DIISOPROPYL SULFATE

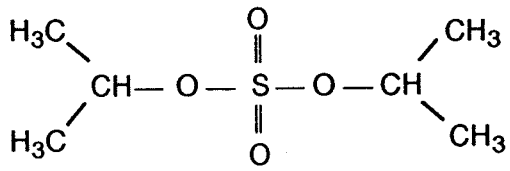
The strong-acid process for producing isopropanol, in which diisopropyl sulfate occurs, was evaluated previously (IARC, 1987).

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Serv. Reg. No.: 2973-10-6
Chem. Abstr. Name: Sulfuric acid, bis(1-methylethyl) ester
IUPAC Systematic Name: Sulfuric acid, diisopropyl ester
Synonyms: Di-isopropylsulphate; diisopropylsulfate; diisopropyl tetraoxosulfate; DIPS; isopropyl sulfate



$C_6H_{14}O_4S$ Mol. wt: 182.24

1.1.2 *Chemical and physical properties*

(*a*) *Description*: Colourless, oily liquid (Druckrey *et al.*, 1973)
(*b*) *Boiling-point*: 94 °C at 7 mm Hg [933 Pa]; 106 °C at 18 mm Hg [2400 Pa] (decomposes) (STN International, 1991)
(*c*) *Melting-point*: –19 °C (STN International, 1991)
(*d* *Density*: 1.0941 at 20 °C/4 °C (STN International, 1991)
(*e*) *Solubility*: 0.5% in water (Druckrey *et al.*, 1973)
(*f*) *Stability*: Highly reactive; degrades rapidly at room temperature, forming coloured species, followed by phase separation resulting in the formation of oligomers (Kingsley *et al.*, 1984); hydrolysed when heated to the monoisopropyl sulfate (Druckrey *et al.*, 1973). Diisopropyl sulfate is an alkylating agent (Wright, 1979).
(*g*) *Conversion factor*: $mg/m^3 = 7.45 \times ppm^a$

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[a]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming normal temperature (25 °C) and pressure (760 mm Hg [101.3 kPa]).

1.1.3 *Technical products and impurities*

Diisopropyl sulfate is not available as a commercial product (Kingsley *et al.*, 1984).

1.1.4 *Analysis*

Sampling and analysis of airborne (personal exposure) diisopropyl sulfate produced in the propylene/sulfuric acid process of isopropanol manufacture have been described (Kingsley *et al.*, 1984). The sample was collected on a solid sorbent (Chromosorb 102), with a filter to prevent the collection of sulfuric acid, and extracted with carbon tetrachloride. The sample was analysed by gas chromatography with sulfur-specific flame photometric detection. The method was shown to be applicable over a range of 0.1–10 ppm [0.75–75 mg/m^3].

1.2 Production and use

1.2.1 *Production*

There is no commercial production of diisopropyl sulfate as such; however, it occurs as an intermediate in the production of isopropanol.

The reaction of olefins with sulfuric acid and water *via* intermediate alkylsulfates to produce alcohols has been known since the middle of the nineteenth century. It was not until the 1920s, however, that the reaction was used commercially to produce isopropanol from propylene. In manufacturing plants, a mixture of propylene and propane is contacted in the absorber with concentrated sulfuric acid. Initially, a sulfuric acid strength of > 90% was required for the reaction to occur (strong-acid process). With time, however, it was found that the acid strength could be reduced to 65–75%, for the propylene reaction ('weak'-acid process) (Lynch *et al.*, 1979).

The reaction of propylene with sulfuric acid is complex, and water plays a major role in determining the concentrations of the intermediate alkyl sulfates.

$$CH_3\text{-}CH=CH_2 + H_2SO_4 \rightarrow (CH_3)_2\text{-}CH\text{-}O\text{-}SO_3H$$
$$(CH_3)_2\text{-}CH\text{-}O\text{-}SO_3H + CH_3\text{-}CH=CH_2 \rightarrow ((CH_3)_2\text{-}CH)_2SO_4$$
$$((CH_3)_2\text{-}CH)_2SO_4 + H_2SO_4 \rightleftharpoons 2(CH_3)_2\text{-}CH\text{-}O\text{-}SO_3H$$
$$((CH_3)_2\text{-}CH)_2SO_4 + H_2O \rightarrow (CH_3)_2\text{-}CH\text{-}O\text{-}SO_3H + (CH_3)_2\text{-}CHOH$$
$$(CH_3)_2\text{-}CH\text{-}O\text{-}SO_3H + H_2O \rightarrow (CH_3)_2\text{-}CHOH + H_2SO_4$$

The more water present in the extracting acid, the less propylene is absorbed to produce the initial monoisopropyl sulfate. In addition, the more water that is present, the more monoisopropyl sulfate, once formed, is converted to isopropanol. Diisopropyl sulfate can also be removed by rapid hydrolysis with acidic water. Therefore, increasing the water content in the sulfuric acid decreases the concentration of diisopropyl sulfate in the acid extract. The concentration of diisopropyl sulfate is reduced by approximately 85% when the sulfuric acid concentration is reduced from 97 to 84 wt%. The diisopropyl sulfate concentration of a 75 wt% propylene–sulfuric acid system is about 1% (Lynch *et al.*, 1979).

Details of the commercial process are presented in the monograph on occupational exposure to mists and vapours from sulfuric acid and other strong inorganic acids (pp. 42–43).

1.2.2 *Use*

Diisopropyl sulfate has no known industrial use; however, it occurs as an intermediate in the production of isopropanol.

1.3 Occurrence

1.3.1 *Natural occurrence*

Diisopropyl sulfate is not known to occur as a natural product.

1.3.2 *Occupational exposure*

No data were available to the Working Group on levels of occupational exposure to diisopropyl sulfate.

Exposure to diisopropyl sulfate in isopropanol manufacturing plants has been inferred from its presence at a concentration of about 20% in acid extracts obtained in the strong-acid processes and about 0.3% in the weak-acid process. The maximal vapour concentration over a spill was calculated to be 520 ppm [3874 mg/m^3] in the strong-acid process and 13 ppm [93 mg/m^3] in the weak-acid process. Actual exposures of workers from spills or leaks would probably be much less, because of dilution in the surrounding air (Lynch *et al.*, 1979). Diisopropyl sulfate might be inhaled as aerosol or vapours during periodic opening of reaction vessels and clean-out operations in these types of plants (Weil *et al.*, 1952; Teta *et al.*, 1992).

Other potential exposures encountered in these processes are described in the monograph on occupational exposure to mists and vapours from sulfuric acid and other strong inorganic acids.

1.4 Regulations and guidelines

No information on the regulatory status of diisopropyl sulfate was found by the Working Group.

2. Studies of Cancer in Humans

Fuller descriptions of the studies summarized below are given in the monograph on occupational exposures to mists and vapours of sulfuric acid and other strong inorganic acids.

2.1 Cohort studies

Weil *et al.* (1952) first raised concern by describing an excess cancer risk associated with work in a US isopropanol unit using a strong-acid process. Cancers at three sites were noted, but significance could be attached only to the few sinonasal cancers and not to the one case of lung and one of laryngeal cancer. Hueper (1966) reviewed the data of Weil *et al.* (1952) and calculated a significant, age-specific excess incidence in men aged 45–54 years, with a relative risk of 21 for cancers of the nasal sinuses and larynx combined.

A cohort study of men at an isopropanol plant in the United Kingdom was reported by Alderson and Rattan (1980). Deaths from cancer gave a nonsignificant standardized

mortality ratio (SMR) of 1.45; one death from nasal cancer was seen, with 0.02 expected, and two each from lung cancer (SMR, 0.78), kidney cancer (SMR, 6.45) and brain tumour (SMR, 16.67). Only the latter was significant.

Enterline (1982), reporting on a US cohort of isopropanol workers, found an SMR for cancer of 0.99, based on 16 deaths; two of these were cancers of the buccal cavity and pharynx (0.50 expected) and seven were of the lung, to give an SMR of 1.18 (not significant). Neither of the subjects with cancers of buccal cavity and pharynx had worked with epichlorohydrin, and their high risk was attributed to employment in the isopropanol unit.

Two cohort studies (Lynch *et al.*, 1979; Teta *et al.*, 1992) have been described not only in the monograph on occupational exposures to mists and vapours from sulfuric acid and other strong inorganic acids but also in the monograph on diethyl sulfate. Lynch *et al.* (1979) demonstrated an excess risk for laryngeal cancer among workers employed in an isopropanol plant (strong- and weak-acid processes) and in an ethanol plant (strong-acid process) in a petrochemical complex. Teta *et al.* (1992) found no effect with the weak-acid process but found an association with work in strong-acid processes, including isopropanol manufacture (one death due to laryngeal cancer and two due to cancer of the buccal cavity and pharynx in men with fewer than five years of employment). The authors noted the inadequate power of their study.

2.2 Case–control studies

The nested case–control study of Soskolne *et al.* (1984), expanded from the study of Lynch *et al.* (1979), found an increased risk for laryngeal cancer in association with exposure to sulfuric acid and demonstrated that there was no confounding of the relationship between exposure to sulfuric acid and laryngeal cancer by employment in either an ethanol or an isopropanol unit: Similar risks were seen after exclusion of workers in these units.

3. Studies of Cancer in Experimental Animals

3.1 Subcutaneous administration

3.1.1 *Mouse*

In a screening assay for lung adenoma induction, groups of 40 A/J or C3H/HeJ mice [sex and age unspecified] received weekly subcutaneous injections of 0.025 ml undiluted diisopropyl sulfate [purity unspecified] or two parts diisopropyl sulfate plus one part diisopropyl oil [purity unspecified] for eight (A/J mice) or 13 (C3H/HeJ mice) weeks. Groups of 40 untreated mice of each strain served as controls. Survival was shorter in the treated groups than in controls. The study was terminated after 24 weeks, and lungs were examined grossly. The incidences of lung adenomas in surviving A/J mice were 9/39 controls, 11/18 ($p < 0.05$) diisopropyl sulfate-treated animals and 10/11 ($p < 0.001$) animals given diisopropyl sulfate plus diisopropyl oil; the incidences in surviving C3H/HeJ mice were 5/40 controls, 14/28 ($p < 0.01$) diisopropyl sulfate-treated animals and 10/37 given diisopropyl sulfate plus diisopropyl oil (Mellon Institute, 1985). [The Working Group noted the limited reporting of the study and the lack of data on animals that died before the end of the study.]

3.1.2 *Rat*

A group of 15 male and female BD-II rats, 100 days old, received weekly subcutaneous injections of 100 mg/kg bw diisopropyl sulfate [purity unspecified] in arachis oil for 15 weeks. Local sarcomas occurred in 14/15 treated rats, which had a mean survival time of 314 ± 24 (standard deviation) days. In a separate experiment, 15 rats received a single subcutaneous injection of 300 mg/kg bw diisopropyl sulfate in arachis oil. Sarcomas developed at the site of injection in 8/15 rats, which had a mean survival time of 476 ± 42 days. In another experiment, 5/18 rats injected subcutaneously with a single dose of 1000 mg/kg bw diisopropyl sulfate in arachis oil developed sarcomas at the site of injection, with a mean induction time of 325 days. No local tumour was found in historical control groups treated with arachis oil (Druckrey *et al.*, 1973). [The Working Group noted that concurrent control groups were not included.]

3.2 Skin application

Mouse: Groups of 28 C3H/HeJ mice [sex and age unspecified] received skin applications [dose unspecified] of a 40% solution of diisopropyl sulfate [purity unspecified] in acetone or a 40% solution of two parts diisopropyl sulfate plus one part diisopropyl oil [purity unspecified] in acetone three times a week for 14 months. A control group of 40 mice received applications of acetone only. Skin papillomas developed in 19/28 mice given diisopropyl sulfate and in 26/28 given diisopropyl sulfate plus diisopropyl oil. Skin carcinomas developed in 12/28 mice given diisopropyl sulfate alone and in 21/28 given the combination. No skin tumour was observed in controls (Mellon Institute, 1985). [The Working Group noted the limited reporting of the study.]

4. Other Relevant Data

No data were available to the Working Group.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Diisopropyl sulfate is an intermediate in the indirect hydration (strong- or weak-acid) process for the preparation of isopropanol from propylene. It has no other known industrial use.

No data were available on levels of occupational exposure to diisopropyl sulfate.

5.2 Human carcinogenicity data

An early US cohort study of isopropanol manufacture using the strong-acid process in a petrochemical plant demonstrated an excess risk for nasal sinus cancer. An increased risk for cancer of the buccal cavity and pharynx was suggested in a cohort of workers at an isopropanol unit in the USA. A cohort study at an isopropanol plant in the United Kingdom indicated an increased risk for nasal cancer (based on one case only) and for brain tumours.

One cohort study at a US isopropanol and ethanol manufacturing plant revealed an increased risk for laryngeal cancer. A subsequent case–control study nested in an expanded cohort at this plant indicated that the increased risk was related to exposure to sulfuric acid; the risk persisted even after exclusion of workers in the ethanol and isopropanol units. A cohort study from a US plant producing ethanol and isopropanol suggested an increased risk for cancers of the larynx, buccal cavity and pharynx, but not of the lung, in strong-acid workers.

No measurement of exposure to diisopropyl sulfate was available for the industrial processes investigated in the epidemiological studies. It is therefore difficult to assess the contribution of diisopropyl sulfate to the increased cancer risks. Furthermore, exposure to mists and vapours from strong inorganic acids, primarily sulfuric acid, probably plays a role.

5.3 Animal carcinogenicity data

Diisopropyl sulfate was tested for carcinogenicity by subcutaneous injection in one strain of rats and by skin application in one strain of mice. It produced local sarcomas in rats and skin papillomas and carcinomas in mice. In a screening study in two strains of mice, an increased incidence of lung adenomas was observed following subcutaneous injection.

5.4 Other relevant data

No data were available to the Working Group.

5.5 Evaluation[1]

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

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

Overall evaluation

Diisopropyl sulfate *is possibly carcinogenic to humans (Group 2B).*

6. References

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[1]For definition of the italicized terms, see Preamble, pp. 26–29.

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