Screening Assessment for the Challenge

Sulfuric Acid, Dimethyl Ester
(Dimethyl Sulfate)

Chemical Abstracts Service Registry Number

77-78-1

Environment Canada
Health Canada

August 2009

Synopsis

The Ministers of the Environment and of Health have conducted a screening assessment of Sulfuric acid, dimethyl ester (Dimethyl sulfate), Chemical Abstracts Service Registry Number 77-78-1. This substance was identified in the categorization of the Domestic Substances List as a high priority for action under the Challenge. Dimethyl sulfate was identified as presenting an intermediate potential for exposure (IPE) to individuals in Canada and had been classified by other agencies on the basis of carcinogenicity and genotoxicity. Since dimethyl sulfate did not meet the criteria for bioaccumulation or inherent toxicity to aquatic organisms, the focus of this assessment relates to human health aspects.

According to data submitted in response to a notice issued under section 71 of CEPA 1999, no companies in Canada reported manufacturing dimethyl sulfate in a quantity greater than or equal to the threshold of 100 kg for the 2006 calendar year. However, it was reported that approximately 1000 kg were imported into Canada in that year. The response to the section 71 notice request indicated that dimethyl sulfate is mainly used in Canada as an intermediate by the pharmaceutical industry. Based on information presented in the available scientific and technical literature, dimethyl sulfate may also be applied as a methylating agent to convert compounds such as phenols and amines to their methyl derivatives in the production of products such as dyes, fragrances, surfactants, and water/sewage treatment flocculants. Other products, such as photographic chemicals, can also be produced through the alkylation of dimethyl sulfate using nitrogen, oxygen and/or sulphur.

Emissions of dimethyl sulfate into the ambient environment are expected to come primarily from anthropogenic sources. Dimethyl sulfate may also be formed in atmospheric emissions from facilities burning fossil fuels containing sulfur. The principal route of exposure for the general population will likely be through inhalation of ambient air; exposure from other media is likely negligible. Consumer exposure to residual dimethyl sulfate in products is also expected to be insignificant.

Based principally on weight of evidence assessments of international and other national agencies, the critical effect for the characterization of risks to human health is carcinogenicity. Increased incidences of tumours were observed in multiple species of experimental animals exposed via inhalation or subcutaneous injection. Tumours were also observed in pups of rats exposed to dimethyl sulfate during pregnancy. Dimethyl sulfate was also consistently genotoxic in a range of in *vivo* and in *vitro* assays and is a strong DNA alkylating agent. While the mode of induction of tumours by dimethyl sulfate has not been fully elucidated, it cannot be precluded that the tumours observed in experimental animals have resulted from direct interaction with genetic material.

On the basis of the carcinogenic potential of dimethyl sulfate, for which there may be a probability of harm at any exposure level, it is concluded that dimethyl sulfate is a substance that is entering or may enter the environment in a quantity or concentration or

under conditions that constitute or may constitute a danger in Canada to human life or health.

Dimethyl sulfate does not meet the criteria for persistence or bioaccumulation as set out in the *Persistence and Bioaccumulation Regulations*. On the basis of low ecological hazards and reported releases of dimethyl sulfate, it is concluded that this substance is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends.

This substance will be included in the upcoming *Domestic Substances List* inventory update initiative. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

Based on the information available, it is concluded that dimethyl sulfate meets one or more of the criteria set out in section 64 of CEPA 1999.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or human health. Based on the results of a screening assessment, the Ministers can propose to take no further action with respect to the substance, to add the substance to the Priority Substances List (PSL) for further assessment, or to recommend that the substance be added to the List of Toxic Substances in Schedule 1 of the Act and, where applicable, the implementation of virtual elimination.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE), and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment, and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance Sulfuric acid, dimethyl ester (Dimethyl sulfate) was identified as a high priority for assessment of human health risk because it was considered to present IPE and had been classified by other agencies on the basis of carcinogenicity and genotoxicity. The Challenge for this substance was published in the *Canada Gazette* on November 17, 2007 (Canada 2007). A substance profile was released at the same time. The substance profile presented the technical human health and ecological information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information were received.

Dimethyl sulfate was determined to be a high priority for assessment with respect to risks to human health under CEPA 1999. However, it was not identified as a priority for assessment of potential ecological risks, based on the evaluation of persistence, potential for bioaccumulation and inherent toxicity to aquatic organisms conducted during the

categorization of the Domestic Substances List. Therefore, this assessment focuses on information relevant to the evaluation of human health risks.

Under CEPA 1999, screening assessments focus on information critical to determining whether a substance meets the criteria for defining a chemical as toxic as set out in section 64 of the Act, where

> "64. […] a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
>
> (*a*) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
>
> (*b*) constitute or may constitute a danger to the environment on which life depends; or
>
> (*c*) constitute or may constitute a danger in Canada to human life or health."

Screening assessments examine scientific information and develop conclusions by incorporating a weight of evidence approach and precaution.

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports, and from recent literature searches, up to June 2008 for the health effects section of the document. Key studies were critically evaluated; modelling results may have been used to reach conclusions. Evaluation of risk to human health includes data relevant to evaluation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization of the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. Screening assessments for the Challenge program do not represent exhaustive or critical reviews of all available data. Rather, they present a summary of the critical information upon which the conclusion is based.

This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. The human health portions of this assessment have undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA), including Dr. Bernard Gadagbui (TERA), Dr. Michael Jayjock (The Lifeline Group) and Dr. Susan Griffin (US EPA). Comments on these sections were also received from Gradient Corporation. The ecological portions of the assessment have also undergone external written peer review/consultation. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. Although external comments were taken into consideration, the final content and outcome of the screening risk assessment remain the responsibility of Health

Canada and Environment Canada. The critical information and considerations upon which the assessment is based are summarized below.

Substance Identity

For the purposes of this document, this substance will be referred to as dimethyl sulfate.

Table 1. Substance identity for dimethyl sulfate

Chemical Abstracts Service Registry Number (CAS RN)	77-78-1
Domestic Substances List (DSL) name	Sulfuric acid, dimethyl ester
Inventory names [1]	*Sulfuric acid, dimethyl ester* (TSCA, DSL, ENCS, AICS, SWISS, PICCS, ASIA-PAC, NZIoC) *Dimethyl sulfate* (ECL, TAIWAN) *Dimethyl sulphate* (EINECS) *Sulfuric acid dimethyl ester* (ECL) *DIMETHYLSULFATE* (PICCS) *METHYL SULFATE* (PICCS) *SULFURIC ACID DIMETHYLESTER* (PICCS)
Other names	*Dimethyl monosulfate* *DMS* *NSC 56194, UN 1595, UN 1595 (DOT)*
Chemical group (DSL stream)	Discrete organics
Major chemical class or group	Sulfates
Major chemical sub-class	Esters
Chemical formula	$C_2H_6O_4S$
Chemical structure	
Simplified Molecular Input Line Entry System (SMILES)	O=S(=O)(OC)OC
Molecular mass	126.13 g/mol

[1] National Chemical Inventories (NCI) 2006: AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Asia-Pacific Substances Lists); ECL (Korean Existing Chemicals List); EINECS (European Inventory of Existing Commercial Chemical Substances); ENCS (Japanese Existing and New Chemical Substances); NZIoC (New Zealand Inventory of Chemicals); PICCS (Philippine Inventory of Chemicals and Chemical Substances); SWISS (Inventory of Notified New Substances); TAIWAN.(List of Toxic Chemical Substances regulated under the Taiwan Toxic Chemical Substances Control Act of 1986); and TSCA (Toxic Substances Control Act Chemical Substances Inventory).

Physical and Chemical Properties

A summary of key physical and chemical properties for dimethyl sulfate is presented in Table 2. At room temperature, dimethyl sulfate is a man-made chemical, found as a colourless, oily liquid with a faint odour.

Table 2. Physical and chemical properties for dimethyl sulfate

Property	Type	Value	Rating[1]	Reference
Melting point (°C)	Experimental	-27		CRC Handbook 2006
Boiling point (°C)	Experimental	188		Merck Index 1996
Density (kg/m^3 at 20°C)	Experimental	1333		Merck Index 1996
Vapour pressure (Pa)[2]	Experimental	90 (0.677 mm Hg)	Moderate	HSDB 2008
Henry's Law constant (Pa m^3/mol at 20°C)[3]	Estimated	0.41 (4.0 x10^{-6} atm m^3/mole)	Moderate	Physprop 2006
Water solubility (mg/L)	Experimental	28 000	Very high	HSDB 2008
Log K_{ow} (Octanol-water partition coefficient) (dimensionless)	Modelled	0.16	Low	KOWWIN 2000
Log K_{oc} (Organic carbon-water partition coefficient) (dimensionless)	Modelled	0.93[4] – 1.17[5]	Very low	KOCWIN 2009

[1] qualitative relative rating of the physical-chemical parameter of a substance
[2] Convert from 0.677 mm Hg
[3] Convert from 4.0 x10^{-6} atm m^3/mole
[4] Koc estimated using the Molecular Connectivity Index (MCI) training and validation datasets
[5] Koc estimated from log Kow

Sources

The presence of dimethyl sulfate in the environment results primarily from anthropogenic sources. This chemical may enter the environment during its production and industrial use as a methylating agent in the preparation of a wide variety of intermediates and products (HSDB 2008). Waste products from industries may contain dimethyl sulfate; however, this chemical can be decomposed prior to disposal (IPCS 1985).

Emission of dimethyl sulfate to air occurs also during the combustion of fossil fuels that contain sulphur, eg., in exhaust gases and particulate matter from coal and oil fired power plants (EA 2008).

According to data submitted in response to a notice under section 71 of CEPA 1999, no companies in Canada reported manufacturing dimethyl sulfate in a quantity greater than or equal to the threshold of 100 kg for the 2006 calendar year. However, it was reported that approximately 1000 kg of the substance were imported into Canada in that year (Environment Canada 2008).

Uses

Dimethyl sulfate is reported to be used in Canada only as a pharmaceutical intermediate, according to data submitted under section 71 of CEPA 1999

Based on other available scientific and technical literature, dimethyl sulfate is mainly used in the chemical and pharmaceutical industry. Dimethyl sulfate is a powerful alkylating agent that may be used in the preparation of a wide variety of substances and products, especially dyes, agricultural chemicals, drugs and other specialty products. Methylation of phenols to make ether serves as an intermediate in the manufacture of commercial products such as dyes and fragrances. Methylation with amine to make quaternary ammonium salts, which are used as surfactants, fabric softeners and flocculants in water treatment such as sewage sludge control (McCormack 2000, DuPont 2002, HSDB 2008). However, the use of dimethyl sulfate as a reagent in the synthesis of quartenary ammonium salts for use as surfactants in agricultural chemicals and fabric softeners has not been identified in Canada. Also, no information was found on its use as a flocculant in waste water treatment in Canada.

Other products, such as photographic chemicals are also produced from alkylation reaction of dimethyl sulfate with nitrogen, oxygen or sulphur. Dimethyl sulfate may also be used as an agent for sulfonation, as a solvent, a stabilizer, or a catalyst for the production of other organic chemicals (DuPont 2002).

This chemical is currently not listed on Health Canada's Cosmetic Ingredient Hotlist as a prohibited substance in cosmetic products (Health Canada 2008a). In Canada, dimethyl sulphate is not approved as a food additive, nor has it been used in food packaging materials and incidental additives used in food plants (2009email from Food Directorate to Existing Substance Bureau, Health Canada, unreferenced. This substance is not registered as an active ingredient in pest control products, nor is it present as a formulant in pest control products (PMRA 2008). Dimethyl sulphate is not listed in the Drug Product Database, the Natural Health Products Ingredients Database nor the Licensed Natural Health Products Database; therefore, it is not used in Canada as a direct medicinal or non-medicinal ingredient in pharmaceuticals, natural health products or veterinary drugs. It has not been identified as being present in these products during initial screening exercises. However, as dimethyl sulfate is used in the manufacture of a

chemical intermediate which is used in pharmaceuticals and possibly in natural health products or veterinary drugs, it is possible that dimethyl sulphate may be present in these products as an impurity. The *Controlled Products Regulations* established under the *Hazardous Products Act* requires this substance to be disclosed on the Material Safety Data Sheet that must accompany workplace chemicals when it is present at a concentration of 0.1% or greater as specified on the Ingredient Disclosure List (Health Canada 2008b)

Releases to the Environment

Production and processing of dimethyl sulfate normally occur in closed systems, and no monitoring data on emissions are available. Dimethyl sulfate is not manufactured in Canada and domestic supply is met by imports.

Emissions of dimethyl sulfate into the environment may occur during use as a methylating agent in the preparation of a wide variety of intermediates and products. Fugitive emission or venting during the handling, transport or storage of dimethyl sulfate could also be a source of emission to the atmosphere. Direct release to the environment from the methylating process is possible; however, only a small fraction of dimethyl sulfate would likely be released to the environment from disposal as it is mainly used as a chemical intermediate in a closed system (EURAR 2002).

The burning of sulphur containing coal/fuel from power plants may also contribute to the emission of dimethyl sulfate (EURAR 2002). Dimethyl sulfate has been detected in the particulate matter and the gas phase of plumes downwind of coal and oil fired power plants, suggesting that this substance may be a product of atmospheric reaction of SO_2 with organics in the aerosol (Hanson et al. 1985). However, any dimethyl sulfate in the atmosphere is likely washed out in rain and rapidly hydrolyzed.

There have been no reportable releases of dimethyl sulfate under the National Pollutant Release Inventory (NPRI) since 2001, with on-site releases to air of 4 and 13 kg reported in 2000 and 1999, respectively (NPRI 2008). In recent information with respect to dimethyl sulfate, gathered under CEPA 1999 through a section 71 notice, companies reported no release of this substance in 2006 (Environment Canada 2008).

Environmental Fate

Based on the results of a Level III fugacity model (Table 3), dimethyl sulfate will remain predominantly in the environmental compartment to which it is released. Dimethyl sulfate is expected to exist solely as a vapour in ambient atmosphere, based on its moderate vapour pressure (Table 2).

Table 3. Results of the Level III fugacity modelling (EQC 2003)[1]

	Fraction of substance partitioning to each medium (%)			
Substance released to:	**Air**	**Water**	**Soil**	**Sediment**
Air (100%)	96.2	1.80	1.97	0
Water (100%)	0.10	99.9	0	0
Soil (100%)	0.60	2.60	96.8	0
Air, water, and soil (33.3% each)	31.3	34.7	34	0

1. Identical hydrolysis rate values were used for the water, soil and sediment compartments.

Dimethyl sulfate is highly soluble in water, where it is expected to hydrolyze fairly rapidly (see Table 4); depending on the pH and temperature, monomethyl sulfate, methanol and sulphuric acid have been identified as hydrolysis products (EURAR 2002). As indicated by a low estimated Henry's Law constant of 0.41 Pa m^3/mole, volatilization is not expected to be a major loss process from water; dimethyl sulfate is not expected to adsorb significantly to suspended solids or sediments, based on its low estimated log K_{OC} values. Its low adsorption potential also indicates that, if released to soil, it would be highly mobile. Hydrolysis is likely to be the dominant loss process in moist soils.

Persistence and Bioaccumulation Potential

Environmental Persistence

Empirical degradation data for dimethyl sulfate are presented in Table 4.

Table 4. Empirical data for persistence of dimethyl sulfate

Medium	Fate process	Degradation value	Degradation endpoint / units	Reference
Air	Photooxidation	> 16	half-life (days, calculated)[a]	Japar et al. 1990, EURAR 2002
	Hydrolysis	< 1	half life (hours)	Lee et. al. 1980
		> 1.38	half life (days)[b]	Japar et al. 1990
Water	Hydrolysis	< 24	half-life (hours)	Lee et. al. 1980
	Hydrolysis	1.15	half-life (hours, calculated)[c]	Robertson and Sugamori 1966, HDSB 1983-
Water	Ready-biodegradation	>60	% degradation (CO_2 evolution) in 28 days	Industry report 1998 cited in EURAR 2002

[a]: Calculated from an atmospheric lifetime of ≥ 23 days for clean tropospheric conditions ([OH] = 1.1 x 10^6 cm^{-3}) using a reaction rate constant ≤5 x 10^{-13} cm^3 $molecule^{-1}$ s^{-1} measured by Japar et al. (1990).
[b]: Calculated from an atmospheric lifetime of > 2 days for clean tropospheric conditions ([H_2O] = 15 Torr) using a reaction rate constant < 1.1 x 10^{-23} cm^3 $molecule^{-1}$ s^{-1} measured by Japar et al. (1990).
[c]: Calculated using a measured hydrolysis rate constant of 1.66 x 10^{-4} s^{-1} (Robertson and Sugamori 1966).

In air, degradation of dimethyl sulfate via photochemically produced hydroxyl radicals is not expected to be a major fate process for dimethyl sulfate, based on its half life of >16 days (Japar et al. 1990). It is also not expected to degrade via direct photolysis. However, the substance is expected to degrade more rapidly via hydrolysis as suggested by a calculated atmospheric half-life value of > 1.38 days (Japar et al. 1990). And in fact, because of its high water solubility, dimethyl sulfate is likely to become incorporated into fog and cloudwater, where it will undergo rapid hydrolysis with a half-life of <1 hour based on data from Lee et al. (1980) Therefore, dimethyl sulfate is not stable in air and is not subject to long range transport. Thus, dimethyl sulfate is not considered to be persistent in air, based on criterion specified in the *Persistence and Bioaccumulation Regulations* (half life in air ≥ 2 days) (Canada 2000).

In water, experimental hydrolysis half-life values of less than 24 hours demonstrate that this chemical is likely to be rapidly transformed. Primary hydrolysis of dimethyl sulfate produces monomethyl sulfate and methanol (Robertson and Sugamori 1966, Lee et al. 1980), while ultimate hydrolysis produces methanol and sulfuric acid. Also, there is evidence that dimethyl sulfate and its hydrolysis products are readily biodegradable (EURAR 2002; Industry report 1998), indicating that the substance undergoes rapid primary and ultimate biodegradation. Considering the empirical hydrolysis and biodegradation data, it is concluded that dimethyl sulfate is not persistent in water as set out in the *Persistence and Bioaccumulation Regulations* (half-life in water ≥182 days) (Canada 2000).

Using an extrapolation ratio of 1:1:4 for a water: soil: sediment biodegradation half-life (Boethling et al 1995), the half-life in soil is also <182 days and the half-life in sediments is <365 days. Thus, dimethyl sulfate is not expected to be persistent in soil and sediment according to the criteria specified in the *Persistence and Bioaccumulation Regulations* (half-life in soil ≥ 182 days and half-life in sediment ≥ 365 days) (Canada 2000).

Potential for Bioaccumulation

The predicted log K_{ow} value of 0.16 (Table 2) suggests that dimethyl has low potential to bioaccumulate in the environment.

Since no experimental bioaccumulation factor (BAF) and/or bioconcentration factor (BCF) data are available for dimethyl sulfate, a model approach was applied (Table 5). The modelled BAF value of 1.03 L/kg indicates that dimethyl sulfate does not have the potential to bioaccumulate in the environment. Modelled BCF factors of 1 to 12 L/kg (Table 5) support the low bioaccumulation potential of this substance.

Considering their physical and chemical properties the principal hydrolysis products, monomethyl sulfate and methanol, are also expected to have a low potential to bioaccumulate (BCFWIN 2000).

Table 5. Modelled bioaccumulation data for dimethyl sulfate

Test organism	Endpoint	Value wet weight (L/kg)	Reference
Fish	BAF	1.03	Gobas BAF middle trophic level (Arnot and Gobas 2003)
Fish	BCF	1.02	Gobas BCF middle trophic level (Arnot and Gobas 2003)
Fish	BCF	12.00	OASIS Forecast 2005
Fish	BCF	11.2	Baseline BCF model without mitigating factors (Dimitrov et al. 2005)
Fish	BCF	4.14	Baseline BCF model with mitigating factors (Dimitrov et al. 2005)
Fish	BCF	3.16	BCFWIN 2000

Based on the available kinetic-based and other modelled values, dimethyl sulfate does not meet the bioaccumulation criteria (BCF or BAF ≥ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000)

Potential to Cause Ecological Harm

As indicated earlier, dimethyl sulfate does not meet the persistence or bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Based on available experimental data, dimethyl sulfate is not expected to cause a high level of harm to aquatic organisms at low concentrations (LC/EC_{50}s are expected to be > 1.0 mg/L**)**. A European Union assessment of dimethyl sulfate (EURAR 2002) cites empirical toxicity values ranging from a 96-hr LC_{50} for fish of 14 mg/L (Hoechst 1981), to a 48-hr EC_{50} for daphnia of 17 mg/L (Hoechst 1990), to a 72-hr EC_{50} for algae of 46.9 mg/L (Hoechst 1988). Finally, considering the hydrolysis products, monomethyl sulfate, methanol and sulfuric acid, empirical toxicity data for these compounds indicate that neither would be expected to cause significant harm to aquatic organisms at low concentrations (acute LC/EC_{50}s are expected to be > 1 mg/L) (EURAR 2002 and Environment Canada 1984).

The quantity of dimethyl sulfate imported into Canada (approximately 1000 kg) (Environment Canada 2008) is not exceptionally large and it is mostly used in closed systems as a chemical intermediate; therefore, releases into the Canadian environment are expected to be very low. Dimethyl sulfate in the atmosphere resulting from combustion of sulphur containing fossil fuels is likely washed out in rain and rapidly hydrolysed so

exposure in this medium is expected to be negligible. Significant exposure of organisms in other environmental media is also considered unlikely.

Therefore, based on available information, dimethyl sulfate is unlikely to cause ecological harm in Canada.

Uncertainties in Evaluation of Ecological Risk

Experimental data for ecotoxicity and degradation were limited, and there were no relevant experimental data for bioaccumulation identified. Estimation of this property relied primarily on QSARs. While there are uncertainties associated with the use of QSAR models to estimate chemical and biological characteristics, the approaches used are considered to yield credible results based on the chemical structure of the substance.

Also, the evaluation primarily focused primarily on data on toxicity to organisms in the pelagic aquatic environment. Although the release and partitioning of this substance can result in the exposure of organisms living in other media (air, soil), no relevant toxicity data have been identified.

Potential to Cause Harm to Human Health

Exposure Assessment

There were no measured concentrations of dimethyl sulfate in environmental media in Canada or elsewhere except for two ambient air studies conducted in the US in 1983. Five different samplers were simultaneously used to collect gaseous and particulate phase dimethyl sulfate samples during both daytime and night time in the Los Angeles Basin. Concentrations of gas-phase dimethyl sulfate ranged from 11–164 nmol/m^3 (1.39-20.6 μg/m^3) with a mean of 8.19 μg/m^3. However, concentrations in airborne particulate matter were significantly lower, with a range of 0.1 to 8.7 nmol/m^3 (0.01-1.09 μg/m^3) (Eatough et al 1986). In another study, in a US urban location, a similar mean concentration of 7.4 μg/m^3 was measured (Shah and Heyerdahl 1988). According to the US Toxic Release inventory (TRI), industries reported release and disposal of dimethyl sulfate in a quantity of more than 7000 lbs in 1994 (with 94% being emitted to air), and approximately 2000 lbs in 2006. In Canada, under the National Pollutants Release Inventory (NPRI), companies reported a release and disposal of 11 kg in 1994, the earliest year of available data but no reportable release volume since 2001.

Combustion of sulphur in fossil fuels in coal and oil-fired generating plants may represent a potential source of exposure to dimethyl sulfate in ambient air. Although it was reported that a large proportion of the dimethyl sulfate in the plumes is formed in the atmosphere, the chemistry regarding its formation and fate is still unknown (Japar et al. 1990). However, fossil fuels currently used for energy generation have a much lower sulphur content than those in use at the time the ambient air studies in the US mentioned

above were conducted. In addition, sulphur dioxide emissions in Canada have decreased by more than 45% since 1980 (Environment Canada 2002). Thus, although no recent data on concentrations of dimethyl sulfate from air in the vicinity of coal and oil fired plants have been identified, it is likely that levels in emissions from such plants would be lower than those reported previously.

In light of the large differences in release volumes of dimethyl sulfate between the United States and Canada, and the apparent decreasing trend in emissions over the years, as well as the likely decreases in the industrial emissions of sulphur-based potential precursor compounds, the use of concentrations of ambient air in the United States from the 1980s to estimate upper bounding exposure for the Canadian population is not considered appropriate.

There are no monitoring data for dimethyl sulfate in water or soil; however, concentrations in these media are likely to be negligible since the substance hydrolyzes very rapidly.

As no releases of dimethyl sulfate to the atmosphere were reported under the recent section 71 notice (Environment Canada 2008), a conservative upper bounding estimate of levels in air, water and soil were modelled, based on the reporting threshold of 0.5 kg. The predicted concentration in air is low at approximately 1 ng/m^3, while concentrations in water and soil are negligible (much lower than 10^{-3} ng/L and 10^{-3} ng/g respectively) (ChemCAN 2003). Likewise, food chain accumulation is unlikely based on a low log K_{ow} value; therefore, concentrations in foods are not expected to be significant.

With respect to potential human exposure as a result of residual levels in products (eg., perfumes, dyes and pharmaceuticals), no data on residuals were identified. Based upon the information provided by the Canadian companies under the recent section 71 notice issued in accordance with CEPA 1999, dimethyl sulfate is mainly used as an intermediate in a closed system and is not a component of consumer products. Thus, consumer exposure is expected to be negligible. The substance was also not included in the US Household Products Database (HPD 2008).

Confidence in the relevant exposure database is considered to be very low to low, as it consists of modelled concentrations of dimethyl sulfate in air, water and soil. However, confidence is high that exposure to the substance by the general population is very limited, in light of the indication that it is not released to the general environment in Canada as well as its very reactive nature.

Health Effects Assessment

An overview of the toxicological database for dimethyl sulfate is presented in Appendix 1.

On the basis of investigations in experimental animals, dimethyl sulfate has been classified by the International Agency for Research on Cancer (IARC) as a Group 2A Carcinogen—"probably carcinogenic to humans" (IARC 1999), by the European Commission as a Category 2 Carcinogen—"should be regarded as if carcinogenic to man"(EURAR 2002), by the United States Environmental Protection Agency (US EPA) as a Group B2 Carcinogen—"probable human carcinogen" (US EPA 1994) and by the National Toxicology Program (NTP) as "reasonably anticipated to be a human carcinogen" (NTP 2005).

The agencies listed above considered dimethyl sulfate to have demonstrated carcinogenic potential in animals based on the same basic dataset: the induction of nasal and respiratory tract tumours following inhalation exposures in rats (Druckrey et al. 1970, Schlögel 1972), hamsters, and mice (Schlöge 1972); local sarcomas following subcutaneous injections in rats (Druckrey et al. 1970); as well as the observation of tumours in rat pups following intravenous injections to pregnant dams (Druckrey et al. 1970). These studies are summarized below and in more detail in Appendix 1 of this assessment.[1]

NMRI mice, Wistar rats and Syrian Golden hamsters were exposed to dimethyl sulfate via inhalation (from 2.6 mg/m^3 for 6 hr/d, 2 d/wk to 10.5 mg/m^3 for 6 hr/d, 1d/2wk, or to 178 mg/m^3 (rat), 252 mg/m^3 (mice) and 105 mg/m^3 (hamsters) for four one hour sessions over a period of fifteen months (Schlögel 1972). Increased incidences of malignant tumours of the respiratory tract (nose and lungs) were reported in all of the three species (Schlögel 1972). In another inhalation study, BD rats were exposed to dimethyl sulfate (17 mg/m^3 or 55 mg/m^3 for 1 hr/d, 5 d/wk) for 130 days (Druckrey et al. 1970). Squamous cell carcinomas of the nasal cavity, tumours in the cerebellum, lymphosarcoma of the thorax, multiple lung lesions, brain neurinoma and esthisio-neuroepithelioma of the olfactory nerve were observed in the exposed animals (Druckrey et al. 1970). Subcutaneous administration of dimethyl sulfate also induced sarcomas at the site of injection in BD rats, with metastasis to the lungs in some animals (Druckrey et al. 1966, Druckrey et al. 1970). The transplacental carcinogenic potential of dimethyl sulfate was also assessed in pregnant female BD rats exposed to dimethyl sulfate via a single intravenous injection on day 15 of gestation. During the one year postnatal observational period, some pups from the exposed dams developed malignant tumours that were mostly of the nervous system (Druckrey et al. 1970). While the above studies contributed to the overall cancer classifications, individual studies are considered limited due to lack of controls, small number of dose groups, small group sizes, limited pathological examination and/or high mortality rates.

Dimethyl sulfate has also been consistently genotoxic in multiple *in vivo* and *in vitro* assays and has been classified as Category 3 for genotoxicity (causes concern for humans owing to possible mutagenic effects) by the European Commission (EURAR 2002). The

[1] Two other cancer studies in mice, including a dermal study (Van Duuren et al. 1974) and an inhalation study (Molodkina et al. 1986) were also cited in the EU risk assessment; however, both were considered insufficient for evaluation of the carcinogenicity of dimethyl sulfate due to several limitations (EURAR 2002) and are therefore only summarized in Appendix 1.

IARC Working Group also concluded that dimethyl sulfate is "a potent genotoxic chemical which can directly alkylate DNA both in vitro and in vivo" (IARC 1999). An overview of the results of available genotoxicity studies is presented in Appendix 1 and briefly summarized below.

Dimethyl sulfate was clastogenic in several *in vivo* tests in rodents, inducing micronuclei, chromosome aberrations and aneuploidy. Dimethyl sulfate also caused DNA damage (strand fragmentation) in multiple tissues of mice and rats. In addition, dimethyl sulfate was shown to be a direct alkylating agent *in vivo* by measurement of DNA adducts (N7-methylguanine) in multiple tissues of rats following intraperitoneal injection and in the nasal cavity and upper respiratory tract of rats following inhalation. Although dimethyl sulfate did not induce dominant lethal mutations in germ cells of mice and rats, mixed results were reported for somatic cell mutations following transplacental exposure (mouse spot test). Furthermore, various mutagenic effects of dimethyl sulfate were also observed in the *Drosophila*. With respect to *in vitro* investigations, dimethyl sulfate consistently tested positive in a range of assays for clastogenicity, mutagenicity, DNA damage and DNA adducts in cultured mammalian cells as well as for mutagenicity in several bacterial and fungal test systems.

Information on the potential carcinogenicity and mutagenicity of dimethyl sulfate in humans is limited to two analytical epidemiological studies and several case reports. Pell (1972) reported a non-statistically significant increase in the incidence of tumours in the respiratory tract for a group of 145 workers. In another investigation, no cases of lung cancer were observed in 24 workers exposed to dimethyl sulfate (Thiess et al. 1969). These data were considered by the IARC Working Group as "inadequate evidence for the carcinogenicity in humans of dimethyl sulfate" (IARC 1999). However, chromosome abberations in lymphocytes and increased levels of methylated hemoglobin adducts (N-methylvaline) have been reported in various studies in workers exposed to dimethyl sulfate (Santosky et al. 1982, Molodkina et al. 1986, Schettgen et al. 2004, Lewalter 1996).

Although a thorough analysis of the potential mode of action for induction of tumours by dimethyl sulfate is beyond the scope of this screening assessment, the US EPA, IARC, NTP and the European Commission have stated that dimethyl sulfate is a strong alkylating agent and has the potential to react with macromolecules such as nucleic acids (IARC 1999, US EPA 1994, NTP 2005, EURAR 2002). Indeed, methylation of DNA (N7-methylguanine, N3-methyladenine) has been observed in various tissues in the internal organs of rats exposed to dimethyl sulfate via intravenous injections as well as in tissues of the nasal passage of rats exposed to dimethyl sulfate via inhalation (Swann and Magee 1968, Mathison et al. 1995 respectively) and elevated levels of hemoglobin adducts have been reported in exposed workers (Santosky et al. 1982, Molodkina et al. 1986, Schettgen et al. 2004, Lewalter 1996, Greim and Lehnert 1999).

The available study accounts indicate that the database on non-cancer effects associated with exposure to dimethyl sulfate is more limited. Acute exposure of dimethyl sulfate to the skin of rabbits resulted in severe edema and necrosis, whereas it was reported to be

extremely irritating and to cause corneal damage in an eye irritation test using rabbits (BASF 1968). Case reports in humans exposed to high concentrations of dimethyl sulfate indicate an initial irritant effect at the site of contact (eyes, respiratory tract, skin) with a delayed onset of more severe corrosion, necrosis and edema in these tissues (ACGIH 2001, EU RAR 2002, IPCS 1985).

The lowest lowest-observed-effect level (LOEL) for long term studies in laboratory animals exposed via inhalation (the predominant route of exposure for the general population) is 2.6 mg/m^3 for lung inflammation in rats exposed for 15 months (Schlögel 1972). In subchronic studies, increased mortality and a "necrotizing effect" in the nasal passages was observed in rats exposed to 17 mg/m^3 dimethyl sulfate (the lowest concentration tested) and above (Druckrey et al. 1970). However, evidence of genetic damage, including DNA methylation (N7-methylguanine) in pulmonary and olfactory mucosa and chromosomal aberrations, was observed in short-term studies of rats exposed to lower concentrations (i.e., as low as 0.24 mg/m^3) (Mathison et al. 2004, Molodkina et al. 1996).

The confidence in the toxicity database in experimental animals is considered to be moderate, as data were identified for acute, repeat-dose, reproductive and developmental toxicity, carcinogenicity and genotoxicity. However, the repeat dose studies are limited and sufficient human epidemiology data are not available. There is also uncertainty regarding the mode of induction of tumours and the levels at which non-cancer effects are induced.

Characterization of Risk to Human Health

Based principally on the weight of evidence assessments of several international agencies (IARC, European Commission, US EPA and NTP), a critical effect for characterization of risk to human health for dimethyl sulfate is carcinogenicity, for which a mode of induction involving direct interaction with genetic material cannot be precluded. Although there are limitations to many of the individual studies, collectively, the evidence is considered sufficient, as dimethyl sulfate is a strong alkylating agent which has induced tumours in multiple species of experimental animals, and consistently induced genotoxic effects in a range of *in vivo* and *in vitro* assays.

With respect to non-cancer effects, comparison of the critical non-neoplastic effect concentration in chronically exposed experimental animals (i.e., 2.6 mg/m^3) with the upper bounding estimate of general population exposure via inhalation (the expected principal route of exposure), based on modelled ambient air concentrations (i.e., approximately 1 ng/m^3), results in a margin of exposure of about 2 600 000. This margin would only be an order of magnitude lower if this upper bounding estimate of population exposure is compared to the concentration associated with genetic damage in short-term studies of experimental animals (i.e., 0.24 mg/m^3). It is noteworthy, though, that this modelled estimate of exposure is based on the reporting limit for direct emissions of dimethyl sulfate to the environment and does not take into account potential formation of

the substance in sulphur based emissions from coal or oil fired energy generating facilities. However, the potential contribution of this source to ambient concentrations is not quantifiable. Thus, in light of the conservative nature of the estimates of exposure in the ambient environment, and taking into consideration the rapid hydrolysis of dimethyl in the atmosphere, the margin of exposure for non-cancer effects for the general population is likely adequately protective to account for uncertainties in the database.

Uncertainties in Evaluation of Risk to Human Health

The scope of this screening assessment does not take into account possible differences between humans and experimental species in sensitivity to effects induced by dimethyl sulfate, particularly in light of the limited data available for humans. In addition, the mechanism of tumour induction has not been fully elucidated. However, the data suggest that the strong alkylation potential of dimethyl sulfate may play a role. Furthermore, there is uncertainty regarding the precise magnitude of exposure to dimethyl sulfate in the general environment, particularly with respect to the potential contribution to overall exposure due to its formation in sulphur based emissions from fuel burning plants. However, in light of the rapid hydrolysis of dimethyl sulfate in environmental media, population exposure is expected to be low. In addition, available sources of information indicate that dimethyl sulfate is not used directly in products which result in exposure of the general population.

Conclusion

Based on the available information, it is concluded that dimethyl sulfate is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the carcinogenicity of dimethyl sulfate, for which there may be a probability of harm at any level of exposure, it is concluded that dimethyl sulfate is a substance that is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that dimethyl sulfate does not meet the criteria in paragraphs 64(a) and 64(b) of CEPA 1999, but it does meet the criterion in paragraph 64(c) of CEPA 1999. Additionally, dimethyl sulfate does not meet criteria for persistence or bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations.*

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Endpoint	Lowest effect levels[ab]/Results
Acute toxicity	**Lowest oral LD_{50}** = 106 mg/kg-bw in rats (BASF 1968) [Additional studies: Kennedy and Graepel 1991; Chemie Bitterfeld-Wolfen 1995; Hoescht 1989, 1996] **Lowest inhalation LC_{50}** = 45 mg/m^3 in rats (Hoescht 1989, 1996; Batsura et al. 1980) [Additional studies: Hein 1971, Kennedy and Graepel 1991] Other effects: Acute exposure of dimethyl sulfate to the skin of rabbits resulted in severe edema and necrosis whereas it was reported to be extremely irritating and cause corneal damage in an eye irritation test using rabbits (BASF 1968).
Short-term toxicity [repeated-dose]	**Lowest inhalation LOEC** (systemic) = 4.0 mg/m^3 (0.77 ppm): Statistically significant reduction in maternal body weight gain in rats exposed from gestation day 7 to 17 (Alvarez et al. 1997). **Lowest inhalation LOEC** = 4.0 mg/m^3 (0.77 ppm): Pathological changes in the nasal cavity of rats (Mathison et al. 2004). **LOEC** (genetic damage) = 0.24 mg/m^3: Increased frequency of chromosome aberrations in bone marrow cells [Mice, unspecified strain/sex, exposed for 2.5 months] (Molodkina et al. 1986). [Additional studies: Morita et al. 1997, Santosky et al. 1982, Fomenko et al. 1983, Epstein and Shafner 1968, Braun et al. 1984, Tsuda et al. 2000, Robbiano and Brambilla 1987; Swann 1968, Mathison et al. 1995, Löfroth et al. 1974, Domshlack 1984, Generoso et al. 1991, Druckrey et al. 1970, Seiler 1977, Bishop et al. 1997]
Subchronic toxicity	**Lowest inhalation LOEC** = 17 mg/m^3 (3 ppm): Increased mortality and "necrotizing effect" in the nasal passages [Rat, BD strain, sex not specified, 3 ppm or 10 ppm for 1 hr/day, 5 days/week, 130 days] (Druckrey et al. 1970). [Additional studies: Molodkina et al. 1986; Santosky et al. 1982]
Chronic toxicity/ carcinogenicity	**Non-neoplastic endpoints:** **Lowest inhalation LOEC** = 0.5 ppm (2.6 mg/m^3): Lower survival, lung inflammation, behavioral changes (apathic, eyes half-open, breathing problems), reduced body weights [Rats, Wistar strain, male and female at 2.6 mg/m^3, 6 hours/day, 2 days/week for 15 months; 10.5 mg/m^3, 6 hours/day, 1 day every 2 weeks for 15 months; 178 mg/m^3 for 1 hour/day, 4 days/year for 15 months] (Schlögel 1972) [Additional studies: Druckrey et al. 1970, Molodkina et al. 1986, Van Duuren et al. 1974, Druckrey et al. 1966, Swann and Magee 1968] **Neoplastic endpoints:** *Inhalation:* CBAxC57BC/GI mice (male and female, 90/group) were exposed to dimethyl sulfate via inhalation for 6 months at concentrations of 0.38, 1.62 or 20.26 mg/m^3 for 2 hours/day, 5 days/week. Statistically significant ($p<0.01$) increases in lung adenomas (4.4%, 9.7%, 13.2%, 21.6% in the control, low, mid, and high exposure groups) were reported

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Endpoint	Lowest effect levels[ab]/Results
	(Molodkina et al. 1986). [The EU RAR noted that "the very limited reporting of the study design and results makes the evaluation of the study impossible" (EU RAR 2002).] NMRI mice (male and female, 15–25/sex/group) were exposed to 3 levels of dimethyl sulfate via inhalation (2.6 mg/m^3, 6 hour/day, 2 days/week for 15 months; 10.5 mg/m^3, 6 hours/day, 1 day every 2 weeks for 15 months; 178 mg/m^3, 1 hr/session, 4 sessions in 15 months). Dimethyl sulfate exposures resulted in an increase in the incidence of malignant tumours (carcinomas) of the respiratory tract (nose and lungs). The incidences of malignant nose and/or lung tumours among the animals examined by Schlögel (1972) were reported as: 0/8, 0/14 and 0/11 (males) and 0/11, 1/18 and 3/14 (females) at 0, 2.6 and 10.5 mg/m^3, respectively (Schlögel 1972). At 178 mg/m^3, no malignant tumours or benign tumours were reported in the male mice. However, in the female mice, 3 incidences of benign trabecular pulmonary adenoma, 1 incidence of benign tubular lung adenoma, 1 incidence of benign papillary lung adenoma and 1 incidence of benign fibroadenoma of the axilla were reported. BD rats (20 and 27/group, sex not specified) were exposed to dimethyl sulfate via inhalation for 130 days at concentrations of 17 mg/m^3 (3 ppm) (n=20 group) or 55 mg/m^3 (10 ppm) (n=27 group) for 1 hr/day, 5 days/week. Five out of 15 surviving rats in the high exposure group developed malignant tumours (3 squamous cell carcinomas of the nasal cavity, 1 tumour in the cerebellum, and 1 lymphosarcoma of the thorax with multiple lung lesions). In the low-exposure group, 3 out of the 12 surviving rats developed tumours (1 squamous cell carcinoma of the nasal cavity, 1 brain neurinoma, and 1 in the esthisio-neuroepithelioma of the olfactory nerve (Druckrey et al. 1970). Wistar rats (males: 15–35/group; females: 15–30/group) were exposed to dimethyl sulfate via inhalation for 15 months at concentrations of either 2.6 mg/m^3 at 6 hours/day and 2 days/week or at 10.5 mg/m^3 at 6 hours/day and 1 day every 2 weeks or at 178 mg/m^3, 1 hr/session, 4 sessions in 15 months. Animals were then observed for 30 months. The incidence of malignant nose and/or lung carcinomas among the animals examined was as follows: 0/25, 0/21, 3/14 and 1/14 (males) and 0/11, 3/16, 3/13 and 1/15 (females) at 0, 2.6, 10.5 and 178 mg/m^3 respectively. The incidence of lung adenomas in females of the 10.5 mg/m^3 exposure group was also reported as "slightly higher" than controls: control (2/25 males, 0/11 females), 2.6 mg/m^3 (0/21 males, 0/16 females) 10.5 mg/m^3 (0/14 males, 3/13 females). Subcutaneous fibromas were also noted but not considered to be exposure-related (Schlögel 1972). Syrian Golden hamsters, (males and females, 15–31/group) were exposed to dimethyl sulfate via inhalation for 15 months at concentrations of either 2.6 mg/m^3 at 6 hours/day and 2 days/week or at 10.5 mg/m^3 at 6 hours/day and 1 day every 2 weeks or at 105 mg/m^3 1 hr/session, 4 sessions in 15 months. Animals were then observed for 30 months. The incidence of malignant nose and/or lung carcinomas among the animals are as follows: 0/5, 0/16 and 0/11 (males) and 0/10, 1/12 and 1/11 (females) at 0, 2.6 and 10.5 mg/m^3. At 105 mg/m^3, no malignant tumors were reported. However, one incidence of a benign trabecular pulmonary adenoma was reported (Schlögel 1972). *Dermal:* ICR/Ha Swiss mice (20/group, sex not specified) were exposed 3 times per week for a period of up to 385 or 475 days to dermal applications of either dimethyl sulfate (0.1mg in 0.1ml acetone) or acetone vehicle alone. Some groups of mice were also exposed to dimethyl sulfate with a tumour promoter (phorbol myristate acetate). No carcinomas or papillomas were reported following the dermal applications of dimethyl sulfate alone.

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Endpoint	Lowest effect levels[ab]/Results
	Papillomas were reported in two mice exposed to dimethyl sulfate combined with phorbol myristate acetate (Van Duuren et al. 1974). [The EU RAR noted the limited number of animals used and only a single tested dose and therefore stated that "the study cannot be evaluated with regard to carcinogenic potential of DMS after dermal exposure" (EU RAR 2002).] *Oral:* N/A (no oral repeated exposure studies were identified) *Other routes:* BD rats (8–12/group, sex not specified in secondary source) were exposed to dimethyl sulfate (in oil) via subcutaneous injections daily at either 8 mg/kg-bw (n=12) for 394 days or 16 mg/kg-bw (n=8) for an unspecified amount of time. In the surviving animals, it was reported that local sarcomas were observed at the injection site of the low-dose group (7/11 survivors with local sarcomas, 3 of which metastasized to the lungs and lymph nodes) and the high dose group (4/6 survivors with local sarcomas and 1 with metastases to the lungs). One rat in the low dose group also developed liver carcinoma and was reported to have died with metastases in the lung and the spleen (Druckrey et al. 1966). BD rats (n=15, sex not specified in secondary source) were exposed to dimethyl sulfate via a single subcutaneous injection at 50 mg/kg-bw (as 0.8% aqueous solution). It was reported that 7 out of 15 rats developed local sarcomas at the injection site with multiple metastases to the lungs in 3 out of the 15 animals (Druckrey et al. 1970). Pregnant female BD rats (n=8) were exposed to dimethyl sulfate via a single intravenous injection at 20 mg/kg-bw on day 15 of gestation. Seven out of fifty-nine pups (one year observation) from the exposed dams developed malignant tumours, mostly of the nervous system (Druckrey et al. 1970).
Reproductive toxicity	**LOEC =** 0.77 ppm (4.0 mg/m^3): Statistically significant ($p<0.05$) decreases in feed consumption and body weight gain in the dams from gestation days 7–17 [rats, CrL:CdBr strain, 25 females/group at 0, 0.12, 0.77 and 1.43 ppm, 6 hours/day during gestation day 7 to 16] (Alvarez et al. 1997). [Additional studies: Molodkina et al. 1986, Santosky et al. 1982, Seiler 1977, Generoso et al. 1991, Bishop et al. 1997]
Developmental toxicity	**NOEC =** 1.43 ppm (7.4 mg/m^3): no significant differences in fetal malformations or variations between control and dimethyl sulfate exposed groups up to the highest dose [rats, CrL:CdBr strain, 25 females/group at 0, 0.12, 0.77 and 1.43 ppm, 6 hours/day during gestation day 7 to 16] (Alvarez et al. 1997). [Additional studies: Molodkina et al. 1986, Santosky et al. 1982, Domshlack 1984, Generoso et al. 1991, Druckrey et al. 1970]
Genotoxicity and related endpoints: *in vivo*	**Clastogenicity:** From the results of six independent tests in several strains of mice, Morita et al. (1997) concluded that dimethyl sulfate was positive for micronuclei induction. Positive findings for micronuclei induction were observed in the peripheral blood of BDF1 mice and MS/Ae mice exposed to dimethyl sulfate via intraperitoneal (i.p.) injection. Dimethyl sulfate did not induce micronuclei in the bone marrow cells of CD1 mice exposed via intraperitoneal injection. Two oral tests in CD1 mice and one i.p. test in MS/Ae mice had inconclusive results for micronuclei induction in the peripheral blood.

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Endpoint	Lowest effect levels[ab]/Results
	Positive in the white rat bone-marrow cells (i.p. study) for chromosome aberrations and aneuploidy (Sharma et al. 1980). Positive in NMRI mouse embryo cells (i.p. study) for chromosome aberrations (Braun et al. 1986). Positive in rat bone marrow cells (inhalation study) for chromosome aberrations (Molodkina et al. 1986). Positive in SHK C57B mice bone marrow cells (inhalation study) for chromosome aberrations (Santosky et al. 1982). Positive in CBWA and WR mice lymphocytes (inhalation study) for chromosome aberrations (Fomenko et al. 1983). **Mutagenicity in germ cells [c]:** Negative in male Swiss mouse (i.p. study) for dominant lethal mutations (Epstein and Shafner 1968). Negative in mice and rats (inhalation study) for dominant lethal mutations (Molodkina et al. 1986). **Mutagenicity in somatic cells:** Negative in mouse pups (i.p. study) for spot tests (Braun et al. 1984). Positive in mouse pups (inhalation study) for spot tests (Santosky et al. 1982). **DNA damage or repair:** Positive in ddY mouse (i.p. study) for DNA breaks (Tsuda et al. 2000). Positive in albino white rats (i.v. study) for DNA breaks (Robbiano and Brambilla 1987). Positive in Wistar rats (parenteral study) for DNA and RNA methylation (Swann 1968). Positive in CrlCD:BR rats (inhalation) for DNA methylation (Mathison et al. 1995, 2004). Positive in NMRI mice (inhalation) for methylation of purines (Löfroth et al. 1974). **Genotoxicity in *Drosophila*:** Positive in sex-linked lethal recessive lethal (SLRL) tests (Vogel and Natarajan 1979a, Alderson 1964). Positive in total and partial sex-chromosome loss (Vogel and Natarajan 1979b). Positive for somatic mutations (Vogel 1989). Positive in somatic recombination eye-mosaic assay (Vogel and Nivard 1993).

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Endpoint	Lowest effect levels[ab]/Results
Genotoxicity and related endpoints: *in vitro*	**Clastogenicity:** Positive in Chinese hamster lung V79 cells for chromosome aberrations (Connell and Medcaff 1982, Natarajan et al. 1984). Positive in Chinese hamster ovary cells for chromosome aberrations (Natarajan et al. 1984). Positive in Chinese hamster lung C1-1 cells for chromosome aberrations (Palitti and Becchetti 1977). Positive in Chinese hamster ovary CHO-WBL cells for micronuclei induction (Sobol et al. 2007). Positive in human fibroblasts for sister chromatid exchanges (Wolff et al. 1977). Positive in Chinese hamster lung V79 cells for sister chromatid exchanges (Connell and Medcaff 1982, Natarajan et al. 1984, Nishi et al. 1984). Positive in Chinese hamster lung C1-1 cells for sister chromatid exchanges (Palitti and Becchetti 1977). **Mutagenicity in mammalian cell lines:** Positive in Chinese hamster ovary cells for mutations on the hgprt locus (Couch et al. 1978, Tan et al. 1983). Positive in Chinese hamster lung V79 cells for mutations on the hgprt locus (Natarajan et al. 1984, Newbold et al. 1980, Nishi et al. 1984). Positive in Chinese hamster lung V79 cells for mutagenicity in ouabain resistance (Newbold et al. 1980). **DNA damage or repair:** Positive in human fibroblasts for unscheduled DNA synthesis (UDS) (Cleaver et al. 1977). Positive in rat primary hepatocytes for UDS (Probst et al. 1981). Positive in F344 rat hepatocytes for DNA strand breaks (Bradley et al. 1987). Positive in L1220 mouse leukemic lympblastoid cells for DNA strand breaks (Durkacz et al. 1981). Positive in human fibroblasts for DNA strand breaks (Teo et al. 1983, Klaude et al. 1996, Yamada et al. 1996). Positive in rat hepatocytes for DNA strand breaks (Sina et al. 1983, Sargent et al. 1991). Positive in human KB cells for DNA strand breaks (Walker 1984). Positive in Chinese hamster lung V79 cells for DNA methylation (Connell and Medcaff

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Endpoint	Lowest effect levels[ab]/Results
	1982, Fox and Brennand 1980, Newbold et al. 1980). Positive in Chinese hamster dermal fibroblasts 4DH2 for DNA methylation (Shiner et al. 1988). Positive in Chinese hamster ovary cells for damage and repair in DHFR gene (Wasserman et al. 1990). Positive in immortalized hamster dermal fibroblasts (4DH2) for cell transformation (Shiner et al. 1988). Positive in calf thymus DNA and other isolated DNA for DNA methylation (Newbold et al. 1980, Park et al. 1989, Tudeck et al. 1992) Positive in calf thymus for DNA covalent binding (Randerath et al. 1981). Positive in isolated DNA for DNA strand break (Kubinski et al. 1981, Mhaskar et al. 1981). **Mutagenicity in bacteria:** Positive in *E. coli* B for forward mutation (Alderson 1964). Positive in *S. typhimurium* for forward mutation (Skopek and Thilly 1983). Positive in *S. typhimurium* (TA1535/ pSK1002) for SOS Umu test (Nakamura et al. 1987). Negative in *E. coli* PQ37 for SOS Umu test (Mersch-Sundermann et al. 1994). Positive in *E. coli* NR3835 (LacI gene) for forward mutation (Zielenska et al. 1989). Positive in *S. typhimurium* (TA 1535, 1537, 1538) for reverse mutation (Braun et al. 1977). Positive in *S. typhimurium* (TS1121, 1157) for reverse mutation (Hoffman et al. 1988). Positive in *S. typhimurium* (JK947) for reverse mutation (Lee et al. 1994). Positive in *S. typhimurium* (TA 98, 100, 1535, 1537, 1538) for reverse mutation (Skopek et al. 1978). Positive in *S. typhimurium* (TA1535, hisG46, hisG428, MT101) for reverse mutation (Tomicic and Franekic 1996). **Mutagenicity in fungal cells:** Positive and negative in *S. cerevisiae* for reverse mutation (Prakash and Sherman 1973). Positive in *S. pombe* (haploid ascspores) for reverse mutation (Heslot 1961). Positive in *Neurospora crassa* for reverse mutation (Westergaard 1957).

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Endpoint	Lowest effect levels[ab]/Results
	Positive in *Aspergillus nidulans* for reverse mutation (Moura Duarte 1971). Positive in *S. cerevisiae* for reverse mutation (Pavlov and Khromov-Borisov 1981). Positive in *S. cerevisiae* (RS112) for homologous recombination (Sobol et al. 2007).
Studies in humans	Case reports in humans exposed to high concentrations of dimethyl sulfate indicate an initial irritant effect at the site of contact (eyes, respiratory tract, skin) with a delayed onset of more severe corrosion, necrosis and edema in these tissues (ACGIH 2001, EU RAR 2002, IPCS 1985). Increased chromosome and chromatid aberrations in lymphocytes have been reported in workers exposed to dimethyl sulfate at concentrations ranging from 0.2 to 20 mg/m^3 (Sanotsky et al. 1982). Chromosome aberrations have been reported in lymphocytes of workers exposed to 100 mg/m^3 dimethyl sulfate (Molodkina et al. 1986). In a biological monitoring study, a concentration-related increase in hemoglobin adducts (N-methylvaline) were observed in workers exposed to 0.01, 0.03, or 0.05 mg/m^3 dimethyl sulfate (Lewalter 1996). In a biological monitoring study, workers that were exposed to dimethyl sulfate (n=62) were compared with non-exposed controls (n=10). Stationary air monitoring indicated that levels of dimethyl sulfate in air was < 10 $\mu g/m^3$. N-methyl valine levels in blood hemoglobin was reported to be not significantly different from that of the control group for 52 out of 62 exposed workers. However for 10 out of the 62 workers, N-methyl valine levels were reported to be up to 4 times higher than that of controls (Schettgen et al. 2004). In a cohort study of 145 workers occupationally exposed to dimethyl sulfate for various periods, IARC (1979) reported that "6 cancer deaths were found versus 2.4 expected; three of these were cancers of the respiratory tract (1.02 expected). Neither the respiratory tract cancers nor the cancer rate at all sites are statistically significant." The exposure to dimethyl sulfate was not fully characterized in secondary reports of this study (Pell 1972). In several case studies, 4 incidences of bronchial carcinoma (Drukrey et al. 1966), 1 incidence of pulmonary carcinoma (Betterndorf 1977) and choroid melanoma (Albert and Puliafito 1977) were reported in workers exposed to dimethyl sulfate. The above data were considered by the IARC Working Group as "*inadequate evidence* for the carcinogenicity in humans of dimethyl sulfate" (IARC 1999). No clinical or X-ray evidence of lung cancers was noted among 24 men that have been exposed to dimethyl sulfate for at least 3 years occupationally. Secondary reports of this study also indicate that 4 cases of lung cancer were observed among 368 men who had historical exposure to dimethyl sulfate. The overall significance of the findings in this study were not provided in secondary sources (Thiess et al. 1969).

[a] LD_{50} = median lethal dose; LC_{50} = median lethal concentration; LOEC = lowest-observed-effect concentration; NOEC = no-observed-effect concentration.

[b] Conversion factor: $mg/m^3 = 5.16 \times ppm$ (IARC 1999).
[c] Both studies for dominant lethal mutations (Epstein and Shafner 1968, Molodkina et al. 1986) were reported as "negative" in the EU RAR (2002); however, it was noted that the evaluation of these results was restricted by either poor reporting or limited study design.