European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

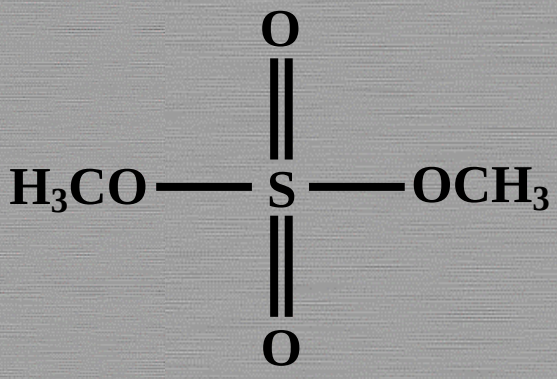
Existing Substances

European Union Risk Assessment Report

CAS No: 77-78-1

EINECS No: 201-058-1

dimethyl sulphate



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RISK ASSESSMENT

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DIMETHYL SULPHATE

CAS No: 77-78-1

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RISK ASSESSMENT

Final report, 2002

The Netherlands

Rapporteur for the risk evaluation of dimethyl sulphate 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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The Netherlands

Date of Last Literature Search :	**1994**
Review of report by MS Technical Experts finalised:	**September 1998**
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.

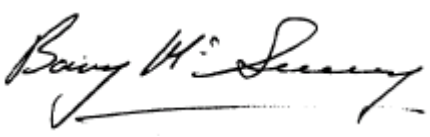
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each 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.

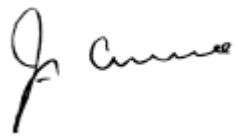
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

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
Joint Research Centre



J. Currie
Director-General
Environment, Nuclear Safety and Civil Protection

[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. 77-78-1
EINECS No. 201-058-1
IUPAC name dimethyl sulphate

Environment

( ) **i)** There is need for further information and/or testing
(X) **ii**) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
( ) **iii**) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Human health (toxicity)

Workers

( ) **i**) There is need for further information and/or testing.
( ) **ii**) There is at present no need for further information and/or testing or for risk. reduction measures beyond those which are being applied.
(X) **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 of:

- concerns for risks for respiratory tract irritation, mutagenicity, and carcinogenicity as a consequence of inhalation exposure arising from production, processing and use of the substance;
- concerns for the pregnant population for additional adverse health effects as a consequence of repeated inhalation exposure arising from the use of the substance as an intermediate.

It is noted that the toxicological database of DMS has gaps with respect to systemic toxicity after repeated exposure, and with respect to effects on reproduction. Furthermore, the carcinogenicity study of Schlögel has serious limitations. However, it is noted that the carcinogenic activity of DMS, i.e., the cancer incidence per mg/m^3 under occupational conditions of exposure, points to very low acceptable exposure levels with regard to the carcinogenic effects, which implies a considerable reduction of the current occupational exposure limits. It is expected that compliance to these low exposure levels will prevent effects other than carcinogenic effects to occur.

Consumers

( ) **i**) There is need for further information and/or testing.
( ) **ii**) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied.
(X) **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 of:

- the risk assessment shows that risks cannot be excluded at any exposure as the substance is identified as a non-threshold carcinogen. However, the risks covered by this risk assessment are not of a magnitude, that immediate action is deemed necessary. Risk reduction measures already being applied are considered sufficient to impose pressure in reducing and controlling exposure to the substance.

Indirect exposure via the environment (industrial emissions)

( ) **i**) There is need for further information and/or testing.
( ) **ii**) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied.
(X) **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 of:

- the risk assessment shows that risks cannot be excluded at any exposure as the substance is identified as a non-threshold carcinogen. However, the risks covered by this risk assessment are not of a magnitude, that immediate action is deemed necessary. Risk reduction measures already being applied are considered sufficient to impose pressure in reducing and controlling exposure to the substance.

In addition to the conclusions according to Council Reg. 793/93/EEC given above, the RAR came to the conclusion concerning emissions from unintentional sources as follows:

Indirect exposure via the environment (unintentional sources)

(X) **i**) There is need for further information and/or testing
( ) **ii**) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
( ) **iii**) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion (**i**) is reached because:

- more information is needed about actual atmospheric concentrations of DMS from unintentional sources. Such data are important to make an up-to-date exposure assessment for this compound, being with a genotoxic carcinogen.

Human health (physico-chemical properties)

Given the physico-chemical data, DMS is considered not to form a risk with respect to flammability, explosive properties, and oxidising properties (**conclusion ii**).

CONTENTS

EUSES Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

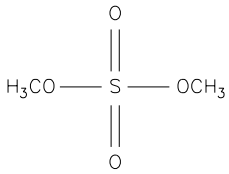
TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No.: 77-78-1
EINECS No.: 201-058-1
IUPAC name: dimethyl sulphate
Molecular formula: $C_2H_6O_4S$

Structural formula:



Molecular weight: 126.13
Synonyms: DMS; methylsulphate; sulphuric acid dimethyl ester; dimethyl monosulphate

1.2 PURITY/IMPURITIES, ADDITIVES

Purity: >99% w/w
Impurity: <= 0.1% w/w methanol (CAS-No. 67-56-1)
<0.5% w/w sulphuric acid (CAS-No 7664-93-9)
<0.5% w/w methyl hydrogen sulphate (CAS-No 75-93-4)
<0.5% w/w dimethyl ether (CAS-No 115-10-6)
Additives: None

1.3 PHYSICO-CHEMICAL PROPERTIES

In **Table 1.1** a list of physico-chemical properties is provided.

Table 1.1 List of physico-chemical properties

Property	Result	Comment
Physical state:	Liquid	a
Melting point:	~ -32°C	a
Boiling point:	188°C	a
Relative density:	1.33 at 20°C	a
Vapour pressure:	65 Pa at 20°C	c
Surface tension:	40.1 mN/cm at 18°C	b
Water solubility:	28 g/l at 20°C	b
Partition coefficient	0.16 (calc.)	b
Flammability:	not flammable	d
Flash point:	83°C	b
Autoflammibility temperature:	450°C	b
Explosive properties:	not explosive	d

Property	Result	Comment
Oxidising properties:	not oxidising	d
Conversion factors (at 20 °C)	1 ppm = 5.24 mg/m³	calculated

[a]More than one apparently independent source. No methods are specified
[b]Result of most reliable test. Other apparently independent sources provide similar results. Most of these methods are not specified
[c]Different values are found in literature. The value presented in the table is considered as most appropriate
[d]Property based on theoretical, structural considerations

These data are mainly derived from Hoechst AG (1996); Merck Index (1983); Kühn et al (1994). For an extended description see the HEDSET.

Conclusion

All relevant physicochemical data were provided. None of the data is based on reports, however the data are considered as sufficiently reliable to fulfil the Annex VIIA requirements.

1.4 CLASSIFICATION

Classification and labelling according to the 26th ATP of Directive 67/548/EEC[4]:

Classification:	Carc. Cat. 2; R45	May cause cancer.
	Muta. Cat. 3; R68[5]	Possible risk of irreversible effects.
	T+; R26	Very toxic by inhalation.
	T; R25	Toxic if swallowed.
	C; R34	Causes burns.
	R43	May cause sensitisation by skin contact.

Labelling: T+ R: 45-25-26-34-43 S: 53-45

Specific concentration limits:

C ≥25%:	T+; R45-25-26-34-43
10% ≤C <25%:	T+; R45-22-26-34-43
7% ≤C <10%:	T+; R45-22-26-36/37/38-43
5% ≤C <7%:	T; R45-22-23-36/37/38-43
3% ≤C <5%:	T; R45-22-23-43
1% ≤C <3%:	T; R45-23-43
0,1% ≤C <1%:	T; R45-20
0,01% ≤C <0,1%:	T; R45

[4] The classification of the substance is established by Commission Directive 2001/32/EC of 19 May 2000 adapting to technical progress for the 26th time Council Directive 67/548 on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (OJ L 136, 8.6.2000, p.1).

[5] The entries were amended by replacing 'Muta.Cat. 3; R40' to 'Muta. Cat. R68' according to the 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

The production of dimethyl sulphate (hereafter referred to as DMS) at tonnages of >1,000 tpa is located at three sites in the European Union (**Table 2.1**). The total EU production volume for 1994 was estimated to be between 20,000 and 30,000 tpa. An amount of 5,000-10,000 tpa is exported (outside EU) and a small quantity of <1,000 tpa is imported. About 20,000 tpa is industrially used within the EU.

Table 2.1 Production sites of dimethyl sulphate (> 1,000 tpa) in the EU

Company	Location
Hoechst AG	Frankfurt a.M., Germany
Chemieproduktionsgesellschaft GmbH Bitterfeld-Wolfen	Bitterfeld, Germany
Rhone-Poulenc Chimie	Courbevoie, France

2.1.1 Production process

The production and transferral of DMS takes place in a closed continuous system. Liquid SO_3 is added to gaseous dimethylether in a reaction vessel, containing about 97% DMS, sulphuric acid and monomethyl sulphate which are continuously withdrawn and purified by vacuum distillation over sodium sulphate. The reaction system has an underpressure to avoid leakages of DMS.

2.2 USE PATTERN

Table 2.2 shows the industrial and use categories of DMS for the European market.

Table 2.2 Industrial and use categories of DMS

Industrial category	EC No.	Use category	EC No.	Main category
Chemical industry: used in synthesis	3	Intermediates	33	I b Intermediates stored on site I c Intermediates stored off site

DMS is mainly used as a chemical intermediate. Its major applications are as a methylating agent of many organic chemicals (e.g. amines, carbon acids, thiols and phenols) both in industry and laboratories. DMS is for example used in the manufacturing of dyes, perfumes, pharmaceuticals, for the separation of mineral oils, and for the analysis of automobile fluids (HSDB, 1996). The substance has also sulphating properties with applications in the manufacturing of various products (e.g. dyes and fabric softeners etc.). Formerly, DMS was used as a war gas. The major chemical industries in the EU that are processing DMS are presented in **Table 2.3**.

Table 2.3 Processing sites of dimethyl sulphate (> 1,000 t/y) in the EU

Company	Location
Hoechst AG	Frankfurt a.M., Germany
BASF AG	Ludwigshafen, Germany
Ciba Geigy AG	Basel, Switzerland*

*Non-EU Country

3 ENVIRONMENT

3.1 EXPOSURE ASSESSMENT

3.1.1 General

DMS may enter the environment during its production and industrial use (processing), and in emissions from power plants that are burning sulphur-containing coal/fuel (see section 3.1.2.2).

General characteristics of DMS that are relevant for the exposure assessment are discussed below.

3.1.1.1 Degradation

Photodegradation

In the atmosphere DMS will be subject to gravitational settling and wash out by rain as well as reaction with photochemically produced hydroxyl radicals. The calculated (QSAR) half-life time for this indirect photolysis is 84.3 days (Hoechst, 1996). The method of calculation is according to the Technical Guidance Document (EC 1996). In addition, the reactivity of DMS towards OH-radicals has been determined experimentally and the rate constant for this reaction is $< 5 \cdot 10^{-13}$ $cm^3 \cdot molecule^{-1} \cdot sec^{-1}$ (Japar, 1990). This rate constant corresponds with an atmospheric lifetime of > 23 days and a DT_{50} of >16 days ([OH]= $1.1 \cdot 10^6$ $molec \cdot cm^{-3}$). For the PECair-calculations the DT_{50} of 84 days is chosen. However, it has to be noted that atmospheric hydrolysis may occur faster (see below).

Hydrolysis

Dimethyl sulphate hydrolyses in water. Reaction rate and type of hydrolysis products depend on pH and temperature. In neutral or acid medium methanol and sulphuric acid are formed, whereas under alkaline conditions the reaction products are methanol and monomethyl sulphate (room temperature) or methanol and sulphate (elevated temperature), respectively. Several estimates for the hydrolysis rate are reported in literature. The half-life at room temperature and pH 7 is about 24 hours; at room temperature and pH 10 it is about 86 seconds. Other observed degradation times are: >70 hours at 8°C, 14 hours at 23°C, and 70 min. at 40°C. In another study a half-life of 1.2 hours is reported for the hydrolysis of DMS under neutral conditions at 25°C. The EHC document (1985) mentions additional DT_{50} values of 4.5 h (temperature unknown) and 40 minutes (at 20°C), at neutral conditions.

According to Lee et al. (1980) the first methylgroup is removed much more rapidly than the second with hydrolysis of dimethyl sulphate being complete in a 24-hour period in water dilute acid or dilute base; the monomethyl species persists over a period of several weeks. The same authors also report that DMS is likely to become incorporated into fog and cloudwater and give a DT_{50} for hydrolysis in air of 30-60 minutes. Howard (1993) gives an estimated life-time value of <1 day for atmospheric transformation (reaction with liquid water).

The overall conclusion is that DMS is hydrolysed very rapidly in water and air (DT_{50} < 1 day).

Biodegradation

In an inherent biodegradation study (modified Zahn-Wellens) in industrial, aerobic, non-adapted activated sludge, the degradation of the hydrolysis products of dimethyl sulphate is reported to be 80% after 15 days. Details of this study are not available.

In a recently performed Modified OECD Screening Test (301 E) with a municipal/industrial activated sludge, DMS (and hydrolysis products) was found to be ready biodegradable (Industry report 1998). An important deviation from the OECD test protocol was that the inoculum was pre-exposed to the test concentration. The relevance of this test is therefore limited to industrial Sewage Treatment Plants (STPs) (regular DMS inflow).

It is difficult to classify DMS into one of the current biodegradation categories on the basis of the above-mentioned information. It should be noticed, however, that the high hydrolysis rate of the substance would anyhow lead to a high removal percentage of DMS in an STP in the present risk assessment. DMS will be regarded as readily biodegradable in industrial STPs.

Recently another biodegradation test result became available. In an OECD 301B, CO_2 Evolution Test MMS was found to be ready biodegradable (Hoechst Marion Roussel report, 1998a). This result supports the OECD 301 E test result for DMS.

3.1.1.2 Distribution

For the adsorption of dimethyl sulphate in a soil-water system a log K_{oc} of 1.38 is calculated according to the TGD (EC 1996). From this it can be concluded that DMS has a low adsorption potential and thus a high mobility/leaching potential.

For the volatility of DMS from water to air a Henry constant of 0.39 $Pa.m^3/mol$ is calculated at a temperature of 25^oC and a vapour pressure of 87 Pa. This means that the compound shows no tendency to evaporate from water.

3.1.1.3 Accumulation

On the basis of the high water solubility, the hydrolysis rate of DMS and the low calculated log K_{ow} of 0.16, no bioaccumulation of DMS is expected.

3.1.2 Emission scenarios

3.1.2.1 Local releases from production and processing

DMS releases

All EU production and large (>1,000 tpa) processing sites of DMS as mentioned in, respectively, **Table 2.1** and **Table 2.3**, submitted site specific information on the environmental releases of the substance DMS. These local environmental releases of DMS from the various production and large processing sites are described below.

Production site 1

Production occurs in a closed system under nitrogen pressure. The concentration in air exhaust of the plant was measured and found to be below the 0.05 ppm (vol/vol) detection limit (less than 1 g/h ~ 0.024 kg/d). The waste of the process is treated with sodium hydroxide and subsequently incinerated on site. No release of DMS is expected to water.

Production site 2

Production occurs in a closed system (under reduced pressure). The main waste gas flow is burned at 1,200°C. A national institute (TÜV/Rheinland) measured 3-4 mg DMS/h in air. Based on these measurements a calculated figure for release to air of 35 g/a is given. This emission occurs after the alkaline absorption of air in the DMS-tanks. No releases to wastewater occur.

Production/processing site 3

Production occurs under elevated temperature and in closed systems (reduced pressure). Releases to wastewater do not occur because the excess of DMS is removed from the reaction process by an alkaline treatment at elevated temperatures. Exhaust gasses of the process chambers are also led through an alkaline washing bath. According to the company the maximum release to air is theoretically $\leq$0.7 kg/a. This value is derived from the detection limit.

Processing site 4

DMS is processed in closed systems. Exhaust gasses of the methylising process are led through a special treatment bath for hydrolysation. Measurements indicate levels below 0.2 mg/m^3. This figure is probably derived from occupational exposure. No measurements are given for wastewater and exhaust gas. No release to wastewater is expected.

Processing site 5

DMS is processed in closed systems. According to the German emissions registers (1994) there are no releases to air. In addition, no release of DMS to wastewater occurs, as after reaction of DMS at processing, the excess DMS is hydrolised at temperatures >60°C and controlled pH.

There is no site-specific information on DMS releases at smaller processing sites in the EU, but there are emission data for the hydrolysis products for these sites.

Monomethylsulphate/sulphate releases

In part I of this section site-specific information on the environmental releases of the parent compound DMS is given. However, as DMS is known to hydrolyse very rapidly into monomethylsulphate and methanol (see section 3.1.1), it might be more relevant to focus the risk assessment on the hydrolysis products, in particular monomethylsulphate. A prudent attempt is made to carry out such a risk assessment for the aquatic compartment. The hydrolysis product monomethylsulphate can be removed from the industrial process in two ways:

- by hydrolytic cleavage before the Waste Water Treatment Plant (WWTP). Methylsulphate is hydrolysed by boiling and recycling of methanol. This means that only anorganic sulphate will remain in the waste stream which is directed to the WWTP.
- in the WWTP, where monomethylsulphate is expected to be biodegraded rapidly (87% removal, see results of biodegradation test in section 3.1.0). In Annex 5 default estimates are made for sulphate and monomethylsulphate releases for one production site and a number of users. Emission factors of 0.3% (TGD Table A1.1) and 85% (TGD Table A3.2 Processing Basic Chemicals IC=2) are assumed for, respectively, production and processing of DMS. Further conversion factors of 1.13 and 1.06 were used for calculating, respectively, the sodium sulphate and sodium monosulphate releases.

Non-EU information

According to the U.S. Toxic Release Inventory in 1994 an amount of 3,180 kg of DMS is released to the environment (Toxics Release Inventory 1994). From this, 3,045 kg is released to air and the remaining 135 kg to surface water. The U.S. emissions of DMS were found to be reduced compared to figures from 1988: 5,159 kg (total). In the Seventh U.S. Annual Report on Carcinogens (1994) it is reported that: 'investigators have found the chemical in wastewater streams and air emissions from plants where it is made or used'.

Individual emission data for 38 DMS producing/using plants in the U.S. are now available. Most of these use DMS as a reactant for various applications that seem to be comparable to those in the EU. Data indicate that DMS emissions to water are negligible (37 out of 38 facilities indicate that water emissions are 0). DMS emissions to air were reported for almost all plants (33 out of 38). The highest atmospheric emission was 2.7 kg/d and for 12 sites the emissions are between 0.3 and 0.6 kg/d.

Conclusion

Similar to the EU, the U.S. emissions of DMS to water are negligible, but on the other hand also understandable as hydrolysis is very rapid. Emission data of hydrolysis products would have been more relevant from a risk assessment perspective (see section above). Emissions to air seem to be higher in U.S. than in the EU. At present, there is no plausible explanation for this difference.

3.1.2.2 Releases from other (unintentional) sources

The reaction of SO_2 with organic compounds in the atmosphere results in the formation of a variety of gas phase and aerosol organic compounds including DMS and monomethyl sulphuric acid (Hansen et al., 1985). The combustion of sulphur-containing fossil fuels has been reported to cause atmospheric contamination by DMS adsorbed on particulate matter (EHC, 1985) and in the gas phase (Hansen et al., 1985). No release figures are available.

DMS has not been identified as a natural product in the environment (EHC, 1985).

3.1.3 Local Predicted Environmental Concentrations

In section 3.1.2.1 it is indicated that the production and large processing sites of DMS all contain closed systems. At these production and processing sites there is no emission to wastewater due to treatment of wastewater with alkaline baths and incineration of waste products. For this reason no PECS in water will be calculated for DMS itself. Local PECs are calculated, however, for the DMS hydrolysis products sulphate and monomethylsulphate for a number of production and processing sites (large and smaller ones). This was done according to the TGD and using both default emission rates and site-specific information on tonnages and river flows. The calculated PECs are shown in Annex 4.

Exhaust gasses after production and processing are treated with alkalic baths. Therefore emissions to air are, theoretically, assumed to be zero. Four companies submitted measured or calculated release data of DMS to air. Three of them indicated that measured levels are found to be below the detection limits. For site No. 2, however, an estimated air release figure of 35 g/a is reported and this value will be used in this exposure assessment. The local PEC in air is calculated according to the TGD (section 2.3.8.2). Assuming a number of production days of 300 and thus a daily atmospheric release of 117 mg, the calculation results in a local PEC air of 32 pg/m^3 (total annual average).

3.1.4 Measured data

There are no measured environmental concentrations available for any of the DMS production and/or processing sites. However, a number of measured concentrations of DMS in air in the vicinity of coal or oil fired heating plants have been reported (**Table 3.1**). One report refers to U.S. data from an industrial process using DMS as reactant. These data have not been extensively (re-)evaluated.

Table 3.1 Measured concentrations of DMS in air

Concentration	Remarks	Reference
8.1 μg/m^3	1 location with 3 samples (US); Median figure; probably populated area (?); data from VOC data base (EPA); regional or local concentrations?;	Kelly et al., 1994
830 ppm	-coal-fired heating plant (US); fly ash and in airborne particulate matter (mono and dimethyl)	Lee et al., 1979
40-50 ppb (~0.26 mg/m^3)	-vicinity of industrial process using DMS as reactant (US)	Hansen et al., 1985
1000 ppm (~5250 mg/m^3) 0.02 ppb	-gas phase; flue line and plume of oil-fired power plant (US); after 1 hour -gas phase; after 20 days and 20 km; integrated concentration	Hansen et al., 1985
0.3-2 ppb (~0.01 mg/m^3)	-Los Angeles Basin (day and night); gas phase; urban area (extreme polluted area in US)	Hansen et al., 1985
<50 ppm 500 ppm 70 and 180 ppm	-flue line and plume of coal-fired power plant (US); both in particles and gas phase; at stack -5 km downwind of plume (gas phase) -plume particles (same age of plume as above)	Hansen et al., 1985

It is difficult to draw a conclusion on the results given in **Table 3.1**. Firstly, most presented monitoring data are rather outdated (before 1985). Nowadays fossil fuel has a lower sulphur contents than twenty years ago. Therefore, current figures will probably be much lower. The concentration of around 0.26 mg/m^3 in the area around an industrial process using DMS is originally from 1975. Further, the data represent a variety of sampling locations of which several are irrelevant for the current risk assessment (e.g. flue line data). However, taking into account both the large uncertainty of the calculated local DMS concentration of 32 pg/m^3 (site-specific scenario) (see paragraph 3.1.2) and the unknown representativity of the data set in **Table 3.1**, it can nevertheless (prudently) be concluded that 1) DMS may occur in our atmospheric environment (more actual monitoring data are needed), but that 2) the contribution of DMS emissions from production/processing sites will be very low compared to those from unintentional sources.

3.1.5 Regional concentrations

Regional concentrations of DMS in the various environmental compartments are considered to be negligible. Therefore no risk characterisation is carried out for the regional scenario.

3.2 EFFECTS ASSESSMENT

3.2.1 Aquatic compartment

3.2.1.1 Short term toxicity to fish

In all studies with aquatic organisms the observed toxicity concerns the toxicity of DMS and its hydrolysis products (methyl sulphate and methanol).

For a static study (temperature 23°C, pH 7.6-7.9, hardness 55 mg/l as $CaCO_3$) with *Lepomis macrochirus* (33-75 mm) a "best fit" 96-hour LC_{50} of 7.5 mg/l is reported (Dawson et al., 1977). This value is derived from a concentration-effect range that is considered not reliable. At 7.5 mg/l the survival percentage is 90%. For *Leuciscus idus melanotus* (1.6-2.6 g, static test, pH 7.5-8.4, hardness 110 mg/l as $CaCO_3$) the LC_{50} is 14 mg/l (Hoechst, 1981).

There are no long-term tests available either for freshwater or marine fish.

In a static test in artificial seawater (salinity not reported, temperature 20°C) with *Menidia beryllina* the "best fit" 96-hour LC_{50} is 15 mg/l (Dawson et al., 1977).

The behaviour pattern of the marine fish *Kuhlia sandvicensis* was tested after exposure to DMS at a concentration up to 20 mg/l (Hiatt et al., 1953). Only at the highest dose of 20 mg/l a slight reaction (e.g. mouth movements, vertical swimming) was reported.

Genetic effects were observed in fish embryos following treatment of sperm with DMS and disturbances in the nucleoli of oocytes from fish have been reported following exposure to DMS-contaminated water (EHC, 1985).

3.2.1.2 Acute toxicity to aquatic invertebrates (e.g. Daphnia)

In a study with *Daphnia magna*, performed according to OECD guidelines, the 48-hour EC_{50} is 17 mg/l (Hoechst, 1990). No details on test water and test conditions are available.

3.2.1.3 Toxicity to aquatic plants (e.g. algae)

In a study with *Scenedesmus subspicatus*, performed according to OECD guidelines (pH 6.1-8.4, temperature 24° C), the 72-hour EC_{50} for growth rate is 46.9 mg/l (Hoechst, 1988).

3.2.1.4 Toxicity to microorganisms (e.g. bacteria)

In an activated sludge test, performed according to OECD guidelines (pH 7, temperature 23°C), the 3 hour-EC_{50} for bacterial respiration inhibition is 377 mg/l (Hoechst, 1990).

In a test for the determination of damage to anaerobic effluent bacteria (fermentation tube method) a toxicity threshold limit of 2000 mg/l is given (Hoechst, 1980). Too little information is available to check the reliability of this test.

3.2.1.5 PNEC for the aquatic compartment

The PNEC for the aquatic compartment is extrapolated from the lowest short term toxicity result, i.e. 14 mg/l for the goldfish, using an extrapolation factor of 1000. This results in a PNEC of 14 µg/l.

$PNEC_{water}$ = 14 µg/l

It has to be borne in mind that this PNEC is in fact based on the toxicity of DMS and its hydrolysis products (methyl sulphate and methanol). From the available ecotoxicity data for methanol (96 h LC_{50} fish: 19,000 mg/l; 24 h EC_{50} daphnids: >10,000 mg/l; EC_{50} algae: 36,000 mg/l, ECETOC, 1996) it can be concluded that the toxicity can mainly be attributed to DMS and methyl sulphate.

As in the current report also a (prudent) risk assessment is carried out for sulphate and monomethylsulphate, PNECs are needed for these substances as well.

Very recently an acute toxicity test result for monomethylsulphate became available. In an OECD 203 test with *Brachidanio rerio* the 96-hour LC_{50} was found to be >10 g/l (Hoechst Marion Roussel report, 1998b). Although normally a PNEC is not set on the basis of one toxicity value a worst-case estimate for the PNEC of monomethylsulphate would be >10 mg/l (10g/l/1000). This estimate of the PNEC is used in the current risk assessment. However, as the rapporteur realises that there is no base set fulfilment for monomethylsulphate and no validation of the zebra fish test yet, also the PNEC for DMS i.e. 14 µg/l, will be used as a "shadow" worst-case approach. A rather worst-case PNEC for sodium sulphate is 630 µg/l (630 mg/l/1000; see IUCLID data set on sodium sulphate).

3.2.1.6 PNEC for micro-organisms in STP

The PNEC for microorganisms in an STP is extrapolated from the activated sludge test result, i.e. an EC_{50} of 377 mg/l, using an extrapolation of 100. This results in a PNEC of 3.8 mg/l.

$PNEC_{microorganisms}$= 3.8 mg/l

Similarly to the $PNEC_{water}$, the $PNEC_{microorganisms}$ is based on the toxicity of DMS and its hydrolysis products. However, due to the short exposure period (3 hours) in the activated sludge test the fraction of DMS will probably be higher than that in the aquatic tests (48-96 hours).

3.2.2 Terrestrial compartment

Toxicity to terrestrial plants

Chromosomal aberrations have been induced by DMS in a variety of vascular plants including *Vicia faba*, wheat, sunflower, and Norway spruce (EHC, 1985). In another experiment the seeds of three rice cultivars were continuously shaken in solutions containing DMS concentrations of 300, 500 or 1000 mg/l during 12 hours. After this treatment the seeds were washed for 60 min. and allowed to recover in fresh water for 3 hours and sown directly in seed beds. In cultivar No. 1 cytologically abnormal plants were detected at all concentrations of DMS. However, the frequency of aberrant plants decreased with increasing dose: 45.5%, 33.3% and 22.2% for 300, 500 and 1000 mg/l, respectively. In cultivar nr.2 25% aberrant plants were observed at 300 mg/l, 33.3% at 1000 mg/l and no aberrant plants at 500 mg/l. A dose response relationship could not be established. The same was seen in cultivar nr.3 with 16.6% aberrants at 300 mg/l, 0% at 500 mg/l, and 40% at 1000 mg/l. The most common type of abnormality noticed involved the

nucleolus; the number of nucleoli varied from two to many and persistent nucleolar bodies of varying sizes were also recorded. Other abnormalities included lagging of chromosomes and bridges with or without fragments (Seetharami Reddi and Reddi, 1985).

3.2.2.1 PNEC for terrestrial compartment

The data from the toxicity tests with terrestrial plants are not suitable for deriving a PNEC for the terrestrial compartment. Therefore the PNEC for the terrestrial compartment was estimated from the PNEC for aquatic organisms using the equilibrium partitioning method (TGD). This results in a $PNEC_{soil}$ of 2 μg/kg.

$PNEC_{soil}$ = 2 μg/kg

3.2.3 Atmosphere

No data available.

3.2.4 Non compartment specific effects relevant to the food chain

No specific data available.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment

Local PECs have been calculated for two major hydrolysis products of DMS, i.e. monomethylsulphate and sulphate (see Annex 4). PNECs for monomethylsulphate and sulphate are, respectively, 14 μg/l and 640 μg/l. All PEC/PNEC ratios were found to be below 1 **(conclusion ii)**.

Sediment

There are no toxicity data for sediment-dwelling organisms and also measured data for the concentration of DMS in sediment are lacking. Thus a quantitative risk characterisation of DMS for sediment can not be performed. However, the low absorption potential of DMS and its high hydrolysis rate suggest that sediment is most probably not a relevant compartment for the environmental risk assessment of DMS (and its hydrolysis products).

3.3.2 Terrestrial compartment

There are no releases of DMS to the aquatic compartment and thus the sludge application route does not contribute to elevated DMS levels in soil. Deposition of DMS is considered to be negligible (low atmospheric releases and high hydrolysis rate of DMS in air) **(conclusion ii).**

No terrestrial risk characterisation is carried out for the hydrolysis products of DMS.

3.3.3 Atmospheric compartment

No ecotoxicity data are available for the atmospheric compartment and therefore no environmental risk characterisation can be carried out for air.

3.3.4 Non compartment specific exposure relevant to the food chain

Because of the negligible environmental exposure of DMS via water and soil and the low K_{ow} of DMS, food chain accumulation is not likely **(conclusion ii)**.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

At room temperature DMS is a colourless oily fluid. It has a low volatility with a vapour pressure of approximately 60 Pa at room temperature. In contact with moist air it decomposes to methylalcohol and ether. Inhalation and dermal contact are the most obvious routes of exposure to humans. Ocular exposure is possible due to hand-eye contact.

DMS is an industrial chemical (the use and main category is given in chapter 2) that is mainly used as an alkylating agent. The substance is used in the manufacture of methylesters, ethers, and amines in dyes, drugs and perfumes (NIOSH, 1979). DMS is also used as a solvent in the separation of mineral oils and as an intermediate in the manufacture of many pharmaceuticals and pesticides (Kirk & Othmer, 1985). DMS is a component of polyurethane-based adhesives (NTP, 1994).

4.1.1.2 Occupational Exposure

Persons exposed to DMS are workers involved in production, manufacturing and use of DMS mainly in the chemical industry.

In some countries occupational limit values for DMS are established (**Table 4.1**).

Table 4.1 Occupational limit values for DMS

Country	Occupational limit	Value (mg/m^3)
Germany	TRK[1]	0.1 (production); 0.2 (use)
USA	PEL[2]	5
The Netherlands	MAC[3]	0.5
Denmark		0.05

1. Technische Richtkonzentrationen (The DFG Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work area – the German MAK)
2. Permissible exposure limit (USA, OSHA = Occupational Safety and Health Administration)
3. Maximum Allowable Concentration (NL, DECOS = The Dutch Expert Committee on Occupational Standards)

Occupational exposure occurs in industries where DMS is produced and in industries where DMS is added to processes. Routes of exposure to DMS in all mentioned industries are by inhalation and by dermal contact.

Relevant populations occupationally exposed are workers in the above mentioned industries, specifically those workers dealing with processes involving DMS, being:

- workers involved in the production of DMS;
- workers drumming DMS;
- workers transferring DMS as intermediate for other products;
- workers responsible for maintenance and cleaning of the equipment used in the production of (products of) DMS.

The following data (if available) are used for the occupational exposure assessment:

- physico-chemical data of DMS and products containing DMS, such as physical appearance and vapour pressure at room temperature;
- data regarding methods of use and use pattern of the substance and of products potentially containing DMS;
- exposure control pattern in the relevant industries (from the HEDSET or other sources);
- exposure data for DMS from the HEDSET or other sources (literature, exposure databases);
- results from exposure models if applicable (EASE model, EPA transfer model); in the exposure models the above mentioned types of data are used.

In this part of the assessment, external (potential) exposure is assessed using relevant models and other available methods in accordance with the Technical Guidance Documents 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 personal protective equipment 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 may reduce the external exposure with 85%. For respiratory protection the efficiency depends largely on the type of protection used. Without specific information, a tentative reduction efficiency of 90% may 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. They will not be used directly in the exposure and risk assessment. Furthermore, the 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 the model estimates with normal assumptions for input parameters in the assessed exposure scenarios are expected not to lead to a reasonable assessment of exposure. For situations with high risk of direct acute effects, such as manual handling of corrosive substances and hot materials, or possible inhalation exposure of substances with severe acute effects on the respiratory tract, the total level of containment given by all exposure control measures is assumed to be higher than for similar scenarios with other substances. For estimating

a single day exposure an extra protection is assumed, reducing exposure with 90%. The extra protection can be reached by a combination of technical and organisational control measures and personal protective equipment. If the extra protection is reached (mainly) by using personal protective equipment, this is an unwanted situation that should be changed by further technical and organisational control measures.

The estimate of repeated dermal exposure depends on the knowledge of a "maximum non-corrosive concentration". If such a concentration can be estimated, this concentration will be used in estimating repeated dermal exposure. Otherwise the estimate for single day exposure will be used.

In this part of the assessment, external (potential) exposure is assessed using relevant models and other available methods in accordance with the Technical Guidance Documents 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).

For the occupational exposure assessment the exposure to DMS can be clustered in 2 scenarios based on type of handling or use of DMS. In the first scenario the production of DMS is considered. Cleaning and maintenance of the system are tasks included in this scenario, so is drumming of DMS. The second scenario deals with the use of DMS as an intermediate in various industries. It is assumed that DMS is not used for other purposes in Europe. The possible use of DMS as a solvent in the separation of mineral oils or in the analysis of automobile fluids that is mentioned in some older references are considered to be not relevant for the present situation in Europe.

Scenario 1: Chemical industry; production of DMS
Scenario 2: Chemical industry; use of DMS as an intermediate

Scenario 1: Chemical industry; production of DMS

In this scenario the production of DMS and cleaning and maintenance of the closed production system is included. Drumming of the liquid into rail cars, tank trucks and vessels is also included but is, due to the characteristics of the process, mentioned separately.

It has been known for many years that DMS is very toxic, therefore production and transferral of DMS takes place in a continuous (closed) process. Liquid sulphur tri-oxide is added to gaseous dimethyl ether in a reaction vessel, containing 96-97% DMS, sulphuric acid and monomethyl sulphate which are continuously withdrawn and purified by vacuum distillation over sodium sulphate (NIOSH, 1979; Company D, 1995). The closed system used for the synthesis of DMS has an underpressure so in case of leakage, air will get in instead of DMS leaking out. The small amount of waste products will be led through sulphuric acid and finally burned at 1200°C. The crude DMS is purified by excretion of dimethylether and by-products and then stored directly in a tank. The distillation process is done under vacuum so DMS leaking out of the system is unlikely (Company D, 1995; Industry, 1997).

The production and transfer take place in closed systems. A closed system is not fully closed in such a way that the system must have opening possibilities for maintenance, cleaning and sampling. It is not an exception that in such cases valves will be opened manually. Also (very limited) leaking because of bad or old junctions cannot be excluded. After production, DMS will be drummed into tank car and vessels (Wendt, 1979). Industry reports that continuous monitoring systems are generally used to indicate the occurrence of leaks (Industry, 1997).

Full PPE is reported to be used if breaching of the closed system is necessary or suspected (e.g. after accidental spillage of DMS). The PPE includes liquid-tight gloves, clothes and boots and respiratory protection with suitable filters.

Cleaning of process equipment is done by flushing with aqueous ammonia solutions to destroy the DMS, followed by flushing with water. No details on the possibly remaining concentrations of DMS are available. Transport drums are reported to be either used only once or are cleaned by flushing with ammonia solutions in an automated cleaning machine (Industry, 1997; Company E, 1997).

Measured data

Production

A small number of exposure data has been provided by the producers or was found in a literature search. Air concentrations were reported at 9 potentially leaking points in 2 sites handling DMS in the USA, varying from 1 to 5.24 mg/m3 (ACGIH, 1980). Number of measurements, measuring time and circumstances in which the measurements took place, were not mentioned. In a later study (ACGIH, 1980) at one of the two sites, peak air concentrations were measured between 1 and 1.6 mg/m^3. Another survey reported long-term concentrations of more than 0.36 mg/m^3 in 53% of 48 air samples taken near the DMS production process, and in 70% of the samples taken near the purification process. An air concentration of 12.3 mg/m3 was measured near a manhole. Nothing is mentioned about the duration of these stationary measurements. All the measurements were done at one factory, and during measurements several tasks (sampling, opening reactors to reduce pressure) were carried out (Molodkina et al., 1979). Personal long-term exposures with a 90% percentile value of 0.01 mg/m3 were reported in another study. It concerned 6 measurements at one factory during production and process control (Industry, 1996).

Because of the use of closed systems, dermal exposure is rather uncommon. In the available literature, skin exposure to DMS is only mentioned due to accidental leakage of DMS. Some of the activities in the production of DMS require manual handling, for instance opening valves, but in such cases special precautions are taken (PPE) to limit the potential contact. Contamination of workers' skin and clothes was mentioned in one source (Molodkina et al., 1979), but quantitative information is not given. In case of dermal contact with DMS, inhalation can be a route of exposure due to the fact that DMS may evaporate from the warm skin resulting in possible effects upon the respiratory system (de Grosz, 1937).

Tanker filling and drumming

Details of tanker filling and drumming have been received from one of the producers. Several steps are taken to reduce the possibility of evaporation of DMS (e.g. vapour retour systems) and to preclude direct skin contact (Company A, 1997). The filling of drums is by half automated equipment reducing the possibilities of exposure of workers (Industry, 1997). Full personal protective equipment is worn during connecting and disconnecting of transfer lines. Similar precautions are advised to the customers of the producers for unloading of DMS (Company A, 1997). Stationary measurements carried out in a drum-filling unit resulted in an average concentration of 0.1 mg/m^3 at a distance of 0.5 m of the hopper and an average concentration of 0.025 mg/m^3 at 2 m of the hopper. Nothing is mentioned about the number of measurements and the duration of measurements. Only the average values of the stationary measurements are given. The measurements were carried out at one workplace during the filling of drums. No DMS was detected in personal samples in the breathing zone of the workers at the filling unit. These workers

only reached the contact zone in case of changing the drums (Company D, 1995). Personal sampling in another study resulted in a 90% percentile long-term exposure value of 0.02 mg/m^3 (12 measurements in 4 factories) for drumming vessels in the presence of Local Exhaust Ventilation (LEV). The same value was found for short-term exposure (<1 hour; Industry, 1996). During filling drums in a third study, 0.42 mg/m3 was found to be the highest (worst case) value of stationary site samples taken at one factory. Drumming was an intermittent process (Olguin and Morgan, 1976).

Models

An estimation of possible inhalation exposure to DMS can be made using the EASE model with the following assumptions: DMS is produced in a closed system, which is breached for quality sampling and maintenance. The use pattern is non-dispersive use with LEV. EASE estimates an exposure to DMS of 0.5-3 ppm (2.6-15.7 mg/m3). If the systems are fully closed, EASE estimates a level of 0-0.1 ppm (0-0.5 mg/m3). Since the EASE model for "low volatility" substances is built to accommodate substances with vapour pressures of 0-1,500 Pa, this model may overestimate exposure levels for substances with vapour pressures in the lower range of this category.

According to the EASE dermal exposure model, extensive potential dermal contact is theoretically possible during cleaning. Cleaning starts with flushing with ammonia solution, followed by flushing with water. According to industry this will lead to complete reaction and removal of DMS. Since DMS is a very corrosive substance, additional control measures are assumed to be taken to reduce exposure even further, including a very strict use of good personal protective equipment. Therefore it is concluded that actual dermal exposure will only occur in the case of accidents.

Exposure during drumming of liquids is estimated by means of the USEPA transfer model (Annex 1). Drumming of the substance in containers of 200 l results in a worst-case concentration of vapour in air of 219 mg/m^3. It has to be noted that the estimated value of the USEPA transfer model probably overestimates the actual exposure; the reason for this assumption is that in case of opening the closed system special precautions will be taken to limit the exposure of the workers by using local exhaust ventilation (LEV). Given the highly toxic nature of DMS efficient LEV is to be expected. Assuming an effectivity of 95%, the estimated concentration is in worst-case situation 11 mg/m3 ($0.05 \cdot 219$). The typical full shift value for drumming is estimated to be 2.44 mg/m3.

Drumming into drums is done with half automated systems and remote opening and closing of the transfer lines. Several control measures are used to avoid the possibility of dermal contact, such as direct neutralisation of possible DMS on lids by putting the lid into lime and using a clean lid every time after a lid has been removed from a drum (Company A, 1997). It is assumed that similar control measures are used throughout the producing industry. These control measures are assumed to lower possible contacts to a minimum. It is therefore assumed that actual dermal exposure will only occur accidentally.

The frequency of drumming into drums is assumed to be up to 25 days per year.

Conclusions

For this scenario measured exposure data concerning production and drumming of DMS are available. Occupational exposure during drumming is expected to be higher than during production itself. The reason for this is the assumed higher level of emission during drumming. In this scenario however, measured exposure levels during drumming were lower than exposure levels measured at the production site. The reason for this might be the advanced drumming

systems used from which less emission takes place than assumed. Exposure during drumming is also estimated by means of the USEPA transfer model. The exposure values resulting from this model were much higher than the measured values. It seems that the model overestimates the exposure level. A reason could be that the calculations of the model are based on a less closed system than the real situation. In that case the USEPA model calculates an exposure level considering that emission takes place on a larger scale than in the real situation. Given the extent of the measurements (12 measurements in 4 factories supported by some results of stationary sampling), more weight is given to the measurements. In this scenario the same exposure levels will be assessed for production as well as drumming.

Regarding the data from literature, the values obtained from the EASE model (that probably overestimate exposure, due to the wide vapour pressure ranges in EASE) and the USEPA transfer model, the following values are derived for the risk assessment:

- worst-case short-term exposure: 5 mg/m3 (mainly based on measured exposure data);
- reasonable worst-case full-shift exposure: 0.05 mg/m^3 (based on exposure data and EASE)
- assuming a fully closed system and considering the expected overestimation by EASE;
- typical full-shift exposure: 0.01 mg/m^3 (mainly based on measured personal exposure levels).

The proper use of adequate PPE can be an important risk reduction method for the handling of substances with acute and serious effects at estimated occupational exposure levels. This situation may be present for the assessed substance in this scenario.

Due to the very strict control measures shown for several activities leading to potential exposure and the known corrosive effects of DMS it is concluded that the possibility of potential dermal exposure is largely avoided by technical means and that actual dermal exposure will only occur due to accidents.

Scenario 2: Chemical industry; use of DMS as an intermediate

In this scenario the further use of DMS is discussed. This scenario describes applications of DMS in the chemical industry and the pharmaceutical industry. DMS is used in these industries as an intermediate, mainly as an alkylating agent, for instance for the alkylation of phenols and amines. These are important intermediates in the dye, pharmaceutical and perfumery industries (NIOSH, 1979). Other possible uses of DMS are considered not to be relevant in Europe. DMS, used as intermediate, is fully reacted in the process. Adding of DMS takes place from vessels to a closed system in which the alkylation takes place. After this process the excess of DMS is destroyed by hydrolysis at temperature above 60°C and controlled pH. Because of the hydrolysis no DMS is present further in the process (Company C, 1995).

Details of actual processes, techniques and control measures are not available. However, according to industry the type of control measures is similar as during production (Industry, 1997). At least one producer gives extensive guidance to customers on the safe handling of DMS (Company A, 1997).

A reasonable worst-case vapour pressure of 60 Pa (at 20°C) is assessed (Kühn, 1994), so DMS is categorised to be of low volatility. Due to this low volatility and the conversion of DMS during the alkylation, the exposure of workers to DMS is limited to adding of DMS to the system, where it will be totally transformed.

Measured data

A large number of measurements is reported by industry. A compilation of reported exposure levels is presented in **Table 4.2**

Table 4.2 Compilation of reported exposure levels

Process or activity	Number of measurements N) and facilities (n)	50-Percentile (mg/m3)	90-Percentile (mg/m3)	Range (mg/m3)	Source and remarks
Measurements for more than 1 hour, reported as full shift levels					
Connection of transfer lines	N = 5 n = 2	15	16	0.01-2.1	Industry, 1996 In open air
Pumping DMS from vessels in reaction system	N = 12 n = 7	2	3	n.a.	Industry, 1996 Under LEV
Cleaning and maintenance of system	N = 5 n = 4	2	15	0.01-0.27	Industry, 1996*
Process control	N = 151 n = 20	4	4	up to 0.3	Industry, 1996* Under LEV
Process handling and sampling	N = 83 n = 14	4	4	up to 2.6	Industry, 1996* Under LEV
Laboratories	N = 174 n = 28	4	4	up to 0.3	Industry, 1996* Under LEV
Further processing	N = 135 n = 7	25	1	< 0.0025-0.27	Company F, 1996* Closed systems
Laboratories	N = 180 n = 31	< 0.0025	5	< 0.0025-0.24	Company F, 1996* Small scale handling under LEV
Test installations	N = 46 n = 6	25	25	< 0.0025-0.025	Company F, 1996* Closed systems and LEV
Further processing	N = 15	8	44	0.02-3.6	Company B, 1995* Only data reported when short term levels above 0.2 mg/m3 were found
Connecting transfer lines	N = 1 n = 1	n.a.	n.a.	< 0.02	Company C, 1997* In open air
Pumping	N = 3 n = 2	n.a.	n.a.	< 0.02	Company C, 1997* Under LEV
Cleaning and maintenance	N = 2 n = 2	n.a.	n.a.	< 0.02-0.02	Company C, 1997* Under LEV
Process handling and sampling	N = 15 n = 6	2	n.a.	< 0.02-0.03	Company C, 1997* Under LEV

Table 4.2 continued overleaf

Table 4.2 continued

Process or activity	Number of measurements (N) and facilities (n)	50-Percentile (mg/m3)	90-Percentile (mg/m3)	Range (mg/m3)	Source and remarks
Short term measurements (< 1 hour)					
Near a deflective flange	n.a.	n.a.	n.a.	0.25-0.3	Ellgehausen, 1975
Connecting transfer lines	N = 4 n = 1	6	32	n.a.	Industry, 1996* In open air
Pumping	N = 1 n = 1			2	Industry, 1996* Under LEV
Process control	N = 3 n = 2	2	3	n.a.	Industry, 1996* Under LEV
Process handling and sampling	N = 2 n = 2			2	Industry, 1996* Under LEV
Further processing	N = 47	15	49	0.2-5.7	Company B, 1995* Only short term values above 0.2 have been reported

n.a. = Not available

*All data reported by company C (1997) and a large part of the data reported by company F (1996) and company B (1995) is also included in the data reported by Industry (1996). The data by Industry (1996) are compiled from 5 companies. The short-term levels reported by Company B (1995) do not appear to be included in the data by Industry (1996). Company F (1996) has included results of measurements done after the compilation of data by Industry (1996)

Most of the processes involved are either in closed systems (pumping, reactions) or are done under LEV. Activities that require opening of closed systems are connection of transfer lines, sampling and laboratory work. The latter only involves small scale handling of DMS under LEV by trained laboratory personnel. The data presented by Company B (1995) probably overestimate true 50- and 90-percentile in this company, since it appears that only data have been presented for shifts when the short-term exposure level was (at any measurement) above 0.2 mg/m^3.

Models

Assumptions made in EASE to estimate the possible exposure to DMS were: use pattern is non-dispersive, LEV is present. EASE estimates an exposure to DMS of 0.5-3 ppm (2.6-15.7 mg/m^3). For closed systems assuming no breaching EASE estimates 0-0.1 ppm (0-0.5 mg/m^3).

Technical control measures in this scenario are generally very similar to those in the production facilities, partly because the producers are also major users in further processing. It is therefore concluded that the potential dermal exposure is largely avoided by technical control measures and that actual dermal exposure will only occur due to accidents.

Conclusions

Short-term exposure levels of up to 5.7 mg/m3, with a 90-percentile of 4.9 mg/m^3 have been reported by one company. Therefore 5 mg/m3 will be used as a reasonable worst-case short-term exposure level for the inhalation exposure of this scenario.

EASE probably overestimates the exposure levels for substances with lower volatility. The data for full shift exposure in this scenario are almost all lower than 2 mg/m^3. Many of these measurements however, are less than 1 mg/m3. The 90-percentiles of full shift measurements reported are in the range of 0.0025 to 1.6 mg/m3, where 1.6 mg/m3 is an outlier reported only for a specific activity and derived from a limited number of measurements. Considering that production workers generally rotate over positions and come into contact with several of the mentioned activities, the reasonable worst-case estimate for full shift exposure level is 0.2 mg/m^3, based on the reported measurements. Typical full shift exposure levels are estimated to be around 0.04 mg/m^3 (based on measured data). The estimates by EASE ("closed system" for full shift exposure and "closed system breached" for short term exposure) agree reasonably well with the measured data.

The proper use of adequate personal protective equipment (PPE) can be an important risk reduction method for the handling of substances with acute and serious effects at estimated occupational exposure levels. This situation may be present for the assessed substance in this scenario.

Dermal exposure is considered to occur only accidentally.

Table 4.3 Conclusions of the exposure assessment

Scenario	Exposure		Estimated inhalation exposure level (mg/m3)						Estimated skin exposure level (mg/day)
	Duration (hr/day)	Frequency (days/year)	Long term				Short term		
			Typical		Reasonable worst case				
			Level	Method	Level	Method	Level	Method	
1. Production *Breaching of closed system*	6-8 < 1	100-200 100-200	0.01	Lit.	0.05	EASE, Lit.	5	Lit., EASE	only accidental exposure
2. Use as an intermediate *Breaching of closed system*	6-8 < 1	100-200 100-200	0.04	Lit.	0.2	Lit.	5	Lit., EASE	only accidental exposure

Lit = Mainly based on measured data
EASE = Based on EASE, taking account of measured data

4.1.1.3 Consumer exposure

Several Member States responded to the exposure questionnaire, primary answering the question whether consumer use was known. Canada stated that there is no consumer use, whereas in Denmark DMS is found in 6 products (intermediates and laboratory chemicals), however, direct consumer use is not identified (DPR, 1996). In the Finnish product register only 1 product, used in the production of drugs, is known containing DMS. Other countries (UK, Czech republic, US, AUS and S) are not aware of any consumer use.

Potential human exposure to DMS may occur as a result of the presence of trace contaminants in formulated endproducts (e.g. perfumes, dyes, pharmaceuticals and pesticides). However, based on data from industry it can be concluded that residual amounts of DMS in formulated endproducts are negligible (see also chapter 4.1.1.2 scenario 2).

Potential exposure may also occur from eating food that has come into contact with packaging containing dimethylsulphate residues. In the US this use is regulated by the Food, Drug and Cosmetic act; migration of DMS to food is not expected under the conditions of use specified in the adhesive regulation (NTP, 1994).

European producers are not aware of customers using dimethylsulphate as raw material for any type of adhesives or as constitutive part of raw materials, used for adhesives. It is therefore concluded, also based on the U.S. data, that migration of DMS to food is not expected to occur.

Conclusion

Exposure to DMS in consumer products is considered to be negligible.

4.1.1.4 Indirect exposure via the environment

Man may be exposed to DMS from industrial emissions and other sources.

In section 3.1.2, emission scenarios are described for the production, large processing sites and for smaller EU processors of DMS. Production and processing in large quantities occurs in closed systems. At these sites no release to waste water occurs and emissions to air are, theoretically, assumed to be zero. However, for production site 2 an estimated release figure of 35 g/a is given, resulting in a PEC_{air} of 32 pg/m^3.

Release figures from other sources (reaction of SO_2 with organic compounds and combustion of fossil containing fuels) are not available.

It is difficult to draw sound conclusions on the available measured data from a variety of sampling locations (recent figure ≈ 8.1 μg/m^3) found in literature. As stated in chapter 3.1.4, it can nevertheless (prudently) be concluded that 1) DMS may occur in the atmosphere but that 2) the contribution of DMS emissions from production/processing sites will be very low compared to those from unintentional sources.

Regional concentrations of DMS are considered to be negligible (see section 3.1.5). Therefore no risk characterisation is carried out for the regional scenario.

4.1.2 Effects assessment: Hazard identification and Dose (concentration)-response (effect) assessment

4.1.2.1 Toxico-kinetics, metabolism, and distribution

DMS can be absorbed via respiratory and oral routes. For oral absorption this is concluded from toxicodynamic data. No information is provided on the metabolism of DMS in animals following oral administration. The information on inhalatory or dermal exposure is limited and no quantitative conclusion can be drawn.

In an inhalatory study in rats a rapid disappearance of DMS from the exposure chamber was reported (40 minutes after exposure to 4.7-127 mg/m^3). Blank chambers (DMS, no animal) were run as controls. At the higher dose levels (50.3 and 127 mg/m^3) the disappearance rate was decreased, probably due to a decreased minute volume caused by DMS (Mathison, 1995). This study provides information on uptake of DMS, however does not allow quantification of the percentage of absorption.

In the urine of mice exposed by inhalation to ^{3}H-DMS (average concentration 16.3 mg/m³ and 0.32 mg/m³ for 135 and 60 min resp.) 84-94% of the radiolabel was collected from urine at 48 hours. Less than 0.5% of estimated dose was recovered in the urine as labelled methylated purines (Löfroth, 1974). Due to the limited report this study is considered not suitable for quantitative evaluation.

After an intravenous injection of 75 mg/kg bw in the rat, DMS was no longer detectable in the blood after 3 minutes (Swann, 1968B).

After inhalatory and dermal exposure DMS is reported to be slowly hydrolysed to methanol and sulphuric acid in the tissues, however no quantitative data are provided (Kühn, 1994). Other minor metabolites may be methylsulphate, formaldehyde, and formate. Methylsulphate is stated not to decompose to sulphate (Mathison, 1995), however this statement is not understandable. When rat liver- and nasal microsomes were incubated with DMS (2 mM in water) only minor amounts of formaldehyde were found with liver microsomes and traces with rat nasal microsomes (Dahl, 1983).

Conclusion

The data are insufficient to quantify the kinetic behaviour of DMS after inhalatory exposure, however, apparently absorption is high. No quantitative information on absorption via the oral and dermal route of exposure is available.

4.1.2.2 Methylating properties

DMS is considered to be a strong methylating agent, which is predicted to react with tissue nucleophilic groups, e.g. in nucleic acids.

Inhalation

In an inhalation test with male NMRI mice (16.3 mg/m³ ^{3}H-DMS for 135 min or 0.32 mg/m³ for 60 min, 4 animals per group) a minor part (<0.5% see above) of the radioactive label was excreted in urine as 7-methylguanine (half-life of approximately 1 day). 3-Methyladenine and 1-methyladenine were present in very small amounts. The pattern of excretion in urine of methylated products was independent of the exposure concentration (Löfroth 1974). Adult male CD-rats (6 animals per group) were exposed nose only to 0, 5.3, 15.7, 42, 115 mg/m^3 DMS for

20 minutes. Methylation of the DNA (N^7-methylguanine and N^3-methyladenine) in the respiratory and olfactory mucosa was found to increase with increasing concentration. In the lung DNA-methylation was found to be low, but nevertheless concentration related (not statistically significant) (Mathison, 1995).

Other routes

Intravenous dosing of 6 male Wistar rats (80 mg/kg in the tail vein) with ^{14}C-DMS showed radioactive N^7-methyl guanine to be concentrated in liver, kidney, and lung RNA and in liver, kidney, lung, and brain DNA (Swann, 1968A, see **Table 4.4**).

In vitro

DNA-methylation by DMS was found in several *in vitro* systems, hamster dermal fibroblasts, V-79 cells and calf thymus DNA.

Main methylation products were N^7-methylguanine and N^3-methyladenine (Shiner 1988, Newbold 1980, Fox 1980, see **Table 4.4**).

Table 4.4 Methylation of nucleic acids by DMS

Testing system	Dose	Survival	Result	Reference
Hamster dermal fibroblasts 4DH2	10 mg/ml	survival 82%	Main methylation products: N^7 -MeGua 80 mmol/mol DNA-P N^3-MeAd 9.8 mmol/mol DNA-P O^6-MeGua not detectable	Shiner et al. (1988)
V-79 cells	8, 15 mg/ml	survival 82 and 58 %	Main methylation products as perc of total methylation (8, 15 mg): N^7 -MeGua 48.1%, 92.4% N^3-MeAd 8.8 %, 12.0% O^6-MeGua not detectable, 0.5%	Newbold et al., 1980
Calf thymus DNA	6 , 60 mCi/ml	no data	Main methylation products as % of total methylation (6,60 mCi/ml): N^7 -MeGua 70.9%,74.5% N^3-MeAd 14.6% ,15.2% O^6-MeGua 0.3%,0.4%	Newbold et al., 1980
V 79-cells	0.8 mM, incubation 1 hour with [^{3}H]DMS	surviving fraction 0.73	Main methylation products are N^7- methylguanine and N^3-methyl adenine	Fox et al., 1980
Wistar albino male rats	single dose of 80 mg [^{14}C]-DMS/kg bw in tail vein and killed 4 hours later	-	7-methylated guanine was found in the DNA and RNA of liver, kidney and lung, and in brain DNA	Swann et al., 1968

Conclusion

The methylating capacities of DMS concentrate mainly on the N^7-guanine sites in the nucleic acids.

4.1.2.3 Acute toxicity

Animal data

Several studies have been carried out with different species and by different routes. They are summarised in **Table 4.5**.

All data on acute toxicity of DMS are of limited quality. DMS has to be classified as toxic after oral treatment (based on the study of BASF, 1968). In inhalation studies the compound is found to be very toxic.

No signs of toxicity other than death are reported, except in the studies of Druckrey (1966), BASF (1968), and Batsura et al. (1980). Druckrey reports convulsions and dyspnoea in rats exposed to DMS s.c. and i.v. Autopsy revealed pulmonary oedema, hepatic congestion and intestinal bleedings. In the BASF study rats (p.o.) and mice (i.p.) were reported to experience dyspnoea and convulsions, rats were apathic and remained in a hunched posture. Autopsy showed gastrectasy and terminal lung oedema (BASF, 1968).

In an inhalation study by BASF (1968) rats (6-12 per group) were exposed to saturated DMS vapour (according to the rapporteur 592 ppm ≈ 3100 mg/m^3 l, 20°C [6]). However, this study of BASF is not suitable for the determination of a LC_{50}.

In rats the LC_{50} level after a 4 hr-inhalative exposure to DMS is reported to be 45 mg/m^3. Groups of animals were sacrificed immediately following exposure and at intervals thereafter. The rats were dyspnoeic with cyanosis of the mucosae, hyperemia of the lung, and hemorrhage in the internal organs. Some animals had nasal discharge. Histological and electron microscopic examination of lung tissue revealed hemorrhage and coagulated proteins in the alveoli. After a latent period of 5-6 hr, accumulation of edematous fluid in the air spaces developed progressively over 24-48 hr (Batsura et al., 1980).

[6]Formulas (Chemiekaartenboek)

Saturated vapour concentrations (ppm)	Csp=10000 · vp/1013
Saturated vapour concentrations (mg/m³)	Csat=(M · vp · 273 · 10000 ·)/(22.4 · 1013 · T)

Input parameters
DMS: M=126.1 vp=60 Pa
Result:
Csp 592.3 ppm
Csat 3106.7 mg/m3
N.B. The HSE criteria document (1996) mentioned 6000 ppm (calc.) for the saturated vapour concentration, however the vapour pressure used for this calculation is not indicated.

Table 4.5 Summary of acute toxicity studies

Route	Species	Protocol	LD_{50}/LC_{50}	Reference
p.o.	rat	no data	LD_{50}=440 mg/kg bw	Merck 1976, Kennedy 1991, Chemie Bitterfeld-Wolfen 1995
p.o.	rat	no data	LD_{50}=205 mg/kg bw	Hoechst 1989, 1996
p.o.	rat	0.5-1% DMS in aq. Emulsion, 7 days observation*	LD_{50}=106 mg/kg bw	BASF 1968
Inhalation	rat	no data	LC_{50}=335 mg/m^3, 1 hour	Hein 1971
Inhalation	rat	no data	LC_{50}=45 mg/m^3, 4 hours	Hoechst AG, 1989,1996 Batsura et al., 1980
Inhalation	rat	no data	LC_{50}= 168 mg/m^3, 4 hours	Kennedy 1991
Inhalation	mouse	no data	LC_{50}=513 mg/m^3, 1 hour	Hein 1971
Inhalation	guinea pig	no data	LC_{50}=168 mg/m^3, 1 hour	Hein 1971
Inhalation	hamster	no data	LC_{50}=293 mg/m^3, 1 hour	Hein 1971
i.p.	mouse	DMS in sunfloweroil (0.1 ml solution/10 g mouse), 8 animals*	LD_{50}=61 mg/kg bw	Fisher 1975
i.p.	mouse	0.5-1% DMS in aqueous emulsion, 7 days observation*	LD_{50}=47 mg/kg bw	BASF 1968
s.c.	rat	no data	LD_{50}=100 mg/kg bw	Druckrey 1966,1970, Chemie Bitterfeld-Wolfen 1995
i.v.	rat	no data	LD_{50}=40 mg/kg bw**	Druckrey 1966

*Limited report
**In later publications the LD_{50} i.v. is reported to be 90 mg/kg bw (Druckrey, 1970, Chemie Bitterfeld-Wolfen, 1995)

Human data

Several case reports on inhalatory and dermal exposure to DMS were found.

One of two men died after exposure to DMS-vapour for three hours at 4°C without protective clothing (Rossmann 1952). In the person that died, symptoms of intoxication appeared after several hours and consisted of irritation of the upper-respiratory tract and fever. In the hospital he developed irritation of the conjunctivae and glottis oedema. He finally died after 3 days. Autopsy revealed oedema of the lung and brain. Histopathological examination confirmed the pulmonary oedema and showed corrosion of the respiratory tract. The other person reported nasal secretion, dyspnoea, and conjunctivitis of both eyes. The second day of hospitalisation, he also developed fever, after which his general condition improved and with only minor lung problems he was released from hospital on day eight.

Several cases of dermal exposure to DMS were reported (Thiess, 1968) leading to erythema and oedema of the exposed areas, both lasting for about two weeks.

Short-lasting inhalatory exposure to DMS was found to induce irritation of the nose and the eyes, sometimes followed by respiratory problems. All these effects were temporary (Thiess, 1968).

In all case-reports a rather long period of latency before signs of intoxication were experienced was reported.

Conclusion

Despite the fact that the information on acute toxicity is limited, the data submitted are acceptable with regard to the basic requirements as specified in the Annex VIIA of Directive 67/548/EC. For classification according to Annex 1 of Directive 67/548/EC, see Chapter 1.

4.1.2.4 Irritation and Corrosivity

Animal data

Skin

In rabbits (number unknown) DMS was applied undiluted to the back for 1, 5, or 15 minutes. Scoring was carried out after 24 hours and after 8 days. Application for 1 minute caused no effects. Five minutes of treatment induced slight erythema at 24 hours, but after 8 days the effect had disappeared. After the 15 minutes application period slight erythema was seen after 24 hours; strong erythema and slight oedema were reported after 8 days. Scores in this study are not according to EC-guidelines, but the effects are classified using an in-house (BASF) scoring system (BASF, 1968).

When applied for 20 hours to the back of rabbits (number not indicated) DMS, undiluted, caused severe necrosis, severe oedema and very strong erythema after 24 hours. After 8 days very severe necrosis with ulceration was found. DMS was also applied to rabbit's ears for a period of 20 hours. Twenty-four hours later very strong erythema, extensive necrosis, and strong oedema was scored (BASF-scoring system). The effect seen 8 days after application of DMS to the ear was indicated as mummification (BASF, 1968).

Despite the fact that the above-mentioned studies were not performed according to current guidelines, they allow DMS to be considered as corrosive.

Eyes

In a limited report DMS was found to be irritating to rabbit's eyes. The dose applied was 0.05 ml, which is considered to be too low according to EC-guidelines. After 1 hour eyes were totally swollen. After 24 hours very strong oedema, strong redness, and corneal opacity were reported. Even after 8 days strong redness, corneal opacity, and strong chemosis with suppuration and staphyloma remained (BASF 1968). Despite the limited report this study indicates that DMS should be considered as an eye irritant with risk for serious damage to the eyes. Guillot (1982) further investigated the irritating potencies of DMS. Six rabbits were observed after 1 hour, 1, 2, 3, 4, and 7 days. DMS (0.1 ml) was applied with and without rinsing the eyes after treatment. The result presented as an acute ocular irritation score (the most severe of the mean score per treatment group) justifies the classification extremely irritating. The effects observed are in agreement with the conclusion of the above-mentioned study.

Respiratory tract

DMS (3.7 or 6.3 mg/m^3) is considered irritating to the respiratory tract in rats based on the limited reported repeated-dose study of Frame (1993) (see section 4.1.2.6).

Human data

In case reports irritating properties of DMS are reported (see 4.1.2.3). No other data are available.

Conclusion

Although none of the tests is performed according to the OECD guidelines, the data are considered acceptable with regard to the basic requirements as specified in Annex VII of Directive 67/548/EC. For classification according to Annex I of Directive 67/548/EC, see Chapter 1.

4.1.2.5 Sensitisation

Animal data

Sensitising activity of DMS was tested in a murine local lymph node assay. Topical dosing of DMS (0.25, 0.5, and 1.0% in acetone/olive oil 80/20 v/v, number of animals not indicated) increased thymidine isotope incorporation in the lymph nodes more than 3-fold compared with vehicle-treated controls. A threefold increase was considered to be determinant of sensitising capacity (Ashby et al., 1995). It is noted that the positive response with DMS may be due to the corrosive properties. The Ear-Flank Test, however, showed an irregular reaction in a group of six guinea pigs treated with 10% DMS in olive oil. Interpretation of this result by the author was that DMS is a compound that does not cause sensitisation (Stevens, 1967). However this test is considered not suitable for evaluation, because the time between induction and challenge is considered to be too short.

Human data

No data on humans are available.

Conclusion

The murine local lymph node assay can be used as a first stage in the assessment of skin sensitisation potential. A positive result indicates the test compound is a potential sensitiser and ‘it may not be necessary to conduct a further guinea pig test’ (OECD 406). The guinea pig test by Stevens (1967), a statement only, is not a standard test and provides only very limited information on the effects of DMS. Therefore this test is not suitable for evaluation.

The data submitted are considered acceptable with regard to the basic requirements as specified in the Annex VIIA of Directive 67/548/EC under the restriction that the positive result in the LNA test is accepted. Therefore, it is concluded that DMS is a potential sensitiser (R43). For classification according to Annex I of Directive 67/548/EC, see Chapter 1.

Note that if the conclusion is not followed, additional testing may be needed.

4.1.2.6 Repeated dose toxicity

Animal data

Oral and dermal

No oral or dermal repeated dose studies with DMS were reported.

Inhalation

In a two-week inhalation study in rats (Frame 1993) DMS was found to induce nasal epithelial cell proliferation at all concentrations tested (0.5, 3.7 and 6.3 mg/m^3 6hr/day 5 d/wk). The 2.0-3.7 fold increase in 2-bromo-5'-deoxyuridine (BrdU) incorporation in nasal epithelium is larger than could be expected from DNA repair only. In respiratory epithelium BrdU incorporation was statistically increased in the highest exposure group only. At the two highest exposure concentrations lesions of the nasal and respiratory epithelium were found, including erosion, ulceration, and atrophy, which increased in severity with exposure concentration and decreased in severity from anterior to posterior regions. Hypertrophy, hyperplasia, and squamous metaplasia were observed in the respiratory epithelium only. The study, however, is insufficiently reported to allow any conclusion on the impact of the observed cell proliferation on the possible carcinogenic action of DMS (section 4.1.2.8).

In a carcinogenicity study, rats, mice, and hamsters were exposed to 2.6 mg/m^3 DMS (6 hr/d, 2d/wk)[7], 10.5 mg/m^3 once every two weeks or a sublethal dose for about 15 months (Schlögel, 1972).

This study is reviewed in section 4.1.2.8. It is considered not suitable for evaluation as repeated dose study according to the guidelines, because no haematology, no clinical biochemistry and very limited histopathological examinations were performed.

Inflammation of the nasal cavity was seen in rats that were exposed to DMS (15.7 and 25.2 mg/m^3, 1 hr/d, 5 d/wk for 130 days) in a study of Druckrey (1970) (see section 4.1.2.8).

It is reported that repeated inhalative exposure of rats and guinea-pigs for 4 months to 2.64±0.43 mg/m^3 induced changes in nervous system function, liver (fatty degeneration of single hepatocytes), kidney (degeneration of single renal tubuli), respiratory organs (bronchitis), and peripheral blood parameters. All changes except of bronchitis were reversible after a recovery period. A 4 month-exposure to 0.29±0.02 mg/m^3 induced only marginal changes. According to the authors these changes were without toxicological relevance (increased body weight, decreased hippuric acid elimination). No morphological changes could be found. In both concentration groups no effects on reproductive organs, spermatogenesis and sperm morphology were detected (Molodkina et al., 1986).

This study is considered not suitable for evaluation as repeated dose study because of the very limited reporting of study design and results. There are e.g. no data on number of animals per group, exposure duration per day, and a list of parameters studied is lacking. Furthermore the results were not substantiated with quantitative data. The conclusion of the authors that 0.29 mg/m^3 is the NOAEL for repeated-dose toxicity of DMS in their studies is not suppported. In another part of the repeated-dose inhalation studies with rats (exposure 4 months) and mice (exposure 2.5 months), reported in the same publication, and performed to assess the genotoxic activity of DMS,

[7] In the first exposure month animals of the 2.6 mg/m^3 group were exposed to 10.5 mg/m^3 (5 d/wk, 6 hrs/d), during the second month they were exposed to 5.3 mg/m^3 (3 d/wk, 6 hrs/d), and starting from the third month to 2.6 mg/m^3 (2 d/wk, 6 hrs/d).

it is found that concentrations of 0.24 mg/m^3 and higher induce an increase in the percentage of bone marrow cells with chromosome aberrations. This study is summarised in section 4.1.2.7.

Human data

No data are available.

Conclusion

The available data are considered insufficient to derive a NOAEL for repeated exposure. The study of Frame provides insufficient information on the character of the observed effects. The study of Schlögel is considered not suitable for evaluation as repeated dose study according to the guidelines, because no haematology, no clinical biochemistry and very limited histopathological examinations were performed. The data submitted do not fulfil the basic requirements as specified in Annex VIIA of Directive 67/548/EC.

4.1.2.7 Mutagenicity

Tables 4.6, **4.7**, and **4.8** summarises the results of mutagenicity tests performed with DMS. Only studies that are considered suitable for evaluation are included.

Table 4.6 Tests with DMS in bacterial systems and yeasts (see also chapter 4.1.2.2)

Strain	Protocol	Test concentration	Toxic concentration	Result	Comments	References
Reverse Mutation tests in *S. typhimurium*						
TA98, TA100, TA1535 TA1537, TA1538	preincubation for 60 min	100, 200, 300 mM	50% survival at 100 mM	+	Positive in all strains	Skopek et al., 1978
TA 1535, TA 1537, TA1538	spot test	0.1, 1, 10 mmol/plate	no data	+	positive in all strains at the highest dose only	Braun et al., 1977
TS1121, TS1157	preincubation 30 min at 37°	0, 0.5, 1, 2, 4 mM/ 0.5 ml	survival at 1 mM 68%, at 2 mM < 50%	+	dose dependent induction of *trp*+ and *his*+ revertants	Hoffman et al., 1988
Forward mutation assay in *S. typhimurium*						
TM35, TM677	preincubation for 60 min	100, 200, 300 mM	50% survival at 100 mM	+	8-Azaguanine resistant fraction is measured	Skopek et al., 1978
E. coli PQ37	SOS test (Umu), incubation 2 h (37°C)	not given		-		Mersch-Sundermann et al., 1994 Quillardet et al.,1985 (method)
S. typhimurium TA1535/pSK1002	SOS test (Umu) incubation 2 h (37°C)	39 mg/ml		+	lowest concentration which induces umu-gene expression 2-fold over background level.	Nakamura et al., 1987

Table 4.6 continued overleaf

Table 4.6 continued

Strain	Protocol	Test concentration	Toxic concentration	Result	Comments	References
Host-mediated assay with *S. typhimurium* (indicator test)						
TA1950	bacteria i.p. NMRI mice (m), incubation 3 hours	2500 and 5000 mmol/kg bw p.o.	animal survival: 66.5% at 2500 mmol/kg, 30% at 5000 mmol/kg	+	Increase in his+ revertants is 2.35 at 2500 mmol/kg bw. No dose-response analysis has been possible due to the high animal toxicity.	Braun et al., 1977
Fungal assays (reverse mutation)						
S.cerevisiae (different strains)	incubation 10 min (30°C)	0.22 ml of 0.1% DMS	50-100% survival	+/-	Base-pair substitutions are found in several strains	Prakash et al. 1973
S. pombe (haploid ascospores)	incubation 1 h (25°C)	0.14-1.18 mM (8 doses)	no data	+	dose dependent increase in number of revertants	Heslot, 1961
Neurospora crassa	incubation 30 min	0.005M	44% survival	+	64 backmutations per 10^6 macroconidia of an initially adenine requiring strain	Westergaard, 1957
Aspergillus nidulans	backmutation test incubation (20 or 30 min)	0.005M	no data	+	reversion of methionine dependent strain	Moura Duarte, 1971

Table 4.7 Tests with DMS in mammalian cells (see also chapter 4.1.2.2)

Cell type	Protocol	Test concentration	Toxic concentration	Result	Comments	References
Chinese Hamster V 79-cells	chromosomal aberration test, incubation 40 min	0.005-0.08 mM	survival 50 % at 0.06 mM (day 7)	+	dose dependent increase in structural chromosome aberrations measured after 7 days	Connell et al., 1982
CHO-cells	HGPRT assay, incubation 16 hours	several doses between 0-80 mM	survival 9% at 80 mmol (day 7)	+	dose dependent increase in number of mutants/ 10^6 cells measured after 7 days	Couch et al., 1978
V 79-cells	HGPRT assay, incubation hours	8, 15 mg/ml	survival 82% (8 mg/ml) 58% (15 mg/ml)	+	mutation frequency 10 and 34/ 10^5 survivors respectively	Newbold et al., 1987

Table 4.7 continued overleaf

Table 4.7 continued

Cell type	Protocol	Test concentration	Toxic concentration	Result	Comments	References
Indicator tests						
V 79 cells	SCE, incubation 40 min	8 concentrations : 0.005- 0.08 mM	50 % survival at 0.06 mM	+	dose dependent increase in number of SCE's at 36 (doses £ 0.05) and 48 hours.	Connell et al., 1982
Human fibroblasts (GM637, XP12RO	SCE, incubation 48 hours	10^{-6}, 10^{-5}, $5 \cdot 10^{-5}$, 10^{-4} M	no data	+	similar dose dependent increase in both normal and xeroderma pigmentosum cells	Wolff et al., 1977
Human fibroblasts (XP12RO)	UDS, incubation 45 min	200, 400 mg/ml	n.d.	+	Induction of DNA-repair	Cleaver et al., 1977
Primary Rat Hepatocytes	UDS, auto-radiographic assay incubation 5 hours	7 exposure concentrations 0.5-1000 nmol/ml	n.d.	+	Positive compared to control (DMSO) at 100-1000 nmol/ml. No further details given	Probst et al., 1981
Hamster dermal fibroblasts 4DH2	DNA-methylation, incubation for 4 hours	10 mg/ml	survival at 10 mg/ml 82%	+	Main methylation products: N^7 -MeGua 80 mmol/mol DNA-P N^3-MeAd 9.8 mmol/mol DNA-P O^6-MeGua not detectable	Shiner et al. (1988)
V-79 cells	DNA-methylation, incubation 3 hours	8, 15 mg/ml	survival 82 and 58 %	+	Main methylation products as perc of total methylation (8, 15 mg/ml): N^7 -MeGua 48.1%, 92.4% N^3-MeAd 8.8 %, 12.0% O^6-MeGua not detectable, 0.5%	Newbold et al., 1980
alf thymus DNA	DNA-methylation, incubation 1 hour	6 , 60 mCi/ml	no data	+	Main methylation products as % of total methylation (6,60 mCi/ml): N^7 -MeGua 70.9%,74.5% N^3-MeAd 14.6% ,15.2% O^6-MeGua 0.3%,0.4%	Newbold et al., 1980
rat hepatocytes (male F344)	determina-tion of DNA SS- and DNA DS-breaks by alkaline elution, incubation 3 hours	0.03, 0.30, 3.00 mM	at 0.30 mM 8% survival	+	dose-related increase in single strand breaks at 0.03 and higher doses; double strand breaks at toxic doses only	Bradley et al., 1987
V 79-cells	DNA-methylation incubation 1 hour with [^{3}H]DMS	0.8 mM	survival 73%	+	Main methylation products are N^7- methylguanine and N^3-methyl adenine	Fox et al., 1980
CHO-cells	incubation for 0 ,0.5, 2, 4, 8 and 24 hour at °C	150 mM	no data	+	Damage formation and repair in the DHFR gene was examined	Wasserman et al., 1990

n.d. = not determined

Table 4.8 Tests in vivo
(see also chapter 4.1.2.2)

Test description	Species, treatment, doses	Result	Comments	References
Tests in *Drosophila melanogaster*				
SLRL test	adult male feeding (Muller-5), $3.8 \cdot 10^{-4}$ M in ethanol/water, control vehicle	+	2.11% sex linked recessive lethal mutations in F1, control 0.25%	Alderson, 1964
SLRL test	adult male feeding (1.25, 2.5, 5.0, 10.0 mM) and injection (2.5, 5.0, 10.0 mM)	+	statistically sinificant increase, after feeding less clear	Vogel et al.1979(A)
Total and partial sex- chromosome loss	adult male feeding (2.5, 5.0, 10.0 mM) and injection (2.5, 5.0 mM)	+	statistically significant increase, after feeding not	Vogel et al. 1979(B)
Somatic recombination, Eye-mosaic assay	larval feeding, 1ml DMS of 10 mM in water	+	increased clone size and significantly higher frequency of spots	Vogel et al., 1993
tests in mammals				
Dominant lethal assay	Male Swiss mice CD-1, 5 per group, 23 mg/kg (=LD_5) i.p., with a mating schedule of 3 virgin females for 8 weeks. Females are replaced every 7 days	-	Limited reported study: single dose tested in group of 5 male animals only.	Epstein et al., 1968
Mouse spot test	25 and 50 mg/kg bw i.p. at day 10 of gestation; cross C57B1 · NMRI or T-stock · DBA	-	OECD 484 no significant difference from saline treated controls	Braun et al. 1984
Indicator tests				
Alkaline elution of brain cell DNA	male albino SD-rats, single dose 0.25 mmol/kg i.v. killed 1 hour after treatment	+	statistically significant increase of DNA breaks ($p<0.01$)	Robbiano et al. 1987
DNA/RNA-binding	Wistar albino male rats were given a single dose of 80 mg [^{14}C]-DMS/kg bw in tail vein and killed 4 hours later	+	7-methylated guanine was found in the DNA and RNA of liver, kidney and lung, and in brain DNA	Swann et al., 1968

DMS is a directly acting mutagen, which methylates DNA especially at the N^7-guanine and the N^3-adenine sites (Shiner 1988, Newbold 1980, see chapter 4.1.2.2, **Table 4.4**.).

*Bacterial and fungal systems (see **Table 4.6**)*

DMS induced reverse mutations in different strains of *S. typhimurium* and in various fungi, and was found positive in a forward mutation assay. Primary DNA damage was reported in assays in *E. coli, P. mirabilis* and *S. typhimurium*. A host-mediated assay with Salmonella was positive.

*Mammalian cells in vitro (see **Table 4.7**)*

DMS induced an increase in cells with chromosomal aberrations in V79-cells. An induction of HPRT gene mutations was found in CHO- and in V79-cells. Moreover, DMS induced an increase in SCE's and UDS in mammalian cells in vitro.

Studies *in vivo* (see **Table 4.8**)

Drosophila

Assays in *Drosophila melanogaster* were positive, i.e., in tests for somatic gene-mutations and recombination, for sex-linked recessive lethals, and in tests for sex chromosome loss.

Mammals

DMS administrated to male mice (23 mg/kg bw i.p.), did not induce dominant lethal mutations as appeared from pregnancy rate, number of total implants, and early and late deaths. However, only one dose-group of 5 animals was tested (Epstein, 1968). No indication was given on toxicity, therefore it is not possible to establish whether the dose was sufficiently high. The toxicological significance of this study cannot be assessed because of the limited study design.

In the mouse spot test (performed according to OECD 484), DMS was administered to pregnant mice (25 or 50 mg/kg bw i.p.). The number of somatic coat colour patches was not increased compared to controls (Braun, 1984).

A brief paper reported DMS positive in a cytogenetic assay in rat bone marrow cells, however, the results are not suitable for evaluation due to the poor reporting (Sharma, 1980 not in **Table 4.8**).

The number of DNA breaks increased significantly after alkaline elution of brain DNA of rats treated with 0.25 mmol/kg i.v. DMS (Robbiano, 1987). The methylating capacity of DMS is demonstrated in several tissues *in vivo* in Wistar rats (Swann, 1968).

In a publication of Molodkina et al. it is stated that repeated inhalative exposure to 20.26±1.34, 2.64±0.43, and 0.29±0.02 mg/m^3 for 4 months did not induce dominant lethal mutations in germ cells of rats. Inhalative exposure to DMS at concentrations of 0, 0.29±0.02 and 2.69±0.43 mg/m^3 in rats, and at concentrations of 0, 0.24±0.2, 4.32±0.75, and 22.1±2.35 mg/m^3 in mice (8 animals per group and species) induced a dose-dependent increase in chromosomal aberrations in bone-marrow cells. (Molodkina et al., 1986). The study is considered not suitable for evaluation of the genotoxicity of DMS in mammals *in vivo*, because of the very limited reporting of study design and results.

Conclusion

The data submitted are in accordance with the basic requirements as specified in Annex VIIA of Directive 67/548/EC. Several tests indicate that DMS is an alkylating agent *in vivo* and *in vitro* (see chapter 4.1.2.2). DMS is a potent direct acting genotoxicant in bacteria and mammalian cells *in vitro*. It is positive in tests for primary DNA damage, gene mutations, and chromosome aberrations *in vitro*. DMS is mutagenic in Drosophila. From the results of the tests with mammals it is concluded that DMS did not induce an increase in dominant lethals in mouse and there were no indications for induction of gene mutations *in vivo*.

According to EC criteria DMS is considered a category 3 mutagen and classified as R40. For classification according to Annex I of Directive 67/548/EC, see Chapter 1.

4.1.2.8 Carcinogenicity

Animal data

Oral

No data on carcinogenic properties of DMS after oral administration are reported.

Dermal

Dermal application of 0.1 mg DMS in 0.1 ml acetone 3 times per week for a period of 385 or 475 days in ICR/Ha Swiss mice (n=20) did not lead to of papillomas or carcinomas. Even when DMS was combined with the tumour promotor phorbol myristate acetate (2.5 μg/0.1 ml acetone (n=20)) the number of papillomas and carcinomas did not exceed that in controls. The number of animals in these studies was limited and only one dose was tested. No findings on non-neoplastic changes were reported (Van Duuren, 1974). The study cannot be evaluated with regard to carcinogenic potential of DMS after dermal exposure.

Inhalation

BD-rats (sex unspecified) were exposed to 55 mg/m^3 (n=27) and 17 mg/m^3 (n=20) DMS in an inhalation chamber for 130 days (1 hr/d, 5 d/wk). It has to be noted that the concentrations mentioned were calculated, maximum concentrations and that the decrease of this maximal concentration with time was not taken into account. Several deaths due to inflammation of the nasal cavity or pneumonia were reported. Five of fifteen surviving rats in the high dose group developed malignant tumours: three squamous cell carcinomas of the nasal cavity, one tumour in the cerebellum, and one lymphosarcoma of the thorax with multiple lung metastases. In the low dose group of 12 surviving animals three were found with a squamous cell carcinoma of the nasal cavity, a brain neurinoma, or an esthesioneuroepithelioma of the olfactory nerve, respectively (Druckrey, 1970). This study points to carcinogenic properties of DMS, although only two dose groups were used, the number of animals was small and pathological examinations were minimal.

The very limited reporting of study design and results makes the evaluation of the study impossible.

In a 6 month-inhalation study groups of 90 male and female mice (CBAxC57BC/GI) were exposed to DMS at concentrations of 0.38±0.08, 1.62±0.17, or 20.26±1.34 mg/m^3 (2 hr per day, 5 days per week). A statistically significant increase in tumours was observed in the high and intermediate dose groups (mainly lung adenoma) (Molodkina et al., 1986). The very limited reporting of the study design and results makes the evaluation of the study impossible.

Male and female rats (Wistar), mice (NMRI), and hamsters (Syrian Golden) were exposed to 2.6 mg/m^3 DMS (6 hr/d, 2d/wk), to 10.5 mg/m^3 (6hr/d, 1d/2wk), or to a sublethal concentration (4 times per year for 1 hour, 178 mg/m^3 (rats), 252 mg/m^3 (mice), 105 mg/m^3 (hamsters)) for about 15 months (Schlögel, 1972). Animals were observed for at least 30 months after start of exposure. Examinations included clinical signs, mortality, body weights, lung weights, macroscopy, and histopathology. Histopathological examination was restricted to lungs and trachea. When gross examination revealed a tumour in other tissues/organs, this tissue/organ was included for histopathological examination.

The results of the study are presented in **Tables 4.9** and **4.10**.

After exposure, the behaviour of exposed animals was affected: animals were apathic, eyes were half-open or closed and breathing problems were apparent. These effects clearly showed a concentration dependency in severity, total duration and time of onset. Body weight gain in DMS-exposed hamsters, rats and mice was distinctly lower than in control animals. In general, survival in groups exposed to DMS was lower than in controls, but the mean survival time varied considerably between the various groups (see **Table 4.9**). A remarkable finding was the very low survival time in male and female rats of the 2.6 mg/m^3 group which was distinctly lower than the survival time in rats of the control or the 10.5 mg/m^3 group. The same phenomenon was seen in mice although less pronounced. The lower survival time in the 2.6 mg/m^3 group is probably due to the initial high exposure regimen applied to this exposure group (see note b, **Table 4.10**).

An increase in the incidence of inflammation of the lungs was reported in DMS-exposed animals in all species. Bronchiopneumonia occurred to about the same degree in control and DMS exposed animals.

The incidence of benign tumours of subcutis and lungs is given in **Table 4.9** and **Table 4.10** gives the incidence of animals with malignant respiratory tract tumours per number of animals examined with histological classification of the tumours. DMS exposure resulted in an increased incidence of malignant tumours in the respiratory tract (nose and lungs). Rats were most sensitive to the tumour inducing activity of DMS, while hamsters were the least sensitive. In all three animal species females appeared more sensitive than males. In female rats of the 10.5 mg/m^3 group the incidence of lung adenomas was slightly higher than in control females. There were no indications that DMS exposure induced an increase in subcutaneous fibromas.

The highest incidence of animals with treatment-related malignant respiratory tract tumours was found in rats exposed to 10.5 mg/m^3 group. The incidence in the 2.6 mg/m^3 group was distinctly lower although the total dose in the low dose group was comparable or higher than that in the 10.5 mg/m^3 group. This lower incidence might be related to the lower mean survival time in the 2.6 mg/m^3 group, which in its turn may be a consequence of the initially high exposure scheme applied to this group.

Exposure to the sublethal DMS concentrations induced treatment-related tumours in rats only. In this context it must be realised that the exposure scheme applied for the sublethal concentrations leads to a lower total dose than that used with the 2.6 - and 10.5 mg/m^3-groups. Moreover most animals of the sublethal groups have been exposed four times only.

The study design does not fulfil to the requirements of OECD 451. However, the results of this study can be used to give a indication on the carcinogenic potential of DMS.

Other routes

BD-rats (no data on sex) were injected subcutaneously once a week (8 mg/kg, n=12, 394 days; 16 mg/kg, n=8, duration not indicated). In the low dose group one animal died preliminary of a liver carcinoma with metastases in lung and spleen; in the high dose group 2 rats died of pneumonia. A majority of surviving animals developed local (at the site of injection) sarcomas (all survivors at 16 mg/kg and 7 of 11 surviving animals at 8 mg/kg). After necropsy three of the surviving rats in the low dose group showed also metastases in the lung, lymph nodes, or kidneys, respectively. Two of the animals with local sarcomas in the high dose group were reported to have metastases in the lung (Druckrey, 1966).

A single dose of 50 mg/kg s.c. caused death in 7 of 15 BD-rats between post-dosing days 314 and 740. The animals had large local sarcomas and three of them had multiple lung metastases (Druckrey, 1970).

Weekly dosing of 2 and 4 mg/kg DMS i.v. in BD-rats (12 per dosing group) for a period of 800 days did not induce any tumours (Druckrey, 1970). However, the report was very limited and several shortcomings in the study design were found.

Eight pregnant rats were dosed with DMS (single 20 mg/kg bw i.v.) at day 15 of gestation. The offspring (n=59) showed no apparent abnormalities and was raised for one year. During this period 7 animals developed malignant tumours in the brain, thyroid gland, liver and uterus. No other toxicological endpoints except carcinogenicity were evaluated (Druckrey, 1970). No information on controls was provided.

Table 4.9 Results: Survival, mean lung weight, and number of animals with benign tumours per treatment group (Schlögel 1972)

Species	Number	Concentration (mg/m^3)	Mean survival (days)	Mean lung weight (g/kg bw)	Benign tumours	
					Tumours of the subcutis[a]	Lungadenomas
Rat	30 20	0	839617	7.34 7.47	1/25 (fibroma) 3/11 (2 fibromas, 1 mammary fibro-adenoma)	2/25 0/11
Rat	35 30	2.6[b]	266301	7.48 11.68	0/21 1/16 (fibroma)	0/21 0/16
Rat	15 15	10.5	590 637	10.54 12.14	0/14 1/13 (fibroma)	1/14 3/13
rat	15 15	178	605279	10.76 10.51	1/14 (fibroma) 0/15	1/14 0/15
Mouse	25 25	0	303 539	13.21 14.30	0/8 7/11 (fibroma)	1/8 3/11
Mouse	25 25	2.6[b]	287370	18.44 18.73	0/14 0/18	1/14 3/18
Mouse	15 15	10.5	308 392	12.73 15.78	0/11 1/14 (fibroma)	4/11 2/1[c]
Mouse	15 15	252	248325	14.32 14.56	0/6 1/11 (axillary fibroadenoma)	0/6 3/11
Hamster	16 16	0	246 302	10.32 10.17	0/5 0/10	0/5 0/10
Hamster	20 19	2.6[b]	261 244	10.96 11.17	0/16 0/12	0/16 0/12
Hamster	15 15	10.5	147 171	13.41 11.14	0/11 0/11	0/11 0/11
Hamster	31 31	105	253 144	9.73 9.92	0/25 0/26	1/25 0/26

[a]Tumours of the subcutis, when no further specification is provided

[b]During the first month animals were exposed 5 days per week (6 hours per day) to 10.5 mg/m^3. The following month animals were exposed 3 times per week to 5.3 mg/m^3. During the rest of the study animals were exposed 2 times per week to 2.6 mg/m^3

[c]A female mouse with both adenomas and carcinomas of the lung is not included here but only in Table 4.10, giving the number of tumour bearing animals with a malignant tumour of the respiratory tract

Table 4.10 Incidence of malignant tumours of the respiratory tract per number of animals examined with histological classification of the tumours
(Schlögel 1972)

Conc species	0 mg/m³	2.6 mg/m³ [a]	10.5 mg/m³	Sublethal dose	Other tumours
Rat	0/36	m : 0/21 f : 3/16 1 nasal carcinoma, 1 nasal carcinoma/ adenocarcinoma, 1 lung carcinoma	m : 3/14 f : 3/13 5 nasal carcinomas, 1 nasal carcinoma + lung carcinoma	m : 1/14 f : 1/15 1 nasal carcinoma + lung carcinoma, 1 lungcarcinoma + anaplastic carcinoma of the left eye	1 stomach adenocarcinoma in controls
Mouse	0/19	m : 0/14 f : 1/18 1 lung adenocarcinoma	m : 0/11 f : 3/14 3 lung carcinomas	m : 0/6 f : 0/11	1 a urinary bladder carcinoma in controls, 1 thorax sarcoma at 2.6 mg/m³
Hamster	0/15	m : 0/16 f : 0/12	m : 0/11 f : 1/11 1 lung carcinoma	m : 0/25 f : 0/26	none

[a]During the first month animals were exposed 5 days per week (6 hours per day) to 10.5 mg/m³. The following month animals were exposed 3 times per week to 5.3 mg/m³. During the rest of the study animals were exposed 2 times per week to 2.6 mg/m³

Human data

An epidemiological study of Pell is quoted in many reports (EHC 1985, HSE 1996). The data obtained in this study show no excess incidence of cancers of the respiratory system among the DMS workers (exposure data not known). In groups of workers (n=386 or 43,000) the number of cases with lung cancer was 4 and 257 respectively. No information on exposure concentrations is available (Thiess, 1968, 1969). All human data are of limited quality; no information on other clinical signs or controls is provided.

Conclusion

A number of carcinogenicity studies with DMS is available. However, the quality of these studies is limited; the number of animals is limited, dose-levels are high, and duration of exposure is in almost all cases short. Moreover, the studies suffer from limited reporting (e.g. no or limited information on histopathological findings). It is noted that OECD guidelines were not compulsory at the time the carcinogenicity studies with DMS were conducted. However, the inhalation study from Schlögel is considered only suitable for giving indication on the carcinogenic potential of DMS.

Information obtained from human studies is minimal and cannot be used for risk assessment. IARC concluded that DMS produces mainly local tumours in rats following inhalation or subcutaneous injection and that there is sufficient evidence to classify DMS as an animal carcinogen (2A). This conclusion is in agreement with the conclusion of the rapporteur. IARC's statement on tumours of the nervous system after prenatal exposure of laboratory animals could not be verified by the rapporteur, because the data (Druckrey et al., 1970) submitted to the rapporteur were too scarce to allow a proper evaluation. Given the results of the mutagenicity studies, it is assumed that DMS acts via a genotoxic mechanism. According to EC criteria DMS is classified as a category 2 carcinogen and labelled with R45. For classification according to Annex I of Directive 67/548/EC, see Chapter 1.

4.1.2.9 Toxicity for reproduction

Fertility

There are neither data on fertility nor on effects on male and female reproductive organs after repeated exposure to DMS.

Developmental toxicity

In a teratogenicity study, pregnant rats (25 per dose group) were exposed nose only to 0, 0.5, 3.7, or 7.9 mg/m^3 DMS, 6 hours per day during day 6-15 of gestation (Alvarez et al.,1997). In pregnant rats exposed to 3.7 and 7.9 mg/m^3 a decrease in food consumption and weight gain was reported. The NOAEL for maternal toxicity was established at 0.5 mg/m^3. No significant differences in malformations and variations were reported between the fetuses in the control and the experimental groups. At the highest concentration tested, a very slight decrease of fetal weights is reported. Therefore it is concluded that a NOAEL of 7.9 mg/m^3 for developmental effects can be derived.

In a publication of Molodkina et al., it is stated that repeated inhalative exposure to 2.64±0.43 and 0.29±0.02 mg/m^3 of male and female rats for 4 months did not induce toxic effects on reproductive organs, spermatogenesis and sperm morphology. In addition, following repeated exposure of pregnant Wistar rats, SHK- and CBAxC57BC/GI mice to DMS at concentrations of 0.46±0.05, 12.6±2.2, 20.8±4.7 mg/m^3 (CBA mice) over the whole gestation period (sacrifice of rats on day 21, sacrifice of mice on day 18) no embryotoxic effects were detected in rats and SHK mice at 0.29±0.02 and 2.69±0.43 mg/m^3. In CBAxC57BC/GI mice DMS produced an increase in preimplantation and postimplantation loss (20.5 to 29.1%, control: 11.8%, no further details) (Molodkina et al., 1986). The very limited reporting of study design and results makes the evaluation of the study impossible and it has not be used for risk characterisation.

Conclusion

It is concluded that DMS only induced slight developmental toxicity after inhalation at maternal toxic concentrations.

In order to fulfil the basic requirements of Annex VII of Directive 67/548/EC, reproductive organs should have been investigated in a 90-day repeated dose toxicity test or otherwise a reproduction study should have been performed.

4.1.3 Risk characterisation

4.1.3.1 General aspects

DMS is a methylating agent, which is found to react with nucleic acids. No data on interference with other nucleophilic macromolecules, e.g. proteins, were provided.

DMS can be absorbed via respiratory and oral routes. Data on dermal absorption are limited and insufficient to draw conclusions. For oral absorption this is concluded from toxicodynamic data. Rapid respiratory absorption is observed in rats exposed to dose levels up to 50.3 mg/m^3. At higher dose levels uptake was decreased, probably due to a decreased minute volume. No information is provided on the metabolism of DMS in animals following oral administration. The information on metabolism after inhalatory or dermal exposure is limited. DMS may be hydrolysed to methanol, sulphuric acid, and methyl sulphate, and, may be metabolised to a lesser extent to formaldehyde, and formate.

The toxicokinetic studies do not allow derivation of quantitative figures on absorption that can be used in risk characterisation.

The available acute toxicity data indicates that, according to the EC-criteria, DMS is toxic after oral administration, and very toxic after exposure by inhalation.

DMS is corrosive to the skin and should be considered to cause risk of serious damage to eyes in laboratory animals. Irritation of the respiratory tract was observed in a poorly reported inhalation experiment with rats.

Local effects of DMS after dermal and respiratory exposure were also seen in humans.

Based on the results of the local lymph node assay, it is concluded that DMS has sensitising properties.

The repeated-dose inhalation studies do not permit the establishment of a NOAEL. No oral and dermal repeated dose toxicity studies are available. The data submitted do not fulfil the basic requirements as specified in Annex VIIA of Directive 67/548/EC.

DMS is a potent direct-acting genotoxicant in bacteria and mammalian cells *in vitro*, it is positive in tests for primary DNA damage, gene mutations, and chromosome aberrations *in vitro*. DMS appears genotoxic in various *in vivo* tests in Drosophila, i.e., in tests for somatic mutations and recombination, for sex-linked recessive lethals, and for sex chromosome loss. From the results of the tests with mammals it is concluded that DMS may have clastogenic activity in somatic cells *in vivo*, but there are no indications for the induction of gene mutations *in vivo*. No tests are available to assess the genotoxicity of DMS in germ cells in mammals.

Evidence on human carcinogenicity is inadequate. The conclusion of IARC is that DMS produces mainly local tumours in rats following inhalation or subcutaneous injection and that there is sufficient evidence to classify DMS as an animal carcinogen (2A). This conclusion is in agreement with the conclusion of the rapporteur. IARC's statement on tumours of the nervous system after prenatal exposure of laboratory animals could not be verified by the rapporteur. Given the results of the mutagenicity studies, it is assumed that the carcinogenicity of DMS is based on a genotoxic mode of action.

The study design of the study of Schlögel does not fulfil to the requirements of OECD 451. However, the results of this study can be used to give a indication of the carcinogenic potency of DMS.

The toxicological database of DMS has gaps with respect to systemic toxicity after repeated exposure, and with respect to effects on reproduction. There are no data available on toxicological parameters such as haematology and clinical chemistry. Furthermore, no data are available on fertility effects of DMS.

It is concluded that DMS only induced slight developmental toxicity after inhalation at maternal toxic concentrations. In order to fulfil the basic requirements of Annex VII of Directive 67/548/EC, reproductive organs should have been investigated in a 90-day repeated dose toxicity test or a reproduction study should have been performed.

4.1.3.2 Workers

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

Acute toxicity

Given the very toxic properties of DMS in the acute inhalation studies (LC_{50} 168 mg/m^3, 4 hr) and the anticipated occupational exposure levels (short term 5 mg/m^3 in both scenarios, estimated without protective equipment), concern for lethality is indicated for unprotected workers. However, the remaining risk for workers using typical PPE is expected to be rather low in this situation, given the MOS for the unprotected worker and the indicative value that may be assumed for protective effects of the PPE (see paragraph 4.1.1.2) (**conclusion ii**).

An acute dermal toxicity study is not available. However, as DMS is considered to be corrosive, dermal exposure has to be prohibited by risk reduction measures and so the risk after dermal exposure will be negligible (**conclusion ii**).

Irritation and corrosivity

Skin

No quantitative conclusions can be drawn from the available data. Because dermal exposure is limited to accidental events, there is no concern for workers involved in production and formulation (**conclusion ii**).

Eyes

Given the industries in which DMS is produced and used, incidental exposure to the eyes by splashing is not likely to occur, because adequate protection measures will be applied in view of the corrosive properties. Therefore, no further risk reduction measures need to be taken to protect the worker (**conclusion ii**).

There are no data available on effects of exposure of the eyes to DMS vapour.

Respiratory tract

Indications for nasal irritation were obtained from observations in rats exposed to 3.7 mg/m^3 for 14 days (6 hr/d, 5 d/wk). The dose level causing no irritation in rat was only 0.5 mg/m^3. Although this rat study is poorly reported and does not allow quantitative risk characterisation, the margin between exposure concentrations in humans (0.05-0.2 mg/m^3) and the NOAEL and LOAEL for irritation in this rat study is considered to be rather small. The remaining risk for workers using typical PPE properly may still be substantial in this situation, given the MOS for the unprotected worker and the indicative value for protective effect of the PPE. Therefore, **conclusion (iii)** is drawn.

It is noted that respiratory irritation was also observed in humans.

Sensitisation

Skin

From the murine local lymph node assay it is concluded that DMS is sensitising to the skin. However, because dermal exposure to DMS is possible accidentally, it is not likely that skin sensitisation becomes apparent in workers exposed to DMS (**conclusion ii**).

Respiratory tract

There are neither data from human experience nor other indications for respiratory sensitisation. Therefore at present there is no need to request further information (**conclusion ii**).

Repeated-dose toxicity

In principal, additional studies resulting in a NOAEL are needed for quantitative risk characterisation, as no reliable repeated-dose studies were provided and exposure to DMS at the workplace cannot be excluded. However, it is noted that the carcinogenic activity of DMS, i.e., the cancer incidence per mg/m^3 under occupational conditions of exposure, points to very low acceptable exposure levels with regard to the carcinogenic effects (see the paragraph on carcinogenicity as given below). It is expected that compliance to these low exposure levels will prevent effects other than carcinogenic effects to occur.

Mutagenicity

From the results of the mutagenicity studies it is concluded that DMS is genotoxicant and classified as category 3 mutagen. Therefore control measures to limit the risks for the workers are needed, which should be in accordance with European legislation regarding worker protection (**conclusion iii**)

Carcinogenicity

DMS is regarded as a genotoxic carcinogen (Carc. Cat 2: R45). Therefore **conclusion (iii)** is applicable.

Despite the limitations of the study of Schlögel, the results can be used to give an indication of the risk for carcinogenic effects, as was also done by the Dutch Expert Committee for Occupational Standard (Health Council of the Netherlands, 1998)[8].

The highest incidence of animals with treatment-related malignant respiratory tract tumours was found in rats exposed to 10.5 mg/m^3. The incidence in the 2.6 mg/m^3 group was distinctly lower although the total dose in the low dose group was comparable or higher than that in the 10.5 mg/m^3 group. This lower incidence might be related to the lower mean survival time in the 2.6 mg/m^3 group, which in turn may be a consequence of the initially high exposure scheme applied to this group. In view of these findings the results from the 10.5 mg/m^3 group are selected to assess the

[8]The Committee is aware that the HBC-OCRV derived from the study of Schlögel is loaded with a greater degree of uncertainty than usually because of the limitations of the design of the rat study (small group size, poor survival, the data do not allow the assessment of a dose-response relationship), and the clear cytotoxicity of DMS at an exposure level of 10.5 mg/m^3, in particular since even at 0.5 mg/m^3 nasal cytotoxicity has been found. Despite these serious shortcomings the study is used for quantitative risk assessment, since in the opinion of DECOS calculating cancer risk-values for DMS based on the available carcinogenicity study is more appropriate than performing no calculations at all. The Committee emphasises that DMS is a potent carcinogen and regrets the unavailability of a more adequate carcinogenicity study.

carcinogenic activity of DMS, according to the method described in the report of the Health Council of the Netherlands (1995).

The carcinogenic activity for life span exposure per unit air concentration is calculated according to the following formula, assuming a linear dose response relationship.

$$I_{conc} = \frac{I_E - I_C}{C \cdot (X_{po} / L) \cdot (X_{pc}/L) \cdot \text{exposure hours per day}/24 \cdot \text{exposure days per week}/7}$$

I_{conc}	carcinogenic activity attributable to the exposure to the substance per unit concentration (expressed per mg/m^3)
I_E	tumour incidences in exposed animals
I_C	tumour incidences in control animals
C	concentration in experiment (mg/m^3)
X_{po}	exposure period
X_{pe}	experimental period
L	standard lifespan for the animal species in question

From the incidence under lifespan exposure conditions the additional lifetime cancer risk under occupational exposure conditions (the Health-based Calculated Occupational Cancer Risk Value (HBC-OCRV)) can be calculated, assuming that the average man lives 75 years, is exposed 8 hours per day during 5 days per week, 48 weeks per year, and inhales 10 m^3 per 8-hour working day.

$$\text{HBC-OCRV} = I_{conc} \cdot 40\text{y}/75\text{y} \cdot 48 \text{ wks}/52 \text{ wks} \cdot 5 \text{ days}/7 \text{ days} \cdot 10 \text{ m}^3/18 \text{ m}^3$$

*Calculations based on the incidence in rats exposed to 10.5 mg/m^3 (see also **Table 4.10**)*

I_E	6/27
I_C	0/36
X_{po}	15 months, i.e., 456 days
X_{pe}	mean survival time found in the exposure group, i.e. 613 days
L	mean survival time found in the control group, i.e. 728 days

$$pI_{conc} = \frac{6/27 - 0/36}{10.5 \cdot 456/728 \cdot 613/728 \cdot 6/24 \cdot 1/14} = 2.2 \text{ per mg/m}^3$$

$$\text{HBC-OCRV} = 2.2 \cdot 40/75 \cdot 48/52 \cdot 5/7 \cdot 10/18 = 4.4 \cdot 10^{-1} \text{ per mg/m}^3$$

In **Table 4.11** the carcinogenic risk is estimated for the occupational exposure scenarios.

Table 4.11 Risk assessment for DMS for carcinogenic effects after repeated inhalation exposure at the workplace

	Risk characterisation for inhalation exposure		
Scenario/subscenario	Estimated inhalation exposure (mg/m³)	HBC-OCRV[a]	Carcinogenic risk
1: Production of DMS	1	$4.4 \cdot 10^{-1}$	$4.4 \cdot 10^{-3}$
2: Use as intermediate	0.2	$4.4 \cdot 10^{-1}$	$0.8 \cdot 10^{-1}$

[a]Cancer risk per mg/m³ under occupational exposure conditions

The TD25 calculated based on the carcinogenicity study of Druckey (1970) is presented in Annex 2. The presented data lead to **conclusion (iii**), based on the expected cancer risks.

Reproductive toxicity

Fertility

With respect to the effects on fertility, the basis requirements of Annex VII of Directive 67/548/EC are not fulfilled. In principal, reproductive organs should have been investigated in a 90-day inhalation study or otherwise a reproduction study should have been performed. However, it is noted that the carcinogenic activity of DMS, i.e., the cancer incidence per mg/m3 under occupational conditions of exposure, points to very low acceptable exposure levels with regard to the carcinogenic effects (see the paragraph on carcinogenicity as given above), which implies a considerable reduction of the current limit values (TRK-values, see paragraph 4.1.1.2). It is expected that compliance to these low exposure levels will prevent effects other than carcinogenic effects to occur.

Developmental toxicity

An inhalatory developmental toxicity study with DMS in rats is available. Developmental toxicity occurred only at maternally toxic levels. The substance is not teratogenic. The NOAEL for developmental effects is 7.9 mg/m^3 (highest concentration tested) and the NOAEL for maternal toxicity 0.5 mg/m^3. At 3.6 mg/m^3 effects were observed on maternal bodyweight gain and food consumption. The NOAEL for maternal toxicity is used to characterise the risk for the pregnant population. It is noted that this risk characterisation is only valid for the maternal effects studied in this study. The MOS between the inhalation NOAEL and the respiratory exposure levels are shown in **Table 4.12**.

The MOSs can be evaluated by comparison with the minimal MOS. In Annex 3, this approach is given together with the assessment factors used to establish the minimal MOS (**Table A1** of this Annex). If this approach is used, then there is concern when the MOS is lower than the minimal MOS.

Table 4.12 Occupational risk assessment of DMS for the pregnant population

Scenario	Risk characterisation for inhalation exposure		
	Estimated inhalation exposure (mg/m³)	MOS[a]	Conclusion[b]
1. Production	0.05	10	ii
2. Use as intermediate	0.2	2.5	iii

[a]Based on a NOAEL of 0.5 mg/m³

[b]The conclusion is reached by considering the magnitude the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Annex 2, Table A.1

Based on the risk assessment as given in **Table 4.12**, it is concluded that adverse effects on the pregnant population due to repeated inhalation exposure cannot be excluded in scenario 2 (**conclusion iii**). It is noted that this risk characterisation is limited to the effects as were studied in the developmental study available. It might be possible that in some industrial premises worker protection measures are already being applied.

The data available do not allow a definite conclusion on reproductive effects after dermal exposure, because studies on these parameters tested via the dermal route were not available. However, the risk for reproductive effects after occupational dermal exposure is considered to be low, because (1) DMS is very reactive and will bind primarily to the application site, and (2) developmental effects in the inhalation developmental study occurred only at clear-cut maternally toxic concentrations, and (3) the dermal exposure is limited to accidental events **(conclusion ii)**.

Occupational limit values

Based on the strong carcinogenic potential, it should be considered whether the occupational limit values as mentioned in chapter 4.1.1.2 (**Table 4.1**) were low enough for worker protection. Based on the HBC-OCRV as calculated above the cancer risk at 0.05 mg/m^3 (lowest mentioned OEL, Denmark) and 5 mg/m^3 (highest mentioned OEL, USA) amount $2.2 \cdot 10^{-2}$ and 2.2, respectively.

Based on the toxicity data available it cannot be excluded that systemic effects might occur even at the lowest value of 0.1 mg/m^3 cited in **Table 4.1**. This can be illustrated by applying the methods outlined in Annex 3. Following this approach, a theoretical Health-based Occupational Reference Value (HBORV) of 0.1 mg/m^3 is based on a fictive NOAEL of 9 mg/m^3 from a semichronic inhalation study, or a NOAEL of 0.9 mg/m^3 from a chronic inhalation study[9]. Comparison of these fictive NOAELs with the available toxicological data from repeated inhalation studies shows that NOAELs lower than 0.9 or 9 mg/m^3 for systemic toxic effects cannot be excluded. In a two-week inhalation study with rats exposed to concentration levels of 0.5, 3.7 and 6.3 mg/m^3 increased cell proliferation of nasal epithelium cells was seen at al dose levels. In the carcinogenicity study of Schlögel effects were observed at all dose levels ($\geq$2.6 mg/m^3), and in the teratogenicity study the NOAEL for maternal toxicity amounted to 0.5 mg/m^3. Therefore it cannot be excluded that a repeated-dose inhalation study with rats may lead to a NOAEL <0.9 or 9 mg/m^3 and thus a HBORV <0.1 mg/m^3.

However, the risk assessment for carcinogenic effects indicates that the occupational exposure limits should be lowered considerably. The reference concentrations associated with the target risk levels of $4 \cdot 10^{-3}$ and $4 \cdot 10^{-5}$ under occupational conditions of exposure amount to 9 and 0.09 µg/m^3, respectively. Because DMS acts mainly locally at the place of first contact and the

[9]Assessments according to Hakkert et al. (1996); factor for interspecies differences 3, factor for intraspecies differences 3, and default factor for extrapolation from semichronic to chronic exposure duration 10.

calculated reference values are rather low, it seems reasonable to assume that these concentrations are low enough to prevent adverse systemic effects.

4.1.3.3 Consumers

As concluded in chapter 4.1.1.3 consumer exposure to DMS is considered to be negligible. DMS is an animal carcinogen and given the results of the mutagenicity studies, it is concluded that the carcinogenicity of DMS is based on a genotoxic mechanism. Hence, **conclusion (iii**) is drawn. However, since consumer exposure is considered to be negligible, the risk will also be negligible.

4.1.3.4 Indirect exposure via the environment

DMS emissions from production/processing sites are rather low (calculated concentration in air for one site 32 pg/m^3). Much higher DMS emissions may occur from unintentional sources.

DMS is an animal carcinogen and given the results of the mutagenicity studies, it is concluded that the carcinogenicity of DMS is based on a genotoxic mechanism. Hence, **conclusion (iii**) is drawn. However, since DMS emissions from production/processing sites are rather low, the risk will also be rather low.

Taking into account the nature of the substance (being a genotoxic carcinogen) more information on actual release figures and/or concentrations from combustion processes are needed (**conclusion i,** unintentional sources).

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

Given the physico-chemical data, DMS is considered not to form a risk with respect to flammability, explosive properties, and oxidising properties (**conclusion ii**).

5 RESULTS

5.1 ENVIRONMENT

( ) **i**) There is need for further information and/or testing.
(X) **ii**) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied.
( ) **iii**) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account.

5.2 HUMAN HEALTH

Human health (toxicity)

Workers

( ) **i**) There is need for further information and/or testing.
( ) **ii**) There is at present no need for further information and/or testing or for risk. reduction measures beyond those which are being applied.
(X) **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 of:

- concerns for risks for respiratory tract irritation, mutagenicity, and carcinogenicity as a consequence of inhalation exposure arising from production, processing and use of the substance;
- concerns for the pregnant population for additional adverse health effects as a consequence of repeated inhalation exposure arising from the use of the substance as an intermediate.

It is noted that the toxicological database of DMS has gaps with respect to systemic toxicity after repeated exposure, and with respect to effects on reproduction. Furthermore, the carcinogenicity study of Schlögel has serious limitations. However, it is noted that the carcinogenic activity of DMS, i.e., the cancer incidence per mg/m^3 under occupational conditions of exposure, points to very low acceptable exposure levels with regard to the carcinogenic effects, which implies a considerable reduction of the current occupational exposure limits. It is expected that compliance to these low exposure levels will prevent effects other than carcinogenic effects to occur.

Consumers

( ) **i**) There is need for further information and/or testing.
( ) **ii**) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied.
(X) **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 of:

- the risk assessment shows that risks cannot be excluded at any exposure as the substance is

identified as a non-threshold carcinogen. However, the risks covered by this risk assessment are not of a magnitude, that immediate action is deemed necessary. Risk reduction measures already being applied are considered sufficient to impose pressure in reducing and controlling exposure to the substance.

Indirect exposure via the environment (industrial emissions)

( ) **i**) There is need for further information and/or testing.
( ) **ii**) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied.
(X) **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 of:

- the risk assessment shows that risks cannot be excluded at any exposure as the substance is identified as a non-threshold carcinogen. However, the risks covered by this risk assessment are not of a magnitude, that immediate action is deemed necessary. Risk reduction measures already being applied are considered sufficient to impose pressure in reducing and controlling exposure to the substance.

In addition to the conclusions according to Council Reg. 793/93/EEC given above, the RAR came to the conclusion concerning emissions from unintentional sources as follows:

Indirect exposure via the environment (unintentional sources)

(X) **i**) There is need for further information and/or testing
( ) **ii**) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
( ) **iii**) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

Conclusion (**i**) is reached because:

- more information is needed about actual atmospheric concentrations of DMS from unintentional sources. Such data are important to make an up-to-date exposure assessment for this compound, being with a genotoxic carcinogen.

<u>Human health (physico-chemical properties)</u>

Given the physico-chemical data, DMS is considered not to form a risk with respect to flammability, explosive properties, and oxidising properties (**conclusion ii**).

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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*, *b.w.*
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
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
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 [1]
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
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
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)

Annex 1 Estimation of concentrations due to transfer operations - USEPA Transfer model

The USEPA transfer model is a model in which the equilibrium concentrations reached in a room during liquid transfer is calculated. Theses calculations actually consist of two parts. In the first part the generation of vapours by displacement of air from containers during liquid transfer is calculated. The generation rate of the vapour is then used as an input variable in a mass balance ventilation model.

For several input parameters typical and worst case default values have been established from empirical knowledge. If more specific information is lacking, the default values can be used to calculate concentrations. These concentrations are spatially averaged concentrations. To calculate exposure levels from these concentrations the time workers spend in this and other environments and the concentrations in the other environments should be known or estimated. As a worst-case assumption it can be assumed that workers spend a whole shift transferring liquids, since transferral is often the activity with the highest levels of emission.

The formula to calculate the concentrations is given in formula 1.

$$C_m = 1000 \cdot (f \cdot M \cdot V \cdot r \cdot P)/(R \cdot T_l \cdot Q \cdot k) \qquad \text{formula 1.}$$

f	= saturation factor	R	= universal gas constant (= 8.3144 J/mol.K)
M	= molar weight (mg/mol)	T_1	= temperature of the liquid (K)
V	= volume of container (m^3)	Q	= ventilation rate (m^3/h)
r	= fill rate (h^{-1})	k	= mixing factor
P	= vapour pressure of subst.(Pa)	C_m	= calculated concentration level (mg/m^3)

The following input data are standard for each assessment in this Annex:

Input:	data			Transfer operations:	
M	126	Twc	293	a	drum
kwc	0.1	Tnorm	293	c	tank truck
knorm	0.5	p	60		

The results are presented in the table below

Worst Case

	f	M	V	r	P	Tl	Q	k	Cm
a	1.0	126	0.200	30	60	293	850	0.1	219,28
c	1.0	126	19.000	2	60	293	1203000	0.1	0,98

Typical case

	f	M	V	r	P	Tl	Q	k	Cm
a	0.5	126	0.200	20	60	293	5100	0.5	2,44
c	1.0	126	19.000	2	60	293	4812000	0.5	0,05

References

Chemical Engineering Branch. Preparation of Engineering Assessments. Volume I: CEB Engineering Manual. Chemical Engineering Branch, Economics and Technology Division, Office of Toxic Substances. U.S. Environmental Protection Agency (Washington, DC), 1991.

Annex 2 Calculation of T25

The calculation of the TD25, based on the results from the study of Druckey (1970) is presented by Sanner (Oslo, 30.03.1998).

Inhalation exposure (Druckrey, 1970) (section 4.1.2.8)

BD rats were treated by inhalation with 3 ppm (a group of 20 rats, sex not specified) or 10 ppm (a group of 20 rats, sex not specified) DMS for 1 h/day, 5 days/week for 19 weeks. 5/15 (33%) of the high-dose rats living more than 643 days developed malignant tumours (3 squamous cell carcinomas of the nasal epithelium, 1 cerebellar tumour, 1 lymphosarcoma). 3/20 (15%) of the low-dose group (2 nervous system tumours, 1 squamous cell carcinoma of the nasal epithelium). No concurrent control group. The spontaneous rate of neurological tumours in BD rats was <1 per 1,000.

Remark on study:

species, strain:	rat, BD, sex not specified
route:	inhalation
tumour:	nervous system and nasal cavity
duration:	1 h, 5 days per week for 19 weeks
exposure start:	not specified
note:	terminated after 92 weeks

Lowest dose with a significant increased tumour incidence

Nervous system and nasal cavity	
control:	0% (historical)
3 ppm:	3/20 (15%)
net %:	15%

Dialy dose per rat during the exposure period

1 hour · inhalation volume · mg DMS m^3 · (5/7) (for 7 days a week)
1h · 6 l/h (def.)[1] · 3 · 126.1/24.45 · 1/1000 · (5/7) = 0.066 mg/rat/day.

Dialy dose per kg bodyweight during the exposure period

Bodyweight is not specified: 350 gram (def.)[10]
i.e. 1000/350 · 0.066 = 0.19 mg DMS/kg bodyweight per day.

[10] In case bodyweights, feed consumption data etc. are not specified, the default data set is used

Dose at this incidence of nasal tumours when administration started after 8 weeks and exposure is for 24 months

19/104 · 92/104 · 0.19 mg DMS/kg/day = 0.031 mg/kg/bodyweight per day (the basis for the calculation is somewhat uncertain, however, the compound is clearly of high potency).

T25 after 24 months

T25 = 25/15 · 0.031 mg/kg/day = 0.052 mg/kg/day
T25 dose descriptor in rats is 0.05 mg/kg/day

Risk Characterisation

Workers

Two scenarios are used for calculation

1. Production of DMS: 0.01 mg/m^3
2. Use as intermediate: 0.2 mg/m^3

In scenarios 1 and 2

Inhalation a working day of light work: 10 m^3. Working week 5 days and 48 weeks. Lifetime 70 years, working time 45 years. Weight 70 kg

0.1 mg/m^3; (0.0 · 10 · 5/7 · 48/52 · 45/70 = 0.00061 mg/kg/day
0.2 mg/m^3; (0.0 · 10 · 5/7 · 48/52 · 45/70 = 0.012 mg/kg/day

Inhalation

T25 = 0.05 mg/kg/day; Dose giving lifetime cancer risk of 10^{-3} = 0.0002 mg/kg/day

Scenario 1. represents a lifetime cancer risk of 0.00061/0.0002 = $3.0 \cdot 10^{-3}$
Scenario 2. represents a lifetime cancer risk of 0.012/0.0002 = $6.0 \cdot 10^{-2}$

References

Druckey H, Kruse H, Preussmann R, Ivankovic S, Landschütz C. Cancerogene alkylierende Substanzen. III. Alkylhalogenide, -sulfate, -sulfonate und ringgespannte Heterocyclen, Z. Krebsforsch 74: 241-273, 1970.

Annex 3 Establishment of the minimal MOSs used for the risk characterisation by the Netherlands[11]

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

Table A.1 Assessment factors applied for the calculation of the minimal MOS for inhalation exposure applicable on the inhalatory developmental study with rats

Aspect	Assessment factors
Interspecies differences	3
Intraspecies differences	3
Differences between experimental conditions and exposure pattern of the worker	1
Type of critical effect	1
Dose-response curve	1
Confidence of the database	1
Overall	9

[11] This annex 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.

DMS Production (Emission 0,3 %, Elimination wwtp 87%)														
Emission of Sodium methylsulfate (MMS)														
Customer name	Location	tpa DMS 1997	Emission factor	tpa MMS 1997	Mass flow effluent (g/s)	River name	MQ m³/s	MNQ m³/s	PEClocal (µg/l)	PNEC DMS (µg/l)	PEC/PNEC DMS	PNEC estimateMMS (µg/l)	PEC/PNEC MMS	
Company A	City 1	14900,00	0,003	47,38	0,2376	River 1	176	87	2,73	14	1,95E-01	10000	2,73E-04	
DMS Customer Use (Emission 85% of Sodium sulfate)														
Emission of Sodium sulfate														
Customer name	Location	tpa DMS 1997	Emission factor	tpa Na sulfate 1997	Mass flow effluent (g/s)	River name	MQ m³/s	MNQ m³/s	PEClocal (µg/l)	PNEC (µg/l)	PEC/PNEC			
Company A	City 1	1303,40	0,85	1251,92	0,4830	River 1	176	87	5,55	630	8,81E-03			
Company K	City 1	2080,50	0,85	1998,32	0,7710	River 1	176	87	8,86	630	1,41E-02			

DMS Customer Use (Emission 85% of Sodium methylsulfate (MMS), Elimination in wwtp 87%)														
Emission of Sodium methylsulfate (MMS)														
GERMANY														
Customer name	Location	tpa DMS 1997	Emission factor	tpa MMS 1997	Mass flow effluent g/s	River name	MQ m³/s	MNQ m³/s	PEC (µg/l)	PNEC DMS (µg/l)	PEC/PNEC DMS	PNEC estimate MMS (µg/l)	PEC/PNEC MMS	Remark
Company B	City 2	0,00	0,85	0,00	0,0000	River 2	1260	420	0,000	14	0	10000	0	
Company C	City 2	948,50	0,85	854,60	4,2862	River 2	1260	420	10,205	14	7,29E-01	10000	1,02E-03	
Company D	City 3	106,20	0,85	95,69	0,4799	River 2	2270	757	0,634	14	4,53E-02	10000	6,34E-05	
Company E	City 3	18,60	0,85	16,76	0,0841	River 2	2270	757	0,111	14	7,93E-03	10000	1,11E-05	
Company F	City 4	5,00	0,85	4,51	0,0226	River 3	5	3	7,532	14	5,38E-01	10000	7,53E-04	
Company G	City 5	12,50	0,85	11,26	0,0565	River 2	1260	420	0,134	14	9,61E-03	10000	1,34E-05	
Company H	City 3	29,00	0,85	26,13	0,1310	River 2	2270	757	0,173	14	1,24E-02	10000	1,73E-05	
Company I	City 3	483,50	0,85	435,63	2,1849	River 2	2270	757	2,888	14	2,06E-01	10000	2,89E-04	
Company J	City 6	161,30	0,85	145,33	0,7289	River 4	209	70	10,413	14	7,44E-01	10000	1,04E-03	
Company L	City 7	3,00	0,85	2,70	0,0136	River 2	1260	420	0,032	14	2,31E-03	10000	3,23E-06	
Company M	City 8	0,00	0,85	0,00	0,0000	River 5	120	40	0,000	14	0	10000	0	
Company N	City 9	5,00	0,85	4,51	0,0226	River 2	1260	420	0,054	14	3,84E-03	10000	5,38E-06	
Company O	City 10	900	0,85	810,90	4,0670	River 2	no data	no data	0,02	14	1,43E-03	10000	2,00E-06	Data from Ciba (1996 data)
Company P	City 2	48,80	0,85	43,97	0,2205	River 2	1260	420	0,525	14	3,75E-02	10000	5,25E-05	
Company Q	City 3	20,10	0,85	18,11	0,0908	River 2	2270	757	0,120	14	8,57E-03	10000	1,20E-05	
Company R	City 11	80,50	0,85	72,53	0,3638	River 6	120	40	9,094	14	6,50E-01	10000	9,09E-04	

European Commission

EUR 19838 EN - European Union Risk Assessment Report
Dimethyl Sulphate, Volume 12

Editors: B.G. Hansen, S.J. Munn, M.Luotamo, S. Pakalin, F. Berthault, J.De Bruijn, S. Vegro, G Pellegrini, C.J.A. Heidorn, R. Allanou, S. Scheer, K. Vormann.

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The report provides the comprehensive risk assessment of the substance Dimethyl Sulphate. 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 dimethyl sulphate concludes that there is at present concern for workers. For consumers and human exposed via the environment the risk assessment concludes that a risk cannot be excluded as the substance is identified as a non-threshold carcinogen. The risks though are low and this should be taken into account when considering the feasibility and practicability of further specific risk reduction measures. The risk assessment for the environment concludes that there is at present no concern for the atmosphere, aquatic ecosystem, terrestrial ecosystem or for micro-organisms in the sewage treatment plant from sources of dimethyl sulphate covered by Regulation 793/93. However, more information is needed about actual atmospheric concentrations of dimethyl sulphate from other sources nor covered by the Regulation.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commission's Committee on risk reduction strategies set up in support of Council Regulation (EEC) 793/93.

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