Health Council of the Netherlands

Dimethyl sulphate

Health-based calculated occupational cancer risk values

2014/27

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Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies *Dimethyl sulphate*
Uw kenmerk : DGV/BMO U-932542
Ons kenmerk : U-8223/BvdV/459-P70
Bijlagen : 1
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Geachte minister,

Graag bied ik u hierbij aan het advies over de gevolgen van beroepsmatige blootstelling aan dimethylsulfaat.

Dit advies maakt deel uit van een uitgebreide reeks, waarin concentratieniveaus in lucht worden afgeleid die samenhangen met een extra kans op (overlijden aan) kanker van 4 per 1.000 en 4 per 100.000 door beroepsmatige blootstelling. De conclusies van het genoemde advies zijn opgesteld door de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en omgeving.

In dit advies concludeert de commissie dat dimethylsulfaat een carcinogene stof is en beveelt aan om deze stof te classificeren in categorie 1B (de stof moet beschouwd worden als kankerverwekkend voor de mens). De commissie is echter van mening dat wegens gebrek aan adequate humane en dierexperimentele gegevens het niet mogelijk is om de extra kans op kanker na blootstelling aan dimethylsulfaat te berekenen.

Ik heb dit advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. J.L. Severens,
vicevoorzitter

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

to:

the Minister of Social Affairs and Employment

No. 2014/27, The Hague, November 3, 2014

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “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).

The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and the Environment, Social Affairs and Employment, Economic Affairs, and Education, Culture and Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

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Contents

Samenvatting

Op verzoek van de Minister van Sociale zaken en Werkgelegenheid, schat de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad, de concentraties van een stof in de lucht die overeenkomen met een vooraf vastgesteld extra risico op kanker (4 per 1.000 en 4 per 100.000 individuen) door beroepsmatige blootstelling gedurende het arbeidzame leven. Het gaat om kankerverwekkende stoffen die door de Gezondheidsraad of de Europese Unie geclassificeerd zijn in categorie 1A of 1B en die kankerverwekkend zijn via een stochastisch genotoxisch mechanisme. Voor de schatting maakt de commissie gebruik van de *Leidraad Berekening risicogetallen voor carcinogene stoffen* van de Gezondheidsraad.[1] In dit advies onderzoekt de commissie de mogelijkheid om zo'n schatting te maken voor dimethylsulfaat. Dimethylsulfaat wordt gebruikt als methylerende stof bij de productie van kleurstoffen, parfums, geneesmiddelen, voor de scheiding van minerale oliën, en voor de analyse van motoroliën. Ook de sulfaterende eigenschappen worden toegepast in de productie van verschillende producten (bv. kleurstoffen en textielverzachters).

De commissie concludeert dat dimethylsulfaat een carcinogene stof is met een stochastisch genotoxisch werkingsmechanisme. De commissie beveelt aan om deze stof onder te brengen in categorie 1B (*stof moet beschouwd worden als kankerverwekkend voor de mens*).

De commissie is echter van mening dat wegens gebrek aan adequate humane en dierexperimentele gegevens het niet mogelijk is om de extra kans op kanker na blootstelling aan dimethyl sulfaat exact te berekenen.

Executive summary

At the request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, derives so-called health-based calculated - occupational cancer risk values (HBC-OCRVs) associated with excess cancer risk levels of 4 per 1,000 and 4 per 100,000 as a result of working life exposure to substances. It concerns substances which are classified by the Health Council or the European Union in category 1A or 1B, and which are considered stochastic genotoxic carcinogens. For the estimation, the Committee uses the *Guideline for the calculation of occupational cancer risk values* of the Health Council.[1] In this report the Committee evaluates the possibility to establish such estimates for dimethyl sulphate. Dimethyl sulphate is used as a methylating agent in the manufacturing of dyes, perfumes, pharmaceuticals, for the separation of mineral oils, and for the analysis of automobile fluids. Also its sulphating properties are applied in the manufacturing of various products (e.g. dyes and fabric softeners, etc.).

In this report, the Committee concludes that dimethyl sulphate is a carcinogenic substance with a stochastic genotoxic mechanism. The Committee recommends dimethyl sulphate to be classified in category 1B *(substance presumed to be carcinogenic to humans*).

The Committee is further of the opinion that due to a lack of adequate human and animal data, it is not possible to exactly establish the health-based calculated occupational cancer risk values for dimethyl sulphate.

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for genotoxic 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 Safety (DECOS), a Committee of the Health Council of the Netherlands, at request of the Minister of Social Affairs and Employment (Annex A). This evaluation should lead, for genotoxic substances with a non stochastic mechanism, to a health-based recommended occupational exposure limit for the concentration of the substance in air. Such an exposure limit cannot be derived if the toxic action can not be evaluated using a threshold model, as is the case for substances with stochastic genotoxic carcinogenic properties. In that case, an exposure-response relationship is recommended for use in regulatory standard setting, i.e. 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 stochastic genotoxic carcinogens by the European Union or by the Committee.

For the establishment of the HBC-OCRV's, the Committee generally uses a linear extrapolation method, as described in the Committee's reports *Calculating cancer risk* and *Guideline for the calculation of occupational cancer risk values*.[1,2] 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 determines the official occupational exposure limits.

1.2 Committee and procedure

The present document contains the evaluation of the DECOS, hereafter called the Committee. The members of the Committee are listed in Annex B. The Committee requested the DECOS Subcommittee on the Classification of Carcinogenic Substances to evaluate the genotoxic mechanism of dimethyl sulphate (see Annex F and G). The recommendations of the Subcommittee were used by DECOS to decide on the appropriate approach to risk assessment. The submission letter (in English) to the Minister can be found in Annex C. In April 2014, the president of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex D. The Committee has taken these comments into account in deciding on the final version of the advisory report. The received comments, and the replies by the Committee, can be found on the website of the Health Council.

1.3 Data

The Committee's recommendation has been based on scientific data, which are publicly available. Data were obtained from the online databases Chemical Abstracts, XToxline, and Medline, using 'carcinogen', 'cancer', 'tumour' or 'neoplast' and CAS registry number as keywords. In addition, in preparing this report reviews by IARC[3], European Union[4] and the Dutch Expert Committee on Occupational Standards (DECOS)[5] were consulted. The last search was performed in September 2014.

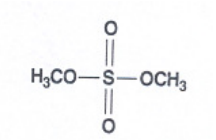
Chapter 2

Identity, toxicity profile and classification

2.1 Identity and physical and chemical properties

Dimethyl sulphate is mainly used as a methylating agent in the manufacturing of dyes, perfumes, pharmaceuticals, for the separation of mineral oils, and for the analysis of automobile fluids. Also its sulphating properties are applied in the manufacturing of various products (e.g. dyes and fabric softeners, etc.). Formerly, dimethyl sulphate was used as a war gas.[6]

The identity and some physicochemical properties of dimethyl sulphate are given below.[4,7]

Chemical name	:	dimethyl sulphate
CAS registry number	:	77-78-1
EC number	:	201-058-1
RTECS number	:	WS8225000[7]
IUPAC name	:	dimethyl sulphate
Synonyms	:	dimethyl monosulphate, DMS, methyl sulphate, sulphuric acid dimethyl ester
Molecular formula	:	$C_2H_6O_4S$
Physical description and colour	:	clear colourless, oily liquid with a very ‘faint’ or no odour
Structure	:	

Molar mass	:	126.13 g/mol
Melting point	:	approximately -32 °C
Boiling point	:	188 °C (with decomposition) at 100 kPa
Relative density (air = 1)	:	1.33 at 20 °C
Solubility in water	:	28 g/L at 20 °C
Solubility in organic solvents	:	Miscible with many polar organic solvents and aromatic hydrocarbons but sparingly soluble in carbon disulphide and aliphatic hydrocarbons
Log P (n-octanol/water)	:	0.16 (calc.)
Vapour pressure	:	65 Pa at 20 °C
Relative vapour density (air = 1):		4.35[6]
Flash point (closed cup)	:	83 °C
Odour threshold	:	Not available
Conversion factor (20 °C, 101.3 kPa)	:	1 ppm = 5.24 mg/m^3 air at 20 °C; 1 mg/m^3 = 0.19 ppm

2.2 Classification as a carcinogenic substance

IARC concluded in 1999 that dimethyl sulphate is *probably carcinogenic to humans* (group 2A).[3] In addition, dimethyl sulphate has been classified by the European Union as a substance which is *presumed to have carcinogenic potential for humans* (GHS category 1B).[4,8] In the 12th NTP Report on Carcinogens dimethyl sulphate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.[6]

DECOS concluded in 1990 that there was insufficient evidence that dimethyl sulphate is carcinogenic to humans while the compound is carcinogenic to animals.[5]

In the present evaluation (September 2014) the Committee (DECOS) follows the recommendation of the DECOS Subcommittee on the Classification of Carcinogenic Substances and classified dimethyl sulphate in category 1B (*substance presumed to be carcinogenic to humans*) (see Annex F and G).

2.3 Genotoxicity

Dimethyl sulphate is a potent direct-acting genotoxicant in bacteria and mammalian cells both in vitro and in vivo.[4] Dimethyl sulphate methylates DNA especially at the N^7-guanine and the N^3-adenine sites.[3,5] It is positive in tests for primary DNA damage, gene mutations, and chromosome aberrations in vitro.

From the results of tests with mammals it is concluded that dimethyl sulphate has genotoxic activity in somatic cells in vivo.[3-5]

The Committee concludes in accordance with the recommendation of the DECOS Subcommittee on the Classification of Carcinogenic Substances (see Annex F) that dimethyl sulphate is a stochastic genotoxic carcinogen.

2.4 Non-carcinogenic effects

Dimethyl sulphate can be absorbed by all routes (oral, respiratory and dermal) but data are limited. Rapid respiratory absorption is observed in rats exposed to dose levels up to 50.3 mg/m^3. At higher dose levels uptake was decreased, probably due to a decreased minute volume. After inhalatory and dermal exposure dimethyl sulphate is hydrolysed to methanol, sulphuric acid and methyl sulphate, and metabolized to a lesser extent to formaldehyde and formate.[4]

Dimethylsulphate is toxic after oral, dermal and inhalation exposure. The LD50 for oral administration is 106-440 mg/kg bw, for inhalation 45-168 mg/m^3 (4 hours), and for subcutaneous administration 100 mg/kg bw in rats.[4]

Dimethyl sulphate is corrosive to skin, is considered an eye irritant with risk for serious damage to eyes and is irritating to the respiratory tract. Dimethyl sulphate was positive in the murine local lymph node assay. Although the positive response may be due to the corrosive properties, dimethyl sulphate is considered a potential skin sensitizer in the absence of further data.[4,9]

No repeated-dose toxicity studies with dimethyl sulphate suitable for the establishment of a NOAEL (No Observed Adverse Effect Level) are reported. In a 2-week inhalation study with rats, a slightly increased proliferation of nasal epithelium cells was still seen at the lowest concentration examined, i.e. 0.5 mg/m^3.[4]

No data on toxicity to fertility are available. From a prenatal developmental toxicity study in rats exposed to concentrations of 0.5 to 7.9 mg/m^3, the NOAEL for maternal toxicity after inhalation was established to be 0.5 mg/m^3 based on decreased food consumption and reduced weight gain. The NOAEL for developmental toxicity was determined to be 7.9 mg/m^3.[4] In another prenatal developmental toxicity study in mice exposed to 25 mg/kg bw once via the intraperitoneal route an increased incidence of resorptions, gestational deaths and increased incidence of live fetuses with malformations was noted following treatments at 1, 6 and 9 hours after mating.[3] The substance is not classified as reprotoxic in the European Union.[9]

2.5 Existing occupational exposure limits and classifications

An inventarisation of occupational exposure limits for dimethyl sulphate in various countries is given in Table 1. Only for the German TRK value it is reported that the critical effects of dimethyl sulphate are its respiratory irritation and genotoxic and carcinogenic effects. In Germany, dimethyl sulphate has been classified as a category A2 carcinogen.[10] In the UK, dimethyl sulphate is listed as a carcinogen.[11] In the US, ACGIH has classified the compound as an A3 carcinogen, i.e. an animal carcinogen and OSHA as a potential occupational carcinogen.[12] Dimethyl sulphate is not classified for reproduction toxic properties in any of the countries listed below. No information on biological limit values could be found. In most countries dimethyl sulphate has a skin notation (see Table 1). Following the decision tree for 'skin notation'[13], it is concluded

Table 1 Occupational exposure limits (OELs) of dimethyl sulphate.

Country (organization)	OEL (ppm)	OEL (mg/m^3)	TWA	Type of exposure limit[a]
The Netherlands[15]	-	-		
European Union (SCOEL)[15]	-	-		(skin)
Denmark[15]	0.01	0.05	8h	(skin)
Finland[15]	0.01	0.052	15min	
France (INRS)[15]	0.1	0.5	8h	
United Kingdom (HSE) [11,15]	0.05	0.26	8h	WEL (skin, carc*)
Germany (DFG)[10]				MAK (skin, carc A2**)
production	(0.02)	(0.1)	TRK	
use	(0.04)	(0.2)	TRK	
Norway[15]	0.01	0.05	8h	(skin)
Austria[15]				
production	0.02	0.1	8h	(skin)
use	0.04	0.2	8h	
production	0.08	0.4	15min	
use	0.16	0.8	15min	
Switzerland[15]	0.02	0.1	8h	(skin)
Belgium[15]	0.1	0.53	8h	(skin)
Spain[15]	0.05	0.26	8h	(skin)
USA (ACGIH)[12]	0.1	0.5	8h	TLV (skin, carc A3***)
USA (NIOSH)[12]	0.1	0.5	10h	REL (skin, carco****)
USA (OSHA)[12]	1	5	8h	PEL (skin)

[a] WEL = workplace exposure limit; MAK = Maximum; TLV = threshold limit value; REL = recommended exposure limit; PEL = permissible exposure limit; skin = skin notation.
* carc = capable of causing cancer and/or heritable genetic damage; ** carc A2 = DFG classifies dimethyl sulphate as a category A2 carcinogen, i.e., an animal carcinogen; DFG category A carcinogens are not assigned a health-based occupational exposure limit, but a so called TRK-value (TRK = Technische Richtkonzentrationen), a concentration feasible with currently available means. TRK-values are given in brackets; *** carc A3 = confirmed animal carcinogen with unknown relevance to humans; **** carco = potential occupational carcinogen.

that in the EU the skin notation for dimethyl sulphate is based on human experience indicating the importance of skin penetration.[4,14]

Chapter 3

Carcinogenicity studies

3.1 Observations in humans

A very limited number of case reports and epidemiological studies concerning carcinogenicity of dimethyl sulphate is available in the older literature and has been reviewed repeatedly.[3,4,6,9] The Committee did not identify data of a more recent date.

Druckrey et al. (1966) reported a case of a 47-year-old male who died from bronchial cancer after 11 years of occupational exposure to dimethyl sulphate. Three out of ten co-workers also died from bronchial cancer.[16] Bettendorf (1977) reported a case of lung cancer in a chemist exposed by inhalation to dimethyl sulphate for over 7 years; however, in this case, there was concomitant exposure to other alkylating agents (notably dichlorodimethyl ether) that were present at higher concentration.[17] Albert and Puliafito (1977) reported a case of choroidal melanoma in a man exposed to dimethyl sulphate for 6 years.[18]

In workers (n=145), who had been exposed to dimethyl sulphate for various periods between 1932 and 1972 (concentrations unknown), no significant increase in deaths from lung cancer was reported.[3,5,9,19,20]

In two studies with workers (n=386 and 43,000 respectively) exposed to unknown concentrations of dimethyl sulphate, the number of cases with lung cancer was 4 and 257, respectively (Thiess & Goldman, 1968; Thiess et al., 1969). No information on concurrent control groups was available.[21,22]

The Committee is of the opinion that the human epidemiological data on the carcinogenicity of dimethyl sulphate do not allow a qualitative or quantitative risk assessment . This conclusion is in agreement with the conclusions from HSE and IARC.[3,23,24]

3.2 Carcinogenicity studies in animals

Animal carcinogenicity data are summarized in the Table 2 in Annex E. A number of animal studies concerning carcinogenicity of dimethyl sulphate is available in the older literature and has been reviewed repeatedly.[3,4,6,9]

Inhalation studies in three species showed tumours of the nasal cavity, sometimes accompanied by lung tumours.[25-27] Druckrey et al. (1970) exposed BD-rats (sex unspecified) for 130 days to 55 mg/m^3 [10 ppm] and 17 mg/m^3 [3 ppm] (1 hr/d, 5 d/wk). At 55 mg/m^3 5/15 of the rats developed malignant tumours (nasal cavity, cerebellum, thorax) . At 17 mg/m^3 3/12 showed carcinomas (nasal cavity). Benign tumours were found in the cerebellum and the olfactory nerve. Several deaths due to inflammation of the nasal cavity or pneumonia were reported.[25] However, this study was poorly reported (purity of dimethyl sulphate was unknown and no information on control animals, and on the observational and pathological examinations was reported).

Key data were reported in a doctoral thesis by Schlögel (1970, 1972).[26,27] Male and female rats (Wistar), mice (NMRI) and hamsters (Syrian Golden) were exposed to 2.6-10.5 mg/m^3 [0.5 ppm] dimethyl sulphate (6 hr/d, 2d/wk), to 10.5 mg/m^3 [2 ppm] (6hr/d, 1d/2wk) or to a sublethal concentration (4 times per year for 1 hour, 178 mg/m^3 (rats), 252 mg/m^3 (mice), 105 mg/m^3 (hamsters)) for about 15 months (Schlögel 1972).[26] The animals were exposed for about 15 months and observed for at least 30 months. The Committee notes that in the first exposure month, animals of the 2.6-10.5 mg/m^3 group were exposed to 10.5 mg/m^3 (5 d/wk, 6 hrs/d), during the second month they were exposed to 5.3 mg/m^3 (3 d/wk, 6 hrs/d), and starting from the third month to 2.6 mg/m^3 (2 d/wk, 6 hrs/d).

In general, survival in the groups exposed to dimethyl sulphate was lower than in controls, although the mean survival time varied considerably between the various exposure groups (see Annex E). The survival time in male and female rats of the 2.6 mg/m^3 group was distinctly lower than the survival time in rats of the control or the 10.5 mg/m^3 group. The same phenomenon was seen in mice although less pronounced. The lower survival time in the 2.6-10.5 mg/m^3 group is probably due to the initially high exposure regimen applied to this exposure group (see also Annex E, footnote).

Annex E lists the observed incidence of benign and malignant lung tumours and malignant tumours of the nose in animals surviving to the end of the study period. Dimethyl sulphate exposure resulted generally in an increased incidence of malignant tumours in the respiratory tract (nose and lungs) compared to the respective control groups. Rats were most sensitive to the tumour inducing activity of dimethyl sulphate, while hamsters were the least sensitive. In all three animal species, females appeared more sensitive than males. Female rats exposed to 10.5 mg/m^3 showed a slightly higher incidence of lung adenomas than the control females.

The highest incidence of treatment-related malignant respiratory tract tumours was found in rats exposed to 10.5 mg/m^3 group. The incidence in the 2.6-10.5 mg/m^3 group was distinctly lower although the total dose in the low dose group was comparable to or higher than that in the 10.5 mg/m^3 group. This lower incidence might be related to the lower mean survival time in the 2.6 mg/m^3 group, which in its turn may be a consequence of the initially high exposure scheme applied to this group. Exposure to sublethal dimethyl sulphate concentrations induced treatment-related tumours in rats only. In this context it is important to realize that the exposure scheme applied for the sublethal concentration (178 mg/m^3) leads to a lower total dose than that used with the 2.6-10.5 and 10.5 mg/m^3 groups, moreover most animals of the sublethal groups have been exposed four times only.

The Committee is aware that the study of Schlögel has shortcomings i.e. small group size, for each concentration a different dosing regimen was used, and poor survival, especially in the low dose (2.6-10.5 mg/m^3) group.[26] Moreover, it was not clear to the Committee which of the histologically assessed animals actually died from cancer or from other causes.

According to the study by van Duuren et al. (1974) dermal exposure of mice did not result in skin papillomas or carcinomas (even not after challenge with a tumour promotor) at a level beyond that of controls.[28] In the offspring of 8 rats, dosed intravenously with dimethyl sulphate (single dose 20 mg/kg bw), 7 out of 59 animals developed malignant tumours after one year. Duckrey et al. (1966, 1970) showed that subcutaneous injection of dimethyl sulphate caused local sarcomas with metastases to the lung.[16,25] There were no oral carcinogenicity studies.

The Committee is of the opinion that the data show that dimethyl sulphate is carcinogenic to animals. There is species specificity of the carcinogenic response and difference in target organs between species. All studies presented here have shortcomings and deviate in one or more aspects from guideline studies (see also Table 2 in Annex E).

3.3 Risk assessment

Epidemiological studies are not conclusive regarding carcinogenicity of dimethyl sulphate. However, sufficient evidence is available that dimethyl sulphate has carcinogenic potency to animals. The Committee classifies dimethyl sulphate in category 1B (*substance presumed to be carcinogenic to humans*) and concludes that a stochastic genotoxic mechanism underlies carcinogenicity.

The logical approach to risk assessment would be the derivation of health-based calculated occupational cancer risk values (HBC-OCRVs). However, none of the animal studies is sufficiently adequate for quantitative risk assessment. Therefore the Committee concludes that due to a lack of adequate human and animal data, it is not possible to exactly establish the health-based calculated occupational cancer risk values for dimethyl sulphate.

3.4 Additional consideration

In spite of this conclusion above (paragraph 3.3), the Committee emphasizes that dimethyl sulphate is a potent carcinogen and that performing no calculations at all may not be appropriate. Therefore, the Committee decided to use, by lack of more adequate studies, the data from Schlögel to speculate on exposure levels related to additional life-time cancer risk.[26]

The Committee performed its calculations using the data from the 10.5 mg/m^3 treatment group (see calculations in Annex H). Being aware of the shortcomings of the Schlögel rat study [small group size, poor survival, no information on the cause of death (tumours or other causes)] the Committee decided not to include the data from the 2.6-10.5 and the 178 mg/m^3 group in the calculations.

From the data of the 10.5 mg/m^3 group the Committee estimated an additional lifetime cancer risk of 4 cases per 1,000 at occupational exposure concentrations of 30 µg dimethyl sulphate/m^3 during a working life (8 hr/day, 40 yrs). The Committee is aware that this value is below any of the existing exposure limits (see Table 1). The Committee recommends that occupational exposures to dimethyl sulphate should be minimized.

The non-carcinogenic toxicity data, as summarized in paragraph 2.4, do not allow to derive an exposure limit for toxicity below the concentration levels associated with additional lifetime cancer risk.

References

1 Health Council of The Netherlands. Guideline for the calculation of occupational cancer risk values. The Hague: The Netherlands; 2012: publicationno. 2012/16E.

2 Health Council of The Netherlands. Calculating cancer risk. The Hague, The Netherlands: 1995: publication no. 1995/06WGD.

3 International Agency for Research on Cancer. Dimethyl sulfate. In: IARC monographs on the evaluation of carcinogenic risks to humans (volume 71): Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (part 2). Lyon, France: 1999: 575-588.

4 European Union Risk Assessment Report, Volume 12. Dimethyl sulphate. European Chemicals Bureau, European Commission; 2002.

5 Werkgroep van Deskundigen (WGD). Rapport inzake grenswaarde dimethyl- en diethylsulfaat. The Hague, The Netherlands: Servicecentrum SDU Uitgevers; 1990: RA 12/90.

6 Dimethyl sulphate. In: Report on Carcinogens (12th edition). National Toxicology Program, Department of Health and Human Services; 2011: 174-175.

7 Dimethyl sulphate. In: Pohanish R, editor. Sittig's Handbook of Toxic and Hazardous Chemicals. Oxford, UK: Elsevier; 2012: 1069-1070.

8 Dimethyl sulphate (77-78-1). Annex VI to Regulation 1272/2008 of the European Parliament and of the Council. http://esis.jrc.ec.europa.eu/index.php?PGM=cla consulted: 1-10-2014.

9 Recommendation from the Scientific Committee on Occupational Exposure Limits for dimethyl sulphate. European Commission; 2004: SCOEL/SUM/111.

10 Deckblatt zu Dimethylsulfat. The MAK Collection for Occupational Health and Safety. http://onlinelibrary.wiley.com/book/10.1002/3527600418 consulted: 1-10-2014.

11 EH40/2005 Workplace exposure limits. Health and Safety Executive (HSE), UK; 2011.

12 Dimethyl sulphate. Hazardous Substances Data Bank. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB consulted: 1-10-2014.
13 Strategy for assigning a 'skin notation'. Brussels, Belgium: European Centre for Ecotoxicology and Toxicology of Chemicals; 1993: 31(revised).
14 Schettgen T, Broding HC, Angerer J, Drexler H. Dimethyl sulphate; a hidden problem in occupational medicine. Occup Environ Med 2004; 61(1): 73-75.
15 Dimethylsulfaat. SER: Databank Grenswaarden Stoffen op de Werkplek (GSW). http://www.ser.nl/nl/taken/adviserende/grenswaarden.aspx consulted: 1-10-2014.
16 Druckrey H, Preussmann R, Nashed N, Ivankovic S. [Carcinogenic alkylating substances. I. Dimethylsulfate, carcinogenic action in rats and probable cause of occupational cancer]. Z Krebsforsch 1966; 68(1): 103-111.
17 Bettendorf U. [Occupational lung cancer after inhalation of alkylating compounds: dichlordimethyl ether, monochlordimethyl ether and dimethyl sulphate (author's transl)]. Dtsch Med Wochenschr 1977; 102(11): 396-398.
18 Albert DM, Puliafito CA. Choroidal melanoma: possible exposure to industrial toxins. N Engl J Med 1977; 296(11): 634-635.
19 Pell S. Mortality of workers exposed to dimethyl sulphate, 1992-1974. Wilmington, Delaware, E I Dupont de Nemours & Co , Inc , 1976; 47pp.
20 Dimethyl Sulfate, Environmental Health Criteria 48, International Programme on Chemical Safety. http://www.inchem.org/documents/ehc/ehc/ehc/48.htm consulted: 1-10-2014.
21 Thiess AM, Goldmann PJ. [Industrial medical problems in connexion with dimethylsulfate poisoning. Observations over 30 years in the BASF]. Zentralbl Arbeitsmed 1968; 18(7): 195-204.
22 Thiess AM, Oettel H, Uhl C. [Contribution to the problems of lung cancer due to occupation. Long term observations from the Badischen Anilin- und Soda-Fabrik AG in Ludwigshafen on the Rhine]. Zentralbl Arbeitsmed 1969; 19(4): 97-113.
23 International Agency for Research on Cancer. Dimethyl sulphate (Group 2A). In: IARC monographs on the evaluation of carcinogenic risks to humans (Suppl 7): Overall evaluations of carcinogenicity: An updating of IARC monographs volumes 1 to 42. Lyon, France: 1987: 200-201.
24 Cartlidge G, Cain J, Brown R. Dimethyl and diethyl sulphates. In: Criteria document for an occupational exposure limit. Sudbury, UK: HSE Books; 1996:
25 Druckrey H, Kruse H, Preussmann R, Ivankovic S, Landschuetz C. [Cancerogenic alkylating substances. 3. Alkyl-halogenides,-sulfates,-sulfonates and strained heterocyclic compounds]. Zeitschr Krebsforsch 1970; 74(3): 241-270.
26 Schlögel F. Cancerogenität und chronische Toxicität inhalierten Dimethylsulfats. Dissertation, Wurzburg: 1972.
27 Schlögel F, Bannash P. [Toxicity and carcinogenic properties of inhaled dimethyl sulfate]. Naunyn Schmiedebergs Arch Pharmacol 1970; 266(4): 441.
28 Van Duuren B, Goldschmidt B, Katz C, Seidman I, Paul J. Carcinogenic activity of alkylating agents. J Natl Cancer Inst 1974; 53(3): 695-700.

29 Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague, The Netherlands: 2010: publication no. A10/07E.

A	Request for advice
B	The Committee
C	The submission letter (in English)
D	Comments on the public review draft
E	Animal studies
F	Evaluation of the Subcommittee on the Classification of Carcinogenic Substances
G	Carcinogenic classification of substances by the Committee
H	Health-based calculated occupational risk values based on the rat study by Schlögel

Annexes

Annex **A**

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 advice 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 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.

Annex **B**

The Committee

- RA Woutersen, *chairman*
  Toxicologic Pathologist, TNO Innovation for Life; and Professor of Translational Toxicology, Wageningen University and Research Centre, Wageningen
- P.J. Boogaard
  Toxicologist, Shell International BV, The Hague
- D.J.J. Heederik
  Professor of Risk Assessment in Occupational Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- R. Houba
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- H. van Loveren
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- T.M. Pal
  Occupational Physician, Netherlands Center for Occupational Diseases, Amsterdam
- A.H. Piersma
  Professor of Reproductive Toxicology, National Institute for Public Health and the Environment, Bilthoven

- H.P.J. te Riele
  Professor of Molecular Biology, VU University Amsterdam; and Netherlands Cancer Institute, Amsterdam
- I.M.C.M. Rietjens
  Professor of Toxicology, Wageningen University and Research Centre, Wageningen
- F.G.M. Russel
  Professor of Molecular Farmacology and Toxicology, Radboud University, Nijmegen
- G.M.H. Swaen
  Epidemiologist, Maastricht University, Maastricht
- R.C.H. Vermeulen
  Epidemiologist, Institute for Risk Assessment Sciences, Utrecht
- P.B. Wulp
  Occupational Physician, Labour Inspectorate, Groningen
- B.P.F.D. Hendrikx, *advisor*
  Social and Economic Council, The Hague
- G.B. van der Voet, *scientific secretary*
  Toxicologist, Health Council of the Netherlands, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

The submission letter (in English)

Subject : Submission of the advisory report *dimethyl sulphate*
Your Reference: DGV/MBO/U-932342
Our reference : U-8223/BvdV/459-P70
Enclosed : 1
Date : November 3, 2014

Dear Minister,

I hereby submit the advisory report on the effects of occupational exposure to dimethyl sulphate.

This advisory report is part of an extensive series in which carcinogenic substances are evaluated for the possibility to establish health-based occupational cancer risk values in accordance with European Union guidelines. This involves substances to which people can be exposed while pursuing their occupation.

The advisory report was prepared by the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council. The advisory report has been assessed by the Health Council's Standing Committee on Health and the Environment.

In this report, the Committee concludes that dimethyl sulphate is a carcinogenic substance (category 1B, substance presumed to be carcinogenic to humans).

The Committee is of the opinion that due to a lack of adequate data, it is not possible to estimate the additional lifetime cancer risk for dimethyl sulphate.

I have today sent copies of this advisory report to the State Secretary of Infrastructure and the Environment and to the Minister of Health, Welfare and Sport, for their consideration.

Yours sincerely,
(signed)
Professor J.L. Severens,
Vice President

Annex **D**

Comments on the public review draft

A draft of the present report was released in April 2014 for public review. The following organization and persons have commented on the draft document:

- T. Lentz, PhD, P. Erdely, PhD, A. Rengasamy, PhD, R. Streicher, Ph.D, National Institute for Occupational Safety and Health (NIOSH), Cincinnati OH, USA.

Annex **E**

Animal studies

Table 2 All studies presented here are non-guideline studies and deviate in one or more aspects from a guideline study.

Study design and animal species	Data on exposure and effect endpoints	Results	Remarks
Schlögel, 1972[26] carcinogenicity study; rat, Wistar; control: 30 M, 20 F 15-30 F	Inhalation;	TBA (tumor bearing animals)	mean survival in days ± SD for M and F, respectively
	1) 0 (30 M, 20 F)	1 lung adenomas M 2/25, F 0/11 malignant lung tumours M 0/25, F 0/11 malignant nasal tumours M 0/25, F 0/11	1) 839 ± 26; 617 ± 87
	2) 2.6 mg/m^3 *, 6 hr/d, 2 d/wk (35 M, 30 F)	2 lung adenomas M 0/21, F 0/16 malignant lung tumours M 0/21, F 1/16 malignant nasal tumours M 0/21, F 2/16	2) 226 ± 27; 301 ± 56 (initially high exposure)
	3) 10.5 mg/m^3, 6 hr/d, 1 d/2 wks (15 M, 15 F)	3 lung adenomas M 1/14, F 3/13 malignant lung tumours M 0/14, F 0/13 malignant nasal tumours M 3/14, F 3/13	3) 590 ± 62; 637 ± 61
	4) 178 mg/m^3, 4 times per year for 1 hr (15 M, 15 F) Xpo = 15 months, Xpe = 30 months	4 lung adenoma M 1/14, F 0/15 malignant lung tumours M 0/14, F 0/15 malignant nasal tumours M 1/14, F 1/15	4) 605 ± 84; 279 ± 72

Schlögel, 1972[26] carcinogenicity study; mouse, NMRI; control: 25/sex; treated: 15-25/sex	Inhalation; 1) 0 (25 M, 25 F) 2) 2.6 mg/m^3 *, 6 hr/d, 2 d/wk (25 M, 25 F) 3) 10.5 mg/m^3, 6 hr/d, 1 d/2 wks (15 M, 15 F) 4) 252 mg/m^3, 4 times per year for 1 hr (15 M, 15 F)Xpo = 15 months, Xpe = 30 months	TBA 1 lung adenomas M 1/8, F 2/11 malignant lung tumours M 0/8, F 0/11 2 lung adenomas M 1/14, F 3/18 malignant lung tumours M 0/14, F 1/18 3 lung adenomas M 4/11, F 2/14 malignant lung tumours M 0/11, F 3/14 4 lung adenomas M 0/6, F 3/11 malignant lung tumours M 0/6, 0/11	mean survival in days ± SD for M and F, respectively 1) 304 ± 59; 540 ± 35 2) 287 ± 39; 371 ± 38 (initially high exposure) 3) 308 ± 34; 393 ± 62 4) 249 ± 33; 325 ± 23
Schlögel, 1972[26] carcinogenicity study; hamster, Syrian golden; control: 16/sex; treated: 15-31/sex	Inhalation; 1) 0 (16 M, 16 F) 2) 2.6 mg/m^3 *, 6 hr/d, 2 d/wk (20 M, 16 F) 3) 10.5 mg/m^3, 6 hr/d, 1 d/2 wks (15 M, 15 F) 4) 105 mg/m^3, 4 times per year for 1 hr (31 M, 31 F) Xpo = 15 months, Xpe = 30 months	TBA 1 lung adenomas M 0/5, F 0/10 malignant lung tumours M 0/5, F0/10 2 lung adenomas M 0/16, F 0/12 malignant lung tumours M 0/16, 0/12 3 lung adenomas M 0/11, F 1/11 malignant lung tumours M 0/11, F 1/11 4 lung adenomas M 1/25, F 0/26 malignant lung tumours M 0/25, F 0/26	mean survival in days ± SD for males and females, respectively 1) 247 ± 54; 303 ± 49 2) 262 ± 34; 244 ± 44 3) 148 ± 25; 171 ± 32 4) 253 ± 29; 144 ± 19
Druckrey, 1970[25] rat, BD; n=20, n=27	inhalation 1) 17 mg/m^3, 1 h/d, 5 d/wk, 2) 55 mg/m^3, 1 h/d, 5 d/wk Xpo = 130d Xpe = until life end	Death: 8/20, 12/27 with inflammation of the nasal cavity, 1 3/12 survivors with treatment related tumours: one rat with squamous cell carcinoma of the nasal cavity, one with brain neuroma and a third with an esthesioneuroepithelioma of the olfactory nerve; 2 5/15 survivors with treatment related tumours: 3 squamous cell carcinomas of the nasal cavity, one cerebellum tumour, and one lymphosarcoma of the thorax with lung metastases.	purity: ?; no concurrent control group; sex unspecified; observations and pathological examination were reported limitedly
Van Duuren, 1974[28] carcinogenicity study; mouse, ICR/Ha Swiss; n=20 F	dermal; 3 times per week, 475 days, 0.1 mg/0.1 ml acetone	Medium survival 437 days. No papillomas or carcinomas found	purity: ?; no information on controls; numbers too limited
Van Duuren, 1974[28] two stage carcinogenesis study; mouse, ICR/Ha Swiss; n=20 F	dermal; challenge with single dose 0.1 mg/0.1 ml acetone, followed by phorbol myristate acetate 3 times a week 14 days after challenge	2 papillomas 0 in controls (challenge with acetone only (n=50) or untreated (n=100)	purity: ? (DMS was distilled at 93 °C at 50 mm Hg)

Druckrey, 1970[25] developmental toxicity study; rat, BD; 8 pregnant F	intravenous; single dose, 20 mg/kg bw at day 15 of gestation; examination of F1 (n=59) at 1 year	7 tumours in brain, liver, uterus, and thyroid gland in F1 animals after 1 year	purity: ?; no information on controls; no information on observational and pathological examinations
Druckrey, 1970[25] carcinogenicity study; rat, BD; n=15	subcutaneous; single dose, 50 mg/kg bw, observation for 740 days	7 deaths with sarcomas at the injection site, 3 of these animals had multiple lung metastases	purity: ?; limited report; no information on controls; no information on observational and pathological examinations
Druckrey, 1966[16] carcinogenicity study; rat, BD;	subcutaneous; once a week		purity: ?; no information on controls; no information on observational and pathological examination
1) n=12	1) 8 mg/kg bw	1 one death with liver carcinoma with spleen and lung metastases, 7 animals with injection site tumours (3 of these accompanied with metastases in lungs and lymph-nodes and kidneys).	
2) n=15	2) 16 mg/kg bw	2 two deaths due to pneumonia, all survivors with tumours at the injection site (2 of these accompanied with metastases in the lung)	
	Xpo=56 wks Xpe=until natural death		

* In first exposure month, animals of the 2.6 mg/m^3 group were exposed to 10.5 mg/m^3 (5 d/wk, 6 hrs/d), during the second month they were exposed to 5.3 mg/m^3 (3 d/wk, 6 hrs/d), and starting from the third month to 2.6 mg/m^3 (2 d/wk, 6 hrs/d).

Xpo exposure period; Xpe total experimental/observation period

Annex **F**

Evaluation of the Subcommittee on the Classification of Carcinogenic Substances

IARC concluded in its most recent evaluation (1999) that dimethyl sulphate is probably carcinogenic to humans (group 2A).[1] In addition, dimethyl sulphate has been classified by the European Union as a substance which is *presumed to have carcinogenic potential for humans* (GHS category 1B).[2] [In the 12th NTP Report on Carcinogens dimethyl sulfate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.[3]]

DECOS concluded in 1990 that there was insufficient evidence that dimethyl sulphate was carcinogenic to humans, while the compound was carcinogenic to animals.[4] Dimethyl sulphate was classified by DECOS in 1990 as a genotoxic carcinogen.[4]

In the present evaluation (November 2013) the DECOS Subcommittee on the Classification of Carcinogenic Substances evaluated the existing and new information regarding human, animal and in vitro studies on carcinogicity and genotoxicity of dimethyl sulphate.

Human studies

A very limited number of case reports and epidemiological studies concerning carcinogenicity of dimethyl sulphate is available in the older literature and repeatedly reviewed (IARC, 1999; EU-RAR, 2002; SCOEL, 2004; NTP-RoC, 2011).[1,3,5,6] The Subcommittee did not identify human data of a more recent date.

Druckrey et al. (1966) reported a case of a 47-year-old male who died from bronchial cancer after 11 years of occupational exposure to dimethylsulphate.[7] Three out of ten co-workers also died from bronchial cancer. Bettendorf (1977) reported a case of lung cancer in a chemist exposed by inhalation to dimethyl sulphate for over 7 years; however, in this case, there was concomitant exposure to other alkylating agents (notably dichlorodimethyl ether) that were present at higher concentrations.[8] Albert and Puliafito (1977) reported a case of choroidal melanoma has been reported in a man exposed to dimethyl sulphate for 6 years.[9]

In workers (n=145), who had been exposed to dimethyl sulphate for various periods between 1932 and 1972 (concentrations unknown), no significant increase in deaths from lung cancer was reported (Pell, 1972).[1,4,6,10,11]

In two studies (Thiess & Goldman 1968; Thiess et al. 1969) with workers (n=386 or 43,000) exposed to unknown concentrations of dimethyl sulphate, the number of cases with lung cancer was 4 and 257, respectively. [12,13] No information on concurrent control groups was available.

The Subcommittee agrees with IARC that the data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to dimethyl sulfate.

Animal studies (see Table 2 in Annex E)

A number of animal studies concerning carcinogenicity of dimethyl sulphate is available in the older literature and repeatedly reviewed (IARC, 1999; EU-RAR, 2002; SCOEL, 2004; NTP-RoC, 2011).[1,3,5,6] The Subcommittee did not identify animal data of a more recent date. Although these older studies were not designed to fulfil the requirements of the OECD the Subcommittee decided not to exclude these studies from her evaluation.

Inhalation studies in three species showed tumours of the nasal cavity, sometimes accompanied by lung tumours.[14-16] Druckrey et al. (1970) showed in a study with BD-rats (sex unspecified) for 130 days (55 mg/m^3 [10 ppm] and 17 mg/m^3 [3 ppm], 1 hr/d, 5 d/wk) 5/15 that rats developed malignant tumours (nasal cavity, cerebellum, thorax) at 55 mg/m^3. At 17 mg/m^3 3/12 showed carcinomas (nasal cavity). Benign tumours were found in the cerebellum and the olfactory nerve. Several deaths due to inflammation of the nasal cavity or pneumonia were reported.[14] However, this study was poorly reported (purity of dimethyl sulphate was unknown and no information on control animals, and on the observational and pathological examinations was reported).

Key data were reported in a doctoral thesis by Schlögel (1970, 1972).[15,16] Male and female rats (Wistar), mice (NMRI) and hamsters (Syrian Golden) were

exposed to 2.6 mg/m^3 [0.5 ppm] dimethyl sulphate (6 hr/d, 2d/wk), to 10.5 mg/m^3 [2 ppm] (6hr/d, 1d/2wk) or to a sublethal concentration (4 times per year for 1 hour, 178 mg/m^3 (rats), 252 mg/m^3 (mice), 105 mg/m^3 (hamsters)) for about 15 months. The animals were exposed for about 15 months and observed for at least 30 months after the start of exposure provided they survived. DMS exposure resulted in an increased incidence of malignant tumours in the respiratory tract (nose and lungs) of rats and mice. Rats were most sensitive to the tumour-inducing activity of dimethyl sulphate, while hamsters were the least sensitive (only one tumour at 10.5 mg/m^3 [2 ppm] dimethyl sulphate). In all three animal species females appeared more sensitive than males. In female rats of the 10.5 mg/m^3 group, the incidence of lung adenomas was slightly higher than in control females.

Dermal exposure of mice did not result in skin papillomas or carcinomas (even not after challenge with a tumour promotor) at a level beyond that of controls (van Duuren et al., 1974).[17] In the offspring of 8 rats, dosed intravenously with dimethyl sulphate (single dose 20 mg/kg bw), 7 out of 59 animals developed malignant tumours after one year. Druckrey et al.(1966, 1970) showed that subcutaneous injection of dimethyl sulphate caused local sarcomas with metastases to the lung.[7,14] There were no oral carcinogenicity studies.

The Subcommittee agrees with IARC that sufficient evidence exists that dimethyl sulphate is carcinogenic to animals.

Mechanism of genotoxicity

Dimethyl sulphate is a potent direct-acting alkylating genotoxic substance in bacteria, and mammalian cells in vitro and in vivo.[5] Dimethyl sulphate methylates DNA especially at the N^7-guanine and the N^3-adenine sites.[1,4] It is positive in tests for primary DNA damage, gene mutations, and chromosome aberrations in vitro. From the results of the tests with mammals it is concluded that dimethyl sulphate has genotoxic activity in somatic cells in vivo.[1,4,5]

DECOS Subcommittee is of the opinion that a stochastic genotoxic mechanism may underly the carcinogenicity of dimethyl sulphate.

Recommendation

Epidemological studies are not conclusive regarding carcinogenicity of dimethyl sulphate. However, sufficient evidence is available that dimethyl sulphate is carcinogenic to animals. Therefore, the Subcommittee recommends to classify dimethyl sulphate in category 1B (*substance presumed to be carcinogenic to*

humans). Moreover, the Subcommittee is of the opinion that a stochastic genotoxic mechanism may underly carcinogenicity. The Subcommittee recommends health-based calculated occupational cancer risk values (HBC-OCRVs) to be calculated for regulatory standard setting.

References

1 International Agency for Research on Cancer. Dimethyl sulfate. In: IARC monographs on the evaluation of carcinogenic risks to humans (volume 71): Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (part 2). Lyon, France, 1999: 575-588.

2 Dimethyl sulphate (77-78-1). Annex VI to Regulation 1272/2008 of the European Parliament and of the Council. http://esis.jrc.ec.europa.eu/index.php?PGM=cla consulted: 1-10-2014.

3 Dimethyl sulphate. In: Report on Carcinogens (12th edition). National Toxicology Program, Department of Health and Human Services, 2011:174-175.

4 Werkgroep van Deskundigen (WGD). Rapport inzake grenswaarde dimethyl- en diethylsulfaat. The Hague, The Netherlands: Servicecentrum SDU Uitgevers, 1990: RA12/90.

5 European Union Risk Assessment Report, Volume 12. Dimethyl sulphate. European Chemicals Bureau, European Commission, 2002

6 Recommendation from the Scientific Committee on Occupational Exposure Limits for dimethyl sulphate. European Commission, 2004: SCOEL/SUM/111.

7 Druckrey H, Preussmann R, Nashed N, Ivankovic S. [Carcinogenic alkylating substances. I. Dimethylsulfate, carcinogenic action in rats and probable cause of occupational cancer]. Z Krebsforsch 1966; 68(1): 103-111.

8 Bettendorf U. [Occupational lung cancer after inhalation of alkylating compounds: dichlordimethyl ether, monochlordimethyl ether and dimethyl sulphate (author's transl)]. Dtsch Med Wochenschr 1977; 102(11): 396-398.

9 Albert DM, Puliafito CA. Choroidal melanoma: possible exposure to industrial toxins. N Engl J Med 1977; 296(11): 634-635.

10 Pell S. Mortality of workers exposed to dimethyl sulphate, 1992-1974. Wilmington, Delaware, E I Dupont de Nemours & Co, Inc, 1976, 47pp.

11 Dimethyl sulfate, Environmental Health Criteria 48, International Programme on Chemical Safety, 1985. http://www.inchem.org/documents/ehc/ehc/ehc48.htm consulted 1-10-2014.

12 Thiess AM, Goldmann PJ. [Industrial medical problems in connexion with dimethylsulfate poisoning. Observations over 30 years in the BASF]. Zentralbl Arbeitsmed 1968; 18(7): 195-204.

13 Thiess AM, Oettel H, Uhl C. [Contribution to the problems of lung cancer due to occupation. Long term observations from the Badischen Anilin- und Soda-Fabrik AG in Ludwigshafen on the Rhine]. Zentralbl Arbeitsmed 1969; 19(4): 97-113.

14 Druckrey H, Kruse H, Preussmann R, Ivankovic S, Landschuetz C. Carcinogene alkylierende Substanzen, III. Alkyl-halogenide-sulfate-sulfonate and ringgespannte Heterocyclen. Zeitschr Krebsforsch 1970; 74(3): 241-270.

15 Schlögel F, Bannash P. Toxicity and carcinogenic properties of inhaled dimethyl sulfate. Naunyn Schmiedebergs Arch Pharmacol 1970; 266(4): 441.

16 Schlögel F. Cancerogenität und chronische Toxicität inhalierten Dimethylsulfats. Dissertation, Wurzburg, 1972.

17 Duuren B van, Goldschmidt B, Katz C, Seidman I, Paul J. Carcinogenic activity of alkylating agents. J Natl Cancer Inst 1974; 53(3): 695-700.

The Subcommittee

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- G.B. van der Voet, *scientific secretary*
  Toxicologist, Health Council of The Netherlands

Date meeting: November 11, 2013

Annex **G**

Carcinogenic classification of substances by the Committee

The Committee expresses its conclusions in the form of standard phrases:

Category	Judgement of the Committee (GR_{GHS})	Comparable with EU Category	
		67/548/EEC before 12/16/2008	EC No 1272/2008 as from 12/16/2008
1A	The compound is known to be carcinogenic to humans. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	1	1A
1B	The compound is presumed to be as carcinogenic to humans. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	2	1B
2	The compound is suspected to be carcinogenic to man.	3	2
(3)	The available data are insufficient to evaluate the carcinogenic properties of the compound.	not applicable	not applicable
(4)	The compound is probably not carcinogenic to man.	not applicable	not applicable

Source: Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.[29]

Annex **H**

Health-based calculated occupational risk values based on the rat study by Schlögel

Data

Epidemiological studies are not conclusive regarding carcinogenicity of dimethyl sulphate. However, sufficient evidence is available that dimethyl sulphate is a potent carcinogen for experimental animals. A stochastic genotoxic mechanism underlies carcinogenicity. The proper approach to risk assessment would be the derivation of health-based occupational risk values. However, all animal studies presented are non-guideline studies and deviate in one or more aspects from a guideline study (see also Table 2 in Annex E). The Committee is aware that none of the studies is sufficiently adequate for quantitative risk assessment.

That being said, the Committee emphasizes that dimethyl sulphate is a potent carcinogen and that performing no calculations at all may not be appropriate. Therefore, the Committee decides to use the data from the study by Schlögel to speculate on the exposure levels related to additional life-time cancer risk.[26]

In the study by Schlögel, groups of male and female rats, mice and hamsters were exposed to 0, 2.6-10.5 mg/m^3 (6 hr/day, 2 days/week), 10.5 mg/m^3 once every two weeks (6 hr/day), or 178 mg/m^3 dimethyl sulphate (a sublethal concentration), 4 times per year for 1 hour. Animals were exposed for about 15 months and observed for at least 30 months. The three concentration groups had different exposure regimens and survival was more affected in 2.6-10.5 mg/m^3

group than in 10.5 or 178 mg/m^3 group. This might be explained by the initial higher dosage regimens, i.e. in the first exposure month, animals of the 2.6 mg/m^3 group were exposed to 10.5 mg/m^3 (5 d/wk, 6 hrs/d), during the second month they were exposed to 5.3 mg/m^3 (3 d/wk, 6 hrs/d), and starting from the third month to 2.6 mg/m^3 (2 d/wk, 6 hrs/d).

The incidence of rats with malignant respiratory tract tumours amounted to 0/36, 3/37, 6/27 and 2/29 in the 0, 2.6, 10.5 and 178 mg/m^3 groups.

Being aware of the shortcomings of the Schlögel rat study (small group size, poor survival no information on cause of death (tumours or other causes) the Committee decided not to use the data from both the 2.6-10.5 mg/m^3 and the 178 mg/m^3 group in the calculations.

The Committee calculated the occupational exposure related to additional life-time respiratory cancer risk based on the data from the 10.5 mg/m^3 group.

Procedure

First, the incidence per µg/m^3 per day (lifespan conditions, assuming a linear dose-response relationship) is calculated as follows:

$$I_{concentration} = \frac{I_e - I_c}{C \times (X_{po}/L) \times (X_{pe}/L) \times \text{hours exposure per day}/24 \times \text{days exposure per week}/7}$$

Where:

- $I_{concentration}$ is the carcinogenic activity attributable to the exposure to the substance per unit daily dose under lifespan conditions, assuming a linear dose response relationship, usually expressed per mg/m^3 or per mg/kg bw/day.
- I_e and I_c are the incidence of tumour bearing animals or tumours in exposed and control animals, respectively.
- X_{po} and X_{pe} (see Table 2 in Schlögel) are the exposure and experimental periods, respectively.
- L is the standard lifespan for the animals in question (L rat in this experiment is 728 days, equal to the mean survival time found in the controls).

Furthermore, it is assumed that the average man lives 75 years, weighs 70 kg, and is exposed 24 hours per day 7 days/week, 52 weeks per year for lifetime.

To estimate the additional lifetime risk of cancer in humans under workplace exposure conditions, it is assumed that the average man lives 75 years, is exposed 8 hours per day, 5 days per week, 48 weeks per year for 40 years and inhales 10 m^3 per 8-hour-working day.

Using as starting point the estimated incidence, $I_{concentration}$, the additional life-time cancer risk per µg/m^3 under occupational exposure conditions (= HBC-OCRV) amounts to:

$$HBC\text{-}OCRV = I_{concentration} \times \frac{40\ years}{75\ years} \times \frac{48\ weeks}{52\ weeks} \times \frac{5\ days}{7\ days} \times \frac{8\ hours}{24\ hours} \times \frac{10\ m^3/day}{18\ m^3/day}$$

Calculations for the 10.5 mg/m^3 exposure group

$$I_{concentration} = \frac{6/27 - 0/36}{(10.5x10^3\ \mu g/m^3) \times (456/728) \times (613/728) \times 6/24 \times 1/14} =$$

$$= 2.2x10^{-3}\ [\mu g/m^3]^{-1}$$

$$HBC\text{-}OCRV = 2.2x10^{-3} \times \frac{40\ years}{75\ years} \times \frac{48\ weeks}{52\ weeks} \times \frac{5\ days}{7\ days} \times \frac{8\ hours}{24\ hours} \times \frac{10\ m^3/day}{18\ m^3/day} =$$

$$= 1.4 \times 10^{-4}\ [\mu g/m^3]^{-1}$$

Based on the HBC-OCRV of 1.4 x 10^{-4} per µg/m^3 the additional life-time cancer risk amounts to:

- 4 per 1,000 (4 x 10^{-3}), for 40 years of exposure to 29 µg/m^3
- 4 per 100,000 (4 x 10^{-5}), for 40 years of exposure 0.29 µg/m^3.

Health Council of the Netherlands

Advisory Reports

The Health Council's task is to advise ministers and parliament on issues in the field of public health. Most of the advisory reports that the Council produces every year are prepared at the request of one of the ministers.

In addition, the Health Council issues unsolicited advice that has an 'alerting' function. In some cases, such an alerting report leads to a minister requesting further advice on the subject.

Areas of activity

Optimum healthcare
What is the optimum result of cure and care in view of the risks and opportunities?

Prevention
Which forms of prevention can help realise significant health benefits?

Healthy nutrition
Which foods promote good health and which carry certain health risks?

Environmental health
Which environmental influences could have a positive or negative effect on health?

Healthy working conditions
How can employees be protected against working conditions that could harm their health?

Innovation and the knowledge infrastructure
Before we can harvest knowledge in the field of healthcare, we first need to ensure that the right seeds are sown.

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