloride; ultraviolet/visible detector specifically targeting bromate	USEPA (2001)
Ion chromatograph/ conductivity and ultraviolet/visible detectors	USEPA Method 326.0 (Revision 1.0*)	1.6 (ClO ₂ ⁻) 0.17 (BrO ₃ ⁻)	8.0 (ClO ₂ ⁻) 0.9 (BrO ₃ ⁻)	ClO ₂	Similar to 300.1; post-addition of KI and Mo(VI); ultraviolet/visible detector specifically targeting bromate	USEPA (2002)
Ultraviolet/visible spectrophotometric Lissamine Green B	USEPA Method 327.0 (Revision 1.0*)	78 (ClO ₂) 78 (ClO ₂ ⁻)	100 (ClO ₂) 100 (ClO ₂ ⁻)	Free Cl ₂ (eliminated with glycine) and ClO ₂ (removed by sparging with inert gas)	Adequate for utility use in conjunction with daily monitoring; two-step procedure	USEPA (2003b)
Flow injection analysis – iodometric	Flow injection analysis	130 (ClO ₂) 10 (ClO ₂ ⁻) 20 (ClO ₃ ⁻)	650 (ClO ₂) 50 (ClO ₂ ⁻) 100 (ClO ₃ ⁻)	Specific interferences are removed using masking agents	Identify ClO ₂ , ClO ₂ ⁻ and ClO ₃ ⁻ ; may be automated and on-line	Novatek (1991)

^a Asterisk (*) indicates proposed United States Environmental Protection Agency (USEPA) methods.

^b Method detection limit (MDL): a measure of a method's sensitivity, defined as the minimum concentration of a substance that can be reported with 99% confidence that the analyte concentration is greater than zero (USEPA, 1995).

^c Practical quantification limit (PQL): the lowest concentration of an analyte that can be reliably measured within specified limits of precision and accuracy during routine laboratory operating conditions. A PQL may be determined either through the use of interlaboratory study data or, in the absence of information, through the use of a multiplier of 5–10 times the MDL (USEPA, 2003a).

Source: Adapted from Health Canada (1998)

4.2 Treatment and control methods and performance

Where chlorite formation is a concern, the control of treatment processes to reduce disinfectant demand and the control of disinfection processes to reduce chlorine dioxide doses are recommended. If chlorine dioxide and chlorite ion are not removed prior to post-chlorine disinfection, they will react with free chlorine to form chlorate ion. Chlorate ion is persistent and difficult to remove (Gallagher, Hoehn & Dietrich, 1994; USEPA, 1999a).

It is possible to reduce the concentration of chlorine dioxide effectively to zero (<0.1 mg/L) by reduction; however, it is normal practice to supply water with a chlorine dioxide residual of a few tenths of a milligram per litre to provide some protection against microbial regrowth during distribution. The presence of chlorite ion below 0.7 mg/L may suppress nitrification in distribution systems (McGuire et al., 2009).

There are several available treatment options for lowering chlorite ion concentrations in drinking-water at the municipal scale. They include granular activated carbon (Dixon & Lee, 1991), sulfur reducing agents, such as sulfite, metabisulfite and thiosulfate (Griese et al., 1991) and ferrous iron (Fe^{2+}), and anion exchange (Griese, Kaczur & Gordon, 1992; Iatrou & Knocke, 1992; Hurst & Knocke, 1997). Furthermore, precise operation (“tuning”), proper maintenance and the generation technology employed with the chlorine dioxide generator have a large bearing on the chlorine dioxide production efficiency and the rate at which chlorite and other undesirable by-products are formed (Gordon, 2001).

Chlorate production is a concern for hypochlorite solutions that are stored at warm temperatures for extended periods of time. This applies to its presence in purchased hypochlorite solutions that are not fresh, as well as hypochlorite solutions stored on site. The rate of formation of chlorate is a function of temperature, pH and hypochlorite concentration (Gordon, Adam & Bubnis, 1995; Gordon et al., 1997; AWWA, 2009; Stanford et al., 2011). Contamination by transition metals such as iron, copper or nickel may catalyse the conversion. The best control approach would be to purchase fresh hypochlorite solutions that are of an appropriate quality, store them in a cool place and out of direct sunlight, and use the hypochlorite as soon as possible after purchase (e.g. within a month, if possible). Purchased hypochlorite solutions are typically in the range of 12–15% hypochlorite. It is also possible to carefully dilute the solution to slow down the rate of conversion to chlorate. New hypochlorite solutions should not be added to containers containing old hypochlorite solutions, as this will accelerate chlorate formation. A decrease in chlorine concentration in the hypochlorite solution will lead to dosing of more hypochlorite in order to maintain disinfection targets. As such, an increased hypochlorite dose could result in higher chlorite and chlorate concentrations in the treated water (Bouland, Duguet & Montiel, 2005).

Currently, there is no readily available and low-cost treatment available to remove chlorate ion once it has been formed in drinking-water. Although anion exchange and reverse osmosis are possible technologies for the removal of chlorate (Alfredo et al., 2015), they are high-cost treatment options. Granular activated carbon is generally not effective, as chlorate is reversibly adsorbed on granular carbon (Gonce & Voudrias, 1994).

As much as 35% of the chlorate concentration found in a distribution system can be attributed to the type and performance (tuning) of the chlorine dioxide generator. If chlorite ion is present in water and is not removed, it will react with any applied free chlorine to produce chlorate and chloride ions. In order to control persistent disinfection by-product formation, it

CHLORINE DIOXIDE, CHLORATE AND CHLORITE IN DRINKING-WATER

is important to minimize production of chlorate ion in the chlorine dioxide generation process and to remove the chlorite ion before adding chlorine (Gallagher, Hoehn & Dietrich, 1994).

In summary, it is possible to reduce the concentrations of chlorine dioxide and chlorite effectively to zero (<0.1 mg/L) by chemical reduction; however, it is normal practice to supply water with a chlorine dioxide residual of a few tenths of a milligram per litre to provide some protection against microbial regrowth during distribution. Chlorate ion arises from the use of either sodium hypochlorite or chlorine dioxide. With chlorine dioxide disinfection, the concentrations of chlorate and chlorite depend on process conditions (in both the chlorine dioxide generator and the water treatment plant) and applied dose of chlorine dioxide. As there is no low-cost option for reducing concentrations of chlorate once it is formed, control of chlorate concentration must rely on preventing its addition (from sodium hypochlorite) or formation (from chlorine dioxide). Chlorite ion is also an inevitable by-product arising from the use of chlorine dioxide. Concentrations of chlorite can be reduced using ferrous iron, sulfur reducing agents or activated carbon and may particularly be needed when chlorine dioxide is used as a pre-oxidant.

5. PROVISIONAL GUIDELINE VALUES

JECFA (WHO, 2008) concluded that the available toxicological data were sufficient to assess the safety of ASC by setting acceptable daily intakes (ADIs) for chlorite and chlorate.

5.1 Chlorine dioxide

Any chlorine dioxide remaining at the consumer's tap will be reduced to chlorite and chloride upon ingestion. Consequently, a guideline value for chlorine dioxide has not been established. The provisional guideline values for chlorite and chlorate (see below) are adequately protective for potential toxicity from chlorine dioxide. The taste and odour threshold for chlorine dioxide is approximately 0.2–0.4 mg/L.

5.2 Chlorite

For chlorite, JECFA established an ADI of 0–0.03 mg/kg bw on the basis of the NOAEL of 3 mg/kg bw per day for reduced liver weight of F₀ females and F₁ males and females in a two-generation reproductive toxicity study in rats (NOAEL identified from unpublished data in support of the Gill et al., 2000 study) and a safety factor of 100 to allow for interspecies and intraspecies variability. This ADI is supported by the results of studies in human volunteers showing no adverse effects at this intake (Lubbers, Chauhan & Bianchine, 1981, 1982; Lubbers & Bianchine, 1984; Lubbers et al., 1984a,b).

Using the upper bound of the ADI of 30 µg/kg bw, a typical human body weight of 60 kg, the assumption that drinking-water contributes 80% of the total exposure and a typical consumption of 2 L of water per day, the provisional guideline value is calculated to be 0.7 mg/L (rounded figure). This guideline value is designated as provisional because use of chlorine dioxide as a disinfectant may result in the chlorite guideline value being exceeded, and difficulties in meeting the guideline value must never be a reason for compromising adequate disinfection.

5.3 Chlorate

For chlorate, JECFA concluded that the most sensitive effects were changes to the thyroid gland of male rats. Rats are considered to be highly sensitive (more so than humans) to the effects of agents that disrupt thyroid hormone homeostasis. JECFA considered that humans are likely to be less sensitive than rats to these effects and that a safety factor for interspecies variation was not required. However, JECFA noted deficiencies in the database, particularly with respect to investigation of possible neurodevelopmental effects. This is a concern relating to reduced iodide transport to the thyroid in pregnant women who are also seriously iodine deficient. Numerous other anions, including dietary perchlorate, nitrate, thiocyanate and bromide, have similar mechanisms, and smokers have the most significant concerns due to high levels of cyanide that is converted to thiocyanate in vivo (Tonacchera et al., 2004; Tarone, Lipworth & McLaughlin, 2010). JECFA therefore established an ADI of 0–0.01 mg/kg bw for chlorate on the basis of the BMDL₁₀ of 1.1 mg/kg bw per day for non-neoplastic effects on the thyroid of male rats in a carcinogenicity study (NTP, 2005), a safety factor of 10 to allow for intraspecies variability and an additional factor of 10 to allow for the deficiencies in the database. The rationale for selection of a tenfold uncertainty factor (as opposed to, for example, a threefold uncertainty factor) was not additionally specified by JECFA.

Using the upper bound of the unrounded ADI of 11 µg/kg bw, a typical human body weight of 60 kg, the assumption that drinking-water contributes 80% (default ceiling value based on drinking-water as the predominant source of exposure) of the total exposure and a typical consumption of 2 L of water per day, a health-based value of 0.3 mg/L (rounded figure) could be calculated. As noted in Section 2.2 above, chlorate concentrations arising from the use of sodium hypochlorite are generally below the health-based value, although higher concentrations have been noted (Stanford et al., 2011). As well, the concentration of chlorate arising from the use of hypochlorite as a disinfectant depends heavily on process conditions, and control of chlorate concentrations must rely on preventing its formation. Control of storage conditions is considered to be most difficult in small, resource-limited water supplies, and so the potential for the health-based value to be exceeded is also greater under these circumstances.

In view of the above considerations, the previous provisional guideline value of 0.7 mg/L is retained. It is essential to ensure the availability of hypochlorite and chlorine dioxide for disinfection purposes. The guideline value is designated as provisional because use of aged hypochlorite or of chlorine dioxide as disinfectants may result in the chlorate guideline value being exceeded, and difficulties in meeting the guideline value must never be a reason for compromising adequate disinfection.

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CHLORINE DIOXIDE, CHLORATE AND CHLORITE IN DRINKING-WATER

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