
Diethylsulphate

Health based calculated occupational cancer risk values

Aanbiedingsbrief



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Health based calculated occupational cancer risk values

Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of the Netherlands

to

the Minister and State Secretary of Social Affairs and Employment

No. 1999/08OSH, The Hague, 20 December 1999

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Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid schat de Commissie WGD van de Gezondheidsraad het extra kankerrisico bij beroepsmatige blootstelling aan stoffen die door de Europese Unie of door de Commissie WGD als genotoxisch kankerverwekkend zijn aangemerkt. In dit rapport bekijkt zij of zo'n schatting mogelijk is voor diethylsulfaat. Zij heeft daarbij gebruik gemaakt van de methode die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06WGD) (Hea95).

De commissie is echter van mening dat wegens een gebrek aan voldoende gegevens het niet mogelijk is om het extra kankerrisico voor diethylsulfaat te berekenen.

Executive summary

On request of the Minister of Social Affairs and Employment the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, estimates the additional cancer risk associated with occupational exposure to substances that have been classified by the European Union or the DECOS as genotoxic carcinogen. In this report the committee studies if such estimates can be calculated for diethylsulphate. It has used the method described in the report 'Calculating cancer risks due to occupational exposure to genotoxic carcinogens' (1995/06WGD) (Hea95).

The committee is of the opinion that due to a lack of sufficient data, it is not possible to estimate the additional cancer risk for diethylsulphate.

Scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, on request of the Minister of Social Affairs and Employment (annex A). This evaluation should lead to a health-based recommended exposure limit for the concentration of the substance in air. Such an exposure limit cannot be derived if the toxic action cannot be evaluated using a threshold model, as is the case for substances with genotoxic carcinogenic properties.

In this case an exposure-response relationship is recommended for use in regulatory standard setting, ie. the calculation of so-called health-based calculated occupational cancer risk values (HBC-OCRVs). The committee calculates HBC-OCRVs for compounds which are classified as genotoxic carcinogens by the European Union or by the present committee.

For the establishment of the HBC-OCRV's the committee generally uses a linear extrapolation method, as described in the committee's report 'Calculating cancer risk due to occupational exposure to genotoxic carcinogens' (1995/06WGD). The linear model to calculate occupational cancer risk is used as a default method, unless scientific data would indicate that using this model is not appropriate.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister of Social Affairs and Employment on the feasibility of using the

HBC-OCRVs as regulatory occupational exposure limits. In the final step of the procedure the Minister sets the official occupational exposure limits.

1.2 Committee and procedure

The present document contains the derivation of HBC-OCRVs by the committee for diethylsulphate. The members of the committee are listed in Annex B. The first draft of this report was prepared by H Stouten and MI Willems, from the TNO Nutrition and Food Research Institute in Zeist, by contract with the Ministry of Social Affairs and Employment.

Diethylsulphate

2.1 Introduction

Diethyl ether has been classified as a genotoxic carcinogen by DECOS (WGD90).

This evaluation of the carcinogenicity and other toxic effects of diethylsulphate has been based on the reviews by the Commission of the European Communities (CEC) (Ber89), the Dutch Expert Committee on Occupational Standards (WGD90), the Deutsche Forschungsgemeinschaft (DFG; Gre95), the UK Health and Safety Executive (HSE; Car96) and IARC (IARC92). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature has been retrieved from the online data bases Chemical Abstracts, Toxline, and Medline, covering the period 1965-1966 to December 1995/ January 1996.

2.2 Identity and physical and chemical properties*

Chemical name	:	diethylsulphate
CAS registry number	:	64-67-5
CAS name	:	sulfuric acid, diethyl ester
EEC number	:	016-027-00-6
EINECS	:	200-589-6
Synonyms	:	diethyl sulfate, diethyl monosulphate, ethyl sulphate, ethyl sulfate, diethyl tetraoxosulfate
Description	:	colourless oily liquid, with a faint peppermint odour
Molecular formula	:	$(C_2H_5)_2SO_4$
Structure	:	
Molecular weight	:	154.19
Boiling point (101.3 kPa)	:	208-209.5 °C (decomposes at temperatures > 100 °C)
Melting point	:	-25 °C
Relative density (25 °C/4 °C)	:	1.2
Vapour pressure (20 °C)	:	25 Pa
Relative density of saturated vapour/air mixture (air=1; 20 °C)	:	1.0
Saturated vapour concentration	:	247 ppm ^a
Relative vapour density (air=1)	:	5.3
Flashpoint	:	104 °C
Solubility in water	:	0.7 g/100 ml at 20 °C; hydrolyses slowly at 25 °C; reacts rapidly at temperatures > 50 °C
Solubility in organic solvents	:	miscible with ethanol and diethyl ether
Log P _{oct/w}	:	1.14 (experimental)
Conversion factors (20 °C, 101.3 kPa)	:	1 ppm = 6.41 mg/m ³ air 1 mg/m ³ = 0.16 ppm
EEC labeling	:	R: 45-46-20/21/22-34 S: 53-45
EEC classification	:	Carc cat 2; R 45; mut cat 2; R 46 Xn; R 20/21/22; C; R 34

^a Calculated using the equation: vol% = (100* p)/1013, p = vapour pressure in mbar at 20 °C, and 1 vol% = 10.000 ppm

* data from IARC92, NLM95, Stu95

2.3 Carcinogenicity studies and selection of study suitable for risk estimation in the occupational situation

CEC, HSE, and IARC concluded from the available epidemiological literature that the evidence for the carcinogenicity of diethylsulphate to humans was insufficient (Ber89; Car96; IARC92).

Animal carcinogenicity data are summarized in Table 1 (Annex D). There were no carcinogenicity inhalation studies. The studies available showed the carcinogenic properties of diethylsulphate. However, only local and no systemic tumours were induced. These studies are considered inappropriate for a quantitative extrapolation to a health-based occupational lifetime cancer risk value for inhalation exposure. The committee is of the opinion that due to a lack of sufficient data, it is not possible to estimate the additional lifetime cancer risk for diethylsulphate.

2.4 Existing occupational exposure limits

No occupational exposure limits are listed for diethylsulphate in The Netherlands, Germany, Sweden, Denmark, or the USA (ISZW99, DFG99, NBO93, Arb96, Hun97, ACG99). In Germany, diethylsulphate has been classified as a category A2 carcinogen. Category A carcinogens are not assigned a health-based occupational exposure limit, but a so called TRK-value (TRK = Technische Richtkonzentration), a concentration feasible with currently available technical means, in this case 0.2 mg/m³ (0.03 ppm) (DFG99). In Sweden, diethylsulphate has been classified as a Class B carcinogen (NBO93). In the UK, diethylsulphate is listed as carcinogen for the purpose of the COSHH regulations 1999. The maximum exposure limit (MEL) for diethylsulphate has been set at 0.32 mg/m³ (0.05 ppm) (HSE99).

2.5 Toxicity profile

According to the European classification/labelling, diethylsulphate is a corrosive compound that can cause skin burns. It is harmful following inhalation, oral, and dermal exposure (CEG93). The LD₅₀s are 350-1000 mg/kg bw by oral administration in rats, 350 mg/kg bw by sc injection in rats, 150 mg/kg bw by ip injection in mice, and 600 mg/kg bw by dermal administration in rabbits (IARC92). When rats were exposed to saturated vapours (i.e., ~250 ppm at 20 °C) for two hours, no mortality was observed. Inhalation of 250 ppm for 24 hours caused 0/6 deaths in rats, while 6/6 deaths occurred following exposure to 500 ppm for four hours (NLM95). No other toxicity data were available.

The Hague, 20 December 1999,
for the committee

dr ASAM van der Burght,
scientific secretary

A handwritten signature in black ink, consisting of a large, stylized initial 'G' followed by a horizontal line and a shorter vertical stroke.

Prof. dr GJ Mulder,
chairman

References

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- Hea95 Health Council of the Netherlands, Dutch Expert Committee on Occupational Standards (DECOS). Calculating cancer risks, THE HAGUE, The Netherlands. 1995; pub no 1995/06 WGD.
- HSE99 Health and Safety Executive (HSE). Occupational exposure limits 1999. Sudbury (Suffolk), UK: HSE Books, 1999.
- Hun97 Hunter WJ, Aresini G, Haigh R *et al.* Occupational exposure limits for chemicals in de European Union. *Occup. Environ. Med.*, 1997; 54:217-22.
- IARC92 International Agency for Research and Cancer (IARC). Diethyl sulfate. In: Occupational exposures to mists and vapours from strong inorganic acids; and other industrial chemicals. Lyon, France: IARC, 1979: 429-48 (IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans; Vol 54).
- ISZW99 Inspectiedienst van het Ministerie van Sociale Zaken en Werkgelegenheid (I-SZW). De nationale MAC-lijst 1999. The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1999.
- NBO93 National Board of Occupational Safety and Health (NBOSH). Occupational exposure limits. Solna, Sweden: NBOSH, 1993: 74 (Ordinance AFS 1993/9).
- NIO95 National Institute of Occupational Safety and Health (NIOSH). Registry of Toxic Effects of Chemical Substances (RTECS). SilverPlatter International NV, 1995; CD-Rom, May 1995.
- NLM95 US National Library of Medicine (NLM). Hazardous Substances Data Bank (HSDB). SilverPlatter International NV, 1995; CD-Rom, May 1995.
- Ric92 Richardson ML, Gangolli S, ed. D292. Diethyl sulfate. In: The dictionary of substances and their effects. Cambridge, UK: Royal Society of Chemistry, 1993: 442-3 (Vol 3).
- Stu95 Studiegroep Chemiekaarten, eds. Diethylsulfaat In: Chemiekaarten: gegevens voor het veilig werken met chemicaliën. 11th ed. Alphen a/d Rijn, The Netherlands: Samson HD Tjeenk Willink bv, 1995: 322.
- WGD90 Werkgroep van Deskundigen (WGD). Rapport inzake grenswaarde dimethyl- en diethylsulfaat. The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1990; rep no RA 12/90.
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- A Request for advice
 - B The committee
 - C Comments in the public draft
 - D Animal studies

Annexes

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advise the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in
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the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

The Committee

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- GJ Mulder, *chairman*
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 - PJ Borm
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The first draft of the present advisory report was prepared by H Stouten and M Willems, from the Department of Occupational Toxicology of the TNO Nutrition and Food Research Institute, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: E Vandenbussche-Parméus.

Lay-out: J van Kan.

Comments on the public draft

A draft of the present report was released in 1999 for public review. No organizations and persons have commented on the draft document:

Animal Studies

See next page.

Table 1 Carcinogenicity studies with diethylsulphate (data from IARC92; WGD90, unless otherwise noted).

authors (ref)	species/route	experimental	findings, tumours	remark
Druckrey <i>et al</i> , 1970	rat (BD; n=12/group) gavage	25, 50 mg/kg bw/d once/week, 81 w	one forestomach squamous cell carcinoma in each dose group; forestomach papillomas in 6/24 (distribution by group not specified)	purity: ?; vehicle: arachis oil sex unspecified; no concurrent control group total dose: 1.9, 3.7 g/kg bw animals observed until death; time of death not specified
Druckrey <i>et al</i> , 1970	rat (BD; n=12/group subcutaneous	25, 50 mg/kg bw/d once/week, 49 w	low dose: local tumours at injection site in 6/12 (3 fibrosarcomas, 2 spindle cell sarcomas, 1 myosarcoma); high dose: idem in 6/11 (3 fibrosarcomas, 3 spindle cell sarcomas, 3 myosarcomas, 1 polymorphocellular sarcoma, 1 glandular carcinoma of unknown origin), two cases of lung metastasis; no such tumours in vehicle-treated historical controls	purity: ?; vehicel: arachis oil sex unspecified; no concurrent control group total dose: 0.8, 1.6 mg/kg bw animals observed until death (295-685 d); mean survival time: low dose: 415 d; high dose: 350 d
Druckrey <i>et al</i> , 1970	rat (BD, pregnant female; n=3) subcutaneous	85 mg/kg bw/d single at gestational day 15	malignant nervous system tumours in 2/30 of the offspring (1 of the cauda equina, 1 of the lumbal nerve); no such tumours found in untreated historical controls	purity: ?; vehicle: arachis oil ? sex of offspring not specified; no concurrent control group offspring observed until death (not specified)
Carnegie- Mellon Institute of Research, 1979 (NIO95)	mouse (C3H/HeJ, male, n=40/ group) dermal	0, 7.4 mg/mouse 3 times/week, for life	malignant skin neoplasms in 21/40; total cancer incidence: 87.5% (median latent periods of appearance: 15.7, 16.2 for neoplasms and cancer, resp) ; no skin tumours in vehicle control group	abstract of unpublished report submitted to USEPA purity: ?; vehicle: acetone all treated mice dead after 23 mo