WHO/SDE/WSH/05.08/86
English only

Chlorite and Chlorate in Drinking-water

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

© World Health Organization 2005

This document may be freely reviewed, abstracted, reproduced and translated in part or in whole but not for sale or for use in conjunction with commercial purposes. Inquiries should be addressed to: permissions@who.int.

The designations employed and the presentation of the material in this document do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.

Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...."

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 on selected chemicals in 1998 and on microbiological aspects in 2002. The third edition of the GDWQ was published in 2004, and the first addendum to the third edition was published in 2005.

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 public 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 lead institution prepared a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the documents for the third edition and addenda.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert meetings, 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 FAO/WHO Meetings 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 internet site and in the current edition of the GDWQ.

Acknowledgements

The first draft of Chlorite and Chlorate in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, was prepared by Dr S. Grant-Trusdale, Health Canada, to whom special thanks are due.

The work of the following working group coordinators was crucial in the development of this document and others contributing to the first addendum to the third edition:

Dr J. Cotruvo, J. Cotruvo Associates, USA (*Materials and chemicals*)
Mr J.K. Fawell, United Kingdom (*Naturally occurring and industrial contaminants*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Chemicals – practical aspects*)
Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)

The draft text was discussed at the Working Group Meeting for the first addendum to the third edition of the GDWQ, held on 17–21 May 2004. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants in the meeting is gratefully acknowledged.

The WHO coordinator was Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters. Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters. Mr Robert Bos, Water Sanitation and Health Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms Penny Ward provided invaluable administrative support at the Working Group Meeting and throughout the review and publication process. Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

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 comment are greatly appreciated.

Acronyms and abbreviations used in the text

CAS	Chemical Abstracts Service
CI	confidence interval
FAO	Food and Agriculture Organization of the United Nations
GAC	granular activated carbon
GDWQ	*Guidelines for Drinking-water Quality*
IPCS	International Programme on Chemical Safety
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
OR	odds ratio
TDI	tolerable daily intake
THM	trihalomethane
WHO	World Health Organization

Table of 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 1
   1.5 Environmental fate 2

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE 2
   2.1 Water 2
   2.2 Food 2
   2.3 Estimated total exposure and relative contribution of drinking-water 2

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS 2

4. EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS 3
   4.1 Chlorine dioxide 3
      4.1.1 Short-term exposure 3
      4.1.2 Long-term exposure 4
      4.1.3 Reproductive and developmental toxicity 4
      4.1.4 Mutagenicity and related end-points 6
      4.1.5 Carcinogenicity 7
   4.2 Chlorite 7
      4.2.1 Acute exposure 7
      4.2.2 Short-term exposure 7
      4.2.3 Long-term exposure 8
      4.2.4 Reproductive and developmental toxicity 8
      4.2.5 Mutagenicity and related end-points 11
      4.2.6 Carcinogenicity 11
   4.3 Chlorate 12
      4.3.1 Acute exposure 12
      4.3.2 Short-term exposure 12
      4.3.3 Carcinogenicity 12
      4.3.4 Reproductive and developmental toxicity 13
      4.3.5 Mutagenicity and related end-points 13

5. EFFECTS ON HUMANS 13
   5.1 Chlorine dioxide 13
   5.2 Chlorite 15
   5.3 Chlorate 15

6. PRACTICAL ASPECTS 16
   6.1 Analytical methods and analytical achievability 16
   6.2 Treatment and control methods and treatment achievability 16

7. PROVISIONAL GUIDELINE VALUES 18
   7.1 Chlorine dioxide 18

7.2 Chlorite 18
7.3 Chlorate 19

8. REFERENCES 19

1. GENERAL DESCRIPTION

1.1 Identity

Compound	*CAS No.*	*Molecular formula*
Chlorine dioxide	10049-04-4	ClO_2
Chlorite (sodium salt)	7758-19-2	$NaClO_2$
Chlorate (sodium salt)	7775-09-0	$NaClO_3$

1.2 Physicochemical properties (NAS, 1987; Budavari et al., 1989; Meister, 1989)

Property	*Chlorine dioxide*[1]	*Sodium chlorite*	*Sodium chlorate*
Boiling point (°C)	11	–	>300 (decomposes)
Melting point (°C)	-59	180–200 (decomposes)	248
Density at 0 °C (g/cm^3)	1.64 (liquid)	–	2.5
Vapour pressure at 25 °C	–	Negligible	–
Water solubility (g/litre)	3.01 (25 °C)	390 (17 °C)	–

1.3 Organoleptic properties

The taste and odour threshold for chlorine dioxide in water is 0.4 mg/litre (NAS, 1987).

1.4 Major uses and sources in drinking-water

Chlorite and chlorate are disinfection by-products resulting from the use of chlorine dioxide as a disinfectant and for odour/taste control in water. Chlorine dioxide is also used as a bleaching agent for cellulose, paper pulp, flour and oils and for cleaning and detanning leather. Sodium chlorite is used in on-site production of chlorine dioxide; as a bleaching agent in the production of paper, textiles and straw products; and in the manufacture of waxes, shellacs and varnishes. Sodium chlorate is used in the preparation of chlorine dioxide; in the manufacture of dyes, matches and explosives; for tanning and finishing leather; and in herbicides and defoliants (NAS, 1987; Budavari et al., 1989; Meister, 1989).

Chlorate and chlorite ions are also formed during the slow decomposition of sodium hypochlorite solutions (Adam et al., 1992; Hutchison et al., 1994). 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

[1] Conversion factor in air: 1 ppm = 2.8 mg/m^3.

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 occur.

1.5 Environmental fate

Chlorine dioxide rapidly decomposes into chlorite, chlorate and chloride ions in treated water, chlorite being the predominant species. This reaction is favoured by alkaline conditions.

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Water

Chlorite occurs in drinking-water when chlorine dioxide is used for purification purposes. The levels of chlorite in water reported in one study ranged from 3.2 to 7.0 mg/litre (Michael et al., 1981).

2.2 Food

Chlorine dioxide, chlorite and chlorate may occur in foodstuffs as a result of their use 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) (US EPA, 1983; CMA, 1989; US FDA, 1990).

2.3 Estimated total exposure and relative contribution of drinking-water

The major route of environmental exposure to chlorine dioxide, chlorite and chlorate is through drinking-water.

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Chlorine dioxide is rapidly absorbed from the gastrointestinal tract. No particular organ appears to selectively concentrate the dose following exposure (Abdel-Rahman, 1985). 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). Excretion is mainly via the urine, smaller amounts being excreted in faeces (Abdel-Rahman et al., 1982).

Chlorite was readily absorbed when administered to rats, then randomly distributed throughout the tissues (Abdel-Rahman et al., 1982). It was transformed mainly into

chloride in rats, smaller amounts appearing as unchanged chlorite. Excretion was mainly via the urine, followed by faeces (Abdel-Rahman et al., 1985).

Chlorate was readily absorbed and randomly distributed throughout the tissues of rats (Abdel-Rahman et al., 1982). It was excreted mainly in the form of chloride in the urine, smaller amounts appearing as chlorite and chlorate (Abdel-Rahman et al., 1985).

4. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

4.1 Chlorine dioxide

4.1.1 Short-term exposure

Drinking-water containing 0, 10 or 100 mg of chlorine dioxide per litre (equivalent to approximately 0, 1.5 or 15 mg/kg of body weight per day) was administered to mice (10 per dose) for 30 days with no apparent effects on blood parameters. The NOAEL for this study was 15 mg/kg of body weight per day (Moore & Calabrese, 1982).

Twelve African green monkeys were exposed to water containing chlorine dioxide at concentrations of 0, 30, 100 or 200 mg/litre (corresponding to doses of 0, 3.5, 9.5 and 11 mg/kg of body weight per day) using a rising-dose protocol for up to 8 weeks. Each dose was maintained for 30–60 days (Bercz et al., 1982). A review by IPCS (2002) stated that the two highest concentrations were equivalent to approximately 9 mg/kg of body weight per day due to impaired palatability leading to reduced water intake. Treatment at the highest dose was stopped after 1 week due to signs of dehydration. Although the authors claimed that there was a significant reversible thyrotoxic effect after 4 weeks of administration of 100 mg of chlorine dioxide per litre, IPCS (2002) determined that the few data did not clearly support this. Overall, at 200 mg of chlorine dioxide per litre, there were clear indications of irritation of the oral cavity, leading to palatability problems. At 100 mg/litre (approximately 9 mg/kg of body weight per day) or less, there were no clear effects among these primates over an 8-week exposure period (IPCS, 2002).

Six monkeys were treated for 8 weeks with drinking-water containing chlorine dioxide at 100 mg/litre, corresponding to an average measured dose of about 4.6 mg/kg of body weight per day (Harrington et al., 1986). According to IPCS (2002), there were no consistent changes seen in thyroxine levels. In the same study, drinking-water containing chlorine dioxide at 0, 100 or 200 mg/litre was administered to male rats (12 per dose) (equivalent to 0, 10 or 20 mg/kg of body weight per day). A dose-dependent decrease in thyroxine levels was observed after 8 weeks of treatment; there was no rebound. According to IPCS (2002), it is not possible to draw any firm conclusions from this study, given the limited extent of observations (e.g., no histopathology was reported) and the fact that changes in thyroid hormone levels were within the control range of values.

Sprague-Dawley rats (10 per sex per dose) were exposed to chlorine dioxide in drinking-water for 90 days at dose levels of 0, 25, 50, 100 or 200 mg/litre (corresponding to 0, 2, 4, 6 or 12 mg/kg of body weight per day for males and 0, 2, 5, 8 or 15 mg/kg of body weight per day for females). Water consumption was decreased in both sexes at the three highest dose levels, most likely because of reduced palatability. Food consumption was decreased in males receiving the highest dose. Goblet cell hyperplasia was significantly increased in the nasal turbinates of females given 8 or 15 mg/kg of body weight per day and males at all doses. Inflammation of the nasal cavity was observed in males at 2 mg/kg of body weight per day and in both sexes at higher doses. The lesions were likely caused by inhalation of chlorine dioxide vapours at the drinking-water sipper tube or from off-gassing of the vapours after drinking, rather than by ingestion of drinking-water. The authors concluded that the lowest dose (2 mg/kg of body weight per day) was a LOAEL (Daniel et al., 1990).

4.1.2 Long-term exposure

In a drinking-water study, chlorine dioxide was administered to rats (seven per sex per dose) at concentrations of 0, 0.5, 1, 5, 10 or 100 mg/litre (highest dose equivalent to about 13 mg/kg of body weight per day) for 2 years. At the highest dose level, survival rate was substantially decreased in both sexes, and mean life span was reduced compared with that for control animals. No correlation was observed between treatment and histopathological findings. In this study, a NOAEL of 10 mg/litre (1.3 mg/kg of body weight per day) was identified (Haag, 1949), although it should be noted that this 1949 study has serious limitations.

4.1.3 Reproductive and developmental toxicity

In a one-generation study carried out with Long-Evans rats, chlorine dioxide was administered by gavage at doses of 0, 2.5, 5 or 10 mg/kg of body weight per day to males (12 per group) for 56 days prior to and during mating to female rats (24 per group) that were dosed (same as males) from 14 days prior to mating and throughout pregnancy until weaning on day 21 of lactation. Fertility measures were not significantly different among the dose groups. There were no dose-related changes in sperm parameters (i.e., concentration, motility, progressive movement or morphology). Thyroid hormone levels were altered significantly, but not in a consistent pattern (Carlton et al., 1991). IPCS (2002) concluded that this study did not demonstrate any impairment of reproductive function and that there were no signs of developmental effects among rats receiving up to 10 mg of aqueous chlorine dioxide per kg of body weight per day.

Female rats were exposed to 0, 1, 10 or 100 mg of chlorine dioxide per litre in drinking-water (equivalent to 0, 0.1, 1 or 10 mg/kg of body weight per day) for 2.5 months before mating and throughout gestation. At the highest dose, there was a slight reduction in the number of implants and live births per pregnancy. No effects

were observed at 1 mg/kg of body weight per day, which was identified as the NOAEL (Toth et al., 1990).

Female Sprague-Dawley rats (13–16 per dose) were supplied with drinking-water containing 0, 2, 20 or 100 mg of chlorine dioxide per litre for 2 weeks before mating and throughout gestation and lactation, until pups were weaned on postnatal day 21. No significant effect on the body weight of either the dams or the pups was observed at any dose tested. At 100 mg/litre (14 mg/kg of body weight per day for the pregnant dam), a significant depression of serum thyroxine and an increase in serum triiodothyronine were observed in the pups at weaning, but not in the dams. Neurobehavioural exploratory and locomotor activities were decreased in pups born to dams exposed to 100 mg/litre but not to those exposed to 20 mg/litre (3 mg/kg of body weight per day), which was considered a NOAEL (Orme et al., 1985).

In a second experiment, rat pups were exposed directly (by gavage) to 14 mg of chlorine dioxide per kg of body weight per day (equivalent to the dose received by a pregnant dam drinking water containing 100 mg of chlorine dioxide per litre) on postnatal days 5–20. In this study, serum thyroxine levels were depressed, a somewhat greater and more consistent delay in the development of exploratory and locomotor activity was seen and pup body weight gain was reduced. The decrease in serum triiodothyronine levels was not statistically significant. Based on decreased pup development and decreased thyroid hormone levels, a LOAEL of 14 mg/kg of body weight per day (the only dose tested) was identified (Orme et al., 1985).

Cell number was significantly depressed in the cerebellum of 21-day-old rat pups born to dams supplied during gestation and lactation with water containing 100 mg of chlorine dioxide per litre (about 14 mg/kg of body weight per day to the dam). A group of 12 rat pups dosed directly by gavage with 14 mg/kg of body weight per day had depressed cell numbers in both the cerebellum and forebrain at postnatal day 11 and displayed decreased voluntary running wheel activity at postnatal days 50–60, despite the fact that chlorine dioxide treatments were terminated at 20 days of age. These data suggest that chlorine dioxide is capable of influencing brain development in neonatal rats. In this study, a LOAEL of 14 mg/kg of body weight per day, the only dose tested, was identified (Taylor & Pfohl, 1985).

The developmental neurotoxic potential of chlorine dioxide was evaluated in a study in which it was administered to rat pups by oral intubation at 14 mg/kg of body weight per day on postnatal days 1–20. Forebrain cell proliferation was decreased on postnatal day 35, and there were decreases in forebrain weight and protein content on postnatal days 21 and 35. Cell proliferation in the cerebellum and olfactory bulbs was comparable to that in untreated controls, as were migration and aggregation of neuronal cells in the cerebral cortex. Histopathological examination of the forebrain, cerebellum and brain stem did not reveal any lesions or changes in these tissues. In this study, a LOAEL of 14 mg/kg of body weight per day (the only dose tested) was identified (Toth et al., 1990).

Female Sprague-Dawley rats received chlorine dioxide at approximately 0, 0.07, 0.7 or 7 mg/kg of body weight per day in drinking-water. After approximately 10 weeks of exposure, females were mated with untreated males and continued to receive chlorine dioxide throughout gestation. On day 20 of gestation, the dams were sacrificed, their uteri were removed and weighed, and the fetuses were examined; half of the fetuses were examined for skeletal and half for visceral abnormalities. There were no clinical signs of toxicity and no exposure-related mortalities among the dams. There was a slight, but not statistically significant, reduction in body weight gain among dams at 0.7 and 7 mg/kg of body weight per day during pregnancy (approximately 14% reduction compared with controls). There was a slight reduction in the mean number of implants per dam in the two highest dose groups, which was statistically significant at 7 mg/kg of body weight per day (10.3 per dam compared with 12.3 per dam in controls). A similar change in the number of live fetuses was also observed at the two highest doses. These effects may have been related to maternal toxicity, as there was a slight reduction in body weight gain among dams at the two highest exposure levels. The incidence of litters with anomalous fetuses was unaffected by treatment (5/6, 4/6, 6/6 and 7/8 among animals receiving 0, 0.07, 0.7 and 7 mg/kg of body weight per day, respectively) (Suh et al., 1983).

4.1.4 Mutagenicity and related end-points

Chlorine dioxide was mutagenic in *Salmonella typhimurium* strain TA100 in the absence of a metabolic activation system (Ishidate et al., 1984). No sperm head abnormalities were observed in male mice following chlorine dioxide gavage (Meier et al., 1985). No chromosomal abnormalities were seen in either the micronucleus test or a cytogenetic assay in mouse bone marrow cells following gavage dosing with chlorine dioxide (Meier et al., 1985).

In an *in vitro* cytogenetics assay, Chinese hamster ovary cells were treated with 0, 2.5, 5, 10, 15, 30 or 60 µg of 0.2% chlorine dioxide per ml in phosphate-buffered saline solution without metabolic activation (-S9). A second experiment was conducted with Chinese hamster ovary cells treated at 0, 6, 13, 25, 50 or 75 µg/ml with metabolic activation (+S9). In the first experiment, cell toxicity was observed 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. In the second experiment (with metabolic activation), cell toxicity and 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 $TK^{+/-}$), cells were treated with 0–65 µg of chlorine dioxide per ml in phosphate-buffered saline with and without metabolic activation (S9). Without S9, marked toxicity was observed at the highest concentration used, 37 µg/ml. The relative growth at the next two concentrations (15 and 24 µg/ml) was 13–18%. There was a dose-related increase in mutant frequency. With S9, marked toxicity was observed at the highest

concentration, 65 µg/ml, and there was also a dose-related increase in mutant frequency, indicating positive results both with and without metabolic activation in this test system (Cifone & Myhr, 1986).

4.1.5 Carcinogenicity

Tumours were not observed in rats following 2-year exposures to chlorine dioxide in drinking-water, although it should be noted that this study is over 50 years old and has serious limitations (Haag, 1949).

4.2 Chlorite

4.2.1 Acute exposure

An oral LD_{50} of 105 mg/kg of body weight has been reported in rats (Musil et al., 1964). Quail were more resistant than rats; the LD_{50} was 493 mg/kg of body weight (Fletcher, 1973).

4.2.2 Short-term exposure

Single doses of sodium chlorite administered orally to cats produced methaemoglobinaemia (Heffernan et al., 1979). A dose of 20 mg of chlorite per litre (equivalent to approximately 1.5 mg of chlorite per kg of body weight) caused up to 32% of the haemoglobin to be in the methaemoglobin state and was considered to be the LOAEL. A dose-dependent increase in methaemoglobinaemia and anaemia was observed in 12 African green monkeys treated with sodium chlorite at 0, 25, 50, 100 or 400 mg/litre in drinking-water using a rising-dose protocol. Doses of chlorite were approximately 0, 3, 6, 13 and 50 mg/kg of body weight per day, and each dose level was maintained for 30–60 days (Bercz et al., 1982).

A more recent study employed doses of sodium chlorite administered by gavage to male and female Crl:CD (SD) BR rats (15 per sex per group). Doses of 0, 10, 25 or 80 mg of sodium chlorite per kg of body weight per day were administered daily by gavage for 13 weeks (equivalent to 0, 7.4, 18.6 or 59.7 mg of chlorite per kg of body weight per day). This study is important because it includes many of the standard parameters of subchronic toxicological studies, whereas previous studies had focused almost entirely on blood parameters. A gavage dose of 80 mg/kg of body weight per day produced death in a number of animals. It also resulted in morphological changes in erythrocytes and significant decreases in haemoglobin concentrations. At 80 mg/kg of body weight per day, red blood cell counts in both sexes were significantly less than control values. In males only, haematocrit and haemoglobin levels were significantly less than control values, and methaemoglobin level and neutrophil count were significantly greater than control values. A slight increase in reticulocyte count was observed at 80 mg/kg of body weight per day in males, but the increase was not statistically significant. These changes were due to marked changes in two individual males, which died shortly after the 13-week bleeding. At 80 mg/kg of body weight per

day, methaemoglobin levels in females were significantly less than control values. A statistical trend test indicated a dose-related downward trend for red blood cell count in females at 25 mg/kg of body weight per day and in males at 10 mg/kg of body weight per day. Statistical significance was not confirmed by direct comparison with the control group, and the group mean values were within the background range; therefore, a direct association with treatment could not be conclusively established. As would be expected where haemolysis is occurring, splenic weights were increased. Adrenal weights were increased in females at 25 and 80 mg/kg of body weight per day, whereas statistically significant changes were observed only at 80 mg/kg of body weight per day in males. Histopathological examination of necropsied tissues revealed squamous cell epithelial hyperplasia, hyperkeratosis, ulceration, chronic inflammation and oedema in the stomach of 7 out of 15 males and 8 out of 15 females given 80 mg/kg of body weight per day doses. This effect was observed in only 2 out of 15 animals at the 25 mg/kg of body weight per day dose and not at all at the 10 mg/kg of body weight per day dose. Microscopic evaluations were made in 40 additional tissues, but no treatment-related abnormalities were found. The NOAEL for this study was determined to be 7.4 mg/kg of body weight per day for stomach lesions and increases in spleen and adrenal weights (Harrington et al., 1995a).

Rats were exposed to chlorite ion at 0, 10, 50, 100, 250 or 500 mg/litre in drinking-water (equivalent to 0, 1, 5, 10, 25 or 50 mg/kg of body weight per day) for 30–90 days. Haematological parameters were monitored, and the three highest concentrations produced transient anaemia. At 90 days, red blood cell glutathione levels in the 100 mg/litre group were 40% below those of controls; there was at least a 20% reduction in the rats receiving 50 mg/litre. In this study, a NOAEL of 1 mg/kg of body weight per day was identified (Heffernan et al., 1979).

4.2.3 Long-term exposure

The effect of sodium chlorite in drinking-water at 0, 1, 2, 4, 8, 100 or 1000 mg/litre on the survival and postmortem pathology of albino rats (seven per sex per dose) was examined in a 2-year study. The life span of the animals was not significantly affected at any dose. No effects were observed in animals exposed to 8 mg/litre (0.7 mg/kg of body weight per day) or less. Animals exposed to 100 or 1000 mg/litre (9.3 or 81 mg/kg of body weight per day) exhibited treatment-related renal pathology; the author concluded that this was the result of a non-specific salt effect. Based on renal effects, this study identifies a NOAEL of 8 mg/litre (0.7 mg/kg of body weight per day) and a LOAEL of 100 mg/litre (9.3 mg/kg of body weight per day). This study has limited value, since there was an insufficient number of animals tested per group, pathology was conducted on a small number of animals and the study did not provide adequate evaluations of more sensitive parameters (Haag, 1949).

4.2.4 Reproductive and developmental toxicity

Female mice (10 per dose) were treated with sodium chlorite at 0 or 100 mg/litre in drinking-water (equivalent to 0 and 22 mg/kg of body weight per day) (US EPA, 2000) from day 1 of gestation and throughout lactation. Conception rates were 56%

for controls and 39% for treated mice. The body weights of pups at weaning were reduced (14% below the controls) in treated mice relative to controls, so that 22 mg/kg of body weight per day is the LOAEL for this study (Moore & Calabrese, 1982).

In a series of three experiments, sodium chlorite was administered to male rats (12 per dose) in drinking-water for 66–76 days at concentrations of 0, 1, 10, 100 or 500 mg/litre (equivalent to 0, 0.1, 1, 10 and 50 mg/kg of body weight per day). No compound-related abnormalities were observed on histopathological examination of the reproductive tract. Abnormal sperm morphology and decreased sperm motility were seen at the two highest dose levels, but no sperm effects were observed at 1 mg/kg of body weight per day, which can be identified as the NOAEL. In another part of the same study, male rats were bred with female rats treated at 0, 0.1, 1.0 or 10 mg of sodium chlorite per kg of body weight per day dose levels. Males were exposed for 56 days and females for 14 days prior to breeding and throughout the 10-day breeding period. Females were also exposed throughout gestation and lactation, until the pups were weaned on day 21. There was no evidence of any adverse effects on conception rates, litter size, day of eye opening or day of vaginal opening. Decreases in the concentrations of triiodothyronine and thyroxine in blood were observed on postnatal days 21 and 40 in male and female pups exposed to 100 mg/litre. Based on reproductive effects, a NOAEL of 10 mg/kg of body weight per day, the highest dose tested in this experiment, was identified (Carlton et al., 1987).

Fetuses from maternal Sprague-Dawley rats exposed for 2.5 months prior to mating and throughout gestation to chlorite ion via drinking-water at levels of 1 or 10 mg/litre were examined. There was an increase in the incidence of anomalies at both concentrations; however, because the treatment groups were small (6–9 females per group), the effects were not considered statistically significant (Ishidate et al., 1984).

Groups of female Sprague-Dawley rats (12 per group) were exposed for 9 weeks to drinking-water containing 0, 20 or 40 mg of sodium chlorite per litre (0, 3 or 6 mg of chlorite per kg of body weight per day) beginning 10 days prior to breeding with untreated males and until the pups were sacrificed at 35–42 days post-conception. Pups were culled at birth to eight pups per litter (all males if possible). From days 31 to 42 post-conception, six litters of each treatment group were assessed for the development of exploratory activity. Pups exposed to a dose of 6 mg/kg of body weight per day exhibited a consistent and significant depression in exploratory behaviour on post-conception days 36–39, but not on day 40. Exploratory activity was comparable between treated and control groups after post-conception day 39. Based on behavioural effects, the NOAEL was identified as 3 mg/kg of body weight per day (Mobley et al., 1990).

In a two-generation study, Sprague-Dawley rats (30 per sex per dose) received drinking-water containing 0, 35, 70 or 300 mg of sodium chlorite per litre for 10 weeks and were then paired for mating. Males were exposed throughout mating, then sacrificed. Exposure for the females continued through mating, pregnancy, lactation and until necropsy following weaning of their litters. Twenty-five males and females

from each of the first 25 litters to be weaned in a treatment group were chosen to produce the F_1 generation. The F_1 pups were continued on the same treatment regimen as their parents. At approximately 14 weeks of age, they were mated to produce the F_{2a} generation. Because of a reduced number of litters in the 70 mg/litre F_1–F_{2a} generation, the F_1 animals were remated following weaning of the F_{2a} generation to produce the F_{2b} generation. Doses for the F_0 animals were 0, 3.0, 5.6 or 20.0 mg of chlorite per kg of body weight per day for males and 0, 3.8, 7.5 or 28.6 mg of chlorite per kg of body weight per day for females. For the F_1 animals, doses were 0, 2.9, 5.9 or 22.7 mg of chlorite per kg of body weight per day for males and 0, 3.8, 7.9 or 28.6 mg of chlorite per kg of body weight per day for females. There were reductions in water consumption, food consumption and body weight gain in both sexes in all generations at various times throughout the experiment, primarily in the 70 and 300 mg/litre groups; these were attributed to lack of palatability of the water. At 300 mg/litre, reduced pup survival, reduced body weight at birth and throughout lactation in F_1 and F_2, lower thymus and spleen weights in both generations, lowered incidence of pups exhibiting a normal righting reflex, delays in sexual development in males and females in F_1 and F_2 and lower red blood cell parameters in F_1 were noted. Significant reductions in absolute and relative liver weights in F_0 females and F_1 males and females, reduced absolute brain weights in F_1 and F_2 and a decrease in the maximum response to auditory startle stimulus on postnatal day 24 but not at postnatal day 60 were noted in the 300 and 70 mg/litre groups. Minor changes in red blood cell parameters in the F_1 generation were seen at 35 and 70 mg/litre, but these appeared to be within normal ranges based on historical data. The NOAEL in this study was 35 mg/litre (2.9 mg/kg of body weight per day), based on lower auditory startle amplitude, decreased absolute brain weight in the F_1 and F_2 generations and altered liver weights in two generations (CMA, 1997; TERA, 1998).

The developmental toxicity of chlorite was examined in New Zealand white rabbits. The rabbits (16 per group) were treated with 0, 200, 600 or 1200 mg of sodium chlorite per litre in their drinking-water (equivalent to 0, 10, 26 or 40 mg of chlorite per kg of body weight per day) from day 7 to day 19 of pregnancy. The animals were necropsied on day 28. Food consumption was depressed at the top two doses, and water consumption was depressed at all doses, but more notably in the top two dose groups. Mean fetal weights were slightly lower at the top two doses as well, with a slightly higher incidence of incomplete ossification of some bones. There were no dose-related increases in defects identified. Minor skeletal anomalies were observed as the concentration of chlorite in water was increased and maternal food consumption was depressed. A NOAEL of 200 mg/litre (10 mg/kg of body weight per day) and a LOAEL of 600 mg/litre (26 mg/kg of body weight per day) were identified based on a decrease in fetal weight and delayed ossification, decreased food and water consumption of the dams and decreased body weight gain in the dams. There was some uncertainty surrounding the interpretation of the results because of inadequate reporting of the number and types of specific abnormalities and variations. In addition, there was some uncertainty as to whether the decreases in food and water consumption and body weight gain in the dams were caused by unpalatability or a direct toxic effect of the chlorite (Harrington et al., 1995b).

4.2.5 Mutagenicity and related end-points

Sodium chlorite produced an increase in revertant colonies in *Salmonella typhimurium* strain TA100 in both the presence and absence of metabolic activation (Ishidate et al., 1984). No chromosomal abnormalities were seen in either the mouse micronucleus test or a cytogenetic assay in mouse bone marrow cells following gavage dosing with chlorite (Meier et al., 1985).

In a micronucleus test in bone marrow from male ddY mice after a single intraperitoneal injection of sodium chlorite at 0, 7.5, 15, 30 or 60 mg/kg of body weight, a statistically positive response was observed at 15 and 30 mg/kg of body weight only: 0.38% and 1.05%, respectively, compared with 0.18% for the control group (Hayashi et al., 1998).

4.2.6 Carcinogenicity

In a long-term study, F344 rats received sodium chlorite in drinking-water at doses of 300 or 600 mg/litre (corresponding to 18 and 32 mg/kg of body weight per day for males and 28 and 41 mg/kg of body weight per day for females) for 85 weeks. All groups of rats were infected with the Sendai virus. A slight dose-related decrease in body weight gain was observed, within 10% of that of the control group. However, no adverse effects on survival or chlorite-related increases in tumour incidence were observed (Hayashi et al., 1998).

Sodium chlorite was administered at concentrations of 0, 250 or 500 mg/litre to $B6C3F_1$ mice (50 per sex per group) for 80 weeks followed by distilled water only for an additional 5 weeks. The concentrations corresponded to doses of approximately 0, 38.1 and 59.3 mg/kg of body weight per day for females and 0, 43 and 68.6 mg/kg of body weight per day for males. All animals were sacrificed after 85 weeks. The incidence of tumour-bearing animals was 32% (control), 34% (low dose) and 26% (high dose) in female mice and 46% (control), 57% (low dose), and 53% (high dose) in male mice. The type and incidence of neoplasms that occurred frequently in each group of both sexes were similar to those observed spontaneously in $B6C3F_1$ mice. The incidence of lymphomas/leukaemias found in the high-dose group was lower than that in the control group: 2% versus 15%, respectively. The incidence of pulmonary adenomas in the high-dose group for males (12%) was higher than the incidence in the controls (0%). The authors suggested either that the higher incidence of lung adenomas in the high-dose group could be attributed to a statistical variation resulting from the low adenoma incidence in control males or that there was a strong case for further studies on the carcinogenicity of sodium chlorite. Overall, no dose-related increases of adenoma or adenocarcinoma incidences were observed, and there was no clear evidence of carcinogenic potential of sodium chlorite in $B6C3F_1$ mice (Kurokawa et al., 1986).

4.3 Chlorate

4.3.1 Acute exposure

An acute oral dosing study in dogs demonstrated lethality at levels of sodium chlorate as low as 600 mg of chlorate ion per kg of body weight (Sheahan et al., 1971).

4.3.2 Short-term exposure

Beagle dogs (four per sex per dose) were exposed by gavage to sodium chlorate at doses of 0, 10, 60 or 360 mg/kg of body weight per day for 3 months. There was no significant effect at any dose level on body weight, food consumption, clinical chemistry, organ weights, ophthalmic effects, gross necropsy or tissue histopathology. Haematological changes were limited to a slight elevation in methaemoglobin level in highest-dose animals, but this appeared to be within normal limits and was not judged to be treatment-related. In this study, a NOAEL of 360 mg/kg of body weight per day in dogs was identified (Bio/dynamics, Inc., 1987a).

Sprague-Dawley rats (14 per sex per dose) were exposed by gavage to sodium chlorate at doses of 0, 10, 100 or 1000 mg/kg of body weight per day for up to 3 months. No treatment-related effects were observed on mortality, physical appearance or behaviour, body weight, food consumption, clinical chemistry, gross necropsy or organ histopathology. At the highest dose, haematological changes indicative of anaemia included decreases in erythrocyte count, haemoglobin concentration and erythrocyte volume fraction (haematocrit). In this study, a NOAEL of 100 mg/kg of body weight per day was identified (Bio/dynamics, Inc., 1987b).

In a 90-day study, chlorate at concentrations of 3, 12 or 48 mmol/litre in drinking-water was provided to both male and female Sprague-Dawley rats. These concentrations correspond to 250, 1000 and 4000 mg of chlorate per litre, equivalent to 30, 100 or 510 mg/kg of body weight per day in males and 42, 164 or 800 mg/kg of body weight per day in females, based on measured water consumption of each group. Body weight gain was sharply curtailed in both sexes at the highest concentration. These effects were generally paralleled by lower organ weights (except for brain and testes). Some decreases in haemoglobin, haematocrit and red blood cell counts were observed at this same dose. Pituitary lesions (vacuolation in the cytoplasm of the pars distalis) and thyroid gland colloid depletion were observed in both the mid- and high-dose groups of both sexes. The NOAEL in this study was 30 mg/kg of body weight per day (McCauley et al., 1995).

4.3.3 Carcinogenicity

There are no studies dealing with the carcinogenic potential of chlorate alone. Sodium and potassium chlorate were evaluated as promoters of renal tumours in *N*-ethyl-*N*-hydroxyethyl-nitrosamine-initiated F344 rats. Sodium chlorate resulted in an increase

in the number of renal tumours, but the effect was not statistically significant due to the small number of animals used (Kurokawa et al., 1985).

4.3.4 Reproductive and developmental toxicity

No studies were available examining the reproductive or embryotoxic potential of chlorate. Sodium chlorate was administered to pregnant CD rats by gavage at doses of 0, 10, 100 or 1000 mg/kg of body weight per day on days 6–15 of gestation. There were no maternal deaths in treated animals or treatment-related effects on maternal body weight gain, food consumption, clinical observations, number of implantations or gross necropsy. Examination of fetuses on day 20 revealed no effects on fetal weight or sex ratio, and no external, visceral or skeletal abnormalities were detected. In this study, a developmental NOAEL of 1000 mg/kg of body weight per day in rats was identified (Bio/dynamics, Inc., 1987c).

4.3.5 Mutagenicity and related end-points

Chlorate has long been known to select nitrate reductase-deficient mutants of *Aspergillus nidulans* (Cove, 1976). However, it has been demonstrated that there is also a mutagenic effect of chlorate in *Chlamydomonas reinhardtii* and *Rhodobacter capsulatus*. Chlorate failed to induce mutations in the BA-13 strain of *Salmonella typhimurium*. The positive mutagenic effects were separated from simple selection of nitrate reductase mutants by incubating cells in nitrogen-free media. Lack of nitrogen prevents cell division during the treatment period. In the case of *C. reinhardtii*, significant increases in mutants were observed at concentrations of 4–5 mmol/litre and above (Prieto & Fernandez, 1993).

No chromosomal abnormalities were seen in either the micronucleus test or a cytogenetic assay in mouse bone marrow cells following gavage dosing with chlorate (Meier et al., 1985).

5. EFFECTS ON HUMANS

5.1 Chlorine dioxide

Six different doses of chlorine dioxide (0.1, 1, 5, 10, 18 or 24 mg/litre) in drinking-water were administered to each of 10 male volunteers using a rising-dose protocol. Serum chemistry, blood count and urinalysis parameters were monitored. A treatment-related change in group mean values for serum uric acid was observed, which the authors concluded was not physiologically detrimental. The highest dose tested, 24 mg/litre (about 0.34 mg/kg of body weight per day), can be identified as a single-dose NOAEL (Lubbers et al., 1981).

The same male volunteers drank 0.5 litres of water containing 5 mg of chlorine dioxide per litre each day for approximately 12 weeks and were then kept under observation for 8 weeks. Serum chemistry, blood counts and urinalysis revealed no abnormalities, except for a slight change in blood urea nitrogen, which the authors

concluded was of doubtful physiological or toxicological significance. This exposure, equivalent to 36 µg/kg of body weight per day, can be considered a NOAEL (Lubbers et al., 1981).

In a prospective study of 197 persons, a portion of the population of a rural village exposed for 12 weeks to a chlorine dioxide-treated water supply (containing 0.25–1.1 mg of chlorine dioxide per litre and 0.45–0.91 mg of free chlorine per litre) experienced no significant changes in haematological parameters, serum creatinine or total bilirubin (Michael et al., 1981).

A cross-sectional study was conducted of 548 births at Galliera Hospital in Genoa, Italy, and 128 births at Chiavari Hospital in Chiavari, Italy, during 1988–1989 to mothers residing in each city. Women in Genoa were exposed to filtered water disinfected with chlorine dioxide (Brugneto River wells, reservoir water and surface water) and/or chlorine (Val Noci reservoir). Women residing in Chiavari used untreated well water. Assignment to a water source and type of disinfectant was based on the mother's address (undisinfected well water, chlorine, chlorine dioxide or both). Municipal records were used to determine family income, and hospital records were used to obtain information about mother's age, smoking, alcohol consumption and education level and birth outcomes — low birth weight (≤2500 g), preterm delivery (≤37 weeks), body length (≤49.5 cm), cranial circumference (≤35 cm) and neonatal jaundice. Neonatal jaundice was almost twice as likely (OR = 1.7; 95% CI = 1.1–3.1) in infants whose mothers resided in the area where drinking-water from surface water sources was disinfected with chlorine dioxide as in infants whose mothers used undisinfected well water. Chlorinated surface water did not produce a similar effect. Large increased risks of smaller cranial circumference and body length were associated with water from surface water sources disinfected with chlorine or chlorine dioxide. The risks for smaller cranial circumference for infants of mothers residing in areas with chlorine dioxide-treated surface water, compared with infants of mothers residing in areas with untreated well water, were as follows: OR = 2.2; 95% CI = 1.4–3.9. For smaller body length, the risks were as follows: OR = 2.0; 95% CI = 1.2–3.3. Risks of low birth weight were also increased for infants of mothers residing in areas with drinking-water disinfected with either chlorine or chlorine dioxide, but they were not statistically significant. For preterm delivery, there were small but non-significant increased risks associated with chlorine or chlorine dioxide disinfection. This study suggests possible risks associated with surface water disinfected with either chlorine or chlorine dioxide, but the results should be interpreted very cautiously. The THM levels were low in both the chlorine-treated (8–16 µg/litre) and chlorine dioxide-treated (1–3 µg/litre) surface water, so it seems unlikely that they could be the causal agents. No information was collected to assess the mothers' water consumption or nutritional habits, and the age distribution of the mothers was not considered. It is possible that bottled water consumption could have confounded the results, particularly if mothers in areas with chlorinated or chlorine dioxide-treated water elected to drink bottled water more than those in the area served by untreated well water. In addition, there are concerns about incomplete ascertainment of births and whether the populations may be different in respects other than the studied water system differences. On the other hand, if the observed associations with water source

and disinfection are not spurious, a question is raised about what water contaminants may be responsible. Exposures to surface water and groundwater sources are compared in this study, and no information is presented about other possible water quality differences (Kanitz et al., 1996).

5.2 Chlorite

The effects of sodium chlorite on humans were evaluated in 10 male volunteers in a rising-dose protocol. Single doses of 0.01, 0.1, 0.5, 1.0, 1.8 and 2.4 mg of chlorite ion per litre in 1 litre of drinking-water were ingested by each subject. Changes in group mean values for serum urea nitrogen, creatinine and urea nitrogen/creatinine ratio were observed, which the authors concluded were not adverse physiological effects. The highest dose tested, 2.4 mg/litre (0.034 mg/kg of body weight per day), can be identified as a single-dose NOAEL (Lubbers et al., 1981).

The same volunteers ingested 0.5 litres of water per day containing 5 mg of sodium chlorite per litre for approximately 12 weeks and were then kept under observation for 8 weeks. Treatment was associated with a change in group mean corpuscular haemoglobin; however, as there was no trend over time for this change and values were within the normal ranges, the authors were reluctant to attach physiological significance to the observation. The dose tested, equivalent to 36 µg/kg of body weight per day, was identified as the NOAEL (Lubbers et al., 1981).

5.3 Chlorate

Because of its use as a weed killer, a large number of cases of chlorate poisoning have been reported (NAS, 1987). Symptoms include methaemoglobinaemia, anuria, abdominal pain and renal failure. For an adult human, the oral lethal dose is estimated to be as low as 20 g of sodium chlorate (230 mg of chlorate per kg of body weight) (NAS, 1980).

Ten male volunteers were given six separate doses of sodium chlorate following a rising-dose protocol, single doses of 0.01, 0.1, 0.5, 1.0, 1.8 and 2.4 mg of chlorate ion per litre in 1 litre of drinking-water being ingested by each volunteer. Very slight changes in group mean serum bilirubin, iron and methaemoglobin were observed, but the authors concluded that they were not adverse physiological effects. The highest dose tested, 2.4 mg/litre (34 µg/kg of body weight per day), can be identified as a single-dose NOAEL (Lubbers et al., 1981).

The volunteers also ingested 0.5 litres of water per day containing 5 mg of sodium chlorate per litre (36 µg/kg of body weight per day) for approximately 12 weeks and were then kept under observation for 8 weeks. Treatment was associated with slight changes in group mean serum urea nitrogen and mean corpuscular haemoglobin, but the authors concluded that these were not physiologically significant, as values remained within the normal range for each parameter. The NOAEL was 36 µg/kg of body weight per day (Lubbers et al., 1981).

6. PRACTICAL ASPECTS

6.1 Analytical methods and analytical achievability

Methods are available for the determination of chlorine dioxide, chlorite and chlorate and total available chlorine (APHA et al., 1995a,b). The limits of detection for these methods are 8 µg/litre for chlorine dioxide, 10 µg/litre for chlorite and chlorate and 4 µg/litre for total chlorine.

6.2 Treatment and control methods and treatment achievability

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 levels are recommended (US EPA, 2003). If chlorine dioxide and chlorite ion are not removed prior to post-chlorine disinfection, they will react with free chlorine to form chlorate ion. Once chlorate ion is present in water, it is very persistent and very difficult to remove (Gallagher et al., 1994; US EPA, 1999).

There are four available treatment options for lowering chlorite ion concentrations in drinking-water at the municipal scale: activated carbon, sulfur reducing agents, iron reducing agents, and tuning of the chlorine dioxide generator.

Activated carbon will remove chlorite ion through adsorption and chemical reduction. Early break-through has been reported in granular activated carbon (GAC) filters when the adsorptive sites have been exhausted, perhaps by competing organic compounds, and only the reduction mechanism remains. The performance of GAC filters for chlorite removal is further complicated by the oxidation of chlorite to chlorate, which may occur if free chlorine is present in the feed water. Short bed life, high operating costs, and the potential for chlorate formation make GAC an impractical choice for chlorite removal at the municipal scale (Dixon & Lee, 1991).

Sulfur agents such as sulfite, metabisulfite, and thiosulfate will reduce chlorine dioxide and chlorite ion, thereby lowering their concentrations in water. In the presence of dissolved oxygen, sulfite and metabisulfite will reduce chlorite to form chloride ion and the undesirable chlorate ion and, as such, is not recommended for the removal of chlorite in drinking water. Thiosulfate is effective at reducing chlorine dioxide and chlorite and does not form chlorate as a by-product, but it requires a long contact time and is pH dependent, which may limit its effectiveness (Griese et al., 1991).

Ferrous iron (Fe^{2+}) will chemically reduce chlorite ion, thereby lowering its concentrations in water. Chlorate ion will form only if the pH drops below 5, which can occur at localized application points where acidic reducing agents such as ferrous chloride are added to the water. Good application and rapid mix and/or pH adjustment to neutral pH 7 may prevent the occurrence of micro-regions of low pH and the subsequent formation of chlorate (Griese et al., 1992). When the pH exceeds 7, the subsequent reaction of chlorite and ferrous iron forms insoluble ferric hydroxide,

which may be beneficial by aiding clarification (Iatrou & Knocke, 1992). However, if the pH exceeds 9, elevated dissolved oxygen and dissolved organic carbon levels impede the effectiveness of ferrous iron and require increased ferrous dosages to attain adequate chlorite removal (Hurst & Knocke, 1997). Any residual chlorite will react with chlorine to form chlorate and should be removed before post-chlorine disinfectant is applied. Ferrous iron or thiosulfate, when used as treatment options for chlorite removal, may be fed in excess of the demand and can complicate post-disinfection (US EPA, 2001).

Chlorine dioxide generator design and performance have a large impact on the amount of chlorite ion formed during chlorine dioxide production. 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 such as chlorate, hydrogen peroxide, and perchlorate are formed. Current commercial chlorine dioxide generators may be broadly classified as chlorite based, chlorate based, or electrochemical systems.

Chlorite ion-based systems rely on the oxidation of chlorite ion to chlorite through the use of an acid, which may attain a maximum conversion efficiency of 80% by stoichiometry; or through the use of chlorine gas, which can result in chlorite carry-through if the chlorine gas feed is too low and chlorate formation if the chlorine gas feed is too high.

Recently developed chlorate ion-based systems typically depend on the reduction of chlorate ion through the reaction of sodium chlorate with an acid and hydrogen peroxide. The product may be quite acidic, and the risk of high hydrogen peroxide and perchlorate levels in the water may detract from the viability of this method.

Electrochemical systems can either directly or indirectly generate chlorine dioxide. The direct method involves the electrolysis of chlorite ion to chlorine dioxide at the anode, and the indirect method is the production of an acid or chlorine gas as a precursor chemical, resulting in the formation of chlorine dioxide, again at the anode. When the chlorine dioxide is formed at the anode, it must be extracted as a gas from the solution by gas-stripping columns, eductors/venturis, low-pressure air flow over a packed bed, or perstraction, which involves the use of a gas-permeable hydrophobic membrane. Proper balance and control are required with these systems to prevent the formation and carry-through of impurities such as acid, chlorate ion, perchlorate ion, and chlorine (Gordon, 2001).

Currently, there is no known treatment available to remove chlorate ion once it has been formed in drinking-water. 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 is important to

minimize production of chlorate ion in the chlorine dioxide generation process and to remove the chlorite ion before adding post-chlorine (Gallagher et al., 1994).

7. PROVISIONAL GUIDELINE VALUES

7.1 Chlorine dioxide

Chlorine dioxide has been shown to impair neurobehavioural and neurological development in rats exposed perinatally. Experimental studies with rats and monkeys exposed to chlorine dioxide in drinking-water have shown some evidence of thyroid toxicity; however, because of the studies' limitations, it is difficult to drawn firm conclusions.

A guideline value has not been established for chlorine dioxide because of its rapid hydrolysis to chlorite and because the chlorite provisional guideline value (see below) is adequately protective for potential toxicity from chlorine dioxide. The taste and odour threshold for this compound is 0.4 mg/litre.

7.2 Chlorite

IARC (1991) has concluded that chlorite is not classifiable as to its carcinogenicity to humans (Group 3).

The primary and most consistent finding arising from exposure to chlorite is oxidative stress resulting in changes in the red blood cells (Heffernan et al., 1979; Harrington et al., 1995a). This end-point is seen in laboratory animals and, by analogy with chlorate, in humans exposed to high doses in poisoning incidents. There are sufficient data available to estimate a TDI for humans exposed to chlorite, including chronic toxicity studies and a two-generation reproductive toxicity study. Studies in human volunteers for up to 12 weeks did not identify any effect on blood parameters at the highest dose tested, 36 µg/kg of body weight per day (Lubbers et al., 1981). Because this study did not identify an effect level, it is not informative for establishing a margin of safety.

In a two-generation study in rats, a NOAEL of 2.9 mg/kg of body weight per day was identified based on lower startle amplitude, decreased absolute brain weight in the F_1 and F_2 generations and altered liver weights in two generations (CMA, 1997; TERA, 1998). Application of an uncertainty factor of 100 to this NOAEL (10 each for inter- and intraspecies variation) gives a TDI of 30 µg/kg of body weight. This TDI is supported by human volunteer studies.

Using the TDI of 30 µg/kg of body weight, 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 litres of water per day, the provisional guideline value is calculated as 0.7 mg/litre (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.

7.3 Chlorate

Like chlorite, the primary concern with chlorate is oxidative damage to red blood cells. Also like chlorite, 36 µg of chlorate per kg of body weight per day for 12 weeks did not result in any adverse effects in human volunteers (Lubbers et al., 1981). Although the database for chlorate is less extensive than that for chlorite, a recent well conducted 90-day study in rats is available, which identified a NOAEL of 30 mg/kg of body weight per day based on thyroid gland colloid depletion at the next higher dose of 100 mg/kg of body weight per day (McCauley et al., 1995). Application of an uncertainty factor of 1000 to this NOAEL (10 each for inter- and intraspecies variation and 10 for the short duration of the study) gives a TDI of 30 µg/kg of body weight. This TDI is also supported by the human volunteer studies.

Using the TDI of 30 µg/kg of body weight, 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 litres of water per day, the provisional guideline value is calculated as 0.7 mg/litre (rounded figure). This guideline value is designated as provisional because use of chlorine dioxide as a disinfectant 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.

A long-term study is currently in progress that should provide more information on the effects of chronic exposure to chlorate.

8. REFERENCES

Abdel-Rahman MS (1985) Pharmacokinetics of chlorine obtained from chlorine dioxide, chlorine, chloramine and chloride. In: Jolley RL et al., eds. *Water chlorination: Environmental impact and health effects.* Vol. 5. Chelsea, MI, Lewis Publishers, pp. 281–293.

Abdel-Rahman MS, Couri D, Bull RJ (1982) Metabolism and pharmacokinetics of alternate drinking water disinfectants. *Environmental Health Perspectives*, 46:19–23.

Abdel-Rahman MS, Couri D, Bull RJ (1985) The kinetics of chlorite and chlorate in rats. *Journal of Environmental Pathology, Toxicology and Oncology*, 6(1):97–103.

Adam LC et al. (1992) Hypochlorous acid decomposition in the pH 5–8 region. *Inorganic Chemistry*, 31:3534–3541.

APHA, AWWA, WEF (1995a) Method 4500, chlorine. In: *Standard methods for the examination of water and wastewater*, 19th ed. Washington, DC, American Public Health Association, American Water Works Association, Water Environment Federation, pp. 4.45–4.67.

APHA, AWWA, WEF (1995b) Method 4500, chlorine dioxide. In: *Standard methods for the examination of water and wastewater*, 19th ed. Washington, DC, American Public Health Association, American Water Works Association, Water Environment Federation, pp. 4.75–4.83.

Bercz JP et al. (1982) Subchronic toxicity of chlorine dioxide and related compounds in drinking water in the nonhuman primate. *Environmental Health Perspectives*, 46:47–55.

Bio/dynamics, Inc. (1987a) *A subchronic (3-month) oral toxicity study in the dog via gavage administration with sodium chlorate*. East Millstone, NJ (Report No. 86-3114 for Sodium Chlorate Task Force, Oklahoma City, OK).

Bio/dynamics, Inc. (1987b) *A subchronic (3-month) oral toxicity study of sodium chlorate in the rat via gavage*. East Millstone, NJ (Report No. 86-3112 for Sodium Chlorate Task Force, Oklahoma City, OK).

Bio/dynamics, Inc. (1987c) *A teratogenicity study in rats with sodium chlorate*. East Millstone, NJ (Report No. 86-3117 for Sodium Chlorate Task Force, Oklahoma City, OK).

Budavari S, O'Neill M, Smith A, eds. (1989) *The Merck index. An encyclopedia of chemicals, drugs and biologicals*, 11th ed. Rahway, NJ, Merck.

Carlton BD et al. (1987) Sodium chlorite administration in Long-Evans rats: reproductive and endocrine effects. *Environmental Research*, 42:238–245.

Carlton BD et al. (1991) Reproductive effects in Long-Evans rats exposed to chlorine dioxide. *Environmental Research*, 56:170–177.

Cifone M, Myhr B (1986) *Mutagenicity evaluation of chlorine dioxide in the mouse lymphoma forward mutation assay.* Kensington, MD, Litton Bionetics Inc. (Report No. 20989).

CMA (1989) *A review of the uses, chemistry and health effects of chlorine dioxide and the chlorite ion*. Washington, DC, Chemical Manufacturers Association.

CMA (1997) *Sodium chlorite: drinking water rat two-generation reproductive toxicity study*. Washington, DC, Chemical Manufacturers Association (Quintiles Report CMA/17/96).

Cove DJ (1976) Chlorate toxicity in *Aspergillus nidulans*: Studies of mutants altered in nitrate assimilation. *Molecular and General Genetics*, 146:147–159.

Daniel FB et al. (1990) Comparative subchronic toxicity studies of three disinfectants. *Journal of the American Water Works Association*, 82:61–69.

Dixon K, Lee RG (1991) The effect of sulfur-based reducing agents and GAC filtration on chlorine dioxide by-products. *Journal of the American Water Works Association*, 83:48–55.

Fletcher D (1973) *Acute oral toxicity study with sodium chlorite in bobwhite quail*. Industrial Bio-Test Laboratory's report to Olin Corporation (IBT No. J2119).

Gallagher DL, Hoehn RC, Dietrich AM (1994) *Sources, occurrence, and control of chlorine dioxide by-product residuals in drinking water*. Denver, CO, American Water Works Association Research Foundation.

Gordon G (2001) Is all chlorine dioxide created equal? *Journal of the American Water Works Association*, 93:163–173.

Griese MH et al. (1991) Using reducing agents to eliminate chlorine dioxide and chlorite ion residuals in drinking water. *Journal of the American Water Works Association*, 83:56–61.

Griese MH, Kaczur JJ, Gordon G (1992) Combining methods for the reduction of oxychlorine residuals in drinking water. *Journal of the American Water Works Association*, 84:69–77.

Haag HB (1949) *The effect on rats of chronic administration of sodium chlorite and chlorine dioxide in the drinking water.* Report to the Mathieson Alkali Works from the Medical College of Virginia.

Harrington RM, Shertzer HG, Bercz JP (1986) Effects of chlorine dioxide on thyroid function in the African green monkey and the rat. *Journal of Toxicology and Environmental Health*, 19:235–242.

Harrington RM et al. (1995a) Subchronic toxicity of sodium chlorite in the rat. *Journal of the American College of Toxicology*, 14:21–33.

Harrington RM, Romano RR, Irvine L (1995b) Developmental toxicity of sodium chlorite in the rabbit. *Journal of the American College of Toxicology*, 14:108–118.

Hayashi M et al. (1998) Micronucleus tests in mice on 39 food additives and 8 miscellaneous chemicals. *Food and Chemical Toxicology*, 26(6):487–500.

Heffernan WP, Guion C, Bull RJ (1979) Oxidative damage to the erythrocyte induced by sodium chlorite, *in vivo. Journal of Environmental Pathology and Toxicology*, 2:1487–1499.

Hurst GH, Knocke WR (1997) Evaluating ferrous iron for chlorite ion removal. *Journal of the American Water Works Association*, 89:98–105.

Hutchison J, Mole N, Fielding M (1994) Bromate and chlorate in water: the role of hypochlorite. In: *Proceedings of the First International Research Symposium on Water Treatment By-products.* Organized by Groupement de Recherche Universitaire sur les Techniques de Traitement et d'Epuration des Eaux (GRUTTEE), Poitiers, 29–30 September.

IARC (1991) *Chlorinated drinking-water; chlorination by-products; some other halogenated compounds; cobalt and cobalt compounds.* Lyon, International Agency for Research on Cancer, pp. 45–359 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 52).

Iatrou A, Knocke WR (1992) Removing chlorite by the addition of ferrous iron. *Journal of the American Water Works Association*, 84:63–68.

IPCS (2002) *Chlorine dioxide (gas)*. Geneva, World Health Organization, International Programme on Chemical Safety (Concise International Chemical Assessment Document 37).

Ishidate M et al. (1984) Primary mutagenicity screening of food additives currently used in Japan. *Food and Chemical Toxicology*, 22:623–636.

Ivett J, Myhr B (1986) *Mutagenicity evaluation of chlorine dioxide in an in vitro cytogenetic assay*. Kensington, MD, Litton Bionetics Inc. (Report No. 20990).

Kanitz S et al. (1996) Association between drinking water disinfection and somatic parameters at birth. *Environmental Health Perspectives*, 104(5):516–520.

Kurokawa Y et al. (1985) Lack of promoting effect of sodium chlorate and potassium chlorate in two-stage rat renal carcinogenesis. *Journal of the American College of Toxicology*, 4:331–337.

Kurokawa Y et al. (1986) Long-term *in vivo* carcinogenicity tests of potassium bromate, sodium hypochlorite and sodium chlorite conducted in Japan. *Environmental Health Perspectives*, 69:221–235.

Lubbers JR, Chauhan S, Bianchine JR (1981) Controlled clinical evaluations of chlorine dioxide, chlorite and chlorate in man. *Fundamental and Applied Toxicology*, 1:334–338.

McCauley PT et al. (1995) The effects of subchronic chlorate exposure in Sprague-Dawley rats. *Drug and Chemical Toxicology*, 18:185–199.

Meier JR et al. (1985) Evaluation of chemicals used for drinking water disinfection for production of chromosomal damage and sperm-head abnormalities in mice. *Environmental Mutagenesis*, 7:201–211.

Meister R, ed. (1989) *Farm chemicals handbook*. Willoughby, OH, Meister Publishing Co.

Michael GE et al. (1981) Chlorine dioxide water disinfection: a prospective epidemiology study. *Archives of Environmental Health*, 36:20–27.

Mobley SA et al. (1990) Chlorine dioxide depresses T_3 uptake and delays development of locomotor activity in young rats. In: Jolley RL, Condie LW, Johnson JD, eds. *Water chlorination: Chemistry, environmental impact and health effects*. Vol. 6. Ann Arbor, MI, Lewis Publishers, pp. 347–360.

Moore GS, Calabrese EJ (1982) Toxicological effects of chlorite in the mouse. *Environmental Health Perspectives*, 46:31–37.

Musil J et al. (1964) Toxicologic aspects of chlorine dioxide application for the treatment of water containing phenols. *Technology of Water*, 8:327–346.

NAS (1980) *Drinking water and health*. Vol. 4. Washington, DC, National Academy of Sciences, National Academy Press.

NAS (1987) *Drinking water and health.* Vol. 7. Washington, DC, National Academy of Sciences, National Academy Press.

Orme J et al. (1985) Effects of chlorine dioxide on thyroid function in neonatal rats. *Journal of Toxicology and Environmental Health*, 15:315–322.

Prieto R, Fernandez E (1993) Toxicity and mutagenesis by chlorate are independent of nitrate reductase in *Chlamydomonas reinhardtii*. *Molecular and General Genetics*, 237:429–438.

Sheahan BJ, Pugh DM, Winstanley EW (1971) Experimental sodium chlorate poisoning in dogs. *Research in Veterinary Science*, 12:387–389.

Suh D, Abdel-Rahman M, Bull R (1983) Effect of chlorine dioxide and its metabolites in drinking water on fetal development in rats. *Journal of Applied Toxicology*, 3(2):75–79.

Taylor DH, Pfohl RJ (1985) Effects of chlorine dioxide on the neurobehavioral development of rats. In: Jolley RL et al., eds. *Water chlorination: Environmental impact and health effects.* Vol. 5. Chelsea, MI, Lewis Publishers, pp. 355–364.

TERA (1998) *Health risk assessment/characterization of the drinking water disinfection by-products chlorine dioxide and chlorite*. Cincinnati, OH, Toxicology Excellence for Risk Assessment (8W-0766-NTLX).

Toth GP et al. (1990) Effects of chlorine dioxide on the developing rat brain. *Journal of Toxicology and Environmental Health*, 31:29–44.

US EPA (1983) Sodium chlorate: exemption from the requirement of a tolerance. US Environmental Protection Agency. *Federal Register*, 48:19028.

US EPA (1999) *Alternative disinfectants and oxidants guidance manual*. Washington, DC, US Environmental Protection Agency, Office of Water, April (EPA 815-R-99-014, http://www.epa.gov/safewater/mdbp/alternative_disinfectants_guidance.pdf).

US EPA (2000) *Toxicological review of chlorine dioxide and chlorite, in support of summary information on the Integrated Risk Information System (IRIS).* Washington, DC, US Environmental Protection Agency, September (EPA/636/R-00/007).

US EPA (2001) *Controlling disinfection by-products and microbial contaminants in drinking water*. Washington, DC, US Environmental Protection Agency, December (EPA/600/R-01/110; http://www.epa.gov/ordntrnt/ORD/NRMRL/Pubs/600R01110/600r01110completedocument.pdf).

US EPA (2003) Proposed rules. US Environmental Protection Agency. *Federal Register*, 68(159):49665.

US FDA (1990) *Food and drugs.* Vol. 21, Parts 170–179. Washington, DC, US Food and Drug Administration, Office of the Federal Register.