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Concise International Chemical Assessment Document 10

2-Butoxyethanol

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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 Organisation (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.

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 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 to ensure that it meets the specified criteria for CICADs.

The second stage involves 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.

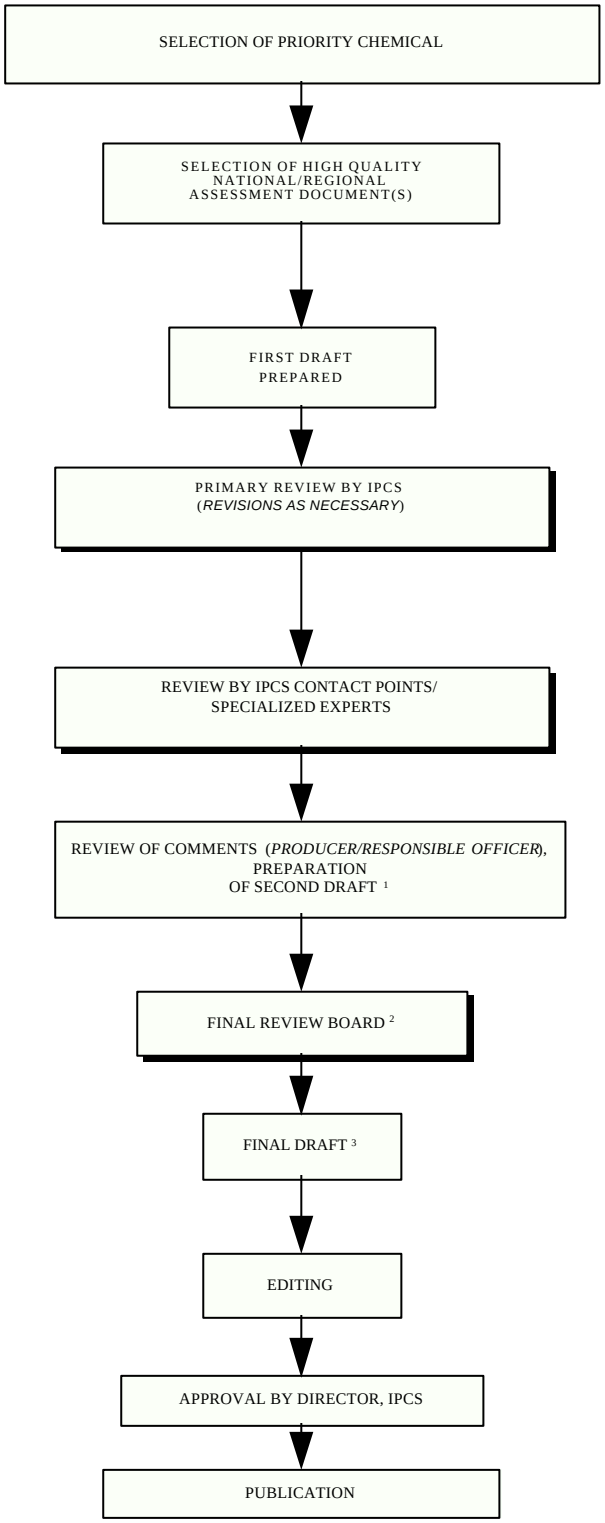
The CICAD Final Review Board has several important functions:

- 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

[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.

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 2-butoxyethanol was based upon reviews prepared by the National Institute for Occupational Safety and Health (NIOSH, 1990) and the Agency for Toxic Substances and Disease Registry (ATSDR, 1996). Additional data were identified through an updated literature search to May 1997, as well as during the peer review of this CICAD. Information on the nature of the peer review and availability of the source documents 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 Berlin, Germany, on 26–28 November 1997. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card (ICSC 0059) produced by the International Programme on Chemical Safety (IPCS, 1993) has also been reproduced in this document.

2-Butoxyethanol (CAS no. 111-76-2) is a high-production-volume glycol ether. It is a colourless liquid that is miscible in water and soluble in most organic solvents. 2-Butoxyethanol is used widely as a solvent in surface coatings, such as spray lacquers, quick-dry lacquers, enamels, varnishes, varnish removers, and latex paint. It is also used in metal and household cleaners. 2-Butoxyethanol exists in the atmosphere almost entirely as a vapour; because the chemical has an atmospheric half-life of approximately 17 h, the risk for transport via the atmosphere should be small. The estimated half-life of 2-butoxyethanol in water is approximately 1–4 weeks, and the chemical is likely readily biodegraded in aerobic soil and water. Its potential for bioaccumulation is low. Based upon limited data, ambient exposures in air are generally in the :g/m^3 range. Indirect exposure of the general population to 2-butoxyethanol is most likely from inhalation and dermal absorption during the use of products containing the chemical. Levels of airborne 2-butoxyethanol in occupational settings are typically in the mg/m^3 range.

2-Butoxyethanol is readily absorbed following inhalation, oral, and dermal exposure. The chemical is metabolized primarily via alcohol and aldehyde dehydrogenases, with the formation of 2-butoxyacetaldehyde and 2-butoxyacetic acid, the principal metabolite, although other metabolic pathways have also been identified.

2-Butoxyethanol has moderate acute toxicity and is irritating to the eyes and skin; it is not a skin sensitizer. The principal effect exerted by 2-butoxyethanol and its metabolite 2-butoxyacetic acid is haematotoxicity, with the rat being the most sensitive species. The results of *in vitro* studies indicate that human red blood cells are not as sensitive as rat red blood cells to the haemolytic effects of 2-butoxyethanol and 2-butoxyacetic acid and also that red blood cells are more sensitive to haemolysis by 2-butoxyacetic acid than to haemolysis by 2-butoxyethanol. In rats, adverse effects on the central nervous system, kidneys, and liver occur at higher exposure concentrations than do haemolytic effects. In animals, adverse effects on reproduction and development have not been observed at less than toxic doses. Although the results of *in vitro* tests for mutagenicity of 2-butoxyethanol were inconsistent, the absence of structural alerts and the negative findings from *in vivo* studies are sufficiently reassuring to allow the conclusion that 2-butoxyethanol is not mutagenic. Based on limited data from case reports and one laboratory study, similar acute effects — including haemolytic effects as well as effects on the central nervous system — are observed in humans and rats exposed to 2-butoxyethanol, although the effects are observed at much higher exposure concentrations in humans than in rats. Based upon the development of haemolytic effects in pregnant rats exposed during gestation, a sample tolerable concentration for humans of 13.1 mg 2-butoxyethanol/m^3 has been derived.

Based upon extremely conservative assumptions, the highest predicted concentrations of 2-butoxyethanol in surface waters in the immediate vicinity of effluent streams may, in some cases, exceed predicted no-observed-effect concentrations. However, more realistic assumptions based on the available data suggest that risk to aquatic organisms is low. Owing to the short half-life of 2-butoxyethanol in the atmosphere, measured or predicted concentrations of this chemical in air are considered to have no environmental significance.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

2-Butoxyethanol (CAS no. 111-76-2; $C_6H_{14}O_2$; ethylene glycol monobutyl ether, monobutyl glycol ether, 2-butoxy-1-ethanol, 2-*n*-butoxyethanol) is a synthetic glycol ether. It is a colourless liquid with a mild ether odour; the odour threshold is approximately 0.10 ppm (0.48 mg/m^3) (Amoore & Hautala, 1983). At ambient temperature, 2-butoxyethanol is miscible in water and soluble in most organic solvents. 2-Butoxyethanol has a boiling point of 171 °C, a vapour pressure of 0.1 kPa at 20 °C, and a log octanol/water partition coefficient of 0.83. The conversion equation for 2-butoxyethanol is 1 ppm = 4.83 mg/m^3 (at 25 °C, 101.3 kPa). Additional physical and chemical properties are presented in the International Chemical Safety Card

reproduced in this document. The structural formula for 2-butoxyethanol is $CH_3CH_2CH_2CH_2$-O-CH_2CH_2OH.

3. ANALYTICAL METHODS

Laboratory analysis for 2-butoxyethanol in environmental samples is usually by gas chromatography (GC) in combination with flame ionization detection (FID), electron capture detection (ECD), or mass spectrometric (MS) detection; infrared absorption spectrophotometry is also sometimes used. The detection limits of these analytical methods in air range from 0.031 ppm (0.15 mg/m^3) for a 48-litre sample (OSHA, 1990) to 0.01–0.02 mg for 2- to 10-litre samples (NIOSH, 1994). Multidimensional GC-MS has been used to improve the detection limit to 5–7 ：g per sample (Kennedy et al., 1990).

Biological monitoring is a useful adjunct to environmental measurements in assessing human exposure to 2-butoxyethanol, as it accounts for both dermal and respiratory uptake. A variety of GC methods combined with FID, ECD, or MS detection and high-performance liquid chromatography (HPLC) methods coupled with ultraviolet or radiochemical detection have been developed for the analysis of 2-butoxyethanol and its metabolite 2-butoxyacetic acid in the urine and blood of exposed workers or rats.

In general, these methods are based on either extraction or lyophilization of the blood or urine followed by derivatization and then analysis (Smallwood et al., 1984, 1988; Groeseneken et al., 1986, 1989; Johanson et al., 1986, 1988; Rettenmeier et al., 1993; Sakai et al., 1993, 1994; Corley et al., 1994). The detection limits range from 0.03 to 0.1 mg 2-butoxyacetic acid/litre. 2-Butoxyethanol and 2-butoxyacetic acid in rat and human blood can be analysed by a GC-MS derivatization method with a detection limit range of 16–18 ng/g blood (Bormett et al., 1995). The National Institute for Occupational Safety and Health reviewed the available data and developed guidelines for biological monitoring of 2-butoxyacetic acid (NIOSH, 1990).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

2-Butoxyethanol does not occur naturally. It is usually produced by reacting ethylene oxide with butyl alcohol, but it may also be made by the direct alkylation of ethylene glycol with an agent such as dibutyl sulfate (Rowe & Wolf, 1982). Temperature, pressure, reactant molar ratios, and catalysts are selected to give the product mix desired.

2-Butoxyethanol is widely used as a solvent in surface coatings, such as spray lacquers, quick-dry lacquers, enamels, varnishes, varnish removers, and latex paint (Leaf, 1985; Sax & Lewis, 1987). In surface coatings, it imparts blush resistance, gloss, and good flow-out. 2-Butoxyethanol is also used as a coupling agent in metal and household cleaners; as an intermediate in 2-butoxyethanol acetate production; and in herbicides, automotive brake fluids, printing inks, spot removers, and cosmetics (Leaf, 1985; ATSDR, 1996). In 1994, 176 900 tonnes of 2-butoxyethanol were produced in the USA (US ITC, 1996). Within the European Community, the total production capacity of 2-butoxyethanol was approximately 70 000–90 000 tonnes in the same year (ECETOC, 1994; CEFIC, 1995).

2-Butoxyethanol may be released into air or water by facilities that manufacture, process, or use the chemical (ATSDR, 1996; US NLM, 1997). Products containing 2-butoxyethanol may also release the substance into the air. Solvent-based building materials such as silicone caulk will release 2-butoxyethanol to air as they dry. There is potential for the release of 2-butoxyethanol from hazardous waste sites, although quantitative data have not been identified. Based upon the detection of 2-butoxyethanol in samples of groundwater and surface water taken near municipal landfills and hazardous waste sites, 2-butoxyethanol may be released to water in leachates from these sites (ATSDR, 1996). Information on the total estimated release of 2-butoxyethanol into the environment in the USA was not identified. In Canada, emissions to the environment between 1992 and 1994 have been reported to range from 1.4 to 3.1 tonnes per year (Canadian Chemical Producers' Association, 1996).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

In the atmosphere, 2-butoxyethanol is expected to exist in the vapour phase. Owing to its water solubility, wet deposition is likely to be more important than dry deposition (ATSDR, 1996). The chemical will not persist in the atmosphere; it has an atmospheric half-life of approximately 17 h, based on an estimated rate constant for reaction with hydroxyl radicals (US NLM, 1997).

The miscibility of 2-butoxyethanol in water suggests that volatilization from water, adsorption, and bioconcentration are not important fate processes and that the chemical should not bioconcentrate in aquatic organisms. Based upon aerobic biodegradation rates, the half-life of 2-butoxyethanol in water is estimated to range from 1 to 4 weeks (Howard et al., 1991). 2-Butoxyethanol is not likely to undergo direct hydrolysis in the aquatic environment, and it is likely readily biodegraded (ATSDR, 1996). Five-day theoretical biological oxygen demand values range from 5% (without acclimation) to 73% (with acclimation); 10-day theoretical biological oxygen demand values range from 57% to 74%. The maximum theoretical biological oxygen demand value reported is 88% for 20 days (US NLM, 1997). Biodegradation is likely to be the most important mechanism for the removal of 2-butoxyethanol from aerobic soil and water.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

Limited data are available on the concentration of 2-butoxyethanol in environmental media. Reported levels of 2-butoxyethanol in samples of ambient air taken from Nepal and Europe and from Antarctica have ranged from 0.1 to 1.59 μg/m^3 and from 1.26 to 14.85 μg/m^3, respectively (Ciccioli et al., 1993, 1996). 2-Butoxyethanol was detected at a concentration of 23 μg/litre in one of seven groundwater samples collected near the Valley of Drums, Kentucky, USA (ATSDR, 1996). Additional monitoring data on the concentration of 2-butoxyethanol in surface waters and information on levels in soils or sediments have not been identified. Levels below 100 μg 2-butoxyethanol/litre have been reported in samples of industrial wastewater effluents in the USA (ATSDR, 1996). Water samples obtained from a highly polluted site on the Hayashida River in Japan, where effluent entered the river from the leather industry, contained 1310 and 5680 μg 2-butoxyethanol/litre (Yasuhara et al., 1981).

6.2 Human exposure

Quantitative information on levels of 2-butoxyethanol in drinking-water and foodstuffs has not been identified, although the chemical has been detected (levels not specified) in drinking-water in six US cities, and there is the potential for the presence of 2-butoxyethanol in foods arising from labelling or packaging materials. Data on concentrations of 2-butoxyethanol in indoor air in the USA are limited to one report, in which the daily arithmetic mean concentration was 0.214 ppbv (1 μg/m^3) for samples obtained from 14 non-industrial offices. 2-Butoxyethanol at a concentration of 8 μg/m^3 was detected in one of six samples of indoor air collected from 14 homes in northern Italy (ATSDR, 1996).

2-Butoxyethanol is present in a variety of consumer products, including cleaning agents and surface coatings, such as paints, lacquers, and varnishes. The average concentration of 2-butoxyethanol in household products marketed in the USA in 1977 was 2.8%. Levels of 2-butoxyethanol in industrial and household window-cleaning agents have been reported to range from 1% to 30% (v/v) (ATSDR, 1996). Based upon available data, indirect exposure of the general population to 2-butoxyethanol is most likely via inhalation and dermal absorption during the use of products containing this chemical.

Based on information from the National Occupational Exposure Survey (NIOSH, 1983), the number of workers potentially exposed to 2-butoxyethanol in the workplace in the USA during 1981–1983 was estimated at about 1.7 million, although it has probably increased since then. Data on the occurrence of airborne 2-butoxyethanol in the workplace obtained from facilities in the USA indicate that, in general, most mean time-weighted-average exposures are below 7 ppm (33.8 mg/m^3) (NIOSH, 1990; ATSDR, 1996). Time-weighted average 2-butoxyethanol exposures have ranged from 1.1 to 5.4 ppm (5.3–26.1 mg/m^3), with an average of 3.5 ppm (16.9 mg/m^3), for silk screening; average exposures of 6.8 ppm (32.8 mg/m^3) for silk screeners, 2.6 ppm (12.6 mg/m^3) for silk screen spray painters, and 1.8 ppm (8.7 mg/m^3) for printing have also been reported (NIOSH, 1990; ATSDR, 1996). In a study of various industrial operations, geometric mean atmospheric exposures to 2-butoxyethanol ranged from 1.5 to 17.7 mg/m^3 for printing, from 3.4 to 93.6 mg/m^3 for painting, and from 0.2 to 1774 mg/m^3 in a mirror manufacturing plant (Veulemans et al., 1987). Workers employed in varnish production facilities have been reported to have individual exposures ranging from <0.1 to 8.1 ppm (<0.5–39.1 mg/m^3) (Angerer et al., 1990; Sohnlein et al., 1993). In a study of automobile cleaners using products containing 2-butoxyethanol, time-weighted-average personal exposures ranged from <0.1 to 7.33 ppm (<0.5–35.4 mg/m^3) (Vincent et al., 1993).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Results of animal and human studies (most of the available data are from studies conducted with rats) indicate that 2-butoxyethanol is readily absorbed following inhalation, oral, and dermal exposure and is oxidized to 2-butoxyacetic acid (Jonsson & Steen, 1978). 2-Butoxyethanol is metabolized primarily via alcohol and aldehyde dehydrogenases, with the formation of 2-butoxyacetaldehyde and 2-butoxyacetic acid, the principal metabolite (Ghanayem et al., 1987b; Medinsky et al., 1990). This is the favoured metabolic pathway for lower systemic doses of 2-butoxyethanol. Alternative pathways include *O*-dealkylation to ethylene glycol and conjugation to 2-butoxyethanol glucuronide and/or 2-butoxyethanol sulfate (Medinsky et al., 1990). In the study conducted by Medinsky et al. (1990), higher relative concentrations of 2-butoxyacetic acid and ethylene glycol were obtained at lower vapour concentrations of 2-butoxyethanol; higher 2-butoxyethanol glucuronide levels were observed at the high exposures to 2-butoxyethanol, possibly owing to saturation of the pathways leading to the formation of 2-butoxyacetic acid and ethylene glycol. In human but not animal studies, the amino acid conjugate of 2-butoxyethanol, *N*-butoxyacetylglutamine, has been identified as a metabolite (Rettenmeier et al., 1993).

In general, the metabolism of 2-butoxyethanol to 2-butoxyacetic acid is linearly related to exposure concentration up to levels causing mortality. In one study, after inhalation exposure in rats, 2-butoxyethanol and 2-butoxyacetic acid were analysed in blood, muscle, liver, and testes. The kinetic profile of 2-butoxyacetic acid tissue concentrations was similar to that of 2-butoxyethanol tissue concentrations. Sixty-four per cent of the inhaled dose of 2-butoxyacetic acid was eliminated in urine, and the rate of urinary excretion of 2-butoxyacetic acid was dose-dependent (Johanson, 1994).

In humans exposed to 20 ppm (96.6 mg/m^3) 2-butoxyethanol for 2 h via inhalation, the concentration of 2-butoxyethanol in the blood reached a plateau of 7.4 μmol/litre within 1–2 h, and the chemical could no longer be detected in the blood 2–4 h after exposure. The mean elimination half-time was 40 min. Less than 0.03% of the total uptake of 2-butoxyethanol was excreted in the urine, whereas urinary excretion as 2-butoxyacetic acid ranged from 17% to 55% (Johanson et al., 1986). Similarly, after percutaneous uptake of 2-butoxyethanol, the urinary excretion of 2-butoxyacetic acid peaked 3 h after exposure and subsequently declined, with an average half-life of 3.1 h. The accumulated excretion of 2-butoxyacetic acid ranged from 8.7 to 313 μmol, corresponding to 2.5–39% of uptake (Johanson et al., 1988).

Several physiologically based pharmacokinetic (PBPK) models of 2-butoxyethanol absorption, metabolism, disposition, and excretion have been developed. One model examined human inhalation exposures during rest and exercise (Johanson et al., 1986; Johanson & Boman, 1991), whereas another addressed high-to-low-dose extrapolation and route of administration extrapolation based on animal data (Shyr et al., 1993). In the Shyr et al. (1993) model, 2-butoxyethanol is metabolized to 2-butoxyacetic acid and ethylene glycol. An additional model combined aspects of the preceding models and addressed the disposition of 2-butoxyacetic acid in rats and humans (Corley et al., 1994). The Corley et al. (1994) PBPK model describes the uptake, distribution, metabolism, and elimination of 2-butoxyethanol and its metabolite 2-butoxyacetic acid. It was developed by expanding a previous inhalation model for 2-butoxyethanol (Johanson et al., 1986) and is composed of two separate models for 2-butoxyethanol and 2-butoxyacetic acid that are joined through metabolism in the liver. Both the 2-butoxyethanol and 2-butoxyacetic acid models have the same eight compartments, with an additional kidney compartment in the 2-butoxyacetic acid model. Unlike the original model of Johanson et al. (1986), the muscle and skin compartments have been separated. Corley et al. (1994) also incorporated protein binding and saturable elimination of 2-butoxyacetic acid by the kidneys. Equations for additional routes of exposure (oral, dermal, and intravenous infusion) were also added. Physiological and biochemical parameters were allometrically scaled rather than using standard values for a 70-kg human. This allows simulations to be conducted for specific data sets. A rat version of the model was also developed.

The Corley et al. (1994) model accurately predicted animal data at dose levels that did not cause haemolysis, the principal effect exerted by 2-butoxyethanol (see below). At dose levels causing haemolysis, the model overpredicted the amount of 2-butoxyacetic acid excreted in the urine. This overprediction is assumed to be caused by toxicity in the kidneys that is secondary to haemolysis. The model does not accommodate toxicity in the kidneys and assumes that the kidneys will continue to function as normal, thereby leading to the overprediction of 2-butoxyacetic acid levels in the urine. The results of the Johanson & Boman (1991) study indicated that during whole-body exposure to 2-butoxyethanol vapour, dermal uptake accounted for approximately 75% of the total uptake of the chemical. The Corley et al. (1994) model was able to accurately predict the Johanson & Boman (1991) human whole-body exposure blood data when it was assumed that the

sampled blood did not represent systemic venous blood but instead represented venous blood draining from the skin compartment. This blood had not yet been diluted by the venous blood pool. Corley et al. (1994, 1997) suggested that the blood samples collected by Johanson & Boman (1991) were not representative of systemic blood concentrations and that dermal uptake is approximately 21% of the total, rather than the 75% suggested by Johanson & Boman (1991). An additional study further addresses dermal uptake in humans from the vapour phase but does not address direct skin contact with liquid containing 2-butoxyethanol (Corley et al., 1997).

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

8.1 Single exposure

Many acute toxicity studies of 2-butoxyethanol have led to the establishment of LC_{50}s or LD_{50}s in a variety of species by inhalation, oral, and dermal exposure. Inhalation LC_{50}s for 2-butoxyethanol of 486 ppm (2347 mg/m^3) (male rats, 4 h), 450 ppm (2174 mg/m^3) (female rats, 4 h), 700 ppm (3381 mg/m^3) (mice, 7 h), and >650 ppm (3140 mg/m^3) (guinea-pigs, 1 h) have been reported. Oral LD_{50}s for rats (2500 mg/kg body weight), mice (1400 mg/kg body weight), guinea-pigs (1200 mg/kg body weight), and rabbits (320 mg/kg body weight) have also been reported. Dermal LD_{50}s of 404–502 and 2000 mg/kg body weight have been reported for rabbits and guinea-pigs, respectively. Effects observed in rats, mice, and guinea-pigs exposed by inhalation to the LC_{50} or by ingestion to the LD_{50} include loss of coordination, ataxia, sluggishness, muscular flaccidity, enlarged kidney, blood in the bladder, haemoglobinuria, splenic lesions, and pulmonary congestion (Werner et al., 1943a; Carpenter et al., 1956; Dodd et al., 1983; Gingell et al., 1997). Inhalation exposures of female rats to 62 ppm (299 mg/m^3) 2-butoxyethanol for 4-h periods resulted in increased osmotic fragility of erythrocytes (Carpenter et al., 1956).

Ghanayem et al. (1987a) indicated that the haemolytic activity of 2-butoxyethanol in rats is age-dependent, with older rats being more susceptible than younger animals. In their study, 2-butoxyethanol (0, 125, or 500 mg/kg body weight) was administered orally to young (4- to 5-week-old) and adult (9- to 13-week-old) male F344 rats, and haematotoxicity was assessed from 2 to 48 h later. A decrease in red blood cells, haemoglobin, and haematocrit was accompanied by a significant ($p < 0.05$) dose-dependent increase in free haemoglobin plasma levels in both age groups administered 500 mg 2-butoxyethanol/kg body weight; in both groups, there was a gradual recovery after 48 h. Although no significant haematotoxic effects were observed in the younger rats administered 125 mg 2-butoxyethanol/kg body weight, effects in older animals administered this dose included a significant decrease ($p \# 0.05$) in the number of red blood cells, haematocrit, and haemoglobin. Free haemoglobin plasma levels were significantly increased ($p \# 0.05$) in adult rats 8 h after oral administration of 125 mg/kg body weight; there was no effect on free haemoglobin plasma levels in young animals. Histopathological evaluation of tissues collected 24 h after 2-butoxyethanol administration to rats of various ages revealed dose- and age-dependent liver and kidney changes. These histopathological changes exhibited signs of regression when examined 48 h following exposure. Severe acute haemolytic anaemia was evidenced by a decrease in circulating red blood cells, an increase in the concentration of free haemoglobin in plasma, and the development of haemoglobinuria. Using a laser-based haematology analyser, Ghanayem et al. (1987a) indicated that the acute haemolysis in 2-butoxyethanol-exposed rats was caused by a time- and dose-dependent decrease in the number of red blood cells, in haemoglobin concentrations, and in haematocrit, with little or no change in mean cell volume. In a follow-up study in which the authors used both a laser-based haematology analyser and an impedance-based analyser, haematology profiles from the impedance-based haematology analyser revealed a time- and dose-dependent increase in haematocrit and mean cell volume; the laser-based analyser was unable to detect early increases in haematocrit and mean cell volume in the exposed animals. Based on these data, Ghanayem et al. (1990) concluded that 2-butoxyethanol causes spherical swelling of red blood cells followed by haemolysis.

To investigate the induction of tolerance, Ghanayem et al. (1992) assessed haematological parameters in naive or previously bled rats administered a single dose of 125 or 250 mg 2-butoxyethanol/kg body weight. The bled/recovered rats were less sensitive to 2-butoxyethanol than the naive animals. *In vitro* incubations with 2-butoxyacetic acid revealed that red blood cells from the bled/recovered rats were less sensitive than those cells from naive animals. Ghanayem et al. (1992) concluded that young red blood cells formed during the regeneration process were less sensitive to 2-butoxyacetic acid than older red blood cells. Chronic exposure to 2-butoxyethanol would be expected to result in tolerance to 2-butoxyethanol-induced haemolytic anaemia. The mechanism is probably related to the greater susceptibility of older cells to 2-butoxyacetic acid; haemolysis of these cells during the initial exposure followed by their replacement with less susceptible younger cells may account for the development of tolerance.

Toxic effects in the kidneys have been observed in rabbits exposed percutaneously to 2-butoxyethanol (Carpenter et al., 1956). Necropsy of rabbits exposed for 24 h to undiluted 2-butoxyethanol (0.48–0.64 ml/kg body weight) revealed congestion of the kidneys, haemoglobinuria, pale livers, and engorged spleens (Carpenter et al., 1956).

When 2-butoxyethanol (200, 260, 320, 375, or 500 mg/kg body weight) was applied to the shaved dorsal skin of groups of female rats, increased mean cell volume, a lowered erythrocyte count and haemoglobin level, and haemoglobinuria were observed within 6 h of exposure to the highest dose; no haemolytic effects were observed at the lowest dose tested (Bartnik et al., 1987). 2-Butoxyethanol at doses of 260, 320, and 375 mg/kg body weight produced similar effects in at least some animals in each group; however, there was no discernible dose–response relationship, which was attributed to the inherent biological variation in percutaneous absorption and haemolytic susceptibility and to the small number of animals ($n = 3$) in these dose groups.

8.2 Irritation and sensitization

2-Butoxyethanol is irritating to the eyes and skin. In rabbits, instillation of an unspecified amount of undiluted 2-butoxyethanol caused severe eye irritation, including conjunctival hyperaemia and oedema (von Oettingen & Jirouche, 1931). More recent ocular tests in rabbits revealed that 30% and 70% concentrations of 2-butoxyethanol were moderately irritating (Kennah et al., 1989). When applied to the skin of rabbits for 4 h, 2-butoxyethanol caused mild irritation; extending the period of contact increased the severity of irritation (Tyler, 1984). 2-Butoxyethanol was classified as a severe cutaneous irritant when the Draize method was used (Zissu, 1995).

2-Butoxyethanol did not induce skin sensitization in guinea-pigs (Unilever, 1989, as cited in ECETOC, 1994; Zissu, 1995).

8.3 Short-term exposure

In older studies, haematotoxic effects (e.g. increased osmotic fragility, decreased haemoglobin, decreased numbers of red blood cells) have been observed in rats (54–320 ppm; 261–1546 mg/m^3), dogs (200–385 ppm; 966–1860 mg/m^3), and monkeys (210 ppm; 1014 mg/m^3) exposed repeatedly via inhalation to 2-butoxyethanol for up to approximately 30–35 days (Werner et al., 1943b; Carpenter et al., 1956).

Dodd et al. (1983) exposed Fischer 344 rats of both sexes to 0, 20, 86, or 245 ppm (0, 97, 415, or 1183 mg/m^3) 2-butoxyethanol, 6 h/day for 9 days in total (5 consecutive days of exposure, followed by 2 days of no exposure, then 4 additional consecutive days of exposure). In both sexes, exposure to 245 ppm (1183 mg/m^3) was associated with a significant reduction in red blood cell counts ($p < 0.001$), haemoglobin levels ($p < 0.001$), and mean cell haemoglobin concentration ($p < 0.01$), as well as a significant increase ($p < 0.001$ in all cases) in mean cell volume, nucleated red blood cells, and reticulocytes. Fourteen days post-exposure, a substantial recovery of the affected erythroid parameters was observed; however, statistically significant differences from controls were still observed for the males (i.e. red blood cell count [$p < 0.01$], mean cell volume [$p < 0.001$], and mean cell haemoglobin [$p < 0.001$]). Exposure of both sexes to 86 ppm (415 mg/m^3) 2-butoxyethanol was associated with a significant but less profound effect on erythroid parameters. The no-observed-adverse-effect level (NOAEL) in this study is 20 ppm (97 mg/m^3).

In a study designed primarily to assess developmental effects, Tyl et al. (1984) exposed pregnant Fischer 344 rats (36 per group) and New Zealand white rabbits (24 per group) to 2-butoxyethanol (0, 25, 50, 100, or 200 ppm; 0, 121, 242, 483, or 966 mg/m^3) for 6 h/day on days 6–15 of gestation for the rats and on days 6–18 of gestation for the rabbits. In rats, there were significant reductions in red blood cell count and significant increases in haemoglobin and haematocrit at 200 ppm (966 mg/m^3) ($p < 0.001$); the red blood cell count was also reduced at 100 ppm (483 mg/m^3) ($p < 0.001$). In dams exposed to 100 or 200 ppm (483 or 966 mg/m^3) 2-butoxyethanol, mean cell volume and mean cell haemoglobin were significantly increased relative to controls; the mean cell haemoglobin concentration was significantly reduced at 100 ppm (483 mg/m^3) 2-butoxyethanol ($p < 0.01$) and 200 ppm (966 mg/m^3) 2-butoxyethanol ($p < 0.001$), relative to controls. In the rabbits, statistically significant increases in haemoglobin content and haematocrit were observed at 100 ppm (483 mg/m^3) ($p < 0.01$) but not at 200 ppm (966 mg/m^3) 2-butoxyethanol. The results of this study indicate that rats are more sensitive than rabbits to the haemolytic effects of 2-butoxyethanol. The NOAEL in this study is 50 ppm (242 mg/m^3) 2-butoxyethanol.

The oral administration of 500 or 1000 mg 2-butoxyethanol/kg body weight per day for 4 consecutive days to male F344 rats produced a pronounced dose-dependent effect on circulating red and white blood cells (Grant et al., 1985); however, some effects were reversible following the end of exposure. Reduced erythrocyte counts, haematocrit, haemoglobin levels, and leukocyte counts and elevated mean cell volume, reticulocyte counts, and mean cell haemoglobin concentration ($p < 0.001$) were observed in animals in the high-dose group. Similar, although less severe, effects were observed in the low-dose group.

To assess the development of tolerance to the haemolytic effects of 2-butoxyethanol exposure in laboratory animals, male F344 rats were administered (by gavage) 125 mg 2-butoxyethanol/kg body weight per day for 0, 1, 2, 3, 6, and 12 days, and haematological parameters (red blood cell counts, haemoglobin content, haematocrit) were determined after exposure (Ghanayem et al., 1987a). Administration of 2-butoxyethanol for 2 and 3 days caused significant haemolysis of red blood cells, although after the third day there was a gradual increase in the number of red blood cells and haemoglobin content. After 12 days, red blood cells and haemoglobin approached pre-exposure levels, indicative of the development of tolerance to the haemolytic effects of 2-butoxyethanol. In a follow-up study, Ghanayem et al. (1992) assessed the haemolytic effects of 2-butoxyethanol (administered as a single dose of 0, 125, or 250 mg/kg body weight) in untreated (control) or 2-butoxyethanol-pretreated male F344 rats. The pretreated animals were administered (by gavage) 125 mg 2-butoxyethanol/kg body weight per day for 3 days and then allowed to recover for 7 days prior to study. The pretreated animals were less sensitive to the haemolytic effects of subsequent exposure to 2-butoxyethanol than the untreated controls. *In vitro* incubations with 2-butoxyacetic acid revealed that red blood cells from the 2-butoxyethanol-pretreated group were less sensitive than cells from the untreated controls. The authors suggested that the development of tolerance to the haemolytic effects of 2-butoxyethanol might be due in part to the reduced sensitivity of young erythrocytes formed during the blood regeneration process.

In mice orally administered 500 or 1000 mg 2-butoxyethanol/kg body weight per day, 5 days/week for 5 weeks, no effect upon white blood cell counts, mean cell volume, or haemoglobin levels was observed; however, red blood cell counts were reduced at both doses (Nagano et al., 1979). The oral administration of 222, 443, or 885 mg 2-butoxyethanol/kg body weight per day, 5 days/week for 6 weeks, to male rats principally affected red blood cells, whereas white blood cell counts were unaffected (Krasavage, 1986).

In a study in which F344/N rats and $B6C3F_1$ mice were administered 2-butoxyethanol in drinking-water daily for 2 weeks, estimates of 2-butoxyethanol intake by rats and mice ranged from 70 to 300 mg/kg body weight per day and from 90 to 1400 mg/kg body weight per day, respectively (NTP, 1993). Survival of both species was not affected by exposure to 2-butoxyethanol. Statistically significant decreases ($p < 0.05$) in relative and absolute thymus weights were noted in male mice receiving 400 or 650 mg 2-butoxyethanol/kg body weight per day. No haematological tests were conducted in this study.

8.4 Long-term exposure

8.4.1 Subchronic exposure

In older studies, haematotoxic effects (e.g. increased osmotic fragility, decreased haemoglobin, decreased red blood cell numbers) have been observed in mice (100–400 ppm; 483–1932 mg/m^3), dogs (415 ppm; 2004 mg/m^3), and monkeys (100 ppm; 483 mg/m^3) exposed repeatedly by inhalation to 2-butoxyethanol for up to approximately 90 days (Werner et al., 1943c; Carpenter et al., 1956). More recent studies on effects associated with the subchronic exposure of laboratory animals to 2-butoxyethanol are limited.

Dodd et al. (1983) exposed Fischer 344 rats of both sexes (16 per group) to 0, 5, 25, or 77 ppm (0, 24, 121, or 372 mg/m^3) 2-butoxyethanol by inhalation, 6 h/day, 5 days/week, for 13 weeks. After 6 weeks, animals exposed to 77 ppm (372 mg/m^3) 2-butoxyethanol had a slight but statistically significant decrease in red blood cell counts ($p < 0.01$) and haemoglobin level (statistics not reported), accompanied by an 11% increase in mean cell haemoglobin concentration ($p < 0.001$). At the end of the study, these effects had either lessened or returned to the ranges of control values. The only significant haemolytic effect for male rats in the 77 ppm (372 mg/m^3) 2-butoxyethanol exposure group was a 5% decrease in red blood cell count after 66 exposures to 2-butoxyethanol (statistics not provided). The NOAEL in this study is 25 ppm (121 mg/m^3).

Groups of F344/N rats and $B6C3F_1$ mice (10 per sex per concentration) were administered 2-butoxyethanol in drinking-water (0, 750, 1500, 3000, 4500, or 6000 mg/litre) daily for 13 weeks; estimated intakes by rats and mice ranged from 70 to 500 mg/kg body weight per day and from 100 to 1300 mg/kg body weight per day, respectively (NTP, 1993). Effects observed in both species included decreased body weight gain and water consumption. In rats, reduced red blood cell counts and histopathological lesions in the liver, spleen, and bone marrow were observed in males and females (at concentrations of 3000–6000 mg/litre and 750–6000 mg/litre, respectively). Reduced thymus weights (at concentrations of 4500 and 6000 mg/litre in males and females, respectively), diminished uterine size (at 4500 and 6000 mg/litre in females), and diminished sperm concentration (750–6000 mg/litre in males) were also noted. A NOAEL could not be identified owing to a mild to moderate anaemia present in most dose groups of rats. In mice, the only effect observed was reduced body weight gain in males and females at concentrations of 3000–6000 mg/litre.

8.4.2 Chronic exposure and carcinogenicity

Published information on effects associated with the chronic exposure of laboratory animals to 2-butoxyethanol was not identified.[1]

8.5 Genotoxicity and related end-points

2-Butoxyethanol has been tested for genotoxicity in a range of *in vitro* and *in vivo* assays (see Elliott & Ashby, 1997, for a recent review). In standard tests in bacteria, 2-butoxyethanol was not mutagenic in *Salmonella typhimurium* strains TA1535, TA1537, TA97, TA98, TA100, and TA102 (Zeiger et al., 1992; Hoflack et al., 1995; Gollapudi et al., 1996). However, the results for strain TA98a were inconsistent, with one report of mutagenicity observed in both the presence and absence of metabolic activation (Hoflack et al., 1995) and another report of no mutagenicity (Gollapudi et al., 1996).

2-Butoxyethanol was not mutagenic at the HPRT locus in Chinese hamster ovary cells in either the presence or absence of metabolic activation (McGregor, 1984; Chiewchanwit & Au, 1995). However, there was evidence that it caused gene mutations at the HPRT locus in Chinese hamster lung (V79) cells (Elias et al., 1996). An *in vitro* assay for unscheduled DNA synthesis in rat hepatocytes yielded equivocal results (Elliott & Ashby, 1997). 2-Butoxyethanol produced sister chromatid exchanges in human peripheral lymphocytes but not in Chinese hamster lung (V79) or ovary cells. *In vitro* cytogenetic assays conducted with human peripheral lymphocytes, Chinese hamster lung (V79) cells, and Chinese hamster ovary cells revealed no induction of chromosomal aberrations. An *in vitro* micronucleus assay in Chinese hamster lung (V79) cells, which incorporated a test for aneuploidy, yielded equivocal results (Elliott & Ashby, 1997).

In vivo mutagenicity tests have yielded uniformly negative results for 2-butoxyethanol. These assays have included three bone marrow micronucleus tests utilizing intraperitoneal injection in rats and mice (Elias et al., 1996; Elliott & Ashby, 1997); a [^{32}P]post-labelling assay for DNA adducts in the brain, kidney, liver, spleen, and testes of orally dosed rats (Keith et al., 1996); an assay for DNA methylation in the brain, kidney, liver, spleen, and testes of rats and in FVB/N transgenic mice carrying the v-Ha-*ras* oncogene (Keith et al., 1996); as well as a test for tumour formation in FVB/N transgenic mice (Keith et al., 1996). Although the results of *in vitro* tests for mutagenicity of 2-butoxyethanol are inconsistent, the absence of structural alerts as well as the negative results from *in vivo* studies are sufficiently reassuring to allow the conclusion that 2-butoxyethanol is not mutagenic.

Mutagenicity studies have also been performed on two metabolites of 2-butoxyethanol — 2-butoxyacetic acid and 2-butoxyacetaldehyde. 2-Butoxyacetic acid was not mutagenic in a series of *in vitro* assays, in addition to an *in vivo* micronucleus assay in mice administered the chemical by intraperitoneal injection (Hoflack et al., 1995; Elias et al., 1996; Elliott & Ashby, 1997). 2-Butoxyacetaldehyde exhibited mutagenic potential in several *in vitro* studies (including tests for HPRT gene mutation, chromosomal aberrations, micronuclei, aneuploidy, and sister chromatid exchange); however, in the absence of data from *in vivo* studies, it is not possible to reach a final conclusion concerning the possible mutagenic hazard of this metabolite (Chiewchanwit & Au, 1995; Hoflack et al., 1995; Elias et al., 1996; Elliott & Ashby, 1997).

8.6 Reproductive and developmental toxicity

Effects on the testes were not observed in studies in which Alpk/Ap (Wistar-derived) rats were exposed by inhalation to 800 ppm (3864 mg/m^3) 2-butoxyethanol for 3 h (Doe, 1984), JCL-ICR mice were orally administered 2-butoxyethanol at doses ranging from 500 to 2000 mg/kg body weight per day, 5 days/week, for 5 weeks (Nagano et al., 1979), or rats were administered 2-butoxyethanol (by gavage) at doses ranging from 222 to 885 mg/kg body weight per day, 5 days/week, for 6 weeks (Krasavage, 1986). Testicular damage was not observed in groups of Alpk/Ap (Wistar-derived) rats administered a single oral dose of 174, 434, or 868 mg 2-butoxyacetic acid/kg body weight (Foster et al., 1987).

No adverse effects were observed in either the dams or pups (number of resorptions, fetal weights, and incidence of malformations) in a study in which Sprague-Dawley rats were exposed by inhalation for 7 h/day on days 7–15 of gestation to 150 or 200 ppm (725 or 966 mg/m^3) 2-butoxyethanol (Nelson et al., 1984); exposure to 250 or 500 ppm (1208 or 2415 mg/m^3) 2-butoxyethanol caused death in the dams.

Tyl et al. (1984) exposed pregnant Fischer 344 rats (36 per group) and New Zealand white rabbits (24 per group) to 0, 25, 50, 100, or 200 ppm (0, 121, 242, 483, or 966 mg/m^3) 2-butoxyethanol for 6 h/day on days 6–15 of gestation for the rats and on days 6–18 of gestation for the rabbits. No adverse reproductive or developmental effects were observed in rats or rabbits exposed to 25 ppm or 50 ppm (121 or 242 mg/m^3) 2-butoxyethanol. In rats, exposure to 200 ppm (966 mg/m^3) 2-butoxyethanol was associated with a reduction in maternal weight gain,

[1] Results of a US National Toxicology Program 2-year carcinogenesis bioassay completed in July 1995 were not available at the time this CICAD was prepared.

a significant ($p < 0.01$) increase in the number of totally resorbed litters, and a reduction in the number of viable implants ($p < 0.001$) and in the percentage of live fetuses ($p < 0.01$) per litter. However, there were no statistically significant increases in incidences of external, visceral, skeletal, or total malformations associated with exposure to 2-butoxyethanol. Exposure to 200 ppm (966 mg/m^3) 2-butoxyethanol was also associated with a significant increase ($p < 0.05$) in the number of litters with one or more fetuses with unossified skeletal elements and poorly ossified skeletal elements. There was a decreased incidence of bilobed cervical centrum 5, bilobed thoracic centra 9 and 13, as well as poorly ossified proximal phalanges of the hindlimb. Following maternal exposure to 100 ppm (483 mg/m^3) 2-butoxyethanol, skeletal ossification in the fetuses was retarded, with a significant ($p < 0.05$) decreased (primarily because at these exposure concentrations this skeletal element was largely unossified) incidence of bilobed cervical centrum 5 and an increased incidence ($p < 0.05$) of unossified cervical centrum 6. In rabbits, exposure to 200 ppm (966 mg/m^3) 2-butoxyethanol produced a significant reduction in maternal body weight, gravid uterine weight, and numbers of total implants and viable implants. No significant increases in the number of fetuses or litters with malformations were observed in any treatment group; however, exposure to 200 ppm (966 mg/m^3) 2-butoxyethanol was associated with a significant ($p < 0.05$) reduction in unossified sternebra 6 and in rudimentary rib at the first lumbar rib. The occurrence of unossified skeletal elements in both rats and rabbits was an indication of delayed development in rats and rabbits exposed to 2-butoxyethanol under maternally toxic conditions (Tyl et al., 1984).

Maternal deaths and a reduction in the number of viable litters were observed in a study in which CD-1 mice were orally administered 4000 mg 2-butoxyethanol/kg body weight per day on days 7–14 of gestation (Schuler et al., 1984).

Heindel et al. (1990) used a continuous breeding protocol (Heindel et al., 1989) to assess the reproductive toxicity of 2-butoxyethanol. Male and female Swiss CD-1 mice were administered 2-butoxyethanol in drinking-water (0, 0.5, 1.0, or 2.0%; equivalent to 0, 0.7, 1.3, and 2.1 g/kg body weight per day) 7 days prior to and during a 98-day cohabitation period (20 pairs of mice per dose). Exposure to 1.0% or 2.0% 2-butoxyethanol in drinking-water was associated with increased mortality in the females and a significant reduction ($p < 0.05$) in the number of live pups per litter, the proportion of pups born alive, and the live pup weights (both absolute and adjusted). The authors noted that these effects occurred in the presence of maternal toxicity, as evidenced by decreased body weight, decreased water consumption, and increased kidney weight in the female mice. Necropsy revealed that testes and epididymis weights were normal, as were sperm number and motility. The reproductive toxicity of 2-butoxyethanol was evident only in female mice, at doses that also elicited general toxicity (Heindel et al., 1990).

No maternal, embryotoxic, fetotoxic, or teratogenic effects were detected when 2-butoxyethanol (106 mg) was applied to the shaved interscapular skin of female Sprague-Dawley rats, four times daily on days 7–14 of gestation (Hardin et al., 1984).

8.7 Immunological and neurological effects

Effects on the immune system were examined in two studies in which 2-butoxyethanol was administered orally, by drinking-water or gavage. In the first study, Sprague-Dawley rats were administered 2-butoxyethanol at 0, 2000, or 6000 mg/litre (males) or 0, 1600, or 4800 mg/litre (females) in drinking-water for 21 consecutive days. Exposure to 2-butoxyethanol had no effect on antibody production, delayed-type hypersensitivity reactions, and interferon or interleukin-2 production. However, natural killer cell cytotoxicity responses were enhanced ($p \# 0.05$) in rats receiving the lowest concentrations of 2-butoxyethanol (Exon et al., 1991). In the second study, male Fischer rats were administered (by gavage) 0, 50, 100, 200, or 400 mg 2-butoxyethanol/kg body weight per day for 2 consecutive days, following immunization with trinitrophenyl-lipopolysaccharide. A reduction ($p < 0.05$) in the serum haemagglutination titre was observed 3 days later in rats administered 200 mg 2-butoxyethanol/kg body weight per day. All animals in the highest dose group died (Smialowicz et al., 1992).

No specific investigations on potential neurological effects associated with exposure to 2-butoxyethanol were identified. However, adverse effects on the central nervous system associated with exposure to 2-butoxyethanol have been observed. These included loss of coordination, sluggishness, narcosis, muscular flaccidity, and ataxia (Carpenter et al., 1956; Dodd et al., 1983; Hardin et al., 1984; Krasavage, 1986).

8.8 *In vitro* haemolytic effects

Bartnik et al. (1987) examined the effects of 2-butoxyethanol and 2-butoxyacetic acid on human (from healthy males) and rat (four male Wistar) erythrocytes *in vitro*. Under these conditions 175, 200, 225, and 250 mmol 2-butoxyethanol/litre induced complete lysis of rat erythrocytes, whereas only 200, 225, and 250 mmol 2-butoxyethanol/litre induced complete lysis of human erythrocytes. Although 3.75–7.5 mmol 2-butoxyacetic acid/litre caused complete lysis of rat erythrocytes, lysis of human erythrocytes was not observed at these concentrations. These results indicate that rats may be more susceptible than humans to the haemolytic effects of

2-butoxyethanol and its metabolite 2-butoxyacetic acid (Bartnik et al., 1987).

Ghanayem (1989) examined the effect of 2-butoxyethanol and 2-butoxyacetic acid on blood collected by cardiac puncture from male F344 rats. The addition of 2-butoxyethanol to whole blood to concentrations of 5 or 10 mmol/litre had no effect on haematocrit, whereas a concentration of 20 mmol/litre caused significant haemolysis ($p < 0.05$). The addition of 2-butoxyacetic acid to rat erythrocytes to concentrations of 0.5 or 1 mmol/litre caused a time- and concentration-dependent increase in haematocrit followed by haemolysis. Incubation with 2 mmol 2-butoxyacetic acid/litre caused a faster time-dependent increase in haematocrit, with the haematocrit reaching a maximum after 2 h, followed by nearly complete haemolysis after 4 h. Also examined was the effect of 2-butoxyacetic acid (0.5, 1, 2, 4, or 8 mmol/litre) on human blood obtained from healthy young male and female volunteers (Ghanayem, 1989). No significant changes in haematocrit or haemolysis were observed at 2-butoxyacetic acid concentrations of 4 mmol/litre or less; at 8 mmol 2-butoxyacetic acid/litre, there was a slight but significant increase in haematocrit ($p < 0.05$), followed by a slight but significant haemolysis ($p < 0.05$) of erythrocytes.

In a subsequent study, Ghanayem & Sullivan (1993) assessed the haemolytic activity of 2-butoxyacetic acid (1 or 2 mmol/litre) in blood collected from a variety of species (i.e. rats, mice, hamsters, baboons, rabbits, pigs, guinea-pigs, dogs, cats, and humans). 2-Butoxyacetic acid caused a time- and concentration-dependent increase in mean cell volume and haematocrit of blood from rats, rabbits, hamsters, mice, and baboons. However, no or minimal effects were observed on blood from humans, guinea-pigs, dogs, cats, and pigs (Ghanayem & Sullivan, 1993), demonstrating the sensitivity of rat erythrocytes and the relative insensitivity of human erythrocytes to the haemolytic effects of 2-butoxyacetic acid.

The effect of 2-butoxyacetic acid on red blood cells from healthy young and older individuals (Udden & Patton, 1994) and individuals with a possible susceptibility to 2-butoxyethanol-induced haemolysis (i.e. sickle cell and spherocytosis patients) (Udden, 1994, 1996) has also been examined. Along with haemolysis, 0.2 and 2 mmol 2-butoxyacetic acid/litre caused decreased red blood cell deformability and increased mean cellular volume in rat red blood cells (Udden & Patton, 1994). However, none of the human blood samples exhibited prehaemolytic changes (i.e. decreased deformability and increased mean cellular volume) or haemolysis after treatment with 2 mmol 2-butoxyacetic acid/litre for up to 4 h (Udden, 1994, 1996; Udden & Patton, 1994). The results of these *in vitro* studies provide further evidence that rat erythrocytes are more susceptible than human erythrocytes to 2-butoxyacetic acid-induced haemolysis.

9. EFFECTS ON HUMANS

Information on human health effects associated with exposure to 2-butoxyethanol are limited to a few case reports and one laboratory investigation; epidemiological studies have not been identified. The principal human health effects attributed to 2-butoxyethanol exposure have involved the central nervous system, the blood, and the kidneys (ATSDR, 1996).

In one report involving a number of small studies, the exposure of two males to 113 ppm (546 mg/m^3) 2-butoxyethanol for 4 h produced nose and eye irritation as well as disturbed taste, but there was no evidence of haemolytic effects. Similar effects were observed in a second study in which two males and one female were exposed to 195 ppm (942 mg/m^3) 2-butoxyethanol for two 4-h periods, separated by a 30-min period of no exposure. When two males and two females were exposed to 100 ppm (483 mg/m^3) 2-butoxyethanol for 8 h, the effects included vomiting and headache. No clinical signs of haemolysis were observed in any of the subjects; however, following exposure to 195 ppm (942 mg/m^3) 2-butoxyethanol, increased osmotic fragility of erythrocytes was observed *in vitro* (Carpenter et al., 1956).

Haemoglobinuria, erythropenia, and hypotension (Rambourg-Schepens et al., 1988; Gijsenbergh et al., 1989), metabolic acidosis, shock, non-cardiogenic pulmonary oedema, and albuminuria (Bauer et al., 1992), and metabolic acidosis, hepatic laboratory abnormalities, and haematuria (Gualtieri et al., 1995) have been reported in case-studies of individuals who had attempted suicide by ingesting 2-butoxyethanol-containing cleaning solutions (involving an estimated ingestion of 25–60 g 2-butoxyethanol). In two of the cases, haemodialysis was employed, and all patients recovered fully with appropriate treatment. A survey of paediatric poisonings identified 24 children who had ingested 5–300 ml of glass cleaners containing 2-butoxyethanol (Dean & Krenzelok, 1992). The two children with the highest intake exhibited no evidence of haemolytic effects. 2-Butoxyethanol is reportedly not a skin sensitizer in humans (Greenspan et al., 1995).

Table 1: Acute and long-term studies on toxicity to aquatic organisms.

Species	End-point[a]	Concentration (mg/litre)	Reference
Freshwater			
Bacterium (*Pseudomonas putida*)	16-h LOEC (growth)	700	Bringmann & Kuhn, 1980a
Sewage sludge bacteria	16-h IC_{50}	>1000	Union Carbide, 1989
Protozoan (*Entosiphon sulcatum*)	72-h LOEC (growth)	91	Bringmann & Kuhn, 1980a
Protozoan (*Chilomonas paramecium*)	48-h EC_5 (growth)	911	Bringmann & Kuhn, 1980b
Protozoan (*Uronema parduczi*)	48-h EC_5 (growth)	463	Bringmann & Kuhn, 1980b
Cyanobacterium (*Microcystis aeruginosa*)	8-day LOEC (growth)	35	Bringmann & Kuhn, 1980a
Green alga (*Scenedesmus quadricaudata*)	7-day LOEC (growth)	900	Bringmann & Kuhn, 1980a
Green alga (*Selenastrum capricornutum*)	7-day NOEC 7-day EC_{50}	125 >1000	Dow, 1988
Water flea (*Daphnia magna*)	24-h LC_{50} 24-h LC_{50} 24-h LC_{50} 48-h LC_{50}	1720 1698–1940 5000 835	Bringmann & Kuhn, 1977 Bringmann & Kuhn, 1982 CMA, 1994 Dow, 1979
Guppy (*Poecilia reticulata*)	7-day LC_{50}	982	Koenemann, 1981
Golden ide (*Leuciscus idus melanotus*)	48-h LC_{50} 48-h LC_{50}	165–186 1880	Junke & Ludemann, 1978 CMA, 1994
Bluegill sunfish (*Lepomis macrochirus*)	96-h LC_{50}	1490	Dawson et al., 1977
Goldfish (*Carassius auratus*)	24-h LC_{50} 24-h LC_{50}	1700 1650	Bridie, 1979 Verschueren, 1983
Fathead minnow (*Pimephales promelas*)	96-h LC_{50}	2137	Dow, 1979
Emerald shiner (*Notropus atherinoides*)	72-h LC_{50}	>500	Dill, 1995
Rainbow trout (*Oncorhynchus mykiss*)	96-h LC_{50}	>1000	Environment Canada, 1997
Estuarine/marine			
Oyster (*Crassostrea virginica*)	96-h LC_{50}	89	US EPA, 1984
White shrimp (*Penaeus setiferus*)	96-h LC_{50}	130	OECD, 1997
Grass shrimp (*Palaemonetes pugio*)	96-h LC_{50}	5.4	Environment Canada, 1997
Brown shrimp (*Crangon crangon*)	48-h LC_{50} 96-h LC_{50}	600–1000 550–950	Verschueren, 1983
Brine shrimp (*Artemia salina*)	24-h LC_{50}	1000	Price et al., 1974
Inland silverside (*Menidia beryllina*)	96-h LC_{50}	1250	Dawson et al., 1977
Sheepshead minnow (*Cyprinodon variegatus*)	96-h LC_{50}	116	OECD, 1997

[a] NOEC = no-observed-effect concentration; LOEC = lowest-observed-effect concentration.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

Results of acute and long-term studies on toxicity to aquatic organisms are summarized in Table 1. Long-term studies are restricted to microorganisms and unicellular algae, for which 72 h is the cut-off point for the designation of acute/long-term studies.

10.2 Terrestrial environment

Information on the toxicological effects of 2-butoxyethanol on terrestrial organisms was not identified.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

In general, effects associated with exposure to 2-butoxyethanol have been identified from studies in animals. 2-Butoxyethanol has moderate acute toxicity following inhalation, ingestion, or dermal exposure. It is an eye and skin irritant, but it is not a skin sensitizer. 2-Butoxyethanol is readily absorbed via inhalation, dermal exposure, and ingestion. The pharmacokinetic models of Corley et al. (1994, 1997) and Johanson & Boman (1991) consider dermal absorption from the vapour phase to account for approximately 21–75% of the total uptake. Pathways for the metabolism of 2-butoxyethanol are similar in animals and humans; the principal metabolite is 2-butoxyacetic acid.

The principal effect exerted by 2-butoxyethanol and its metabolite 2-butoxyacetic acid is haematotoxicity, with rats being the most sensitive species. Older rats are more sensitive than younger animals to the haemolytic effects of 2-butoxyethanol and 2-butoxyacetic acid. Critical effects observed in inhalation studies conducted with rats were decreased haemoglobin and mean cell haemoglobin; increased haematocrit and mean cell volume (NOAEL = 20 ppm [97 mg/m^3]; lowest-observed-adverse-effect level [LOAEL] = 86 ppm [415 mg/m^3] in animals exposed for 9 days; Dodd et al., 1983); decreased red blood cells and haemoglobin (NOAEL = 25 ppm [121 mg/m^3]; LOAEL = 77 ppm [372 mg/m^3]) in animals exposed subchronically (Dodd et al., 1983); and decreased red blood cells and increased mean cell volume (NOAEL = 50 ppm [242 mg/m^3]; LOAEL = 100 ppm [483 mg/m^3]) in pregnant animals exposed on days 6–15 of gestation (Tyl et al., 1984). The results of *in vitro* studies indicate that human red blood cells are not as sensitive as rat red blood cells to the haemolytic effects of 2-butoxyethanol and 2-butoxyacetic acid and also that red blood cells are more sensitive to haemolysis by 2-butoxyacetic acid than to haemolysis by 2-butoxyethanol (Bartnik et al., 1987; Ghanayem, 1989; Ghanayem & Sullivan, 1993; Udden, 1994; Udden & Patton, 1994).

In rats, adverse effects on the central nervous system, kidneys, and liver occur at higher exposure concentrations than do haemolytic effects. 2-Butoxyethanol (and, in one study, 2-butoxyacetic acid) did not cause adverse reproductive or developmental effects in either sex at less than toxic doses (Nagano et al., 1979; Doe, 1984; Hardin et al., 1984; Nelson et al., 1984; Tyl et al., 1984; Foster et al., 1987; Heindel et al., 1990). Although sperm concentration was reduced in rats administered drinking-water containing 2-butoxyethanol (NTP, 1993), the reduction was not dose-dependent, and no change in sperm cell morphology was observed. Although the results of *in vitro* tests for mutagenicity of 2-butoxyethanol were inconsistent, the absence of structural alerts and the negative findings from *in vivo* studies are sufficiently reassuring to allow the conclusion that 2-butoxyethanol is not mutagenic. 2-Butoxyethanol has not been found to have an adverse effect on the immune system (Exon et al., 1991; Smialowicz et al., 1992).

Based on limited data from case reports and one laboratory study, similar acute effects — including haemolytic effects as well as effects on the central nervous system — are observed in humans and rats exposed to 2-butoxyethanol, although the effects are observed at much higher exposure concentrations in humans than in rats.

11.1.2 Criteria for setting guidance values for 2-butoxyethanol

The following guidance is provided as a possible basis for derivation of limits of exposure and for judgement of the quality of environmental media by relevant authorities. Available data indicate that the haematotoxicity associated with exposure to 2-butoxyethanol is similar in laboratory animals and humans, although available data do not permit quantification of dose–response for the latter. The guidance value provided here is derived, therefore, on the basis of studies conducted in animals. Based on limited data in humans, the rat is likely more sensitive to the haemolytic effects of 2-butoxyethanol exposure (Carpenter et al., 1956; Bartnik et al., 1987).

The dose–response for haematotoxicity in rats has been consistent in an inhalation study of developmental toxicity, in which pregnant animals were exposed to 2-butoxyethanol on days 6–15 of gestation (Tyl et al., 1984), and in a subchronic inhalation toxicity study (Dodd et al., 1983). In the developmental study, the NOAEL and LOAEL in the dams were 50 ppm (242 mg/m^3) and 100 ppm (483 mg/m^3), respectively (Tyl et al., 1984). In the subchronic inhalation study, the NOAEL and LOAEL were 25 ppm (121 mg/m^3) and 77 ppm (372 mg/m^3), respectively (Dodd et al., 1983). A tolerable concentration (TC) has been derived as follows:

$$TC = [(242\ mg/m^3)/10] \times [6/24] \times [(0.16\ m^3\ per\ day/0.215\ kg)/(22\ m^3\ per\ day/64\ kg)]$$

$$= 13.1\ mg/m^3$$

where:

- 242 mg/m^3 (50 ppm) is the NOAEL from the study (Tyl et al., 1984) providing the best bounding of dose–response in the most sensitive species;

- 10 is the uncertainty factor to account for intra-species variability in humans. No additional factor was incorporated to address interspecies variability on the basis of limited data in humans and several *in vitro* studies that indicate that rat erythrocytes are far more sensitive than human erythrocytes to the haemolytic effects associated with exposure to 2-butoxyethanol (and its metabolite 2-butoxyacetic acid). No additional factor was incorporated to account for the short duration of exposure in the critical study, as there is no indication that effect levels vary with increased exposure duration;

- 6/24 is the conversion from 6 h/day to continuous exposure; and

- [(0.16 m^3 per day/0.215 kg)/(22 m^3 per day/64 kg)] is the scaling factor from rats to humans, based on the assumed inhalation volume and body weight for rats (0.16 m^3 per day and 0.215 kg, respectively) and humans (22 m^3 per day and 64 kg, respectively). The PBPK model of Corley et al. (1994, 1997) would not result in an appreciably different TC at this level of exposure.

It should be noted that the TC was based on a study involving the whole-body exposure of rats and an assumption that 100% of the inhaled 2-butoxyethanol was retained. The extent of skin absorption has not been formally taken into account in the development of this TC and may be greater than intake via inhalation.

11.1.3 Sample risk characterization

The extremely limited nature of the available data to serve as a basis for estimation of exposure should be borne in mind in interpreting the comparisons presented here for indirect exposure of the general population to 2-butoxyethanol. The concentration of 8 ：g 2-butoxyethanol/m^3 measured in a sample of indoor air collected in northern Italy is approximately 1600-fold lower than the TC developed in the preceding section. Levels of 2-butoxyethanol are considerably higher in some occupational settings. In addition, skin absorption may be of greater importance than respiratory absorption.

11.2 Evaluation of environmental effects

11.2.1 Aquatic environment

Data on measured levels of 2-butoxyethanol in surface waters are insufficient for risk characterization. However, a sample risk characterization for the aquatic environment is presented in which the ratio between a predicted (local) environmental concentration (PEC_{local}) and a predicted no-effect concentration (PNEC) is calculated.

PEC_{local}s for surface waters have been derived based upon data from Australia (OECD, 1997) as well as information on all reported releases to the environment in 1993 from individual industrial plants in the USA (Staples et al., 1998). Calculations of expected surface water concentration were based on worst-case scenarios for local river flows identified from a US Geological Survey database. Site-specific estimates were made for 36 industrial plants, of which 26 discharged through sewage treatment plants and 10 discharged directly to rivers. Both studies relied on fugacity modelling to predict the environmental distribution of 2-butoxyethanol, yielding slightly different results. However, both approaches indicated that most (84–96%) of the chemical will partition to water, with almost all of the remainder volatilizing to air. There is negligible binding of 2-butoxyethanol to particulates, and no bioconcentration in organisms is expected. In addition, 2-butoxyethanol is readily degraded by microorganisms.

A PEC for surface water in Sydney, Australia, based on the assumption that all local usage passes through a single sewage treatment plant and releases at a point source to a river, was calculated as follows:

$$PEC_{local\ (water)} = C_{effluent}/[(1 + K_{p(susp)} \times C_{(susp)}) \times D]$$

$$= 50.4 \text{ ：g/litre}$$

where:

- $C_{effluent}$ is the concentration (g/litre) of the chemical in the sewage treatment plant effluent, calculated as $C_{effluent} = W \times (100 - P)/(100 \times Q)$
  where:
  - W = emission rate: 1400 kg/day (OECD, 1997)
  - P = % removal by biodegradation in the sewage treatment plant (modelled as 91% using the SIMPLETREAT model)
  - Q = volume of wastewater: 250 000 m^3/day (OECD, 1997)

- $K_{p(susp)}$ is the suspended matter/water adsorption coefficient), calculated as $K_{p(susp)} = F_{oc(susp)} \times K_{oc}$
  where:
  - $F_{oc(susp)}$ = the fraction of organic carbon in suspended matter (0.01)
  - K_{oc} = $0.411 \times K_{ow}$
    where:
    - K_{ow} = the octanol/water partition coefficient (6.76)

- $C_{(susp)}$ is the concentration of suspended matter in river water (default value = 15 mg/litre)

- D is the dilution factor for river flow (default value = 10)

As degradation in the sewage treatment plant is a large component of the assumptions, and as it cannot be assumed that this level of sewage treatment occurs in all countries globally, this calculation can be revised assuming no sewage treatment (i.e. P = 0), yielding a PEC of 560 μg/litre. This value assumes that all local release is diluted with general wastewater from the urban centre. No values were available for individual industrial plants in Sydney, Australia, and therefore concentrations released directly to rivers cannot easily be calculated.

Using the other approach of site-specific estimation (Staples et al., 1998), 36 industrial plants in the USA were selected from 814 reporting emissions, on the basis of availability of river flow values and worst-case releases. Calculations were based on local stream flows, taking a value for the lowest flow expected over any single 7-day period once in 10 years. For plants emitting via a sewage treatment system, degradation rates of 90% were assumed. Calculated concentrations are "instantaneous," assuming no dilution by the receiving stream, no degradation in the receiving waters, and no distribution to media other than water. These are conservative assumptions. Calculated in-stream concentrations ranged from 0.0002 to 21.7 mg/litre for emissions via sewage treatment (annual release ranged from 18 000 to 974 000 kg for the 26 plants with sewage treatment) and from 0.000 01 to 4.66 mg/litre for untreated emissions (annual release ranged from 1870 to 35 000 kg for the 10 plants with no sewage treatment). The highest reported concentration of 2-butoxyethanol in surface waters was 5.7 mg/litre following release by the leather industry into the Hayashida River in Japan, before treatment was introduced (Yasuhara et al., 1981). These measured and estimated surface water concentrations are summarized in Table 2.

As a guide for those wishing to perform similar calculations using local use/release figures, the Staples et al. (1998) study estimates that the annual release of total glycol ethers (assuming that 50% of released compounds would be 2-butoxyethanol) leading to instantaneous 2-butoxyethanol concentrations in surface waters of 1 mg/litre would be 18 000 kg with sewage treatment and 1800 kg without sewage treatment for streams with very low flow at 0.03 m^3/s (equivalent to 2.5 million litres/day).

A PNEC for surface waters may be calculated as follows:

Table 2: PEC/PNEC ratios.

Location	Sewage treatment	Highest concentration (mg/litre)	PEC/PNEC ratio[a]
Australia[b] (Sydney)	Yes	0.05	0.3
	No	0.56	3.4
USA (site specific)[c]	Yes	21.7	131.5
	No	4.66	28.2
Japan[d]	No	5.7	34.5

[a] Based on a PNEC of 165 μg/litre (see text).
[b] Modelled.
[c] Modelled, but based on known annual release for each site.
[d] Measured.

PNEC = (165 mg/litre)/1000

= 165 μg/litre

where:

- 165 mg/litre is the lowest reported effect level for a lethality end-point in aquatic species (48-h LC_{50} in the golden ide [*Leuciscus idus melanotus*], a freshwater fish); and

- 1000 is the uncertainty factor. The range of organisms tested in short-term tests would justify application of an uncertainty factor of 100, yielding a PNEC of 1.65 mg/litre, based on the lowest reported LC_{50} in fish. However, there is some indication that estuarine species may be more sensitive, although the lowest reported LC_{50} for the grass shrimp (*Palaemonetes pugio*) (96-h LC_{50} = 5.4 mg/litre) is such an extreme outlier compared with the range of other data that it is difficult to justify its use as the basis for the PNEC calculation. Application of an uncertainty factor of 1000 to the lowest freshwater value would be protective for both freshwater and estuarine environments, yielding margins relative to the 96-h LC_{50}s for the grass shrimp (5.4 mg/litre) and the oyster (*Crassostrea virginica*) (89 mg/litre), the most sensitive of the estuarine invertebrates, of 33 and 540, respectively. For freshwater organisms, the threshold concentration for inhibition of growth in algae (long-term effect) cannot be justified as the basis for application of uncertainty factors to establish a PNEC.

As the highest measured concentration in surface waters (at 5.7 mg/litre) is almost identical to the lowest reported LC_{50} concentration (at 5.4 mg/litre for the grass shrimp), it is not surprising that high risk factors are generated. High-volume usage and emissions to surface waters in a range of industries would lead to locally high concentrations, principally where sewage treatment was

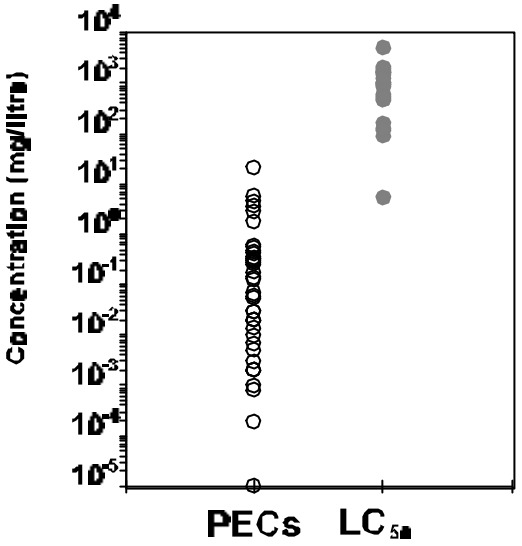


Figure 1: Plot of estimated and measured concentrations in surface waters and reported acute toxicity values for 2-butoxyethanol

not in operation and river flow was low. It can be expected that concentrations would exceed those likely to produce effects in some aquatic species under these circumstances. However, the majority of reported acute toxicity effect levels are 100 mg/litre or higher, and most exceed 800 mg/litre. Four of 38 estimated surface water concentrations exceed 2 mg/litre, with the remainder less than, and usually substantially less than, 1 mg/litre (Figure 1). Most of these estimates also fail to account for dilution in rivers. Using an uncertainty factor of 100, justified by the range of toxicity data, on the lowest reported freshwater LC_{50} and typical estimates of water concentrations yields PEC/PNEC ratios of #1. Therefore, for most releases to surface waters, the risk is considered to be low. It is also unlikely that 2-butoxyethanol would be toxic to sewage treatment plant bacteria, as the only reported effect level for bacteria is an IC_{50} of >1000 mg/litre (Union Carbide, 1989).

11.2.2 Terrestrial environment

Data are inadequate to characterize the risks to terrestrial organisms of exposure to 2-butoxyethanol. A $PEC_{local(air)}$ of 537 :g/m^3, based upon the use patterns of this chemical in Australia, has been reported (OECD, 1997). Although available monitoring data are limited, this predicted concentration is much higher than levels measured in ambient air (see section 6). As 2-butoxyethanol is expected to have a half-life in the atmosphere of less than 1 day, these concentrations are considered to have no environmental significance.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

Previous evaluations of 2-butoxyethanol published by WHO, the International Agency for Research on Cancer (IARC), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), or the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) were not identified. A *Screening Information Dataset (SIDS) Initial Assessment Report* has been prepared under the Organisation for Economic Co-operation and Development (OECD) High Production Volume (HPV) Chemicals Programme (OECD, 1997). Information on international hazard classification and labelling is included in the International Chemical Safety Card that has been reproduced in this document.

13. HUMAN HEALTH PROTECTION AND EMERGENCY ACTION

Human health hazards, together with preventative and protective measures and first aid recommendations, are presented in the International Chemical Safety Card (ICSC 0059) reproduced in this document.

13.1 Human health hazards

2-Butoxyethanol is toxic to humans. Following long-term or repeated exposure, effects on the blood may be observed.

13.2 Advice to physicians

In case of intoxication, immediate supportive measures should be given, as central nervous system depression, respiratory paralysis, hypotension, and metabolic acidosis have been observed in the few hours post-exposure. Close monitoring for renal toxicity and possible haemodialysis are mandatory in the subsequent days (renal insufficiency may develop 2–3 days post-exposure) until recovery is achieved, on average by the second week post-exposure.

13.3 Health surveillance advice

Periodic medical examination of the haematopoietic system should be included in a health surveillance programme.

13.4 Spillage

As 2-butoxyethanol is toxic and absorbed through the skin, emergency crews need to wear proper equipment, including a mask with cartridge for organic vapour, for handling spills. The chemical should not be allowed to enter drains or watercourses.

14. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

Information on national regulations, guidelines, and standards can be found in the International Register of Potentially Toxic Chemicals (IRPTC), available from UNEP Chemicals (IRPTC), Geneva.

The reader should be aware that regulatory decisions about chemicals taken in a certain country can be fully understood only in the framework of the legislation of that country. The regulations and guidelines of all countries are subject to change and should always be verified with appropriate regulatory authorities before application.

2-BUTOXYETHANOL

0059
April 1993

CAS No: 111-76-2
RTECS No: KJ8575000
UN No: 2369
EC No: 603-014-00-0

Ethylene glycol monobutyl ether
Monobutyl glycol ether
$C_6H_{14}O_2$ / $CH_3(CH_2)_2CH_2OCH_2CH_2OH$
Molecular mass: 118.2

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Combustible.	NO open flames. NO contact with oxidizing agents.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Above 61°C explosive vapour/air mixtures may be formed.	Above 61°C closed system, ventilation.	In case of fire: keep drums, etc., cool by spraying with water.

EXPOSURE		PREVENT GENERATION OF MISTS!	IN ALL CASES CONSULT A DOCTOR!
Inhalation	Cough, drowsiness, headache, nausea.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest, and refer for medical attention.
Skin	MAY BE ABSORBED! Dry skin (further see Inhalation).	Protective gloves, protective clothing.	Remove contaminated clothes, rinse skin with plenty of water or shower, and refer for medical attention.
Eyes	Redness, pain, blurred vision.	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	Abdominal pain, diarrhoea, nausea, vomiting (further see Inhalation).	Do not eat, drink, or smoke during work.	Rinse mouth, give plenty of water to drink, induce vomiting (ONLY IN CONSCIOUS PERSONS!), and refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING	
Collect leaking and spilled liquid in sealable containers as far as possible, wash away remainder with plenty of water.	Xn Symbol R: 20/21/22-37 S: 24/25 UN Hazard Class: 6.1 UN Pack Group: III	Airtight. Do not transport with food and feedstuffs.

EMERGENCY RESPONSE	STORAGE
NFPA Code: H 2; F 2; R 0	Separated from strong oxidants, food and feedstuffs; keep in the dark.

IPCS
International Programme on Chemical Safety

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SEE IMPORTANT INFORMATION ON THE BACK.

IMPORTANT DATA

Physical State; Appearance
COLOURLESS LIQUID, WITH CHARACTERISTIC ODOUR.

Chemical Dangers
The substance can form explosive peroxides. The substance decomposes, producing toxic fumes. Reacts with strong oxidants, causing fire and explosion hazard.

Occupational Exposure Limits
TLV: 25 ppm; 121 mg/m^3 (as TWA) (skin) (ACGIH 1992-1993)

Routes of Exposure
The substance can be absorbed into the body by inhalation and through the skin, and by ingestion.

Inhalation Risk
A harmful contamination of the air will be reached rather slowly on evaporation of this substance at 20°C.

Effects of Short-term Exposure
The substance irritates the eyes, the skin, and the respiratory tract. Exposure could cause central nervous system depression and liver and kidney damage.

Effects of Long-term or Repeated Exposure
The liquid defats the skin. The substance may have effects on the haematopoietic system, resulting in blood disorders.

PHYSICAL PROPERTIES

Boiling point: 171°C
Melting point: -75°C
Relative density (water = 1): 0.90
Solubility in water: miscible
Vapour pressure, kPa at 20°C: 0.10
Relative vapour density (air = 1): 4.1
Relative density of the vapour/air-mixture at 20°C (air = 1): 1.00
Flash point: (c.c.) 61°C
Auto-ignition temperature: 238°C
Explosive limits, vol% in air: 1.1-12.7
Octanol/water partition coefficient as log Pow: 0.830

ENVIRONMENTAL DATA

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

NOTES

Depending on the degree of exposure, periodic medical examination is indicated. Check for peroxides prior to distillation; render harmless if positive. Keep in dark because of possible formation of explosive peroxides.

ADDITIONAL INFORMATION

LEGAL NOTICE Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible for the use which might be made of this information

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APPENDIX 1 — SOURCE DOCUMENTS

NIOSH (1990)

Copies of this source document (*Criteria for a recommended standard. Occupational exposure to ethylene glycol monobutyl ether and ethylene glycol monobutyl ether acetate*; NIOSH Publication No. 90-118) are available from:

Publications Office
National Institute for Occupational Safety and Health
4676 Columbia Parkway
Cincinnati, OH 45226
USA
(513) 533-8471

This document was prepared by Joann Wess and reviewed internally by staff of the National Institute for Occupational Safety and Health. The draft document was reviewed externally by Dr F. Mirer, United Auto Workers; Mr M. Gillen, Workers' Institute for Safety and Health; Mr F. Burkhardt, International Brotherhood of Builders and Allied Trades; Dr J. McCuen, ARCO Chemical Company; Mr W. Lypka, Graphic Communications International Union; Dr H. Veulemans, Laboratorium voor arbeidshygienne en-toxicologie; Dr E.M. Johnson, Jefferson Medical College; Dr J.V. Rodricks, Dr J.S. Ferguson, Dr R.M. Putzrath, Mr M. Fitzgerald, Chemical Manufacturers Association; Dr L. Welch, George Washington University; Dr P. Sharma, Utah State University; Dr R. Elves, Department of the Air Force; and Dr F. Welsch, Chemical Industry Institute of Toxicology.

ATSDR (1996)

Copies of the ATSDR's *Toxicological profile for 2-butoxyethanol and 2-butoxyethanol acetate* (draft for public comment) may be obtained from:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, GA 30333
USA

This ATSDR draft document has undergone internal ATSDR review. The document has also been reviewed by an expert panel of nongovernmental reviewers consisting of the following members: Dr W. Decker, Private Consultant, El Paso, TX; Dr A. Gregory, Private Consultant, Sterling, VA; and Dr R. Rubin, Johns Hopkins School of Public Health, Baltimore, MD.

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on 2-butoxyethanol 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:

BASF, Ludwigshafen, Germany

Chemical Manufacturers Association, Arlington, USA

Department of Health, London, United Kingdom

Environment Canada, Ottawa, Canada

Health and Safety Executive, Liverpool, United Kingdom

Health Canada, Ottawa, Canada

Ministry of Health and Welfare, Government of Japan, Tokyo, Japan

National Chemicals Inspectorate (KEMI), Solna, Sweden

National Institute of Occupational Health, Budapest, Hungary

National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands

National Occupational Health & Safety Commission, Sydney, Australia

Oxygenated Solvents Producers Association, Brussels, Belgium

United States Department of Health and Human Services (National Institute of Environmental Health Sciences, Research Triangle Park)

United States Environmental Protection Agency (National Center for Environmental Assessment, Washington, DC)

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Berlin, Germany, 26–28 November 1997

Members

Dr H. Ahlers, Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Mr R. Cary, Health Directorate, Health and Safety Executive, Bootle, United Kingdom

Dr S. Dobson, Institute of Terrestrial Ecology, Huntingdon, United Kingdom

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers & Veterinary Medicine, Berlin, Germany *(Chairperson)*

Mr J.R. Hickman, Health Protection Branch, Health Canada, Ottawa, Ontario, Canada

Dr I. Mangelsdorf, Documentation and Assessment of Chemicals, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany

Ms M.E. Meek, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada *(Rapporteur)*

Dr K. Paksy, Department of Reproductive Toxicology, National Institute of Occupational Health, Budapest, Hungary

Mr V. Quarg, Ministry for the Environment, Nature Conservation & Nuclear Safety, Bonn, Germany

Mr D. Renshaw, Department of Health, London, United Kingdom

Dr J. Sekizawa, Division of Chemo-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Prof. S. Soliman, Department of Pesticide Chemistry, Alexandria University, Alexandria, Egypt *(Vice-Chairperson)*

Dr M. Wallen, National Chemicals Inspectorate (KEMI), Solna, Sweden

Ms D. Willcocks, Chemical Assessment Division, Worksafe Australia, Camperdown, Australia

Dr M. Williams-Johnson, Division of Toxicology, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

Dr K. Ziegler-Skylakakis, Senatskommission der Deutschen Forschungsgemeinschaft zuer Pruefung gesundheitsschaedlicher Arbeitsstoffe, GSF-Institut fuer Toxikologie, Neuherberg, Oberschleissheim, Germany

Observers

Mrs B. Dinham,[1] The Pesticide Trust, London, United Kingdom

Dr R. Ebert, KSU Ps-Toxicology, Huels AG, Marl, Germany (representing ECETOC, the European Centre for Ecotoxicology and Toxicology of Chemicals)

Mr R. Green,[1] International Federation of Chemical, Energy, Mine and General Workers' Unions, Brussels, Belgium

Dr B. Hansen,[1] European Chemicals Bureau, European Commission, Ispra, Italy

Dr J. Heuer, Federal Institute for Health Protection of Consumers & Veterinary Medicine, Berlin, Germany

Mr T. Jacob,[1] DuPont, Washington, DC, USA

Ms L. Onyon, Environment Directorate, Organisation for Economic Co-operation and Development, Paris, France

Dr H.J. Weideli, Ciba Speciality Chemicals Inc., Basel, Switzerland (representing CEFIC, the European Chemical Industry Council)

Secretariat

Dr M. Baril, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr R.G. Liteplo, Health Canada, Ottawa, Ontario, Canada

Ms L. Regis, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Mr A. Strawson, Health and Safety Executive, London, United Kingdom

Dr P. Toft, Associate Director, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

[1] Invited but unable to attend.

RÉSUMÉ D'ORIENTATION

Ce CICAD relatif au 2-butoxyéthanol a été rédigé sur la base d'évaluations préparées par le National Institute for Occupational Safety and Health (NIOSH, 1990) et l'Agency for Toxic Substances and Disease Registry (ATSDR, 1996). Une étude de la littérature publiée jusqu'en mai 1997 a fourni des données complémentaires, à quoi se sont ajoutés les éléments d'information obtenus lors de l'évaluation par des pairs du présent CICAD. Des informations concernant la nature de l'évaluation par les pairs et la disponibilité des documents originaux figurent à l'appendice 1. Des informations sur cette évaluation sont données à l'appendice 2. Ce CICAD a été approuvé en tant qu'évaluation internationale lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Berlin (Allemagne) du 26 au 28 novembre 1997. La liste des participants à la réunion du Comité d'évaluation finale figure à l'appendice 3. La fiche d'information sur la sécurité chimique (ICSC 0059), préparée par le Programme international sur la sécurité chimique (IPCS, 1993), est également reproduite dans le présent document.

Le 2-butoxyéthanol (CAS N° 111-76-2) est un éther du glycol produit en quantités industrielles. C'est un liquide incolore miscible à l'eau et soluble dans la plupart des solvants organiques. Il est très largement utilisé dans les enduits, les laques à séchage rapide, les émaux, les vernis, les dissolvants et les peintures au latex. On l'utilise également dans les nettoyants pour métaux et certains produits ménagers. Dans l'atmosphère, il est présent entièrement à l'état gazeux et comme sa demi-vie à ce niveau est d'environ 17 heures, il n'y a guère de risque de transport atmosphérique. Dans l'eau, on estime sa demi-vie à environ 1-4 semaines. Il est probablement décomposé sans difficulté en aérobiose dans le sol et dans l'eau. Son potentiel de bioaccumulation est faible. Selon les données limitées dont on dispose, les concentrations auxquelles on peut être exposé dans l'air sont de l'ordre du : g/m^3. S'il y a exposition indirecte de la population, c'est très probablement par inhalation ou absorption percutanée lors de l'utilisation de produits qui contiennent du 2-butoxyéthanol. La concentration du 2-butoxyéthanol sur le lieu de travail est de l'ordre du mg/m^3.

Après exposition par la voie respiratoire, buccale ou percutanée, le 2-butoxyéthanol est facilement résorbé. La métabolisation s'opère essentiellement sous l'action de l'alcool- et de l'aldéhyde-déshydrogénase et conduit à la formation de 2-butoxyacétaldéhyde et d'acide 2-butoxyacétique, le principal métabolite. Il existe toutefois d'autres voies métaboliques.

Le 2-butoxyéthanol présente une toxicité aiguë modérée et peut irriter la peau et les yeux; il n'entraîne aucune sensibilisation cutanée. Les principaux effets du 2-butoxyéthanol et de son principal métabolite, l'acide 2-butoxyacétique, sont dus à l'hématotoxicité de ces composés. Le rat est l'espèce la plus sensible. Les résultats des études *in vitro* montrent que les hématies humaines ne sont pas aussi sensibles que celles du rat aux effets hémolytique du 2-butoxyéthanol et de l'acide 2-butoxyacétique et que l'effet hémolytique de ce dernier est plus prononcé. Chez le rat, l'action toxique se manifeste aussi au niveau du système nerveux central, des reins et du foie, mais à une concentration plus élevée que dans le cas des effets hémolytiques. On n'a pas observé chez l'animal d'effets toxiques sur la reproduction à des doses inférieures aux doses toxiques. Les épreuves de mutagénicité *in vitro* ont donné des résultats irréguliers mais en l'absence d'indices structuraux et compte tenu des résultats négatifs obtenus *in vivo*, on peut avec une confiance suffisante, considérer que le 2-butoxyéthanol n'est pas mutagène. Les données limitées que l'on a pu tirer d'un certain nombre de cas d'intoxication de même que les résultats d'une étude en laboratoire, montrent que des effets analogues — notamment des effets hémolytiques et des effets au niveau du système nerveux central — se produisent chez l'homme comme chez le rat, mais à des concentrations beaucoup plus élevées. Compte tenu des effets hémolytiques observés chez des rattes gravides exposées pendant la période de gestation, on a estimé à 13,1 mg/m^3 la concentration tolérable pour l'homme.

En s'en tenant à des hypothèses extrêmement prudentes, on peut considérer que la concentration estimative maximale de 2-butoxyéthanol dans les eaux de surface très proches des effluents est susceptible de dépasser parfois la valeur prévisible de la concentration maximale sans effet observable. Toutefois, selon des hypothèses plus réalistes fondées sur les données disponibles, il semblerait que ce composé ne soit que faiblement toxique pour les organismes aquatiques. Comme la demi-vie atmosphérique du 2-butoxyéthanol est brève, on estime que la concentration mesurée ou calculée de cette substance dans l'air ne pose pas de problème écologique.

RESUMEN DE ORIENTACIÓN

El presente documento abreviado de evaluación internacional de productos químicos (CICAD) sobre el 2-butoxietanol se basó en los exámenes preparados por el Instituto Nacional para la Seguridad y Salud del Trabajo (NIOSH, 1990) y la Agencia para el Registro de Sustancias Tóxicas y Enfermedades (ATSDR, 1996). Se identificaron datos adicionales en una investigación de publicaciones actualizada hasta mayo de 1997, así como en el curso del examen por homólogos del presente CICAD. En el apéndice 1 se halla información sobre la naturaleza del examen por homólogos y la disponibilidad de los documentos de origen. En el apéndice 2 se presenta información sobre el análisis por homólogos del presente CICAD. Este CICAD fue aprobado como evaluación internacional en una reunión de la Junta de Examen Final, celebrada en Berlín (Alemania) los días 26-28 de noviembre de 1997. En el apéndice 3 se halla la lista de los participantes en la reunión de la Junta de Examen Final. También se ha reproducido en el presente documento la ficha internacional de seguridad química (ICSC 0059) producida por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993).

El 2-butoxietanol (CAS N^{o} 111-76-2) es un éter glicólico de alto volumen de producción. Es un líquido incoloro miscible en agua y soluble en la mayor parte de los disolventes orgánicos. El 2-butoxietanol se utiliza ampliamente como disolvente en revestimientos de superficies, y en lacas en nebulización, lacas de secado rápido, esmaltes, barnices, eliminadores de barnices y pintura látex. También se utiliza en productos limpiadores de metales y domésticos. El 2-butoxietanol existe en la atmósfera casi totalmente en forma de vapor; dado que el producto químico tiene una semivida atmosférica de unas 17 horas, el riesgo de transporte por la atmósfera debe ser pequeño. La semivida estimada del 2-butoxietanol en agua es aproximadamente de 1-4 semanas; probablemente experimenta una biodegradación rápida en el suelo aerobio y en el agua. La capacidad de acumulación es baja. Basándose en datos limitados puede indicarse que la exposición ambiental en el aire se halla en general en la gama de : g/m^3. La exposición indirecta de la población general al 2-butoxietanol se produce muy probablemente por inhalación y absorción cutánea durante el empleo de productos que contienen la sustancia química. Las concentraciones del 2-butoxietanol en el aire en entornos laborales se hallan típicamente en la gama de mg/m^3.

El 2-butoxietanol se absorbe fácilmente después de la exposición por inhalación o por vías oral y cutánea. El producto químico es metabolizado principalmente por la deshidrogenasa de alcoholes y aldehídos, con formación de 2-butoxiacetaldehído y de ácido 2-butoxiacético, el principal metabolito, aunque también se han identificado otras vías metabólicas.

El 2-butoxietanol presenta una moderada toxicidad aguda y es irritante para los ojos y la piel; no es un sensibilizador cutáneo. El principal efecto del 2-butoxietanol y de su metabolito, el ácido 2-butoxiacético, es la hematotoxicidad, siendo la rata la especie más sensible. Los resultados de estudios *in vitro* muestran que los eritrocitos humanos no son tan sensibles como los eritocitos de rata a los efectos hemolíticos del 2-butoxietanol y del ácido 2-butoxiacético, y también que los eritrocitos son más sensibles a la hemólisis por el ácido 2-butoxiacético que por el 2-butoxietanol. En la rata, los efectos adversos sobre el sistema nervioso central, los riñones y el hígado se producen con concentraciones de exposición más altas que los efectos hemolíticos. En animales no se han observado efectos adversos sobre la reproducción y el desarrollo con dosis inferiores a las tóxicas. Aunque los resultados de las pruebas *in vitro* de mutagenicidad del 2-butoxietanol son incoherentes, la ausencia de elementos estructurales de alerta y los resultados negativos de los estudios *in vivo* son suficientemente alentadores para permitir llegar a la conclusión de que el 2-butoxietanol no es mutagénico. Basándose en datos limitados procedentes de estudios de casos y de un estudio de laboratorio, se han señalado efectos agudos análogos (incluidos efectos hemolíticos y otros sobre el sistema nervioso central) en personas y ratas expuestas al 2-butoxietanol, aunque los efectos se observaron con concentraciones de exposición mucho más altas en personas que en ratas. Basándose en la aparición de efectos hemolíticos en ratas grávidas expuestas durante la gestación, se ha deducido una concentración tolerable de muestra para las personas de 13,1 mg de 2-butoxietanol/m^3.

Sobre la base de supuestos extremadamente conservadores, las concentraciones previstas máximas de 2-butoxietanol en aguas superficiales situadas cerca de corrientes de efluentes pueden, en algunos casos, exceder de las concentraciones previstas de efectos no observados. Sin embargo, supuestos más realistas basados en los datos disponibles permiten indicar que el riesgo para los seres acuáticos es escaso. Debido a la corta semivida del 2-butoxietanol en la atmósfera, las concentraciones medidas o previstas de este producto químico en el aire se consideran exentas de importancia ambiental.