DIMETHYL SULFATE

Data were last reviewed in IARC (1974) and the compound was classified in *IARC Monographs* Supplement 7 (1987a).

1. Exposure Data

1.1 Chemical and physical data

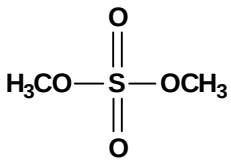
1.1.1 *Nomenclature*

Chem. Abstr. No.: 77-78-1

Chem. Abstr. Name: Sulfuric acid, dimethyl ester

Synonyms: Dimethyl monosulfate; methyl sulfate

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_2H_6O_4S$ Relative molecular mass: 126.13

1.1.3 *Chemical and physical properties of the pure substance*

From IARC (1974)

(*a*) *Description*: Colourless, oily liquid

(*b*) *Boiling point*: 188°C (with decomposition); 76°C at 2 kPa

(*c*) *Melting point*: –27°C

(*d*) *Solubility*: Miscible with many polar organic solvents and aromatic hydrocarbons, but sparingly soluble in carbon disulfide and aliphatic hydrocarbons

(*e*) *Vapour pressure*: 13 Pa at room temperature

(*f*) *Stability*: Stable at room temperature; hydrolysis in water is rapid.

(*g*) *Reactivity*: An active alkylating agent

(*h*) *Conversion factor*: $mg/m^3 = 5.16 \times ppm$

1.2 Production and use

Dimethyl sulfate has been produced commercially since at least the 1920s. It is used mainly as a methylating agent for converting active-hydrogen compounds such as phenols, amines and thiols to the corresponding methyl derivatives.

No information was available on production. During 1967–70, only five companies worldwide reported manufacturing it (IARC, 1974).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997) as many as 10 000 workers in the United States were potentially exposed to dimethyl sulfate (see General Remarks). No information was available as to the operations in which these exposures might have occurred.

1.3.2 *Environmental occurrence*

No information on environmental exposures was available to the Working Group.

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 0.52 mg/m^3 as the 8-h time weighted average threshold limit value for occupational exposures to dimethyl sulfate. Values used as standards or guidelines have ranged from 0.05 to 0.50 mg/m^3 in other countries (International Labour Office, 1991).

2. Studies of Cancer in Humans

As previously summarized, four cases of bronchial carcinoma were reported in men exposed occupationally to dimethyl sulfate (IARC, 1974). Additional case reports have since appeared: a case of pulmonary carcinoma in a man exposed for seven years to 'small amounts' of dimethyl sulfate but to larger amounts of bis(chloromethyl)ether and chloromethyl methyl ether (IARC, 1987b), and a case of choroidal melanoma in a man exposed for six years to dimethyl sulfate (IARC, 1987a).

3. Studies of Cancer in Experimental Animals

Dimethyl sulfate has been tested for carcinogenicity in rats by inhalation, subcutaneous and intravenous injection, and following prenatal exposure. It produced local sarcomas and tumours of the nervous system (IARC, 1974).

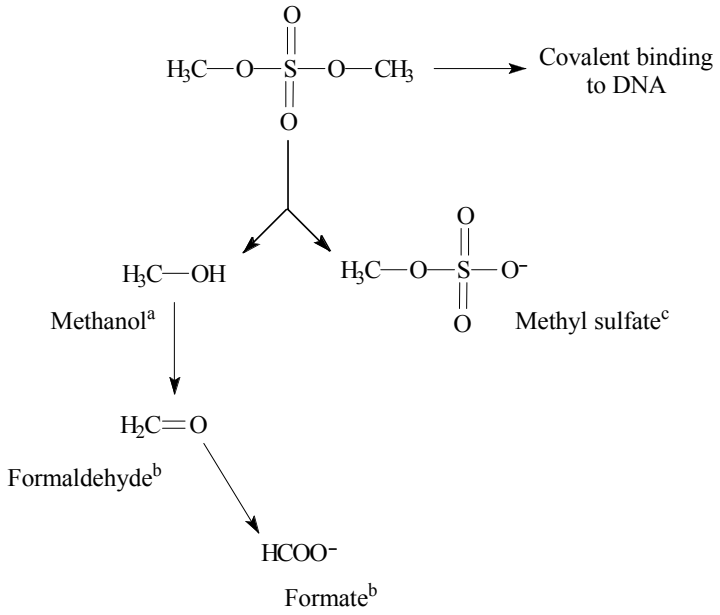
4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

As previously summarized, after an intravenous injection of 75 mg/kg bw in the rat, dimethyl sulfate was no longer detectable in blood after three minutes. No other data

were available to the Working Group (IARC, 1974). Dimethyl sulfate rapidly decomposes on contact with water to methanol and methyl sulfate (Figure 1) (Mathison *et al.*, 1995).

Figure 1. Dimethyl sulfate biotransformation and decomposition pathways *in vivo*



From Mathison *et al.* (1995)
[a] Primary products expected from hydrolysis of dimethyl sulfate
[b] Minor metabolites expected to be produced following further oxidation or hydrolysis of methanol
[c] Methyl sulfate does not further decompose to sulfate or function as a DNA methylating intermediate.

4.2 Toxic effects

4.2.1 *Humans*

Exposure to dimethyl sulfate causes corrosion or irritation to the skin, eyes and respiratory tract, with inflammation and tissue necrosis upon acute exposure. Death is commonly a result of respiratory failure (Molodkina *et al.*, 1985; Wang *et al.*, 1988; Ip *et al.*, 1989).

4.2.2 *Experimental systems*

No data were available to the Working Group.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Groups of adult female (C3H/R1 × 101/R1)F_1 mice were treated with 25 mg/kg bw dimethyl sulfate once by intraperitoneal injection of 25 mg/kg bw within four days before mating or at 1, 6, 9 or 25 h after mating with untreated males. Control groups were treated with vehicle only (1 mL water) four days before mating or 6 or 25 h after mating. Control and treated females were killed and their uterine contents examined 17–18 days after mating. Resorptions were significantly increased ($p < 0.01$) following treatment at 1, 6, 9 and 25 h after mating (63%, 57%, 50% and 34%, respectively) in comparison with before mating and 6 h and 25 h after mating control group frequencies of 4.8, 4.3% and 5.3%, respectively. Treatment before mating had no effect on the frequency of resorptions. The frequency of midgestational deaths was significantly increased at 1 h (6%) compared with control group frequencies of 0.3–0.6%. Late gestational deaths were significantly increased following the 1, 6 and 9 h treatments (11%, 10% and 5%, respectively), compared with a control group frequency of 0.3%. No effect was observed at other times. The incidences of live fetuses with malformations were (numbers of fetuses examined in parentheses): before mating control, 1.0% (298), treated (with, exceptionally, 75 mg/kg bw), 2.6 % (269); pooled after mating controls, 1.1% (650), treated at 1 h, 30% (40); treated at 6 h, 25% (120); treated at 9 h, 13% (134); treated at 25 h, 2% (187). In contrast to other alkylating agents with similar DNA-binding properties but different effects upon exposed zygotes, there appeared to be no site-specific alkylation product identifiable as the critical target. The authors speculated that the effects were due to an epigenetic disruption in the normal programming of gene expression during early embryogenesis (Generoso *et al*., 1991).

4.4 Genetic and related effects

The genetic effects of dimethyl sulfate have been reviewed by Hoffmann (1980).

4.4.1 *Humans*

Chromosome aberrations have been reported in lymphocytes of workers exposed to 100 mg/m^3 dimethyl sulfate (Molodkina *et al.*, 1985).

4.4.2 *Experimental systems* (see Table 1 for references)

Dimethyl sulfate induced mutation in bacteria and DNA damage in prophage. It forms a variety of alkylated bases, including *N*7-methylguanine, *N*3-methyladenine and *N*7-methyladenine with DNA *in vitro.*

In single studies, dimethyl sulfate induced somatic mutations in *Drosophila melanogaster* and in stamen hairs of *Tradescantia* clone BNL 4430.

In experiments conducted with mammalian cells *in vitro*, in the absence of exogenous metabolic activation, dimethyl sulfate induced morphological transformation, chromosomal aberrations, sister chromatid exchanges and gene mutations; it induced DNA strand breaks and formed *N*7-methylguanine, *N*3-methyladenine and *N*7-methyladenine in DNA.

Dimethyl sulfate forms *N*7-methylguanine in DNA when administered to rats *in vivo*. Urine collected from rats up to 48 h after exposure to airborne concentrations of ^{3}H-

Table 1. Genetic and related effects of dimethyl sulfate

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, Prophage, induction, SOS repair test, DNA strand breaks, cross-links or related damage	+	NT	252	Tudek *et al.* (1992)
PRB, Prophage, induction, SOS repair test, DNA strand breaks, cross-links or related damage	+	NT	1% in air	Dianov *et al.* (1991)
ECD, *Escherichia coli pol A*, differential toxicity	+	NT	6500	Fluck *et al.* (1976)
SAF, *Salmonella typhimurium*, forward mutation	+	NT	2.02	Skopek & Thilly (1983)
SAS, *Salmonella typhimurium* TA1535/pUC8, reverse mutation	+	NT	1.9	Tomicic & Franekic (1996)
SAS, *Salmonella typhimurium* hisG46/pUC8, reverse mutation	+	NT	1.9	Tomicic & Franekic (1996)
SAS, *Salmonella typhimurium* hisG428/pUC8, reverse mutation	+	NT	1.9	Tomicic & Franekic (1996)
SAS, *Salmonella typhimurium* MT101/UC8, reverse mutation	+	NT	1.9	Tomicic & Franekic (1996)
SAS, *Salmonella typhimurium* JK947, reverse mutation	+	NT	50	Lee *et al.* (1994)
ECF, *Escherichia coli* B, forward mutation	+	NT	126	Alderson (1964)
ECF, *Escherichia coli* NR3835, *LacI* gene, forward mutation	+	NT	164	Zielenska *et al.* (1989)
SCH, *Saccharomyces cerevisiae*, homozygosis	(+)	NT	240	Pavlov & Khromov-Borisov (1981)
SCR, *Saccharomyces cerevisiae*, reverse mutation	(+)	NT	240	Pavlov & Khromov-Borisov (1981)
TSM, *Tradescantia* clone BNL 4430, stamen hair mutation	+	NT	163	Shima & Ichikawa (1995)
DMM, *Drosophila melanogaster*, somatic mutation	+		5044 feed	Vogel (1989)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DMX, *Drosophila melanogaster*, sex-linked lethal recessive mutations	+		48 feed	Alderson (1964)
DIA, DNA strand breaks/cross-links, L1220 mouse leukaemic lymphoblastoid cells *in vitro*	+	NT	0.25	Durkacz *et al.* (1981)
DIA, DNA strand breaks *in vitro*	+	NT	252	Kubinski *et al.* (1981)
DIA, DNA strand breaks in PM2 DNA *in vitro*	+	NT	6.3	Mhaskar *et al.* (1981)
DIA, DNA strand breaks/cross-links, rat hepatocytes *in vitro*	+	NT	4	Sina *et al.* (1983)
DIA, DNA strand breaks, rat hepatocytes *in vitro*	+	NT	0.8	Sargent *et al.* (1991)
DIA, DNA strand breaks, Fischer 344 rat hepatocytes *in vitro*	+	NT	3.8	Bradley *et al.* (1987)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	+	NT	12.60	Probst *et al.* (1981)
GCO, Gene mutation, Chinese hamster ovary CHO cells *in vitro*	+	NT	1.3	Couch *et al.* (1978)
GCO, Gene mutation, Chinese hamster ovary CHO cells, *hprt* locus *in vitro*	+	NT	5	Tan *et al.* (1983)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	+	NT	8	Newbold *et al.* (1980)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	+	NT	6.3	Natarajan *et al.* (1984)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	+	NT	5	Nishi *et al.* (1984)
G9O, Gene mutation, Chinese hamster lung V79 cells, ouabain resistance *in vitro*	+	NT	NG	Newbold *et al.* (1980)
SIC, Sister chromatid exchange, Chinese hamster lung CP-1 cells *in vitro*	(+)	NT	6.3	Palitti & Becchetti (1977)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	1.3	Natarajan *et al.* (1984)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	NT	6.3	Natarajan *et al.* (1984)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	NT	1.3	Connell & Medcalf (1982)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	NT	5	Nishi *et al.* (1984)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CIC, Chromosomal aberrations, Chinese hamster lung Cl-1 cells *in vitro*	(+)	NT	6.3	Palitti & Becchetti (1977)
CIC, Chromosomal aberrations, Chinese hamster lung V79 cells *in vitro*	+	NT	6.3	Connell & Medcalf (1982)
CIC, Chromosomal aberrations, Chinese hamster lung V79 cells *in vitro*	+	NT	6.3	Natarajan *et al.* (1984)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	NT	6.3	Natarajan *et al.* (1984)
TCL, Cell transformation, immortalized hamster dermal fibroblasts (4DH2)	+	NT	10	Shiner *et al.* (1988)
DIH, DNA strand breaks, human fibroblasts *in vitro*	+	NT	19	Teo *et al.* (1983)
DIH, DNA strand breaks/cross-links, human KB cells (line of HeLa cells) *in vitro*	+	NT	50	Walker (1984)
DIH, DNA strand breaks, human fibroblasts *in vitro*	+	NT	3.1	Yamada *et al.* (1996)
DIH, DNA strand breaks, human fibroblasts *in vitro*	+	NT	63	Klaude *et al.* (1996)
SHT, Sister chromatid exchange, transformed human cells *in vitro*	+	NT	1.5	Wolff *et al.* (1977)
CBA, Chromosomal aberrations, white rat bone-marrow cells *in vivo*	+		325 ip × 1	Sharma *et al.* (1980)
COE, Chromosomal aberrations, NMRI mouse embryos *in vivo*	+		25 ip × 1	Braun *et al.* (1986)
AVA, Aneuploidy, rat bone-marrow cells *in vivo*	+		325 ip × 1	Sharma *et al.* (1980)
BID, Formation of *N*3-methylguanine, O^6-methylguanosine in DNA *in vitro*	+	NT	NG	Lawley *et al.* (1972)
BID, Alkylated purines, Chinese hamster lung V79 cells *in vitro*	+	NT	100	Fox & Brennand (1980)
BID, Formation of *N*7-methylguanine, *N*3-methyladenine, O^6-methylguanine, *N*3-methylguanine in DNA of Chinese hamster lung V79 cells *in vitro*	+	NT	8	Newbold *et al.* (1980)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	NT	5675	Randerath *et al.* (1981)
BID, Formation of *N*7-methylguanine, O^6-methylguanine, *N*3-methyladenine in DNA of Chinese hamster lung V79 cells, *in vitro*	+	NT	10	Connell & Medcalf (1982)
BID, Formation of *N*7-methylguanine, *N*7-methyladenine, *N*3-methyladenine in DNA of Chinese hamster C4DH2 cells, *in vitro*	+	NT	10	Shiner *et al.* (1988)
BID, Formation of *N*7-methylguanine in DNA *in vitro*	+	NT	1576	Park *et al.* (1989)
BID, Formation of *N*7-methylguanine in DNA *in vitro*	+	NT	32	Tudek *et al.* (1992)
BVD, Formation of *N*7-methylguanine in DNA and RNA from rat liver *in vivo*	+		80 inj × 1	Swann & Magee (1968)

[a] +, positive; (+), weak positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; NG, not given; inj, injection; ip, intraperitoneal

labelled dimethyl sulfate of 0.32 and 16.3 µg/L contained *N*7-methylguanine, *N*3-methyladenine and *N*1-methyladenine (Löfroth *et al.*, 1974). Dimethyl sulfate (lowest effective dose 25 mg/kg bw i.p.) induced chromosomal aberrations in NMRI mouse embryos at day 10 of gestation following its transplacental administration.

4.4.3 *Mechanistic considerations*

Dimethyl sulfate is a monofunctional alkylating agent that reacts with DNA through a bimolecular substitution (S_N2) reaction, forming a transition complex with strong nucleophiles, particularly base nitrogens such as the N7 position of guanine and the N3 position of adenine. It reacts far less extensively with weaker nucleophilic centres in DNA, such as O^6-position of guanine (Lawley, 1974). Thus, *N*7-methylguanine, and *N*3-methyladenine are the major DNA adducts formed when dimethyl sulfate reacts with DNA *in vitro* or *in vivo*, *O*^{6}-methylguanine being formed at very low levels (Singer & Grunberger, 1983). Of these adducts, only *O*^{6}-methylguanine is firmly established as directly mispairing, resulting in GC→AT transition mutations (Singer & Grunberger, 1983). Experiments conducted in mammalian cells *in vitro* (Newbold *et al*., 1980; Connell & Medcalf, 1982; Natarajan *et al.*, 1984; Shiner *et al.*, 1988) and carcinogenicity studies *in vivo* (Lawley, 1984) suggest that S_N2 alkylating agents such as dimethyl sulfate are weak carcinogens because they yield low levels of mispairing adducts such as *O*^{6}-methylguanine, and that their cytotoxic, mutagenic and carcinogenic activities owe more to the indirect effects of depurination, DNA strand breakage and chromosomal damage. This is in contrast to S_N1 alkylating agents, such as *N*-methyl-*N*-nitrosourea, which produces relatively high levels of mispairing adducts such as *O*^{6}-methylguanine, induces high levels of gene mutations at low cytotoxicity, and is a potent carcinogen.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to dimethyl sulfate may occur during its manufacture and its use as a methylating agent.

5.2 Human carcinogenicity data

No epidemiological studies were available to the Working Group. A small number of cases of, mainly, bronchial carcinoma has been reported.

5.3 Animal carcinogenicity data

Dimethyl sulfate was tested for carcinogenicity in rats by inhalation, subcutaneous and intravenous injection, and following prenatal exposure. It produced local sarcomas and tumours of the nervous system.

5.4 Other relevant data

Dimethyl sulfate rapidly decomposes on contact with water, as a result of which it very rapidly disappears from the circulation of dosed rats.

It is corrosive or irritant to the skin, eyes and respiratory tract of exposed people, and may result in death caused by respiratory failure.

Dimethyl sulfate is embryotoxic to rats and causes malformations among surviving foetuses.

Workers exposed to dimethyl sulfate have developed chromosomal aberrations in their circulating lymphocytes. Dimethyl sulfate has been subjected to a broad range of in-vitro tests for genotoxic activity, in which positive results were consistently found without the need for exogenous metabolic activation systems. It has also consistently produced positive responses in the small number of in-vivo tests to which it has been subjected. It forms a variety of alkylated bases with DNA *in vitro* and the same alkylated bases are formed *in vivo*.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity in humans of dimethyl sulfate.

There is *sufficient evidence* for the carcinogenicity in experimental animals of dimethyl sulfate.

Overall evaluation

Dimethyl sulfate is *probably carcinogenic to humans (Group 2A)*.

In making the overall evaluation, the Working Group took into consideration that dimethyl sulfate is a potent genotoxic chemical which can directly alkylate DNA both *in vitro* and *in vivo*.

6. References

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