DIETHYL SULFATE

Data were last evaluated in IARC (1992a).

1. Exposure Data

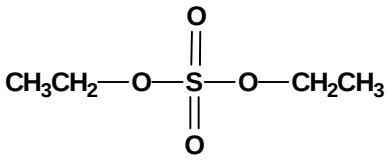
1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 98503-29-8

Chem. Abstr. Name: Sulfuric acid, diethyl ester

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_4H_{10}O_4S$ Relative molecular mass: 154.19

1.1.3 *Physical properties* (for details, see IARC, 1992a)

(*a*) *Boiling point*: 208–209.5°C

(*b*) *Melting point*: –25°C

(*c*) *Conversion factor*: $mg/m^3 = 6.31 \times ppm$

1.2 Production, use and human exposure

Diethyl sulfate is manufactured from ethylene and sulfuric acid. It is used principally as an intermediate (ethylating agent) in the manufacture of dyes, pigments and textile chemicals, and as a finishing agent in textile production. It is an intermediate in the indirect hydration (strong acid) process for the preparation of synthetic ethanol from ethylene. No data were available on levels of occupational exposure to diethyl sulfate (IARC, 1992a).

2. Studies of Cancer in Humans

2.1 Cohort studies

Exposure to diethyl sulfate occurs in ethanol production. One cohort study at an isopropanol (see this volume) and ethanol manufacturing plant in the United States revealed

a significantly increased risk for laryngeal cancer (standardized mortality ratio [SMR], 5.0 (95% CI, 1.4–12.9), based on four cases; after including some additional groups of workers, the SMR was 3.2 (95% CI, 1.3–6.6) based on seven cases (IARC, 1992a).

A cohort study at two plants producing ethanol and isopropanol in the United States showed nonsignificant excess risks based on two cancers of the larynx and three buccal cavity and pharynx cancers in strong-acid workers (IARC, 1992a).

2.2 Case–control studies

A subsequent case–control study nested in an expanded cohort at the aforementioned isopropanol and ethanol manufacturing plant in the United States indicated that the increased risk of laryngeal cancer was related to exposure to sulfuric acid; the risk persisted even after exclusion of workers in the ethanol and isopropanol units (IARC, 1992a).

An association between estimated exposure to diethyl sulfate and risk for brain tumours was suggested in a case-control study of workers at a petrochemical plant in the United States. Seventeen glioma cases and six times as many controls were included and an odds ratio of 2.1 (90% confidence interval [CI], 0.6–7.7) was obtained; a parallel study of 21 cases (including the 17 of this other study) and with another set of controls showed no clear increase in risk, however (IARC, 1992a).

[No measurement of exposure to diethyl sulfate was available for the industrial processes investigated in the epidemiological studies. It is therefore difficult to assess the contribution of diethyl sulfate to the increased cancer risks. Furthermore, exposure to mists and vapours from strong inorganic acids, primarily sulfuric acid (see IARC, 1992b), may play a role in increasing these risks.]

3. Studies of Cancer in Experimental Animals

Diethyl sulfate was tested for carcinogenicity by oral and subcutaneous administration in one strain of rats. After subcutaneous administration, a high incidence of malignant tumours at the injection site was observed. Following oral gavage of diethyl sulfate, tumours of the forestomach were observed. A low incidence of malignant tumours of the nervous system was observed in the same strain of rats after prenatal exposure (IARC, 1992a).

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

4.1 Absorption, distribution, metabolism and excretion

In male rats administered diethyl sulfate solution by gavage or by intraperitoneal or subcutaneous injection, ethylmercapturic acid and a sulfoxide were identified as metabolites (IARC, 1992a).

4.2 Toxic effects

Diethyl sulfate is a strong skin irritant in animals. No other data were available to the Working Group (IARC, 1992a)

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 diethyl sulfate by a single intraperitoneal injection of 150 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 (0.1 mL dimethyl sulfoxide) 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 1, 6 or 9 h after mating (30%, 24% and 14%, respectively) in comparison with available control group frequencies of 4.1%, 10% and 3.9%. Treatment had no effect if given before mating or 25 h after mating. Midgestational and late deaths were significantly increased at 1 h (15% and 14%, respectively) and at 6 h (16% and 21%, respectively), in comparison with available control frequencies of 0.9% and 1.3%. No effect was observed at other times. The incidences of live fetuses with malformations were (numbers of fetuses examined in parentheses): before mating control, 0.6% (338), treated, 0.2% (441); 1 h after mating control, 0.3% (371), treated, 15% (113); 6 h treated, 25% (157); 9 h treated, 3% (213); 25 h treated, 2% (314). 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 lethal effects were due to an epigenetic disruption of gene expression during early embryogenesis (Generoso *et al.*, 1991).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

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

As previously summarized, diethyl sulfate induced mutation and DNA damage in bacteria and induced reverse mutation and mitotic recombination in yeast. In plant cells, diethyl sulfate induced chromosomal aberrations. In a single study, diethyl sulfate did not induce heritable translocation in *Drosophila melanogaster* but did induce autosomal recessive lethal mutations, sex-linked recessive lethal mutations and genetic crossing-over. In cultured mammalian cells, diethyl sulfate induced chromosomal aberrations, micronucleus formation, sister chromatid exchanges, forward mutation and DNA single-strand breaks; it also induced unscheduled DNA synthesis in primary cultures of rat

Table 1. Genetic and related effects of diethyl 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	30	De Oliveira *et al*. (1986)
PRB, Prophage, induction, SOS repair test, DNA strand breaks, cross-links or related damage	NT	+	0.2	Nakamura *et al*. (1987)
PRB, Prophage, induction, SOS repair test, DNA strand breaks, cross-links or related damage	+	NT	40	Barbé *et al*. (1983)
PRB, *Salmonella typhimurium* TA1535/pSK1002, *umu* test,	+	NT	1170	Vericat *et al*. (1986)
SAF, *Salmonella typhimurium* SV50, forward mutation, arabinose resistance test (Ara test)	+	NT	75	Xu *et al*. (1984)
SAF, *Salmonella typhimurium* TM677, forward mutation	+	NT	65	Skopek & Thilly (1983)
SAF, *Salmonella typhimurium* BA13 and BAL13, forward mutation, arabinose resistance test (Ara test)	+	NT	154	Roldán-Arjona *et al*. (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	NG	McCann *et al*. (1975)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	2500	Waskell (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	NG	Probst *et al*. (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	NT	NG	McCann *et al*. (1975)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	NT	2500	Levin *et al*. (1982)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	NT	2500	Levin *et al*. (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500	Waskell (1978)
SAS, *Salmonella typhimurium* TA97 (*hisO1242 hisD6610* pKM101), reverse mutation	+	NT	2500	Levin *et al*. (1982)
SAS, *Salmonella typhimurium* TA90 (*hisO1242 hisD6610*), reverse mutation	+	NT	2500	Levin *et al*. (1982)
SAS, *Salmonella typhimurium* TA88 (*hisO1242 hisD6610*), reverse mutation	+	NT	5000	Levin *et al*. (1982)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SAS, *Salmonella typhimurium* TA2637 (*hisC3076* pKM101), reverse mutation	+	NT	2500	Levin *et al*. (1982)
SAS, *Salmonella typhimurium* TR3243 (*hisD6610*), reverse mutation	+	NT	5000	Levin *et al*. (1982)
SAS, *Salmonella typhimurium hisC3076*, reverse mutation	+	NT	5000	Levin *et al*. (1982)
SAS, *Salmonella typhimurium hisD3052*, reverse mutation	–	NT	5000	Levin *et al*. (1982)
SAS, *Salmonella typhimurium* TS1121 (*aroC321 hisG46*), reverse mutation	+	NT	600	Hoffmann *et al*. (1988)
SAS, *Salmonella typhimurium* TS1157 (*aroC321 hisG46* pKM101), reverse mutation	+	NT	600	Hoffmann *et al*. (1988)
ECK, *Escherichia coli* K12, forward or reverse mutation	+	NT	308	Mohn & Van Zeeland (1985)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	+	NT	NG	Probst *et al*. (1981)
EC2, *Escherichia coli* WP2, reverse mutation	+	NT	NG	Probst *et al*. (1981)
SCH, *Saccharomyces cerevisiae*, homozygosis by mitotic recombination or gene conversion	+	NT	4500	Zimmermann *et al*. (1966)
SCR, *Saccharomyces cerevisiae*, reverse mutation	+	NT	4500	Zimmermann *et al*. (1966)
ACC, *Allium cepa*, chromosomal aberrations	–	NT	4600	Gohil & Kaul (1983)
PLC, Plant cells, chromosomal aberrations	+	NT	1200	Floria & Ghiorghita (1980)
PLC, Plant cells, chromosomal aberrations	+	NT	3850	Gohil & Kaul (1983)
DMG, *Drosophila melanogaster*, genetic crossing-over or recombination	+		6000 feed	Pelecanos (1966)
DMM, *Drosophila melanogaster*, autosomal recessive lethal mutations	+		6000 feed	Pelecanos (1966)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		NG	Abraham *et al*. (1979)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		1500 inj	Vogel (1989)
DMC, *Drosophila melanogaster*, heritable translocations	–		6000 feed	Pelecanos (1966)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DIA, DNA strand breaks, cross-links or related damage, Chinese hamster ovary CHO cells *in vitro*	+	NT	154	Abbondandolo *et al*. (1982)
DIA, DNA strand breaks, cross-links or related damage, Chinese hamster ovary CHO cells *in vitro*	+	NT	385	Dogliotti *et al*. (1984)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	+	NT	15.4	Probst *et al*. (1981)
GCO, Gene mutation, Chinese hamster ovary CHO cells *in vitro*	+	NT	46	Couch *et al*. (1978)
GCO, Gene mutation, Chinese hamster ovary CHO cells, *hprt* locus *in vitro*	+	NT	154	Bignami *et al*. (1988)
GCO, Gene mutation, Chinese hamster ovary CHO cells, Na/K ATPase *in vitro*	+	NT	154	Bignami *et al*. (1988)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	+	NT	308	Mohn & Van Zeeland (1985)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	+	NT	100	Nishi *et al*. (1984)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	NT	100	Nishi *et al*. (1984)
MIA, Micronucleus test, Chinese hamster lung V79 cells *in vitro*	+	NT	154	Bonatti *et al*. (1986)
MIA, Micronucleus test, Chinese hamster lung V79 cells *in vitro*	+	NT	40	De Ferrari *et al*. (1988)
MIA, Micronucleus test, Chinese hamster lung V79 cells *in vitro*	+	NT	460	Nüsse *et al*. (1989)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	NT	100	Asita (1989)
DIH, DNA strand breaks, cross-links or related damage, human leukocytes *in vitro*	+	NT	154	Schutte *et al*. (1988)
MIH, Micronucleus test, human lymphocytes *in vitro*	+	NT	154	De Ferrari *et al*. (1988)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	154	De Ferrari *et al*. (1988)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
AIH, Aneuploidy, human lymphocytes *in vitro*	+	NT	15	De Ferrari *et al*. (1988)
DVA, DNA strand breaks, cross-links or related damage, SD rat brain cells *in vivo*	+		40 iv × 1	Robbiano & Brambilla (1987)
MST, Mouse spot test, C57BL/6 Jena XT mice *in vivo*	?		225 ip × 1	Braun *et al*. (1984)
SLP, Mouse specific locus test, (101/E1 × C3H/E1)F_1 mice, post-spermatogonia *in vivo*	(+)		200 ip × 1	Ehling & Neuhäuser-Klaus (1988)
MVM, Micronucleus test, ddY mice *in vivo*	+		400 ip × 1	Asita *et al*. (1992)
COE, Chromosomal aberrations, NMRI mice embryos *in vivo*	+		150 ip × 1	Braun *et al*. (1986)
DLM, Dominant lethal test, (101/E1 × C3H/E1)F_1 mice *in vivo*	+		100 ip × 1	Ehling & Neuhäuser-Klaus (1988)
Micronucleus test, *Pleurodeles waltl*, larvae erythrocytes	+		6 (water)	Jaylet *et al.* (1986)
BVD, Binding (covalent) to DNA, (102/E1 × C3H/E1)F_1 mouse germ/testis/bone-marrow/liver *in vivo*	+		48 ip × 1	Van Zeeland *et al*. (1990)

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

[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, intraperitoneally; iv, intravenous

hepatocytes. Diethyl sulfate induced chromosomal aberrations, micronucleus formation and aneuploidy in cultured human lymphocytes. It induced alkali-labile sites in cultured human leukocytes in one study. It was clastogenic in mice and newts (*Pleurodeles waltl*), induced DNA damage in mice and rats and ethylated DNA in mice. Diethyl sulfate induced specific locus mutations in mouse germ-line cells. In mice, diethyl sulfate alkylated DNA to produce mainly *N*7-ethylguanine in germ cells, testis tubules, bone marrow and liver (IARC, 1992a).

DNA base sequence changes were analysed in 31 transmissible *vermilion* mutants recovered from *Drosophila melanogaster*, the male germ cells of which had been treated with diethyl sulfate. There were 93% base-pair substitutions and 7% deletions. The most frequent base-pair changes were GC→AT transitions (73%) and AT→TA transversions (10%) (Sierra *et al.*, 1993).

5. Evaluation

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

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

Overall evaluation

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

In making the overall evaluation, the Working Group took into account that diethyl sulfate is a strong direct-acting alkylating agent which ethylates DNA and that, as a result, it is genotoxic in virtually all test systems examined, including induction of potent effects in somatic and germ cells of mammals exposed *in vivo*.

6. References

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