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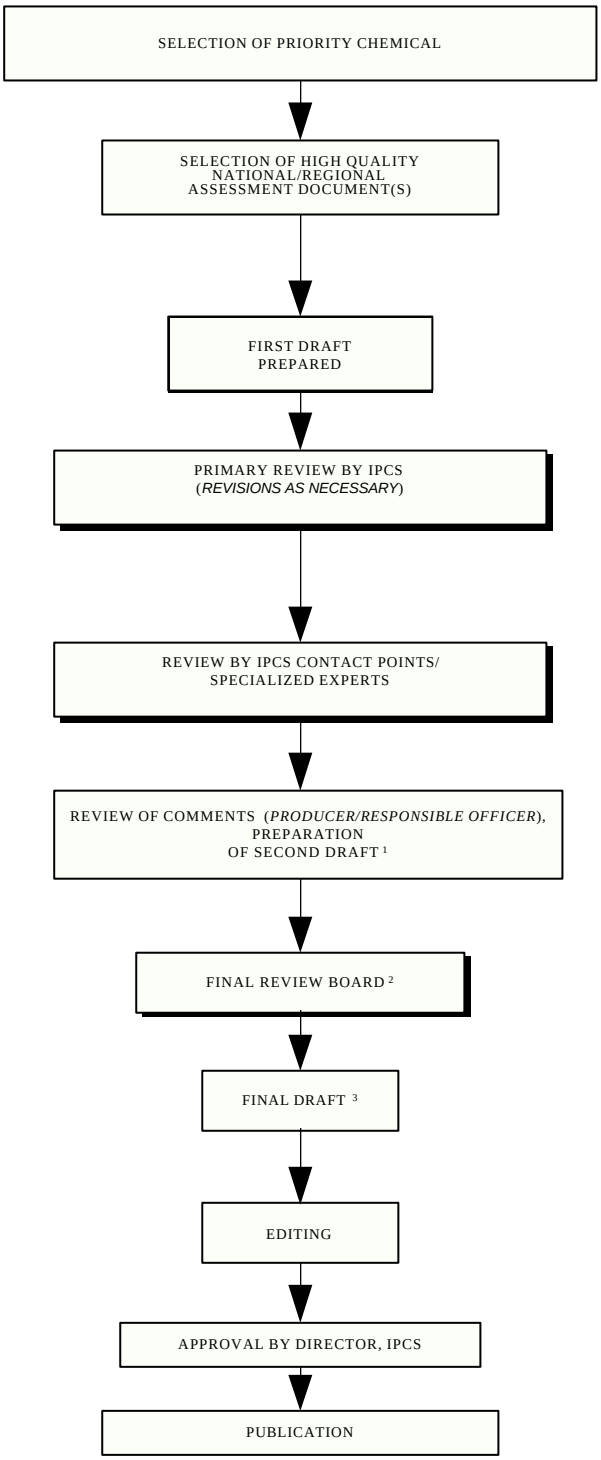
[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170).

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:

$$^{\oplus}O=Cl=O^{\ominus}$$

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.

[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.

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-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 “de-gassing” 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, animals were killed at 6, 24, and 48 h post-administration and 50

metaphase cells taken from the bone marrow of each animal for analysis of chromosome aberrations. A negative result was obtained for micronucleus formation, and there were no increases in the number of structural or numerical chromosome aberrations (including an assessment of hyperploidy and polyploidy). Apparently, there were no overt signs of general toxicity.

Groups of five male ICR mice received a single intraperitoneal injection of approximately 0, 9, 21, 28, or 39 mg aqueous chlorine dioxide/kg body weight (Ivett & Myhr, 1984b). Following subcutaneous implantation of bromodeoxyuridine and 26 h after chlorine dioxide administration, approximately 25 bone marrow metaphase cells from each animal were assessed for sister chromatid exchange. Shortly after administration of aqueous chlorine dioxide, all animals showed hyperactive behaviour. There were no significant increases in sister chromatid exchange among any of the chlorine dioxide-treated groups.

8.6.4 Studies in germ cells

The only study available (an unpublished dominant lethal assay in rats; Moore & Myhr, 1984) employed the intraperitoneal route of administration using up to 20 mg aqueous chlorine dioxide/kg body weight. This study did not show any mutagenic effects on male germ cells, and the result does provide some reassurance, in that even at levels affecting fertility and producing mortality, no evidence of mutagenic activity is seen. However, in addition, the results of *in vivo* mutagenicity studies conducted using this exposure route showed no evidence for effects in the bone marrow; hence, effects in the germ cells would not be expected.

8.6.5 Other studies

Positive results for chlorine dioxide were claimed in various test systems (e.g., Ames test, *in vitro* cytogenetics, *in vivo* bone marrow micronucleus, *in vivo* chromosome aberrations). However, in general, the conduct of these tests was poorly described, and it has subsequently emerged that aqueous sodium chlorite solutions were tested rather than chlorine dioxide (Ishidate et al., 1984; Hayashi et al., 1988; Fujie & Aoki, 1989).

8.7 Reproductive toxicity

There are no studies available using chlorine dioxide gas. A number of studies are available using aqueous chlorine dioxide or preparations that generate chlorine dioxide.

8.7.1 Effects on fertility

In a one-generation study, groups of 12 male Long-Evans rats received 0, 2.5, 5, or 10 mg/kg body weight per day of aqueous chlorine dioxide by oral gavage 7 days/week for 56 days prior to mating and throughout the 10-day mating period (Carlton et al., 1991). Similarly, groups of 24 females received aqueous chlorine dioxide for 14 days prior to mating and then throughout the mating, gestation, and lactation periods until weaning on day 21 of lactation. Examinations included pre-terminal blood samples for assessment of thyroid hormones T_3 and T_4 and weights and histopathological examination of male reproductive organs. Samples were also taken for analysis of sperm motility and morphology. Dams were observed for fertility, length of gestation, body weight gain, and any signs of behavioural abnormality. Pre-terminal blood samples were taken, and animals were examined macroscopically, with an additional microscopic evaluation of reproductive organs. Overall, this study did not demonstrate any impairment of reproductive function, and there were no signs of developmental effects among rats receiving up to 10 mg aqueous chlorine dioxide/kg body weight per day.

Reduced male fertility (reduced number of pregnant females) was observed among males receiving a single intraperitoneal injection of 20 mg aqueous chlorine dioxide solution/kg body weight in a dominant lethal assay (see section 8.6.4; Moore & Myhr, 1984). However, as this dose level was also associated with high mortality, it is unlikely that this result indicates a specific effect on fertility. In addition, the parenteral route of exposure used makes the results of doubtful relevance to human health.

Groups of 10 male mice received oral gavage doses of up to approximately 16 mg freshly prepared aqueous chlorine dioxide/kg body weight on each of 5 consecutive days (Meier et al., 1985). Animals were killed 1, 3, and 5 weeks after the last administration, and caudal epididymides were removed for analysis of 1000 sperm-heads from each animal. There were no differences seen in the percentage of abnormal sperm-heads at any time point.

8.7.2 Developmental toxicity

Groups of female Sprague-Dawley rats received approximately 0, 0.07, 0.7, or 7 mg/kg body weight per day (assuming body weight of 300 g and water consumption of 20 ml/day) of aqueous chlorine dioxide in drinking-water (Suh et al., 1983). 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 killed, their uteri were removed and weighed, and 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 body weight per day during pregnancy (about 14% reduction compared with controls). There was a slight reduction in the mean number of implants per dam in the top two dose groups, which attained statistical significance among animals at 7 mg/kg body weight per day (10.3 per dam compared with 12.3 per dam in controls), with a similar change in the number of live fetuses. This may be related to maternal toxicity at these two exposure levels, as there was a slight reduction in body weight gain among dams. 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 body weight per day, respectively).

In a study aimed at assessing thyroid function in neonates exposed directly to aqueous chlorine dioxide or potentially exposed *in utero*, groups of 15–18 Sprague-Dawley rat pups born to unexposed dams received 0 or 14 mg aqueous chlorine dioxide/kg body weight per day by oral gavage between days 5 and 20 post-partum (Orme et al., 1985). In addition, groups of 13–16 females received 0, 2, 20, or 100 mg aqueous chlorine dioxide/litre in drinking-water from 2 weeks prior to mating until pups were weaned (day 21 postpartum). Observations included food and water consumption, body weight, the age of eye opening, and locomotor activity. Terminal blood samples were taken from dams and pups for analysis of thyroid hormones T_3 and T_4. No clear information was presented on the general health of the dams (although body weight was apparently unaffected), making it difficult to determine the significance of any developmental effects in pups. Limited data were presented on body weight effects, although reduced body weight gain was noted for the pups born to chlorine dioxide-exposed dams between days 14 and 21 postpartum (50% lower between days 14 and 21). Locomotor effects were slight, variable, and transient, and hence of doubtful importance.

For the pups born to dams receiving chlorine dioxide, there were some changes in T_3 and T_4 values that attained statistical significance, but values fell within the range of concurrent control values, and there was a lack of an obvious dose–response. Overall, no evidence for an effect on thyroid hormone status was obtained, and there was no clear evidence for developmental toxicity following oral exposure of neonates to chlorine dioxide or to offspring exposed *in utero* and via lactation.

8.8 Immunological and neurological effects

There are no data specifically relating to immunological effects.

In a study specifically designed to study effects on the brain, groups of 112–178 neonatal Long-Evans rat pups received 0 or 14 mg aqueous chlorine dioxide/kg body weight per day by oral gavage on days 1–20 post-partum (Toth et al., 1990). Pups were killed 11, 21, and 35 days postpartum. Investigations included the following: forebrains were examined histopathologically from females killed on day 35; terminal blood samples were taken for analysis of T_3 and T_4 levels; and liver mitochondria were analysed for "-glycerophosphate dehydrogenase activity (this enzyme is reported by the authors to be an enzyme significantly decreased in hypothyroidism). In addition, protein synthesis in the forebrain, cerebellum, and olfactory bulbs was assessed by measuring the uptake of ^{14}C-leucine, and total DNA content in those areas of the brain was also measured.

There were a large number of deaths (about 30% of all newborns) among the neonatal pups that were attributed to gavage errors. There was a slight reduction in body weight (7% reduction between days 11 and 35), and there were related reductions in tissue weights, total protein, and DNA content. There were no significant histopathological changes noted in the brain except a reduction in the number of dendritic spine counts in one region. There were no other significant changes. The authors attributed the change in dendritic spine counts and reductions in total DNA and protein content as being indicative of a specific neurotoxic effect. However, there is no reasonable evidence for this; only a small number of samples (4–6) were used for analysis of spine counts, there were no other histopathological abnormalities recorded, and no clinical signs of toxicity were reported. Overall, there were some slight signs of reduced body weight gain at 14 mg/kg body weight per day in these neonates, and it would seem likely that the slight changes in the brain were related to this.

9. EFFECTS ON HUMANS

Very few data are available relating to single exposures in humans. From the reports that are available (Dalhamn, 1957; Gloemme & Lundgren, 1957; Kennedy et

al., 1991; Salisbury et al., 1991; Anon, 1997), it would appear that single high-level exposures may lead to eye irritation, respiratory tract lesions, and possibly permanent impairment of lung function. However, the quality of the data available is poor, often involving mixed exposures with other irritant gases, such as chlorine or sulfur dioxide, and there is no dose–response information.

9.1 Drinking-water studies

As with animal studies using this route of administration, human studies using drinking-water administration are of limited value in relation to occupational considerations; the inhalation and dermal routes would be expected to be the main routes of exposure. The following studies are summarized to help complete the toxicological profile for chlorine dioxide.

In a series of extensive human volunteer studies on water disinfectants, groups of 10 males received aqueous chlorine dioxide in drinking-water by a range of different protocols (a sequence of rising concentrations of up to around 0.34 mg/kg body weight over a 16-day period, approximately 0.035 mg/kg body weight on every third day for 12 weeks, or approximately 3.6×10^{-5} mg aqueous chlorine dioxide/kg body weight per day daily for 12 weeks) (Lubbers et al., 1982, 1984; Lubbers & Bianchine, 1984). Observations included physical examination (blood pressure, respiration rate, pulse, oral temperature, and electrocardiography), extensive blood biochemistry, haematology, and urinalysis, and the subjective recording of taste. There were no significant adverse effects recorded for any of the parameters measured.

A prospective epidemiological survey was performed on a group of 197 people exposed to chlorine dioxide-treated drinking-water on a seasonal basis (Michael et al., 1981). Haematology and blood biochemistry samples were taken before and after a 12-week chlorine dioxide exposure period. Reliable quantification of exposure was almost impossible due to the difficulties associated with estimating water consumption and the rapid decay of aqueous chlorine dioxide. There were no significant changes as a result of chlorine dioxide exposure in any of the parameters recorded.

In a retrospective study, hospital records relating to the morbidity and mortality of infants born between 1940 and 1955 were studied from a community in the USA (Tuthill et al., 1982). Tap water was treated with chlorine dioxide between 1944 and 1958, and comparisons were made with a nearby community, which, in part, used the same three hospital facilities and apparently did not receive chlorine dioxide-treated tap water. There were no clear demographic differences between the populations studied. A statistically significant increase in premature births was noted among members of the community that received chlorine dioxide-treated tap water. However, the identification of prematurity was on the basis of the physician's assessment, there were no objective measures, and the proportion of premature births differed markedly between hospitals. There were no other significant differences in the condition of neonates between the two communities. Due to the lack of information on the extent of chlorine dioxide exposure, the uncertainties attached to the diagnoses of prematurity at the hospitals, and lack of adequate consideration of confounding factors such as smoking and socioeconomic status, no conclusions can be drawn from this study.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

An EC_{50} for inactivation of *Cryptosporidium parvum*, a protozoan parasite that can infect the digestive tract of humans and other warm-blooded animals, was measured at 1.3 mg/litre; parasite inactivation was monitored by infectivity (Korich et al., 1990).

Spores of the giant kelp (*Macrocystis pyrifera*) were exposed to nominal concentrations of chlorine dioxide for 48 h at 15 °C with constant illumination by cool fluorescent lamps. A no-observed-effect concentration (NOEC) was determined at 2.5 mg/litre, with lowest-observed-effect concentrations (LOECs) for germination and germ tube length at 25 and 250 mg/litre, respectively (Hose et al., 1989).

Embryos of the purple sea urchin (*Strongylocentrolus purpuratus*) were exposed to nominal concentrations of chlorine dioxide at 15 °C for 48 h. Abnormalities recorded included pre-hatch malformations, retarded development, post-hatch abnormalities, skeletal malformations, and gut malformations. The NOEC was determined at 25 mg/litre, with a LOEC for malformations at 250 mg/litre (Hose et al., 1989).

Bluegill sunfish (*Lepomis macrochirus*) and fathead minnow (*Pimephales promelas*) 96-h LC_{50} values were reported at 0.15 and 0.02–0.17 mg/litre, respectively. Exposure was by release of chlorine dioxide stock solutions into the test medium for approximately 1 h in each 24 h (Wilde et al., 1983).

The NOEC for survival of kelp bass (*Paralabrax clathratus*) eggs exposed to chlorine dioxide for 48 h at 20 °C without aeration was 25 mg/litre (Hose et al., 1989).

A major field incident occurred in Sweden in the early 1980s, when it was recorded that the bladderwrack (*Fucus vesiculosus*), the major component of brackish water communities in Sweden, had disappeared from an area of 12 km^2 (Lindvall & Alm, 1983). It was subsequently demonstrated in laboratory experiments and model ecosystems that chlorate was responsible (Rosemarin et al., 1985; Lehtinen et al., 1988). It was also shown that brown algae of many species are sensitive to chlorate, with a threshold concentration at around 10–20 µg/litre for prolonged exposure (4–5 months) when exposure took place in nitrate-limited brackish water with a salinity of 0.7–0.8‰ (Rosemarin et al., 1994). A requirement to treat wastewater from pulp mills to reduce chlorate (derived from use of chlorine dioxide) to chloride has diminished the problem (Landner et al., 1995).

Data on the effects of chlorine dioxide on terrestrial organisms were not available.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

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 occured 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, animals showed 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. Also in rats, 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 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. 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).

Repeated oral exposure studies are available in humans and animals but are of very little relevance to occupational considerations and were generally of limited design and/or quality. The results show no consistent evidence of thyroid toxicity (which has been most extensively studied) or of other systemic toxicity associated with chlorine dioxide administered in the drinking-water or by gavage.

There are no data available on the effects of repeated dermal exposure and no useful data in relation to chronic exposure or carcinogenicity.

No conclusions can be drawn from genotoxicity studies of chlorine dioxide in bacteria because of limitations in reporting and/or study design. Studies in mammalian cells using aqueous solutions of chlorine dioxide indicate that it 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.

Well conducted studies in rats have shown that oral exposure at parentally toxic levels 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.

11.1.2 Criteria for setting tolerable intakes/ concentrations or guidance values for chlorine dioxide gas

The main health effect in relation to occupational exposure to chlorine dioxide is irritation of the respiratory tract, skin, and eyes. There are no reliable quantitative human data. The animal studies are old and of poor quality, and no long-term studies are available; the likely target tissue, the nasal tract, was not investigated, and studies focused on the lungs. A NOAEL for respiratory tract effects of 1 ppm (2.8 mg/m^3) derived from inhalation studies in rats of up to a 2-month duration thus is based on very limited data.

11.1.3 Sample risk characterization

The scenario chosen as an example is occupational exposure in the United Kingdom; the available measured occupational exposure data and the exposure levels predicted using the EASE model indicate a maximum likely exposure of 0.1 ppm (0.28 mg/m^3), 8-h TWA.

In occupational settings, a pragmatic approach (so-called "margin of safety") may be used by comparison of NOAELs for the key end-point of concern with the exposure levels achieved under occupational conditions to help determine the adequacy of current practices in terms of protecting human health. Applying this approach for chlorine dioxide, comparison of the predicted exposure level with the NOAEL of 1 ppm (2.8 mg/m^3) suggests that there is no cause for concern in relation to the development of irritation of the respiratory tract and of the eyes in workers occupationally exposed to chlorine dioxide.

11.2 Evaluation of environmental effects

Insufficient data are available with which to conduct an environmental risk assessment. Chlorine dioxide would be degraded in the environment to yield chlorite and chlorate in water. However, almost all release is to the atmosphere, with decomposition to chlorine and oxygen. 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.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

Previous evaluations on gaseous chlorine dioxide by other international bodies were not identified. IPCS, based on data on chlorite, proposed an oral tolerable daily intake of 30 µg/kg body weight per day for chlorine dioxide in drinking-water (IPCS, 2000). Information on international hazard classification and labelling is included in the International Chemical Safety Card (ICSC 0127) reproduced in this document.

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APPENDIX 1 — SOURCE DOCUMENT

Health and Safety Executive (2000) *Chlorine dioxide risk assessment document EH72/14.* Sudbury, Suffolk, HSE Books (ISBN 0 7176 1844 7)

The authors' draft version is initially reviewed internally by a group of approximately 10 Health and Safety Executive experts, mainly toxicologists, but also involving other relevant disciplines, such as epidemiology and occupational hygiene. The toxicology section of the amended draft is then reviewed by toxicologists from the United Kingdom Department of Health. Subsequently, the entire criteria document is reviewed by a tripartite advisory committee to the United Kingdom Health and Safety Commission, the Working Group for the Assessment of Toxic Chemicals (WATCH). This committee comprises experts in toxicology and occupational health and hygiene from industry, trade unions, and academia.

The members of the WATCH committee at the time of the peer review were:

Mr S.R. Bailey (Independent Consultant)
Professor J. Bridges (University of Surrey)
Dr H. Cross (Trades Union Congress)
Mr D. Farrer (Independent Consultant)
Dr A. Fletcher (Trades Union Congress)
Dr I.G. Guest (Chemical Industries Association)
Dr A. Hay (Trades Union Congress)
Dr L. Levy (Institute of Occupational Hygiene, Birmingham)
Dr T. Mallet (Chemical Industries Association)
Mr A. Moses (Independent Consultant)
Dr R. Owen (Trades Union Congress)
Mr J. Sanderson (Independent Consultant)

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on chlorine dioxide gas was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

A. Aitio, World Health Organization, Switzerland

M. Baril, Institut de Recherches en Santé et en Sécurité du Travail du Québec, Canada

R. Benson, US Environmental Protection Agency, Region VIII, USA

J. Dunnick, National Institute of Environmental Health Sciences, USA

P. Edwards, Department of Health, United Kingdom

Elf Atochem SA, France

T. Fortoul, National University of Mexico, Mexico

R. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV), Germany

G. Koennecker, Fraunhofer Institute of Toxicology and Aerosol Research, Germany

Y. Patel, Office of Water, US Environmental Protection Agency, USA

K. Savolainen, Finnish Institute of Occupational Health, Finland

J. Sekizawa, National Institute of Health Sciences, Japan

D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Australia

P. Yao, Chinese Academy of Preventive Medicine, People's Republic of China

K. Ziegler-Skylakakis, GSF - National Research Center for Environment and Health, Germany

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Stockholm, Sweden, 25–28 May 1999

Members

Mr H. Abadin, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA, USA

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CHLORINE DIOXIDE

0127
October 1999

CAS No: 10049-04-4
RTECS No: FO3000000
EC No: 006-089-00-2

Chlorine oxide
Chlorine peroxide
Chlorine(IV)oxide
ClO_2
Molecular mass: 67.5

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Not combustible but enhances combustion of other substances. Many reactions may cause fire or explosion.	NO contact with combustibles.	In case of fire in the surroundings: water in large amounts, water spray.
EXPLOSION	Risk of fire and explosion: see Chemical Dangers.	Closed system, ventilation, explosion-proof electrical equipment and lighting. Do NOT expose to friction or shock.	In case of fire: keep drums, etc., cool by spraying with water. Combat fire from a sheltered position.
EXPOSURE		**AVOID ALL CONTACT!**	**IN ALL CASES CONSULT A DOCTOR!**
Inhalation	Cough. Headache. Laboured breathing. Nausea. Shortness of breath. Sore throat. Symptoms may be delayed (see Notes).	Closed system and ventilation.	Fresh air, rest. Half-upright position. Refer for medical attention.
Skin	Redness. Pain.	Protective gloves. Protective clothing.	First rinse with plenty of water, then remove contaminated clothes and rinse again. Refer for medical attention.
Eyes	Redness. Pain.	Safety goggles or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion			

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Evacuate danger area! Consult an expert! Ventilation. Remove gas with fine water spray. (Extra personal protection: complete protective clothing including self-contained breathing apparatus).	O Symbol T+ Symbol N Symbol R: 6-8-26-34-50 S: (1/2-)23-26-28-36/37/39-38-45-61

EMERGENCY RESPONSE	STORAGE
	Fireproof if in building. Separated from combustible and reducing substances. Cool. Keep in the dark. Ventilation along the floor.

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

SEE IMPORTANT INFORMATION ON THE BACK.

IMPORTANT DATA

Physical State; Appearance
RED-YELLOW GAS, WITH PUNGENT ODOUR.

Physical dangers
The gas is heavier than air.

Chemical dangers
May explode on heating, on exposure to sunlight or if subjected to shock or sparks. The substance is a strong oxidant and reacts violently with combustible and reducing materials. Reacts violently with organics, phosphorus, potassium hydroxide and sulfur, causing fire and explosion hazard. Reacts with water producing hydrochloric acid and chloric acid.

Occupational exposure limits
TLV (as TWA): 0.1 ppm; (ACGIH 1999).
TLV (as (STEL)): 0.3 ppm; (ACGIH 1999).

Routes of exposure
The substance can be absorbed into the body by inhalation.

Inhalation risk
A harmful concentration of this gas in the air will be reached very quickly on loss of containment.

Effects of short-term exposure
The substance irritates severely the eyes, the skin and the respiratory tract. Inhalation of gas may cause lung oedema (see Notes). Exposure far above the OEL may result in death. The effects may be delayed. Medical observation is indicated.

Effects of long-term or repeated exposure
The substance may have effects on the lungs, resulting in chronic bronchitis.

PHYSICAL PROPERTIES

Boiling point: 11°C
Melting point: -59°C
Relative density (water = 1): 1.6 at 0°C (liquid)
Solubility in water, g/100 ml at 20°C: 0.8

Vapour pressure, kPa at 20°C: 101
Relative vapour density (air = 1): 2.3
Explosive limits, vol% in air: 10

ENVIRONMENTAL DATA

This substance may be hazardous to the environment; special attention should be given to water organisms.

NOTES

The symptoms of lung oedema often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential.
Immediate administration of an appropriate spray, by a doctor or a person authorized by him/her, should be considered.
Rinse contaminated clothes (fire hazard) with plenty of water.

ADDITIONAL INFORMATION

RÉSUMÉ D'ORIENTATION

Ce CICAD consacré au dioxyde de chlore repose sur un bilan des problèmes sanitaires (principalement en milieu professionnel) préparé par le *Health and Safety Executive* du Royaume-Uni (Health and Safety Executive, 2000). Ce document vise principalement les voies d'exposition à prendre en considération en milieu professionnel, principalement sur les lieux de production du dioxyde de chlore, mais contient également des informations relatives à l'environnement. Les effets de ce composé sur la santé et son devenir dans l'environnement, de même que les implications sanitaires de son utilisation pour traiter l'eau de boisson comme d'ailleurs celles d'autres dérivés halogénés résultant de l'interaction entre ce désinfectant et d'autres produits présents dans l'eau, étant traités dans un récent document de la série *Critères d'hygiène de l'environnement* (IPCS, 2000), il n'en sera pas question dans ce qui suit en détail. La mise au point rédigée par le *Health and Safety Executive* repose sur une bibliographie arrêtée à septembre 1998. Un dépouillement complémentaire de la litterature à été effectué jusqu'à janvier 1999 afin de recueillir toutes données supplémentaires publiées après l'achèvement de cette étude. En l'absence de documentation sur le devenir du composé et ses effets sur l'environnement, on s'est tourné vers les publications originales pour essayer de trouver des informations sur ce point. Des renseignements sur la nature de l'examen par des pairs et sur les sources documentaires existantes sont données à l'appendice 1. L'appendice 2 contient des informations sur l'examen par des pairs du présent CICAD. Ce CICAD a été approuvé en tant qu'évaluation internationale lors de la réunion du Comité d'évaluation finale qui s'est tenue à Stockholm (Suède) du 25 au 28 mai 1999. La liste des participants à cette réunion figure à l'appendice 3. La fiche internationale sur la sécurité chimique du dioxyde de chlore (ICSC No 0127) établie par le Programme international sur la sécurité chimique (IPCS, 1993) est également reproduite dans le présent CICAD.

Le dioxyde de chlore (ClO_2, No CAS 10049-04-4) se présente à la température ambiante sous la forme d'un gaz jaune verdâtre à orange. Ce gaz est explosif lorsque sa concentration dans l'air dépasse 10 % en volume. Il est soluble dans l'eau et ses solutions aqueuse sont assez stables si on les conserve au frais et à l'abri de la lumière. Il est commercialisé et transporté en solution aqueuse stabilisée (généralement à moins de 1% p/v, car il y a risque d'explosion à concentration plus élevée).

Il peut y avoir exposition professionnelle au dioxyde de chlore lors de sa production, de son utilisation dans l'industrie du papier comme agent de blanchiment, lors de la mise en fûts de la solution aqueuse et également lorsqu'on l'utilise comme agent stérilisant en milieu hospitalier, comme désinfectant pour le traitement de l'eau ou pour l'amélioration de la farine. Lors de la production ou de l'utilisation ultérieure du dioxyde de chlore captif sous forme gazeuse, une surveillance adéquate des ateliers est essentielle du fait du caractère explosif de ce gaz. Il est à noter qu'une fois le gaz en solution dans l'eau, sa volatilité est faible et on peut donc penser que l'exposition par la voie respiratoire est minime.

Il existe quelques données relatives aux limites d'exposition professionnelle sur les lieux de travail où l'on produit ou utilise du dioxyde de chlore; les concentrations mesurées ou estimées indiquent que dans tous les cas, l'exposition atmosphérique individuelle (au Royaume-Uni) est inférieure à 0,1 ppm (0,28 mg/m^3) en moyenne sur 8 h pondérée par rapport au temps et à 0,3 ppm (0,84 mg/m^3) sur la période de référence de 15 minutes.

L'exposition par voie cutanée la plus fréquente peut résulter d'un contact avec des solutions aqueuses contenant jusqu'à 1 % du composé lors de la préparation ou de l'utilisation de ces solutions. On estime que sur les lieux de travail, l'exposition par contact cutané avec des solutions aqueuses devrait se situer entre 0,1 et 5 mg/cm^2 par jour.

Les données toxicocinétiques sont limitées mais il ne semble pas qu'il puisse y avoir une absorption et une distribution de dioxyde de chlore inchangé dans l'ensemble de l'organisme par voie percutanée ou respiratoire. En revanche, il est possible que d'autres dérivés tels que des chlorates, chlorites ou chlorures puissent être absorbés et se répartir largement dans l'organisme. Selon une étude, du « chlore » (forme chimique non précisée) provenant de solutions aqueuses de dioxyde de chlore peut être absorbé par la voie orale et se répartir ensuite largement dans l'organisme avant d'en être rapidement et majoritairement éliminé. On ne possède pas d'informations précises sur l'identité des métabolites mais il est vraisemblable que les produits de dégradation consistent en chlorates, chlorites et chlorures, du moins dans un premier temps.

Etant donné la réactivité du dioxyde de chlore, il est vraisemblable que ses effets soient purement locaux. On ne possède pas de données quantitatives concernant des sujets humains, mais une seule inhalation de dioxyde de chlore se révèle en tout cas très toxique pour le le rat. Après exposition à une concentration de 16 ppm de dioxyde de chlore (45 mg/m^3) pendant 4 h, il n'y a pas eu de mortalité chez les animaux d'expérience malgré la

présence, aux concentrations de 16-46 ppm (45 à 129 mg/m^3), d'un oedème pulmonaire et d'un emphysème dont l'incidence augmentait avec la dose. Le calcul a donné une CL_{50} moyenne de 32 ppm (90 mg/m^3). Dans une autre étude, on a observé un écoulement oculaire, des saignements de nez, un oedème pulmonaire puis la mort lors de l'exposition d'animaux à 260 ppm (728 mg/m^3) pendant 2 h. Chez le rat, l'administration par voie orale d'une seule dose d'une solution de dioxyde de chlore se révèle toxique; aux concentrations de 40 et 80 mg/kg de poids corporel, on a constaté les signes d'une activité corrosive au niveau de l'estomac et des intestins. Le calcul de la DL_{50} par voie orale a donné une valeur de 94 mg/kg de poids corporel.

Les données relatives au pouvoir irritant du dioxyde de chlore pour les muqueuses oculaire et respiratoire sont en nombre limité. Toutefois, on a la preuve que le composé présent dans l'air est irritant pour les voies respiratoires et la muqueuse oculaire sans que l'on sache à quelle concentration. Chez des rats exposés pendant deux heures à la concentration de 260 ppm (728 mg/m^3), on a constaté uen forte irritation des yeux et des voies respiratoires.

On ne signale pas de cas de sensibilisation cutanée ni d'asthme d'origine professionnelle qui soient liés à une exposition au dioxyde de chlore.

Les données fournies par les études comportant une exposition répétée par la voie respiratoire sont généralement de qualité médiocre, aussi faut-il interpréter avec prudence les informations relatives à la relation dose-réponse. On peut d'ailleurs se demander pourquoi les tissus des fosses nasales n'ont pas été examinés, alors même qu'il a été fait état de rhinorrhée lors d'une étude sur le rat à la dose de 15 ppm (42 mg/m^3). Ces observations montrent bien que les fosses nasales pourraient constituer un tissu cible en cas d'inhalation de dioxyde de chlore. D'autres études sur le rat ne font état d'aucun effet nocif à la concentration de 0,1 ppm (0,28 mg/m^3) lors d'une exposition de 5 h par jour pendant 10 semaines, ni à la concentration de 1 ppm (2,8 mg/m^3) pendant 2 à 7 h par jour sur une durée de deux mois. Une exposition répétée à la concentration de 2,5 ppm (7,0 mg/m^3) ou davantage, 7 h par jour pendant 1 mois ou à 10 ppm (2,8 mg/m^3) ou davantage 15 min deux fois par jour pendant 4 semaines a entraîné une atteinte pulmonaire se traduisant par une bronchite, une bronchiolite et de petits foyers d'hémorragie alvéolaire dont la gravité était fonction de la dose. A la concentration de 15 ppm (42 mg/m^3) pendant 15 min 2 à 4 fois par jour sur un mois, on a constaté une mortalité parmi les animaux. Dans les mêmes conditions d'exposition, on n'a constaté, parmi le nombre limité d'observations effectuées, aucun effet nocif à la concentration de 5 ppm (14 mg/m^3).

Les études d'exposition par voie orale portant sur des rats ou des primates sont généralement limitées dans leur conception comme d'ailleurs dans leur qualité, mais les résultats obtenus ne révèlent aucun signe de toxicité générale qui soit imputable au dioxyde de chlore administré aux animaux en solution dans leur eau de boisson ou par gavage. On ne possède aucune donnée sur l'exposition chronique au dioxyde de chlore ni sur sa cancérogénicité éventuelle.

Les études relatives à l'action des solutions de dioxyde de chlore sur les cellules mammaliennes montrent que ce composé est mutagène *in vitro*. Des études *in vivo* bien conduites et portant sur des cellules somatiques ou germinales n'ont en revanche pas permis de constater l'expression de cette activité. Cependant, étant donné la réactivité du composé et du fait que les résultats obtenus *in vitro* sont positifs, on peut s'inquiéter de la possibilité d'effets mutagènes localisés au point de contact, bien qu'aucune étude n'ait porté sur ce type d'effet toxique.

L'exposition au dioxyde de chlore à des doses toxiques pour les géniteurs n'affecte ni la fécondité, ni le développement. Ce résultat s'explique par la réactivité de ce gaz, qui ne lui permet pas de parvenir en quantité importante jusqu'à l'appareil reproducteur.

Les mesures de l'exposition professionnelle (au Royaume-Uni) et le calcul de l'intensité de cette exposition au moyen du modèle d'évaluation de l'exposition utilisé, indiquent que l'exposition professionnelle est vraisemblablement égale à 0,1 ppm (0,28 mg/m^3) au maximum, en moyenne pondérée par rapport au temps sur une durée de 8 h. Si l'on compare ce chiffre à la valeur de la concentration sans effet nocif observable (NOAEL), qui a été établie à partir de données très limitées, on est amené à considérer qu'il n'y a aucune raison de s'inquiéter d'une quelconque action irritante pour les yeux et les voies respiratoires des travailleurs exposés au dioxyde de chlore.

On ne possède pas suffisamment de données pour procéder à une évaluation du risque environnemental. Le dioxyde de chlore libéré dans l'environnement y subirait rapidement une décomposition en chlorite et chlorate. Les quelques données écotoxicologiques disponibles montrent que le dioxyde de chlore peut être très toxique pour les organismes aquatiques; la valeur la plus faible de la CL_{50} qui ait été publiée pour les poissons est de 0,02 mg/litre. On a montré que le chlorate déchargé dans les eaux résiduaires des industries du papier après blanchiment au dioxyde de chlore pouvait faire d'important

dégâts écologiques dans la faune et la flore des eaux saumâtres. Les macroalgues brunes marines sont particulièrement sensibles au chlorate en cas d'exposition prolongée. Le seuil d'apparition des effets est compris entre 10 et 20 µg/litre.

RESUMEN DE ORIENTACIÓN

Este CICAD sobre el dióxido de cloro gaseoso se basó en un examen de los problemas relativos a la salud humana (fundamentalmente profesionales) preparado por la Dirección de Salud y Seguridad del Reino Unido (Dirección de Salud y Seguridad, 2000). Este examen se centra en las vías de exposición de interés para el entorno ocupacional, principalmente en relación con la producción de dióxido de cloro, pero contiene también información sobre el medio ambiente. Los efectos en la salud y el destino y los efectos en el medio ambiente del dióxido de cloro utilizado en el tratamiento del agua potable, junto con los de los productos orgánicos halogenados producidos por la interacción entre el desinfectante y otros materiales presentes en el agua, figuran en un documento reciente de los Criterios de Salud Ambiental (IPCS, 2000) y no se abordan aquí con todo detalle. En el examen de la Dirección de Salud y Seguridad figuran los datos identificados hasta septiembre de 1998. Se realizó una búsqueda bibliográfica ulterior hasta enero de 1999 para localizar cualquier información nueva que se hubiera publicado desde la terminación del examen. Puesto que no se disponía de documentos originales sobre el destino y los efectos en el medio ambiente, se realizó una búsqueda bibliográfica para obtener más información. La información acerca del carácter del examen colegiado y la disponibilidad del documento original figura en el apéndice 1. La información sobre el examen colegiado de este CICAD aparece en el apéndice 2. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final celebrada en Estocolmo (Suecia) del 25 al 28 de mayo de 1999. La lista de participantes en esta reunión figura en el apéndice 3. La Ficha internacional de seguridad química sobre el dióxido de cloro (ICSC 0127), preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993), también se reproduce en el presente documento.

El dióxido de cloro (ClO_2, CAS Nº 10049-04-4) existe en forma de gas de un color entre amarillo verdoso y naranja a temperatura ambiente. El dióxido de cloro gaseoso es explosivo cuando su concentración en el aire es superior al 10% v/v. Es soluble en agua y las soluciones son bastante estables si se mantienen en un lugar refrigerado y oscuro. Se comercializa y transporta como solución acuosa estabilizada, generalmente en una concentración inferior al 1% p/v (las formas más concentradas son explosivas).

Se puede producir exposición ocupacional al dióxido de cloruro gaseoso durante su fabricación, en las industrias de blanqueo de papel y pasta, durante la carga de la solución acuosa en bidones y durante su utilización como agente esterilizante en hospitales, como biocida en el tratamiento del agua y como agente para la mejora de la harina. Durante la fabricación y el posterior uso del gas cautivo, es esencial un buen control de la instalación de elaboración, a causa del carácter explosivo del gas. Además, una vez que el gas se absorbe en el agua, tiene una volatilidad baja. Por estos motivos se prevé una exposición por inhalación mínima.

Hay datos limitados sobre la exposición ocupacional en relación con la fabricación y las aplicaciones del dióxido de cloro; las concentraciones medidas o estimadas indicaron que toda la exposición personal a través del aire (en el Reino Unido) era inferior a 0,1 ppm (0,28 mg/m^3) en un promedio ponderado por el tiempo de ocho horas y de 0,3 ppm (0,84 mg/m^3) en un periodo de referencia de 15 minutos.

La exposición más común puede producirse por contacto con soluciones acuosas de hasta un 1% de la sustancia durante su preparación y uso. Se estima que la exposición cutánea por contacto con la solución acuosa en el entorno del trabajo oscila entre 0,1 y 5 mg/cm^2 al día.

Los datos sobre la toxicocinética son limitados, aunque parece poco probable que se produzca una absorción y distribución sistémica importante de dióxido de cloro intacto por vía cutánea o por inhalación. Es posible que otros derivados, como los iones clorato, clorito y cloruro, se puedan absorber y distribuir ampliamente. En un estudio se ha puesto de manifiesto que el «cloro» (forma química no caracterizada) derivado del dióxido de cloro acuoso se absorbe por vía oral, con una distribución amplia y una eliminación rápida e importante. No se dispone de información clara sobre la identidad de los metabolitos, aunque cabe suponer que los productos de degradación incluyen, por lo menos inicialmente, iones clorato, clorito y cloruro.

Dado el carácter reactivo del dióxido de cloro, parece poco probable que los efectos en la salud se limiten a respuestas locales. No hay datos humanos cuantitativos, pero el dióxido de cloro es muy tóxico en una exposición única por inhalación en ratas. No se observó mortalidad tras la exposición a 16 ppm (45 mg/m^3) durante cuatro horas, aunque se detectaron edema y enfisema pulmonar en todos los animales expuestos a 16-46 ppm (45-129 mg/m^3) de dióxido de cloro, aumentando la incidencia en una manera dependiente de la dosis. La CL_{50} media calculada fue de 32 ppm (90 mg/m^3). En otro estudio se produjo exudación ocular, hemorragia nasal, edema pulmonar y muerte a 260 ppm (728 mg/m^3) durante dos horas. El dióxido de cloro es tóxico cuando se administra en solución mediante una

dosis oral única a ratas; con 40 y 80 mg/kg de peso corporal se detectaron signos de actividad corrosiva en el estómago y el tracto gastrointestinal. La DL_{50} calculada por vía oral fue de 94 mg/kg de peso corporal.

Los datos sobre el efecto irritante en los ojos y las vías respiratorias del dióxido de cloro gaseoso son limitados. Sin embargo, hay pruebas de dicho efecto en personas asociadas con niveles desconocidos de dióxido de cloro gaseoso en el aire. En ratas expuestas a 260 ppm (728 mg/m^3) durante dos horas se observó irritación grave de los ojos y las vías respiratorias.

No se han notificado casos de sensibilización cutánea o asma ocupacional relacionados con el dióxido de cloro.

La calidad de los datos disponibles sobre la exposición por inhalación repetida es generalmente escasa, por lo que la información sobre la relación dosis-respuesta se debe examinar con prudencia. Además, existe el problema de que no se examinó el tejido nasal, aunque en un estudio se notificó rinorrea en ratas con 15 ppm (42 mg/m^3), lo cual indica que el conducto nasal puede ser un tejido destinatario del dióxido de cloro inhalado. Otros estudios en ratas pusieron de manifiesto que no se encontraban efectos adversos con 0,1 ppm (0,28 mg/m^3) cinco horas/día durante 10 semanas o con 1 ppm (2,8 mg/m^3) 2-7 horas/día durante dos meses. Al parecer se producen lesiones pulmonares, en forma de bronquitis, bronquiolitis o pequeñas zonas de alveolitis hemorrágica, con 2,5 ppm (7,0 mg/m^3) o más tras una exposición repetida de siete horas/día durante un mes y con 10 ppm (28 mg/m^3) o más en 15 minutos dos veces al día durante 4 semanas, con una gravedad dependiente de la dosis. Se observó mortalidad con 15 ppm (42 mg/m^3) 15 minutos, dos o cuatro veces al día durante un mes. En el mismo régimen de exposición, no se observaron efectos adversos (entre las observaciones limitadas realizadas) con 5 ppm (14 mg/m^3).

Los estudios de exposición repetida por vía oral en ratas y primates son en general de formulación y/o calidad limitados, pero sus resultados ponen de manifiesto que no hay pruebas de toxicidad sistémica asociada con el dióxido de cloro administrado en el agua de bebida o mediante sonda. No hay datos en relación con la exposición crónica o la carcinogenicidad del dióxido de cloro gaseoso.

Los estudios realizados en células de mamíferos utilizando soluciones acuosas de dióxido de cloro indican que es mutágeno *in vitro*. Esta actividad no se expresó en estudios bien realizados *in vivo* en células somáticas o germinales. Sin embargo, dado su carácter generalmente reactivo y debido al hecho de que se han producido resultados positivos *in vitro*, esta sustancia suscita preocupación por la mutagenicidad local en el punto de contacto, aunque no se han realizado estudios sobre este efecto final.

La exposición oral de ratas a niveles de dióxido de cloro tóxicos para las madres no afecta a la fecundidad o el desarrollo. Esto concuerda con la opinión de que, puesto que el dióxido de cloro es un gas reactivo, sería poco probable que llegara a los órganos reproductivos en cantidades significativas.

Los datos disponibles de medición de la exposición ocupacional (en el Reino Unido) y los niveles de exposición pronosticados utilizando el modelo de estimación y evaluación de la exposición indican una exposición probablemente máxima de 0,1 ppm (0,28 mg/m^3) en una evaluación ponderada por el tiempo de ocho horas. La comparación de este nivel de exposición con la concentración sin efectos adversos observados (NOAEL), que se obtiene a partir de datos muy limitados, parece indicar que no hay motivo de preocupación en cuanto al efecto de irritación de las vías respiratorias y de los ojos de los trabajadores expuestos al dióxido de cloro en el lugar de trabajo.

Los datos disponibles son insuficientes para realizar una evaluación del riesgo para el medio ambiente. El dióxido de cloro se degradaría rápidamente en el medio ambiente para producir clorito y clorato. Los pocos datos de ecotoxicidad disponibles ponen de manifiesto que el dióxido de cloro puede ser muy tóxico para los organismos acuáticos; la CL_{50} más baja para los peces fue de 0,02 mg/l. Se ha demostrado que el clorato, liberado en las aguas residuales de las fábricas de pasta de papel tras la utilización de dióxido de cloro, tiene efectos ambientales importantes en las comunidades de aguas salobres. Las macroalgas pardas son particularmente sensibles al clorato tras una exposición prolongada. El umbral para los efectos es de 10-20 µg/l.

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