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1,4-DIOXANE

CAS No: 123-91-1

EINECS No: 204-661-8

Summary Risk Assessment Report

2002 **Special Publication I.01.68**

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SUMMARY RISK ASSESSMENT REPORT

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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Final report:	**2002**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance 1,4-dioxane that has been prepared by the Netherlands in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the original risk assessment report that can be obtained from the European Chemicals Bureau[1]. The present summary report should preferably not be used for citation purposes.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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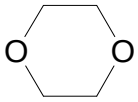
1 GENERAL SUBSTANCE INFORMATION

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

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.

Physico-chemical properties

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	*
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)	**
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 the literature. The value presented in the table is considered as the most appropriate
**** Conclusion based on theoretical, structural considerations.

All relevant physicochemical data were provided. None of the data is based on test reports, however the data are considered as sufficiently reliable to fulfil the Annex VIIA requirements of 67/548/EEC. The substance is not explosive under 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, R19 and S9).

Classification

Classification and labelling according to the 28th ATP of Directive 67/548/EEC[2]:

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

[2] The classification of the substance is established by Commission Directive 2001/59/EC of 6 August 2001 adapting to 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

In Europe, 1,4-dioxane is at present only produced at BASF AG in Ludwigshafen, Germany. The production volume in 1997 was estimated to be 2,000-2,500 tonnes with an export outside the European Community of 575 tonnes. There is no information about import volumes of 1,4-dioxane into the EU.

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. Other uses are for measuring optical activity, for cryoscopic determination and in the manufacturing of membrane filters.

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. 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. Another reason for the decreasing usage is the increasing dioxane recovery in the pharmaceutical industry.

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.

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. These unintentional sources will result in 1,4-dioxane releases. In addition, 1,4-dioxane can also remain as an impurity in several end-products.

General characteristics of 1,4-dioxane which are relevant for the exposure assessment are:

- Degradation: no hydrolysis, no direct photolysis in the lower atmosphere, photo-oxidation in air with DT_{50} of 29 hours and not biodegradable.

- Distribution: based on a Koc of 7.1 l/kg (QSAR non-hydrophobics; log Kow -0.32) it can be concluded that 1,4-dioxane has a low adsorption potential and thus a high mobility/leaching potential. A calculated Henry's law constant of 4.34 $Pa.m^3/mol$ indicates that 1,4-dioxane is moderately volatile from water.

- Accumulation: on the basis of the high water solubility and the low calculated log Kow of -0.32, no bioaccumulation of 1,4-dioxane is expected.

3.1.1 PECs at production, processing and unintentional formation

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

Table 3.1 Exposure scenarios

Exposure scenario (local)	
I-1/II-1.	Production/processing (site-specific)
II-2.	Processing tape (site-specific)
II-3.	Processing pharma. (site-specific)
II-4.	Processing resins (site-specific)
II-5.	Processing glue (site-specific)
II-6.	Processing pharma./pest. (generic)
II-7.	Processing "other uses" (generic)
III-1.	Unintentional processing (site 1) (site-specific)
III-2.	Unintentional processing (site 2) (site-specific)
III-3.	Unintentional PET production (site-specific)
III-4.	Unintentional via AES end-use (actual NL data)

Both site-specific and generic release data are used for calculating the predicted environmental concentrations (PECs) in the various compartments.

Local PECs in the sewage treatment plant and surface water range from, respectively, 0.01 to 183 mg/l and 0.001 to 18.3 mg/l. For air the PECs are between 0.01 and 38 µg/m^3 and for soil all PECs are lower than 0.5 mg/kg wwt. The highest level of 1,4-dioxane in worm and fish is calculated to be 2.3 mg/kg wwt.

3.2 EFFECTS ASSESSMENT

Aquatic compartment

Both short-term and long-term toxicity studies for freshwater and saltwater organisms are available.

There are also a number of studies with bacteria and protozoans. The test result with *Pseudomonas putida* (2,700 mg/l) is used for deriving the $PNEC_{microorganisms}$. According to the TGD no assessment factor is needed when using a NOEC for *P. putida*: **$PNEC_{microorganisms}$** = 2,700 mg/l.

There are three long-term aquatic toxicity 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 tests for three trophic levels) is used, which leads to a **$PNEC_{water}$** of 57.5 mg/l. 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.

Terrestrial compartment and secondary poisoning

Some ecotoxicity data with terrestrial invertebrates and plants are available. Since these data are considered not to be relevant, the $PNEC_{terrestrial}$ is calculated based on equilibrium partitioning. The **$PNEC_{soil}$** is calculated to be 14 mg/kg wwt. The **PNEC for secondary poisoning** is set at 20 mg/kg. This value is based on toxicity data from laboratory mammals.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment

For the risk characterisation the $PNEC_{STP}$ and $PNEC_{water}$ are compared with the corresponding PECs for the various exposure scenarios. **Table 3.2** presents the PEC/PNEC ratios and it shows that all PEC/PNEC ratios are <1 (**conclusion (ii)**)[3].

[3] **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.

Table 3.2 PEC/PNEC ratios for the STP and surface water

Life cycle stage or scenarios		PEC/PNEC STP	PEC/PNEC water
I-1/II-1.	Production/processing	<0.1	<0.01
II-2.	Processing tape	n.r.	<0.01
II-3.	Processing	<0.1	0.06
II-4.	Processing resins	n.r.	<0.01
II-5.	Processing glue	n.r.	<0.01
II-6.	Processing pharma./pest.	0.07	0.3
II-7.	Processing “other uses”	0.05	0.2
III-1.	Unintentional processing	<0.1	<0.01
III-2.	Unintentional processing	<0.1	<0.01
III-3.	Unintentional PET production	<0.1	0.01
III-4.	Unintentional AES	<0.1	<0.01

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 3.3** shows the PEC/PNEC ratios for soil. In none of the exposure scenarios does the PEC exceed the PNEC (**conclusion (ii)**)[3].

Table 3.3 PEC/PNEC ratios for soil.

Life cycle stage or scenarios		PEC/PNEC
I-1/II-1.	Production/processing	<0.01
II-2.	Processing tape	<0.01
II-3.	Processing	<0.01
II-4.	Processing resins	<0.01
II-5.	Processing glue	<0.01
II-6.	Processing pharma./pest.	0.04
II-7.	Processing “other uses”	0.02
III-1.	Unintentional processing	<0.01
III-2.	Unintentional processing	<0.01
III-3.	Unintentional PET production	<0.01
III-4.	Unintentional AES	<0.01

3.3.4 Secondary poisoning

In all exposure scenarios the PEC/PNEC ratios for both worm- and fish-eating birds or mammals are <0.1 (**conclusion (ii)**) [3].

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 Occupational exposure

Occupational exposure to 1,4-dioxane can occur during production, in the formulation industry, and during end-use of the substance or of products containing the substance. Occupational exposure levels have been estimated using measured data and modelling with EASE with relevant assumptions.

Production of 1,4-dioxane takes place in a closed system. Exposure is mainly possible due to quality control sampling and drumming of the substance and fugitive emissions and due to cleaning and maintenance of the production system. The reasonable worst-case full-shift inhalation exposure level for workers drumming and workers in a pilot plant is estimated to be 10 mg/m^3, with typical exposure of 0.2 mg/m^3 and short-term values up to 150 mg/m^3. Dermal exposure is estimated to be highest due to drumming: 42 mg/day.

Cleaning and maintenance of the production system is done during a limited number of days per year and is estimated to lead to a reasonable worst-case full-shift inhalation exposure level of 10 mg/m^3 (typical: 5 mg/m^3) and a dermal exposure level of 65 mg/day.

The formulation of products containing 1,4-dioxane leads to inhalation exposure and dermal exposure mainly due to adding of the substance to mixers. The estimated reasonable worst-case full-shift inhalation exposure level is 180 mg/m^3 (typical: 40 mg/m^3, short term 360 mg/m^3). Addition of 1,4-dioxane is estimated to lead to a dermal exposure level of 420 mg/day.

The end-use of 1,4-dioxane or products containing the substance can be divided into three subscenarios: use of cleaning agents containing 1,4-dioxane, use of paints containing 1,4-dioxane and use of the pure substance in laboratories for the mobile phase in HPLC-techniques. The previously widespread use of 1,4-dioxane in cleaning agents may not be relevant anymore, but since this is not fully clear, it is assessed. Exposure is assumed to be due to widespread manual handling of products containing 1,4-dioxane, leading to a reasonable worst-case full-shift inhalation exposure level of 50 mg/m^3, a typical full-shift inhalation exposure level of 15 mg/m^3 and short-term inhalation exposure levels of 150 mg/m^3. Dermal exposure to two hands is expected to be possible, leading to an exposure level of 1260 mg/day. 1,4-Dioxane is also used in paints for precision instruments, generally in paint baths in which instrument parts are immersed. Adding of paint containing 1,4-dioxane and evaporation from the baths may lead to exposure. The reasonable worst-case full-shift inhalation exposure is estimated to be 11 mg/m^3, with typical values of 2 mg/m^3 and short-term exposures of 33 mg/m^3. Dermal exposure due to filling of the bath is estimated to be done up to once per day, leading to an exposure level of 4 mg/day. Exposure in laboratories related to the HPLC-techniques is mostly due to degassing of the HPLC-fluid and is of short duration. A short-term inhalation exposure level of 166 mg/m^3, a reasonable worst-case full-shift inhalation exposure of 25 mg/m^3 and a typical full-shift exposure level of 5 mg/m^3 are estimated. Dermal exposure is estimated to be 420 mg/day.

It is noted that evaporation from the skin may lower the real dermal exposure levels for all scenarios by an unknown extent.

Table 4.1 Summary of occupational exposure

Scenario	Activity	Frequency (days/year)	Duration (hour)	Reasonable worst case		Typical concentration		Dermal	
				(mg/m^3)	method	(mg/m^3)	method	mg/cm^2/day	dose (mg/day)
Production	full shift *	225	6-8	10	meas.	0.2	measured	0.1-1	42 **
	short-term	225	0-0.5	150	meas., exp.				
	cl.& m.	up to 25	6-8	10	meas., 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	meas., exp.	15	meas., exp.	1.5	1,260
	(short-term)	225	0-0.5	150	meas., 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		5	meas., exp.	1	420
	- degassing		0.25	166	meas.				
	- 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

4.1.1.2 Consumer exposure

Consumer exposure to 1,4-dioxane can result from both the intentional and the unintentional use of 1,4-dioxane. However, from its deliberate use as a solvent/reagent in a wide range of applications direct consumer use could not be identified. Besides, in many cases 1,4-dioxane will not be present in the end-product. Therefore, consumer exposure resulting from the deliberate use of 1,4-dioxane is likely to be negligible.

The unintentional use of 1,4-dioxane relates to its occurrence as an impurity in other materials, as 1,4-dioxane is formed as a reaction by-product in the manufacture of ethoxylated substances (particularly surfactants and emulsifiers). As such, 1,4-dioxane can be found in a variety of consumer products. The data available indicate that the main potential consumer exposure results from exposure to cosmetics/toiletries and household detergents, while consumer exposure to pharmaceuticals, foods, agricultural and veterinary products, and ethylene glycol-based antifreeze coolants can be considered negligible.

Three exposure scenarios have been considered, using measured data for 1,4-dioxane concentrations in cosmetic/toiletry products and household detergents, and the CONSEXPO model (version 2) for the estimation of the exposure: I. shampoo (a rinse-off product), II. baby lotion (a stay-on product), and III. hand dishwashing liquid. For all three scenarios, exposure is considered to occur by the dermal and inhalation route. The results are given in **Table 4.2**.

Although since 1987 progress has been made in reducing 1,4-dioxane levels in products containing wash-active substances, very worst-case exposures have also been calculated, in case reduction measures were not taken or were not effective.

Table 4.2 Summary of consumer exposure

Scenario	Dermal exposure (mg/cm^3)	Inhalatory exposure (mg/m^3)	Total internal dose (μg/kg bw/day)
I	0.03 *0.18*	0.013 *0.0765*	0.92 *5.53*
IIA – child	0.012	$2.9 \cdot 10^{-5}$	3.05
IIB – adult	0.01	$3.5 \cdot 10^{-5}$	2.29
III	$7.2 \cdot 10^{-5}$ *$1.2 \cdot 10^{-3}$*	0.02 *0.3264*	0.132 *2.20*
Combined (I + IIB + III)			3.342 *10.02*

(very worst-case exposures in italics)

4.1.1.3 Humans exposed via the environment

1,4-Dioxane may be released to the environment through wastewater and air effluents at the sites where it is produced, processed, used, and via unintentional formation. Estimated concentrations (EUSES) in the air near the emission sources for the various exposure scenarios ranged from 0.01 to 38.9 $\mu g/m^3$. The calculated total daily human intake via air, drinking water and food for all emission scenarios at the local scale (using EUSES) ranged from 0.1 to 103 μg/kg bw/day for the various exposure scenarios. For the regional scale, the concentration in the air and the total human intake are calculated to be 0.02 $\mu g/m^3$ and $4.5 \cdot 10^{-5}$ mg/kg bw/day, respectively.

Recent drinking water measurements indicate a level of 0.5 μg 1,4-dioxane/l.

4.1.2 Effects assessment

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 after oral and inhalation exposure by rats. After inhalation exposure, 1,4-dioxane was also well absorbed by 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-dioxan-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. 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 need 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 cause 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 the EC criteria the substance needs 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 some other 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 was 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 Risk characterisation

4.1.3.1 Workers

Assuming that oral exposure is prevented by personal hygiene measures, the risk characterisation for workers is limited to the dermal and respiratory routes of exposure. Furthermore, it is assumed that adequate risk reduction measures are taken to prevent accidental exposure. If applicable, quantitative risk characterisation is performed by calculation of the Margin of Safety (MOS - ratio between NOAEL/LOAEL and exposure levels) and comparison of this value with the minimal MOS. This minimal MOS is established via assessment factors, taking into account inter- and intraspecies differences, differences between experimental conditions and the exposure pattern of the worker, type of critical effects, dose-response relationship, confidence of the database and correction for route-to-route extrapolation. A risk is indicated when the MOS is lower than the minimal MOS.

Given the effects observed in the acute respiratory and dermal toxicity studies, there is no concern for lethality after exposure via these routes (**conclusion (ii)**)[3]. In view of the minimal MOS of 27, the calculated MOSs (19-680) between the LOAEL of 6,800 mg/m^3 for neurotoxic effects in rats and the short-term respiratory exposure concentrations do not point to concern for acute neurotoxic effects (**conclusion (ii)**)[3]. 1,4-Dioxane is not irritating to the skin. However, because 1,4-dioxane is a fat solvent and may cause eczema upon prolonged or repeated exposure and dermal exposure is possible in all occupational exposure scenarios there is a need for limiting the risk (**conclusion (iii)**)[4]. Despite the eye irritating properties a risk is not anticipated, because ocular exposure will occur only accidentally by splashing (**conclusion (ii)**)[3]. The MOS between the human NOAEL for respiratory irritation and the short-term exposure levels varies between 2 and 72. 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)**)[3]. The results from the sensitisation and mutagenicity studies do not point to concern for these endpoints (**conclusion (ii)**)[3].

Based on the MOSs between the NOAEL from the repeated dose study by inhalation in rats (400 mg/m^3; highest dose level tested) and the anticipated inhalation exposure levels (10-180 mg/m^3) it is concluded that adverse effects due to exposure in the scenario "formulation" (MOS of 2) cannot be excluded (**conclusion (iii)**)[4]. For the other scenarios (MOSs 8-40) a health risk is

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

not anticipated with regard to this endpoint since the minimal MOS is 9. A suitable dermal repeated dose toxicity study with 1,4-dioxane is not available. The risk assessment for repeated dermal exposure is based on the respiratory NOAEL, because of the clear differences in toxicokinetics of 1,4-dioxane after oral and inhalation exposure. Based on the comparison of the minimal MOS (18) and the calculated MOS (6) between this NOAEL and the anticipated exposure level in the scenario "use in cleaning agents" there is concern (**conclusion (iii)**)[4]. For all other scenarios (MOS 17-2,020) there is no concern for adverse effects after repeated exposure via the skin. There will be no additional risk due to combined exposure. The conclusions for respiratory and dermal repeated dose toxicity are also applicable for the end point carcinogenicity.

There are no indications for concern on fertility caused by 1,4-dioxane (**conclusion (ii)**)[3]. The MOSs between the NOAEL for developmental toxicity (517 mg/kg bw/d) and the occupational exposure levels amount 73-369, 29-10,340 and 18-304 for respiratory, dermal and combined exposure, respectively. It is concluded that these MOS-values do not indicate a risk for adverse effects on progeny (**conclusion (ii)**)[3].

The current occupational limit values for 1,4-dioxane range from 18 mg/m^3 (5 ppm) to 90 mg/m^3 (25 ppm), and are predominantly based on irritation of the mucous membranes and on the epigenetic-cytotoxic mechanism of carcinogenicity. However, in the present report reference is made to additional oral and inhalation studies, which should be taken into account for the establishment of OELs. Therefore, it is recommended to reconsider the current OELs.

4.1.3.2 Consumers

Starting points for the risk assessment for repeated-dose toxicity and reproductive toxicity are the exposure estimates 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. 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 as for repeated-dose toxicity can be taken.

The MOSs between the inhalation exposure estimates and the inhalatory NOAEL are >>10,000 for scenarios I, IIA, IIB and III. The MOSs between the dermal exposure estimates and the calculated dermal NOAEL of 20 mg/kg bw/day are far greater than 1,000 for all scenarios. When comparing the oral NOAEL with the total internal doses for scenarios I, IIA, IIB, III, and for the combined scenario, 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)**)[3].

Even where the announced reduction measures were not taken or were not effective, the total internal doses for scenarios I, IIa, IIB, III, and for the combined scenario 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)**)[3].

4.1.3.3 Humans exposed via the environment

Inhalation exposure

The MOSs between the inhalatory NOAEL of 400 mg/m^3 from the chronic inhalation study in rats and the inhalatory exposure levels 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)**)[3].

Intake via drinking water and total daily intake

The starting points for the risk characterisation for repeated dose toxicity, carcinogenicity and reproductive toxicity are the measured drinking water concentration, the estimated total daily intakes for the different scenarios at local scale and regional scale, and the overall oral NOAEL of 10 mg/kg bw/day from a 2-year drinking water study in rats.

The MOS between the measured drinking water concentration and the oral NOAEL is $7 \cdot 10^{+5}$ and indicates no concern for the three endpoints (**conclusion (ii)**)[3].

With the exception of the processing scenario II-3, the calculated MOSs for repeated dose toxicity, carcinogenicity and reproductive toxicity for all local scenarios are >100, and indicate no concern for the three endpoints (**conclusion (ii)**)[3]. The calculated MOS for the processing 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. Since there is no drinking water intake from this water, **conclusion (ii**)[3] seems to be most appropriate for this scenario.

For the regional scale the MOS ($2.2 \cdot 10^{+5}$) indicates no concern for the three endpoints (**conclusion (ii)**)[3]**.**

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

Given the physico-chemical data, 1,4-dioxane is considered not to form a risk with respect to explosive and oxidising properties (**conclusion (ii)**)[3].

However, it is noted that the substance is highly flammable and should be labelled with respect to this aspect.

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”.

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.