European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

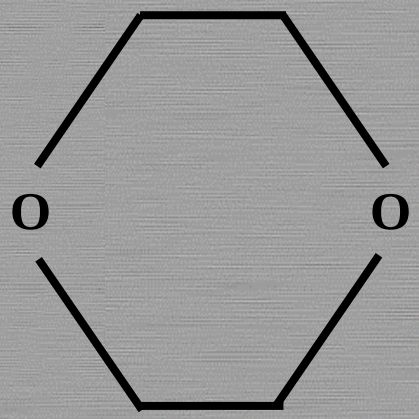
Existing Substances

European Union Risk Assessment Report

CAS No: 123-91-1

EINECS No: 204-661-8

1,4-dioxane



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European Union Risk Assessment Report

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RISK ASSESSMENT

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1,4-DIOXANE

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RISK ASSESSMENT

Final Report, 2002

The Netherlands

Rapporteur for the risk evaluation of 1,4-dioxane is the Ministry of Housing, Spatial Planning and the Environment (VROM) in consultation with the Ministry of Social Affairs and Employment (SZW) and the Ministry of Public Health, Welfare and Sport (VWS). Responsible for the risk evaluation and subsequently for the contents of this report, is the rapporteur.

The scientific work on this report has been prepared by the Netherlands Organisation for Applied Scientific Research (TNO) and the National Institute of Public Health and the Environment (RIVM), by order of the rapporteur.

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Date of Last Literature Search :	**1994**
Review of report by MS Technical Experts finalised:	**1999**
Final report:	**2002**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.

Barry Mc Sweeney
Director-General
DG Joint Research Centre

Catherine Day
Director-General
DG Environment

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1 O.J. No L 084, 05/04/199 p.0001 – 0075

2 O.J. No L 161, 29/06/1994 p. 0003 – 0011

3 Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS no: 123-91-1
EINECS no: 204-661-8
IUPAC name: 1,4-Dioxane

Environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Human health

Human health (toxicity)

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) is reached, because:

- defatting of the skin cannot be excluded for all occupational exposure scenarios;
- repeated-dose toxicity and carcinogenicity for the scenario "formulation" after inhalation exposure at the workplace cannot be excluded;
- repeated-dose toxicity and carcinogenicity after dermal exposure at the workplace cannot be excluded for the subscenario "use in cleaning agents";
- repeated-dose toxicity and carcinogenicity after combined (i.e. respiratory and dermal) exposure at the workplace cannot be excluded for the scenario "formulation" and the subscenario "use in cleaning agents".

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

CONTENTS

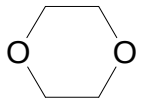
The **EUSES summary file** contains confidential information on the use of the substance and therefore cannot be made publicly available. It can be made available to the Competent Authorities under Regulation 793/93 on request.

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS-No.:	123-91-1
EINECS-No.:	204-661-8
IUPAC name:	1,4-dioxane
Synonyms:	1,4-dioxacyclohexane; diethylene dioxide; diethylene ether; diethylene-1,4-dioxide; dioxane; dioxyethylene ether; glycolethylene ether; NE 220; p- dioxane; tetrahydro-1,4-dioxane; tetrahydro-p-dioxane
Molecular formula:	$C_4H_8O_2$
Structural formula:	



Molecular weight: 88

1.2 PURITY/IMPURITIES, ADDITIVES

Purity:	≥99% w/w
Impurity:	≤0.1% w/w water (CAS-No.7732-18-5) ≤0.1% w/w 2-methyl-1,3-dioxane (CAS-No.497-26-7) ≤0.03% w/w 2-ethyl-1,3-dioxane (CAS-No.2568-96-9) ≤0.001% w/w hydrogen peroxide (CAS-No.7722-84-1) ≤0.03% w/w non volatile components
Additives:	In stabilised dioxane 2,6-tert-butyl-p-cresol is found.

1.3 PHYSICO-CHEMICAL PROPERTIES

In **Table 1.1,** the physico-chemical properties are summarised.

Table 1.1 Physico-chemical properties

Property	Result	Comment
Physical state	Liquid	*
Melting point	12°C	*
Boiling point	101°C	**
Relative density	1.034	**
Vapour pressure	40 hPa at 20°C	***
Surface tension	33.2 mN/m	***
Water solubility	Miscible in all mixtures	*
Solubility	Miscible in most organic solvents	*
Partition coefficient n-octanol/water (log value)	-0.27 (-0.32) [1)]	*
Flash point	11 °C	***
Flammability	Highly Flammable (R11 and R19)	*
Autoflammability temperature	300°C	***
Explosive properties	Not explosive	*
Oxidising properties	Not oxidising	****
Odour (threshold air)	Like ether (24 ppm v/v)	** (Amoore and Hautala, 1983)
Conversion factors (at 20 °C)	1 ppm = 3.6 mg/m^3 1 mg/m^3 = 0.278 ppm	calculated

* More than one apparently independent source. No methods specified.
** Result of most reliable test. Other apparently independent sources provide results of the same order. Most of these methods are not specified.
*** Several values are found in literature. The value presented in the table is considered as the most appropriate
**** Conclusion based on theoretical, structural considerations.
1) Calculated log Kow-value (QSAR; Rorije et al., 1997) is used in EUSES calculations.

These data are mainly derived from BASF (1995), BUA (1992/1994), Grant Chemicals (1977). For an extended description, see entry in IUCLID database.

Conclusion

Information on oxidising properties is not available. However, on theoretical considerations the compound is concluded to be not oxidising. All other required physico-chemical data were submitted. None of these data is based on test results, substantiated with reports. However, the data are considered as sufficiently reliable to fulfil the Annex VIIA of 67/548/EEC requirements. The substance is not explosive under the appropriate storage conditions (stored in the dark and in tightly closed containers). Otherwise peroxides can be formed. The substance should be labelled as highly flammable (R11 and R19). A highly flammable liquid should be labelled with S9.

1.4 CLASSIFICATION

Classification and labelling according to the 28th ATP of Directive 67/548/EEC[4]:

Classification:	F; R11-19	Highly flammable May form explosive peroxides
	Carc. Cat. 3; R40	Limited evidence of a carcinogenic effect
	Xi; R36/37	Irritating to eyes and respiratory system
	R66	Repeated exposure may cause skin dryness or cracking
Labelling:	F; Xn	
	R: 11-19-36/37-40-66	S: (2-)9-16-36/37-46

Specific concentration limits: None

Note: D

[4] The classification of the substance is established by Commission Directive 2001/59/EC of 6 August 2001 adapting to the technical progress for the 28th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (OJ L 225, 21.8.2001, p.1).

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

In Europe, 1,4-dioxane is at present only produced at BASF AG in Ludwigshafen, Germany. Since 1990, Dow Europe s.a. in the Netherlands stopped production (DOW information). The production volume in 1997 was estimated to be 2,000-2,500 tonnes with an export outside the European Community of 575 tonnes (Industry, 1998). There is no information about import volumes of 1,4-dioxane into the EU.

The other producers outside the European Union are Ferro Corp. in the USA and Osaka Yuki and Toho Chem. in Japan (BUA, 1991). The worldwide production capacity in 1985 was estimated to be 11,000 - 14,000 t/a (Surprenant, 1988). In 1995 the production capacity of known producers and the worldwide production volume is estimated at 8,000 t/a and 10,000 t/a, respectively (BASF information). In general the worldwide production of 1,4-dioxane is decreasing because of changing use patterns (see Section 2.2).

2.1.1 Production process

There are three main types of production for 1,4-dioxane (BUA, 1991):

- acid-catalysed conversion of diethylene glycol by ring closure in a closed system. (Weber, 1975; Dittus, 1966; BASF information). The use of mono-, tri- and polyethylene glycol and their ethers as raw material is also reported;
- catalysed cyclo-dimerisation of ethylene oxide (Yamanis and Garland, 1981) on acid ion exchanger resins via oligo-ethylene sulphonates;
- ring closure of 2-chloro-2'-hydroxyethyl ether through heating with 20% sodium hydroxide.

The second and the third processes are especially useful for the production of substituted dioxanes.

Industrially, the first production process is the most important one. This process is used at the German production site. This production is carried out at a temperature of between 130 and 200°C and a pressure ranging from 250 to 1,100 hPa (Weber, 1975; Braun and Young, 1977; BUA, 1991). Dehydration and purification takes place by distillation (BASF, information). For this production, sulphuric acid, phosphoric acid, p-toluenesulphonic acid and strongly acidic ion exchangers are used as catalysts (Weber, 1975). Zeolites can also be used (Anonymous, 1996).

The continuous synthesis (Surprenant, 1988) is carried out in a heated vessel. The raw product forms an azeotrope with water. The dioxane is separated by distillation. Water and volatile by-products are separated by extractive distillation (Weber, 1975). The main by-products are acetaldehyde and 2-methyl-1,3-dioxalane, 2-ethyl-1,3-dioxolane. At a lesser extent, glycol, crotonaldehyde and polyglycol are formed during the production (Weber, 1975; Surprenant, 1988). The crude 1,4-dioxane is further cleaned by heating with acids, distillation (to remove glycol and acetaldehyde), salting out with NaCl, $CaCl_2$ or NaOH and fine subsequent distillation (Weber, 1975; BUA, 1991).

2.2 USE

1,4-Dioxane has a great variety of applications. Because of its physical-chemical properties it is mainly used as a processing solvent (waxes, fat, lacquers, varnishes, cleaning and detergent preparations, adhesives, cosmetics, deodorant fumigants, emulsions and polishing compositions, pulping of wood). It is also used as an extraction medium for animal and vegetable oils and as a laboratory chemical (eluent in chromatography) and in plastic, rubber, insecticides and herbicides (BASF information; HSDB, 1996; BUA, 1991). Other uses are for measuring optical activity, for cryroscopic determination and in the manufacturing of membrane filters (BUA, 1991).

Other applications of 1,4-dioxane outside the EU include its use as a chemical intermediate and part of a catalyst (polymerisation for plastics).

In general, the usage of 1,4-dioxane is decreasing (BUA, 1991). The use of 1,4-dioxane as a stabiliser (3-4%) in 1,1,1-trichloroethane stopped at the end of 1995 because of the ozone depletion potency of 1,1,1-trichloroethane (DOW information; BUA, 1991; BASF information). Another reason for the decreasing usage is the increasing dioxane recovery in the pharmaceutical industry.

In 1985 in the USA about 90% of the 1,4-dioxane produced served as a stabiliser for chlorinated solvents, particularly 1,1,1-trichloroethane. The remaining 10% was used in the solvent area. It is expected that the present situation in the US will be totally different (BUA, 1991).

According to the most recent information from industry, 1,4-dioxane is used in the production processes of the following categories of products: pharmaceuticals/pesticides, magnetic tape, adhesives and others (Industry, 1998). The 1997 mass balance for 1,4-dioxane is confidential and thus not publically available. It can be made available to Member States Competent Authorities on request.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

1,4-Dioxane may enter the environment during its production, processing, formulation and/or use of products. In a number of industrial processes (ethoxylation reactions) 1,4-dioxane may also be formed unintentionally and, in addition, 1,4-dioxane can also remain as an impurity in several end-products (see Section 3.1.1.4). These unintentional sources will also result in 1,4-dioxane releases.

3.1.1 Environmental releases

The environmental exposure assessment of 1,4-dioxane will be based on the expected releases of the substance during the following life cycle stages:

I. Production
II. Processing (pharmaceuticals/pesticides, adhesives, magnetic tape and others)
III. End-use
IV. Unintentional formation

Both site-specific and generic release data are used for calculating the predicted environmental concentrations (PECs) in the various compartments. Generic data (TGD defaults) are used if no data were obtained from either industry or other bodies.

3.1.1.1 Releases from production

At present there is only one production site of 1,4-dioxane in the EU. Besides production at this site also processing takes place (see 3.1.1.2). Site-specific release information is given in the next section (site I-1/II-1).

3.1.1.2 Releases from processing

Site-specific information on 1,4-dioxane emissions has been submitted for five processing sites (see **Table 3.1**).

Table 3.1 Site-specific 1,4-dioxane emissions at various processing sites

Company/Site	Processing	Emission (kg/y) air (a) water (w)	Waste incinerated (tonnes per annum)	Reference
Site I-1/II-1	Production/processing	<25 (a) 26,500 (w)	0.150	Industry
Site II-2	Processing magnetic tapes	21,000 (a) - (w)	82-115	Industry
Site II-3	Processing pharmaceuticals	conf. (a) conf. (w)	-	Industry
Site II-4	Processing resins	120 (a) - (w)	-	DEI, 1996
Site II-5	Processing glues	1,106 (a) - (w)	-	DEI, 1996

Site I-1/II-1: Emission data to air are according to emission registers (1994). Emission data to water are estimated by daily measurements in the STP effluent.
Site II-3: Emission data for air are deduced from a mass balance where the amount of 1,4-dioxane in each waste and final product is chromatographically determined.

The processing of 1,4-dioxane in magnetic tape production (scenario II-2) is known to be fully covered by the above-mentioned site-specific data. The same is most probably true for the use of 1,4-dioxane at adhesive production (scenarios II-4 and II-5). The situation is different, however, for the usage of 1,4-dioxane at the production of pharmaceuticals/pesticides, as only part of the volume is covered by the available site-specific data (scenario II-3). For this reason, a generic scenario (scenario II-6) is carried out for the remaining tonnage for this application (**Table 3.2**). The tonnage is set at 1,000 tonnes, resulting from data and site-specific information from industry. The combination of IC 2 (Chemical industry: basic chemicals) and UC 48 (solvents) is thought to be most appropriate for this usage, as 1,4-dioxane is used as a reaction solvent (pers. comm P.v.d. Poel/RIVM, 29-6-1998). The default release factors of 65% (water) and 25% (air) are very high in comparison with the site-specific (scenario II-3) release factors for the same type of production process: 1% (water) and 3% (air) (Calculation confidential). With US Toxic Release Inventory data of 1995 for 1,4-dioxane (different applications) and the total 1,4-dioxane production tonnage in the US in 1992, average emission factors of 1.7% (air) and 1.8% (water) can be calculated. Although it concerns average emission factors, the US-information also indicates that the TGD defaults are most probably too conservative. One of the reasons for this difference between TGD and actual emission factors is that there is an increasing recovery of 1,4-dioxane in the pharmaceutical industry (see Section 2.2). On the basis of this information it is proposed in the current risk assessment to multiply the site-specific emission factors of scenario II-3 with a factor 10, taking into account the differences in site size, type of product and degree of recovery etc. This results in emission factors of 30% (air) and 10% (water). It is emphasised that the use of a factor 10 for this purpose is not a general rule (case by case).

Table 3.2 Generic scenario II-6 for the use of 1,4-dioxane at the production of pharmaceuticals/pesticides

Tonnage	1,000
Industry category	2 (Chemical Industry: basic chemicals)
Use category	48 (solvents)
Release fraction water	0.10
Release fraction air	0.30
Fraction of main source	0.17 *
Number of emission days	43 **
Release to water (kg/d)	395
Release to air (kg/d)	1,190

* Derivation of fraction of main source is treated as confidential as it includes the number of processing sites
** Estimate based on Table B3.2 of the TGD (0.25f·T)

As there is no site-specific information for other uses, a generic scenario (II-7) is carried out for this usage as well (**Table 3.3**). The input tonnage is set at 125 t/a. Similar to pharmaceuticals/pesticides, the IC/UC combination 2/48 is chosen, as most of "other uses" will be linked with the usage of 1,4-dioxane as a processing solvent for various organic reactions. However, also for this scenario the TGD default emission factors (65% to water and 25% to air) are considered too conservative. Alternative emission factors are derived from the US emission factors, as presented above. This because the US factors are, similar to scenario II-7, also related to a number of different applications. The factors are multiplied with a factor of 10 (see remark above about use of this factor) in order to take into account spread in site size etc., resulting in emission factors of 17% and 18% for, respectively, air and water.

Table 3.3 Generic scenario II-7 for the use of 1,4-dioxane at "other uses"

Tonnage	125
Industry category	2 (Chemical Industry: basic chemicals)
Use category	48 (solvents)
Release fraction water	0.18
Release fraction air	0.17
Fraction of main source	0.3 *
Number of emission days	15 **
Release to water (kg/d)	270
Release to air (kg/d)	255

* Derivation of fraction of main source is treated as confidential as it includes the number of sites
** Estimate based on Table B3.2 of the TGD (0.4 f·T)

3.1.1.3 Releases from use/end-products

The end-products are pharmaceuticals, pesticides, magnetic tapes and other products like paint, lacquers or resins. Information about amounts of 1,4-dioxane in these products and their potential environmental releases is given below:

Magnetic tape

Approximately 1 billion m^2 of tape is produced per year that is sold worldwide (BASF information). This total amount of magnetic tape contains about 2 tonnes of 1,4-dioxane as a residue (BASF, information). Releases of 1,4-dioxane from tape are expected at waste disposal in a widely dispersive manner. No estimate for this type of release will be made because it is assumed to be a minor source and release data are not available.

Pharmaceuticals and pesticides

No generic scenario is considered for pharmaceutical end-products because the 1,4-dioxane amounts in these kinds of products are expected to be negligible. No data could be found to underpin this statement in a quantitative manner.

3.1.1.4 Releases from unintentional sources

It is generally known that 1,4-dioxane can be formed as a by-product in several ethoxylation reactions (BUA, 1991; Aus, 1997).

Release of 1,4-dioxane as a by-product in AES (Alkyl Ether Sulphates)

Detergents with AES (Alkyl Ether Sulphates) as surfactant contain 1,4-dioxane as a by-product. Apart from AES, an anionic surfactant, also products with non-ionic surfactants could contain 1,4-dioxane as a by-product (Aus, 1997). It is reported that in AES manufacturing, the sulphonation step is the major source of 1,4-dioxane formation (Aus, 1997).

Releases from surfactant production

Active raw material (AES) contains 1,4-dioxane at a maximum of 500 ppm (Procter and Gamble, 1997).

Releases via surfactant usage

For Germany, Australia and the Netherlands estimates are available for the environmental releases of 1,4-dioxane from AES usage. In the BUA review(BUA, 1991) the consumption of surfactants in detergents and cleaners in Germany was estimated around 227,000 tonnes in 1989. The release of 1,4-dioxane, as a minor impurity in several groups of surfactants, is estimated to be about 3 tonnes.

In the draft report of Australia 10,000 t/a of AES surfactants are used in Australia and from this, one tonne of 1,4-dioxane (only in AES surfactants) was estimated to be released to the environment. The usage volume of AES in the Netherlands is estimated at 3,500 t/a. Assuming a 1,4-dioxane residue fraction of 200 ppm in AES, 0.7 tonnes of 1,4-dioxane are released annually to the environment in the Netherlands (Procter and Gamble, 1997). The latter figure of 700 kg/a is used for estimating the environmental concentrations of 1,4-dioxane from the use of AES surfactants (scenario III-4 in **Table 3.5**).

Release of 1,4-dioxane as a by-product in other ethoxylated substances

Apart from AES surfactants, a variety of other products which are formed by ethoxylation reactions have the potential to contain 1,4-dioxane as a by-product. These products include chemicals like alkyl-, alkylphenol- and fatty amine ethoxylates, polyethylene glycols and their

esters, and sorbitan ester ethoxylates (Aus, 1997). Their uses cover food, cosmetics, agricultural/veterinary products, therapeutic products, household products and various industrial applications.

In **Table 3.4** three sites are presented where products are made via ethoxylation reactions and for which actual data are available. It has to be emphasised that these three are not representative for the whole EU as there are expected to be many more companies in the EU which produce chemicals via ethoxylation reactions. At present these data are not available. It is felt that the scenarios III-1 and III-2 will most probably cover the local situation for these types of processes. At a regional scale, however, an unknown number of other point sources with similar activities (unintentional processing) may affect regional levels. To take this "unintentional background" into account, the sum of the releases for scenarios III-1 and III-2 are multiplied with a factor 10 for the regional input (see Section 3.1.1.5).

Table 3.4 Local 1,4-dioxane emissions from unintentional processes

Site	Processing	Emission (kg/y)	Reference
Site III-1	Processing	- (a) 800 (w)	DEI, 1996 Eijssen et al., 1993
Site III-2	Processing	- (a) 400 (w)	BUA, 1991
Site III-3	PET production	600 (1996) (a) 900 (1997) (a) 4,600 (1996) (w) 300 (1997) (w)	Zuiveringschap Drenthe, 1997

The reduction in emissions to the hydrosphere at the Dutch plant making poly-ethylene-terephthalate (PET) is due to the fact that most of their wastewater is now being incinerated. According to industry during the further processing cycle of PET (e.g. production of PET bottles) the emissions of 1,4-dioxane are expected to be much lower than those at PET-production, because the levels of free diethyleneglycol are negligible in the PET polymer (the presence of diethyleneglycol is responsible for the unintentional 1,4-dioxane formation).

3.1.1.5 Overview of local emission data and regional release data

An overview of the local emission data for 1,4-dioxane is presented in **Table 3.5**.

Table 3.5 Overview of local release data for 1,4-dioxane

Life cycle stage	Air (kg/d) [1)]	Water (kg/d) [1)]	Scenario
I-1/II-1 Production/processing	< 0.08	88	site-spec.
II-2 Processing tape	70	0	site-spec.
II-3 Processing	conf.	conf.	site-spec.
II-4 Processing resins	0.4	-	site-spec.
II-5 Processing glue	3.7	-	site-spec.
II-6 Processing pharma./pest.	1,190	395	generic
II-7 Processing 'other uses'	250	270	generic
III-1 Unintentional processing	-	2	site-spec.
III-2 Unintentional processing	-	1.3	site-spec.
III-3 Unintentional PET production	2 (1996) 3 (1997) [2)]	15 (1996) [2)] 1 (1997)	site-spec.
III-4 Unintentional AES (end-use)	0	0.004	site spec.

1) Number of emission days is 300 for the site-specific scenarios, except for scenario no. III-4 in which the number of days is 365 and the fraction of the main source is 0.002 instead of 1.
2) Highest figure for scenario III-3 is used for regional input.

Regional and continental releases

The site-specific and generic local data for emission (kg/d) as given in **Table 3.6** are recalculated to annual averages and regional emissions, and then summed up for the estimation of the total regional release. As stated in Section 3.1.1.4, the releases of scenarios III-1 and III-2 are summed up and then multiplied with a factor 10 as a default regional input for releases from unintentional processing. The overall results are shown in **Table 3.6**. Continental input is set equal to regional input. This because extrapolation of all scenarios I and II (incl. generic ones) from regional to continental would result in an unrealistic overestimation of release. In addition, unintentional releases (III) are negligible compared to those from scenarios I and II.

Table 3.6 Estimated regional release of 1,4-dioxane

All life cycle stages	Air (kg/d)	Water (kg/d)	70% via STP (kg/d) 30% via surface water (kg/d)
Regional	965	434	304 130

3.1.1.6 General overview of all relevant (input) data for calculation of the PECs

Emission data and site-specific or generic data for a number of other parameters (e.g. STP-size, flow rate of receiving water etc.) that are needed for calculation of the predicted environmental concentrations (PECs) in the various compartments are shown in **Table 3.7**. The calculations are based on the EU Technical Guidance Document (TGD 96), applying the European System for the Evaluation of Substances (EUSES). The input data and the results of the various EUSES calculations contain confidential information and as such cannot be made publically available. It

can be made available to Member States Competent Authorities for Regulation 793/93 on request.

Table 3.7 General overview of all relevant input data for calculation of the PECs. Production/processing. (Numbers in brackets refer to use pattern in EUSES)

	Site specific			
	Site I-1 *(1)*	Site II-1 *(1)*	Site II-2 *(2)*	Site II-3 *(3)*
Life cycle step	Production	Processing	Processing	Processing
Tonnes/y [1)]	n.r.	n.r.	n.r.	*confidential*
Industrial and Use category	2 and 48	0, 2, 3, 14 and 48	0 and 15 (tape)	
Main category	Ib: continuous production	III: non-dispersive/ multi-purpose equipment	III: non-dispersive	
Fraction of chemical in formulation	-	-	-	
Number of days Fraction of main source	300 1	300 1	300 1	
Release (%) air water	n.r.	n.r.	n.r.	
Amount released air (kg/d) water (kg/d)	<0.0833 see processing site 1	< 0.0833 88.2	70 0	
Waste (t.p.a) incinerated	0.150	0.150	82-115	
Size of STP (m^3/d)	420,000	420,000		
River flow (m^3/d)	$6.3 \cdot 10^7$	$6.3 \cdot 10^7$		
Dilution	151	151		

[1)] Average tonnage of years 1994 and 1995

n.r. = Not relevant

Table 3.7 continued General overview of all relevant input data for calculation of the PECs. Production/processing.

	Site specific for the Netherlands (NL)		Generic	
	Site II-4 *(4)*	Site II-5 *(5)*	Site II-6 *(6)*	Site II-7 *(6)*
Life cycle step	Processing resins	Processing glue	Processing pharma./pest.	Processing other uses
Tonnes/y [1)]	-	-	1,000	125
Industrial and Use category	0 and 48	0 and 48	2/48	2/48
Main category	-	-	III	III
Fraction of chemical in formulation	-	-		
Number of days Fraction of main source	300 1	300 1	43 0.17	15 0.3
Release (%) - air - water	n.r.	n.r.	30 10	17 18
Amount released - air (kg/d) - water (kg/d)	0.4 0	3.7 0	1,190 395	250 270
Waste (t.p.a) incinerated	-	-	-	-
Size of STP (m^3/d)	n.r.	n.r.	2,000 [d)]	2,000 [d)]
River flow (m^3/d)	n.r.	n.r.	-	-
Dilution	n.r.	n.r.	10 [d)]	10 [d)]

[1)] Average tonnage of years 1994 and 1995
n.r. = Not relevant
[d)] Default values

Table 3.7 continued General overview of all relevant input data for calculation of the PECs. Production/processing.

	Unintentional sources (NL)	(Germany)	(NL)	(NL)
	Site III-1 (*7*)	Site III-2 *(8)*	Site III-3 *(9)*	AES use in soap III-4 (10)
Life cycle step	Processing	Processing	PET production	Private use
Tonnes/y [1)]	-	-	-	3,500
Industrial and Use category	15 and 55 (by-product)	15 and 55 (by-product)	15 and 55 (by-product)	5 9
Main category	-	-	-	-
Fraction of chemical in formulation	-	-	-	-
Number of days [d)] Fraction of main source	300	300	300	365 *(table A4.1 of TGD)* 0.002 *(table B4.1 of TGD)*
Release (%) air water	n.r.	n.r.	n.r.	- 0.0002
Amount released air (kg/d) water (kg/d)	 0 2	 0 1.3	 2 [2)] 15 [2)]	 0 0.004
Waste (t.p.a) incinerated	-	-	-	n.r.
Size of STP (m^3/d)	2,000 [d)]	72,000	2,000 [d)]	2,000 [d)]
River flow (m^3/d)	-	-	-	-
Dilution	10 [d)]	23	10 [d)]	10 [d)]

1) Average tonnage of years 1994 and 1995
2) Emission data are from 1996. Wastewater is not incinerated.
n.r. = Not relevant
d) Default values

3.1.2 Environmental fate

3.1.2.1 Degradation

The BUA-report (1991) gives a comprehensive description of the different environmental transformation and degradation routes of 1,4-dioxane. A summary of the various routes is presented below. Details can be found in the BUA-report (1991).

Hydrolysis

There are no experimental data available on the hydrolysis of 1,4-dioxane (BUA, 1991). However, 1,4-dioxane does not contain any hydrolysable groups and ethers are generally classified as resistant to hydrolysis (Aus, 1997).

Photodegradation

There are two possible photo-degradation routes for 1,4-dioxane: direct photolysis and photo-oxidation through reaction with free OH-radicals or ozone.

Photolysis

Studies of direct photolysis of liquid 1,4-dioxane at 185 nm give the following products: formaldehyde, glycol monovinyl ether and ethylene (BUA, 1991). Gas-phase photolysis at 147 nm gives principal products of formaldehyde and ethylene (BUA, 1991). Since the wavelength of light in the troposphere is greater than 290 nm, photolysis does not occur in the lower atmosphere.

Photo-oxidation in air

A rate constant of 10.8 $\pm 1.3 \cdot 10^{-12}$ cm^3.$molecule^{-1}$.s^{-1} has been determined experimentally for the reaction of 1,4-dioxane with OH-radicals. This rate constant corresponds with an atmospheric lifetime and DT_{50} of 36 hours (OH-concentration is $5 \cdot 10^5$ molec.cm^{-3}). According to the TGD 96 QSAR a rate constant of $1.3 \cdot 10^{-11}$ $cm^3 \cdot molecule^{-1} \cdot s^{-1}$ can be calculated, which results in a DT_{50} of 1.2 days (29 hours) (OH-concentration of $5 \cdot 10^5$ molec.cm^{-3}). The calculated value of $1.3 \cdot 10^{-11}$ $cm^3 \cdot molecule^{-1} \cdot s^{-1}$ is further used in the risk assessment.

An experimental photo-oxidation study of 1,4-dioxane in the presence of nitrogen monoxide was mentioned in a BUA-review (1991). The half-life for this reaction is measured to be 3.4 hours.

In BUA (1991) a study is described on abiotic degradation of 1,4-dioxane with ozone. A half-life of 60 hours for 1,4-dioxane in water with an ozone concentration of 10^{-5} mol/l is mentioned.

Biodegradation

Tests on readily biodegradability are not available. BUA (1991) reviewed several biodegradation tests conducted with 1,4-dioxane. From these standardised OECD and non-standardised tests it can be concluded that 1,4-dioxane is not biodegradable.

An actinomycete has been specified in 1,4-dioxane-adapted sludge that grows on the substance as a sole carbon and energy source. As the general occurrence of this actinomycete in wastewater treatment plants is unknown, 1,4-dioxane is treated as non-biodegradable in both industrial and non-industrial exposure scenarios in this risk assessment.

3.1.2.2 Distribution

With regard to the adsorption of 1,4-dioxane in a soil-water system, a K_{oc} of 7.1 l/kg (QSAR non-hydrophobics; log K_{ow} -0.32) has been calculated according to the TGD 96. It can be concluded that 1,4-dioxane has a low adsorption potential and thus a high mobility/leaching potential.

With regard to the volatility of 1,4-dioxane from water to air a Henry's law constant of 4.34 Pa.m^3/mol (vapour pressure is 49.3 hPa at 25ºC) can be calculated at a temperature of 25ºC. From a measured activity coefficient (g) a Henry's law constant of 0.29 Pa.m^3/mol at 20ºC was calculated (BUA, 1991). In addition an experimental value for the air/water partition coefficient at 25ºC (log K_{AW}) was determined. This log K_{AW} of -3.70 corresponds to a Henry's law constant of 0.49 Pa.m^3/mol (BUA, 1991). Overall, it can be concluded that 1,4-dioxane is moderately volatile from water. The calculated Henry's law constant of 4.34 Pa.m^3/mol is further used in the risk assessment. Insufficient information was available about the measured values.

The distribution of 1,4-dioxane in the sewage treatment plant is estimated (EUSES) as follows (log K_{ow}= -0.32 and H= 4.34 $Pa \cdot m^3 \cdot mol^{-1}$):

Fraction directed to air	0.07
Fraction directed to water	0.93
Fraction directed to sludge	0.001
Fraction degraded	0

Elimination of 1,4-dioxane from open systems may occur via stripping (BUA, 1991). Despite its high water solubility and moderate vapour pressure high removal rates have been found in stripping tests (30 to 70%). These stripping rates are much higher than the estimated fraction directed to air from the WWTP (7%: see table above).

3.1.2.3 Accumulation

On the basis of the high water solubility and the low calculated log K_{ow} of -0.32, no bioaccumulation of 1,4-dioxane is expected. This conclusion is supported by the results of a bioaccumulation study in which very low BCF-values (0.2-0.7) were found (Japan Chem. Ind., 1992).

3.1.3 Aquatic compartment (incl. sediment)

3.1.3.1 Calculation of Local Predicted Environmental Concentrations (PEC_{local})

Sewage Treatment Plant (STP)

The predicted environmental concentrations of 1,4-dioxane in the effluent of the sewage treatment plant during emission periods are given in **Table 3.8**. These PECs are calculated from the daily amounts of 1,4-dioxane released to wastewater (**Table 3.7**).

Table 3.8 PECs in the effluent of an STP

Life cycle stage or scenarios	PEC (mg/l) STP
I-1/II-1 Production/processing (1)	0.194
II-2 Processing tape (2)	n.r
II-3 Processing (3)	24
II-4 Processing resins (4)	n.r
II-5 Processing glue (5)	n.r
II-6 Processing pharma./pest. (6)	183
II-7 Processing 'other uses' (6)	125
III-1 Unintentional processing (7)	0.9
III-2 Unintentional processing (8)	0.01
III-3 Unintentional PET production (9)	6.93
III-4 Unintentional AES (10)	0.002

Surface water

The local PECs in surface water, i.e. local PECs in surface water during an emission episode, are presented in **Table 3.9**.

Table 3.9 Local PECs in surface water

Life cycle stage or scenarios	PEC (mg/l) surface water
I-1/II-1 Production/processing (1)	0.002
II-2 Processing tape (2)	0.001
II-3 Processing (3)	3.2
II-4 Processing resins (4)	0.001
II-5 Processing glue (5)	0.001
II-6 Processing pharma./pest.(6)	18.3
II-7 Processing 'other uses' (6)	12.5
III-1 Unintentional processing (7)	0.09
III-2 Unintentional processing (8)	0.002
III-3 Unintentional PET production (9)	0.7
III-4 Unintentional AES (10)	0.001

3.1.3.2 Measured data

Table 3.10 Measured data of 1,4-dioxane in water

Location	Type of site	Levels observed	Year	Literature
NL	Surface water in area in province Drente	1-10 μg/l		TNO, 1997
NL	Drinking water	0.5 μg/l		..
Germany	Ground water near banks of Rhine River	< 10 μg/l (5 different locations)	1996	Industry
Great Britain	Effluent of STP discharging into river Lee	< 1 ng/l (8 hour mixed samples)	?	BUA-report, 1991
USA	Effluent of two STP near lake Michigan	1 μg/l	?	BUA-report, 1991
Unknown	Effluent of STP from a PET manufacturing process	100 mg/l	1995	Internet
USA	Chicago Sanitary and Ship Channel	1 μg/l	1975/76	BUA-report, 1991
USA	Groundwater; near landfill	0.1, 0.5 and 2.4 μg/l (3/8 samples)	1977	BUA-report, 1991
USA	Leachate from the vicinity of 2 landfills for low level radioactive waste	no data	?	BUA-report, 1991
Canada	Groundwater near 3 landfills	<1 μg/l	1983-1986	BUA-report, 1991
Canada	Groundwater beneath landfill	500 μg/l	1982	BUA-report, 1991
USA	Drinking water	dioxane was identified	≤1976	BUA-report, 1991
USA	Drinking water	0.01 μg/l (one sample)	1975	BUA-report, 1991
USA	Drinking water (contaminated)	2,100 μg/l	≤1976	BUA-report, 1991

Note: Most data presented in this table are obtained from the BUA-report (BUA, 1991). Original data were not re-evaluated.

3.1.3.3 Comparison between predicted and measured data

Note: the set of measured data is limited and, in addition, mainly exists for older data from outside the EU. Thus only a limited comparison of measured and calculated information is possible.

STP

The recent measured effluent 1,4-dioxane concentration of 100 mg/l from a PET manufacturing process is higher than the calculated $PECs_{STP}$ of 6.9, 0.01 and 0.9 mg/l (site-specific emission data) for various unintentional 1,4-dioxane releases (**Table 3.10**). It is realised that the source (Internet) of the 100 mg/l figure is questionable.

Surface water

The calculated regional concentration in surface water amounts to 1.3 µg/l. The recent Dutch surface water data of 1-10 µg/l indicate that in specific regions similar levels can be found.

3.1.4 Atmosphere

3.1.4.1 Calculation of Local Predicted Environmental Concentrations (PEC_{local})

From the daily amounts of 1,4-dioxane released to air the EUSES model (OPS module) calculates local atmospheric concentrations. The calculated annual average 1,4-dioxane concentrations in air are presented in **Table 3.11**.

Table 3.11 Local PECs in air

Life cycle stage or scenarios	PEC (µg/m³) air
I-1/II-1 Production/processing (1)	<1.5
II-2 Processing tape (2)	16
II-3 Processing (3)	12.6
II-4 Processing resins (4)	0.1
II-5 Processing glue (5)	0.9
II-6 Processing pharma./pest. (6)	38.9
II-7 Processing 'other uses' (6)	2.9
III-1 Unintentional processing (7)	0.05
III-2 Unintentional processing (8)	0.04
III-3 Unintentional PET production (9)	0.5
III-4 Unintentional AES (10)	0.01

3.1.4.2 Measured data

Table 3.12 Measured data of 1,4-dioxane in air

Location	Type of site	Levels observed	Year	Literature
USA	Three industrialised urban areas	0.036, 0.07 and 0.036 μg/m³ (geometric means: n=111)	1981 (summer)	BUA-report, 1991
USA	Two industrialised urban areas	0.036 μg/m³ (geometric mean: n=26) highest value: 5.31 μg/m³	1982 (winter)	BUA-report, 1991
USA	Ambient air	0.4 μg/m³ (n=24) 0.2 μg/m³ (n=23) 0.1 μg/m³ (n=10)	1984	BUA-report, 191
USA	Various landfills	0.62 and 0.33 g/m³	?	BUA-report, 1991
Germany	Gases from landfill	ppm range	?	BUA-report, 1991
USA	Dioxane gassing out (impurity) at Colgate Palmolive Company	below detection limit (limit not given)	1980	BUA-report, 1991

Note: Most data presented in this table are obtained from the BUA-report (BUA, 1991). Original data were not re-evaluated.

3.1.4.3 Comparison between predicted and measured data

Note: the set of measured data is limited and, in addition, mainly exists for older data from outside the EU. Thus only a limited comparison of measured and calculated information is possible.

The calculated regional air concentration is 0.02 μg/m^3. This figure is below the available US data.

3.1.5 Terrestrial compartment

3.1.5.1 Calculation of Local Predicted Environmental Concentrations (PEC_{local})

The EUSES model takes into account both the application of STP sludge on agricultural soil and the deposition from air for the calculations of 1,4-dioxane levels in the terrestrial compartment.

The PECs of 1,4-dioxane at a local scale are given in **Table 3.13**.

Table 3.13 Local PECs in soil

Life cycle stage or scenarios	PEC terrestrial (mg/kg wet wt)
I-1/II-1 Production/processing (1)	<* $9.2 \cdot 10^{-4}$
II-2 Processing tape (2)	$4 \cdot 10^{-3}$
II-3 Processing (3)	0.07
II-4 Processing resins (4)	$2.6 \cdot 10^{-5}$
II-5 Processing glue (5)	$2.1 \cdot 10^{-4}$
II-6 Processing pharma./pest. (6)	0.5
II-7 Processing 'other uses' (6)	0.35
III-1 Unintentional processing (7)	0.003
III-2 Unintentional processing (8)	0.005
III-3 Unintentional PET production (9)	0.02
III-4 Unintentional AES (10)	$8.1 \cdot 10^{-6}$

* No sludge application to agricultural soil. Real value will be lower

3.1.5.2 Measured data

No measured data available on 1,4-dioxane levels in soil.

3.1.6 Secondary poisoning

Table 3.14 shows the calculated PECs of 1,4-dioxane in fish and worm.

Table 3.14 PECs in fish and worm

Life cycle stage or scenarios	PEC worm (mg/kg wwt)	PEC fish (mg/kg wwt)
I-1/II-1 Production/processing (1)	$5.0 \cdot 10^{-4}$	0.003
II-2 Processing tape (2)	$3.3 \cdot 10^{-3}$	0.002
II-3 Processing (3)	0.02	2.3
II-4 Processing resins (4)	$2.7 \cdot 10^{-5}$	0.002
II-5 Processing glue (5)	$1.8 \cdot 10^{-4}$	0.002
II-6 Processing pharma./pest. (6)	0.17	1.5
II-7 Processing 'other uses' (6)	0.11	0.36
III-1 Unintentional processing (7)	$9 \cdot 10^{-4}$	0.06
III-2 Unintentional processing (8)	$2.8 \cdot 10^{-5}$	0.002
III-3 Unintentional PET production (9)	$6.5 \cdot 10^{-3}$	0.4
III-4 Unintentional AES (10)	$9.6 \cdot 10^{-6}$	0.002

3.1.7 Calculation of regional and continental concentrations

The regional concentrations of 1,4-dioxane in the environmental compartments air, water and soil are calculated from regional and continental release data as presented in **Table 3.6**.

Calculated regional concentrations are given in **Table 3.15**.

Table 3.15 Calculated regional concentrations of 1,4-dioxane

Compartment	PEC regional
Air (µg/m³)	0.02
Water (µg/l)	1.3
Soil (µg/kg)	0.006

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT) ASSESSMENT

3.2.1 Aquatic compartment (incl. sediment)

3.2.1.1 Toxicity test results

3.2.1.1.1 Toxicity to fish

The 1,4-dioxane short-term toxicity studies for freshwater and saltwater fish are summarised in **Table 3.16**.

Table 3.16 Short-term toxicity of 1,4-dioxane to fish

No	Species	LC_{50} (mg/l) 95% C.I.	Method	Reference	R.I.[b]
1	*Pimephales promelas*	13,000 (10,000-17,000) nc [a] (96h)	Static Dow Chemical, 1987	TSCAT, 1989a	1
2	*Pimephales promelas*	9,850 ac [a] (96h)	flow through	Geiger et al., 1990	2
3	*Pimephales promelas*	10,800 ac (96h)	flow through	Geiger et al., 1990	2
4	*Menidia beryllina*	6,700 nc (96h)	semi static synthetic sea water	Dawson et al., 1975/77	2
5	*Lepomis macrochirus*	> 10,000 nc (96h)	semi static	Dawson et al., 1975/77	2
6	*Oryzias latipes*	10,500 nc (48h)	semi static	Japan Chem. Ind., 1992	2
7	*Leuciscus idus*	8,450 (48h)	Static DEV-L15, 1976	Juhnke and Ludemann, 1978	2
8	*Leuciscus idus*	9,630 (48h)	Static DEV-L15, 1976	Juhnke and Ludemann, 1978	2
9	*Cyprinus carpio*	12,000 (48h)	other	Nishiushi, 1981	4
10	*Pimephales promelas*	>100 (72h)	static	Dow Chemical, cited in BUA, 1991	4
11	*Pimephales promelas*	>100 (96h)	static	Dow Chemical, cited in BUA, 1991	4

[a] ac = Actual concentration / nc = Nominal concentration
[b] Reliability index

Table 3.16 clearly shows that the acute toxicity test results for various fish species are all in the same order of magnitude.

In the HEDSET, one long-term toxicity test with fish is reported. A NOEC of >103 mg/l for *Pimephales promelas* was observed in a 32-day test based on survival as the endpoint (TSCAT, 1989a). This NOEC is recalculated from a "maximum acceptable toxicant concentration" (MATC)

according to the TGD (MATC/√2=NOEC). For *Kuhlia sandvicensis* a NOEC is reported of 20 mg/l (Hiatt et al., 1953). This value is not taken into account when deriving the $PNEC_{water}$, since the ecological importance of the endpoint of this test, schooling behaviour, is rather difficult to interpret.

3.2.1.1.2 Toxicity to aquatic invertebrates

Short-term toxicity data on freshwater invertebrates are presented in **Table 3.17**.

Table 3.17 Short-term toxicity of 1,4-dioxane to aquatic invertebrates

No.	Species	EC_{50} (mg/l)	Method	Reference	R.I.[b)]
1	*Daphnia magna*	4,700 nc [a)] (24h, immobility)	other	Bringmann and Kühn, 1977a	2
2	*Daphnia magna*	8,450 (8,040-8,880) nc [a)] (24h, immobility)	other	Bringmann and Kühn, 1982	2
3	*Ceridodaphnia dubia*	163-299 (48h)	other	Dow Chemical (TSCAT), 1989a	4

[a)] nc = Nominal concentration
[b)] Reliability index

For the *Aedes agyptii* midge larvae test a 4h-LC_{50} of 40,000 mg/l was found (Kramer et al., 1983).

In addition to the short-term data for invertebrates, a long-term static renewal test (7 days) with *Ceriodaphnia dubia* has been carried out (Springborn Laboratories Inc., 1989). A NOEC of 625 mg/l (nominal) was found in this test.

The results of the acute Ceriodaphnia test (299 and 163 mg/l for, respectively, 24h EC_{50} and 48 h EC_{50}) are not in line with the other aquatic data and the NOEC of 625 mg/l for the same species. As 1) the original test report could not be obtained and 2) no mechanistic/structural rationale could be given for the very large difference between this test result and all other available data and 3) long-term data are available for three different trophic levels, the short-term Ceriodaphnia data are not used in the derivation of the $PNEC_{water}$.

3.2.1.1.3 Toxicity to algae

No short-term toxicity data of 1,4-dioxane to aquatic algae are reported in the HEDSET. The available long-term toxicity data are presented in **Table 3.18**.

Table 3.18 Long-term toxicity of 1,4-dioxane to aquatic algae

No.	Species	NOEC (mg/l)	Method	Reference	R.I.[b)]
1	*Scenedesmus quadricauda*	5,600 nc [a)] (8d, cell multiplication inhibition)	static	Bringmann and Kühn, 1977b	2
2	*Microcystis aeruginosa*	575 nc [a)] (8d, cell multiplication inhibition)	static	Bringmann and Kühn, 1976	2

[a)] nc = Nominal concentration
[b)] Reliability index

3.2.1.1.4 Toxicity to microorganisms

In **Table 3.18** the toxicity data on 1,4-dioxane for microorganisms together with data for protozoans are presented. With the exception of the *Chilomonas paramecium* test the toxicity data for protozoans and bacteria are quite consistent.

In a short-term respiration inhibition test with sewage-sludge no effect on respiration is found up to a concentration of 2,000 mg/l (BASF information, 1979).

Table 3.19 Toxicity of 1,4-dioxane to microorganisms incl. protozoans

No.	Species	Result (mg/l)	Method	Reference	R.I.[b)]
1	*Chilomonas paramecium*	> 10,000 nc [a)] (48h NOEC, cell multiplication inhibition)	Static	Bringmann et al., 1980	2
2	*Entosiphon sulcatum*	5,340 nc (72h NOEC, cell multiplication inhibition)	static	Bringmann, 1978	2
3	*Pseudomonas fluorescens*	2,700 nc (16h NOEC, glucose assimilation inhibition)	Static modified DEV L8, 1960	Bringmann, 1973	2
4	*Pseudomonas putida*	2,700 nc (16h NOEC, cell multiplication inhibition)	static	Bringmann and Kühn, 1977b	2
5	*Uronema parduczi*	5,620 nc (20h NOEC, cell multiplication inhibition)	static	Bringmann and Kühn, 1980	2
6	*Photobacterium phosphoreum*	6,000 (EC_{50})	other direct assay (luminescence reduction)	Thomulka and McGee, 1992	4
7	*Vibrio harveyi*	16,000 (EC_{50})	other direct assay (luminescence reduction)	Thomulka and McGee, 1992	4
8	*Vibrio harveyi*	6,500 (EC_{50})	other growth assay (luminescence reduction)	Thomulka and McGee, 1992	4

[a)] nc = Nominal concentration
[b)] Reliability index

3.2.1.2 Calculation of Predicted No Effect Concentration (PNEC)

PNEC for micro-organisms

The luminescence assays will not be included in the derivation of the $PNEC_{microorganisms}$ since saltwater organisms are involved in these assays, which are irrelevant for a sewage treatment plant (STP) situation.

The test with P. putida is used for deriving the $PNEC_{microorganisms}$. According to the TGD, no assessment factor is needed when using a NOEC for P. putida.

Thus the **$PNEC_{microorganisms}$ = 2,700 mg/l.**

This PNEC is supported by short-term respiration inhibition test with sewage sludge in which no effects were found up to a concentration of 2,000 mg/l (BASF information, 1979).

PNEC for the aquatic compartment

There are three long-term test results available for 1,4-dioxane for three different trophic levels (fish, invertebrates and algae). The lowest value is the NOEC for fish of >103 mg/l. This value is indicative for the long-term toxicity of 1,4-dioxane for fish. However, as no effects were seen in this test, it is felt more appropriate to use the Mycrocystis aeruginosa NOEC of 575 mg/l for the PNEC derivation. An assessment factor of 10 (three long-term test for three trophic levels) is used, which leads to a **$PNEC_{water}$ of 57.5 mg/l.**

PNEC for sediment-dwelling organisms

Since no data on sediment-dwelling organisms are available the equilibrium partitioning method is used to derive the $PNEC_{sediment}$. The **$PNEC_{sediment}$** is calculated to be **43.3 mg/kg wwt** (EUSES).

3.2.2 Terrestrial compartment

3.2.2.1 Toxicity test results

3.2.2.1.1 Toxicity to terrestrial invertebrates

In a test with pupae of the flesh fly *Sarcophaga crassipalpis*, 5 µl dioxane is applied topically to the pupal cutical (Denlinger et al., 1980). No mortality is observed during diapause. Development and termination of the diapause is monitored based on the oxygen consumption. 32% terminated the diapause prematurely. Out of these, 56% developed normally to adult insects.

This test is not considered relevant to derive a PNEC for the terrestrial compartment.

3.2.2.1.2 Toxicity to terrestrial plants

The germination of *Lactuca sativa* is investigated during a period of 3 days. The test is conducted on agar. An EC_{50} (germination) was found at a concentration of 1,450 mg 1,4-dioxane/l (Reynolds, 1989).

This test is not considered appropriate for the derivation of the $PNEC_{terrestrial}$.

3.2.2.2 Calculation of PNEC for the terrestrial compartment

Since no relevant toxicity data for terrestrial species are available the $PNEC_{soil}$ is calculated based on equilibrium partitioning. The $PNEC_{soil}$ is calculated to be 14 mg/kg wwt (EUSES).

3.2.3 Atmosphere

No data available.

3.2.4 Secondary poisoning

No specific data available. Derivation of PNEC secondary poisoning is given in Section 3.3.4.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment (incl.sediment)

STP

The $PNEC_{microorganisms}$ for 1,4-dioxane was set at 2,700 mg/l. For the risk characterisation this value is compared with the PEC_{STP} for the various exposure scenarios. **Table 3.20** shows the PEC-values and the PEC/PNEC ratios.

Table 3.20 PEC/PNEC ratios for the STP

Life cycle stage or scenarios	PEC (mg/l) STP	PEC/PNEC
I-1/II-1 Production/processing (1)	0.194	<0.1
II-2 Processing tape (2)	n.r	n.r.
II-3 Processing (3)	24	<0.1
II-4 Processing resins (4)	n.r	n.r.
II-5 Processing glue (5)	n.r	n.r.
II-6 Processing pharma./pest. (6)	183	0.07
II-7 Processing "other uses" (6)	125	0.05
III-1 Unintentional processing (7)	0.9	<0.1
III-2 Unintentional processing (8)	0.01	<0.1
III-3 Unintentional PET production (9)	6.93	<0.1
III-4 Unintentional AES (10)	0.002	<0.1

Table 3.20 shows that all PEC/PNEC ratios are <1: **conclusion (ii)**.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Surface water

The calculated PECs in surface water are compared with the $PNEC_{water}$ of 57.5 mg/l for 1,4-dioxane. Table 3.21 shows the PEC-values and the PEC/PNEC ratios for water. In all scenarios the PEC is lower than the PNEC: **conclusion (ii)**.

Table 3.21 PEC/PNEC ratios for surface water

Life cycle stage or scenarios	PEC (mg/l) surface water	PEC/PNEC
I-1/II-1 Production/processing (1)	0.002	<0.01
II-2 Processing tape (2)	0.001	<0.01
II-3 Processing (3)	3.2	0.06
II-4 Processing resins (4)	0.001	<0.01
II-5 Processing glue (5)	0.001	<0.01
II-6 Processing pharma./pest.(6)	18.3	0.3
II-7 Processing "other uses" (6)	12.5	0.2
III-1 Unintentional processing (7)	0.09	<0.01
III-2 Unintentional processing (8)	0.002	<0.01
III-3 Unintentional PET production (9)	0.7	0.01
III-4 Unintentional AES (10)	0.001	<0.01

Sediment

There are no data for sediment-dwelling organisms and also measured data for the concentration of 1,4-dioxane in sediment are lacking. Thus a quantitative risk characterisation of 1,4-dioxane for sediment cannot be performed. However, the low adsorption potential of 1,4-dioxane suggests that sediment is most probably not a relevant compartment for the risk assessment of 1,4-dioxane.

3.3.2 Atmosphere

As no PNEC for air could be derived, no risk characterisation is carried out for the atmospheric compartment.

3.3.3 Terrestrial compartment

The calculated PECs in soil are compared with the $PNEC_{soil}$ of 14 mg/kg wwt for 1,4-dioxane. **Table 3.22** shows the PEC-values and the PEC/PNEC ratios for soil. In none of the exposure scenarios does the PEC exceed the PNEC: **conclusion (ii)**.

Table 3.22 PEC/PNEC ratios for soil

Life cycle stage or scenarios	PEC (mg/kg) terrestrial	PEC/PNEC
I-1/II-1 Production/processing (1)	$< 9.2 \cdot 10^{-4}$	<0.01
II-2 Processing tape (2)	4.10^{-3}	<0.01
II-3 Processing (3)	0.07	<0.01
II-4 Processing resins (4)	$2.6 \cdot 10^{-5}$	<0.01
II-5 Processing glue (5)	$2.1 \cdot 10^{-4}$	<0.01
II-6 Processing pharma./pest. (6)	0.5	0.04
II-7 Processing 'other uses' (6)	0.35	0.02
III-1 Unintentional processing (7)	0.003	<0.01
III-2 Unintentional processing (8)	0.005	<0.01
III-3 Unintentional PET production (9)	0.02	<0.01
III-4 Unintentional AES (10)	$8.1 \cdot 10^{-6}$	<0.01

3.3.4 Secondary poisoning

The PNEC for secondary poisoning is set at 20 mg/kg wwt. This figure is based on the oral NOAEL of 10 mg/kg bw/d (see Section 4) in combination with a conversion factor of 20 (NOAEL to NOEC) and an assessment factor of 10. In all exposure scenarios the PEC/PNEC ratios for both worm and fish eating birds or mammals are <0.1: **conclusion (ii).**

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

The human population can be exposed to 1,4-dioxane at the workplace, from the use of consumer products and indirectly via the environment.

1,4-Dioxane is a colourless liquid substance used as a solvent, a stabiliser or an extractant. It is soluble in water and almost all organic solvents. Exposure to 1,4-dioxane at the workplace occurs most likely via the skin and the respiratory tract.

The substance is hygroscopic and forms peroxides, acetaldehyde, ethylene acetal and acidic materials when it comes in contact with the air (NIOSH, 1977).

1,4-Dioxane is produced by one company (Company A), with the following purposes:

- Solvent in a wide variety of uses such as the production of lacquers, varnishes, cleaning and detergent preparations, adhesives, cosmetics, deodorant fumigants, emulsions and polishing compositions, pulping of wood, extraction medium for animal and vegetable oils, laboratory chemical (eluent in chromatography), cassettes, plastic and rubber, and insecticides and herbicides (Company A, 1997; HSDB, 1996; Grant Chemicals, 1977); in many cases 1,4-dioxane will not be present in the end-product, but is only used as a solvent in the production process.
- Stabiliser in 1,1,1-trichloroethane; this use has diminished considerably as a result of the restriction of the use of substances depleting the ozone layer (Grant Chemicals, 1977);
- Part of a catalyst, for example in vinyl chloride polymerisation of polyvinyl chloride.

It is not completely clear to what extent 1,4-dioxane is presently used as a solvent in end-products.

4.1.1.2 Occupational exposure

Occupational exposure can occur during the production, in the formulation industry, and during the use of the substance. Since there is no detailed information regarding the formulation of several products containing 1,4-dioxane, this is considered in one scenario. The substance is mostly used as a solvent extractant in the pharmaceutical industry. It was also used as a stabiliser of organic solvents. However this use should be discontinued because of the ban of solvents with chlorinated hydrocarbons. It is used as a solvent in lacquers and varnishes, cleaning agents, disinfectants, in cassette production, and as an auxiliary material in textiles. The substance is also used as an eluent in chromatography.

The following data are used for occupational exposure assessment:

- Physico-chemical data of 1,4-dioxane and, when available, of products containing 1,4-dioxane;
- Data regarding production processes of the substance and products containing 1,4-dioxane;
- Temperatures at which production processes take place;
- Amount of 1,4-dioxane used in the products;
- Data regarding use pattern of the products;
- Data from product registers provided by countries of the EU;
- Data from several exposure databases provided by countries of the EU;
- Data from the literature (open and grey) regarding exposure to 1,4-dioxane or analogues.
- Results from models (EASE model).

The exposure is assessed using the available information on substance, processes and work tasks. More detailed information on these parameters may lead to a more accurate exposure assessment.

In this part of the assessment, external (potential) exposure is assessed using relevant models and other available methods in accordance with the Technical Guidance Document (TGD 96) and agreements made at official Meetings of Competent Authorities. Internal dose depends on external exposure and the percentage of the substance that is absorbed (either through the skin or through the respiratory system).

The exposure is assessed without taking account of the possible influence of personal protective equipment (PPE). If the assessment, as based on potential exposure, indicates that risks are to be expected, the use of PPE may be one of the methods to decrease actual risks, although other methods (technical and organisational) are to be preferred. This is in fact obligatory following harmonised European legislation.

Knowledge of effectiveness of PPE in practical situations is very limited. Furthermore, the effectiveness is largely dependent on site-specific aspects of management, procedures and training of workers. A reasonably effective use of proper PPE for skin exposure is tentatively assumed to reduce the external exposure by 85%. For respiratory protection the efficiency depends largely on the type of protection used. Without specific information, a reduction efficiency of 90% will be assumed, equivalent to the assigned protection factors for supplied-air respirators with a half mask in negative pressure mode (NIOSH, 1987). Better protection devices will lead to higher protection. Imperfect use of the respiratory protection will lower the practical protection factor compared to the assigned factor. These estimations of reduction are not generally applicable “reasonable worst-case” estimations, but indicative values based on very limited data. Furthermore, this reduction of external exposure does not necessarily reflect the reduction of absorbed dose. It has to be noted, that the use of PPE can result in a relatively increased absorption through the skin (effect of occlusion), even if the skin exposure is decreased. This effect is very substance-specific. Therefore, in risk assessment it is not possible to use default factors for reduction of exposure as a result of the use of PPE.

In some specific situations a preliminary assessment of the possible influence of PPE on exposure will be made. This regards situations in which the failure to use adequate protective equipment properly will often lead to acute adverse effects on the worker. Examples of such situations are manual handling of very corrosive substances and handling materials with high temperatures.

There is only limited information about processes regarding the production of the products containing 1,4-dioxane. The same holds for the concentration of the substance in the products containing 1,4-dioxane.

In a publication of Petrelli et al. (1993), it was mentioned that 1,4-dioxane could occur as a solvent in pesticides together with cyclohexanol and 2-nitropropane. The concentration of 1,4-dioxane and cyclohexanol was mentioned to be 80%, the concentration of 1,4-dioxane with 2-nitropropane was mentioned to be 5%. Company A (1997) mentioned that when 1,4-dioxane is used as a solvent, the concentration of the substance varies from 10-40%.

Denmark, Sweden and Finland provided information from their product registers. In Denmark the substance was found in 120 products, mainly solvents and cleaning agents. The concentration of the substance in the product varies from 0 to 100%. In 17 of the found products, the concentration of the substance is between 10 and 100% (10 products contain a concentration of 1,4-dioxane between 80 and 100%). The majority of the products contain a minor concentration of 1,4-dioxane (71 products contain 0-1% 1,4-dioxane) (PROBAS, 1996).

In Finland the substance occurs in 5 products (4 solvents and 1 primer). The concentration of the substance in the solvents ranges from 0.1-100%, while the concentration of the substance in the primer was in the range of 1-5% (FEI, 1996). In Sweden the substance is found in 15 products. The Swedish product register (KEMI, 1996) did not provide concentrations of the substance in the formulations.

Company B provided information in which it was stated that 1,4-dioxane was used as a stabiliser in 1,1,1-trichloroethane at 3 to 4%. Since 1995, 1,1,1-trichloroethane may not be used anymore, as it is listed on the Montreal protocol for ozone depletion. This substance is a solvent mainly used in metal degreasing operations as a cold cleaner.

From the above it can be concluded that the concentration of the substance in the products used varies considerably.

Exposure to 1,4-dioxane can occur during production and use of the substance. The most important uses of 1,4-dioxane are considered in the exposure scenarios. Since there is hardly any information regarding the formulation of products containing 1,4-dioxane, this activity is summarised in one scenario.

The following exposure scenarios are considered:

- Scenario 1: production of 1,4-dioxane;
- Scenario 2: formulation of 1,4-dioxane in a product;
- Scenario 3: use of 1,4-dioxane or the product containing 1,4-dioxane.

In this report a general description of the scenario will be given, including measured data, followed by an exposure assessment by modelling for each scenario.

4.1.1.2.1 Occupational exposure from production of 1,4-dioxane (scenario 1)

The substance is produced in the EU by one company (Company A). The manufacturing occurs by dehydration and ring closure of diethylene glycol. Process temperature varies from 130-200°C, under atmospheric pressure (BUA, 1992; Grant Chemicals, 1977). The process is continuous, with dioxane vaporising from the reaction vessel. The vapours are passed through acid trap distillation columns to remove water and to purify the product. Drumming is performed

under nitrogen blanketing using a vapour recovery system. Nitrogen is used to prevent peroxide forming (Locher, 1984). 1,4-Dioxane is hygroscopic and forms peroxides, acetaldehyde, ethylene acetal and acidic materials when it comes in contact with air. Exposure is possible as a result of "breathing" of the system, during quality control sampling, drumming and maintenance. The majority of the dioxane is transported for further processing (Company A, Grant Chemicals, 1977; NIOSH, 1977). Further processing of the substance in company A is considered, when this is performed in a closed system. This will probably lead to a similar or a less high exposure.

Exposure data

There are data available on inhalation exposure during the production of dioxane. Exposure data from company A, from the Finnish Environmental Institute, and from some publications were used. The exposure data are summarised in **Table 4.1**. Exposure measurements from Company A have been presented in two sets, one set covering a period from 1979 to 1996 and a more recent set, covering a period of 1993-1998.

Table 4.1 Exposure data during the production of 1,4-dioxane

Substance	Industries or tasks/activities	n	Exposure levels (mg/m^3)			
			range	arithmetic average	90th percentile	Reference
1,4-dioxane [a)]	syntheses (closed system) storage/drumming pilot plant waste disposal laboratory repairing/maintenance	59 37 264 35 305 10	<0.004-1.3 <0.07-576 0-173 0.036-43 0-166 <0.036-4.7	0.18 [b)] 0.07 [b)] 2.6 [b)] 0.07 [b)] 0.11 [b)] 0.72	0.9 40 47 0.4 0.6	Company A, 1997 full shift personal samples (1979-1996)
1,4-dioxane	syntheses (closed system) storage/drumming pilot plant waste disposal laboratory repairing/maintenance	18 8 52 2 29 -	<0.007-1.14 0.07-12 0.07-30 0.15-4.7 <0.07-0.18 -	0.08 [b)] 0.10 [b)] 0.18 [b)] < 0.07 [b)] -	1.1 10 4.8 0.15	Company A, 1998 full shift personal samples (1993-1998)
1,4-dioxane	dioxane plant, no activities described	1 5 4 5 5		3.6 5.8 ± 1.8 [c)] 7.2 ± 3.6[c] 6.6 ± 1.4 [c)] 4.1 ± 2.2 [c)]		Young et al., 1976 full shift (7.5 hr) personal samples[d]
1,4-dioxane	dioxane production plant	26	0.02-26 [e)]			Thiess et al., 1976 no duration given
1,4-dioxane	production and drumming (personal) (stationary samples) point sources 3 manufacturers (1974-1975) around storage tanks (1968)	 30 44 15 n.g. 2	 0.1-26 2.1-2.7 0.4-85 360, 2,880	 43 15 166 3.9 3.24 23		NIOSH, 1977 [f)] no duration given

[a)] Laboratory work concerns both quality control and use as a solvent in laboratories; [b)] Median; [c)] Arithmetic average ± sd

[d)] In the study of Young et al. (1976), it was mentioned that exposure was measured over a certain period of time; it was however not stated, how many times the exposure was measured;

[e)] Not given during what circumstances exposure measurements were performed; they all concerned stationary samples, in *e.g.* the vicinity of a reaction vessel, during cleaning and maintenance, near leaks in the system and during drumming;

[f)] No duration of measurements given; n.g. = Not given.

To derive an exposure value, personal samples are the most relevant. The stationary measurements can only serve as an indication. Since the available exposure data are not of optimum quality (duration of exposure, division of activities is ambiguous), exposure models are also used (for comparison). The estimations made by the exposure models are discussed in the following paragraph.

Exposure assessment with models

Production of 1,4-dioxane takes place at elevated temperatures (130-200°C) in a closed system. Exposure is mainly possible due to quality control sampling and drumming of the substance.

Cleaning and maintenance is considered separately.

Exposure during the production itself is assumed to be possible due to "breathing" of the system. Concentrations are assumed to be low. Assuming no aerosol formation, a closed system, and no breaching with full containment an exposure of 0-0.1 ppm (≈0-0.4 mg/m^3) is estimated.

It is assumed that the dermal exposure during the production (excluding quality control sampling, drumming and other possible breaching of the system) can be neglected.

Quality control sampling occurs only incidentally. EASE estimates an inhalation exposure of 10-50 ppm (≈36-180 mg/m^3) when it is assumed that this activity is performed at room temperature, with non-dispersive use and LEV.

Dermal exposure during quality control sampling is assumed to concern non-dispersive use, direct handling and incidental contact. This results in a dermal exposure of 0-0.1 mg/cm^2/day. When it is furthermore assumed that the half of one hand is exposed (210 cm^2), a total dermal exposure of 21 mg/day is derived.

Drumming is performed via a transfer line under nitrogen blanketing using a vapour recovery system. This method of drumming can diminish the exposure considerably. Inhalation and dermal exposure can occur as a result of connecting and disconnecting the transfer line, and as a result of leakages of the system (Locher, 1984). EASE estimates an inhalation exposure of 10-50 ppm (≈36-180 mg/m^3), assuming non-dispersive use, in the presence of LEV. Drumming is done by other workers at a location different from the other exposure activities.

Dermal exposure occurs mainly during connecting and disconnecting of the transfer line. When non-dispersive use, direct handling and incidental contact is assumed a dermal exposure of 0-0.1 mg/cm^2/day is estimated. When it is furthermore assumed that the half of both hands could be exposed (420 cm^2) a total dermal exposure of 42 mg/day is estimated.

Exposure data for cleaning and maintenance

Industry reports that before opening of the system, the system is flushed with large amounts of water, and the concentration is checked with a general organic vapour monitor. If organic vapours are not detectable, the system can be opened (Industry, 1998). Ten measured inhalation exposure levels related to cleaning and maintenance were reported by Industry, with a maximum of 4.7 mg/m^3 (Company A, 1997).

One study was found in which dermal exposure was measured (for another substance) during maintenance activities.

A study submitted to EPA by a manufacturer for premanufacture notification (PMN) review has included some dermal exposure data on trichloroketone (TCK). For the study six maintenance workers were chosen (Anonymous, 1996). Two types of maintenance mechanics were distinguished: mechanics responsible for calibrating and maintaining process instruments and electrical equipment components/controls and mechanics responsible for mechanical equipment and pipefitting type activities, including installation/repair of pumps, compressors, flanges and other process equipment. Prior to maintenance activities, all process lines were flushed and blocked out. During the maintenance activities nitrile protective gloves and protective coveralls were worn.

Both protected and unprotected exposure was measured. Unprotected exposure was measured by analysis of the nitrile gloves and the protective clothing, protected exposure was measured by analysis of the inner cotton gloves worn beneath the nitrile gloves and full body cotton underwear worn beneath the protective clothing. The total daily unprotected exposure ranged from 0.0081 to 505.4 mg, with an average of 163.5 mg. The total protected dermal exposure ranged from 0.0098 to 0.241 mg, with an average of 0.080 mg. The major part of the exposure was found on the "hands" (being the nitrile gloves with a surface area of 1,000-1,260 cm^2): more than 99% of the potential exposure of the two highest exposed workers. The protection afforded in this study by the protective gloves was very high (more than 99,9% for the two workers with the highest potential exposure.

Exposure assessment with models for cleaning and maintenance

The system is flushed with large amounts of water before opening. The remaining concentration after flushing is stated by industry to be very low, but is unknown. Based on the measured data for inhalation exposure and on the fact that 1,4-dioxane is highly soluble in water, it is expected that the concentration is no more than 1%. EASE estimates an exposure of 10-50 ppm (≈36-180 mg/m^3), assuming a partial vapour pressure of 0.04 kPa (1% of 4 kPa), non-dispersive use and direct handling in the presence of dilution ventilation.

For dermal exposure assessment the option of use pattern does not have any relation with the process of dermal exposure. While the possibility of transport through the air (dispersion) is very important in inhalation exposure assessment, the possibility of direct contact is much more important for the dermal exposure assessment. The process of cleaning and maintenance is expected to possibly lead to extensive contact with contamination. Industry reports that only carefully trained workers are involved in cleaning and maintenance. Therefore, the option of non-dispersive use is chosen for use pattern.

Dermal exposure during cleaning and maintenance is therefore estimated as 1-5 $mg/cm^2/day$, assuming non-dispersive use, direct handling and extensive contact. When it is furthermore assumed that the fraction of the substance handled is 1% and both hands and a part of the forearms could be exposed (≈1,300 cm^2, comparable to the surface areas of the protective gloves in the TCK study), a total dermal exposure of 65 mg/day is estimated.

Conclusion

There are several groups of exposed workers: those involved in actual production, quality control sampling and tank car filling, those involved in drumming and those involved in cleaning and maintenance. There are also several locations, e.g. the normal production location, the drumming facility and the pilot plant. The exposure during the major part of the production process is assumed to be 0.4 mg/m^3, this exposure could occur full shift. The exposure during

quality control sampling and drumming is assumed to be higher. The duration of quality control sampling is assumed to be rather short, and actual drumming is expected to be up to 4 hours a day.

Considering the 90 percentile values of full-shift exposure measured in the pilot plant and for drumming, and considering the highly skewed distribution of the older data for drumming, the reasonable worst-case exposure is estimated to be 10 mg/m^3. The typical exposure values presented by industry are generally up to 0.2 mg/m^3. Short-term exposure levels have not been measured. Based on the highest full shift exposure levels it is estimated that reasonable worst-case short-term exposure levels may be up to 150 mg/ m^3.

Dermal exposure for workers exposed due to drumming is estimated to be 42 mg/day.

Cleaning and maintenance are assumed to be performed by other workers. Company A (1997) performed some measurements during repair and maintenance activities. The exposure of these workers varied from 0-4.7 mg/m^3, with a mean of 0.72 mg/m^3, the 90 percentile value was not given. Thiess et al. (1976) measured a concentration of 14 mg/m^3 during cleaning of the distillation vessel. Considering the limited number of measured values, the low concentration of 1,4-dioxane to be expected after flushing with water and the estimate made by EASE, inhalation exposure (reasonable worst case) is assessed as 10 mg/m^3. The typical exposure is estimated as 5 mg/m^3, based on the measured data of Company A (1997). It is assumed that this activity could be full shift, though on a limited number of days. The frequency of exposure is estimated to be up to 25 days a year.

When the measured dermal exposure data for the other substance are compared with the assessment made by EASE, it is concluded that the measured data for TCK are substantially higher, than the data estimated by EASE. The result of the EASE model will be taken forward to the risk characterisation, because of the expected very high effectiveness of flushing and the fact that workers are all well-trained. The measured data show that the exposure can be lowered substantially by the use of protective clothing, but that actual exposure is still possible.

Dermal exposure during all activities could be less, due to evaporation of 1,4-dioxane from the skin. The estimated value is therefore probably an overestimation. However, the amount evaporated cannot be estimated.

4.1.1.2.2 Occupational exposure from formulation of products containing 1,4-dioxane (scenario 2)

There is hardly any information provided regarding formulation of products containing 1,4-dioxane. The activities performed during formulating a product are assumed to be adding of the substance to a mixture, mixing and finally drumming or bagging of the product. In case of 1,4-dioxane the highest exposure probably occurs during adding of the substance and drumming of the product.

Company A indicated that the concentration of 1,4-dioxane in solvents varies from 10-40%.

Exposure data

No exposure data during formulation of products containing 1,4-dioxane are available. However, there are data available on the use of a product in which the activities, performed with that product, are similar to the activities performed in formulation (in which the pure substance is

used). Company A (1997) performed exposure measurements during the manufacturing of magnetic tapes. The activities performed during the manufacturing of magnetic tapes are: formulation of dispersions, cleaning activities, research in the laboratory and waste treatment. The data are given in **Table 4.3** (scenario 3). The solvents used in the manufacturing of magnetic tapes contain up to 40% of 1,4-dioxane, while during formulation of products the pure substance is used (Company A, 1997). Therefore higher exposures could occur during formulation activities with the pure substance.

Due to the fact that there are only exposure data from one facility, the exposure is also assessed by modelling.

Exposure assessment with models

Inhalation and dermal exposure can occur during formulation and drumming of paints, lacquers, and cleaning agents and during the formulation of plastics. The formulation of paints, lacquers and cleaning agents is performed at room temperature, while the production of plastics is generally done at approximately 240°C (Eijssen et al., 1993). The mixing process during plastic manufacturing is assumed to be done in a closed system, while mixing of paints, lacquers and cleaning agents often occurs in an open system.

Adding of 1,4-dioxane is assumed to be performed at room temperature for formulating all products. Mixing of plastics is assumed to be performed in a closed system. Mixing of paint and lacquers on the other hand, often occurs in an open system. The same holds for drumming of lacquers and paints.

Estimates of inhalation exposure for these situations are presented in **Table 4.2**.

Table 4.2 Estimates of exposure, using EASE, for formulation of products containing 1,4-dioxane

Exposure situation	Use pattern	LEV (yes/no)	Percentage of substance	Estimated exposure level (ppm)	Estimated exposure level (mg/m³)
Adding dioxane	non-dispersive	yes	100	10-50	37-180
Mixing plastics	closed system			0-0.1	0-0.4
Mixing/drumming (paints, lacquers, cleaning agents)	non-dispersive	yes	40 [a)]	10-50	37-180

[a)] An estimated partial vapour pressure of 1.6 kPa (40% of 4 kPa) is used. The percentage may be too high for paints, lacquers and cleaning agents.

Dermal exposure mostly occurs during adding of the substance to the mixer and during drumming or bagging of the product. A dermal exposure of 0.1-1 mg/cm^2/day is estimated, assuming non-dispersive use, direct handling and intermittent contact. When it is furthermore assumed that the half of both hands could be exposed (420 cm^2), a total exposure due to hand contact is calculated as 420 mg/day.

Dermal exposure during actual mixing is assumed to be negligible, since hardly any contact will occur.

Conclusion

When the exposure data are compared with the estimates made by EASE, and considering the fact that the exposure data during the manufacturing of magnetic tapes does not concern the handling of pure 1,4- dioxane, it can be concluded that the estimated exposure in the presence of LEV agrees reasonably well with the measured values.

The reasonable worst-case estimate during this activity is assumed to be 180 mg/m^3 (upper limit of assessment in the presence of LEV).

The typical value is assessed as 40 mg/m^3, based on measured exposure levels and the lower limit of the estimate made by EASE. Since it is assumed that adding of 1,4-dioxane, drumming of the product and mixing is performed by the same workers, exposure during these activities could occur full shift. Short-term exposure is estimated to be up to twice the full shift exposure (360 mg/m^3, expert judgement).

The dermal exposure is estimated to be 420 mg/day.

Dermal exposure could be less, due to evaporation of 1,4-dioxane from the skin. The estimated value, is therefore probably an overestimation. The amount evaporated can, however, not be estimated.

4.1.1.2.3 Occupational exposure from end-use of 1,4-dioxane or of the product containing 1,4-dioxane (scenario 3)

The end-uses of the substance can be divided into the use of the pure substance or the use of solvents containing 1,4-dioxane in for example laboratories, the pharmaceutical industry and the manufacture of magnetic tapes, and the use of products containing 1,4-dioxane, such as cleaning agents, paints, lacquers and varnishes.

Exposure data

Some exposure data are available for this exposure scenario. The Finnish Environmental Institute (FEI, 1996) provided some exposure data during the use of 1,4-dioxane in a cleaning agent, during the use in a laboratory (probably as the mobile phase in HPLC), and during medicine manufacturing (as an extractant). Company A (1997/1998) provided exposure data during the use of the substance in a laboratory, in the pharmaceutical industry and in the manufacture of cassettes. The measured exposure data are given in **Table 4.3**.

Table 4.3 Exposure data during the use of the substance

Substance	Industries or tasks	n	Exposure levels (mg/m³) full shift			Reference
			Range	Arithmetic average	90th percentile	
1,4-dioxane	Metal cleaning surface Laboratory work Medicine manufacture	4 1 20	15-55 165 1.8-18	31 6.5		FEI, 1996 a) fixed and personal samples
1,4-dioxane	Shirt cleaning area, textile industry	2 3	0.7-1.8 < limit of detection c)	1.1 b)		Kullman, 1989 personal samples
1,4-dioxane	Pharmaceutical production Manufacture of magnetic tapes	<30 >100	<3.6	 37-75 d)		Company A; 1997 personal samples
1,4-dioxane	Laboratory Use (e.g. as solvent) in other productions	305 194	0-166 <0.01-184	0.11 e) 0.11 e)	0.58 1.8	Company A; 1997 personal samples (1979-1996)
1,4-dioxane	Laboratory Use (e.g. as solvent) in other productions	29 49	<0.07-0.18 <0.04-7.2	<0.07 e) 0.07 e)	0.15 0.62	Company A; 1998 personal samples (1993-1998)

a) 12 personal and 13 fixed point samples, 14 measurements or activities (?) were performed continually, the other measurements were performed intermittently; there was, however, no distinction made; mean duration was 46 minutes, with a range of 10 to 100 minutes; in all situations dilution ventilation was present.
b) Measurements performed during the winter period, in which the windows and doors remained closed.
c) Measurements performed in the summer period, in which the doors and windows were open, it was not given in what concentration the substance occurred in the cleaning agent.
d) These were reported to be "typical values".
e) These were medians.

1,4-Dioxane can be used as a stabiliser in concentrations of 3-4% in 1,1,1-trichloroethane (Company B, 1996). This was used as a cleaning agent for metals. Its use is prohibited since 1995, as a result of the agreement in Montreal from 1994 which dealt with the handling of substances depleting the ozone layer (EU, 1994). The University of Louvain, Belgium has made 179 measurements on 1,4-dioxane over the period 1985-1996 in industries in which cleaning/degreasing, painting and the use of adhesives was done. The range of measured concentrations was 0.9-302.4 mg/m^3, with a 90th percentile of 40 mg/m^3. In 97.8% of the samples, also 1,1,1-trichloroethane was present and the correlation between the concentration of the two substances in the samples was r = 0.8. It is therefore concluded, that these data relate to the use of 1,4-dioxane as a stabiliser for 1,1,1-trichloroethane and that these data are not relevant for the present occupational exposure situation (Belgium, 1998). The FEI (1996) provided data on exposure to 1,4-dioxane due to the use of cleaning agents. No details are known of the exact composition of these cleaning agents. It is possible that the data from FEI refer to cleaning agents containing chlorinated hydrocarbons that are no longer in use.

Exposure assessment with models

Several estimates can be made using EASE:

- Use of products containing 1,4-dioxane (*e.g.* cleaning agents, lacquers and paints);
- Use of the pure substance in for example the manufacturing of medicines (extractant) and in laboratories (as the mobile phase in HPLC technique).

Use of the products containing the substance

The most important functions of 1,4-dioxane in products used to be those of a stabiliser in cleaning agents and a solvent in lacquers and paints. It is not clear whether 1,4-dioxane is also an ingredient of cleaning agents without chlorinated hydrocarbons. In the Swedish product register (KEMI, 1996) it is given that the paints and varnishes are used in the industry for precision and optical instruments, watches and clocks. Paint baths are probably the most important coating technique in these industries.

The highest inhalation exposure will probably occur when it is used as a cleaning agent in the metal industry. When it is assumed that cleaning agents contain up to 10% of the substance (expert judgement), EASE assesses an inhalation exposure of 10-50 ppm (≈36-180 mg/m^3) or 50-100 ppm (180-360 mg/m^3). In this assessment the following assumptions were made: non-dispersive use, direct handling with or without LEV.

Dermal exposure during this activity is assessed as 5-15 mg/cm^2/day, assuming wide-dispersive use, direct handling and extensive contact. When it is furthermore assumed that both hands could be exposed (840 cm^2), and it is considered that the product contains 10% of the substance, a total daily dermal exposure of 420-1,260 mg/day is estimated. These assessments are not valid if 1,4-dioxane is not used in cleaning agents.

For the use of 1,4-dioxane in paints and varnishes in the precision instruments industry the following estimates are made for inhalation exposure:

- Paint containing up to 10% of 1,4-dioxane;
- Partial vapour pressure ≈0.4 KPa;
- No aerosol formation;
- Non-dispersive use and effective LEV used;
- Estimate: 0.5-3 ppm (approximately 2-11 mg/m^3).

Dermal exposure in this use is possible due to filling of the painting machine or bath. This is expected to be small scale liquid handling, non-dispersive use with incidental contact of one hand (approximately 420 cm^2), resulting in an exposure level of up to 4 mg/day ($0.1 \cdot 420 \cdot 0.1$).

Use of the pure substance

In the laboratory, exposure to 1,4-dioxane mainly occurs when the mobile phase is prepared (adding of 1,4-dioxane) and when the solution is degassed with helium, nitrogen or in an ultrasonic bath. In several publications it is described that 1,4-dioxane is used as the mobile phase in HPLC (Kleef et al., 1993; Novakovic et al., 1990; Oshima et al., 1990). In the study of Oshima, it was mentioned that the concentration of 1,4-dioxane in the mobile phase was 25%. This indicates that the concentration of dioxane can be relatively high. When this aspect is taken into account the following exposure can be estimated: 200-500 ppm (730-1,800 mg/m^3), assuming non-dispersive use, direct handling, without dilution ventilation, and a concentration of 1,4-dioxane of 50% (partial vapour pressure of 1,4-dioxane is calculated as 2 kPa, 50% of 4 kPa). When dilution ventilation is taken into account a concentration of 100-200 ppm is assessed (360-730 mg/m^3). When the concentration of 1,4-dioxane in the mobile phase is less than 38%, the exposure is estimated as 10-50 ppm (≈37-180 mg/m^3, same assumptions in the presence of LEV), or 50-100 ppm (≈180-366 mg/m^3; without dilution ventilation). During degassing, the exposure is estimated to be above the 1,000 ppm (3,600 mg/m^3). In this estimate aerosol formation, non-dispersive use without dilution ventilation is assumed. When in this assessment

the presence of dilution ventilation is assumed, a concentration of 200-500 ppm (730-1,800 mg/m^3) is estimated. When the concentration 1,4-dioxane in the mobile phase is less than 38%, the concentration is estimated as 200-500 (≈730-1,800 mg/m^3; vp moderate, without dilution ventilation) or 100-200 ppm (≈365-730 mg/m^3; vp moderate, with dilution ventilation). Especially the latter are short-term exposure levels, since the duration of degassing is up to 15 minutes (expert judgement).

Dermal exposure during this activity is assumed to concern non-dispersive use, direct handling and intermittent contact. This results in an exposure of 0.1-1 mg/cm^2/day. When an exposed area of one hand is assumed (420 cm^2) a total dermal exposure of 420 mg/day is estimated.

During the manufacture of medicines, 1,4-dioxane is mainly used as an extractant. It is assumed that an extractant is used in a more or less closed system, which can be breached. When these assumptions are used in EASE together with the assumption that LEV is present, an inhalation exposure of 10-50 ppm (36-180 mg/m^3) is estimated.

Dermal exposure during this activity is assumed to occur incidentally, due to contact with contaminated surfaces. A dermal exposure of 0-0.1 mg/cm^2/day is estimated, assuming non-dispersive use, direct handling and incidental contact. When it is furthermore assumed that the half of both hands (420 cm^2) could be exposed a total exposure due to skin contact of 42 mg/day is assessed.

Conclusion

A distinction will be made between the exposure due to the use of products containing 1,4-dioxane and the use of the pure substance.

Use of products

For the use of products containing 1,4-dioxane the conclusion depends on whether the substance is still used as a component of cleaning agents for metal surfaces. Assuming this is still the case, the following conclusion is reached. When the exposure measurements are compared with the estimated exposure levels, it appears that EASE overestimates the exposure. A typical exposure is assessed as 15 mg/m^3, based on the measured exposure data. The reasonable worst-case estimate used for the risk assessment is 50 mg/m^3, based on the highest exposure measured during cleaning of metal surfaces. It is assumed that the exposure during use of the substance could be full shift. Short-term exposure would be expected to be up to three times the reasonable worst-case exposure level: 150 mg/m^3 (expert judgement). Dermal exposure during this activity is assessed as 1,260 mg/day.

Assuming that the substance is only used in paints and varnishes for precision instruments, the only source of data is the EASE model, resulting for inhalation exposure in a reasonable worst-case full-shift exposure level of approximately 11 mg/m^3, a typical exposure level of 2 mg/m^3 and a short-term exposure of 33 mg/m^3 (three times the reasonable worst-case level; expert judgement). Dermal exposure in this process is expected to be up to 4 mg/day.

Use of the pure substance

For the use of the pure substance the conclusion is different. The short-term exposure is supposed to be highest during the use in the laboratory, this is more or less confirmed by the exposure measurements. Considering the exposure data (exposure between 0 and 166 mg/m^3, with a median of 0.11 mg/m^3) it appears that 166 mg/m^3 is an outlier. This concentration will

therefore be used as the short-term peak level, which will occur during degassing of the HPLC fluid. This exposure could occur during 15 minutes per day. The frequency of this exposure will be less than that for other activities. Considering the exposure data, it appears that EASE overestimates the exposure considerably, probably because the activities with open systems are short-term activities. Based on the measured exposure data a typical value of 5 mg/m^3 is estimated (full shift). The reasonable worst-case exposure is assessed as 20 mg/m^3, which is mainly based on the highest exposure level during the manufacturing of medicines (also full shift).

Dermal exposure during the use of the pure substance is assessed as 420 mg/day.

Dermal exposure during all activities could be less, due to evaporation of 1,4-dioxane from the skin. The estimated value is therefore probably an overestimation. However, the amount evaporated cannot be estimated.

4.1.1.2.4 Summary of occupational exposure

The overall conclusions on occupational exposure are presented in **Table 4.4.**

Table 4.4 Conclusion of the exposure assessment

Scenario	Activity	Frequency	Duration	Reasonable worst case		Typical concentration		Dermal	
		(days/year)	(hr)	(mg/m^3)	method	(mg/m^3)	method	$mg/cm^2/day$	dose (mg/day)
Production	full shift *	225	6-8	10	measured	0.2	measured	0.1-1	42 **
	short-term	225	0-0.5	150	measured, exp.				
	cl.& m.	up to 25	6-8	10	measured, exp.	5	EASE	1.5	65
Formulation	full shift	225	6-8	180	EASE, exp.	40	EASE, exp.	1	420
	short term			360					
End-use [a)]	Use of products								
	- cleaning agent	225	6-8	50	measured, exp.	15	measured, exp.	1.5	1,260
	short-term	225	0-0.5	150	measured, exp.				
	- paint	225	6-8	11	EASE	2	EASE	0.01	4
	short-term	225	0-0.5	33	EASE, exp.				
	use of substance	100-200	6-8	20	measured	5	measured, exp.	1	420
	- degassing		0.25	166					
	- full shift		8	25 ***	calculated				

* The inhalation exposure levels are for the highest subgroups in production (pilot plant and drumming).

** The dermal exposure level is for connecting a transfer line in the process of drumming.

*** The full shift level is calculated with the following equation: $(0.25 \cdot 166 + 7.75 \cdot 20) / 8 \approx 25$.

a) It is not clear whether the use of 1,4-dioxane in cleaning agents is still a relevant use.

4.1.1.3 Consumer exposure

4.1.1.3.1 Intentional use

From the deliberate use of 1,4-dioxane as a solvent/reagent in a wide range of applications (see Section 4.1.1.1), it is difficult to predict direct consumer use. Uses in products like lacquers, varnishes, cleaning and detergent preparations, adhesives, cosmetics, and deodorant fumigants may be applicable to consumers. However, in many cases 1,4-dioxane will not be present in the end-product.

The exposure information provided by several countries did not mention any of the above mentioned uses of dioxane-containing products by consumers. Denmark, Sweden and Finland provided information from their product registers (see also Section 4.1.1.2). The substance was found in several products mainly solvents and cleaning agents. Real consumer use of these products could however not be identified, only the Swedish product register stated that one product, a sealing compound, was available to consumers.

As there is low potential for consumer exposure from the deliberate use of 1,4-dioxane, consumer exposure is likely to be negligible.

4.1.1.3.2 Unintentional formation

1,4-Dioxane can occur as impurity in other materials, as it is formed as a reaction by-product in the manufacture of ethoxylated substances (particularly surfactants and emulsifiers). These substances are used in food, cosmetic, agricultural and veterinary, therapeutic, household and varied industrial applications. A survey undertaken by NICNAS indicated indeed widespread public exposure to 1,4-dioxane from a variety of consumer products including cosmetics/toiletries, household detergents, pharmaceuticals, foods, agricultural and veterinary products, and ethylene glycol-based antifreeze coolants (NICNAS, 1998).

From the limited quantitative data available on 1,4-dioxane levels in pharmaceuticals (100-380 ppm), agricultural and veterinary products (<<10 ppm), and ethylene glycol-based antifreeze coolants (0.1-22 ppm), and taking into account the use pattern and volatility, it was concluded by NICNAS that consumer exposure from these sources would be negligible (NICNAS, 1998). This is also true for consumer exposure to foods, in which 1,4-dioxane occurs either naturally or as an impurity (<10 ppm) from a number of permitted ethoxylated food additives, such as polysorbates (NICNAS, 1998). 1,4-Dioxane has been identified in a number of natural products including shrimp, chicken, tomatoes, coffee and certain condiments (Hartung, 1989). Although no data are available on the level of 1,4-dioxane in these natural products, it is expected to be low.

The main potential consumer exposure results from exposure to cosmetics/toiletries and household detergents. Several measured data are available for 1,4-dioxane concentrations in cosmetic/toiletry products and a selection of these data are presented in **Table 4.5**. However, it should be noted that most of the data are at least seven years old. Since then, progress has been made in reducing the levels of dioxane in shower-gels, bubble bath products, hair-care agents and similar products that contain alkylethers as wash-active substances (BUA, 1992/1994). In Germany, the Commission for Cosmetic products therefore set a residual 1,4-dioxane content of 10 mg/kg as a value capable of being attained and a target to be aimed for (BUA, 1992/1994). It

would be helpful to have more information about the current 1,4-dioxane levels in cosmetics to verify this proposed reduction.

Table 4.5 Monitoring data for 1,4-dioxane in cosmetics/toiletries

Product type	1,4-Dioxane level (ppm) n=[..]	Reference
Shampoo	<50 [4]-300 [2]	Rümenapp and Hild, 1987
Shampoo (anti-dandruff) Shampoo Shampoo Shampoo (anti-dandruff)	10-390, n.d.- 487 n.d.-101 n.d.	Okotest, 1987 Okotest, 1987 Okotest, 1989 Okotest, 1990
Hair lotion	47-108	Scalia and Menegatti, 1991; Scalia, 1992
Bath foam	22-41	Scalia and Menegatti, 1991; Scalia, 1992
Hair lotion	47-108	Scalia and Menegatti, 1991; Scalia, 1992
Douche foam	13-358	Okotest, 1987
Shampoo & douche foam	<3 [12]-470 [1] [total=95]	Weyland and Rooselaar, 1987
Baby lotion	11	Scalia, 1992

n.d. = Not detectable

Some quantitative data are also available for 1,4-dioxane in household detergents. Rümenapp and Hild (1987) detected 1,4-dioxane in hand dishwashing products at levels ranging from <50 (n=3) to 100 ppm (n=3). Weyland and Rooselaar (1987) detected 1,4-dioxane in three hand dishwashing liquids with concentrations ranging from 29-518 ppm. In Germany 1,4-dioxane was detected in hand dishwashing liquid up to 216 mg/kg (Okotest, 1987). 1,4-Dioxane was detected in 39/270 household aerosol products in Japan (a.o. waterproofing agent, ski wax remover, car bumper cleaner) with concentrations ranging from 0.17-2.25% (Mori et al., 1992). However, these data are also rather outdated and are expected nowadays to be less, since technology had improved.

The wide range of cosmetics/toiletries used are either rinse-off or stay-on products. Based on a rather frequent exposure pattern and the high 1,4-dioxane concentrations measured, the (worst-case) consumer exposure is evaluated for shampoo (scenario I) being a representative of a rinse-off product and for baby lotion (scenario II) as a stay-on product.

For the use of household detergents as a worst-case exposure scenario hand dishwashing liquid is evaluated (scenario III).

The following data are used for the consumer exposure assessment:

- Physical chemical data of 1,4-dioxane (molecular weight, Log K_{ow}, vapour pressure at room temperature);
- Contact parameters;
- Concentration parameters (percentage of 1,4-dioxane in shampoo, baby lotion and hand dishwashing liquid);
- The results from a mathematical model (CONSEXPO, version 2; van Veen, 1997) to get an impression of the consumer exposure, as no measured exposure data are available for the use of shampoo, baby lotion and hand dishwashing liquid.

4.1.1.3.3 Consumer exposure from using shampoos (scenario I)

1,4-Dioxane may be a constituent in shampoo as a by-product from ethoxylated substances. Since the concentrations mentioned in **Table 4.5** are rather outdated, and in view of the apparent reduction measures since 1987, a 1,4-dioxane concentration of 50 mg/kg in shampoo is taken as a worst-case assumption. The exposure is considered to occur by dermal and inhalation route, and is estimated by using the contact scenario "personal care". The inhalation exposure scenario is "evaporation from mixture" (assuming that 1,4-dioxane evaporates from the shampoo) and the dermal exposure scenario is "fixed volume of product" (assuming a homogeneous diluted volume of shampoo on the skin).

The model is thought to represent a case at the upper end of normal use of the product. Variability in bodyweight and use frequency is explicitly taken into account.

Details of the parameters used and the results of the modelling are presented in Appendix A.

Result of the model

Assuming the use of the shampoo 2 - 7 times a week for 1 minute (Mennes et al., 1996) with 12 g per event, this results in an average inhalatory exposure per event of 0.013 mg/m^3. The average dermal event exposure was calculated to be low (0.03 mg/cm^3). The yearly average inhalatory exposure was 0.0576 µg/m^3, while the yearly average dermal exposure was 0.136 µg/cm^3. The total internal dose is 0.02 µg/kg bw/day (inhalation) + 0.9 µg/kg bw/day (dermal) = 0.92 µg/kg bw/day.

Remark

In case reduction measures were not taken or were not effective, it is assumed that shampoo may contain 300 mg/kg 1,4-dioxane as a very worst case. In this case, recalculation (see Appendix A) leads to an average inhalatory exposure per event of 0.0765 mg/m^3 and an average dermal event exposure of 0.18 mg/cm^3. The inhalation uptake will then be 0.125 µg/kg bw/day and the dermal uptake 5.4 µg/kg bw/day, resulting in a total internal dose of 5.53 µg/kg bw/day.

4.1.1.3.4 Consumer exposure from using baby lotions (scenario II)

When 1,4-Dioxane is found in baby lotion, the main exposure route is considered to be dermal. Inhalatory exposure is also relevant, but oral exposure is not expected. The measured concentration of 10 mg 1,4-dioxane/kg baby lotion is used as a worst-case approach. The exposure estimation is obtained using the contact scenario "personal care". For the dermal exposure the scenario "fixed volume of product" was taken. For the inhalation exposure scenario the painting model was selected because it considers elimination of 1,4-dioxane from the lotion. It can be fitted to a use different from painting by dismissing the lower layer. The person is in a way painted with lotion.

Details of the parameters used and the results of the modelling are presented in Appendix A.

Results of the model

Child

Assuming the use of the lotion once a day with 2.4 g per event and considering that the lotion remained on the skin until the next day's wash, the dermal exposure was calculated to be 12

µg/cm^3 (average event) resulting in a cumulative worst-case uptake estimate of 3.04 µg/kg bw/day. The average event inhalation exposure was low ($2.9 \cdot 10^{-5}$ mg/m^3) resulting in a cumulative worst-case uptake estimate of $1.157 \cdot 10^{-5}$ mg/kg bw/day. The total internal dose is 3.05 µg/kg bw/day.

Adult

Assuming the use of the lotion 1-2 times a day with 7.5 g/event and considering that the lotion remained on the skin until the next wash, the dermal exposure was calculated to be 0.01 mg/cm^3 (average event), resulting in a cumulative worst-case uptake estimate of 54.1 mg/year (2.277 µg/kg bw/day). The inhalation exposure was calculated to be 0.035 µg/m^3 (average event), resulting in a cumulative uptake of 0.39 mg/year ($1.64 \cdot 10^{-5}$ mg/kg bw/day). The total internal dose is 2.29 µg/kg bw/day.

4.1.1.3.5 Consumer exposure from using dishwashing liquids (scenario III)

The use of dishwashing liquid containing 1,4-dioxane results in exposure mainly via the dermal route and also via the inhalatory route. In view of the apparent reduction measures since 1987, and the rather outdated data available, the amount of 1,4-dioxane in dishwashing liquid is estimated to be 30 mg/kg. The consumer exposure is estimated using the contact scenario "washing dishes". The dermal exposure scenario is "fixed volume of product" and the inhalation scenario is "evaporation from mixture".

Details of the parameters and assumptions (taken from Weegels, 1997) and the results of the modelling are presented in Appendix A.

Results of the model

Assuming dish washing once a day for 20 minutes results in a mean event dermal exposure of 0.072 µg/cm^3 and a mean event inhalatory exposure of 0.02 mg/m^3. The dermal uptake is 0.002 µg/kg bw/day, while the inhalation uptake is 0.13 µg/kg bw/day. The total internal uptake is 0.132 µg/kg bw/day.

Remark

In case reduction measures were not taken or were not effective, dish washing liquid contains 100 mg/kg 1,4-dioxane as a very worst case. In this case, recalculation (see Appendix A) leads to a mean event dermal exposure of 1.2 µg/cm^3 and a mean event inhalatory exposure of 0.3264 mg/m^3. The dermal uptake will be 0.0347 µg/kg bw/day and the inhalation uptake 2.17 µg/kg bw/day. The total internal uptake is then 2.20 µg/kg bw/day.

4.1.1.3.6 Combined exposure from the 3 scenarios

In the worst case that the three scenarios occur, the combined total internal dose will be 0.92 + 2.29 + 0.132 = 3.342 μg/kg bw/day. As a very worst case, in case reduction measures were not taken or were not effective, the combined total internal dose will be 5.53 + 2.29 + 2.20 = 10.02 μg/kg bw/day.

4.1.1.4 Humans exposed via the environment

4.1.1.4.1 Exposure resulting from industrial emissions

1,4-Dioxane may be released to the environment through wastewater and air effluents at the sites where it is produced, processed, after use and via unintentional formation. These indirect exposure routes are taken into account in Section 3.

From the daily amounts of 1,4-dioxane released to air the EUSES model (OPS module) calculates local atmospheric concentrations. The calculated annual average 1,4-dioxane concentrations in air are presented in **Table 4.6**.

Table 4.6 Calculated local annual average concentrations in air

Life cycle stage or scenarios	PEC (μg/m³) air
I-1/II-1 Production/processing (1)	<1.5
II-2 Processing tape (2)	16
II-3 Processing (3)	12.6
II-4 Processing resins (4)	0.1
II-5 Processing glue (5)	0.9
II-6 Processing pharma./pest. (6)	38.9
II-7 Processing “other uses” (6)	2.9
III-1 Unintentional processing (7)	0.05
III-2 Unintentional processing (8)	0.04
III-3 Unintentional PET production (9)	0.5
III-4 Unintentional AES (10)	0.01

The total human intake via air, drinking water and food for all emission scenarios at local scale is given in **Table 4.7** (EUSES).

Table 4.7 Total daily intake via air, drinking water and food at local scale

Life cycle stage or scenarios	Total daily intake (µg/kg/d)
I-1/II-1 Production/processing (1)	0.4
II-2 Processing tape (2)	4.1
II-3 Processing (3)	103
II-4 Processing resins (4)	0.1
II-5 Processing glue (5)	0.2
II-6 Processing pharma./pest. (6)	79.7
II-7 Processing "other uses" (6)	21.1
III-1 Unintentional processing (7)	2.4
III-2 Unintentional processing (8)	0.1
III-3 Unintentional PET production (9)	17.9
III-4 Unintentional AES (10)	0.1

The regional exposure assessment is discussed in Section 3. In **Table 4.8** the total human intake as well as the intake via air are presented.

Table 4.8 Regional scale air concentrations and total human intake

	Regional
Intake (mg/kg/d)	$4.5 \cdot 10^{-5}$
PEC air (µg/m^3)	0.02

4.1.1.4.2 Measured data in the environment

1,4-Dioxane has been detected in drinking water. Rather old data (round 1975) are available from the USA where drinking water concentrations of 0.01 - 2.1 µg/l have been measured. In the Netherlands recently (≥ 1996) 1,4-dioxane has been detected during groundwater extraction. The measured concentrations ranged from <0.1 - 14 µg/l. In drinking water from the same area 0.5 µg 1,4-dioxane/l has been detected, indicating that the substance could not be removed completely with the used purification techniques.

4.1.2 Effects assessment: Hazard identification and Dose (Concentration) - response (effects) assessment

4.1.2.1 Toxicokinetics, metabolism, and distribution

4.1.2.1.1 Studies in animals

Absorption, distribution and excretion

Oral

Male rats (n=3) were given single oral doses of 10, 100 or 1,000 mg ^{14}C-1,4-dioxane/kg bw. Radioactivity in urine, faeces and expired air was determined after 24 hours for rats treated once with 10 mg/kg bw and after 72 hours for rats given once 100 or 1,000 mg/kg bw. In another experiment male rats (n=2) were treated with 10 or 1,000 mg ^{14}C-1,4-dioxane/kg bw for 17 days. Excreta were collected for up to 20 days. At termination the rats were sacrificed and analysed for radioactivity.

Table 4.9 Cumulative excretion of radioactivity in rats after oral dosing

% of the dose					
	Single dose (mg/kg bw)			Multiple doses (mg/kg bw)	
	10	100	1,000	10	1,000
Time (h)	24	72	72	480	480
Urine	98.74	85.52	75.74	98.87	82.32
Faeces	0.95	1.95	1.06	0.46	2.05
Expired 1,4-dioxane	0.43	4.69	25.25	1.33	8.86
Expired $^{14}CO_2$	3.07	3.13	2.39	4.17	6.95
Body	3.11	1.47	1.02	0.63	0.53

After both single and repeated administration high absorption of ^{14}C-1,4-dioxane occurs in rats, as demonstrated by urinary excretion of 75.74 - 98.74% of the applied dose and faecal excretion of only 0.46 - 2.05% of the applied dose. The amount of expired 1,4-dioxane increases dose-relatedly from 0.43% of the administered dose at 10 mg/kg bw to 25.25% at 1,000 mg/kg bw indicating saturation of urinary excretion/metabolism. After multiple dosing, saturation also occurs, and, in addition, the amount of expired CO_2 increases. When 1,000 mg/kg bw was given repeatedly, expired 1,4-dioxane decreased and expired $^{14}CO_2$ increased when compared with single dosing. This effect was not observed when 10 mg/kg bw was given repeatedly (Young et al., 1978).

Dermal

In a skin-penetration study male and female Pitman-Moore Rhesus monkeys (n=3-6) received open applications of ^{14}C-1,4-dioxane in methanol or a skin lotion on the forearm for 24 hours (dose: 4 mg/cm^2; area: 3-15 cm^2). After the 24-hour treatment period the treated area was washed with water and soap. One and five minutes after treatment with 1,4-dioxane in skin lotion 36% and 15% of the applied dose, respectively, were still detectable on the skin. Urine was collected over a 5-day period and was analysed for the radiolabel. Within 24 hours after treatment 2.3% and 3.4% of the applied radioactivity were excreted via the urine. The peak rate

of absorption was within 4 hours after treatment when estimated on urinary excretion (Marzulli et al., 1981). According to Appel (1988), the results could be affected by evaporation because only 15% of the applied dose was detectable after 5 minutes. From this study it can only be concluded that dermal absorption occurs.

In a very limited study by Fairley et al. (1934) repeated application of an 80% aqueous 1,4-dioxane solution to the skin of four rabbits and guinea-pigs under non-occlusive conditions led, within 50 to 100 days to damage of the renal tubulus cells and glomeruli as well as haemorrhages in the renal medulla, and liver degeneration. From this study the only conclusion can be that dermal absorption occurs.

Inhalation

Four male Sprague-Dawley rats with jugular vein cannulas were placed in a 1 litre "head-only" chamber under dynamic air flow conditions. The flow rate of 1,4-dioxane vapour was adjusted to give a chamber concentration of 180 mg/m^3 (50 ppm). During and after the 6-hour exposure urine was collected and analysed.

The radioactivity expressed as 1,4-dioxane in plasma at the end of exposure was 7.3 µg/ml. Thereafter, the plasma concentration of 1,4-dioxane decreased in a log-linear manner until it was not detectable (<0.3 µg/ml) at 11 hours after the start of the experiment. A $t_{½}$ of 1.01 hours was calculated. The amounts of 1,4-dioxane and β-hydroxyethoxyacetic acid (HEAA) in urine during exposure (0-6 h) were 5.1 and 7,613 µg, respectively, and afterward (6-48 h) 1.7 and 13,659 µg, respectively. Hence, more than 99.9% of the total urinary excretion of the inhaled 1,4-dioxane was HEAA. When estimated from the total 1,4-dioxane (6.8 µg) and 1,4-dioxane equivalents of HEAA (21,271 µg · 0.73 [= ratio of molecular weights]) excreted in urine, the rats absorbed at least 72 mg 1,4-dioxane/kg bw during the 6-hour exposure period. Assuming a respiratory minute volume of 240 ml/min for rats, these data indicate complete absorption (Young et al., 1978).

Other

Six rats received i.v. doses of 3, 10, 30, 100, 300 or 1,000 mg ^{14}C-1,4-dioxane/kg bw and samples of blood were obtained via the right jugular vein every 5 minutes for estimating radioactivity in plasma. Two additional rats were used to estimate radioactivity in expired air (1,4-dioxane and $^{14}CO_2$) as well as in urine and faeces. These rats were equipped with jugular and ureter cannulas.

At the lowest i.v. doses given, 3 and 10 mg/kg bw, radioactivity was eliminated from the plasma by apparently linear kinetics with a $t_{½}$ of 1.1 hours. At higher doses, radioactivity was eliminated from plasma progressively more slowly. At dose levels ≥100 mg/kg bw, elimination was retarded till a peak level of ca. 100 µg/ml plasma was reached, whereafter elimination occurred with the same $t_{½}$ as that at lower doses. As the dose increased from 3 to 1,000 mg/kg bw, plasma clearance decreased from 3.33 to 0.25 ml/min. The renal clearance rates of 1,4-dioxane were low, being 0.032 ml/min at 10 mg/kg bw, and 0.029 ml/min at 1,000 mg/kg bw. These values indicate that 1,4-dioxane was extensively reabsorbed by the kidney. The pulmonary clearance of 1,4-dioxane was also low, being 0.032 at 10 mg/kg bw and 0.055 ml/min at 1,000 mg/kg bw. The metabolic clearance (i.e. the difference between plasma clearance and the total of renal and pulmonary clearance) decreased from 2.82 ml/min at 10 mg/kg bw to 0.17 ml/min at 1,000 mg/kg bw. This indicates saturation of the metabolic capacity of rats at high dose levels. The saturation curve for 1,4-dioxane in this experiment suggested that doses of 1,4-dioxane below the plateau of 100 µg/ml plasma are metabolised and eliminated rapidly, while doses of 1,4-dioxane

resulting in higher plasma levels are removed progressively more slowly from the body due to saturation of metabolism.

The excretion of 1,4-dioxane in urine and expired air followed the same pattern of 1,4-dioxane in plasma, indicating first order processes. In both urine and expired air, the total 1,4-dioxane excreted was 5% (4 + 1%, respectively) of the 10 mg/kg bw dose and 38% (11 + 27%, respectively) of the 1,000 mg/kg bw dose. Following 10 mg/kg bw, 92% was excreted as HEAA in urine, while following 1,000 mg/kg bw this was only 60% (Young et al., 1978).

At various times up to 16 hours after i.p injection of 6.97 mg ^{3}H-1,4-dioxane/kg bw to male Sprague-Dawley rats, the distribution of radioactivity was studied in whole blood, liver, kidney, spleen, lung, colon, and skeletal muscle. 1-2 hours after injection the kidneys revealed 1.5-2 fold higher levels of radioactivity than the other tissues, which was explained by excretion via the urine. Distribution among other tissues was more or less uniform. Radioactivity in all examined tissues decreased in time. In blood, radioactivity was higher than in examined tissues at all sampling points, except for kidneys after 1 hour. Studies of the nature of 1,4-dioxane binding revealed that the extent of "covalent" binding (as measured by incorporation of radioactivity into lipid free, acid-insoluble tissue residues) increased up to 6 hours post injection and was clearly higher in the liver, spleen and colon than in other tissues. Much lower amounts of "covalent" binding occurred in the skeletal muscle and blood. Investigations of the subcellular distribution in liver indicated that most of the radioactivity was in the cytosol, followed by the microsomal, mitochondrial and nuclear fractions. The specific activity of all three particulate fractions reached a maximum at 6 hours after 1,4-dioxane administration. The percent "covalent binding" (as measured by incorporation into lipid free, acid insoluble tissue residues) was highest in the nuclear fraction, followed by microsomal and mitochondrial fractions and the whole homogenates. Pre-treatment of rats with inducers of microsomal mixed function oxidases [3-methylcholanthrene (dissolved in corn oil, given as a single i.p. dose of 40 mg/kg bw 24 hours prior to 1,4-dioxane administration), polychlorinated biphenyls (dissolved in corn oil and administered i.p. at 500 mg/kg bw 4 days prior to 1,4-dioxane administration) and phenobarbital (dissolved in 0.9% saline and administered i.p. at a dose of 80 mg/kg bw daily for 4 consecutive days prior to 1,4-dioxane treatment)] had no significant effect on the "covalent binding" of 1,4-dioxane to the various subcellular fractions of the liver. There was no microsome-catalysed *in vitro* binding of ^{3}H- or ^{14}C-dioxane to DNA under conditions which brought about substantial binding of ^{3}H-benzo[a]pyrene (Woo et al., 1977d).

Rats received a single i.p. dose corresponding to 1/10 of the LD_{50} (799-5,600 mg/kg bw) of ^{14}C-1,4-dioxane/kg bw (no details). Six rats/time point were sacrificed after 5, 15 and 30 minutes and after 1, 3 and 6 hours. After 5 minutes a maximal 1,4-dioxane level was found in liver and kidney, and after 15 minutes in blood, brain and testes. The distribution coefficient tissue/blood in the liver is 0.8, remaining constant throughout the experiment, and in kidneys is also 0.8, but increasing to 1.0 at the end of the experiment. In the testes the ratio tissue/blood is 0.6 after 5 minutes and 1.3 at the end of the experiment. In the brain the ratio was 0.7 remaining constant. The ratio subcellular fraction/tissue for the nuclear fraction of liver cells was 0.06 and for mitochondrial liver fractions 0.01 after 6 hours (Mikheev et al., 1990).

Biotransformation

Two male Sprague-Dawley rats received by gavage a single oral dose of 1,000 mg ^{14}C- 1,4 dioxane/kg bw in distilled water. 24-Hour urine was analysed for radioactivity and metabolites were identified by TLC, GC, NMR, GC/MS. HEAA was identified as the major

metabolite in urine and amounted to about 85% of the excreted material. The remaining 15% in urine was attributed to unchanged 1,4-dioxane and diethylene glycol (Braun and Young, 1977).

Rats received once by gavage 10, 100 or 1,000 mg ^{14}C-labeled 1,4-dioxane/kg bw. The pharmacokinetics of 1,4-dioxane appeared to be non-linear. At the low dose level of 10 mg/kg bw almost all of the administered dose was rapidly excreted in the urine as HEAA and only a small amount of parent compound was excreted in the exhaled air. At higher doses (100 and 1,000 mg/kg bw) more unchanged ^{14} C-1,4-dioxane was excreted in the expired air. In rats given a daily oral dose of 1,000 mg ^{14}C-1,4-dioxane/kg bw for 17 days an increased biotransformation of 1,4-dioxane was seen as was demonstrated by a higher excretion of metabolites in urine and exhalation of CO_2. At this dose level induction of the metabolising enzymes had taken place. At repeated administration of 10 mg/kg bw no increase in biotransformation was seen (Dietz et al., 1982; Reitz et al., 1990; Young et al., 1978).

Male Sprague-Dawley rats received i.p. 1,000 (in Woo et al., 1977b: 500) -4,000 mg 1,4-dioxane/kg bw. Urine samples were collected in 8-12 hr intervals for 2 days and analysed for volatile compounds. For sample clean up an acidic system was used. Two major peaks were identified, one for 1,4-dioxane and one for a metabolite which was identified as 1,4-dioxane-2-one. This metabolite was undetectable at pH>12, but reappeared upon reacidification of the urine. The excretion of this metabolite was dose- and time-dependent, reaching a maximum between 20-28 hours after administration. The amount of unchanged 1,4-dioxane in urine accounted for 2.9, 6.8, 10.8 and 10.8% of the dose of 1,000, 2,000, 3,000 and 4,000 mg/kg bw, respectively. At a dose of 3,000 mg/kg bw, 33% was excreted as 1,4-dioxane-2-one (Woo et al., 1977a; 1977b).

Remark

The metabolite identification is pH-dependent. At high pH, HEAA was detected as the major metabolite. At low pH, HEAA will be converted to 1,4-dioxane-2-one, which was then identified as the major metabolite. These two substances are in chemical equilibrium.

The effect of typical inducers and inhibitors of hepatic mixed function oxidases (MFO) on the excretion of 1,4-dioxane-2-one, the main 1,4-dioxane metabolite in urine, was studied in rats treated i.p. with 3 g/kg bw 1,4-dioxane. Pre-treatment with the inducers phenobarbital (dissolved in 0.9% NaCl solution and administered i.p. at a dose of 80 mg/kg bw daily for 4 consecutive days prior to 1,4-dioxane treatment), the polychlorinated biphenyl Aroclor 1254 (dissolved in corn oil and administered as a single oral i.p. of 500 mg/kg bw 4 days prior to 1,4-dioxane administration) and, to a much lesser extent, 3-methylcholanthrene (dissolved in corn oil, given as a single i.p. dose of 40 mg/kg bw 24 hours prior to 1,4-dioxane administration) increased the metabolite excretion and shortened the time of onset of peak excretion of the metabolite. In contrast, inhibitors/repressors of MFO as 2,4-dichloro-6-phenylphenoxyethylamine (dissolved in 0.9% NaCl solution and given i.p at doses of 15.9 mg/kg bw at 0.5 hour before and 8, 16, 24 hours after 1,4-dioxane administration) and cobaltous chloride (injected s.c. at 60 mg/kg bw 24 hours prior to 1,4-dioxane administration) decreased the metabolite excretion. The effects observed were independent of renal excretory function. Of the inducers, phenobarbital had the greatest effect, followed by Aroclor 1254. 3-Methylcholanthrene was the weakest (Woo et al., 1977c; 1978).

The metabolite HEAA accumulates in tissues with an oxidative capacity (Hecht & Young, 1981; Hecht et al., 1983).

Apart from the above-mentioned oxidation products, 1,4-dioxane-2-one and HEAA, Hecht and Young (1981) postulated the formation of 1,4-dioxane-2-ol as a result of hydroxylation. The substance is in equilibrium with the reactive and presumably cytotoxic β–hydroxyethoxy acetaldehyde. Toxicologically significant amounts presumably can be formed in cells in which the oxidative capacity has been saturated by high doses of 1,4-dioxane prohibiting the complex oxidation to HEAA.

Studies of Braun and Young (1977) also show that the HEAA may form 1,4-dioxan-2-one as a cyclisation product, during chromatographic separation of dioxane metabolites under acidic conditions.

The possible metabolic pathways of 1,4-dioxane are depicted below. They include:

- Hydrolysis to diethylene glycol, followed by oxidation of one of the hydroxyl groups,
- Direct conversion via a possible ketoperoxyl radical intermediate, and
- Through α-hydroxylation, followed by the oxidation of the hemiacetal or hydroxyaldehyde inter-mediate (Woo et al., 1977a).

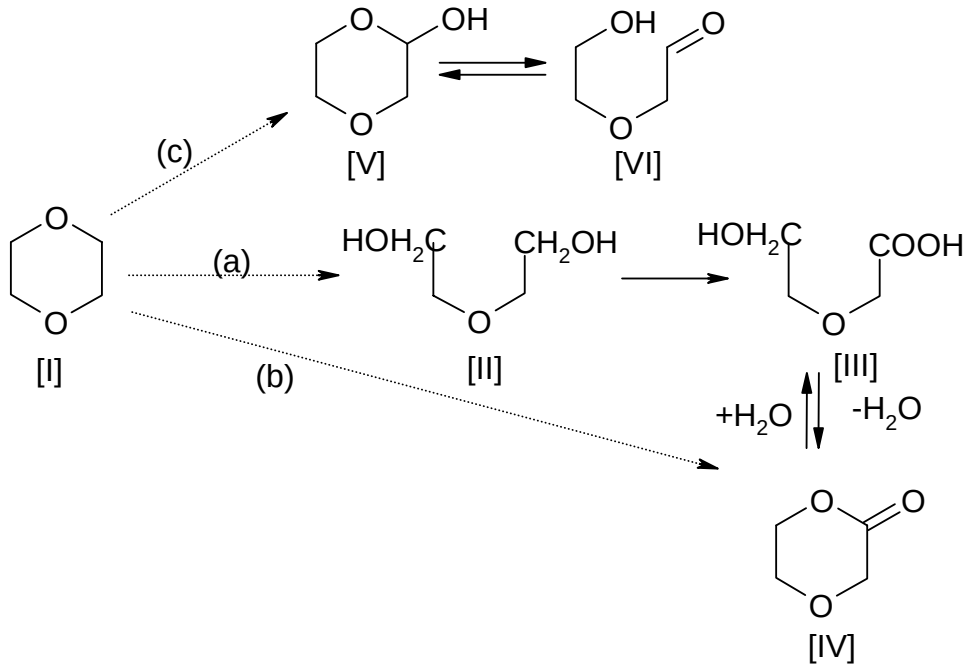


Figure 1 Suggested metabolic pathways of 1,4-dioxane in the rat (Woo et al., 1977a)
(I 1,4-dioxane; II diethylene glycol; III β-hydroxyethoxy acetic acid (HEAA);
IV 1,4-dioxane-2-one; V 1,4-dioxane-2-ol, VI β-hydroxyethoxy acetaldehyde)

4.1.2.1.2 Studies in humans

Oral

No data available.

Dermal

In vitro

The ability of ^{14}C-1,4-dioxane to penetrate excised human skin has been examined. The substance was applied to the epidermis in three different vehicles representative of cosmetic products.

Since ^{14}C-1,4-dioxane is a volatile compound, the evaporation after application to the skin was also determined. When evaporation was prevented, the absorption rate values for 1,4-dioxane in each vehicle were: water, $4.3 \cdot 10^{-4}$ cm hr^{-1}; isopropopyl myristate, $11.2 \cdot 10^{-4}$ cm hr^{-1}; and "popular lotion", $2.7 \cdot 10^{-4}$ cm hr^{-1}. According to the authors, these results rank 1,4-dioxane as a rapidly penetrating compound.

When 1,4-dioxane was applied in the "popular lotion" and evaporation was allowed to occur, skin permeation was reduced approximately 10-20 fold. From separate experiments it was determined that from a thin layer of the lotion, 90% of added ^{14}C-1,4-dioxane evaporated in 15 minutes and most of the remaining compound evaporated slowly over a 24-hour period (Bronaugh et al., 1980; abstract only, no more details present).

Inhalation

The pharmacokinetics and metabolism of 1,4-dioxane were determined in four healthy male volunteers exposed to 50 ppm (180 mg/m^3) for 6 hours in a chamber under dynamic airflow conditions. Blood was sampled at regular intervals up to 12 hours after the start of the experiment. Urine was collected during and after exposure for a total of 48 hours.

During exposure a plateau concentration was reached in plasma after an initial rapid rise. After exposure, the plasma 1,4-dioxane concentration decreased linearly, indicating first-order elimination which was not saturated at 50 ppm. The plasma $t_{½}$ for elimination of 1,4-dioxane was 59 minutes. The plasma HEAA concentration was maximal after 7 hours, whereafter it fell log-linearly. After the exposure period the plasma HEAA concentration was higher than the plasma 1,4-dioxane concentration.

From the total administered 1,4-dioxane 99.3% was eliminated via the urine as HEAA. In the 0-6 h interval 47% of the total HEAA were excreted, and none was detectable after 24 hours. The $t_{½}$ for elimination of HEAA in urine was 2.7 hours. Only 0.7% of the total administered dose was eliminated by excretion of 1,4-dioxane in the urine, 90% of which was already recovered in the 0-6 h period. None was detectable after 12 hours. The $t_{½}$ for elimination of 1,4-dioxane in urine was 48 hours.

When estimated from the total 1,4-dioxane and 1,4-dioxane equivalents of HEAA excreted in urine, at least 5.4 mg 1,4-dioxane/kg bw were absorbed during the 6-hour exposure period (i.e. at least 50% of the administered dose, assuming a respiratory volume of 20 m^3/day). Since a large fraction of both 1,4-dioxane and HEAA was eliminated during the exposure period, the calculated dose of 5.4 mg/kg was not in the body at one time. The maximum amount in the body occurred at 6 hours. To calculate this amount the total 1,4-dioxane and 1,4-dioxane equivalents of HEAA excreted from 0-6 hours were subtracted from the total dose to obtain 2.86 mg equivalents of 1,4-dioxane per kilogram in the body at 6 hours.

A simulation of repeated daily exposures to 180 mg/m^3 1,4-dioxane for 8 hours/day indicated that 1,4-dioxane would never accumulate to concentrations above those attained after a single

8-hour exposure as long as the exposure concentration of 1,4-dioxane was 180 mg/m^3 or less (Young et al., 1977).

1,4-Dioxane and HEAA were found in the urine of 1,4-dioxane plant personnel exposed to a time weighted average concentration of 1.6 ppm (5.8 mg/m^3) for 7.5 hours. The average concentration of 1,4-dioxane and HEAA in samples of urine collected at the end of the working day amounted to 3.5 and 414 µmol/l, respectively. Hence, 1,4-dioxane comprised only 0.8% of the total concentration of 1,4-dioxane and HEAA in urine, suggesting that metabolism of 1,4-dioxane to HEAA in humans is very rapid and not saturated at a vapour concentration of 1.6 ppm (Young et al., 1976).

Special investigation: modelling study

In a paper by Fisher et al. (1997), a physiologically-based pharmacokinetic (PB-PK) lactational model is described. With this model, the transfer of 1,4-dioxane into breast milk was predicted for a simulated exposure of a lactating woman (2-3 months postpartum) throughout an 8-hour period to a constant vapour concentration of 25 ppm (90 mg/m^3). For the modelling purposes, a conservative nursing schedule (i.e. eight 12-min nursing bouts over a 24-hour period) was used to emphasize the lactational transfer of the chemical to the nursing infant. Published human metabolic parameters and human pharmacokinetic models were used for 1,4-dioxane. The model predicted that for the assumed maternal occupational exposure concentration, scenario and nursing schedule, the quantity of ingested dioxane by the infant amounted to 0.559 mg/day. No attempt to validate the model, for instance by comparison with actually measured concentrations, is presented in the paper, while the model performance cannot be adequately assessed because calculated plasma-time curves for dioxane were not given. These are considered serious shortcomings, which preclude quantitative conclusions to be drawn from the study. The study indicates that excretion via the milk may occur.

4.1.2.1.3 Summary of toxicokinetics, metabolism and distribution

Radiolabeled 1,4-dioxane was rapidly and almost completely absorbed after oral and inhalation exposure by rats. After inhalation exposure by humans, 1,4-dioxane was also rapidly and for at least 50% absorbed. For dermal absorption no quantitative conclusions can be drawn. However, based on the studies of Marzulli et al. (1981) and Fairley et al. (1934), it can be concluded that skin absorption occurs. In an *in vitro* study it was demonstrated that 1,4-dioxane can penetrate human skin when occluded, but rapidly evaporates from human skin when not occluded. For the risk assessment 100% absorption is chosen for the oral and inhalatory route, and 50% for the dermal route. The latter is chosen as default because the limited data available indicate that 100% absorption would be a too worst-case assumption for the volatile compound 1,4-dioxane.

Dioxane-related material was predominantly excreted via the urine in both rats and humans. In human urine, the major metabolite was β-hydroxyethoxyacetic acid (HEAA). Both HEAA and 1,4-dioxan-2-one were identified as the major metabolite in rat urine. Identification of these metabolites is pH-dependent. At a high pH, HEAA will be detected and at a low pH, HEAA will be converted to 1,4-dioxan-2-one. These two metabolites are in chemical equilibrium. At low pH the equilibrium is more shifted to 1,4-dioxan-2-one.

In rats and humans the pharmacokinetic and metabolic fate of 1,4-dioxane is rather comparable. In rats it is shown to be dose-dependent due to a limited capacity to metabolise 1,4-dioxane to HEAA. A single oral dose of 10 mg/kg bw to rats was rapidly metabolised and

excreted via the urine, while a single oral dose of 1,000 mg 1,4-dioxane/kg bw saturated the metabolism of 1,4-dioxane to HEAA, resulting in decreased urinary excretion of HEAA and increased 1,4-dioxane in the expired air. In rats, 1,4-dioxane was eliminated from the plasma by linear kinetics with a t½ of 1 hour after i.v. doses up to 10 mg/kg bw and after inhalation exposure to 180 mg/m^3. At higher i.v. doses (≥100 mg/kg bw) elimination occurred progressively more slowly until plasma peak levels of 100 µg/ml were reached, whereafter elimination occurred with the same t½ of lower doses. Hence, saturation of metabolism occurs at 1,4-dioxane doses resulting in plasma levels above 100 µg/ml. After inhalation exposure of humans to 180 mg/m^3 1,4-dioxane, 1,4-dioxane was rapidly eliminated from plasma ($t_{½}$ of 1 h) and excreted via urine. Saturation did not occur.

Repeated oral administration of 1,4-dioxane to rats at high doses causes further alterations in the pharmacokinetics of 1,4-dioxane, such as changes in oxidising enzyme capacity and a reduction in 1,4-dioxane accumulation in plasma. This correlates with the observed reduction in the 1,4-dioxane exhaled with respiratory air and the increase in the amount of CO_2, and possibly also with the shift in the ratio of oxidation products (HEAA, 1,4-dioxane-2-one) to the possible intermediate products (1,4-dioxane-2-ol/β–hydroxyethoxy acetaldehyde).

A PB-PK modeling study indicates that dioxane may also be excreted into human milk.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

Several studies have been carried out with different species and by different routes. The most reliable studies are summarised in **Table 4.10**. It must be noted that most of these studies were old with little detail provided and that none of them were performed according to current guidelines or GLP.

Table 4.10 Summary of acute toxicity data

Route	Species	Protocol	Results LD50/LC50	Reference
Oral	rat	other * other *	ca.5,170 mg/kg bw 5,345 mg/kg bw	BASF, 1973 Laug et al., 1939
		other * other *	ca. 6,200 mg/kg bw 6,370 mg/kg bw	Nelson, 1951 Pozzani et al., 1959
		other *	6,500 mg/kg bw	BASF, 1958
		other *	7,339 mg/kg bw	Smyth et al., 1941
	mouse	other *	5,850 mg/kg bw	Laug et al., 1939
	guinea pig	other *	3,256 mg/kg bw	Smyth et al., 1941
		other *	4,000 mg/kg bw	Laug et al., 1939
	rabbit	other *	ca. 2,100 mg/kg bw	Nelson, 1951
	rabbit	other *	6,500 mg/kg bw	Knoefel, 1935
Dermal	rabbit	unknown	7,855 mg/kg bw	RTECS, 1995
Inhalatory	rat	unknown, 2 hours exposure	46,000 mg/m^3	RTECS, 1995
	rat	unknown, 4 hours exposure	51,300 mg/m^3	Pozzani et al., 1959
	mouse	unknown, 2 hours exposure	37,000 mg/m^3	RTECS, 1995

* See IUCLID

Oral

Signs of toxicity after oral administration to rats, mice and guinea-pigs included narcotic effects, coma, irritation of the gastro-intestinal mucous membranes and damage in liver and kidneys (Laug et al., 1939; Nelson, 1951; Smyth et al., 1941). In rabbits dose-related narcotic effects were seen (Nelson, 1951).

Dermal

In a summary of a dermal LD_{50} study in rabbits only a LD_{50} was given (see **Table 4.9**). Neither clinical signs nor toxic effects were mentioned (RTECS, 1995).

Inhalation

Groups of 3 male and 3 female rats (Sprague-Dawley) were exposed to a nominal concentration of 155,000 mg/m^3 for 1, 3 and 7 hours. The animals were observed for 14 days. After 1 hour exposure no mortalities occurred, after 3 hours 6/12 animals died and after 7 hours 4/18 animals (there is no explanation for this number of animals). Effects observed after inhalation exposure included: dyspnoea, apathy, narcosis, irritation of mucous membranes of the eyes and respiratory tract, eyelid-reflex-loss, unkempt coat and staggering as well as acute heart dilatation, haemorrhagic erosion of the mucous membranes of the stomach and bloody contents in stomach and intestines (BASF, 1980).

Guinea pigs exposed to 3,660, 7,320, 10,980, 36,600, 109,800 mg/m^3 for maximally 8 hours showed irritation of the mucous membranes of the nose and eye. The highest concentration caused mortality within 2 days (Yant et al., 1930).

Male rats were exposed two times for 4 hours within one day to 3,660 or 7,320 mg/m^3 1,4-dioxane. The activities of the serum enzymes ALAT, ASAT and ornithine carbamyl transferase were markedly elevated (Drew et al., 1978).

Other routes

Administration via other routes resulted in LD_{50} values for rats of 799-5,600 mg/kg bw (i.p.) (Lundberg et al., 1986; Woo et al., 1978; Argus et al., 1973) and for the mouse of 4,350 mg/kg bw (s.c.) (BASF, 1958).

After i.p. administration of 1,4-dioxane to mice, a LD_{50} of ca. 5,790 mg/kg bw was derived. Observed effects before death were dyspnoea, narcosis, convulsions and ventral body position. Microscopic examination revealed a discoloured liver (BASF, 1973).

Additional single exposure studies

After implantation with [6-^{3}H]thymidine, groups of 4 male Sprague-Dawley rats received by gavage single doses of 0, 10, 100 or 1,000 mg/kg bw 1,4-dioxane in saline. The animals were sacrificed after 7 days and their livers were examined. Upon acute dosing, 1,4-dioxane did not cause hepatic cytotoxicity, as no significant changes were noted in organ to body weight ratios, the amount of DNA/g tissue, the rate of DNA synthesis as measured by [6-^{3}H]thymidine incorporation, or the presence of histopathological changes in the liver (Stott et al., 1981).

Enzyme induction

Groups of 5 male mice received orally 0, 500, 1,000 or 2,000 mg 1,4-dioxane/kg bw, administered once daily for 2 days. 24 Hours after the last dose the animals were killed and the liver was examined. At 1,000 and 2,000 mg/kg relative liver weight was increased and microsomal protein content in the liver was increased. The same dose levels enhanced the rate of *in vitro* metabolism of aminopyrine, ethylmorphine and acetanilide substrates and increased levels of microsomal NADPH cytochrome c reductase and cytochrome P450 content (Pawar and Mungikar, 1978).

Neurotoxicity

In a neurotoxicity test, the inhibition of propagation and maintenance of an electrically evoked seizure discharge were investigated as a criterion of the acute neurotropic effect of 1,4-dioxane.

The testing was performed in parallel on male albino Wistar rats (4 per group) and female mice (8 per group) of the H strain under two divergent conditions: the shortening of the duration of maximal tonic extension after electroshock was the criterion in male rats exposed to 1,4-dioxane vapour for 4 hours, whereas the slowing of the development of tonic extension after electroshock was determined in female mice exposed for 2 hours. Three concentrations between 25-75% of the maximum effect level were tested (exact concentrations not mentioned). The concentration at which a 30% depression of the maximum attainable effect was obtained was 6,807.6 mg/m^3 for rats and 8,784 mg/m^3 for mice. No attention was paid to behavioural changes (e.g. narcosis or depressed activity) (Frantík et al., 1994).

In a neurotoxicity test by Kanada et al. (1994) the effect of oral administration of 1,4-dioxane on monoamine neurotransmitters and metabolites in the rat brain was investigated. Male Sprague-Dawley rats received a single oral administration of 1,050 mg 1,4-dioxane/kg bw. Two hours after administration rats were killed and acetylcholine, 3,4-dihydroxyphenylalanine (DOPA), dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), norepinephrine, 3-methoxy-4-hydroxyphenylglycol (MHPG), serotonin and 5-hydroxyindoleacetic acid (5HIAA) contents in various brain regions were measured.

Significant effects of 1,4-dioxane administration were: decrease in dopamine and serotonin concentrations in the hypothalamus and decrease of serotonin concentrations in the medulla oblongata. Concentrations of the other neurotransmitters and metabolites were not significantly influenced after the administration of 1,4-dioxane. No attention was paid to behavioural changes (e.g. narcosis or depressed activity).

4.1.2.2.2 Studies in humans

There are no human data on acute toxicity of 1,4-dioxane available.

4.1.2.2.3 Summary of acute toxicity

The oral LD_{50} value of 1,4-dioxane for the rat varied between 5,170 and 7,339 mg/kg bw and the dermal LD_{50} was reported to be 7,855 mg/kg bw for the rabbit. With respect to inhalation the LC_{50} was 36,700 mg/m^3 for mice and 46,000-52,000 mg/m^3 for rats.

According to EC criteria 1,4-dioxane need not be classified on the basis of its acute toxicity.

Four hours exposure of rats to 3,660 or 7,320 mg 1,4-dioxane/m^3 caused elevated ALAT, ASAT and ornithine carbamyl transferase activity. At oral doses of 1,000 and 2,000 mg/kg, dose-dependent induction of drug metabolising enzymes in mice was seen. Depression of tonic extension after electroshock in rats was seen at concentrations ≥6,800 mg/m^3 and an oral administration of 1,050 mg/kg bw caused a decrease in dopamine and serotonin levels in the hypothalamus and a decrease in serotonin in the medulla oblongata.

4.1.2.3 Irritation

4.1.2.3.1 Studies in animals

Skin

In an epicutaneous study in rabbits (1 male and 1 female) a cotton patch sized 2.5·2.5 cm was soaked with undiluted 1,4-dioxane (approximately 0.5 ml) and applied to the shaven back (for 1, 5 and 15 minutes as well as for 20 hours) and on the ear (for 20 hours) under occlusive conditions.

Application to the skin during 1-15 minutes caused very slight erythema after 24 hours and slight scale formation after 8 days. This scale formation is most likely caused by the defatting properties of 1,4-dioxane. 24 Hours after the 20-hour application, slight erythema and slight oedema were observed on the back of 1 animal. Seven days later moderate scale formation was seen. On the ear slight erythema was observed 24 hours as well as 8 days after the 20 hours application. Scores according to OECD were not given (BASF, 1973; Zeller and Kühlem, 1998a).

In a special irritation test by Sekizawa et al. (1994) using 3 male and 3 female Wistar rats and 3 male and 3 female ddY mice, the lowest irritating concentration was 80% 1,4-dioxane in physiological saline. More data about concentrations were not available. Scores according to OECD were not given.

Eyes

Two male White Vienna rabbits received an instillation of 0.05 ml undiluted 1,4-dioxane for an undetermined exposure period. 24 Hours after instillation, slight corneal opacity and conjunctival redness as well as slight to severe chemosis were observed in both rabbits. Additionally, smeary deposition was noted. 8 Days after application, when the study was terminated, slight conjunctival redness was observed in one animal. This finding was expected to reverse if the observation period would have been prolonged. This animal showed small retraction of the eyelid. Because the chosen dose level is very low in comparison to the current guidelines and only two animals were used, 1,4-dioxane is considered as an eye irritant (BASF, 1973; Zeller and Kühlem, 1998b).

In vitro

In an *in vitro* test with isolated bovine cornea, irritation (including changes in opacity and thickness of the isolated cornea) was observed at 1,4-dioxane concentrations of 5-100% (Igarashi and Northover, 1987; Gautheron et al., 1992).

Respiratory tract

Groups of 3 male and 3 female Sprague-Dawley rats were exposed to a nominal concentration of 155,000 mg/m^3 for 1, 3 or 7 hours. After one hour exposure 0/12 rats died, after 3 hours exposure 6/12 rats died and after 7 hours exposure 4/18 rats died. The observed symptoms included irritation of the respiratory tract in rats. In this study histopathology was performed. Animals that died showed swollen lungs. No details were available (BASF, 1980).

Gingell et al. (1994) cited two studies, one in which guinea pigs were exposed for 3 hours to concentrations of 1,000 to 30,000 ppm 1,4-dioxane (Yant et al., 1930), and another in which rats, mice, guinea pigs and rabbits were exposed for 8 hours to 1,4-dioxane concentrations of 4,000 to 11,000 ppm (Gross, 1938). It is stated that at the higher concentrations marked irritation of the mucous membranes was apparent. Deaths occurring during exposure or shortly afterward were usually due to respiratory failure because of lung oedema, but the animals also exhibited congestion of the brain. Delayed deaths were due to pneumonia. Histological evidence of liver and kidney toxicity was observed in animals that died after exposure as well as in surviving animals evaluated several days after exposure.

4.1.2.3.2 Studies in humans

Skin and eye irritation

According to Gingell et al. (1994), 1,4-dioxane is a fat solvent and prolonged and repeated contact can cause eczema. After repeated exposure skin irritation was seen (see Section 4.1.2.6.2. Studies in humans). Eye irritation was reported after inhalation exposure (see Section 4.1.2.3.2. Inhalation).

Wirth and Klimmer (1937) reported no irritation of neat 1,4-dioxane on the skin and slight burning sensation on mucous membranes of the mouth. No details were available.

Inhalation

Wirth and Klimmer (1937) reported throat irritation at 1,000 mg/m^3 and strong throat irritation at 10,000 mg/m^3.

Twelve subjects were exposed to 1,4-dioxane for 15 minutes to observe olfactory fatigue. A concentration of 720 mg/m^3 showed to be the highest concentration acceptable. At 1,080 mg/m^3 irritation of eyes, nose and throat was reported, although the odour was not recognised (Silverman et al., 1946). Immediately slight burning of the eyes accompanied by lacrimation and slight irritation of the nose and throat was reported from an exposure of 5,760 mg/m^3 for 10 minutes. After 19,800 mg/m^3 for 1 minute, eye irritation and burning sensation in the nose and throat were noted. At 36,000 mg/m^3 pulmonary irritation occurred (Gingell et al., 1994; Yant et al., 1930).

4.1.2.3.3 Summary of irritation

Although the base set requirements were not quite met, based on all data provided (including human experience) it can be concluded that 1,4-dioxane is irritating to the eye and the respiratory tract, but not to the skin. However, being a fat solvent, 1,4-dioxane can cause eczema upon prolonged or repeated contact. Classification with R36/37 and R66 is appropiate.

Acute exposure of human beings to concentrations of 1,4-dioxane ≥1,000 mg/m^3, a concentration not recognisable by odour, caused irritation of eyes, nose and throat.

4.1.2.4 Corrosivity

The substance is not corrosive to skin or eyes (see Section 4.1.2.3).

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

In a well-performed maximisation test, according to Guideline 84/449/EEC, 1,4-dioxane did not show skin sensitising properties. After a pre-test, in which undiluted 1,4-dioxane did not cause skin irritation, B6 female Pirbright White guinea pigs were induced with 5% (injection) and 100% (epidermal) test substance in the main test. Upon intradermal induction well-defined signs of erythema and oedema were observed. Upon percutaneous induction incrustation, well-defined erythema and slight oedema were noted, but these were caused by the intradermal induction. After the challenge with the undiluted substance no sensitisation reactions were observed (BASF, 1993).

4.1.2.5.2 Studies in humans

A 52-year old man, who developed dermatitis on his left hand after daily dipping in a 1,4-dioxane containing solvent for 3 years, scored positive in a patch test (0.5% in water) (Fregert, 1974).

4.1.2.5.3 Summary of sensitisation

1,4-Dioxane did not show skin sensitising properties in a guinea pig maximisation test, performed according to OECD guidelines. According to EC criteria the substance does not need to be classified on the basis of the available tests. The human data are too limited to draw conclusions.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

Oral

1,4-Dioxane was administered in several repeated oral studies over longer and shorter periods in time. Most of these studies are not described as being subacute or semi-chronic toxicity studies, but as carcinogenicity studies with shortened application or exposure periods. These studies, including the toxicological effects observed, are described in Section 4.1.2.8 “Carcinogenicity”. Toxicological effects observed in these longer term studies in rats and mice after oral administration in the drinking water included severe effects on the liver, kidneys and nose, with

a LOAEL of 0.02% (equal to 0.016 g/kg bw/d). A dose of 0.01% (equivalent to 10 mg/kg bw/d) showed no effects. The results of the "short-time" studies are given in this paragraph.

In a 2-week study, groups of 10 male and 10 female Crj:BDF1 mice received drinking water containing 0, 1,110, 3,330, 10,000, 30,000 or 90,000 ppm 1,4-dioxane (equal to 0, 0.21, 0.66, 1.38, 2.55 or 3.63 g/kg bw/d for males of the 0-90,000 ppm groups, respectively, and 0, 0.24, 0.75, 1.78, or 3.23 g/kg bw/d for females of the 0-30,000 ppm groups, respectively). Observations included clinical signs, body weight, food and water consumption, necropsy, and histopathological examination (on 2-4 animals per sex per group). Mortality occurred in the top dose male (9/10) and female (10/10) groups. Body weights and food consumption were decreased in males and females at 30,000 and 90,000 ppm. Water consumption was decreased in males ≥10,000 ppm and in females ≥3,330 ppm. In the liver, single cell necrosis and swelling of the central area were observed in both males and females from the 90,000 and 30,000 ppm groups, respectively (Japan Bioassay Research Center, 1998a).

Groups of 10 male and 10 female Crj:BDF1 mice received drinking water containing 0, 640, 1,600, 4,000, 10,000 or 25,000 ppm 1,4-dioxane (equal to 0, 0.10, 0.26, 0.58, 0.92 or 1.83 g/kg bw/d and 0, 0.17, 0.41, 0.92, 1.71 or 2.70 g/kg bw/d for males and females of the 0-25,000 ppm groups, respectively) for 13 weeks. Observations included clinical signs, body weight, food and water consumption, haematology, biochemistry, urinalysis, necropsy, organ weights and histopathological examination.

One male in the 25,000 ppm group died. Body weights and food consumption were slightly reduced in the 10,000 and 25,000 ppm male groups and in the 25,000 ppm female group. Water consumption was decreased in all treated males and in females ≥4,000 ppm. In males, effects on haematology, biochemistry or urinalysis parameters were observed at ≥10,000, ≥4,000 and ≥10,000 ppm, respectively. In females, this occurred at ≥10,000 ppm. Absolute and relative lung weights were increased in males at 25,000 ppm and in females ≥10,000 ppm. In females kidney weight was also increased at these dose levels. Upon histopathology, non-neoplastic lesions were observed in the nasal cavity (nuclear enlargement and eosinophilic change of the olfactory and respiratory epithelium, vacuolic change of the olfactory nerve), trachea (nuclear enlargement of the epithelium), lung (accumulation of foamy cells, degeneration and nuclear enlargement of the bronchial epithelium), and liver (necrosis of single cell and swelling of the central area) in males at 4,000 ppm or greater groups and in females at 1,600 ppm or greater groups. No effects were found on the reproductive organs. Based on the histopathology findings in females at 1,600 ppm, the NOAEL in this study can be established at 640 ppm (equal to 0.17 g/kg bw/d) (Japan Bioassay Research Center, 1998b).

In a 2-week study, groups of 10 male and 10 female F344/DuCrj rats received drinking water containing 0, 1,110, 3,330, 10,000, 30,000 or 90,000 ppm 1,4-dioxane (equal to 0, 0.13, 0.37, 1.01 or 2.96 g/kg bw/d and 0, 0.16, 0.40, 1.04 or 2.75 g/kg bw/d for males and females of the 0-30,000 ppm groups, respectively). Observations included clinical signs, body weight, food and water consumption, necropsy, and histopathological examination (on 2-4 animals per sex per group).

In the 90,000 ppm group, all males and females died. In the 30,000 ppm group 2 females died. Body weights were reduced in the 30,000 and 90,000 ppm male and female groups. Food and water consumption were dose-relatedly decreased in males (≥10,000 and ≥1,110 ppm, respectively) and in females (≥30,000 and ≥3,330 ppm, respectively). Upon histopathology, nuclear enlargement of the olfactory epithelium, swelling and vacuolic change of the central area in the liver, hydropic change of the proximal renal tubule, and vacuolic change in the brain were seen in the 30,000 ppm

male and female groups. Nuclear enlargement of the olfactory epithelium was also seen in the 10,000 ppm male and female groups (Japan Bioassay Research Center, 1998a).

Groups of 10 male and 10 female F344/DuCrj rats received drinking water containing 0, 640, 1,600, 4,000, 10,000 or 25,000 ppm 1,4-dioxane (equal to 0, 0.06, 0.15, 0.33, 0.76 or 1.90 g/kg bw/d and 0, 0.10, 0.20, 0.43, 0.87 or 2.01 g/kg bw/d for males and females of the 0-25,000 ppm groups, respectively) for 13 weeks. Observations included clinical signs, body weight, food and water consumption, haematology, biochemistry, urinalysis, necropsy, organ weights and histopathological examination.

One female in the 25,000 ppm group died. Body weights were reduced in the 10,000 and 25,000 ppm male and female groups. Food consumption was decreased in males at 25,000 ppm and in females ≥10,000 ppm. Water consumption was dose-relatedly decreased in all treated males and in females ≥1,600 ppm. In males, effects on haematology, biochemistry or urinalysis parameters were observed at 25,000, ≥4,000 and ≥4,000 ppm, respectively. In females, this occurred at ≥10,000, ≥4,000 and ≥10,000 ppm, respectively. Absolute and relative kidney weights were increased in females ≥1,600 ppm. Upon histopathology, non-neoplastic lesions were observed in the nasal cavity (nuclear enlargement of the olfactory and respiratory epithelium), trachea (nuclear enlargement of the epithelium), liver (vacuolic change and swelling of the central area, granulation), kidney (hydropic change and nuclear enlargement of the proximal tubule) and brain (vacuolic change) in both males and females at 1,600 ppm or greater groups. No effects were found on the reproductive organs. Based on the findings at 1,600 ppm (histopathology in males and females, and kidney weight changes in females), the NOAEL in this study can be established at 640 ppm (equal to 0.06 g/kg bw/d for males and 0.10 g/kg bw/d for females) (Japan Bioassay Research Center, 1998b).

In a limited repeated dose study 50 white rats of an unspecified inbred strain were given drinking water containing 5% 1,4-dioxane for 1-10 days (corresponding to ca. 4,150 mg/kg bw). Thirty-five rats died and were not examined. The remaining 15 surviving animals were killed for macroscopic and electron microscopic examination of the kidneys on days 1, 3, 5, 7, 8 and 10 during treatment. No further details, i.e. on number of animals sacrificed, are available. Studies on control animals were not mentioned. No macroscopic changes were seen in rats killed during the first 7 days of exposure, but, in rats killed later, frequent enlargements of the kidneys with superficial aberrations were observed. Microscopic examination of the kidneys from rats sacrificed after 3 days of exposure showed swollen epithelial cells in the proximal section of the nephron. Vesicular degeneration of tubular epithelium was first observed after 5 days of exposure and became more severe from the 7th day of exposure onwards. An accumulation of intracellular hyaline droplets was observed by electron microscopy, followed by enlargement of the basal labyrinth. Subsequent changes were noted in the tubular epithelium followed by degeneration, ultimately resulting in necrosis (David, 1964).

Dermal

In a very limited study by Fairley et al. (1934) repeated application of an 80% aqueous 1,4-dioxane solution to the skin of four rabbits and guinea-pigs under non-occlusive conditions led, within 50 to 100 days to damage of the renal tubulus cells and glomeruli as well as haemorrhages in the renal medulla, and liver degeneration. From this study the only conclusion can be that dermal absorption occurs and that the same effects were obtained as after oral administration.

Inhalation

No adequate general short-term toxicity studies by inhalation exposure are available. Torkelson et al. (1974) mentioned some inhalation studies with rats, rabbits, guinea-pigs, and dogs with concentrations ranging from 180 to 360 mg/m^3 during 82 to 136 7-hour exposures. It is stated that in all of these studies no adverse effects were noted with respect to appearance, demeanour, growth, mortality, haematological and clinical chemical studies, organ weights, or gross and microscopic pathological examination (no details available). A special study with inhalatory exposure is described under special investigations below.

A 2-year chronic toxicity and carcinogenicity study using rats was performed. The effects on carcinogenicity are described in Section 4.1.2.8 "Carcinogenicity". The study design and toxicological effects are given here.

Groups of 288 male and 288 female Wistar rats were exposed to air containing 400 mg 1,4-dioxane vapour/m^3 for 7 hours/day, five days a week for a total of 2 years. Based on 100% absorption, 240 ml/min breathed air, a body weight of 400 g and 7-hour exposure/day a dosage of 108 mg/kg bw/day can be calculated. A control group of 192 rats/sex was used.

No effects were seen on clinical signs (including activity, demeanour, eye and nasal irritation, skin condition and respiratory distress), body weights or mortality. Some slight changes were observed in haematological values, but these were within the normal physiological limits and not considered of toxicological importance. BUN and AP values in treated male rats were slightly decreased. Changes in liver, kidney or spleen weights were not observed.

Upon gross and microscopic examination, no treatment-related non-neoplastic effects were found in tissues/organs, including the reproductive organs. The NOAEL for toxic effects can be considered at 400 mg 1,4-dioxane/m^3 (Torkelson et al., 1974).

Special investigations

In a study by Stott et al. (1981), male Sprague-Dawley rats (4-6 per group) received 0, 10 or 1,000 mg 1,4-dioxane/kg bw/day via drinking water for 11 weeks (7days/week). 7 Days prior to termination, the rats received [6-^{3}H]thymidine. After sacrifice the livers were examined. After repeated exposure, 1,4-dioxane was cytotoxic to hepatic tissue at the highest dose level, as evidenced by an increase in liver to body weight ratio and a significant rise in hepatic DNA synthesis as measured by [6-^{3}H]-thymidine incorporation, accompanied by a minimal degree of hepatocellular swelling. No changes relative to controls were observed in rats dosed with 10 mg/kg bw/day.

Behaviour

In a study for effects on behaviour female CFE rats (8-10/group) were exposed to 1,4-dioxane concentrations of 5,490, 10,980 and 21,960 mg/m^3 during 4 hours/day, 5 days/week for 2 weeks.

The avoidance response was dose-relatedly decreased. At 21,960 mg/m^3 a few animals also showed a decreased escape response. Maximal decrease for both parameters was seen after 2 days exposure. Thereafter the effects became less severe. All effects were reversible. Other severe behavioural effects (e.g. motor imbalance, frank depression or ataxia) were not seen (Goldberg et al., 1964).

4.1.2.6.2 Studies in humans

Oral

No data available.

Dermal

See the study of Johnstone (1959) under inhalation below.

A 47-year-old female laboratory technician showed inflammatory skin changes in the upper extremities and to a lesser extent in the face after several weeks of dermal exposure to 1,4-dioxane. Histological examinations of the stripy skin changes showed symptoms of eczema. It should be noted that the involved woman had previously a burn which is a confounder in assessing the skin changes (Sonneck, 1964).

Inhalation

The first records of death caused by exposure to 1,4-dioxane date from 1933 when five patients died 5 to 8 days after the symptoms appeared (Barber, 1934). These symptoms are similar to those described by Johnstone (1959) who reported the case of a 21-year old worker who had been exposed to 1,4-dioxane for one week in a closed, non-ventilated room without respiratory equipment. The 1,4-dioxane concentration ranged from 720 mg/m^3 to 2,340 mg/m^3. Moreover, he had repeatedly dipped his hands into a tub containing liquid 1,4-dioxane. The man had been an alcoholic. The signs experienced included pain in the upper abdomen, emanating into the sides, followed by hypertonia and neurological symptoms. After one week of hospitalisation the man died of kidney failure. Necropsy included renal cortex necrosis with severe interstitial haemorrhages. Severe centrilobular necrosis was found in the liver. The brain showed signs of demyelination and partial loss of nerve fibre tissue.

In vitro

The effect of 1,4-dioxane on human haemoglobin was investigated spectrophotometrically. At concentrations of 0.1-0.5% oxyhaemoglobin was converted into methaemoglobin while at concentrations of 10-20%, in addition to methaemoglobin conversion, haemoglobin-1,4-dioxane complex formation was observed. Protein coagulation occurred as the 1,4-dioxane concentration was further increased (40%) (Baykut et al., 1978).

4.1.2.6.3 Summary of repeated dose toxicity

1,4-Dioxane was administered in several repeated oral dose studies over longer and shorter periods of time. Although most of these studies can be considered as chronic toxicity and carcinogenicity studies or as a study for special investigations, there were some subacute and semi-chronic studies available. In a limited study with rats effects on the kidneys were seen after administration of 5% 1,4-dioxane in the drinking water for 1 to 10 days. In rats a rise in (6-3H)-thymidine incorporation into liver DNA accompanied by a minimal degree of hepatocellular swelling was observed after oral dose levels higher than 10 mg/kg bw for 11 weeks. In the 2- and 13-week oral studies and in the longer term oral studies (see Section 4.1.2.8), with drinking water doses ranging from 0.05-9% for mice and from 0.01-9% for rats, toxicological effects observed in rats and mice after oral administration in the drinking water included severe effects

on the nasal cavity, lungs, liver and kidneys, with a NOAEL of 0.01% (equivalent to 10 mg/kg bw/day) in a 2-yr rat study. The LOAEL for these severe effects was above the cut-off value for R48.

For inhalation exposure a 2-year chronic toxicity and carcinogenicity study with rats was available. In this study the NOAEL for toxic effects was considered to be 400 mg 1,4-dioxane/m^3 (equivalent to 108 mg/kg bw/d), the highest dose tested. In a very limited dermal experiment, using rabbits and guinea-pigs, effects on liver and kidneys were observed, indicating again that the substance was absorbed through the skin. Effects (avoidance response) on the CNS were dose-relatedly increased in rats at concentrations ≥5,400 mg/m^3.

Under extreme conditions, occupational exposure resulted in adverse effects in humans. A woman with a skin burn developed inflammatory skin changes and clinical symptoms of eczema after occupational dermal exposure. In a male alcoholic, occupational inhalation exposure to concentrations of 720 to 2,340 mg/m^3 caused hypertonia and neurological symptoms followed by death due to kidney failure. Necropsy showed renal cortex and centrilobular liver necrosis and brain damage. An *in vitro* experiment on human haemoglobin showed the conversion of oxyhaemoglobin to methaemoglobin at concentrations of 0.1-0.5% of 1,4-dioxane, while formation of haemoglobin-1,4-dioxane complex was observed at concentrations of 10-20%.

4.1.2.7 Mutagenicity

Genotoxicity assays with 1,4-dioxane are summarised in **Table 4.11**. Only qualified tests (performed according to OECD guidelines, or performed in accordance with these guidelines) were presented. Where relevant, the volatility of 1,4-dioxane was taken into account.

Table 4.11 Genotoxicity studies with 1,4-dioxane

Assays	Species	Protocol	Results	References
In vitro studies				
Bacterial gene mutation test	S. typhimurium (4 strains)	other: Ames et al. (1975b)	negative (-/+ S9)	Haworth et al., 1983
Bacterial gene mutation test	S. typhimurium (5 strains)	other: Ames et al. (1975a)	negative (-/+ S9)	Stott et al., 1981
Bacterial gene mutation test	S. typhimurium (2 strains)	other: Ames et al. (1975b)	negative (-/+ S9)	Nestmann et al., 1984
Bacterial gene mutation test	S. typhimurium (5 strains)	other: Ames et al. (1975b)	negative (-/+ S9) *	BASF, 1979a/b/c
Chromosome aberration test	CHO-cells	other: Galloway et al., 1985	negative (-/+ S9)	Galloway et al., 1987
Gene mutation test (HGPRT test)	CHO-cells	OECD 476	negative (-/+ S9)	BASF, 1991

Table 4.11 continued overleaf

Table 4.11 continued Genotoxicity studies with 1,4-dioxane.

Assay	Species	Protocol	Results	References
Aneuploidy test	S. cerevisiae	other: Parry and Zimmerman, 1976	negative	Zimmermann et al., 1985
Sister Chromatid Exchange test	CHO-cells	other: Galloway et al., 1985	positive (-S9); negative (+S9)	Galloway et al., 1987
DNA repair test	*E.coli* K-12 343/113 uvrB$^-$/rec A$^-$ and uvrB$^+$/rec A$^+$	other: Mohn et al., 1984	negative	Héllmer and Bolcsfoldi, 1992
Unscheduled DNA synthesis test	rat hepatocytes	other: Butterworth et al., 1987a	negative	Goldsworthy et al., 1991
Cell transformation assay	Balb/3T3 cells	other: Schechtman and Kouri, 1977	negative (-/+ S9)	Microbiological Associates, 1980a/b
Cell transformation assay	Balb/3T3 cells	other: Sheu et al., 1987	positive (- S9) (+ S9 not tested)	Sheu et al., 1988
Alkaline elution assay	rat hepatocytes	unknown	positive	Sina et al., 1983
In vivo studies				
Dominant lethal assay	mouse	other: Röhrborn and Vogel, 1967 ip 2,500 ml/kg bw	negative	BASF, 1977
SLRL assay	Drosophila melanogaster	unknown	positive	Yoon et al., 1985
Micronucleus assay	B6C3F1 mice	Unknown ip 2,000-4,000 mg/kg bw	negative	McFee et al., 1994
Micronucleus assay	CD-1 mice	Unknown ip 2; 500-3,200 mg/kg bw	negative	Morita, 1994
Micronucleus assay	C57BL6 mice	Unknown po 900-5,000 mg/kg bw	positive	Mirkova, 1994
Micronucleus assay	Balb/c mice	Unknown po 3,600-5,000 mg/kg bw	negative	Mirkova, 1994
Micronucleus assay	CBA mice	Unknown po 1,800 mg/kg bw	negative	Tinwell and Ashby, 1994
Micronucleus assay	C57BL6 mice	Unknown po 3,600 mg/kg bw	negative	Tinwell and Ashby, 1994
Unscheduled DNA synthesis test	rat liver	other: Butterworth et al., 1987b	negative	Goldsworthy et al., 1991
Unscheduled DNA synthesis test	rat nasal epithelial cells	other: Bermudez and Allen, 1984	negative	Goldsworthy et al., 1991
Replicate DNA synthesis test	Fisher 344 rat hepatocytes	other: Uno et al., 1992a/b	negative	Uno et al., 1994
Alkaline elution assay (DNA ss breaks) in liver	Sprague Dawley rats	other	positive	Kitchin and Brown, 1990

* 1,4-dioxane (purity 99%) tested was once containing 2,6-di-tert butyl-p-cresol, once peroxide, and was once peroxide-free.

4.1.2.7.1 Studies *in vitro*

Bacterial assays in *Salmonella typhimurium* have been carried out in 2 to 5 strains at several dose levels according to Ames et al. (1975a/b). All tests were negative with and without metabolic activation (Nestmann et al., 1984; Haworth et al., 1983; Stott et al., 1981; BASF, 1979a/b/c). In a gene mutation assay (HGPRT-test) in CHO cells negative results were found both with and without metabolic activation; although the test concentrations ranged from 0.05-10.0 mg/ml the necessary cytotoxicity was not observed in this assay (BASF, 1991). Also negative results were obtained in a test for chromosomal aberrations both without or with metabolic activation (Galloway et al., 1987). A test for SCE's in CHO-cells was positive without metabolic activation but negative with metabolic activation (Galloway et al., 1987). In yeast there was no increase in aneuploidy (Zimmermann et al., 1985). In an UDS-test using primary isolated rat hepatocytes 1,4-dioxane tested negative (Goldsworthy et al., 1991). A cell transformation assay with Balb/3T3 cells tested without metabolic activation was positive (Sheu et al., 1988), while another test (both with and without metabolic activation) showed negative results (Microbiological Associates, 1980a/b). An alkaline elution test for DNA single strand breaks was positive in rat hepatocytes at cytotoxic concentrations (Sina et al., 1983).

4.1.2.7.2 Studies *in vivo*

In total 6 micronucleus tests were performed. In C57BL6 mice oral application of 1,4-dioxane resulted both in micronucleus induction (Mirkova, 1994) as well as in negative results (Tinwell and Ashby, 1994). Negative results were also observed after oral application of 1,4-dioxane in BALB/c mice (Mirkova, 1994) and CBA mice (Tinwell and Ashby, 1994) as well as after i.p. application in B6C3F1 mice (McFee et al., 1994) and CD-1 mice (Morita, 1994). Except for the oral study with BALB/c mice and the i.p. study with CD-1 mice the ratio PCE/NCE was decreased, indicating that the bone marrow was reached.

A dominant lethal assay in male mouse was negative after a single i.p. injection. The rate of conception, mean number of implantations, percentage of living foetuses and mutagenicity index were unchanged (BASF, 1977). At high dosages positive results were obtained in a sex-linked recessive lethal test in *Drosophila melanogaster* (Yoon et al., 1985).

Neither a single application of 1,000 mg/kg bw, nor treatment with 1% 1,4-dioxane in drinking water for 2 weeks or with 2% 1,4-dioxane for 1 week, induced unscheduled DNA synthesis in primary rat hepatocytes. Negative results for unscheduled DNA synthesis were also found in rat nasal respiratory epithelial cells (from the nasoturbinate or the maxilloturbinate) after treatment of rats with 1% 1,4-dioxane in drinking water for 8 days, or after treatment with 1% in the drinking water for 8 days with an additional single gavage dose of up to 1,000 mg/kg bw 1,4-dioxane (Goldsworthy et al., 1991). In an alkaline elution tests 1,4-dioxane induced DNA single strand breaks in liver cells especially at dose levels higher than 2,500 mg/kg (Kitchin and Brown, 1990).

4.1.2.7.3 Special investigations

In vivo

Rats treated with a single oral dose of 1,000 mg 1,4-dioxane/kg bw after pre-treatment of 0.01, 0.1, 1.0 or 2.0% 1,4-dioxane for 1 day up to 9 weeks in drinking water showed increased

incorporation of [6-^{3}H]thymidine into liver DNA after pre-treatment at concentrations ≥0.1% in drinking water. These effects remained the same after several weeks of administration. Substitution of damaged cells and hence cytotoxicity are probably involved (BASF, 1987; Goldsworthy et al., 1991).

A single gavage administration of 1,000 mg/kg bw 1,4-dioxane to rats did not result in hepatocyte cell proliferation, as no increases in the liver to body weight ratio and the labelling index (with ^{3}H-methyl thymidine) were found. In contrast, continuous administration of 1% 1,4-dioxane in the drinking water for 1 to 2 weeks produced a two-fold increase in the hepatic labelling index, suggesting cell proliferation (Goldsworthy et al., 1991). After mapping the nasal tumours as found in the NCI chronic rat bioassay (see Section 4.1.2.8), Goldsworthy et al. (1991) investigated cell proliferation in the nasal epithelium from those sites were the majority of the tumours originated. No histopathological lesions were present in rats given 1% 1,4-dioxane in the drinking water for up to 2 weeks, and no increases in labelling index (with ^{3}H-methyl thymidine) were observed at any site.

Despite the observed hepatoxicity at 1,000 mg/kg bw/day (see Section 4.1.2.6.1) Stott et al. (1981) observed no *in vivo* DNA alkylation or increase in hepatic DNA repair in rats dosed by gavage at this dose level.

CBA/J mice (number unknown) were injected i.p. seven times over 7 days with 0.5 ml of a 0.1, 1.0, 5, 10 or 20% 1,4-dioxane solution. The 20% concentration caused mortality even before all seven injections were given. No biologically significant changes in ^{3}H-thymidine incorporation rates were recorded for isolated lymphocytes (Thurman et al., 1978).

In vitro

In a study by Thurman et al. (1978) lymphocytes from untreated mice were incubated with 1,4-dioxane in concentrations of 0.25% and 0.5%. The rate of ^{3}H-thymidine incorporation into the lymphocytes fell and the ability of the T-lymphocytes to be stimulated by mitogens was reduced, while that of the B-lymphocytes was greatly increased. Levels of 1.0 % 1,4-dioxane and above were cytotoxic. Human lymphocyte cultures treated for 2 hours with 1,4-dioxane in concentrations of 0.25 to 1.0% showed no significant effects. However, a dioxane level of 2.5% resulted in a marked increase in phyto-haemagglutinine-stimulated DNA synthesis.

In vitro incubation of 1,4-dioxane and DNA in the presence of microsomes showed no signs of covalent DNA binding. Benz[a]pyrene was used as a positive control (Woo et al., 1977d).

4.1.2.7.4 Studies with a metabolite

An Ames test, an UDS test on rat hepatocytes and an HGPRT-test with CHO cells performed with a metabolite of 1,4-dioxane, 1,4-dioxan-2-one, were all negative (BASF, 1979d; Goldsworthy et al., 1991; BASF, 1985). A cell transformation test with Balb/3T3 cells was negative with metabolic activation and positive without metabolic activation (Microbiological Associates, 1981a/b, 1986).

4.1.2.7.5 Summary of mutagenicity

In vitro, clastogenic and mutagenic effects were not reported. *In vivo*, a dominant lethal test was negative and in a test for sex linked recessive lethals in Drosophila melanogaster positive results

were obtained. From 6 performed micronucleus tests one test orally performed with C57BL6 mice showed a positive result. Three other oral tests using C57BL6 mice, BALB/c, and CBA mice and two i.p tests with B6C3F1 and CD-1 mice showed negative results. In 4 of these negative tests the target organ was reached. *In vitro* as well *in vivo* alkaline elution tests pointed to DNA strand breaks at high dose levels. 1,4-Dioxane can also induce sister chromatid exchanges in CHO cells and cell transformation in Balb/3T3 cells.

Although there are some indications that 1,4-dioxane may be weakly genotoxic, 1,4-dioxane is considered a non-genotoxic compound based on the total weight of evidence. This is further supported by the absence of DNA-adducts at hepatotoxic doses.

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

The available studies on carcinogenicity are summarised in table **Table 4.12**.

Table 4.12 Carcinogenicity studies with 1,4-dioxane

Study type	Duration	Result	Reference
Mice 0.5 or 1% in drinking water	90 weeks	liver damage, pneumonia/rhinitis hepatocellular carcinomas	NCI, 1978
Mice 0.05, 0.2 or 0.8% in drinking water	104 weeks	damage to nasal cavity, lungs, kidney hepatocellular carcinomas/adenomas	Yamazaki et al., 1994; Japan Bioassay Research Center, 1998c
Rats 1% in drinking water (equivalent to 1g/kg bw/d)	63 weeks	potential for kidney damage and liver tumours	Argus et al., 1965
Rats 0.75, 1.0, 1.4 or 1.8% in drinking water	13 months	kidney damage nasal and liver carcinomas	Hoch-Ligeti et al., 1970; Argus et al., 1973
Rats 0.01, 0.1 or 1.0 % in drinking water	716 days	kidney and liver damage nasal and liver carcinomas	Kociba et al., 1974
Rats 0.5 or 1% in drinking water	110 weeks	damage to liver, kidney, stomach, pneumonia/ rhinitis	NCI, 1978; Goldsworthy et al., 1991
Rats 0.02, 0.10 or 0.50% in drinking water	104 weeks	damage to nose, liver, kidney nasal carcinomas; liver carcinomas/adenomas	Yamazaki et al., 1994; Japan Bioassay Research Center, 1998c
Guinea pig 0.5-2% in drinking water	23 months	kidney and lung damage potential for liver and gall bladder tumours	Hoch-Ligeti and Argus, 1970
Rats 400 mg/m^3 by inhalation	2 years	slight increase in lymphoreticular cell sarcomas in males and mammary gland adenomas in females	Torkelson et al., 1974

Oral

In a drinking water experiment groups of 50 male and 50 female B6C3F1 mice were exposed to 0, 0.5 and 1% 1,4-dioxane for 90 weeks. The mean doses were 720 and 830 mg/kg bw/day for males and 380 and 860 mg/kg bw/day for females. Observations included clinical signs, body weight, food and water consumption, necropsy and histopathology. Body weights were not consistently affected, although the weight of the high dose females was lower than that of the controls during the second year of the study. Survival rates of the dosed mice (46/50 in low and

45/50 in high dose males, 39/50 in low and 28/50 in high dose females) were lower than those of the controls (48/50 in males and 45/50 in females), but a sufficient number of animals were at risk for development of late-appearing tumours. Treatment-related non-neoplastic lesions in males and females included hepatic cytomegaly, pneumonia and rhinitis. In both sexes an increased incidence in hepatocellular carcinomas was seen. The incidences were 2/49, 18/50 and 24/47 for males and 0/50, 12/48 and 29/37 for females at 0, 0.5 and 1%, respectively. Also an increase in the incidence of hepatocellular adenomas plus carcinomas was seen: at 0, 0.5 and 1% 8/49, 19/50 and 28/47 for males and 0/50, 21/48 and 35/37 for females, respectively. One nasal adenocarcinoma was seen in a low dose female and one in a high dose male. No effects were seen on male and female reproductive organs (NCI, 1978).

In a long-term drinking water experiment groups of 50 male and 50 female mice (Crj:BDF_1) were administered 1,4-dioxane in drinking water for 104 weeks. The dose rates were 0, 0.05, 0.2 or 0.8% (equal to 0, 0.066, 0.25 or 0.77 g/kg bw/d for males and 0, 0.077, 0.32 or 1.07 g/kg bw/d for females, respectively). All animals were examined for clinical signs, body weight, food and water consumption, haematology, biochemistry and urinalysis. After 105 weeks the animals were sacrificed. Necropsy and histopathology were performed on all animals, including dead and moribund animals. The survival of females at the 0.2 and 0.8% groups was significantly lower than those of the controls (17/50 and 5/50 vs 29/50, respectively) due to liver tumours. Mean body weights of females at 0.2 and 0.8% and males at 0.8% were lower than those of controls. Food and water consumption were decreased in high dose males and females. In males, effects on haematology, biochemistry or urinalysis parameters were observed at 0.8%, ≥0.2% and 0.8%, respectively. In females, this occurred at ≥0.2%. Absolute and relative lung weights were increased in males at 0.8% and in females at ≥0.2%. Upon histopathology, non-neoplastic lesions were observed in the nasal cavity (nuclear enlargement and atrophy of the olfactory and respiratory epithelium, inflammation), trachea (atrophy and/or nuclear enlargement of the epithelium), lung (accumulation of foamy cells, nuclear enlargement and atrophy of the bronchial epithelium), kidney (nuclear enlargement of the proximal tubule) in males and females at 0.2% or greater groups. In males, lesions were also observed in liver (angiectasis) at 0.8% and in testis (decreased mineralisation) at ≥0.2%. Hepatocellular carcinomas occurred with significantly increased incidences in males at 0.8% and in all treated female groups (incidence in males was 15/50, 20/50, 23/50 and 36/50 and in females 0/50, 6/50, 30/50 and 45/50 for controls, 0.05, 0.2 and 0.8% groups, respectively). Increased incidences of hepatocellular adenomas were seen in males and females at 0.05 and 0.2% (incidence in males was 7/50, 16/50, 22/50 and 8/50 and in females 4/50, 30/50, 20/50 and 2/50 for controls, 0.05, 0.2 and 0.8% groups, respectively). One nasal esthesioneuroepithelioma was seen in one male at 0.8% and one nasal adenocarcinoma was seen in one female at 0.8%. The LOAEL can be established at 0.05%, equal to 0.066 g/kg bw/d for males and 0.077 g/kg bw/d for females (Yamazaki et al., 1994; Japan Bioassay Research Center, 1998c).

In a drinking water study, 26 Wistar rats received 300 mg 1,4-dioxane/animal (equivalent to 1 g/kg bw/day) for 63 weeks. A control group of 6 animals was used. In two rats that died 21½ weeks after the beginning of the experiment, histological changes appeared in the entire liver. Groups of cells with strongly enlarged hyperchromic nuclei were found, generally located periportally. There were similar changes in rats that died or were killed after 63 weeks on study. In addition groups of large cells with reduced cytoplasmic basophilia were evident. At the end of the treatment, 6 of the treated animals had hepatomas. One of these six had also renal pelvis carcinoma and another myeloid leukaemia. Severe kidney damage was also reported. These changes often resembled glomerulonephritis. There are no data available about the control

group. This study is dated and not performed according to current guidelines; however, the results show a potential for kidney damage and liver tumours (Argus et al., 1965).

In a later study, groups of 30 male Charles River CD rats were given daily via the drinking water (freshly prepared) 0, 0.75, 1.0, 1.4 or 1.8% 1,4-dioxane (equal to 750, 1,000, 1,400 or 1,800 mg/kg bw/day) for 13 months. Tumours of the nasal cavity occurred in 0/30, 1/30, 1/30, 2/30 and 2/30 rats of the control, 0.75, 1.0, 1.4 or 1.8% groups, respectively. The earliest effects observed (time and dose levels were not clear) were an increase in the nuclear size of hepatocytes mostly in the periportal areas. Groups of large cells with reduced cytoplasmic basophilia gave the liver a slightly nodular appearance. Two of the animals in the highest dose group also developed hepatocellular carcinomas. Histological examination at termination showed epidermoidal carcinoma with adenocarcinoma-like areas in the nose. Epithelial papillomas were also observed (Hoch-Ligeti et al., 1970). Argus et al. (1973) reported in a later publication of the same study a dose-dependent increase in liver tumours (nodules and hepatomas). In the control group, 0 nodules were seen, in the 0.75% group, 4, in the 1.0% group, 9, in the 1.4% group, 13 and in the 1.8% group 11 (absolute figures are missing). Hepatomas were seen in the 1.4 and 1.8% group; which amounted to 3 and 12, respectively. Furthermore, marked kidney damage, including glomerulonephritis and pyelonephritis with epithelial thickening of Bowman's capsules, periglomerular fibrosis, localised extended distal tubulus lumina, nuclear atypia and numerous multinuclear giant cells were seen at all dose levels. No data were available about mortality. This study is dated and not performed according to current guidelines; however, the results show a potential for liver tumours.

Groups of 60 male and 60 female Sherman rats received via the drinking water 0, 0.01, 0.1 or 1% 1,4-dioxane (equal to 0, 9.6, 94 or 1015 mg/kg bw/day for males and 0, 19, 148 or 1,599 mg/kg bw/day for females) for 716 days. Within 2 days after initiating the study the body weights of both sexes at 1.0% 1,4-dioxane were significantly lower than controls. The body weights remained depressed throughout the study. The concentration of 1% 1,4-dioxane led within two to four months to a severe reduction of survival rates in both sexes, nearly half of the group succumbing after four months. The survival rate after four months was essentially the same for all groups. No effects on haematology were observed and the only significant alteration in terminal organ weights was a significantly increased liver weight in rats receiving 1% 1,4-dioxane. In rats at 0.1 and 1.0% 1,4-dioxane, gross and histopathological examination revealed variable degrees of renal tubular epithelial and hepatocellular degeneration and necrosis, accompanied by regenerative activities in the liver (hepatocellular hyperplastic nodule formation) and renal tubuli. No effects were seen on male and female reproductive organs. Only in the highest dose group were treatment-related tumours found: in the liver, carcinomas were found in 10/66 animals surviving at 12 months and cholangiomas in 2/66 animals, while squamous cell carcinomas of the nasal cavities were found in 3/66 animals. The NOAEL in this study was 0.01% 1,4-dioxane, equal to 9.6 or 19 mg/kg bw in males and females, respectively (Kociba et al., 1974).

In a NCI (1978) study groups of 35 male and 35 female Osborne-Mendel rats were exposed via the drinking water to 0, 0.5 and 1% 1,4-dioxane for 110 weeks. The mean dose levels were 240 and 530 mg/kg bw/day for male rats and 350 and 640 mg/kg/bw/day for female rats. Observations included clinical signs, body weight, food and water consumption, necropsy and histopathology. Body weights were not consistently affected, although the weight of the high dose animals was lower than that of the controls during the second year of the study. The survival rates of the rats of both dose groups were significantly lower than that of controls, but sufficient animals of each sex were alive at 52 weeks (33/35, 26/35 and 33/35 for males and 35/35, 30/35 and 29/35 for females at 0, 0.5 and 1%, respectively) to be at risk for the

development of late-appearing tumours. Nonneoplastic lesions associated with dioxane treatment were observed in the kidney (tubular degeneration), liver (cytomegaly) and stomach (ulceration). A higher incidence of pneumonia and rhinitis occurred in males and females of both dose groups. Rats of both sexes developed squamous cell carcinomas in the nasal cavities (0/33, 12/33 and 16/34 for control, low and high dosed males and 0/34, 10/35 and 8/35 for control, low and high dosed females, respectively). In one high dose male these carcinomas extended to the retrobulbar tissues of the eye and in one low dose male into the brain. In addition, adenocarcinomas arose from the nasal mucosal epithelium in three high dose males, in one high dose female and one low dose female. The first nasal carcinomas developed after one year. A follow-up examination localised nasal tumours in the front third of the posterior meatus of the nasal cavities (Goldsworthy et al., 1991). Also an increase in hepatocellular adenomas was seen in females. The incidence was 0/31, 10/33 and 11/32 for control, low and high dosed females, respectively. No effects were seen on male and female reproductive organs (NCI, 1978).

In a long-term drinking water study groups of 50 male and 50 female rats (F344/DuCrj) were administered 1,4-dioxane for 104 weeks. The dose levels were 0, 0.02, 0.1 or 0.5% in drinking water (equal to 0, 0.016, 0.081 or 0.398 g/kg bw/d for males and 0, 0.021, 0.103 or 0.514 g/kg bw/d for females, respectively). All animals were examined for clinical signs, body weight, food and water consumption, haematology, biochemistry and urinalysis. After 105 weeks the animals were sacrificed. Necropsy and histopathology were performed on all animals, including dead and moribund animals. The survivals of males and females at 0.5% were significantly lower than those of the control group (22/50 vs 40/50 and 24/50 vs 38/50, respectively) due to nasal and liver tumours. Mean body weights at 0.5% males and females were lower than those of controls. Food and water consumption were not affected. In males, effects on haematology, biochemistry or urinalysis parameters were observed at ≥0.1%, 0.5% and 0.5%, respectively. In females, this occurred at 0.5%, 0.5% and ≥0.1%, respectively. Absolute and relative liver weights were increased in males at ≥0.1% and in females at 0.5%, while in females at this dose level also the lung and kidney weights were increased. Upon histopathology, non-neoplastic lesions were observed in the nasal cavity (see below), liver (see below) and kidney (nuclear enlargement of the proximal tubule) in males at 0.02% or greater groups, and in females at 0.1% or greater groups. Malignant neoplasms of the nasal cavity occurred only in 0.5% males and females, not in controls and 0.02 and 0.1% animals. These tumours included squamous cell carcinoma (3/50 and 7/50 for males and females, respectively), sarcoma (not otherwise specified; 2/50 in males), esthesioneuroepithelioma (1/50 and 1/50) and rhabdomyosarcoma (1/50 in males). Higher incidences of non-neoplastic lesions in the nasal cavity (respiratory metaplasia, nuclear enlargement and atrophy of the olfactory epithelium; nuclear enlargement, squamous cell metaplasia and squamous cell hyperplasia of the respiratory epithelium; hydropic change and sclerosis in the lamina propria; adhesion, inflammation and/or proliferation of the nasal gland) were also observed in 0.5% males and females. The lesions in the olfactory epithelium tended to occur at a somewhat higher incidence also in the 0.1% groups.

Hepatocellular adenomas and carcinomas occurred with significantly increased incidences in high dose males (24/50 and 14/50, respectively) and high dose females (38/50 and 10/50, respectively). Hepatocellular adenomas were seen at low incidences in males at 0.02 and 0.1% and in females at 0.1% (incidences in males were 0/50, 2/50 and 4/49 and in females 1/50, 0/50 and 5/50 for controls, 0.02 and 0.1% groups, respectively). The incidence of non-neoplastic lesions in the liver (including spongiosis and hyperplasia) was increased at 0.1 and 0.5% in both males and females. The incidence of hyperplasia in males was 3/50, 2/50, 10/50 and 24/50 and in females 3/50, 2/50, 11/50 and 47/50 for controls, 0.02, 0.1 and 0.5% groups, respectively. The incidence of spongiosis was dose-relatedly increased in males at all dose levels and in females at

0.5% (incidence in males was 12/50, 20/50, 25/50 and 40/50 and in females 0/50, 0/50, 1/50 and 20/50 for controls, 0.02, 0.1 and 0.5% groups, respectively).

In males the incidences of mesothelioma of the peritoneum, fibroma of the subcutis and fibroadenoma of the mammary gland at 0.5% were greater than in the control group. In females at 0.5% the incidence of adenoma of the mammary gland was increased.

In this study, an effect on the target organ liver (spongiosis) was seen in males even at the lowest dose tested 0.02% (although not statistically significant, there was a dose-related trend). Therefore 0.02% (equal to 0.016 g/kg bw/d) can be established as the LOAEL (Yamazaki et al., 1994; Japan Bioassay Research Center, 1998c).

In a limited study a group of 22 guinea pigs was exposed for 23 months to drinking water containing 1,4-dioxane in concentrations that ranged from 0.5 to 2.0%. An untreated control group was used. Nine treated animals developed peri- or bronchial and nodular mononuclear infiltration in the lung. In addition 2 guinea pigs developed gall bladder carcinomas, three had early hepatomas and one had an adenoma of the kidney. In the control animals 4/10 guinea pigs developed peripheral mononuclear cell accumulation and hyperplasia of the bronchial epithelium was observed in one. This study is dated and not performed according to current guidelines; however, the results show some indication for liver and gall bladder tumours (Hoch-Ligeti and Argus, 1970).

Inhalation

A group of 288 male and 288 female Wistar rats was exposed to air containing 400 mg 1,4-dioxane vapor/m^3 for 7 hours/day, five days a week for a total of 2 years. Based on a 100% absorption, 240 ml/min breathed air, a body weight of 400 g and 7 hours exposure/day a dosage of 108 mg/kg bw/day can be calculated. A control group of 192 rats/sex was used. For general toxicity results see also Section 4.1.2.6 “Repeated dose toxicity”. Upon gross and microscopic examination, no 1,4-dioxane characteristic nasal and liver tumours, as observed after oral administration, were seen. It is however not clear from the text whether or not the nasal cavity was adequately examined. The incidence of tumours observed in other organs/tissues appeared to be unrelated to exposure. The only difference from the control groups was an increase in lymphoreticular cell sarcomas in males (18% (37/206) versus 12% (18/150)) and in mammary gland adenoma in females (13% (29/217) versus 8% (11/139)), which were not statistically significant. For neoplastic effects, the NOAEL appears to be 400 mg/m^3, as there was no increase in tumour incidence and no gross pathological or histopathological evidence of organ injury (Torkelson et al., 1974).

Tumour promotion studies

Groups of 20-40 SENCAR mice were given a single dose of up to 1,000 mg/kg 1,4-dioxane by the oral, subcutaneous or dermal route and were then treated dermally three times a week for 20 weeks with 1.0 mg TPA. After 24 weeks, the papilloma rate had not increased. Therefore, 1,4-dioxane was not functioning as an initiator (the promotional activity was not tested) (Bull et al., 1986).

Groups of 9 male rats were treated by gavage with 100 or 1,000 mg/kg bw/day for 5 days/week for 7 weeks. The animals were initiated with diethylnitrosamine (30 mg/kg, i.p. 24 h after 2/3 partial hepatectomy). Ten days after the last administration the animals were killed and the number and total volume of gammaglutamyltransferase (GGT)-positive foci was studied in liver sections. 1,4-Dioxane at 1,000 mg/kg showed a clear positive result. The control and 100 mg/kg group gave negative results (Lundberg et al., 1987).

Special investigations

Peroxisomal proliferation

In a special study for the induction of peroxisomal proliferation 5 male Fischer 344 rats received 1,4-dioxane in drinking water (concentrations 0.1 and 1.0%) for 5 days. Neither a dose-related increase in liver/body weight, nor an increase in the peroxisomal enzyme palmitoyl-CoA-oxidase was observed (Goldsworthy et al., 1991).

In another study on peroxisomal proliferation (TSCAT, 1989b) male Fischer 344 rats (7/group) received an oral application of 0 or 2000 mg 1,4-dioxane/kg bw in physiologic saline for 9 days over an 11-day period. The animals were killed at 16 hours after the last exposure. Body weights were significantly decreased in comparison to the controls from day 5 and onwards. Absolute and liver weight/body weight ratio's were markedly increased but the protein concentration in the liver remained constant. No induction of palmitoyl-CoA-P activity was observed.

Mode of action

The mechanism behind the organ-specific toxicity and carcinogenic effects of 1,4-dioxane has not yet been elucidated. 1,4-Dioxane is considered as a non-genotoxic compound. The metabolite of 1,4-dioxane, 1,4-dioxan-2-one, is negative in an Ames test, a HGPRT-test with CHO cells and an UDS test on rat hepatocytes, while a cell transformation assay with Balb/3T3 cells was negative with metabolic activation and positive without metabolic activation.

In special studies for peroxisomal proliferation no effect of 1,4-dioxane was observed after oral administration up to 2,000 mg/kg bw, the highest dose tested, to rats during 5-9 days.

Increased incorporation of [6-^{3}H] thymidine into liver DNA was observed in rats given 1% 1,4-dioxane in their drinking water. Since this effect remained the same after several weeks of application, substitution of damaged cells and hence cytotoxicity are probably involved.

Non-linear toxicokinetics was demonstrated in the rat. Saturation of oxidation of 1,4-dioxane to HEAA and 1,4-dioxane-2-one at doses >10 mg/kg bw results in accumulation of 1,4-dioxane. The metabolites 1,4-dioxane-2-ol and β–hydroxyethoxy acetaldehyde may also accumulate in tissues with oxidative capacity. These effects may be related in view of the correlation between increased rates *in vitro* of DNA strand breaks, sister chromatid exchange at cytotoxic concentrations and *in vivo* in the organ-toxic dose range. In combination with the cytotoxicity at high doses this suggests accumulation of toxic metabolites not removed via oxide metabolic pathways.

Based on the above-mentioned findings, the mode of action is most likely cytotoxic in nature. The cytotoxic effects and organ damage via increased cell turnover may pave the way for liver carcinogenesis.

Although the nasal tumours observed cannot be explained from drinking water experiments and the underlying mechanism is unclear, it seems that nasal toxicity (as evidenced by the non-neoplastic lesions in the nasal cavity) plays a role in nasal carcinogenesis. It is believed that this toxicity is more likely associated with cytotoxicity and organ damage triggered by reactive metabolites than by a local effect due to volatilisation, because no tumours were observed after inhalatory exposure. It is noted that no cell proliferation was observed in the nasal epithelium of rats given 1% 1,4-dioxane in their drinking water for 2 weeks (Goldsworthy et al., 1991).

4.1.2.8.2 Studies in humans

In a cross sectional study 74 workers employed in 1,4-dioxane production and aged between 32 and 62 and were exposed for between 3 and 41 years to 1,4-dioxane concentrations of up to around 54 mg/m^3. The group showed no evidence of liver or kidney damage, nor had a higher incidence of cancer deaths than did the population at large. Two pensioned employees contracted cancer. One, 66-year old, died of liver and kidney insufficiency with diabetes mellitus, and was diagnosed having metastasis of a squamous epithelial carcinoma with unknown primary tumour. The other, 69 years old, died of circulatory failure with fluid from the pericardial space and uraemia. Myelifibrotic leukaemia was also noted. In 6 active workers no increased rate of chromosome aberrations in lymphocytes compared to controls was noted (Thiess et al., 1976).

A mortality study conducted on 165 employees engaged for one month to ten years or more in 1,4-dioxane production and exposed (not continuously) to 1,4-dioxane concentrations below 90 mg/m^3 showed no significant difference in observed deaths from overall cancer compared to the expected numbers (Buffler et al., 1978).

An epidemiology study on 151 employees in a textile factory, who were exposed for between one and six years to concentrations of up to 1,350 mg/m^3 of 1,1,1-trichloroethane blended with 4% 1,4-dioxane showed no significant differences in health, particularly on ECG changes and liver damage, when compared to a control group (Kramer et al., 1978).

Investigations on 80 men with potential exposure of 0.18 to 184 mg/m^3 of 1,4-dioxane showed no signs of 1,4-dioxane related health effects (NIOSH, 1977).

4.1.2.8.3 Summary of carcinogenicity

In a two-year inhalation study rats exposed to 400 mg/m^3 showed no 1,4-dioxane characteristic tumours.

From chronic drinking water experiments with rats and mice it can be concluded that 1,4-dioxane causes liver and kidney damage and liver adenomas and carcinomas. Furthermore, in rats nasal adenomas and carcinomas were also seen, accompanied by non-neoplastic lesions in the nasal cavity. These lesions were also observed in mice, but in mice 1,4-dioxane did not induce an increased incidence of nasal tumours.

The liver, kidney and nasal damage were seen at concentrations of 0.02%, 0.1% and 0.1%, respectively, in drinking water, while at 0.01% (equivalent to 10 mg/kg bw/day) no effects were seen. The liver tumours were seen at 1,4-dioxane drinking water concentrations of ≥0.05% for mice and of ≥0.1% for rats. The nasal tumours in rats were observed at 1,4-dioxane drinking water concentrations of ≥0.5%. Some indication for liver tumours were also obtained in guinea-pigs, but no information on non-neoplastic lesions was provided. Based on these results, 1,4-dioxane can be considered as a carcinogen for test animals. Since 1,4-dioxane is considered a non-genotoxic compound a threshold approach seems justified. The liver tumours are considered to be associated with cytotoxicity and organ damage, which seem to occur in particular at dose levels at which 1,4-dioxane metabolism becomes saturated. The nasal tumours cannot be explained from a drinking water study, however, it seems that nasal toxicity plays a role in the nasal carcinogenicity. The overall NOAEL, based on liver damage, can be considered to be 0.01% (equivalent to 10 mg/kg bw/day).

1,4-Dioxane has tumour promoter, but not initiator, properties.

Limited retrospective studies on workers who inhaled 1,4-dioxane concentrations up to 184 mg/m^3 for some years showed no evidence of occupational disease or an increased tumour incidence when compared to the general population. The chromosome aberration rate in lymphocytes in six 1,4-dioxane exposed workers was also comparable to the controls.

Despite the fact that the substance is a carcinogen in two species (rats and mice), with some indication for a third species (guinea pigs), the current classification as category 3 carcinogen (R40) is agreed with because the substance is a low potent carcinogen and the available data indicate a non-genotoxic mechanism. For both liver and nasal tumours, cytotoxic effects and organ damage are considered to be involved, which are subject to non-linear kinetics, implicating a threshold.

Based on a comparable data set, IARC (1999) concluded that there is *inadequate evidence* for the carcinogenicity of 1,4-dioxane in humans and that there is *sufficient evidence* for the carcinogenicity of 1,4-dioxane in experimental animals, and classified 1,4-dioxane as a Group 2B carcinogen (*possibly carcinogenic to humans*).

4.1.2.9 Reproduction toxicity and developmental toxicity

4.1.2.9.1 Studies in animals

In a multigeneration study (modified to include screening for dominant lethal and teratogenic effects) with ICR Swiss mice in which 1,1,1-trichloroethane (containing 3% 1,4-dioxane as stabiliser) and 1,2-dichloroethane were tested via the drinking water, a control group treated with 0.17 mg 1,4-dioxane/ml in 1% Emulphor in deionized water was used beyond a naive control group (deionized water only). As to the 1,4-dioxane/Emulphor control group, no effects were found on adults, reproductive performance, litter survival and growth, teratogenesis and general pathology. With respect to dominant lethal screening the frequency of dominant lethal factors was somewhat increased. Because this study was not performed with 1,4-dioxane as test substance this study is of limited relevance for evaluation (Lane et al., 1982).

In a developmental study testing 1,1,1-trichloroethane containing 3% 1,4-dioxane stabiliser to CD rats the “vehicle control” group contained 0.05% Tween 80 and 0.9 ppm 1,4-dioxane as stabiliser. When compared to the deionized/filtered water control group no significant changes were seen. Only some very minor differences for maternal body weight and water consumption were observed. Because this study was not performed with 1,4-dioxane as test substance, but only as stabiliser this study is of limited relevance for evaluation (George et al., 1989).

Groups of 17-20 pregnant Sprague-Dawley rats received by gavage 0, 0.25, 0.5 and 1.0 ml 1,4-dioxane/kg bw in water during days 6-15 of gestation. The animals were killed on day 21 of pregnancy. The females treated with 1 ml/kg bw showed a slightly smaller weight gain during treatment, which continued during the second stage of gestation. Food consumption in these females was decreased during treatment, especially evident in the first 2 days of treatment. The average weight of live foetuses from dams treated with 1 ml/kg bw was significantly less than controls. Number of implantations and number of foetuses alive was slightly decreased at 1 ml/kg bw and preimplantation loss was slightly increased at this dose level. At this dose level also a delay of ossification was found in the area of the sternum. There was no indication for teratogenicity. The NOAEL in this study for maternal and embryotoxicity can be established at 0.5 ml/kg bw, equivalent to 517 mg/kg bw (Giavini et al., 1985).

4.1.2.9.2 Studies in humans

No data available.

4.1.2.9.3 Summary of reproduction toxicity and developmental toxicity

There is one acceptable teratogenicity study provided, in which rats were treated with 0, 0.25, 0.5 or 1.0 ml 1,4-dioxane/kg bw in the drinking water. At 1 ml/kg slight maternal toxicity was seen together with embryotoxicity. No teratogenic effects were observed. The NOAEL for maternal and embryotoxicity was established at 0.5 ml/kg b.w (equivalent to 517 mg/kg bw/day).

In the oral 13-week studies and in the oral and inhalatory chronic toxicity/carcinogenicity studies no histopathological effects were observed in the reproductive organs of mice and rats (see Sections 4.1.2.6 and 4.1.2.8).

4.1.3 Risk characterisation

4.1.3.1 General aspects

The human population may be exposed by the oral, dermal and inhalatory route.

In the data set for 1,4-dioxane animal studies as well as human studies are available.

Radiolabeled 1,4-dioxane was rapidly and almost completely absorbed by rats after oral and inhalation exposure. After inhalation exposure, 1,4-dioxane was also well absorbed in humans. For dermal absorption no quantitative conclusions can be drawn. Available data indicate that 1,4-dioxane can readily penetrate the skin, but that the amount absorbed is limited due to rapid evaporation. For the risk assessment 100% absorption is chosen for the oral and inhalatory route, and 50% (default) for the dermal route.

Dioxane-related material was predominantly excreted via the urine in both rats and humans. In human urine, the major metabolite was β-hydroxyethoxyacetic acid (HEAA). Both HEAA and 1,4-dioxan-2-one were identified as the major metabolites in rat urine. Identification of these metabolites is pH dependent. At a high pH HEAA will be detected and at a low pH HEAA will be converted to 1,4-dioxane-2-one. These two metabolites are in chemical equilibrium. At low pH the equilibrium is more shifted to 1,4-dioxan-2-one and at high pH to HEAA. A PB-PK modelling study has indicated that dioxane may also be excreted into human milk.

The kinetic and metabolic fate of 1,4-dioxane is rather comparable in rats and humans. In rats, this fate was shown to be dose-dependent due to a limited capacity to metabolise 1,4-dioxane to HEAA and 1,4-dioxane-2-one. A low dose is rapidly metabolised and excreted via the urine, while higher doses (i.e. doses resulting in plasma levels above 100 µg/ml) saturate the metabolism of 1,4-dioxane to HEAA and 1,4-dioxane-2-one, resulting in decreased urinary excretion of metabolites and increased 1,4-dioxane in the expired air.

Repeated oral administration of 1,4-dioxane to rats at high doses causes further alterations in the kinetics of 1,4-dioxane, such as changes in oxidising enzyme capacity and a reduction in 1,4-dioxane accumulation in plasma. This correlates with the observed reduction in the 1,4-dioxane exhaled with respiratory air and the increase in the amount of CO_2, and possibly also

with the shift in the ratio of oxidation products (HEAA, 1,4-dioxane-2-one) to the possible intermediate products (1,4-dioxane-2-ol/β–hydroxyethoxy acetaldehyde).

Assessment of the available data indicates that 1,4-dioxane has a low acute oral, dermal and inhalatory toxicity. According to the EC criteria 1,4-dioxane needs not be classified on the basis of its acute toxicity. Concentrations ≥ 6,800 mg/m^3 or single oral administrations of 1,050 mg/kg bw causes signs of neurotoxicity in rats.

Based on all data provided (including human experience) it can be concluded that 1,4-dioxane is irritating to the eye and the respiratory tract, but not to the skin. However, being a fat solvent, 1,4-dioxane can cause eczema upon prolonged or repeated contact. Classification with R36/37 and R66 is appropriate.

With respect to sensitisation 1,4-dioxane was negative in a guinea-pig maximisation test. Therefore, according to EC criteria the substance need not be classified.

1,4-Dioxane was administered in several repeated oral dose studies over longer and shorter periods. Although most of these studies can be considered as chronic toxicity and carcinogenicity studies, there were some subacute and semi-chronic studies available. Toxicological effects observed in 2- and 13-week studies and in the longer-term studies in rats and mice after drinking water administration included severe effects on the nasal cavity, lungs, liver and kidneys, with an overall NOAEL of 0.01% (equivalent to 10 mg/kg bw/day) in a 2-year rat study. The LOAEL for these severe effects was above the cut-off value for R48.

There exist studies for special investigations from which no NOAEL can be derived.

No adequate repeated general toxicity studies on inhalation exposure are available. In a 2-year toxicity/carcinogenicity study with rats no toxic effects were observed at 400 mg/m^3, the only dose tested. No nasal and liver tumours, as observed after oral administration in drinking water, were seen. The NOAEL can be established at ≥400 mg/m^3 (equivalent to 108 mg/kg bw/d).

Based on the weight of evidence the substance is considered a non-genotoxic compound.

1,4-Dioxane can be considered as a carcinogen for test animals, and is classified as a category 3 carcinogen (R40). In drinking water studies with rats and mice, liver and kidney damage and liver adenomas and carcinomas were induced. In rats also nasal adenomas and carcinomas were observed, accompanied by non-neoplastic lesions in the nasal cavity. These lesions were also observed in mice, but in mice 1,4-dioxane induced no increased incidence of nasal tumours. The liver, kidney and nasal damage were still seen at concentrations of 0.02%, 0.1% and 0.1%, respectively, in drinking water, while at 0.01% (equivalent to 10 mg/kg bw/day) no effects were seen. The liver tumours were seen at 1,4-dioxane drinking water concentrations of ≥0.05% for mice and of ≥0.1% for rats. The nasal tumours in rats were observed at 1,4-dioxane drinking water concentrations of ≥0.5%. Some indication for liver tumours were also obtained in guinea-pigs, but no information on non-neoplastic lesions was provided. For both liver and nasal tumours, cytotoxic effects and organ damage are considered to be involved, which are subject to non-linear kinetics, implicating a threshold. The NOAEL can be established at 0.01% in drinking water, equivalent to 10 mg/kg bw/day, based on liver damage.

No adequate fertility study was available for 1,4-dioxane. In oral 13-week studies and in oral and inhalatory chronic toxicity/carcinogenicity studies no effects were observed on the male and female reproductive organs. In an oral teratogenicity study with rats the NOAEL for maternal and embryotoxicity can be established at 0.5 ml/kg bw, equivalent to 517 mg/kg bw/day.

4.1.3.2 Workers

Assuming that oral exposure is prevented by personal hygiene measures, the risk characterisation for workers is limited to the respiratory and dermal routes of exposure.

4.1.3.2.1 Acute toxicity

1,4-Dioxane is not considered, for classification purposes, as harmful after inhalation and there is no concern with respect to lethality. However, neurotoxic effects were observed in rats (4 hours) and mice (2 hours) exposed to 1,4-dioxane. The LOAEL was 6,800 mg/m^3 (rats). The Margins of Safety (MOSs) between this LOAEL and short-term exposure concentrations in humans are given in **Table 4.13**.

These MOSs can be evaluated by comparison with the minimal MOS (27). In Appendix B this method is explained and assessment factors used to establish the minimal MOS are given (**Table B.1**). If this method is used, then there is concern when the MOS is lower than the minimal MOS. The conclusions are given in **Table 4.13**.

Table 4.13 Risk assessment for 1,4-dioxane for neurotoxicity after short-term respiratory exposure

Scenario/subscenario	Risk characterisation for respiratory exposure		
	Estimated respiratory exposure in mg/m^3 (short-term)	MOS [a]	Conclusion [b]
Production:			
- short-term	150	45	ii
- cleaning and maintenance	10	680	ii
Formulation	360	19	ii
Use:			
- product: cleaning agent	150	45	ii
- product: as paint- pure substance -	33	206	ii
- substance: degassing	166	41	ii

[a] Based on a LOAEL of 6800 mg/m^3

[b] The conclusion is reached by considering the magnitude of the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Appendix B.

In the scenario formulation, the MOS is below the minimal MOS. However, taking into account additional parameters such as the conservative nature of the exposure estimate in this case a conclusion (ii) was considered appropriate.

Consequently, based on the risk assessment for neurotoxicity after short-term inhalation exposure as given in **Table 4.13**, it is concluded that **conclusion (ii)** is applicable for all exposure scenarios.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

The data on acute dermal toxicity of 1,4-dioxane are of limited quality. However, given the data available and the estimated dermal exposure levels, there is no indication that 1,4-dioxane might induce acute toxicity after contact with the skin (**conclusion (ii)**). Local effects are taken into account in the section on irritation and corrosivity.

4.1.3.2.2 Irritation and corrosivity

Skin, repeated exposure

1,4-Dioxane is not irritating to the skin. However, being a fat solvent, 1,4-dioxane can cause eczema upon prolonged or repeated exposure. A concentration-response relationship cannot be derived from the data available. Because dermal exposure is possible in all scenarios, it is concluded that there is need for limiting the risks: **conclusion (iii)**.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Given the information of the industry, it is likely that adequate measures have been applied in the production scenario. However, there is no information for scenarios regarding the formulation and use of dioxane scenarios.

Eyes

1,4-Dioxane is irritating to the eyes. However, because exposure to the eyes is possible only accidentally by splashing, **conclusion (ii)** is reached.

Respiratory irritation, single exposure

Indications for irritation of eyes, nose and throat were obtained from a study in humans (n = 12, exposure for 15 minutes). The dose level causing no subjective signs of irritation was 720 mg/m^3. It is noted that humans were only exposed for 15 minutes. No data are available on the concentration-time relationship with respect to respiratory irritation. Therefore, based on expert judgement, this risk assessment is considered to be only applicable for an exposure duration of maximum half an hour. No conclusions can be drawn for longer exposure duration. The MOSs between this NOAEL and short-term exposure concentrations in humans are mentioned in **Table 4.14**. These MOSs can be evaluated by comparison with the minimal MOS (3). In Appendix B, this method is explained and assessment factors used to establish the minimal MOS are given (**Table B.2**). If this method is used, then there is concern when the MOS is lower than the minimal MOS.

The conclusions are given in **Table 4.14**.

Table 4.14 Risk assessment for 1,4-dioxane for respiratory irritation after short-term respiratory exposure

Scenario/subscenario	Risk characterisation for respiratory exposure		
	Estimated respiratory exposure in mg/m³ (short-term)	MOS [a]	Conclusion [b]
Production: - short-term - cleaning and maintenance	 150 10	 5 72	 ii ii
Formulation	360	2	ii
Use: - product: cleaning agent - product: as paint - pure substance (degassing)	 150 33 166	 5 22 4	 ii ii ii

[a] Based on a human NOAEL of 720 mg/m³

[b] The conclusion is reached by considering the magnitude of the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Appendix B.

Based on the risk assessment as mentioned in **Table 4.14,** there are only indications for a risk of respiratory irritation in scenario 2 (formulation). However, because a human study is used as starting point and because of the worst-case character of the exposure estimate there is no concern for this effect in all occupational exposure scenarios (**conclusion (ii)**).

4.1.3.2.3 Sensitisation

From the guinea pig maximisation test it was concluded that 1,4-dioxane is not sensitising to the skin. There are no indications for respiratory sensitisation. Therefore, **conclusion (ii)** is reached.

4.1.3.2.4 Repeated-dose toxicity

Inhalation

Starting-points for the risk characterisation for workers exposed by inhalation are the occupational exposure levels as estimated in Section 4.1.1.2 (summarised in **Table 4.4**) and the NOAEL of 400 mg/m^3 (only concentration tested) from the chronic inhalation study in rats (Torkelson et al., 1974). No effects were observed in this study. The MOSs between this NOAEL and the inhalatory exposure levels vary between 2 and 40 (see **Table 4.15**).

These MOSs can be evaluated by comparison with the minimal MOS (9). In Appendix B, this method is explained and assessment factors used to establish the minimal MOS are given (Table B.3). If this method is used, then there is concern when the MOS is lower than the minimal MOS. The conclusions are given in **Table 4.15**.

Table 4.15 Risk assessment for 1,4-dioxane for repeated-dose toxicity after respiratory exposure

Scenario/subscenario	Risk characterisation for respiratory exposure		
	Estimated respiratory exposure (mg/m³)	MOS [a]	Conclusion [b]
Production:			
- full shift	10	40	ii
- cleaning and maintenance	10	40	ii
Formulation	180	2	iii
Use:			
-product: cleaning agent	50	8	ii
- product: paint	11	36	ii
- pure substance (full shift)	25	16	ii

a) Based on a NOAEL of 400 mg/m³ in rats

b) The conclusion is reached by considering the magnitude of the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Appendix B.

By considering the magnitude of the MOSs, taking into account a number of additional parameters as described in the TGD, **conclusion (iii)** is reached for scenario 2, formulation. There is no concern with regard to repeated-dose toxicity after occupational inhalation exposure for the production and use scenarios: **conclusion (ii)**. It might be possible that in some industrial premises, worker protection measures are already applied.

Dermal

The results of the dermal repeated dose toxicity study with rabbits and guinea pigs of Fairley et al. (1934) cannot be used quantitatively for risk assessment. However, it is noted that effects on the liver and kidneys were observed. These organs were also the target organs in the drinking water studies with rats (NOAEL 10 mg/kg bw/d). The NOAEL for repeated dose toxicity after inhalation is 400 mg/m^3 (only dose level tested, i.e. 101 mg/kg bw/d). At this dose level no effects were observed and the target organs after inhalation are unknown. Both studies can be used for risk characterisation for systemic effects after repeated dermal exposure by application of route-to-route extrapolation. The occupational exposure levels to be used as starting-point are estimated in Section 4.1.1.2 (summarised in **Table 4.4**).

The MOSs between the oral NOAEL and the dermal exposure levels vary between 0.5 and 200, and between the respiratory NOAEL and the dermal exposure levels between 6 and 2,020 (see **Table 4.16**).

The MOSs can be evaluated by comparison with the minimal MOSs (i.e. 18 for both the oral and the inhalation study as starting point). In Appendix B an approach is described to interpret the MOS by using the minimal MOS concept, along with the assessment factors used to establish the minimal MOS (**Table B.4**). For route-to-route extrapolation correction is made for differences in oral, inhalation, and dermal absorption. Based on the qualitative information from the available studies, for the inhalation and oral route of exposure 100% absorption is taken into account, and for the dermal route 50%. Using this approach a concern is obtained when the MOS is lower than the minimal MOS. The conclusions are given in **Table 4.16**.

Table 4.16 Risk assessment for 1,4-dioxane for repeated-dose toxicity and carcinogenicity after dermal exposure

Scenario/subscenario	Risk characterisation for dermal exposure based on the oral and respiratory NOAEL			
	Estimated dermal exposure in mg/day (mg/kg bw/d) [a]	MOS [b]	MOS [c]	Conclusion [d]
Production: - full shift - cleaning and maintenance	 42 (0.6) 65 (0.9)	 17 11	 168 112	 ii ii
Formulation	420 (6)	2	17	ii
Use: - product: cleaning agent - product: paint - pure substance (full shift)	 1,260 (18) 4 (0.05) 420 (6)	 0.5 200 2	 6 2,020 17	 iii ii ii

a) The estimated dermal exposure in mg/kg bw/d, assuming a worker body weight of 70 kg, is used for calculating MOSs.
b) Based on an oral NOAEL (rats) of 10 mg/kg bw/d.
c) Based on a respiratory NOAEL (rats) of 400 mg/m^3 (i.e., 240 ml/min breathed air, a body weight of 400 g and 7 hr exposure/day results in 101 mg/kg bw/d).
d) The conclusion is reached by considering the magnitude of the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Appendix B.

The results of the toxicity studies suggest that 1,4-dioxane is more toxic after oral exposure than after inhalation exposure. Because in general the dermal route differs more from the oral route than from the inhalation route (because first-pass effects via the liver play only a role after oral absorption) and because of the clear differences in the toxicokinetics of 1,4-dioxane after oral and inhalation exposure (saturation of metabolism plays a role only after oral administration) it is considered justifiable to use the inhalation study as the starting point for drawing conclusions. This means that there is reason for concern only in the scenario "use in cleaning agents": **conclusion (iii)**. In all other scenarios/subscenarios **conclusion (ii)** is applicable. The risk for local effects after repeated dermal exposure cannot be derived from the oral or inhalation toxicity studies.

Combined exposure (dermal and inhalation)

The total body burden (systemic dose) is determined by uptake after dermal as well as inhalation exposure to 1,4-dioxane. In general, a risk characterisation for systemic effects for combined exposure introduces a lot of uncertainties, e.g., due to differences in build-up of the internal exposure after both exposure routes and due to difficulties in the choice of the most appropriate toxicity study as starting point. In case of 1,4-dioxane the inhalation study is used as the starting point for both the risk characterisation after dermal and after inhalation exposure. Therefore, it is considered justifiable to estimate the risk for combined exposure, starting with the NOAEL of 400 mg/m^3 (101 mg/kg bw/d).

In **Table 4.17** the calculation of the systemic dose is given, starting with the estimated dermal and inhalation exposure levels and a dermal and inhalation absorption of 50% and 100%, respectively. The MOS-values for combined exposure are calculated starting with the NOAEL from the chronic inhalation study in rats.

The MOSs can be evaluated by comparison with the minimal MOSs (i.e. 36). In Appendix B, the assessment factors used to establish the minimal MOS are given (**Table B.5**). For inhalation-to-

internal extrapolation correction should be made for inhalation absorption. Based on the qualitative information from the available studies 100% absorption is taken into account. Using this approach there is concern when the MOS is lower than the minimal MOS.

The conclusions are given in **Table 4.17**.

Table 4.17 Risk assessment for 1,4-dioxane for repeated-dose toxicity and carcinogenicity after combined exposure

Scenario/subscenario	Risk characterisation for combined exposure				
	Estimated dermal exposure in mg/day (systemic dose in mg/kg bw/d) [a]	Estimated respiratory exposure in mg/m³ (systemic dose in mg/kg bw/d) [b]	Total systemic dose as result from dermal and inhalation exposure in mg/kg bw/d [c]	MOS [d]	Conclusion [e]
Production: - full shift - cleaning and maintenance	 42 (0.3) 65 (0.5)	 10 (1.4) 10 (1.4)	 1.7 1.9	 59 53	 ii ii
Formulation	420 (3)	180 (25.7)	29	4	iii
Use: - product: cleaning agent - product: paint - pure substance (full shift)	 1260 (9) 4 (0.02) 420 (3)	 50 (7.1) 11 (1.6) 25 (3.6)	 16 1.7 6.6	 6 59 15	 iii ii ii

a) The systemic dose due to dermal exposure in mg/kg bw/d, assuming a worker body weight of 70 kg and 50% dermal absorption
b) The systemic dose due to respiratory exposure in mg/kg bw/d, assuming a worker body weight of 70 kg, a respiratory volume of 10 m³ per workday, and 100% inhalation absorption
c) Total systemic dose, i.e., the sum of the systemic dose due to dermal exposure and the systemic dose due to respiratory exposure
d) Based on a respiratory NOAEL (rats) of 400 mg/m³ (i.e., 240 ml/min breathed air, a body weight of 400 g and 7 hr exposure/day results in 101 mg/kg bw/d)
e) The conclusion is reached by considering the magnitude of the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Appendix B (see Table B.5).

This means that there is concern for the formulation scenario "formulation" and the subscenario "use in cleaning agents" (**conclusion (iii)**), and there is no concern for all other scenarios.

4.1.3.2.5 Mutagenicity

Based on the weight of evidence, 1,4-dioxane is considered to be a non-genotoxic compound. Therefore at present there is no concern and no need to request further information (**conclusion (ii)**).

4.1.3.2.6 Carcinogenicity

1,4-Dioxane is considered to be a carcinogen acting by a non-genotoxic mode of action. Therefore, a threshold approach is appropriate.

Dermal exposure

Carcinogenicity studies performed by the dermal route were not available. After respiratory exposure no carcinogenicity was seen. In a chronic oral study with rats (Kociba et al., 1974) a NOAEL of 10 mg/kg bw/d was observed, based on systemic effects (liver, kidney).

Carcinogenicity (tumours in the nose and the liver) was observed at higher dose levels, but because of the mode of action, the NOAEL for liver and kidney toxicity is used for evaluation of the carcinogenicity. Given the toxicokinetic data after dermal and inhalation exposure in rats it is justifiable to estimate the risk after dermal exposure starting with the chronic inhalation study. Therefore, the risk characterisation and the conclusions for repeated-dose toxicity after dermal exposure, based on the inhalation NOAEL of 400 mg/m^3, are also applicable with respect to carcinogenicity, i.e. **conclusion (ii)** for the production and formulation scenarios and the subscenarios "use of paints containing 1,4-dioxane" and "use as pure substance", and **conclusion (iii)** for the subscenario "use in cleaning agents". The risk for local carcinogenicity after repeated dermal exposure cannot be derived from the oral or inhalation toxicity studies.

Inhalation exposure

In the chronic inhalation study with rats (Torkelson et al., 1974), no effects including carcinogenicity were observed. Therefore, considering the non-genotoxic mode of action and the fact that a threshold approach is appropriate, the risk characterisation and the conclusions for repeated-dose toxicity after inhalation are also applicable with respect to carcinogenicity (**conclusion ii** (production and use) and **conclusion iii** (formulation)).

Combined exposure (dermal and inhalation)

The conclusions for repeated dose toxicity after combined exposure are also applicable for systemic carcinogenicity after exposure via both routes, i.e., **conclusion (iii)** for the formulation scenario, and the subscenarios "use in cleaning agents" and **conclusion (ii)** for all other scenarios.

4.1.3.2.7 Toxicity for reproduction

There are no indications that 1,4-dioxane caused effects on fertility based on the results of the oral and respiratory carcinogenicity studies with mice and rats.

Developmental studies performed by inhalation or dermal exposure were not available. In the oral developmental study with rats a NOAEL of 517 mg/kg bw/d is established for maternal toxicity and embryotoxicity. The substance is not teratogenic.

The NOAEL (517 mg/kg bw/d) for developmental toxicity from the oral teratogenicity study with rats is used for risk characterisation by route-to-route extrapolation.

The MOSs between the oral NOAEL and the respiratory, the dermal and the combined exposure levels are shown in **Tables 4.18**, **4.19**, and **4.20**.

The MOSs can be evaluated by comparison with the minimal MOSs. In Appendix B, the assessment factors which can be used to establish the minimal MOSs are given (**Table B.6**). For route-to-route extrapolation correction is made for differences in absorption between the routes (100% inhalation, 100% oral and 50% dermal absorption). Using this method, there is concern when the MOS is lower than the minimal MOS.

The conclusions are given in **Tables 4.18**, **4.19**, and **4.20**.

Table 4.18 Risk assessment for developmental toxicity after respiratory exposure.

Scenario/subscenario	Risk characterisation for respiratory exposure		
	Estimated respiratory exposure in mg/m³ (mg/kg bw/d) [a]	MOS [b]	Conclusion [c]
Production: - full shift - cleaning and maintenance	 10 (1.4) 10 (1.4)	 369 369	 ii ii
Formulation	180 (25.7)	20	ii
Use: - product: cleaning agent - product: paint - pure substance (full shift)	 50 (7.1) 11 (1.6) 25 (3.6)	 73 323 145	 ii ii ii

a) Estimated respiratory exposure in mg/kg bw/d assuming a worker body weight of 70 kg and a breathing volume of 10 m³/working day, used for calculating MOSs

b) Based on an oral NOAEL of 517 mg/kg bw/d in rats

c) The conclusion is reached by considering the magnitude of the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Appendix B (cf. Table B.6)

Table 4.19 Risk assessment for developmental toxicity after dermal exposure

Scenario/subscenario	Risk characterisation for dermal exposure		
	Estimated dermal exposure in mg/day (mg/kg bw/d) [a]	MOS [b]	Conclusion [c]
Production: - full shift - cleaning and maintenance	 42 (0.6) 65 (0.9)	 861 574	 ii ii
Formulation	420 (6)	86	ii
Use: - product: cleaning agent - product: paint - pure substance (full shift)	 1,260 (18) 4 (0.05) 420 (6)	 29 10,340 86	 ii ii ii

a) Estimated dermal exposure in mg/kg bw/d assuming a worker body weight of 70 kg, used for calculating MOSs

b) Based on an oral NOAEL of 517 mg/kg bw/d with rats

c) The conclusion is reached by considering the magnitude of the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Appendix B (cf. Table B.6)

Table 4.20 Risk assessment for developmental toxicity after exposure via combined routes

Scenario/ subscenario	Risk characterisation for combined exposure				
	Estimated dermal exposure in mg/day (systemic dose in mg/kg bw/d) [a]	Estimated respiratory exposure in mg/m³ (systemic dose in mg/kg bw/d) [b]	Total systemic dose as result from dermal and inhalation exposure in mg/kg bw/d [c]	MOS [d]	Conclusion[e]
Production:					
- full shift	42 (0.3)	10 (1.4)	1.7	304	ii
- cleaning and maintenance	65 (0.5)	10 (1.4)	1.9	272	ii
Formulation	420 (3)	180 (25.7)	29	18	ii
Use:					
- product: cleaning agent	1,260 (9)	50 (7.1)	16	32	ii
- product: paint	4 (0.02)	11 (1.6)	1.7	304	ii
- pure substance (full shift)	420 (3)	25 (3.6)	6.6	78	ii

[a] The systemic dose due to dermal exposure in mg/kg bw/d, assuming a worker body weight of 70 kg and 50% dermal absorption
[b] The systemic dose due to respiratory exposure in mg/kg bw/d, assuming a worker body weight of 70 kg, a respiratory volume of 10 m³ per workday, and 100% inhalation absorption
[c] Total systemic dose, i.e., the sum of the systemic dose due to dermal exposure and the systemic dose due to respiratory exposure
[d] Based on an oral NOAEL of 517 mg/kg bw/d with rats
[e] The conclusion is reached by considering the magnitude of the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Appendix B (cf. Table B.6).

The size of the MOSs listed in the **Tables 4.18**, **4.19**, and **4.20** for respiratory and combined exposure in the scenario formulation are not very large. However, based on the uncertainties present in the risk assessment (e.g. the conservative nature of the occupational respiratory exposure estimate), it is justifiable to conclude that the risk assessment based on the NOAEL for developmental effects does not point to concern after dermal, respiratory or combined exposure to 1,4-dioxane for all scenarios (**conclusion (ii)**).

Occupational limit values

In several countries there are occupational limit values for 1,4-dioxane (see **Table 4.21**).

Table 4.21 Occupational limit values

Country/ organisation	8-hr TWA		15-min STEL		Remarks	References
	mg/m³	ppm	mg/m³	ppm		
USA	90	25	-	-	Skin notation	ACGIH, 1991
The Netherlands	40	11	80	22	Skin notation	DECOS, 1987
UK	90	25	360		-	HSE, 1996
Germany	72	20	-	-	Skin notation Carcinogen IIIb Local irritant	DFG, 1996
Sweden	90	25	180	50	Skin notation Carcinogenic	NBOSH, 1993
Denmark	36	10	-	-	Skin notation	Arbejdstilsynet, 1996a
Norway	18	5	-	-	Skin notation Carcinogen 3	Arbeidstilsynet, 1996b

The ACGIH established a TLV-TWA in 1979 and revised this in 1991. The TLV was based on hepatotoxic and nephrotoxic effects, which have occurred in workers, and have been shown to result in animals from dosages one-tenth those required to produce a significant increase in the occurrence of cancer.

In the DECOS report, a MAC of 11 ppm for 8-hour exposure was established in 1987. This was based on the epigenetic-cytotoxic mechanism of carcinogenicity for 1,4-dioxane and a respiratory chronic toxicity study in which no cytotoxic and hepatotoxic effects occurred (NAEL 111 ppm).

Because of the cytotoxicity and the carcinogenicity of 1,4-dioxane a MAK value was established by Germany in 1996. This value was based on an inhalation study (NAEL 111 ppm), a human metabolism study in which at 50 ppm still eye irritation occurred and a human study with 6-hour exposure, in which at 50 ppm no systemic effects occurred.

In the Swedish report (Scientific Basis for Swedish Occupational Standards XIII) the critical effect of occupational exposure to 1,4-dioxane was described to be irritation of the mucous membranes. In animal experiments 1,4-dioxane has been shown to be carcinogenic.

The documentation on the values established in the UK, Denmark and Norway were not available.

It is apparent that expert committees use different reasoning for the establishment of occupational limit values of 1,4-dioxane. Recent oral studies were not used in most evaluations (e.g. Yamazaki et al., 1994; NCI, 1978). However, the inhalation study (Torkelson et al., 1974), which is already used in most evaluations, is most relevant for establishing occupational limit values.

4.1.3.3 Consumers

From the identified uses attention has been paid to the exposure to 1,4-dioxane from its occurrence in shampoo (scenario I), baby lotion (scenario II) and dishwashing liquid (scenario III). The exposures have been estimated using the CONSEXPO model (see Section 4.1.1.3). For consumers, inhalation and dermal exposure is most relevant in all three scenarios, and for all scenarios it is considered that the exposures occur frequently.

Repeated-dose toxicity, carcinogenicity, reproductive toxicity

Starting points for the risk assessment for repeated-dose toxicity and reproductive toxicity are the exposure estimates (taking into account the announced reduction measures since 1987) and the NOAEL of 400 mg/m^3 from the chronic inhalation study in rats, and the overall NOAEL for oral repeated exposure of 10 mg/kg bw/d from the 2-year drinking water study in rats. Studies to assess the systemic toxicity after dermal exposure were lacking. Route-to-route extrapolation is applied by correction for differences in absorption (oral 100%, dermal 50%), and assuming a body weight of 70 kg and a product volume of 1 cm^3. As 1,4-dioxane is considered to be a non-genotoxic carcinogen, a threshold approach is appropriate. For the risk characterisation for carcinogenicity the same NOAELs can be taken, as in the chronic studies tumour formation was also monitored.

The margins of safety (MOSs) between the inhalation exposure estimates (0.013 mg/m^3, 0.029 µg/m^3, 0.035 µg/m^3 and 0.02 mg/m^3 for scenario I, IIA, IIB and III, respectively, and the NOAEL of 400 mg/m^3 are all >>10,000. The MOSs between the dermal exposure estimates (0.03 mg/cm^3, 0.012 mg/cm^3, 0.01 mg/cm^3 and 0.072 µg/cm^3 for scenario I, IIA, IIB and III, respectively) and the calculated dermal NOAEL of 20 mg/kg bw/day are far greater than 1000. When comparing the oral NOAEL with the total internal doses for scenario I (0.92 µg/kg bw/day),

IIA (3.05 µg/kg bw/day), IIB (2.29 µg/kg bw/day), III (0.132 µg/kg bw/day), and for the combined scenario (3.342 µg/kg bw/day) the MOS-values are all >>3,000.

Taking into account intra- and inter-species differences, the non-genotoxic properties of the substance and the use of NOAELs from chronic studies, these MOSs indicate no concern for consumers by inhalation and dermal exposure (**conclusion (ii)**).

Remark: Even when the announced reduction measures were not taken or were not effective, the total internal doses for scenario I (5.53 µg/kg bw/day), IIA (3.05 µg/kg bw/day), IIB (2.29 µg/kg bw/day), III (2.20 µg/kg bw/day), and for the combined scenario (10 µg/kg bw/day) would result in MOS-values ≥1,000 when compared to the oral NOAEL of 10 mg/kg bw/day. Hence, also in this very worst case, there would be no concern for consumers after inhalation and dermal exposure (**conclusion (ii)**).

4.1.3.4 Humans exposed via the environment

4.1.3.4.1 Exposure resulting from industrial emissions

Inhalation exposure

The starting points for the risk characterisation for repeated dose toxicity and reproductive toxicity are the local PECs in air as presented in **Table 4.6** and the NOAEL of 400 mg/m^3 (only concentration tested) from the chronic inhalation study in rats. No effects were observed in this study. As 1,4-dioxane is considered to be a non-genotoxic carcinogen, a threshold approach is appropriate. For the risk characterisation for carcinogenicity the same NOAEL can be taken, as in this study tumour formation was also monitored.

The MOSs between the NOAEL of 400 mg/m^3 and the inhalatory exposure levels at local scale are given in **Table 4.22**. The MOS between this NOAEL and the inhalatory exposure level at regional scale (0.02 µg/m^3, see **Table 4.8**) is $2.5 \cdot 10^{+7}$.

Table 4.22 MOSs for air at local scale

Life cycle stage or scenarios	MOS
I-1/II-1 Production/processing (1)	$2.6 \cdot 10^{+5}$
II-2 Processing tape (2)	$2.5 \cdot 10^{+4}$
II-3 Processing (3)	$3.2 \cdot 10^{+4}$
II-4 Processing resins (4)	$3.7 \cdot 10^{+6}$
II-5 Processing glue (5)	$4.6 \cdot 10^{+5}$
II-6 Processing pharma./pest. (6)	$1.0 \cdot 10^{+4}$
II-7 Processing 'other uses' (6)	$1.4 \cdot 10^{+5}$
III-1 Unintentional processing (7)	$7.4 \cdot 10^{+6}$
III-2 Unintentional processing (8)	$1.0 \cdot 10^{+7}$
III-3 Unintentional PET production (9)	$8.5 \cdot 10^{+5}$
III-4 Unintentional AES (10)	$2.5 \cdot 10^{+7}$

The margins of safety at local as well as regional scale are all >>1,000. From these high margins of safety it is concluded that there is no concern for human safety with regard to repeated-dose toxicity, carcinogenicity as well as reproductive toxicity by inhalation (**conclusion (ii))**.

Total daily intake

The starting points for the risk characterisation for repeated dose toxicity, carcinogenicity and reproductive toxicity are the total daily intakes for the different scenarios at the local scale as calculated in **Table 4.7** and the overall oral NOAEL of 10 mg/kg bw/day from a 2-year drinking water study in rats. The MOSs are given in **Table 4.23**. The MOS between the NOAEL of 10 mg/kg bw/day and the total daily intake at regional scale ($4.5 \cdot 10^{-5}$ mg/kg bw/day, see **Table 4.7**) is $2.2 \cdot 10^{5}$.

Table 4.23 MOSs for total daily intake at local scale

Life cycle stage or scenarios	MOS
I-1/II-1 Production/processing (1)	$2.4 \cdot 10^{4}$
II-2 Processing tape (2)	$2.4 \cdot 10^{3}$
II-3 Processing (3)	97.5
II-4 Processing resins (4)	$1.5 \cdot 10^{5}$
II-5 Processing glue (5)	$4.2 \cdot 10^{4}$
II-6 Processing pharma./pest. (6)	126
II-7 Processing 'other uses' (6)	474
III-1 Unintentional processing (7)	$4.1 \cdot 10^{3}$
III-2 Unintentional processing (8)	$1.5 \cdot 10^{5}$
III-3 Unintentional PET production (9)	558
III-4 Unintentional AES (10)	$2 \cdot 10^{5}$

For the local scale the calculated margins of safety for repeated dose toxicity, carcinogenicity and reproductive toxicity for scenario II-3 is 97.5. From the EUSES calculations it can be seen that for this scenario the intake via drinking water is by far the major intake route. However, the receiving water for scenario II-3 is an effluent channel/river (a few kilometres long) with tide influence (salinity) from the ocean. There is therefore no drinking water intake from this water. Despite the low MOS of 97.5, **conclusion (ii)** seems to be most appropriate for this scenario. From the margins of safety >100 for all remaining scenarios it is concluded that there is no concern (**conclusion (ii)**). For the regional scale the margin of safety indicates no concern for the three endpoints (**conclusion (ii)**).

4.1.3.4.2 Measured data

In drinking water 1,4-dioxane has been detected in concentrations ranging from <0.1 - 2.1 µg/l. The high concentrations have been found in the 1970s, however recent data from the Netherlands indicate that concentrations of 0.5 µg/l in drinking water occurs. The margin of safety between this value and the NOAEL of 10 mg/kg bw/day from the 2-year rat study is considered sufficient taking into account a drinking water consumption of 2 l/day and a body weight of 70 kg (**conclusion (ii)**).

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Effects assessment: Hazard identification

4.2.1.1 Explosivity

1,4-Dioxane is not explosive.

4.2.1.2 Flammability

1,4-Dioxane is a highly flammable liquid.

4.2.1.3 Oxidising potential

Test data on oxidising properties are not available. However, on theoretical considerations the substance is concluded not to be oxidising.

4.2.2 Risk characterisation

The substance is highly flammable and should be labelled with respect to this aspect. 1,4-dioxane is not considered to pose a risk with respect to explosive and oxidising properties.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5 RESULTS

5.1 ENVIRONMENT

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (**iii)** is reached, because:

- Defatting of the skin cannot be excluded in all occupational exposure scenarios;
- Repeated-dose toxicity and carcinogenicity for the scenario “formulation” after inhalation exposure at the workplace cannot be excluded;
- Repeated-dose toxicity and carcinogenicity after dermal exposure at the workplace cannot be excluded for the subscenario “use in cleaning agents”;
- Repeated-dose toxicity and carcinogenicity after combined (i.e. respiratory and dermal) exposure at the workplace cannot be excluded for the scenario “formulation” and the subscenario “use in cleaning agents”;

Table 5.1 Overview of conclusions with respect to occupational risk characterisation

End point	Conclusions valid for the occupational scenarios					
	Scenario 1		Scenario 2		Scenario 3	
	MOS	conclusion	MOS	conclusion	MOS	conclusion
Acute toxicity						
- dermal	n.a.	ii	n.a.	ii	n.a.	ii
- inhalation (LOAEL rat, neuro 6,800 mg/m³)	45-680	ii	19	ii	41-206	ii
Irritation, repeated exposure						
- dermal	n.a.	**iii**	n.a.	**iii**	n.a.	**iii**
- inhalation (NOAEL human 720 mg/m³)	5-72	ii	2	ii	4-22	ii
- eyes	n.a.	ii	n.a.	ii	n.a.	ii
Sensitisation						
- dermal	n.a.	ii	n.a.	ii	n.a.	ii
- inhalation	n.a.	ii	n.a.	ii	n.a.	ii
Repeated dose toxicity, systemic effects, including carcinogenicity						
- dermal (NOAEL rat 400 mg/m³)	112-168	ii	17	ii	6-2,020	**iii**
- inhalation (NOAEL rat 400 mg/m³)	40	ii	2	**iii**	8-36	ii
- systemic (NOAEL rat 400 mg/m³)	53-59	ii	4	**iii**	6-59	**iii**
Mutagenicity	n.a.	ii	n.a.	ii	n.a.	ii
Reproductive toxicity, developmental effects (oral NOAEL rat 517 mg/kg bw/d)						
- dermal	574-861	ii	86	ii	29-10340	ii
- inhalation	369	ii	20	ii	7-323	ii
- combined	272-304	ii	18	ii	32-304	ii

n.a .= Not applicable

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.2.2 Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / *Bw*, *bw*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 50 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives

JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling

PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA

UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

Appendix A CONSEXPO Report

SHAMPOO

CONSEXPO report

Generated by CONSEXPO 2.0

Compound: 1,4-dioxane (CAS: 123-91-1)
Subject: person
Weight: mean: 65.000 kg (sd 8.500), normal distribution

CONTACT

Contact scenario: Personal care
Parameter definition of scenario:
Duration of contact per event: 10.000 min
Duration of actual use per event: 1.000 min
Frequency of contact: 2.000 - 7.000 1/week, uniform distribution
Start of contact: 0.00e+00 min

INHALATION

Exposure
Scenario: evaporation from mixture
Person uses product.
Mean event concentration (average case): 1.275e-02 mg/m3
Year average (average case): 5.760e-05 mg/m3
Mean event concentration (cumulative worst case): 1.275e-02 mg/m3
Year average (cumulative worst case): 5.760e-05 mg/m3

Exposure estimates based on the following parameters:
Release area: 1200.000 cm2
Temperature: 38.000 Celsius
Ventilation rate: 4.000 m3/hr
Room volume: 1.600 m3
Weight fraction: 50.000 mg/kg
Molweight solvent: 100.000 g/mol

Uptake
Model: fraction model
Average case estimate: 3.302e-01 mg/year
1.391e-05 mg/(kg.day)

Cumulative worst case estimate: 4.953e-01 mg/year
2.086e-05 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 1.000 fraction
Inhalation rate: 10900.000 cm3/min
Respirable fraction: 1.000 fraction

DERMAL

Exposure
Scenario: fixed volume of product
Mean event concentration (average case): 3.000e-02 mg/cm3
Year average (average case): 1.355e-04 mg/cm3
Mean event concentration (cumulative worst case): 3.000e-02 mg/cm3
Year average (cumulative worst case): 1.355e-04 mg/cm3

Exposure estimates based on the following parameters:
Product amount: 12.000 g
Product volume: 2.000 cm3
Applied product volume: 2.000 cm3
Weight fraction of compound: 50.000 mg/kg
Dilution before use: 10.000 times

Uptake
Model: fraction model
Average case estimate: 1.426e+01 mg/year
6.005e-04 mg/(kg.day)
Cumulative worst-case estimate: 2.138e+01 mg/year
9.007e-04 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 100.000 %

ORAL

No exposure

SHAMPOO - very worst case

CONSEXPO report

Generated by CONSEXPO 2.0

Compound: 1,4-dioxane (CAS: 123-91-1)
Subject: person
Weight: mean: 65.000 kg (sd 8.500), normal distribution

CONTACT

Contact scenario: Personal care
Parameter definition of scenario:
Duration of contact per event: 10.000 min
Duration of actual use per event: 1.000 min
Frequency of contact: 2.000 - 7.000 1/week, uniform distribution
Start of contact: 0.00e+00 min

INHALATION

Exposure
Scenario: evaporation from mixture
Person uses product.
Mean event concentration (average case): 7.650e-02 mg/m3
Year average (average case): 3.456e-04 mg/m3
Mean event concentration (cumulative worst case): 7.650e-02 mg/m3
Year average (cumulative worst case): 3.456e-04 mg/m3

Exposure estimates based on the following parameters:
Release area: 1200.000 cm2
Temperature: 38.000 Celsius
Ventilation rate: 4.000 m3/hr
Room volume: 1.600 m3
Weight fraction: 300.000 mg/kg
Molweight solvent: 100.000 g/mol

Uptake
Model: fraction model
Average case estimate: 1.981e+00 mg/year
8.345e-05 mg/(kg.day)
Cumulative worst-case estimate: 2.972e+00 mg/year
1.252e-04 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 1.000 fraction
Inhalation rate: 10900.000 cm3/min
Respirable fraction: 1.000 fraction

DERMAL

Exposure
Scenario: fixed volume of product
Mean event concentration (average case): 1.800e-01 mg/cm3
Year average (average case): 8.131e-04 mg/cm3
Mean event concentration (cumulative worst case): 1.800e-01 mg/cm3
Year average (cumulative worst case): 8.131e-04 mg/cm3

Exposure estimates based on the following parameters:
Product amount: 12.000 g
Product volume: 2.000 cm3
Applied product volume: 2.000 cm3
Weight fraction of compound: 300.000 mg/kg
Dilution before use: 10.000 times

Uptake
Model: fraction model
Average case estimate: 8.554e+01 mg/year
3.603e-03 mg/(kg.day)
Cumulative worst-case estimate: 1.283e+02 mg/year
5.404e-03 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 100.000 %

ORAL

No exposure

BABY LOTION - child

CONSEXPO report

Generated by CONSEXPO 2.0

Compound: 1,4-dioxane (CAS: 123-91-1)
Subject: person
Weight: mean: 8.000 kg (sd 1.000), normal distribution

CONTACT

Contact scenario: Personal care
Parameter definition of scenario:
Duration of contact per event: 1.000 day
Duration of actual use per event: 1.000 day
Frequency of contact: 1.000 1/day
Start of contact: 0.00e+00 min

INHALATION

Exposure
Scenario: evaporation due to painting
Person does not use product.
Mean event concentration (average case): 2.861e-05 mg/m3
Year average (average case): 2.895e-05 mg/m3
Mean event concentration (cumulative worst case): 2.861e-05 mg/m3
Year average (cumulative worst case): 2.895e-05 mg/m3

Exposure estimates based on the following parameters:
Release area: 2031.000 - 4298.000 cm2, uniform distribution
Temperature: 25.000 Celsius
Ventilation rate: 33.800 m3/hr
Room volume: 22.500 m3
Product amount: 2.400 g
product density: 1.200 mg/cm3
Weight fraction: 1.00e-05 fraction
Fraction to upper layer: 0.990 fraction
Molweight solvent: 100.000 g/mol

Uptake
Model: fraction model
Average case estimate: 3.380e-02 mg/year
1.157e-05 mg/(kg.day)
Cumulative worst-case estimate: 3.380e-02 mg/year
1.157e-05 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 1.000 fraction
Inhalation rate: 2220.000 cm3/min
Respirable fraction: 1.000 fraction

DERMAL

Exposure
Scenario: fixed volume of product
Mean event concentration (average case): 1.200e-02 mg/cm3
Year average (average case): 1.214e-02 mg/cm3
Mean event concentration (cumulative worst case): 1.200e-02 mg/cm3
Year average (cumulative worst case): 1.214e-02 mg/cm3

Exposure estimates based on the following parameters:
Product amount: 2.400 g
Product volume: 2.000 cm3
Applied product volume: 2.000 cm3
Weight fraction of compound: 1.00e-05 fraction
Dilution before use: 1.000 times

Uptake
Model: fraction model
Average case estimate: 8.870e+00 mg/year
3.036e-03 mg/(kg.day)
Cumulative worst-case estimate: 8.870e+00 mg/year
3.036e-03 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 100.000 %

ORAL
No exposure

BABY LOTION - adult

CONSEXPO report

Generated by CONSEXPO 2.0

Compound: 1,4-dioxane (CAS: 123-91-1)
Subject: person
Weight: mean: 65.000 kg (sd 8.500), normal distribution

CONTACT

Contact scenario: Personal care
Parameter definition of scenario:
Duration of contact per event: 1.000 day
Duration of actual use per event: 1.000 day
Frequency of contact: 1.000 - 2.000 1/day, uniform distribution
Start of contact: 0.00e+00 min

INHALATION

Exposure
Scenario: evaporation due to painting
Person does not use product.
Mean event concentration (average case): 3.450e-05 mg/m3
Year average (average case): 5.237e-05 mg/m3
Mean event concentration (cumulative worst case): 3.450e-05 mg/m3
Year average (cumulative worst case): 5.237e-05 mg/m3

Exposure estimates based on the following parameters:
Release area: 1200.000 cm2
Temperature: 21.000 Celsius
Ventilation rate: 111.000 m3/hr
Room volume: 74.000 m3
Product amount: 7.500 g
product density: 1.000 g/cm3
Weight fraction: 1.00e-05 fraction
Fraction to upper layer: 1.000 fraction
Molweight solvent: 100.000 g/mol

Uptake
Model: fraction model
Average case estimate: 2.998e-01 mg/year
1.263e-05 mg/(kg.day)
Cumulative worst-case estimate: 3.897e-01 mg/year
1.641e-05 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 1.000 fraction
Inhalation rate: 10883.407 cm3/min (uninspected default)
Respirable fraction: 1.000 fraction

DERMAL

Exposure
Scenario: fixed volume of product
Mean event concentration (average case): 1.000e-02 mg/cm3
Year average (average case): 1.518e-02 mg/cm3
Mean event concentration (cumulative worst case): 1.000e-02 mg/cm3
Year average (cumulative worst case): 1.518e-02 mg/cm3

Exposure estimates based on the following parameters:
Product amount: 7.500 g
Product volume: 7.500 cm3
Applied product volume: 7.500 cm3
Weight fraction of compound: 1.00e-05 fraction
Dilution before use: 1.000 times

Uptake
Model: fraction model
Average case estimate: 4.158e+01 mg/year
1.751e-03 mg/(kg.day)
Cumulative worst-case estimate: 5.405e+01 mg/year
2.277e-03 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 100.000 %

ORAL

No exposure

DISH WASHING

CONSEXPO report

Generated by CONSEXPO 2.0

Compound: 1,4-dioxane (CAS: 123-91-1)
Subject: person
Weight: 70.000 kg

CONTACT

Contact scenario: Washing dishes
Parameter definition of scenario:
Duration of contact per event: 40.000 min
Duration of actual use per event: 20.000 min
Frequency of contact: 1.000 1/day
Start of contact: 0.00e+00 min

INHALATION

Exposure
Scenario: evaporation from mixture
Person does not use product.
Mean event concentration (average case): 1.958e-02 mg/m3
Year average (average case): 5.503e-04 mg/m3
Mean event concentration (cumulative worst case): 1.958e-02 mg/m3
Year average (cumulative worst case): 5.503e-04 mg/m3

Exposure estimates based on the following parameters:
Release area: 0.250 m2
Temperature: 50.000 Celsius
Ventilation rate: 40.000 m3/hr
Room volume: 20.000 m3
Weight fraction: 30.000 mg/kg
Molweight solvent: 18.000 g/mol

Uptake
Model: fraction model
Average case estimate: 3.328e+00 mg/year
1.302e-04 mg/(kg.day)
Cumulative worst-case estimate: 3.328e+00 mg/year
1.302e-04 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 1.000 fraction
Inhalation rate: 11500.000 cm3/min
Respirable fraction: 1.000 fraction

DERMAL

Exposure
Scenario: fixed volume of product
Mean event concentration (average case): 4.500e-05 mg/cm3
Year average (average case): 1.265e-06 mg/cm3
Mean event concentration (cumulative worst case): 7.200e-05 mg/cm3
Year average (cumulative worst case): 2.024e-06 mg/cm3

Exposure estimates based on the following parameters:
Product amount: 2.000 - 10.000 g, uniform distribution
Product volume: 2.000 cm3
Applied product volume: 2.000 cm3
Weight fraction of compound: 30.000 mg/kg
Dilution before use: 2000.000 times

Uptake
Model: fraction model
Average case estimate: 3.326e-02 mg/year
1.301e-06 mg/(kg.day)
Cumulative worst-case estimate: 5.322e-02 mg/year
2.082e-06 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 100.000 %

ORAL

No exposure

DISH WASHING - very worst case

CONSEXPO report

Generated by CONSEXPO 2.0

Compound: 1,4-dioxane (CAS: 123-91-1)
Subject: person
Weight: 70.000 kg

CONTACT

Contact scenario: Washing dishes
Parameter definition of scenario:
Duration of contact per event: 40.000 min
Duration of actual use per event: 20.000 min
Frequency of contact: 1.000 1/day
Start of contact: 0.00e+00 min

INHALATION

Exposure
Scenario: evaporation from mixture
Person does not use product.
Mean event concentration (average case): 3.264e-01 mg/m3
Year average (average case): 9.175e-03 mg/m3
Mean event concentration (cumulative worst case): 3.264e-01 mg/m3
Year average (cumulative worst case): 9.175e-03 mg/m3

Exposure estimates based on the following parameters:
Release area: 0.250 m2
Temperature: 50.000 Celsius
Ventilation rate: 40.000 m3/hr
Room volume: 20.000 m3
Weight fraction: 500.000 mg/kg
Molweight solvent: 18.000 g/mol

Uptake
Model: fraction model
Average case estimate: 5.549e+01 mg/year
2.170e-03 mg/(kg.day)
Cumulative worst-case estimate: 5.549e+01 mg/year
2.170e-03 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 1.000 fraction
Inhalation rate: 11500.000 cm3/min
Respirable fraction: 1.000 fraction

DERMAL

Exposure
Scenario: fixed volume of product
Mean event concentration (average case): 7.500e-04 mg/cm3
Year average (average case): 2.108e-05 mg/cm3
Mean event concentration (cumulative worst case): 1.200e-03 mg/cm3
Year average (cumulative worst case): 3.373e-05 mg/cm3

Exposure estimates based on the following parameters:
Product amount: 2.000 - 10.000 g, uniform distribution
Product volume: 2.000 cm3
Applied product volume: 2.000 cm3
Weight fraction of compound: 500.000 mg/kg
Dilution before use: 2000.000 times

Uptake
Model: fraction model
Average case estimate: 5.544e-01 mg/year
2.168e-05 mg/(kg.day)
Cumulative worst-case estimate: 8.870e-01 mg/year
3.469e-05 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 100.000 %

ORAL

No exposure

Appendix B Establishment of the minimal MOSs used for occupational risk

Characterisation by the Netherlands

NOTE: This appendix represents the views of the Netherlands. In particular it presents the approach used by the Netherlands to determine, in a transparent way, which conclusion is to be drawn for worker risk characterisation base on the magnitude of the MOS.

In the tables below calculations of the minimal MOS-values via assessment factors are given. The assessment factors are based on the report of Hakkert et al. (1996).

Table B.1 Assessment factors applied to an inhalation study in rats for the calculation of the minimal MOS for neurotoxicity after short-term inhalation exposure

Aspect	Assessment factors
Interspecies differences [1)]	3
Intraspecies differences [2)]	3
Differences between experimental conditions and exposure Dose-response [3)]	1 3
Type of critical effect	1
Confidence of the database	1
Overall	27

1) Adjustment via caloric demands is not applicable for inhalatory exposure. The factor 3 concerns a factor for remaining uncertainties
2) A factor 3 is applicable for workers
3) A LOAEL is used as starting-point. Given the effects observed at this concentration and because it was shown in a respiratory repeated dose study for effects on behaviour in rats that the effects became less severe already after 2 days of exposure and they were reversible, a factor 3 is applicable for extrapolation to a NAEL.

Table B.2 Assessment factors applied to an inhalation study in humans for the calculation of the minimal MOS for local respiratory irritation after short-term inhalation exposure

Aspect	Assessment factors
Interspecies differences [1)]	1
Intraspecies differences [2)]	3
Differences between experimental conditions and exposure	1
Type of critical effect Dose-response	1 1
Confidence of the database	1
Overall	3

1) Not applicable, because a human study is used as starting point
2) A factor 3 is applicable for workers

Table B.3 Assessment factors applied to the chronic inhalation study with rats for the calculation of the minimal MOS for systemic effects after chronic inhalation exposure

Aspect	Assessment factors
Interspecies differences [1)]	3
Intraspecies differences [2)]	3
Differences between experimental conditions and exposure	1
Type of critical effect	1
Dose response	1
Confidence of the database	1
Overall	9

[1)] Adjustment via caloric demands is not applicable when extrapolation is based on concentration equivalents in rats and human, because the species breath pro rata of caloric demands
[2)] A factor 3 is applicable for workers

Table B.4 Assessment factors applied to the chronic oral and inhalation studies with rats for the calculation of the minimal MOS for systemic effects after chronic dermal exposure

Aspect	Assessment factors for the oral NOAEL	Assessment factors for the inhalation NOAEL
Interspecies differences [1)]	4 · 3	4 · 3
Intraspecies differences [2)]	3	3
Differences between experimental Conditions and exposure	1	1
Type of critical effect	1	1
Dose-response curve	1	1
Route-to-route extrapolation [3)]	0.5	0.5
Confidence of the database	1	1
Overall	18	18

[1)] Correction for caloric demands is applicable when extrapolation is based on dose equivalents. The respiratory NOAEL is recalculated to a dose in the rat (mg/kg bw/d), and on this dose the assessment factors for interspecies differences were applied
[2)] A factor 3 is applicable for workers
[3)] For route-to-route extrapolation correction is made for differences between dermal and oral and inhalation exposure. Based on the qualitative information from the studies available, for inhalation and oral route of exposure 100% absorption is taken into account, and for the dermal route 50%

Table B.5 Assessment factors applied to the chronic inhalation studies with rats for the calculation of the minimal MOS for systemic effects for risk assessment after combined exposure

Aspect	Assessment factors
Interspecies differences [1]	4 · 3
Intraspecies differences [2]	3
Differences between experimental conditions and exposure	1
Type of critical effect	1
Dose-response curve	1
Route-to-route extrapolation [3]	1
Confidence of the database	1
Overall	36

[1] Correction for calorific demands is applicable when extrapolation is based on dose equivalents. The respiratory NOAEL is recalculated to a dose in the rat (mg/kg bw/d), and on this dose the assessment factors for interspecies differences were applied

[2] A factor 3 is applicable for workers

[3] For route-to-route extrapolation correction is made for inhalation absorption. Based on the qualitative information from the studies available, for inhalation route of exposure 100% absorption is taken into account

Table B.6 Assessment factors applied to the oral developmental study with rats for the calculation of the minimal MOS for reproductive effects after chronic dermal, inhalation, and combined exposure

Aspect	Assessment factors for the oral developmental studies, applicable for dermal risk assessment	Assessment factors for the oral developmental study, applicable for inhalation risk assessment	Assessment factors for the oral developmental study, applicable for inhalation and dermal routes
Interspecies differences [1]	4 · 3	4 · 3	4 · 3
Intraspecies differences [2]	3	3	3
Differences between experimental conditions and exposure	1	1	1
Type of critical effect	1	1	1
Dose response	1	1	1
Route-to-route extrapolation	0.5	1	1
Confidence of the database	1	1	1
Overall	18	36	36

[1] Adjustment for calorific demands together with an uncertainty factor

[2] Because the progeny comprises only a subpopulation of the general population, a factor 3 is considered to be sufficient to compensate for differences within this population

European Commission

EUR 19833 EN **European Union Risk Assessment Report**
1,4-dioxane, Volume 21

Editors: B.G. Hansen, S.J. Munn, C. Musset, M.Luotamo, J. de Bruijn, S. Pakalin
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The report provides the comprehensive risk assessment of the substance 1,4-dioxane. It has been prepared by the Netherlands in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The human health risk assessment for 1,4-dioxane concludes that there is at present concern for workers. There is at present no concern for consumers and humans exposed via the environment. The environmental risk assessment for 1,4-dioxane concludes that there is at present no concern for atmosphere, aquatic ecosystem, terrestrial ecosystem or for microorganisms in the sewage treatment plant.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commissions committee on risk reduction strategies set up in support of Council Regulation (EEC) No. 793/93.

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