

IPCS

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CONCISE INTERNATIONAL CHEMICAL ASSESSMENT DOCUMENT

N° 41

Diethylene Glycol Dimethyl Ether



IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

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



WORLD HEALTH ORGANIZATION

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Concise International Chemical Assessment Document 41

DIETHYLENE GLYCOL DIMETHYL ETHER

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

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

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FOREWORD

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

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

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

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

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as

guidance only. The reader is referred to EHC 170¹ 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

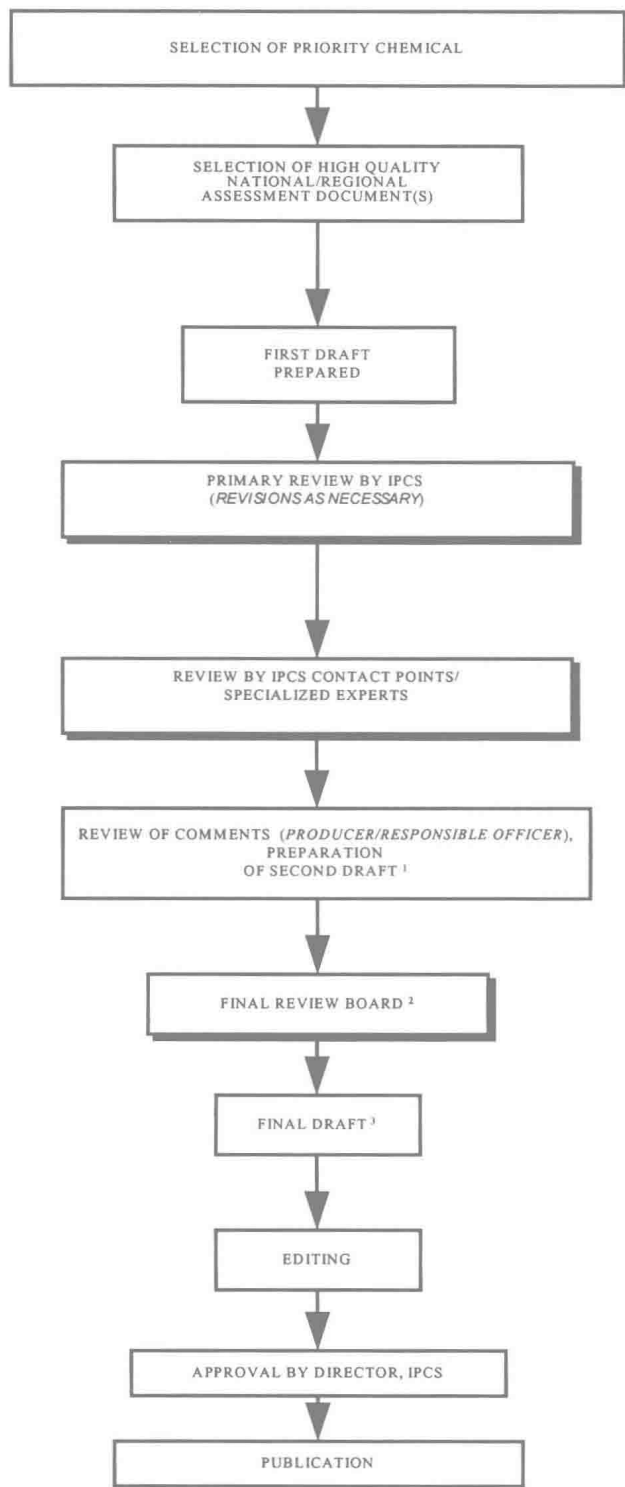
The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Co-ordinator, IPCS, on the selection of chemicals for an IPCS risk assessment, the appropriate form of the document (i.e., EHC or CICAD), and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

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

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

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

CICAD PREPARATION FLOW CHART



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

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

The CICAD Final Review Board has several important functions:

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

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

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

1. EXECUTIVE SUMMARY

This CICAD on diethylene glycol dimethyl ether (in the following called diglyme) was prepared by the Fraunhofer Institute of Toxicology and Aerosol Research, Hanover, Germany. Diglyme was selected for review in the CICAD series owing to concerns for human health, notably potential reproductive effects. The CICAD is based on reports compiled by the GDCh Advisory Committee on Existing Chemicals of Environmental Relevance (BUA, 1993a) and the German MAK-Kommission (Greim, 1994). A comprehensive literature search of relevant databases was conducted in March 2000 to identify any relevant references published subsequent to those incorporated in these reports. Information on the preparation and peer review 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 Geneva, Switzerland, on 8–12 January 2001. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card on diglyme (ICSC 1357), produced by the International Programme on Chemical Safety (IPCS, 2000), has also been reproduced in this document.

Diglyme (CAS No. 111-96-6) is a colourless liquid with a slight, pleasant odour. It is miscible with water and a number of common organic solvents. In the presence of oxidation agents, peroxide may form. Due to its dipolar aprotic properties, diglyme is used mainly as a solvent (semiconductor industry, chemical synthesis, lacquers), as an inert reaction medium in chemical synthesis, and as a separating agent in distillations.

Diglyme liquid or vapour is readily absorbed by any route of exposure, metabolized, and excreted mainly in the urine. The main metabolite is 2-methoxyethoxyacetic acid. 2-Methoxyacetic acid is a minor metabolite; in rats, it amounts to about 5–15% in the urine.

The acute toxicity of diglyme is low after oral exposure or inhalation.

Diglyme is slightly irritating to the skin or eye. No investigations are available on the sensitizing effects of diglyme.

The main targets in male animals after repeated intake of diglyme are the reproductive organs. In 2-week inhalation studies in male rats, dose-dependent decreases in weights of testes, epididymides, prostate, and seminal vesicles were observed. The testes were atrophic, and damage of the spermatocytes was observed. The no-

observed-adverse-effect level (NOAEL) in these studies was 30 ppm (167 mg/m³); the lowest-observed-adverse-effect level (LOAEL) was 100 ppm (558 mg/m³). Experiments with mice showed morphologically altered sperm, mainly with amorphous heads, after exposure to 1000 ppm (5580 mg/m³). After exposure by inhalation to high concentrations, male and female animals also showed effects on the haematopoietic system, such as changes in leukocyte counts and atrophy in spleen and thymus.

No long-term studies are available for diglyme; therefore, all end-points cannot be reliably assessed. Several Ames tests as well as an unscheduled DNA synthesis test did not reveal a genotoxic potential of diglyme *in vitro*. Nor was the number of chromosomal aberrations increased in bone marrow cells *in vivo*.

In a dominant lethal test with rats, the number of pregnancies was significantly reduced after exposure to 1000 ppm (5580 mg/m³) but not to 250 ppm (1395 mg/m³). The positive results may be due to the effects of diglyme on fertility.

In teratogenicity studies with rats, rabbits, and mice, diglyme showed dose-dependent effects on fetal weights, number of resorptions, and incidence of variations and malformations in a wide variety of tissues and organ systems, at concentrations that were not maternally toxic. The LOAEL for developmental effects in an inhalation study with rats was 25 ppm (140 mg/m³); the NOAEL for the oral route was 25 mg/kg body weight in rabbits and 62.5 mg/kg body weight in mice. The reproductive toxicity of diglyme is attributed to the minor metabolite 2-methoxyacetic acid.

Epidemiological studies of female semiconductor workers occupationally exposed to ethylene glycol ethers (EGEs), including diglyme, have found an increased risk of spontaneous abortions and lower fecundity. Workers in the semiconductor industry are exposed to a number of potential reproductive toxicants, however, including EGEs and other chemicals. From these data, it is not possible to determine the contribution of diglyme to the increased risk of adverse reproductive effects. Painters exposed to a variety of metals, organic solvents, and other chemicals, including 2-methoxyethanol, a metabolite of diglyme, but not to diglyme itself, were found to have an increased risk of oligospermia.

The main environmental target compartment of diglyme is the hydrosphere. The chemical is hydrolytically stable. The half-life in air for the reaction of diglyme with hydroxyl radicals is calculated to be about 19 h. Diglyme is inherently biodegradable, with a rather long log phase and significant adsorption to activated

sludge. From the *n*-octanol/water partition coefficient and the water miscibility of the chemical, a negligible potential for bioaccumulation and geoaccumulation is derived.

From valid test results available on the toxicity of diglyme to various aquatic organisms, this compound can be classified as a chemical exhibiting low acute toxicity in the aquatic compartment. The 48-h EC₀ value for daphnia (*Daphnia magna*) and the 72-h EC₁₀ value for algae (*Scenedesmus subspicatus*) were ≥1000 mg/litre (highest measured concentration). For the golden orfe (*Leuciscus idus*), a 96-h LC₀ of ≥2000 mg/litre was determined. Only very few studies concerning the toxicity of diglyme towards terrestrial species are available. The fungus *Cladosporium resinae* exhibited a toxic threshold concentration of about 9.4 g/litre.

From the sample risk characterization for the workplace, there is high concern for possible human health effects. Exposure of the general population to diglyme should be avoided.

The available data do not indicate a significant risk associated with exposure of aquatic organisms to diglyme. Due to the lack of measured exposure levels, a sample risk characterization with respect to terrestrial organisms cannot be performed. However, from the use pattern of diglyme, significant exposure of terrestrial organisms is not to be expected.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Diglyme (CAS No. 111-96-6; relative molecular mass 134.17) is also known as bis(2-methoxyethyl)ether (IUPAC name), diethylene glycol dimethyl ether, DEGDM(E), dimethyl carbitol, and 2,5,8-trioxynonane. It belongs to the group of ethylene glycol ethers (EGEs). The molecular structure of diglyme (C₆H₁₄O₃) is shown below:



Diglyme is a colourless liquid of low viscosity with a slight, pleasant odour. The chemical freezes at about -64 °C. Depending on the presence of impurities, its boiling point is between 155 and 165 °C (Hoechst, 1990). Diglyme is miscible with water and with a number of common organic solvents. It dissolves numerous compounds, such as vegetable oils, waxes and resins, boron hydrides, organic boron compounds, sulfur, sulfur dioxide, hydrogen peroxide, and carbon dioxide. With

water, azeotrope formation is observed at a concentration ratio of 23 wt. % diglyme and 77 wt. % water (BUA, 1993a). Diglyme has an *n*-octanol/water partition coefficient (log *K*_{ow}) of -0.36, determined by a shake flask experiment (Funasaki et al., 1984). Its vapour pressure at 20 °C ranges from 0.23 to 1.1 kPa. The chemical is volatile with water vapour (BUA, 1993a). The calculated Henry's law constant is given as 0.041 Pa·m³/mol (J. Gmehling, personal communication, 1991).

The conversion factors for diglyme for the gas phase (101.3 kPa, 20 °C) are as follows:

$$\begin{aligned} 1 \text{ mg/m}^3 &= 0.18 \text{ ppm} \\ 1 \text{ ppm} &= 5.58 \text{ mg/m}^3 \end{aligned}$$

Diglyme is chemically stable. In the presence of strong oxidation agents, peroxide may form. Commercial products typically contain peroxides at a concentration of 5 mg/kg. To avoid the further formation of peroxides, commercial products may contain antioxidants, such as 2,6-di-*tert*-butyl-4-methylphenol (BUA, 1993a).

Additional physical and chemical properties of diglyme are presented in the International Chemical Safety Card (ICSC 1357) reproduced in this document.

3. ANALYTICAL METHODS

Two general methods for the determination of glycol derivatives in ambient and workplace air are described:

- adsorption onto modified silica containing cyano-propyl groups, synthetic polymers such as XAD 2 or XAD 7, or modified activated charcoal, with subsequent solvent elution (e.g., acetone, dichloromethane, dichloromethane/methanol); and
- adsorption onto TENAX TA with subsequent thermal desorption.

In either case, detection is carried out via gas chromatography/flame ionization detection (GC/FID) or gas chromatography/mass spectrometric detection (GC/MSD) (NIOSH, 1990, 1991, 1996; Stolz et al., 1999). For the determination of diglyme in indoor air, the chemical was adsorbed onto activated charcoal, eluted with dichloromethane/methanol, and determined by capillary GC/MSD (internal standard toluene-d₈ and 1,2,3-trichloropropane). The detection limit was 3 µg/m³; data on recovery rate and standard deviation are not available (Plieninger & Marchl, 1999).

The enrichment of diglyme from water samples is also in general carried out by adsorption onto XAD 4 or XAD 8 material with subsequent solvent elution (e.g., diethylether, dichloromethane) and determination by capillary GC/MSD (Morra et al., 1979; Lauret et al., 1989). Recovery rates and standard deviations are not available. A detection limit of 0.01 µg/litre is reported (Morra et al., 1979).

Analytical methods for the determination of diglyme in soil or sediment are not available.

Diglyme was determined together with other glycol ethers in human urine by enrichment on diatomaceous earth, extraction with dichloromethane/acetone (90:10), and detection by capillary GC/FID. The validation results of the method are given only as ranges for total glycol ethers: detection limits 0.25–1 mg/litre, standard deviation 1.5–17.1% (at 5 mg/litre), and recovery rates 92.0–125.2% (at 2, 5, and 10 mg/litre) (Hubner et al., 1992). [¹⁴C]Diglyme was determined in rat urine for metabolism studies by high-performance liquid chromatography/scintillation detection on a reversed-phase C18 column (gradient elution with methanol/acetic acid) after acidification of the sample (Cheever et al., 1988). Information on detection methods for other biological materials is not available.

The metabolite 2-methoxyacetic acid is assumed to play a major role in the toxic effects of diglyme (see sections 8 and 9). Therefore, common detection methods for this compound in urine after inhalation exposure to related EGEs are described briefly here. The basis of these methods is an esterification of 2-methoxyacetic acid with diazomethane after lyophilization of the alkaline urine solution and uptake in hydrochloric acid/dichloromethane (Groeseneken et al., 1986) or with trimethylsilyldiazomethane after extraction of the acid urine solution with dichloromethane/isopropyl alcohol (Sakai et al., 1993). The determination was carried out in both cases with a GC/FID using a capillary column. The recovery rates were reported to be 31% (Groeseneken et al., 1986) and 98% (Sakai et al., 1993). The detection limits were 0.15 mg/litre (Groeseneken et al., 1986) and 0.05 mg/litre (Sakai et al., 1993).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

4.1 Natural sources

There are no known natural sources of diglyme.

4.2 Anthropogenic sources

Diglyme is manufactured in a closed system by the catalytic conversion of dimethyl ether and ethylene oxide under elevated pressure (1000–1500 kPa) and temperatures (50–60 °C) with a maximum yield of 60%. The by-products tri- and tetraethylene glycol dimethyl ether and small amounts of a high-molecular-mass ethylene glycol dimethyl ether are separated by fractional distillation (Hoechst, 1991). This process is based on the classic Williamson ether synthesis (Rebsdats & Mayer, 1999).

In 1982, about 47 200 tonnes of diglyme were produced in the USA (HSDB, 1983). In 1990, about 400 tonnes of the chemical were manufactured in Germany, of which 200 tonnes were exported (BUA, 1993a). More recent data or data from other countries are not available. Diglyme is registered as a high-production-volume chemical by the Organisation for Economic Co-operation and Development (OECD) (i.e., its production volume in at least one OECD member state is ≥ 1000 tonnes/year) (OECD, 1997).

4.3 Uses

Because of its dipolar aprotic properties and its chemical stability (see sections 2 and 5.2), diglyme is used mainly as a solvent, as an inert reaction medium in chemical synthesis, and as a separating agent in distillations. These uses include industrial applications, such as polymerization reactions (e.g., of isoprene, styrene), the manufacture of perfluorinated organic compounds (BUA, 1993a), reactions in boron chemistry (Brotherton et al., 1999; Rittmeyer & Wietelmann, 1999), and its application as a solvent for, for example, textile dyes, lacquers, and cosmetics (BUA, 1993a; Baumann & Muth, 1997).

Diglyme is also used in the manufacture of integrated circuit boards, primarily as a solvent for the photoresists. These are used as photosensitive materials for the coating of the wafer during microlithographic patterning in the photo/apply process (Messner, 1988; Correa et al., 1996; Gray et al., 1996) and in the production of semiconductors (Corn & Cohen, 1993).

Diglyme is included in the European Inventory of Cosmetics Ingredients in the solvent category (EC, 1996). Its use in cosmetics in Germany and Canada was not reported (BUA, 1993a; Clariant GmbH, personal communication, 2000; IKW [German Trade Association on Cosmetic and Detergent Preparations], personal communication, 2000; R. Gomes, Health Canada, personal communication, 2001). Data for other countries are also not available.

EGEs in general are also used as auxiliary solvents in water-based paints that are industrially applied (e.g., in the spraying of automobiles, metal furniture, household appliances, and machines) (Karsten & Lueckert, 1992; Baumann & Muth, 1997). It is not possible with the available data to estimate the annual amount of diglyme in this field of use or its application in water-based paints for consumer use.

4.4 Estimated global release

The global releases of diglyme cannot be estimated with the available data.

The releases from the production of diglyme at the German manufacturer for the year 1990 are estimated as follows: <2.5 g/tonne released into air, about 133–188 g/tonne released into water, and <7.5 kg/tonne released with solid wastes. The liquid wastes are disposed of in approved chemical waste incinerators (BUA, 1993a).

Data on the degree of recycling of diglyme from its application as a solvent or as an inert reaction medium in industrial processes are not available.

Information on the content of diglyme in consumer products such as cosmetics or paints and lacquers is not available. It is assumed that any diglyme used in this way will end up in ambient air or domestic wastewater.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, TRANSFORMATION, AND ACCUMULATION

5.1 Transport and distribution between media

Diglyme is miscible with water and has a low Henry's law constant (see section 2), leading to a low volatility from aqueous solutions (Thomas, 1990). From this and its use pattern, it is expected that the main target compartment of the chemical will be the hydrosphere.

5.2 Transformation

From GC measurements with an aqueous solution of 47.2 g diglyme/litre (5% v/v) kept in the dark for 21 days (NTP, 1987), it has been concluded that the chemical is hydrolytically stable. This is also to be expected from diglyme's chemical structure (Harris, 1990).

Direct photolysis of diglyme is assumed to be of minor importance due to diglyme's weak absorption at wavelengths above 230 nm (Ogata et al., 1978a,b). NTP (1987) determined no decrease in the concentration of an aqueous solution of diglyme (47.2 g/litre) exposed to room light for 72 h.

The reaction of gaseous diglyme with hydroxyl radicals in the atmosphere has an experimentally determined rate constant K_{OH} of 1.7×10^{-11} cm³/molecule per second (Dagaut et al., 1988). Assuming an average tropospheric hydroxyl radical concentration of about 6×10^5 molecules/cm³ (BUA, 1993b), the half-life of diglyme can be calculated to about 19 h. Due to the miscibility of diglyme with water and its low Henry's law constant (see section 2), diglyme is furthermore expected to be deposited easily with rain or other wet deposition. From this and its short half-life in atmospheric reactions, long-distance transport of diglyme in ambient air is assumed to be negligible.

From a Zahn-Wellens test following OECD Guideline 302B, adsorption of diglyme onto activated sludge was 17% after 3 h, and total removal was 42% after 28 days. The degree of elimination and the degradation curve are indicative of inherent primary degradation, according to OECD criteria (Hoechst, 1989a).

Roy et al. (1994) achieved a similar result in an electrolytic respirometer test with industrial wastewater from a manufacturer of synthetic organic chemicals. In a further experiment in which diglyme was tested together with dioxane and other unspecified organic chemicals, the degree of biodegradation was significantly higher than in the test with diglyme alone (80% after 32 days), suggesting that the biodegradation of diglyme is more efficient in the presence of other carbon sources. High salt concentrations in the wastewater, however, result in a decrease in biodegradation, indicated by a significant increase in the lag phase.

Data on the anaerobic degradation of diglyme are not available.

5.3 Accumulation

The log K_{ow} of diglyme (−0.36; see section 2) indicates a negligible potential for bioaccumulation.

Measurements concerning the geoaccumulation of diglyme are not available. Data on the adsorption of the chemical onto activated sludge in the Zahn-Wellens test (see section 5.2) cannot be used for the estimation of adsorption onto soil. It is to be expected that the oxygen atoms in the diglyme molecule will lead to a high affinity for the microorganisms of the activated sludge but not

for the humic acids or inorganic components of soils. From the physicochemical properties of the substance (miscibility with water, low $\log K_{ow}$; see section 2), a low tendency to sorption onto inorganic and organic soil substances is to be expected.

As a result of its highly hydrophilic character and its low tendency to volatilize from aqueous solutions or to adsorb to soil constituents, diglyme may reach groundwater. EGEs were detected particularly in anoxic groundwater in the vicinity of US landfill sites (Ross et al., 1992). The possibility that the chemical will subsequently enter wells and drinking-water cannot be excluded.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

Data on the concentrations of diglyme in ambient or workplace air are not available.

Diglyme was detected in surface water in the Dutch parts of the river Rhine at concentrations ranging between 0.1 and 0.3 $\mu\text{g/litre}$ (1978; five samples), 0.03 and 0.3 $\mu\text{g/litre}$ (1979; five samples), and 0.5 and 5 $\mu\text{g/litre}$ (1985; six samples) (Morra et al., 1979; Linders et al., 1981; KIWA, 1986). More recent data or data from surface waters in other countries are not available.

In 1987, the chemical was determined in the biologically treated leakage from two French landfills at concentrations in the order of 2–20 $\mu\text{g/litre}$ (Lauret et al., 1989). Diglyme was furthermore determined but not quantified in 1992 in wastewater samples, from a German oil reclaiming company, that had been pre-treated by equalization, neutralization, adsorption to activated sludge, flocculation, and flotation (Gulyas et al., 1994).

Data on the concentration of diglyme in soil or sediment are not available.

Data on the concentration of diglyme in biological material are not available.

6.2 Human exposure

6.2.1 Workplaces

There is a potential for inhalation or dermal contact in the chemical and allied product industries where diglyme is used as a solvent.

During the diglyme production process and its use as a solvent in chemical synthesis, inhalation and dermal contact are assumed to occur mainly during cleaning and maintenance operations, as solvents are handled mainly in closed systems.

No data are available on diglyme exposure concentrations at the workplace. Data on other EGEs that are produced in the same way and that have a comparable use pattern and similar volatilization behaviour may serve as a rough approximation.

ECETOC (1995) reported time-weighted average (TWA) exposures for several other EGEs between 0.01 and 6.5 ppm for the production process. This would correspond to airborne diglyme concentrations between about 0.06 and 36 mg/m^3 , taking its conversion factor for the gas phase into account (see section 2). The dermal exposure to diglyme can be estimated with the calculation model Estimation and Assessment of Substance Exposure (EASE) to be a maximum of 0.1 mg/cm^2 per day, based on the assumption that trained workers incidentally have direct skin contact with diglyme during cleaning and maintenance operations. Assuming further that exclusively the palms (an area about 420 cm^2) are exposed, this would lead to a maximum dermal body dose of 0.6 mg/kg body weight per day (assuming a body weight of 70 kg).

For the use of EGEs in the semiconductor industry, TWA exposure values between 0.01 and 0.55 ppm are reported (workplace operation not specified; ECETOC, 1995). This would correspond to airborne diglyme concentrations between about 0.06 and 3.1 mg/m^3 . As diglyme is obviously used in mixtures with other EGEs (see, for example, Messner, 1988), the diglyme exposure levels cannot be estimated from these data. The maximum dermal dose could be assumed to be equal to the dose estimated for the production process (0.6 mg/kg body weight per day). Some authors report significant permeation of protective gloves of different materials by EGEs. Gloves made of nitrile and butyl rubber or neoprene provide the best protection (breakthrough rates ≥ 45 min) and are now the ones being used most frequently in the semiconductor industry (for review, see Paustenbach, 1988).

For the use of glycol ethers in professional painting operations, the geometric means of the TWA exposure values were between 1.7 and 5.6 ppm, with maximum concentrations up to about 37.6 ppm (workplace operation not specified; ECETOC, 1995). For diglyme, this would correspond to airborne concentrations between 9.5 and 31 mg/m³, with a maximum of 210 mg/m³. The maximum dermal exposure could be assumed to be equal to the dose estimated for the production and solvent use of diglyme in chemical synthesis (incidental contact during transferring/weighing/mixing or cleaning and maintenance procedures, exposure of palms [420 cm²] only: 0.1 mg lacquer/cm² per day). Assuming a maximum diglyme content of the lacquer of 25% (Baumann & Muth, 1997), this results in a maximum dermal body dose of about 0.15 mg diglyme/kg body weight per day.

6.2.2 Consumer exposure

The main target compartment of diglyme is the hydrosphere (see section 5.1). The chemical is inherently biodegradable with a rather long log phase and a significant tendency to adsorb onto activated sludge (see section 5.2). From this and from its suspected use as a solvent in consumer products such as lacquers and cosmetics, the main route of exposure of the general population to diglyme is likely via the ingestion of drinking-water and via dermal contact with the respective consumer products.

The database is not sufficient to estimate the daily intake of diglyme by the general population.

Data on the concentration of diglyme in drinking-water are not available.

Quantitative information on dermal exposure to diglyme via cosmetic products is not available. Although diglyme is included in the European Union's Inventory on Cosmetics Ingredients, its use was not reported for Germany or Canada (see section 4.3). For other countries, data are also not available.

Measured data on exposure to diglyme-containing water-based paints and lacquers for consumer use are not available. Furthermore, the relevance of diglyme as an auxiliary solvent in paints for consumer use cannot be estimated with the available data. Due to the low tendency of volatilization of diglyme from aqueous solutions (see section 5.1), inhalation exposure is assumed to be of minor importance. Dermal exposure cannot be quantified with the available data.

6.2.3 Biological monitoring

As dermal exposure is significant, measurement of diglyme in air is not sufficient for exposure monitoring. Therefore, biological monitoring of the metabolite 2-methoxyacetic acid, which belongs to the metabolic pathway that is responsible for the developmental effects and effects on the reproductive system, is preferable. Methods for detecting this metabolite in urine are described in section 3.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

7.1 Absorption

Studies on the metabolism of diglyme in rats show that diglyme is absorbed from the gastrointestinal tract (Cheever et al., 1986, 1988). Absorption following inhalation can be concluded from the observation of poisoning symptoms in studies on single- and repeated-dose exposure to diglyme and in analogy with other glycol ethers.

In an *in vitro* study with human skin, the high percutaneous absorption of glycol ethers (ECETOC, 1995; Johanson, 1996) was confirmed. The permeability constant was 1×10^{-3} cm/h, and the lag time was approximately half an hour. With these findings, diglyme was among the glycol ethers with the highest absorption rate (Filon et al., 1999).

Dermal absorption of glycol ether liquids or vapours is very high (Johanson & Boman, 1991; ECETOC, 1995; Kezic et al., 1997; Brooke et al., 1998; Johanson, 2000). With 2-methoxyethanol, for example, dermal absorption of the vapour is approximately as high as absorption via inhalation. Dermal uptake of the liquid is very high: exposure of an area of 2000 cm² for 1 h resulted in a body dose of 5920 mg in a study with human volunteers (Kezic et al., 1997).

7.2 Distribution and accumulation

No studies are available that investigate the distribution of radioactively labelled diglyme within the body. Glycol ethers in general are readily distributed throughout the body (ECETOC, 1995).

The metabolite 2-methoxyacetic acid has shown evidence of accumulation in animals and humans. In

Table 1: Metabolites in the urine after single oral application of diglyme.

	Male Sprague-Dawley rats					Pregnant CD-1 mice	
	Cheever et al. (1988)		Cheever et al. (1989a)		Richards et al. (1993)	Daniel et al. (1986)	Daniel et al. (1991)
Dose (mg/kg body weight)	6.84	684	684	684	684	300	500
Application at day of gestation	—	—	—	—	—	12	11
Duration of urine collection (h)	96	96	96	96	48	48	48
Pretreatment	—	—	22 days diglyme	22 days phenobarbital	—	—	—
	% of dose						
Metabolite I (not identified)	<0.1	0.3	0.4	0.7	n.g. ^a	n.g.	n.g.
N-(Methoxyacetyl)glycine	0.1	0.3	0.7	0.9	n.g.	n.g.	n.g.
Diglycolic acid	6.7	3.9	2.2	4.6	n.g.	n.g.	n.g.
Metabolite IV (not identified)	2.5	1.0	1.1	1.6	n.g.	n.g.	n.g.
2-Methoxyacetic acid^b	5.8	6.2	10.0	13.4	n.g.	26.1–27.0	28.0
2-Methoxyethanol	2.2	0.8	2.1	1.5	n.g.	n.g.	n.g.
2-Methoxyethoxyacetic acid^b	70.3	67.9	68.5	64.2	67.0	64.5–67.1	63.0
Metabolite VIII (not identified)	0.4	1.2	2.3	1.0	n.g.	n.g.	n.g.
2-(2-Methoxyethoxy)ethanol	0.3	<0.1	1.2	0.7	n.g.	n.g.	n.g.
Diglyme	0.4	1.8	1.3	0.3	n.g.	n.g.	n.g.
Total	88.7	83.4	88.8	88.9	81.0	n.g.	n.g.

^a n.g. = not given.^b Bold indicates main metabolites.

humans, its half-life was calculated as 77.1 h (ECETOC, 1995).

7.3 Metabolism

The metabolites identified in the urine following oral application in different studies are given in Table 1. The metabolic pathway of diglyme is shown in Figure 1.

The principal pathway of biotransformation of diglyme involves *O*-demethylation with subsequent oxidation to form the main metabolite 2-methoxyethoxyacetic acid, which accounts for about 60–70% of the dose in the urine of rats and pregnant mice after 48–96 h (Daniel et al., 1986; Cheever et al., 1988; Toraason et al., 1996) (see Table 1).

In addition, cleavage (*O*-dealkylation) of the central ether bond results in the formation of 2-methoxyethanol, which is subsequently oxidized to 2-methoxyacetic acid. This metabolite accounts for about 5–15% of the dose in the urine of rats after 48–96 h (Cheever et al., 1988, 1989a). In the urine of pregnant mice, it was found in higher concentrations (26–28% of the dose; Daniel et al., 1986, 1991) (see Table 1). Also, humans may form this metabolite in higher concentrations. Based on nmol 2-methoxyethanol generated per nmol P-450, human

microsomes were found to be 7 times more effective than rat microsomes in converting diglyme to 2-methoxyethanol (Tirmenstein, 1993; Toraason et al., 1996).

There is no apparent quantitative difference in the spectrum of metabolites, including 2-methoxyethoxyacetic acid and 2-methoxyacetic acid, over a 100-fold dose range (6.84–684 mg/kg body weight; see Table 1).

Repeated doses of diglyme or induction with phenobarbital or ethanol increases the cleavage of the central ether linkage of diglyme as a result of cytochrome P-450 enzyme induction in the liver (Cheever et al., 1988, 1989a; Tirmenstein, 1993; ECETOC, 1995; Toraason et al., 1996).

Although the main metabolite in rat urine is 2-methoxyethoxyacetic acid, numerous studies indicate that 2-methoxyacetic acid is the metabolite responsible for the toxicity of diglyme for the male reproductive organs (see also section 8.7) (Cheever et al., 1985, 1988; BUA, 1993a). Further, 2-methoxyacetic acid was transferred to the fetus and found as the sole metabolite in the fetus (no parent compound was detected in the fetus either) after dosing diglyme to mice at day 11 or 12 of pregnancy (Daniel et al., 1986, 1991). The highest levels for the average embryo (whole embryos analysed) were

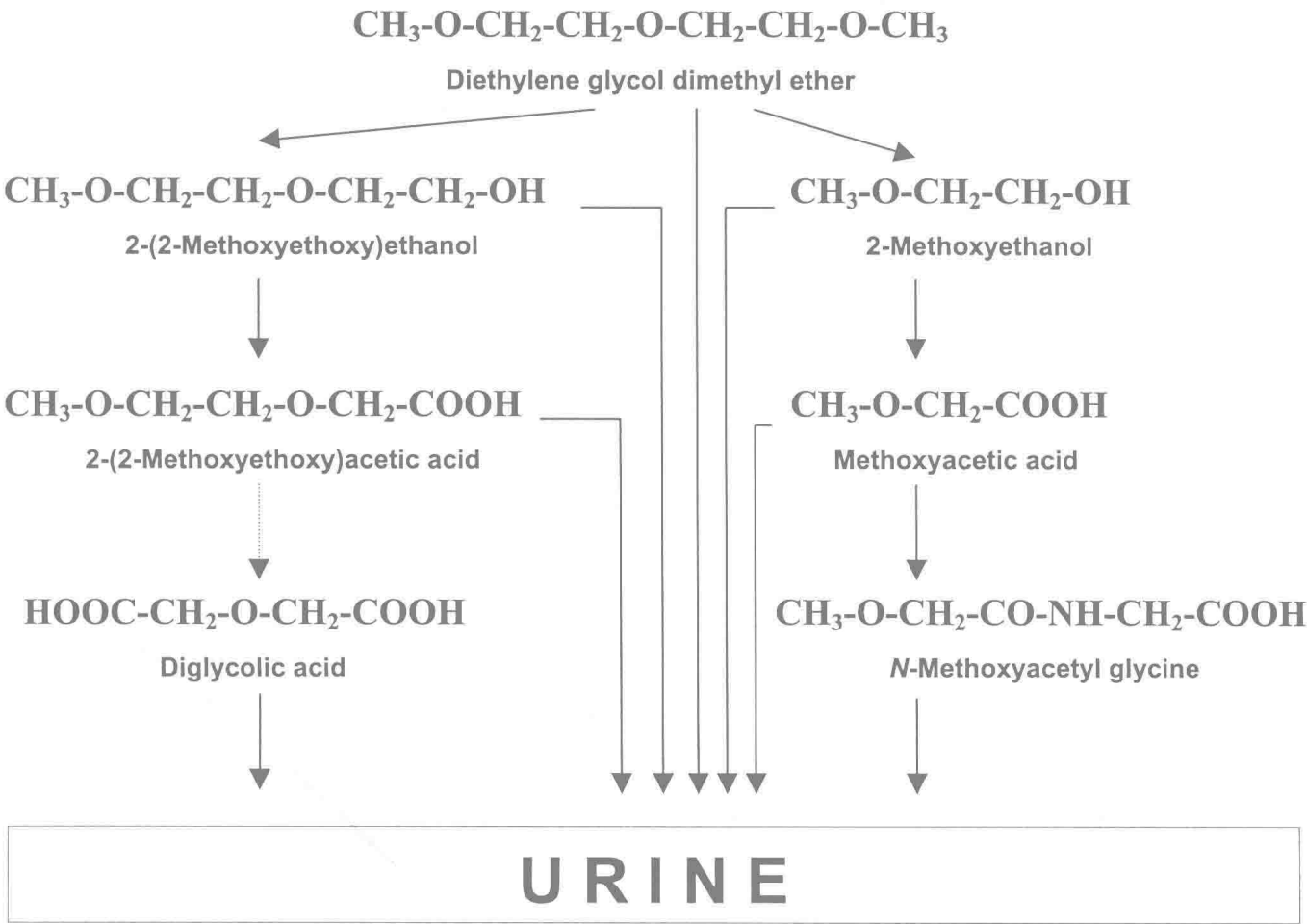


Figure 1: Metabolism and disposition of diethylene glycol dimethyl ether.

detected at 6 h after dosing. Significantly lower amounts were detected in blood taken from the dam at that time point (Daniel et al., 1991).

7.4 Elimination

The major route of elimination is through the urine. Ninety-six hours after oral application of 6.84 mg diglyme/kg body weight to male Sprague-Dawley rats, 90% of the dose was excreted via urine, 3.6% as carbon dioxide, and 2.9% in the faeces. Only 1.7% of the dose remained in the carcass (Cheever et al., 1988).

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

8.1 Single exposure

8.1.1 Inhalation

A 7-h nose-only exposure (inhalation hazard test) to an atmosphere saturated with diglyme at room temperature (about 10 g/m^3) caused restlessness, narrowing of palpebral fissures, and irregular breathing in rats. All animals survived. Necropsy 14 days after exposure revealed no macroscopic findings (Hoechst, 1979a).

8.1.2 Oral administration

The acute oral toxicity of diglyme is low. The oral LD_{50} for the female rat is 4760 mg/kg body weight (Hoechst, 1979b) and for the female mouse is 2978 mg/kg body weight (Plasterer et al., 1985). Poisoning symptoms were restlessness and breathing difficulties.