2-Methylaziridine (propylene imine)

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. 1999/10OSH, The Hague, 20 December 1999

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Contents

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 maakt zij zo'n schatting voor 2-methylaziridine (propyleen imine). Zij heeft daarbij gebruik gemaakt van de methode die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06WGD) (Dec95a).

Naar schatting van de commissie is de extra kans op kanker voor 2-methylaziridine (propyleen imine):

- 4×10^{-5} bij 40 jaar beroepsmatige blootstelling aan 0.6 $\mu g/m^3$
- 4×10^{-3} bij 40 jaar beroepsmatige blootstelling aan 60 $\mu g/m^3$

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 lifetime 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 presents such estimates for 2-methylaziridine. It has used the method described in the report 'Calculating cancer risks due to occupational exposure to genotoxic carcinogens' (1995/06WGD) (Dec95a).

The committee estimated that the additional lifetime cancer risk for 2-methylaziridine amounts to:

- 4×10^{-5} for 40 years of occupational exposure to 0.6 $\mu g/m^3$
- 4×10^{-3} for 40 years of occupational exposure to 60 $\mu g/m^3$

Chapter 1

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 for 2-methylaziridine by the committee. The members of the committee are listed in Annex B. The first draft of this report was prepared by MI Willems, from the TNO Nutrition and Food Research Institute in Zeist, by contract with the Ministry of Social Affairs and Employment.

Chapter 2

2-Methylaziridine (propylene imine)

2.1 Introduction

2-Methylaziridine has been classified as a genotoxic carcinogen by the European Union as a carcinogenic compounds (EU category 2).

The toxicity and carcinogenicity of 2-methylaziridine (CAS no. 75-55-8) have been evaluated by IARC (IARC75) and ACGIH (ACG91)*. In addition, literature was retrieved from online databases Medline, Toxline and Chemical Abstracts, covering the period 1966 to January 1996.

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

No epidemiological studies could be retrieved on the incidence of cancer due to exposure to 2-methylaziridine. Only data (1 study) on cancer in rats after oral (by gavage) administration, is available for calculating the risk of cancer (Table 1, Annex D). In this study, the total incidence of rats with a mixture of tumors was 37/52 for the low dose group (10 mg/kg bw/d) (Ull71).

* After completion of the report IARC concluded in 1999 that 2-methylaziridine was a IARC-group 2B-compound (IARC99).

2.3 Carcinogenic activity in experimental animals, lifetime low-dose exposure

To calculate the carcinogenic activity expressed as the incidence per unit dose 2-methylaziridine per day, the observed number of tumour-bearing animals (male plus female rats) of the study of Ulland *et al* (Ull71) are used. The committee is of the opinion that the available data do not indicate that the use of the linear model is not appropriate

The incidence of tumour bearing animals per mg test substance/kg bw/day (lifespan conditions, assuming a linear dose response relationship), I_{dose}, is calculated as follows:

$$I^*_{dose} = \frac{I_e - I_c}{C \times (X_{po}/L) \times (X_{pe}/L) \times \text{exposure hours per day}/24 \times \text{exposure days per week}/7}$$

$$= \frac{37/52 - 1/12}{10 \times (60 \times 7/1000) \times (60 \times 7/1000) \times 24/24 \times 2/7} = 1.25 \text{ [mg/kg.d]}^{-1}$$

2.4 Health risk to humans

To estimate the additional lifetime risk of cancer in humans under lifespan conditions on the basis of results in animal experiments, it is assumed that no difference exists between experimental animals and man with respect to toxicokinetics, mechanism of tumour induction, target, susceptibility etc, unless specific information is available which justifies a different approach. Furthermore, it is assumed that the average man lives 75 years, and is exposed 24 hours per day 7 days/week, 52 weeks per year for lifetime.

2.5 Calculation of the HBC-OCRV

To estimate the additional lifetime risk of cancer in humans under workplace conditions, it is assumed that the average man lives 75 years, is exposed 8 hours per day, five days a week, 48 weeks a year, for 40 years, and inhales 10 m^3 air per 8 hour-working day. Using as starting point the estimated incidence, I_{dose}, of 1.25 per mg/kg bw/day, the

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* I_{dose} = 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 per m^3 or as mg per kg body weight per day.
C is the concentration to which the animals are exposed, expressed as mg/m^3 or as mg/kg bw/day.
I_e and I_c = incidence of tumour bearing animals or tumours in exposed and control animals, respectively,
Xpo = exposure period, Xpe = experimental period
L = standard lifespan for the animals in question (L rat is assumed to be 1000 days)

additional lifetime cancer risk per mg/m^3 under occupational conditions, the HBC-OCRV, amounts to:

$$\text{HBC-OCRV} = 1.25\ x\frac{40y}{75y}x\frac{48w}{52w}x\frac{5d}{7d}x\frac{10m^3}{70kg} = 6.3 \times 10^{-2}\ [\text{mg/m}^3]^{-1}$$

Based on the HBC-OCRV of 6.3x10^{-2} per mg/m^3 the reference additional lifetime cancer risks correspond to:

- 4x10^{-5} for 40 years of exposure to 0.6 µg/m^3
- 4x10^{-3} for 40 years of exposure to 60 µg/m^3

2.6 Existing exposure limits

Table 2 summarizes the occupational exposure limits established by regulatory authorities in Germany, United Kingdom, and Sweden, and by the USA-ACGIH. No occupational exposure limits has been established in The Netherlands, Germany or in Sweden.

The lowest occupational exposure limit set amounts to 4.7 mg/m^3. This concentration is a factor 78 higher than the concentration leading to an additional cancer risk of 4 x 10^{-3} (i.e., 0.06 mg/m^3).

Table 2 Occupational exposure limits for 2-methylaziridine.

country	level		time relation	notations	ref.
	ppm	mg/m^3			
The Netherlands[a]	-	-	-	-	-
Germany[b]	-	-	-	skin	DFG96
UK[c]	-	-	-	-	HSE95
Sweden[d]	-	-	-	-	NBO93
USA-ACGIH[e]	2	4.7	8-h TWA	skin	ACG96

[a] 2-methylaziridine is listed as carcinogen

[b] The DFG classifies methylaziridine as a category A2 carcinogen; therefore, no MAK-value has been assigned. A so-called "Technische Richtkonzentration"(i.e., a concentration feasible with currently available technical means) is not given.

[c] Defined as carcinogen, labeled with risk phrase "R45".

[d] Substance is listed under section 9: carcinogen, and may only be handled by permission of the Labour Inspectorate.

[e] Classified as a A3 carcinogen: animal carcinogen.

2.7 Toxicity profile of 2-methylaziridine

Apart from an acute inhalation study with rats no data on the toxicity of 2-methylaziridine (other than on carcinogenicity) were found. From this study ACGIH proposed an occupational exposure limit of 4.7 mg/m^3 (after comparison with data on ethyleneimine) (ACG91).

In conclusion, the committee believes that an occupational exposure limit for 2-metylaziridine derived from data other than on genotoxicity/carcinogenicity would in all likelihood be expected to be higher than the concentration levels associated with the referential cancer risk levels.

The Hague, 20 December 1999,
for the committee

dr ASAM van der Burght,
scientific secretary

prof. dr GJ Mulder,
chairman.

References

ACG91 American Conference of Governmental Industrial Hygienists (ACGIH). Propylene imine. In: - Documentation of the Threshold Limit Values and Biological Exposure Indicies, 6th ed. Cincinnati OH, USA; ACGIH, 1991: 1314.

ACG96 American Conference of Governmental Industrial Hygienists (ACGIH). 1996. TLVs(R) and BEIs(R). Threshold Limit Values for chemical substances and physical agents.Biological Exposure Indices. Cincinnati OH, USA; ACGIH, 1995: 32.

DEC95a Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards (DECOS). Calculating cancer risk. The Hague: Health Council of the Netherlands, 1995 publication no 1995/06WGD.

DFG96 Deutsche Forschungsgemeinschaft (DFG): Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. MAK- und BAT-Werte-Liste 1996. Maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleranzwerte. Weinheim, FRG: VCH Verlagsgesellschafft mbH, 1996: 87, 109, 130 (Mitteilung 32).

HSE95 Health and Safety Executive (HSE). Occupational exposure limits 1995. Sudbury (Suffolk), UK: HSE Books, 1995: 21, 49 (Guidance note EH 40/95).

IARC75 International Agency for Research on Cancer (IARC). 2-Methylaziridine. Some aziridines, N-, S- and O-mustards and selenium. Lyon, France: IARC, 1975: 61-65 (In: IARC monographs on carcinogenic risk of chemicals to man, Vol 9.

IARC99 International Agency for Research on Cancer (IARC). Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (part two). 1999; 71: 1497-1502.

ISZW95 Inspectiedienst van het Ministerie van Sociale Zaken en Werkgelegenheid (ISZW). De Nationale MAC-lijst 1995. The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1995: 47, 63 (pub no P145).

NBO93 National Board of Occupational Safety and Health (NBOSH). Occupational exposure limits. Solna, Sweden: NBOSH, 1993: 75 (Ordinance AFS 1993/9).

Ull71 Ulland B, Finkelstein M, Weisburger EK, *et al*. Carcinogenicity of industrial chemicals propylene imine and propane sultone. Nature 1971; 230: 460-1.

Wei81 Weisburger EK, Ulland BM, Nam J, *et al*. Carcinogenicity tests of certain environmental and industrialchemicals. J Natl Cancer Inst, 1981; 67: 75-88.

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

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- PJ Borm
  toxicologist; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- VJ Feron,
  professor of toxicology; TNO Nutrition and Food Research Institute, Zeist
- DJJ Heederik
  epidemiologist; Wageningen University, Wageningen
- LCMP Hontelez, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- G de Jong
  occupational physician; Shell International Petroleum Maatschappij, The Hague
- J Molier-Bloot
  occupational physician; BMD Akers bv, Amsterdam
- IM Rietjens
  professor in Biochemical toxicology; Wageningen University, Wageningen.

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, Den Haag
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- HG Verschuuren
  toxicologist; DOW Europe, Horgen (Switzerland)
- AAE Wibowo
  toxicologist; Coronel Institute, Amsterdam
- F de Wit
  occupational physician; Labour Inspectorate, Arnhem
- CA Bouwman, *scientific secretary*
  Health Council of the Netherlands, Den Haag
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, Den Haag

The first draft of the present advisory report was prepared by 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.

Annex **C**

Comments on the public draft

A draft of the present report was released in 1998 for public review. The following organizations and persons have commented on the draft document:

- WF ten Berge, DSM, Heerlen

Annex **D**

Animal studies

Table 1 Carcinogenicity studies with 2-methylaziridine.

authors	species[a]	exposure characteristics	dose	exposure and experimental period[b]	findings	remark
Ulland *et al* (Ull71) Weisburger *et al* (Wei81)	rat male and female (26) Charles River CD	oral (gavage) 2 x/w	0, 10.17, 20.74 mg/kg bw/d (see remark)	Xpo = 60 w (low dose), 88 w (high dose) Xpe = 60 w	high dose: 22/52 tumour bearing animals, male: 3 gliomas, 3 earduct squamous-cell carcinomas, 2 intestinal adenocarcinomas, 6 leukaemias. female: 10 breast tumours (mainly adenocarcinomas), 1 glioma, 3 miscellaneous tumours (not specified). low dose: 37/52 tumour bearing animals, male: 4 gliomas, 3 ear-duct squamous-cell carcinomas, 2 intestinal adenocarcinomas, 4 leukaemias, 4 miscellaneous tumours (not specified). female: 20 breast tumours, 2 gliomas, 3 earduct squamous-cell carcinomas, 3 miscellaneous tumours. control: 1 pituitary adenoma among 6 males and 6 females	during exposure period treatment discontinued for 2 w followed by administration of lower doses (doses given are weighted mean doses) high mortality: survived at w 52: 11 males, 3 females in low dose group; 3 males, 2 females in high dose group

[a] The number between parenthese represents the number of animals exposed per sex per group.

[b] Xpo = exposure period; Xpe = experimental period.