Workplace Exposure Standard (WES) review

DIETHYL SULPHATE
(CAS NO: 64-67-5)

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New Zealand Government

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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for diethyl sulphate should be changed.

The WES review considers the potential for exposures to diethyl sulphate in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposures given currently available analytical methods.

The review includes a recommendation to change the WorkSafe WES for diethyl sulphate, which is currently set at a **WES-TWA** of 0.05**ppm** [0.32mg/m^3] for **inhalable fraction** with a ***skin*** notation, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Ed., November 2019 (WorkSafe, 2019).

Terms that are **bold** (first occurrence only) are further defined in the Glossary.
Synonyms: Diethyl sulfate; Sulphuric acid, diethyl ester; Sulfuric acid, diethyl ester; Ethyl sulphate.

2.0 Chemical and physical properties

Diethyl sulphate is a clear, colourless, oily liquid with a faint peppermint/ethereal or no odour at room temperature (**NICNAS**, 2014; **SCOEL**, 2009; **DFG**, 2003).

The odour threshold for diethyl sulphate is reported to be too low to provide adequate warning of exposure (DFG, 2003).

Chemical and physical properties diethyl sulphate include:

Molecular weight	154.2g/mol
Formula	$C_4H_{10}O_4S$
Specific gravity	1.17g/cm^3 at 25°C
Melting point	-25°C
Boiling point	209.5°C [with decomposition]
Vapour pressure	0.3hPa at 20°C; 0.212mmHg at 25°C
Relative vapour density [air = 1]	5.31
Flash point	104°C
Log KOW	1.14
Solubility	Water: 7.0g/L at 20°C; miscible with alcohol, diethyl ether, and most polar solvents
Decomposition products	Readily decomposes in hot water to ethyl hydrogen sulphate and ethanol
Conversion factors	1mg/m^3 = 0.156ppm 1ppm = 6.409mg/m^3

NTP RoC, 2016; SCOEL, 2009; DFG, 2003.

TABLE 1: Physicochemical properties of diethyl sulphate

Health-related hazard classifications for diethyl sulphate:

	HSNO CLASSIFICATION
Substance	Diethyl sulphate
CAS No.	64-67-5
Classification	6.1D (All); 6.1D (O); 6.1D (D); 6.1D (I); 6.6A; 6.7A 8.2C; 8.3A

TABLE 2:
HSNO health-related hazard classifications of diethyl sulphate (**EPA**, 2019)

For a full listing of all HSNO health-related hazardous substances classification codes and their descriptions, see Appendix 2.

[All] Overall classification for that endpoint.

[O] Oral exposure route.

[D] Dermal exposure route.

[I] Inhalation exposure route.

3.0
Uses

Diethyl sulphate is primarily used as a chemical intermediate [ethylating agent] in the synthesis of ethyl derivatives of phenols, amines, and thiols; as an accelerator in the sulphation of ethylene; and, in some sulphonation processes (NTP RoC, 2016).

Diethyl sulphate is used to manufacture dyes, pigments, carbonless paper, and textiles; as an intermediate in the indirect hydration [strong-acid] process for the preparation of synthetic ethanol from ethylene; and, smaller quantities are used in household products, cosmetics, agricultural chemicals, pharmaceuticals, and laboratory reagents (NTP RoC, 2016).

Occupational exposure to diethyl sulphate can occur during production, storage, transportation and end-use.

Workers can be exposed to diethyl sulphate via inhalation, ingestion and eye or dermal contact (NTP RoC, 2016).

The number of workers exposed or potentially exposed to diethyl sulphate in New Zealand workplaces is unknown.

Statistics New Zealand 2019 data indicate that 6,310 New Zealand workers were working in the areas of:

- synthetic fibre textile manufacturing
- basic organic chemical manufacturing
- fertiliser and pesticide manufacturing
- pharmaceutical and medicinal product manufacturing
- cleaning compound and toiletry preparation manufacturing (NZ.Stat, 2019).

4.0
Health effects

IN THIS SECTION:

4.1 Non-cancer

Humans

The DFG review of diethyl sulphate noted that:

> "Unlike for dimethyl sulfate, for which there are numerous reports of acute intoxications and of long-term exposures suspected of causing cancer in man (see "Dimethylsulfate" in Volume 4 of the present series), for diethyl sulfate there are no reports of effects of short-term or long-term exposure or of toxicity resulting from handling the substance at work." (DFG, 2003).

The SCOEL recommendation on diethyl sulphate summarised the irritation/corrosion potential in humans:

> "According to older publications diethyl sulphate is clearly caustic to the skin, although to a lesser extent that dimethyl sulphate (compiled by DFG 1980)." (Reference cited in SCOEL, 2009).

The New Zealand EPA classifies diethyl sulphate as a 6.1D substance – a substance that is acutely toxic.

Animals

The DFG review of diethyl sulphate summarised the acute toxicity in experimental animals:

> "After administration by most routes in animal studies, diethyl sulfate is less acutely toxic than dimethyl sulfate (Weber 1902, Wachtel 1920, Carpenter and Smyth 1946, Alderson 1964, Druckrey *et al*. 1970); only after intravenous administration are the two substances said to be of equal toxicity (Wachtel 1920)."
>
> "The symptoms of diethyl sulfate intoxication are like those caused by other alkylating substances: 20 minutes after dosing, the animals become apathetic, progressive dyspnoea develops and after several hours pulmonary oedema which is fatal within 10 to 20 hours. In animals which survive longer, haemorrhagic diarrhoea is sometimes observed. The results of the histological examination always include haemorrhagic pulmonary oedema, and severe damage in the intestinal mucosa and often also in the liver (Druckrey *et al*. 1970)." (References cited in DFG, 2003).

The DFG review of diethyl sulphate summarised the irritation/corrosion potential in experimental animals:

> "Diethyl sulfate is also less corrosive than dimethyl sulfate (Weber 1902, Wachtel 1920); this is in accordance with its much slower hydrolysis in water (Wachtel 1920). However, the severity of the corrosive action of diethyl sulfate on the skin cannot be determined definitively from the unclear reports in the early literature (Weber 1902, Wachtel 1920) or from other brief descriptions (Smyth *et al*. 1949, Union Carbide 1971).
>
> "Diethyl sulfate causes necrosis on the dorsal skin of rabbits (Smyth *et al*. 1949) and on the more sensitive abdominal skin erythema and swelling like that seen in mild first degree burns (Union Carbide 1971).
>
> "In the rabbit eye, solutions containing 40% diethyl sulfate and more cause severe corrosion and necrosis; milder effects have been described after application of solutions containing as little as 15% diethyl sulfate (Carpenter and Smyth 1946, Smyth *et al*. 1949)." (References cited in DFG, 2003).

The New Zealand EPA classifies diethyl sulphate as an 8.2C and 8.3A substance – a substance that is corrosive to dermal and occur tissue.

The NICNAS review of sulfuric acid, diethyl ester summarised the sensitisation potential in experimental animals:

> "The chemical at a 10% concentration produced positive results for skin sensitisation in a mouse local lymph node assay (**LLNA**) (Ashby *et al*., 1995 cited in **REACH**). However, considering the corrosive nature of the chemical and possibility of generating false positive results for corrosive chemicals in the LLNA (Basketter & Kimber, 2007), it is not considered appropriate to classify the chemical as a skin sensitiser." (References cited in NICNAS, 2014).

The NICNAS review of sulfuric acid, diethyl ester summarised the reproductive/ developmental toxicity in experimental animals:

> "Groups of adult female mice were treated with the chemical at 150**mg/kg bw**, via a single **i.p.** injection either four days before mating or at one, six, nine or 25 hours after mating with untreated males. Resorptions increased significantly in mice that received the chemical at one, six or nine hours after mating (30%, 24% and 14%, respectively). Mid and late gestational deaths were increased significantly in the mice receiving the chemical one hour after mating (15% and 14%, respectively) and six hours after mating (16% and 21% respectively). The observed effects were reported to be due to 'altered programming of gene expression during embryogenesis' (Generoso *et al*., 1991 cited in IARC, 1999)." (References cited in NICNAS, 2014).

The NICNAS review of sulfuric acid, diethyl ester summarised the genotoxic potential in experimental animals and *in vitro* test systems:

> "As an alkylating agent, the chemical reacts with the RNA and DNA bases of the cell nucleus, causing alkylation of oxygen sites, including the O6-position of guanine 'which is considered to play a special role in the mutagenic and carcinogenic activity' (Hoffman, 1980 cited in MAK, 2012).
>
> "As a result of the alkylation mechanism, the chemical produced positive results in the following *in vitro* assays (**IARC**, 1992; IARC, 1999):
>
> - forward and reverse mutations in bacterial systems (for example, strains of Salmonella typhymurium)
> - unscheduled DNA synthesis (**UDS**) in rat hepatocytes
> - mutations at the hprt locus in Chinese hamster ovary (**CHO**) and V79 lung cells
> - sister chromatid exchange in V79 cells, and
> - micronuclei in cultured human lymphocytes.
>
> "The chemical induced genotoxic effects *in vivo*, including in germ cells (IARC, 1992; IARC, 1999):
>
> - micronucleated erythrocytes in larvae of newts exposed to the chemical
> - DNA fragmentation in brain cells of male rats treated intraperitoneally (i.p.) with the chemical
> - micronuclei in mouse peripheral reticulocytes
> - specific locus mutations in mouse germ-line cells
> - DNA alkylation in mice, producing **N**7-ethylguanine in germ cells, bone marrow and liver

- dominant lethal mutations (chromatid breaks and gaps) in mouse embryonal cells after transplacental treatment, and
- sex-linked recessive lethal mutations in Drosophila melanogaster fed or injected with the chemical." (References cited in NICNAS, 2014).

The New Zealand EPA classifies diethyl sulphate as a 6.6A substance – a substance that is a known or presumed mutagen.

4.2 Cancer

The International Agency for Research on Cancer [IARC] evaluation of diethyl sulphate concluded that:

> There is *inadequate evidence* for the carcinogenicity in humans of diethyl sulphate.
>
> There is *sufficient evidence* for the carcinogenicity of diethyl sulphate in experimental animals.

With an overall evaluation that:

> Diethyl sulphate 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*." (IARC, 1999).

The US National Toxicology Program [NTP] Report on Carcinogens [RoC], Fourteenth Edition concluded that:

> "Diethyl sulfate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals." (NTP RoC, 2016).

The New Zealand EPA classifies diethyl sulphate as a 6.7A substance – a substance that is a known or presumed human carcinogen.

Humans

The SCOEL recommendation on diethyl sulphate summarised the carcinogenicity data in exposed humans:

> "Industrial exposure to diethyl sulphate occurs primarily in ethanol production ("strong-acid process"). One cohort study at an isopropanol 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, 1992).

"A cohort study at two plants producing ethanol and isopropanol in the United States showed non-significant excess risks based on two cancers of the larynx and three buccal cavity and pharynx cancers in strong-acid workers (IARC, 1992). 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 sulphuric acid; the risk persisted even after exclusion of workers in the ethanol and isopropanol units (IARC, 1992).

"An association between estimated exposure to diethyl sulphate 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 (IARC, 1992)." (References cited in SCOEL, 2009).

Animals

The SCOEL recommendation on diethyl sulphate summarised the carcinogenicity data in experimental animals:

"No chronic inhalation studies have been reported. Long-term feeding and injection studies were performed with rats (see Table 1), with the following results:

"After oral application (gavage) of 25 or 50mg/kg BD rats (12 per group), once weekly, over 81 weeks and surveillance of the animals until their natural death there was 1 squamous cell carcinoma of the forestomach in each animal of the treated groups, and in 6 rats there was a (not reported) number of benign papillomas. The authors discussed that diethyl sulphate was quickly hydrolysed in the stomach and had therefore no systemic carcinogenic effect (Druckrey *et al*. 1970).

"After weekly subcutaneous injections of 25 or 50mg/kg to rats (12 per group) for 49 weeks all animals of the higher dose group developed local tumours at the injection site; one animal died from pneumonia. The tumours were sarcomas (spindle-cell, fibrosarcomas, myosarcomas, polymorph-cell sarcomas), and one adenocarcinoma. Six of the 12 rats of the lower dose group contracted local fibrosarcomas (3), spindle-cell sarcomas (2), or myosarcoma (1) (Druckrey *et al*. 1970).

"After a single sub-cutaneous dose of 50mg/kg diethyl sulphate to BD rats 17 out of 24 animals developed local tumours. The observation time was not noted, nor was there mentioning of control group(s).

"The transplacental carcinogenicity of diethyl sulphate was also studied in preliminary form by Druckrey *et al*. (1970). Three pregnant rats received 85mg/kg **i.v.** (about 1/4 LD-50) at the 15th gestational day. Thirty offspring animals were raised until their natural death. Malformations were not found, but 2 animals developed malignant tumours of the CNS (neurinomas). The mother animals later developed multiple mammary carcinomas (also reported in: Druckrey 1973).

"Although there are only older publications that do not match modern experimental standards, a strong carcinogenic activity of diethyl sulphate is evident (IARC 1974, 1992; DFG 1980, 2000).

> "Similar results had been obtained by the same group with the analogous compound, dimethyl sulphate (Druckrey *et al*. 1966, 1970; see DFG 1985). Hence, diethyl and dimethyl sulphate appear comparable regarding both their mode of carcinogenic action and their carcinogenic activity." (References cited in SCOEL, 2009).

4.3 Absorption, distribution, metabolism and excretion

The SCOEL recommendation on diethyl sulphate summarised the **ADME**:

> "The metabolism of diethyl sulphate has been studied in rats (**s.c.**, i.p., oral administration; Kaye 1974). The metabolism proceeds via conjugation to glutathione; the urinary excretion product is ethyl mercapturic acid. Owing to its alkylating properties diethyl sulphate reacts with DNA, primarily at N7 of guanine, and to minor extents at several positions of adenine and cytosine (DFG 1980).
>
> "Based on the structural similarity to dimethyl sulphate (SCOEL/SUM/111) a skin absorption of diethyl sulphate appears likely, although experimental or human data are not available." (References cited in SCOEL, 2009).

The DFG review of diethyl sulphate summarised the mechanistic data for carcinogenesis:

> "The development of local tumours after subcutaneous injection and forestomach tumours after oral administration to rats was to be expected because diethyl sulfate is highly reactive. However, the development of neurinomas in rats exposed prenatally by subcutaneous injection into the dams demonstrates that diethyl sulfate can also have systemic effects.
>
> "In biochemical studies it was demonstrated that diethyl sulfate reacts with RNA and DNA bases, predominantly with the **N**-7 of guanine but also with the N-1, N-3 and N-7 of adenine and the N-1 and N-3 of cytosine (Singer and Fraenkel-Conrat 1975, Sun and Singer 1975, Singer 1977; see also Loveless 1966, Lawley and Brookes 1963). Diethyl sulfate also reacts with all nucleophilic centres of uracil (Kusmierek and Singer 1976).
>
> "In addition, as well as all the other oxygen atoms in nuclein bases, diethyl sulfate ethylates the **O**-6 of guanine which is considered to play a special role in the mutagenic and carcinogenic activity of alkylating substances (Singer and Fraenkel-Conrat 1975, Singer 1977)." (DFG, 2003).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows diethyl sulphate exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2019).

JURISDICTION OR ADVISORY BODY	8-HOUR LIMIT VALUE		SHORT-TERM LIMIT VALUE	
	ppm	mg/m³	ppm	mg/m³
Austria[1]	0.03	0.2	0.12	0.8
Hungary				0.2
Ireland	0.05			
New Zealand	0.05	0.32		
Switzerland	0.03	0.2		
UK	0.05	0.32		

TABLE 3: Exposure standards for diethyl sulphate from around the world

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on diethyl sulphate were SCOEL and DFG.

5.2 SCOEL

The Scientific Committee on Occupational Exposure Limits [SCOEL] review of diethyl sulphate concluded that:

> "It is recommended that dimethyl sulphate and diethyl sulphate should be regulated and controlled in a similar way. Based on its very clearcut genotoxic and alkylating potency, the compound is assigned to the SCOEL carcinogen group A (non-threshold carcinogen; Bolt and Huici-Montagud 2008). A health-based **OEL** cannot be derived.
>
> "As for dimethyl sulphate, occupational exposures to diethyl sulphate should strictly be minimised, taking every possible technical precaution." (Reference cited in SCOEL, 2009).

The rationale for their conclusions was:

> "Diethyl sulphate is a strong alkylating agent. It is clearly directly mutagenic in virtually all test systems examined. It has been 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 sulphate, 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, 1992). Hence, the compound is carcinogenic locally and systemically.
>
> "Inhalation carcinogenicity studies have not been performed. However, the available carcinogenicity data are generally comparable to those obtained with the structural analogue, dimethyl sulphate, for which long-term inhalation exposure conditions for rats at 0.5ppm (6h, twice per week) were clearly carcinogenic (see SCOEL/SUM/111)."

[1] **TRK** value [based on technical feasibility].

> "By analogy to dimethyl sulphate, a "skin notation" is applied.
>
> "No data are reported on biological monitoring of diethyl sulphate. By analogy to dimethyl sulphate (see SCOEL/SUM/111) it appears plausible that the haemoglobin adduct (N-ethylvaline at the N-terminus of haemoglobin) could be a useful parameter, which should be employed in occupation al field studies." (References cited in SCOEL, 2009).

5.3 DFG

The Deutsche Forschungsgemeinschaft [DFG, German Research Foundation] review of diethyl sulfate concluded that diethyl sulfate is considered to be clearly carcinogenic in experimental animals, and therefore it is not possible to establish a MAK value (DFG, 2003).

The rationale for their conclusions was:

> "In rats, the only species tested to date, diethyl sulfate causes malignant tumours at the injection site after subcutaneous injection, in the stomach after administration by gavage, and neurinomas after transplacental exposure. Long-term feeding studies did not yield clearly positive results presumably because of inactivation of the substance before it came into contact with sensitive structures. Long-term inhalation studies and effects in man have not been described. However, numerous positive results of mutagenicity tests in various systems have been published."
>
> "Especially the results of the dominant lethal test and the specific locus test (Ehling und Neuhäuser-Klaus 1988) demonstrate that diethyl sulfate increases the mutation rate in the progeny of exposed mammals. That diethyl sulfate has systemic activity has also been demonstrated by the induction of neurinomas after prenatal exposure of rats by subcutaneous injection of the substance into the dams. Therefore diethyl sulfate is classified in Germ cell mutagen category 2." (DFG, 2003).

5.4 DECOS

For dimethyl sulphate, the Dutch Expert Committee on Occupational Standards (DECOS) of the Health Council of the Netherlands calculated, based on animal data, that occupational exposure to dimethyl sulphate at 0.29µg/m^3 (0.00006ppm) corresponded to the acceptable risk level of 4 extra cancer cases per 100,000 occupationally exposed people [8 hours/day; 5 days/per week; 40 years working life], and concentrations of 29µg/m^3 (0.006ppm) corresponded to the **tolerable risk** level of 4 extra cancer cases per 1,000 exposed workers (DECOS, 2014).

5.5 ECB

For dimethyl sulphate, the European Chemicals Bureau (ECB) – an agency of the European Union and predecessor of the ECHA – calculated that occupational exposure to dimethyl sulphate at 0.09µg/m^3 (0.00002ppm) corresponded to the risk level of 4 extra cancer cases per 100,000 occupationally exposed workers [8 hours/day; 240 days/year; 45 years working life], and concentrations of 9µg/m^3 (0.002ppm) corresponded to the risk level of 4 extra cancer cases per 1,000 exposed workers (ECB, 2002).

5.6 Safe Work Australia

Safe Work Australia have not proposed an exposure standard due to insufficient data to derive a concentration.

In their review, they say, “Evidence in animals and humans suggest that carcinogenicity may be due to a mutagenic mode of action. However, insufficient data exists to recommend a suitable TWA.” (Safe Work Australia, 2019).

6.0 Analytical methods for the assessment of airborne diethyl sulphate

A common method to measure diethyl sulphate exposure is using **HSE MDHS** 89 (HSE, 1998).

Using this method an air sample is collected onto a sampling train consisting of a sorbent tube containing 200mg of Tenax TA, with the sampling train set at a flow rate of 0.2 litres per minute. Following desorption of the analyte, the sample is analysed using gas chromatography with mass spectrometry.

A modification of this method, available in New Zealand, can achieve a detection limit of 0.01ppm per sample. It is acknowledged that this could not quantify samples at airborne concentrations below 0.01ppm [0.06mg/m^3], which is the proposed 8-hour TWA.

7.0
Discussion

WorkSafe's WES for diethyl sulphate has been unchanged since adoption in 2001.

The toxicological database reviewed above indicates diethyl sulphate is locally toxic to humans, causing skin, eye and respiratory tract irritation/corrosion; and locally and systematically toxic to laboratory species causing skin, eye and respiratory tract irritation/corrosion, and malignant tumours in rats after adult or prenatal exposure.

Based on the aforementioned documentation, informed by the conclusions of the SCOEL and DFG reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 0.05ppm [0.32mg/m^3] for inhalable fraction of diethyl sulphate to be inadequate to manage health risks from possible workplace exposure:

- Diethyl sulphate induced a high incidence of malignant tumours at the injection site in rats after subcutaneous injection, and forestomach tumours after oral administration. In addition, diethyl sulphate induced a low incidence of malignant tumours of the nervous system [neurinomas] in rats exposed *in utero* (SCOEL, 2009).
- Diethyl sulphate is a strong alkylating agent and reported as a direct-acting mutagen in almost all *in vitro* and *in vivo* studies (SCOEL, 2009; DFG, 2003).
- The mechanism(s) by which diethyl sulphate induces cancer appear to be stochastic genotoxic reactions with DNA, notably the ethylation of the O–6 of guanine and N-7 of guanine (DFG, 2003).
- Neither SCOEL nor DFG review proposed OELs or tolerable cancer risk estimates for workplace exposures to diethyl sulphate, because of the established genotoxicity, which precluded a threshold OEL, and the lack of robust data to calculate a cancer risk.
- The SCOEL and DFG reviews noted the parallels in toxicity profiles between diethyl sulphate and dimethyl sulphate, an IARC classified Group 2A carcinogen (SCOEL, 2009; DFG, 2003; IARC, 1999).
- For dimethyl sulphate, DECOS calculated, based on animal data, that occupational exposure to dimethyl sulphate at 0.29µg/m^3 (0.00006ppm) corresponded to the **acceptable risk** level of 4 extra cancer cases per 100,000 occupationally exposed people, and concentrations of 29µg/m^3 (0.006ppm) corresponded to the **tolerable risk** level of 4 extra cancer cases per 1,000 exposed workers (DECOS, 2014).
- For dimethyl sulphate, ECB calculated that occupational exposure to dimethyl sulphate at 0.09µg/m^3 (0.00002ppm) corresponded to the risk level of 4 extra cancer cases per 100,000 occupationally exposed workers, and concentrations of 9µg/m^3 (0.002ppm) corresponded to the risk level of 4 extra cancer cases per 1,000 exposed workers (ECB, 2002).

- The proposed WES-TWA of 0.01ppm [0.06mg/m^3] for diethyl sulphate is set to be protective against all non-carcinogenic endpoints, but due to the lack of specific data for diethyl sulphate may not be fully protective against cancer risks.
- A *skin* notation is justified for diethyl sulphate, based on the cross-reference to dimethyl sulphate that can cause systemic toxicity after dermal absorption which was considered potentially to be the primary route of occupational exposure (SCOEL, 2004).
- Available information indicates that diethyl sulphate is not a sensitiser, so a *sen* notation is not warranted.

8.0 Recommendations

WorkSafe considers its current WES-TWA of 0.05ppm [0.32mg/m^3] for inhalable fraction of diethyl sulphate to be inadequate to protect workers exposed in the workplace.

It is proposed that WorkSafe:

1. adopt a WES-TWA for diethyl sulphate of 0.01ppm [0.06mg/m^3] [inhalable fraction]
2. retain the *skin notation* for diethyl sulphate.

Noting that the proposed WES-TWA of 0.01ppm for diethyl sulphate may not eliminate all risk, due to lack of data on the extent of genotoxic and carcinogenic potential of diethyl sulphate and the impact of dermal absorption, so exposures should be minimised.

It is acknowledged that currently there are no available analytical methods that would allow determination of airborne levels of diethyl sulphate at the proposed WES-TWA. WorkSafe recommends substituting alternative substances so far as is reasonably practicable.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
95%CI/ CI95%	95% Confidence Interval.
Acceptable [cancer] risk	EU criterion: 4 extra cases in a population of 10,000 until 2013; 4 extra cases in a population of 100,000 after 2013 [see Tolerable risk].
ADME	Absorption, Distribution, Metabolism and Excretion.
CHO	Chinese hamster ovary.
CI	Confidence Interval.
DECOS	Dutch Expert Committee on Occupational Standards - a Committee [DECOS] of the Health Council of the Netherlands. The latter was established in 1902 as an independent scientific advisory body with a remit: "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance.
DNA	Deoxyribonucleic acid.
ECB	European Chemicals Bureau – an agency of the European Union and predecessor of the ECHA.
EPA	The New Zealand Environmental Protection Authority.
HSE	Health and Safety Executive, UK.
HSNO	Hazardous Substances and New Organisms Act 1996, New Zealand.
IARC	The International Agency for Research on Cancer – an agency of the World Health Organisation.
IFA	Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung [Institute for Occupational Safety and Health of the German Social Accident Insurance].
Inhalable fraction	Inhalable particulate fraction is that fraction of dust that can be breathed into the nose or mouth. Particulate size: mostly <100µm, 50% cut point. For sampling purposes the inhalable dust is to be collected according to the method set out in AS 3640-2009: Workplace Atmospheres – Method for Sampling and Gravimetric Determination of Inhalable Dust (Standards Australia, 2009b). (*cf.* Respirable fraction) (Also referred to as: inhalable aerosol; inhalable particulate matter)
i.p.	Intraperitoneal.
i.v.	Intravenous.
LLNA	Local lymph node assays.
MAK	Maximale Arbeitsplatz-Konzentration, (maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (for example, by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. A value set by the DFG.
MDHS	Methods for the Determination of Hazardous Substances. Laboratory methods produced by the HSE's Health and Safety Laboratory.
µg/m^3	Micrograms of substance per cubic metre of air.
mg	Milligram or one thousandth of a gram.
mg/kg	Milligrams per kilogram.
mg/kg b.w. or mg/kg bw	Milligram of substance per kilogram body weight.
mg/m^3	Milligrams of substance per cubic metre of air.

TERM	MEANING
N	Nitrogen [Number suffixes indicate position in associated molecule].
NICNAS	National Industrial Chemicals Notification and Assessment Scheme is the Australian government's regulatory body for industrial chemicals.
NOAEL	No Observed Adverse Effect Level.
NTP	National Toxicology Program, US Department of Health and Human Services.
O	Oxygen [Number suffixes indicate position in associated molecule].
OEL	Occupational Exposure Limit (equivalent to a WES).
ppm	Parts of vapour or gas per million parts of air.
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals. An EU program and regulation.
RNA	Ribonucleic Acid.
RoC	Report on carcinogens.
s.c.	Subcutaneous.
SCOEL	The Scientific Committee on Occupational Exposure Limits is a committee of the European Commission, established in 1995 to advise on occupational health limits for chemicals in the workplace within the framework of Directive 98/24/EC, the chemical agents directive, and Directive 90/394/EEC, the carcinogens at work directive.
sen	A substance that can 'sensitise' the respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
skin	Skin absorption – applicable to a substance that is capable of being significantly absorbed into the body through contact with the skin. A WorkSafe term.
SMR	Standardised Mortality Ratio is a measure of the strength or association between exposure and mortality; a form of Relative Risk (RR) in which the outcome is death. The SMR is the ratio of the number of deaths (due to a given disease arising from exposure to a specific risk factor) that occurs within the study population to the number of deaths that would be expected if the study population had the same rate of mortality as the general population (the standard). By convention, the figure is usually multiplied by 100 [an SMR of 200 corresponds to a RR of 2.0]. A *value greater than 100/1.0 indicates a positive association between exposure and disease*. (This may be causal, or have other explanations, such as bias, chance or confounding). (WHEC, 2017).
Tolerable [cancer] risk	EU criterion: 4 extra cases in a population of 1,000 [see Acceptable risk].
TRK	Technische Richtkonzentration [technical guidance concentration level].
UDS	Unscheduled DNA Synthesis.
WES	Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A WorkSafe term.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A WorkSafe term.

Appendix 2: HSNO health-related hazardous substance classifications

This is the full list of all health-related hazardous substances classifications that are listed by the NZ EPA, including those that apply to this substance.

CLASSIFICATION CODE	MEANING
Acutely toxic	
6.1A	Substances that are acutely toxic – Fatal
6.1B	Substances that are acutely toxic – Fatal
6.1C	Substances that are acutely toxic – Toxic
6.1D	Substances that are acutely toxic – Harmful
6.1E	Substances that are acutely toxic – May be harmful, aspiration hazard
Skin irritant	
6.3A	Substances that are irritating to the skin
6.3B	Substances that are mildly irritating to the skin
Eye irritant	
6.4A	Substances that are irritating to the eye
Sensitisation	
6.5A	Substances that are respiratory sensitisers
6.5B	Substances that are contact sensitisers
Mutagens	
6.6A	Substances that are known or presumed human mutagens
6.6B	Substances that are suspected human mutagens
Carcinogens	
6.7A	Substances that are known or presumed human carcinogens
6.7B	Substances that are suspected human carcinogens
Reproductive/developmental toxicants	
6.8A	Substances that are known or presumed human reproductive or developmental toxicants
6.8B	Substances that are suspected human reproductive or developmental toxicants
6.8C	Substances that produce toxic human reproductive or developmental effects on or via lactation
Target organ toxicants	
6.9A	Substances that are toxic to human target organs or systems
6.9B	Substances that are harmful to human target organs or systems
Skin corrosive	
8.2A	Substances that are corrosive to dermal tissue (UN PGI)
8.2B	Substances that are corrosive to dermal tissue (UN PGII)
8.2C	Substances that are corrosive to dermal tissue (UN PGIII)
Eye corrosive	
8.3A	Substances that are corrosive to ocular tissue

Source: www.epa.govt.nz/industry-areas/hazardous-substances/rules-for-hazardous-substances/hazardous-substances-classification-codes

Appendix 3: References

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Notes

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