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N° 37

Chlorine Dioxide (Gas)

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among UNEP, ILO, FAO, WHO, UNIDO, UNITAR and OECD

WORLD HEALTH ORGANIZATION

Concise International Chemical Assessment Document 37

CHLORINE DIOXIDE (GAS)

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170[1] for advice on the derivation of health-based guidance values.

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Co-ordinator, IPCS, on the selection of chemicals for an IPCS risk assessment, the appropriate form of the document (i.e., EHC or CICAD), and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS and one or more experienced authors of criteria documents to ensure that it meets the specified criteria for CICADs.

The draft is then sent to an international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments.

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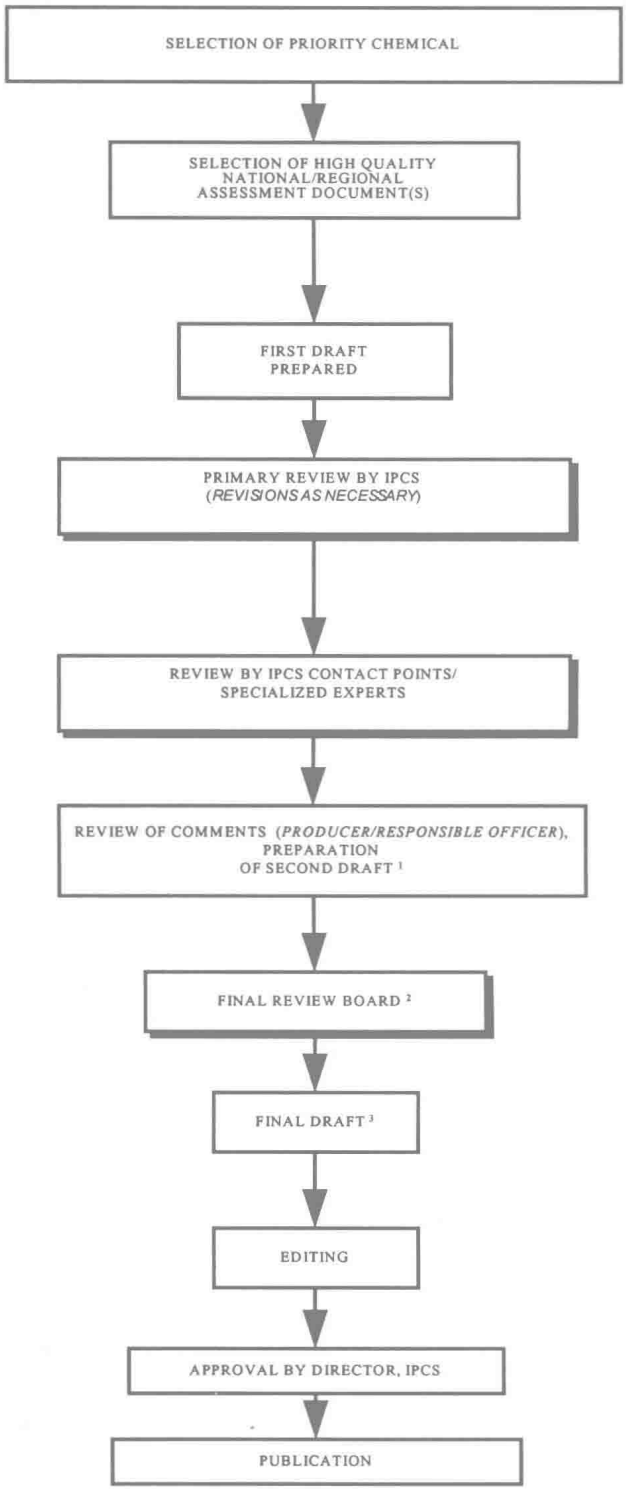
[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170).

CICAD PREPARATION FLOW CHART



1 Taking into account the comments from reviewers.
2 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.
3 Includes any revisions requested by the Final Review Board.

A consultative group may be necessary to advise on specific issues in the risk assessment document.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD on chlorine dioxide gas was based on a review of human health concerns (primarily occupational) prepared by the United Kingdom's Health and Safety Executive (Health and Safety Executive, 2000). This document focuses on exposures via routes relevant to occupational settings, principally related to the production of chlorine dioxide, but also contains environmental information. The health effects and environmental fate and effects of chlorine dioxide used in the treatment of drinking-water, together with those of halogenated organics produced by the interaction between the disinfectant and other materials present in the water, are covered in a recent Environmental Health Criteria document (IPCS, 2000) and are not dealt with in detail here. Data identified as of September 1998 were covered in the Health and Safety Executive review. A further literature search was performed up to January 1999 to identify any additional information published since this review was completed. Since no source document was available for environmental fate and effects, the primary literature was searched for relevant information. Information on the nature of the peer review and availability of the source document is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Stockholm, Sweden, on 25–28 May 1999. Participants at the Final Review Board meeting are presented in Appendix 3. The International Chemical Safety Card for chlorine dioxide (ICSC 0127), prepared by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

Chlorine dioxide (ClO_2, CAS No. 10049-04-4) exists as a greenish yellow to orange gas at room temperature. Chlorine dioxide gas is explosive when its concentration in air exceeds 10% v/v. It is water soluble, and solutions are quite stable if kept cool and in the dark. It is marketed and transported as a stabilized aqueous solution, generally less than 1% w/v (more concentrated forms are explosive).

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. Furthermore, once the gas is absorbed in water, it has a low volatility. For these reasons, inhalation exposure is anticipated to be minimal.

Limited occupational exposure data are available in relation to the manufacture and uses of chlorine dioxide; the measured or estimated concentrations indicated that all personal airborne exposures (in the United Kingdom) were below 0.1 ppm (0.28 mg/m^3) 8-h time-weighted average (TWA) and 0.3 ppm (0.84 mg/m^3) 15-min reference period.

The most common dermal exposure may arise from contact with aqueous solutions of up to 1% of the substance during preparation and use. It is predicted that dermal exposure from contact with the aqueous solution in occupational settings will range from 0.1 to 5 mg/cm^2 per day.

Toxicokinetic data are limited, although it would seem unlikely that there would be any significant systemic absorption and distribution of intact chlorine dioxide by dermal or inhalation routes. It is possible that other derivatives, such as chlorate, chlorite, and chloride ions, could be absorbed and widely distributed. One study shows that "chlorine" (chemical form not characterized) derived from aqueous chlorine dioxide is absorbed by the oral route, with a wide distribution and rapid and extensive elimination. No clear information is available on the identity of metabolites, although breakdown products are likely to include, at least initially, chlorites, chlorates, and chloride ions.

Given the reactive nature of chlorine dioxide, it seems likely that health effects would be restricted to local responses. There are no quantitative human data, but chlorine dioxide is very toxic by single inhalation exposure in rats. There were no mortalities following exposure to 16 ppm (45 mg/m^3) for 4 h, although pulmonary oedema and emphysema were seen in all animals exposed to 16–46 ppm (45–129 mg/m^3) chlorine dioxide, the incidence increasing in a dose-related manner. The calculated mean LC_{50} was 32 ppm (90 mg/m^3). In another study, ocular discharge, nosebleeds, pulmonary oedema, and death occurred at 260 ppm (728 mg/m^3) for 2 h. Chlorine dioxide is toxic when administered in solution by a single oral dose to rats; at 40 and 80 mg/kg body weight, there were signs of corrosive activity in the stomach and gastrointestinal tract. The calculated oral LD_{50} was 94 mg/kg body weight.

Data on the eye and respiratory tract irritancy of chlorine dioxide gas are limited in extent. However, there is evidence for eye and respiratory tract irritation in humans associated with unknown airborne levels of chlorine dioxide gas. Severe eye and respiratory tract

irritancy has been observed in rats exposed to 260 ppm (728 mg/m^3) for 2 h.

There are no reports of skin sensitization or occupational asthma associated with chlorine dioxide.

The quality of the available repeated inhalation exposure data in animals is generally poor, such that the information on dose–response must be viewed with some caution. In addition, there is concern that the nasal tissues were not examined, although rhinorrhoea was reported in one study in rats at 15 ppm (42 mg/m^3), indicating that the nasal passages may be a target tissue for inhaled chlorine dioxide. Other rat studies indicated that no adverse effects were reported at 0.1 ppm (0.28 mg/m^3) for 5 h/day for 10 weeks or at 1 ppm (2.8 mg/m^3) for 2–7 h/day for 2 months. Lung damage, manifested by bronchitis, bronchiolitis, or small areas of haemorrhagic alveolitis, appears to develop at 2.5 ppm (7.0 mg/m^3) or more following repeated exposure for 7 h/day for 1 month and at 10 ppm (28 mg/m^3) or more for 15 min twice per day for 4 weeks, with dose-dependent severity. Mortalities occurred following exposure at 15 ppm (42 mg/m^3) for 15 min, 2 or 4 times per day, for 1 month. In the same exposure regime, there were no adverse effects reported (among the limited observations performed) at 5 ppm (14 mg/m^3).

The results of repeated oral exposure studies in rats and primates are generally of limited design and/or quality but show no evidence of systemic toxicity associated with chlorine dioxide administered in the drinking-water or by gavage. There are no data in relation to chronic exposure to or carcinogenicity of chlorine dioxide gas.

Studies in mammalian cells using aqueous solutions of chlorine dioxide indicate that chlorine dioxide is an *in vitro* mutagen. This activity was not expressed in well conducted studies *in vivo* in somatic or germ cells. However, given the generally reactive nature of this substance and the fact that positive results have been produced *in vitro*, there is cause for concern for local "site-of-contact" mutagenicity, although no studies have been conducted for this end-point.

Oral exposure to chlorine dioxide at parentally toxic levels in rats does not impair fertility or development. This is consistent with the view that as chlorine dioxide is a reactive gas, it would be unlikely to reach the reproductive organs in significant amounts.

The available measured occupational exposure data (in the United Kingdom) and the exposure levels predicted using the Estimation and Assessment of Substance Exposure model indicate a maximum likely exposure of 0.1 ppm (0.28 mg/m^3), 8-h TWA. Comparison of this exposure level with the no-observed-adverse-effect level (NOAEL), which is derived from very limited data, suggests that there is no cause for concern in relation to the development of irritation of the respiratory tract or of the eyes in workers occupationally exposed to chlorine dioxide.

Insufficent data are available with which to conduct an environmental risk assessment. Chlorine dioxide would be degraded rapidly in the environment to yield chlorite and chlorate. The few ecotoxicity data available show that chlorine dioxide can be highly toxic to aquatic organisms; the lowest reported LC_{50} for fish was 0.02 mg/litre. Chlorate, released in pulp mill wastewaters following use of chlorine dioxide, has been shown to cause major ecological effects on brackish water communities. Brown macroalgae (seaweeds) are particularly sensitive to chlorate following prolonged exposure. The threshold for effects is between 10 and 20 µg/litre.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Chlorine dioxide (ClO_2, Chemical Abstracts Service [CAS] No. 10049-04-4), a free radical, exists as a greenish yellow to orange gas at room temperature with a characteristic pungent chlorine-like odour. Chlorine dioxide gas is strongly oxidizing; it is explosive in concentrations in excess of 10% v/v at atmospheric pressure and will easily be detonated by sunlight or heat (Budavari et al., 1996). Its melting point is -59 °C, its boiling point is 11 °C (at 101.3 kPa), and its vapour density is 2.34 (air = 1).

Owing to the difficulties in transportation associated with the explosive nature of aqueous solutions of chlorine dioxide, marketed products are usually stabilized by the addition of substances such as sodium hydrogen carbonate, which leads to the formation of an aqueous sodium chlorite solution rather than chlorine dioxide. However, chlorine dioxide is then generated at the site of intended use by a displacement reaction (such as by the addition of an acid). Its solubility in water is 3 g/litre at 20 °C, and its specific gravity is 1.642 (Budavari et al., 1996).

Some of the more commonly used synonyms for chlorine dioxide include chlorine oxide, chlorine peroxide, chloroperoxyl, chlorine(IV) oxide, and chlorine dioxide hydrate.

The chemical structure of chlorine dioxide is shown below:

·O=Cl=O·

The conversion factor for chlorine dioxide in air at 20 °C and 101.3 kPa is 1 ppm = 2.8 mg/m^3.

Additional physical/chemical properties are presented on the International Chemical Safety Card (ICSC 0127) reproduced in this document.

At room temperature and pressure, the natural form of chlorine dioxide is a gas that is unstable, highly reactive (an oxidizing agent), and explosive. Consequently, very few toxicological studies are available that relate to the gaseous form. Some studies have been conducted via the oral route using aqueous solutions of chlorine dioxide. Several of these studies were conducted using "stabilized aqueous chlorine dioxide," sometimes by maintaining a constant pH using sodium carbonate and sodium hydrogen carbonate. However, it is recognized that this would effectively lead to the formation of aqueous sodium chlorite (which can subsequently generate chlorine dioxide by acid displacement). These studies are felt to be less relevant than those using stabilized aqueous chlorine dioxide and are not summarized in this review. The reasons for this are that chlorine dioxide dissolves discretely in water (i.e., it does not dissociate into ions), forming a solution of around pH 5 or less, whereas an aqueous solution of sodium chlorite has a different, ionized composition and a pH of approximately 8. The explosive nature of this substance has limited the concentration of chlorine dioxide in aqueous solutions to a maximum of about 1% w/v.

3. ANALYTICAL METHODS

3.1 Workplace air monitoring

The US Occupational Safety and Health Administration (OSHA) has published Method ID 202, "Determination of chlorine dioxide in workplace atmospheres" (Björkholm et al., 1990; OSHA, 1991; Hekmat et al., 1994). This describes a method for making personal exposure measurements of chlorine dioxide. Samples are collected by drawing air through a midget fritted glass bubbler, or impinger, containing 0.02% potassium iodide in a sodium carbonate/sodium bicarbonate buffer solution, at a flow rate of 0.5 litres/min. Chlorine dioxide is trapped and converted to chlorite (ClO_2^-), which is subsequently measured by suppressed ion chromatography using a conductivity detector. The method has a reported detection limit of 0.004 ppm (0.011 mg/m^3) for a 4-h sampling time and 0.06 ppm (0.17 mg/m^3) for a 15-min sampling time. However, it is recommended that a sampling time of less than 1 h be used in order to avoid possible negative interference from chlorine and acid gases.

3.2 Biological monitoring in humans

Because of the rapid formation of chloride ions following absorption of chlorine dioxide and the high normal, physiological levels of chloride in biological fluids, biological monitoring cannot detect occupational exposure to chlorine dioxide. Hence, there are no published biological monitoring methods available for chlorine dioxide.

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

The most significant uses of chlorine dioxide worldwide appear to be in bleaching paper pulp and cellulose. However, owing to the nature of the source document of this CICAD (Health and Safety Executive, 2000), this section focuses mainly on the production of chlorine dioxide.

Potential occupational exposure to chlorine dioxide gas may occur during its manufacture, 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 (Health and Safety Executive, 2000). There will also be potential exposure to aerosol if aqueous solutions of chlorine dioxide are agitated or splashed, such as may occur during the charging of drums. During manufacture and subsequent captive use of the gas, good process plant control is essential because of the explosive nature of the gas. Furthermore, once the gas is absorbed in water, it has a low volatility. For these reasons, inhalation exposure is anticipated to be minimal.

Additional uses are reported in bleaching flour, leather, fats and oils, textiles, and beeswax; water purification and taste and odour control of water; cleaning and detanning leather; and manufacture of chlorate salts, oxidizing agents, bactericides, antiseptics, and deodorizers (Budavari et al., 1996). However, no exposure data are available for these uses.

It is estimated that up to 1400 tonnes of aqueous chlorine dioxide are used per year in the United Kingdom (Health and Safety Executive, 2000). In North

America (USA and Canada), the estimated production in 1980 was 243 000 tonnes per year, and in 1990, it was around 509 000 tonnes per year (Clayton & Clayton, 1994). In Sweden, approximately 75 000 tonnes per year were manufactured (principally in pulp mills) in 1992 (Landner et al., 1995).

Release to the environment is almost exclusively to the air. The US Toxic Release Inventory reports total releases of chlorine dioxide in 1996 at approximately 550 tonnes to the atmosphere, of which more than 98% was via stacks and the remainder fugitive air releases. The majority of reported releases were from use of chlorine dioxide in pulp bleaching, with the remainder in food processing.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

Chlorine dioxide is readily volatilized from aqueous solution at between 10 °C and 15 °C (Budavari et al., 1996). It is quite stable in solution if kept cool, in the dark, and in a closed vessel. Chlorides in solution catalyse decomposition, even in the dark. Volatilized chlorine dioxide decomposes to chlorine and oxygen with noise, heat, flame, and a minor pressure wave at low concentrations; it decomposes explosively at >40 kPa partial pressure.

At pHs between 4.8 and 9.8, up to 50% of chlorine dioxide is hydrolysed to chlorite. A chlorite concentration of 0.72 mg/litre was obtained following treatment with chlorine dioxide at 1.5 mg/litre (Moore & Calabrese, 1980).

Use of chlorine dioxide in pulp mills leads to the formation of chlorate. This is reduced to chloride in treatment plants, where present (Landner et al., 1995).

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

No data are available on levels of chlorine dioxide in the environment. Chlorine dioxide would be degraded in the environment to yield chlorite and chlorate in water, so no water concentrations of chlorine dioxide are expected. However, almost all release is to the atmosphere, with decomposition to chlorine and oxygen.

6.2 Occupational exposure

The main source of occupational exposure worldwide would appear to be from the paper and pulp industry. Limited data are available, although one review (Jappinen, 1987) quotes ranges in pulp bleaching of 0–2 ppm (0–5.6 mg/m^3) (from Ferris et al., 1967; measured data were from around 1958, although it was not clear if these were from personal monitoring or static samples) and more recent (1965–1972) measurements by the Finnish Institute of Occupational Health of <0.1–2.5 ppm (<0.28–7.0 mg/m^3).

Limited occupational exposure data were received from one manufacturer of the gas. The data indicated that all personal exposures during drum charging were below 0.1 ppm (0.28 mg/m^3) 8-h TWA and 0.3 ppm (0.84 mg/m^3) 15-min reference period (Health and Safety Executive, 2000).

Limited occupational exposure data were also received from companies using the substance as a biocide in hot and cold water systems and as a sterilizing agent in hospitals. No data were received from firms using it for reducing foul smells and odours in water treatment. During its use as a sterilizing agent in hospitals, all occupational exposures were found to be well below 0.1 ppm (0.28 mg/m^3) 8-h TWA and less than 0.3 ppm (0.84 mg/m^3) 15-min reference period. During its use for treating and controlling *Legionella*, personal exposures and static sampling concentrations of the gas were found to be less than 0.03 ppm (0.084 mg/m^3) 8-h TWA.

In all situations where the gas is produced in a closed plant with full containment, the Estimation and Assessment of Substance Exposure (EASE) model, version 2 (a knowledge-based computer system for predicting exposures in the absence of measured occupational exposure data), predicted inhalation exposure to the gas of between 0 and 0.1 ppm (0 and 0.28 mg/m^3). It is expected that the potential for inhalation exposure to chlorine dioxide gas will be greater from an aqueous solution that has been agitated or activated by the addition of an acid than during production.

The gas is highly reactive, and there may be the potential for skin contact, particularly when the humidity is high and the gas is absorbed in the moisture and may settle on cold surfaces. In this situation, therefore, those without gloves may be exposed to the aqueous form. However, the most common dermal exposure may arise

from contact with up to 1% aqueous solutions of the substance during preparation and use. The EASE model (refer to European Union Technical Guidance Document[1]) predicts that dermal exposure from contact with the aqueous solution will vary from 0.1–1.0 mg/cm^2 per day during drum charging and its use in water treatment to 1–5 mg/cm^2 per day during its use as a sterilizing agent in hospitals.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

There are no data available regarding dermal or inhalation routes of exposure to the gaseous form of chlorine dioxide, although it would seem unlikely that there would be any significant systemic absorption and distribution of intact chlorine dioxide by these routes. It is possible that other derivatives, such as chlorate, chlorite, and chloride ions, could be absorbed and widely distributed.

One study (Abdel-Rahman et al., 1980; also reported in Abdel-Rahman et al., 1982) shows that "chlorine" (chemical form not characterized) derived from aqueous chlorine dioxide is absorbed by the oral route, with a wide distribution and rapid and extensive elimination. In this study, groups of four rats received a single oral gavage dose of approximately 1.5 or 4.5 mg $^{36}ClO_2$/kg body weight. Blood samples were collected for up to 48 h post-administration, and at 72 h, animals were killed, with samples taken from kidneys, lungs, small intestine, liver, spleen, thymus, bone marrow, and testes. ^{36}Cl was found in all tissues except testes, skin, and the remaining carcass, although levels in these tissues each accounted for less than 1% of the administered dose. No clear information is available on the identity of metabolites, although breakdown products are likely to include, at least initially, chlorites, chlorates, and chloride ions. About 40% of the ^{36}Cl was recovered in urine, expired air, and faeces, although the urine accounted for most (about 30%).

[1] Technical Guidance Document in support of the risk assessment directive (93/67/EEC) for substances notified in accordance with the requirements of Council Directive 67/548/EEC; published May 1994.

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

Chlorine dioxide is very toxic by inhalation in rats. Groups of five male and five female rats were exposed, nose only, to 0, 16, 25, 38, or 46 ppm (0, 45, 70, 106, or 129 mg/m^3) chlorine dioxide gas for 4 h (Schorsch, 1995[2]). There were no mortalities at 16 ppm (45 mg/m^3) or in controls. However, there were 3/5, 4/5, and 5/5 deaths among males and 5/5, 2/5, and 4/5 deaths among females at 25, 38, and 46 ppm (70, 106, and 129 mg/m^3), respectively. Clinical signs of toxicity included respiratory distress. Macroscopically, pulmonary oedema and emphysema were seen in all groups of chlorine dioxide-exposed animals, with the incidence increasing in a dose-related manner (severity was not described). The calculated mean LC_{50} was 32 ppm (90 mg/m^3).

Ocular discharge, nosebleeds, pulmonary oedema, and death occurred in rats exposed to 260 ppm (728 mg/m^3) for 2 h (Dalhamn, 1957). In this study, no further exposure levels were used.

Chlorine dioxide is toxic when administered in solution by the oral route to rats. Groups of five male and five female rats received a single oral gavage dose of 10, 20, or 40 ml aqueous 0.2% w/v chlorine dioxide/kg body weight (not 2%, as stated in the test reports) (Tos, 1995[2]). However, as correctly stated, the administered doses corresponded to 20, 40, and 80 mg chlorine dioxide/kg body weight. Two males and two females receiving 80 mg chlorine dioxide/kg body weight died, and a further two males at 40 mg/kg body weight also died within 48 h of administration. There were no deaths at 20 mg/kg body weight. General clinical signs of toxicity were observed among all treated groups of animals; in addition, there were occasional observations of red nasal discharge. Macroscopically, at 40 and 80 mg/kg body weight only, animals showed signs of corrosive activity in the stomach and gastrointestinal tract. There were no other treatment-related macroscopic abnormalities. The calculated oral LD_{50} was 94 mg/kg body weight.

Groups of five male Sprague-Dawley rats received approximately 0, 0.12, 0.24, or 0.48 mg aqueous chlorine dioxide/kg body weight by oral gavage (Abdel-

[2] Unpublished data, conducted according to Organisation for Economic Co-operation and Development (OECD) guidelines, in compliance with Good Laboratory Practice, and with quality assurance inspection. Peer-reviewed by European Union Member States as part of classification and labelling activity.

Rahman et al., 1980). Samples of blood were taken at 15, 30, 60, and 120 min post-administration for analysis of glutathione and methaemoglobin levels and osmotic fragility; methaemoglobin formation was not observed, and the other parameters measured were only slightly affected, with no clear dose–response relationship.

8.2 Irritation and sensitization

The limited data available (Dalhamn, 1957; see section 8.1) indicate that chlorine dioxide is a respiratory tract irritant. In relation to skin irritation, there are no data on gaseous or aqueous forms of chlorine dioxide; in relation to eye irritation, the limited data from the single exposure study by Dalhamn (1957) (see section 8.1) indicate that ocular discharge may occur as a result of exposure to gaseous chlorine dioxide.

There is no useful information regarding skin or respiratory tract sensitization in animals.

8.3 Short-term exposure

8.3.1 Inhalation

All of the studies reported in this section suffer from inadequacies in reporting detail and study design. In addition, a further brief and unconventional study by Dalhamn (1957) and another by Paulet & Desbrousses (1971) were not included due to evidence of concurrent infection or extremely poor reporting.

Groups of five rats were exposed, whole body, to either 0 or about 0.1 ppm (0.28 mg/m^3, the approximate mean over 10 weeks, but with a range down to 0.05 ppm [0.14 mg/m^3] and up to 0.3 ppm [0.84 mg/m^3] on one occasion) chlorine dioxide gas (Dalhamn, 1957) for 5 h/day, 7 days/week, for 10 weeks. There were no deaths and no clinical signs of toxicity. Body weight gain was reduced by approximately 6% compared with controls. Histopathological examination showed no exposure-related effects on kidneys, liver, or lungs (which appear to have been the only organs studied) of treated animals. No further useful information was available. Overall, although investigations were limited, no adverse effects were observed in this study. However, no information was presented regarding nasal effects, and the nose could reasonably be anticipated to be a target tissue.

Unknown numbers of rats and rabbits were exposed to 1, 2.5, 5, 10, or 15 ppm (2.8, 7.0, 14, 28, or 42 mg/m^3) chlorine dioxide gas for 2–7 h/day for 1 or 2 months (Paulet & Desbrousses, 1974). Reduced body weight, leukocytosis, and pulmonary lesions (broncho-alveolitis) were claimed for exposures to 5 or 10 ppm (14 or 28 mg/m^3). At 2.5 ppm (7.0 mg/m^3), 7 h/day for 1 month, the report indicated that there were small areas of haemorrhagic alveolitis in the lungs, and no effects were reported at 1 ppm (2.8 mg/m^3). No experimental data were presented, and there was no indication of the extent of investigations or if control animals were used. The reliability of these findings is limited by poor reporting.

Groups of 10–15 rats were exposed to 0, 5, 10, or 15 ppm (0, 14, 28, or 42 mg/m^3) chlorine dioxide gas for 15 min, 2 or 4 times per day, for 1 month (Paulet & Desbrousses, 1974). Investigations included body weight, haematology, and histopathological examination of lungs and liver only. At 5 and 10 ppm (14 and 28 mg/m^3), there were no mortalities and no "oculo-nasal catarrh." At 15 ppm (42 mg/m^3), one animal in each exposure group died, and survivors were reported to have "oculo-nasal catarrh with weeping mucus"; between weeks 2 and 4, animals showed a marked decrease in body weight. However, changes in other groups were not directly comparable with controls, as the group mean weights at the start of the study showed considerable variation. There were no clear effects on total red and white cell counts among any of the exposed groups. Histopathologically, for animals exposed twice per day to 15 ppm (42 mg/m^3), "congestion of vessels" and peribronchiolar infiltration were observed at 2 weeks. After 4 weeks, bronchitis, thickening of alveolar walls, oedematous alveolitis, catarrhal alveolitis, and bronchio-pneumonitic nodules were additionally reported. For animals exposed 4 times per day, findings were similar, but more severe. At 10 ppm (28 mg/m^3), bronchitis, bronchiolitis, and "alveolar irritation" were less marked than at 15 ppm (42 mg/m^3), and at 5 ppm (14 mg/m^3), there were no signs of toxicity related to exposure. There were no effects seen in the liver.

Investigations were limited in this study. For the effects that were reported, the degree of severity was not well described, nor was the incidence of findings. Given these limitations, it is difficult to draw many firm conclusions. However, this study indicates that repeated inhalation exposure to 10 ppm (28 mg/m^3) or more chlorine dioxide gas 15 min per occasion, 2–4 times per day, over a 4-week period resulted in respiratory tract lesions, with mortalities seen at 15 ppm (42 mg/m^3).

8.3.2 Oral

Oral studies are of limited value with respect to occupational considerations, as the inhalation and dermal routes would be expected to be the main routes of occupational exposure. Furthermore, as chlorine dioxide is a very reactive substance, most effects would be expected to be local, again making the oral studies of limited relevance in the occupational context. Many of

these studies have focused on investigations of thyroid hormone levels, based on the hypothesis that chlorine dioxide could inhibit thyroid function by interacting with endogenous iodide. The following studies are summarized to help complete the toxicological profile for chlorine dioxide.

In a study focusing on thyroid function, groups of 12 male Sprague-Dawley rats received 0, 100, or 200 mg/litre aqueous chlorine dioxide for 8 weeks (Harrington et al., 1986). Body weight gain was reported to be significantly decreased in treated animals, although no data were presented, and there was no indication of the magnitude of the effect. Apparently, there was also a reduction in water consumption thought to be related to unpalatability. There was no effect seen on radioactive iodide uptake in the thyroid (measured on completion of 8 weeks of treatment). Over the 8-week treatment period, T_4 levels showed a decrease among chlorine dioxide-exposed animals compared with controls. However, given the limited extent of observations (for instance, no histopathology was reported) and the fact that changes in thyroid hormone levels were within the control range of values, it is not possible to draw any firm conclusions.

Groups of African Green monkeys (*Cercopithecus aethiops*) received aqueous chlorine dioxide at concentrations of 30, 100, or 200 mg/litre in a rising-dose protocol (each step lasting 30–60 days) in drinking-water for up to 8 weeks (Bercz et al., 1982). Due to impaired palatability leading to reduced water intake, the two highest concentrations were both equivalent to about 9 mg/kg body weight per day. Haematology and blood biochemistry investigations were performed (including T_4 levels). No histopathology was performed. At 200 mg/litre, erythema and ulceration of the oral mucosa and increased nasal mucous discharge were observed. However, due to signs of dehydration, treatment of this group was stopped after 1 week. The increased nasal mucous secretion may be due to "degassing" of chlorine dioxide from the solution with subsequent irritation of the nasal tract by the gas. The authors claimed that there was a significant reversible thyrotoxic effect after 4 weeks of administration of 100 mg chlorine dioxide/litre, but the few data did not clearly support this. Overall, at 200 mg/litre aqueous chlorine dioxide, there were clear indications of irritation of the oral cavity, leading to palatability problems. At concentrations of 100 mg/litre (approximately 9 mg/kg body weight per day) or less, there were no clear effects among these primates over an 8-week exposure period.

Similarly, groups of female African Green monkeys received 100 mg/litre freshly prepared aqueous chlorine dioxide in drinking-water for up to 8 weeks (Harrington et al., 1986). Investigations were focused on thyroid hormone levels and some associated parameters, such as iodide uptake and oestradiol levels. Again, there were no consistent changes seen in iodide uptake or T_4 levels, and no other effects were remarked on.

8.4 Medium-term exposure

Groups of 10 male and 10 female Sprague-Dawley rats received approximately 0, 2, 4, 6, or 12 mg/kg body weight per day and 0, 2, 5, 8, or 15 mg/kg body weight per day, respectively, of aqueous chlorine dioxide in drinking-water for 90 days (Daniel et al., 1990). Examinations included clinical observation, body weight, food and water consumption, pre-terminal haematology and blood biochemistry, a comprehensive range of organ weights, and extensive macroscopic and microscopic examinations. There were no treatment-related deaths or clinical signs of toxicity. Water consumption was reduced, in a dose-related manner, among all treated groups, but this was probably related to palatability. Related to this effect, there were reductions in body weight gain and food consumption at the highest exposure level. There were no toxicologically significant effects on haematology, blood biochemistry, or organ weights. The only target tissue that was identified was the nasal cavity, which showed an increased incidence of goblet cell hyperplasia, squamous metaplasia, and inflammatory responses. These effects may have arisen from the evolution of chlorine dioxide gas from the drinking-water.

Groups of four male Sprague-Dawley rats received 0, 1, 10, 100, or 1000 mg chlorine dioxide/litre in drinking-water for 4 months (Abdel-Rahman et al., 1980). Blood samples were taken at 2 and 4 months for analysis of glutathione and methaemoglobin levels and for determination of osmotic fragility and erythrocyte morphology (using electron microscopy). Overall, this study showed some indication of reduced glutathione levels (about 10–20% lower than controls), which may be associated with the reactive nature of chlorine dioxide and the formation of free radicals, and also some changes in haematology parameters (osmotic fragility, erythrocyte morphology). None of these changes displayed any clear dose–response pattern. Hence, the toxicological significance of these findings is unclear.

8.5 Long-term exposure and carcinogenicity

There are no chronic inhalation or dermal studies available, and no conventional carcinogenicity studies are available.

Groups of 10 male Sprague-Dawley rats received 0, 1, 10, 100, or 1000 mg/litre freshly prepared aqueous chlorine dioxide in drinking-water for up to 12 months (Abdel-Rahman et al., 1981). No clear treatment-related changes in any of the measured parameters (water consumption, haematology, glutathione levels, tritiated thymidine incorporation in liver, kidney, testes, and small intestine) were observed. However, the interpretation is complicated by a marked decrease in actual body weight among all groups, including controls. No histopathological investigations were performed. Overall, no useful information can be gained from this report.

8.6 Genotoxicity and related end-points

8.6.1 *Studies in bacteria*

In a modified Ames test, 10, 100, and 1000 mg/litre of an aqueous extract from chlorine dioxide gas sterilization of a medical device was tested against *Salmonella typhimurium* TA1535 only, with and without S9 (Jeng & Woodworth, 1990). A negative result was obtained, although there are considerable doubts about whether or not the extract tested contained any chlorine dioxide.

The same authors (Jeng & Woodworth, 1990) performed another Ames test again using only TA1535 apparently against 10, 100, and 1000 mg chlorine dioxide gas/litre with and without metabolic activation. No further details of the techniques used were reported, and, although a negative result was claimed, no details were recorded.

8.6.2 *In vitro studies in mammalian systems*

In an unpublished but well conducted *in vitro* cytogenetics assay, Chinese hamster ovary cells were treated with 0, 2.5, 5, 10, 15, 30, or 60 µg 0.2% chlorine dioxide/ml in phosphate-buffered saline solution in the absence of metabolic activation and 0, 6, 13, 25, 50, or 75 µg/ml in the presence of metabolic activation (Ivett & Myhr, 1986). Cell toxicity was observed at 60 µg/ml (-S9), and there was an absence of mitotic cells at 30 µg/ml. At 2.5–15 µg/ml, there was a marked dose-related, statistically significant increase in the number of metaphases with chromosome aberrations. In the presence of 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.

In a mouse lymphoma forward mutation assay using the L5178Y $TK^{+/-}$ system, cells were treated with 0–65 µg chlorine dioxide/ml in phosphate-buffered saline in the presence and absence of metabolic activation (Cifone & Myhr, 1986). In the absence of metabolic activation, marked toxicity was observed at the highest concentration used, 37 µg/ml. The relative growth (compared with control cultures) at the next two concentrations (15 and 24 µg/ml) was 13–18%. There was a dose-related increase in mutant frequency. Similarly, in the presence of metabolic activation, 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.

An unpublished *in vitro* cell transformation assay is available in which BALB/3T3 cells were administered 0–6 µg aqueous chlorine dioxide/ml (Rundell & Myhr, 1986). The frequency of transformed foci was within the range of spontaneous transformations observed in historical controls, indicating a negative result.

8.6.3 *In vivo studies in mammalian systems*

In a bone marrow cytogenetics assay, groups of five male and five female CD-1 mice received a single intraperitoneal injection of approximately 0, 2, 5, or 15 mg aqueous chlorine dioxide/kg body weight (Ivett & Myhr, 1984a). Bone marrow cells were analysed for chromosome aberrations at 6, 24, and 48 h. There were no clear effects on the mitotic index, but two males receiving approximately 15 mg chlorine dioxide/kg body weight died, and other signs of toxicity (poor grooming) were also observed at the highest dose level. There were no increases in the frequency of chromosome aberrations among treated animals at any of the sacrifice times when compared with controls.

Groups of five male and five female CD-1 mice received five daily oral gavage doses of approximately 0, 5, 10, or 20 mg aqueous chlorine dioxide/kg body weight (Meier et al., 1985). Animals were killed 6 h after the last administration, and 1000 polychromatic erythrocytes from the bone marrow of each animal were analysed for micronucleus formation. In addition, groups of four male and four female CD-1 mice were used for analysis of chromosome aberrations from bone marrow samples. Animals were exposed to the same doses as above, either as a single administration or using a repeated-exposure regime. Following single exposure,