Aziridine (ethylene imine)

Health based calculated occupational cancer risk values

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

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Bij brief van 3 december 1993, nr DGV/BMO-U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen.

Per 1 januari 1994 heeft mijn voorganger daartoe een commissie ingesteld die de werkzaamheden voortzet van de Werkgroep van Deskundigen (WGD). De WGD was een door genoemde minister ingestelde adviescommissie.

Hierbij bied ik u - gehoord de Beraadsgroep Gezondheid en Omgeving - een publicatie van de commissie aan over aziridine (ethyleen imine).
Deze publicatie heb ik heden ter kennisname aan de Minister van Volksgezondheid Welzijn en Sport en aan de Minister van Volkshuisvesting Ruimtelijke Ordening en Milieubeheer gestuurd.

w.g.
prof. dr JJ Sixma

Aziridine (ethylene imine)

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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. 2000/13OSH, The Hague, 6 September 2000

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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 maakt zij zo'n schatting voor aziridine. Zij heeft daarbij gebruik gemaakt van de methode die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06WGD) (Dec95).

Naar schatting van de commissie is de extra kans op kanker voor aziridine:

- 4×10^{-5} bij 40 jaar beroepsmatige blootstelling aan 0.9 $\mu g/m^3$
- 4×10^{-3} bij 40 jaar beroepsmatige blootstelling aan 90 $\mu g/m^3$

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 aziridine. It has used the method described in the report 'Calculating cancer risks due to occupational exposure to genotoxic carcinogens' (1995/06WGD) (Dec95).

The committee estimated that the additional lifetime cancer risk for aziridine amounts to:

- 4×10^{-5} for 40 years of occupational exposure to 0.9 $\mu g/m^3$
- 4×10^{-3} for 40 years of occupational exposure to 90 $\mu g/m^3$

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 aziridine 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.

In 1998, 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 C. The committee has taken these comments into account in deciding on the final version of the report.

Chapter 2

Aziridine (ethylene imine)

2.1 Introduction

The carcinogenicity of aziridine (CAS no. 115-56-4) has been evaluated by IARC (IARC75), ACGIH (ACG91) and DFG in 1970 and 1985 (Gre95). IARC has concluded that the degree of evidence for carcinogenicity of aziridine to animals is limited (IARC87). In addition, aziridine has been classified as a category 2 carcinogen by the European Union.

This evaluation of the carcinogenicity was based on a review by IARC (IARC87). In addition, literature was retrieved from online databases Medline, Toxline and Cancerlit covering the period 1975 to 1996*.

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

No case reports or epidemiological studies were available.

Table 1 (annex D) summarizes the carcinogenicity studies with experimental animals. Aziridine is carcinogenic in two strains of mice after oral administration, producing an increased incidence of liver-cell and pulmonary tumours (IARC75, Inn69). Subcutaneous injection of single doses in suckling mice produced an increased incidence

* After completion of the report, IARC concluded in 1999 that aziridine was a IARC group 2B compound. No additional animal studies were presented (IARC99).

of lung tumours in males. In one experiment in rats, the incidence of tumours at the injection site following its subcutaneous injection in oil is increased (IARC75).

In the absence of inhalation studies, the oral studies of Innes *et al* (1969) are used for the calculation of the potential cancer risk at the workplace. In this study, the incidences of mice ((C57Bl/6xC3H/Anf)F_1) with (mixtures of) different tumours after exposure to aziridine are 16/17 (male), 15/15 (female) and 31/32 (male and female) (Inn69) (for exposure regime see annex D). The committee is of the opinion that the available data do not indicate that the use of the linear model is not appropriate.

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

To calculate the carcinogenic activity expressed as incidence per mg aziridine per kg bw per day, the number of tumour-bearing male and female mice of the (C57B1/6xC3H/Anf)F_1 strain are used as starting point (Inn69). The average dose per day amounts to: (4.64 x 22 + 13 x 0.12 x 524)/(78 x 7) = 1.68 mg/kg bw per day.

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

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

$$\frac{31/32 - 30/166}{1.68 \times 546/750 \times 546/750 \times 24/24 \times 7/7} = 8.9 \times 10^{-1}\ [\text{mg/kg/d}]^{-1}$$

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, weights 70 kg and is exposed 24 hours per day 7 days/week, 52 weeks per year for lifetime.

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* I_{dose} = the carcinogenic activity attributable to the exposure to the substance per unit daily dose under lifespan conditions assuming a linear dose response relationship
Ie and Ic = incidence of tumour bearing animals or tumours in exposed and control amnimals, respectively,
Xpo = exposure period, Xpe = experimental period
and L = standard lifespan for the animals in question (L rat is assumed to be 1000 days)

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 of 8.9 x 10^{-1} per mg/kg bw/day, the additional lifetime cancer risk per mg/m^3 under occupational conditions, the HBC-OCRV, amounts:

$$\text{HBC-OCRV} = 8.9x10^{-1}\ x\frac{40y}{75y}x\frac{48w}{52w}x\frac{5d}{7d}x\frac{10m^3}{70kg} = 4.5 \text{ x } 10^{-2}[mg/m^3]^{-1}$$

Based on the HBC-OCRV of 4.5 x 10^{-2} per mg/m^3 the reference additional lifetime cancer risk amounts to:

- 4 x 10^{-5} for 40 years of exposure to 0.9 µg/m^3
- 4 x 10^{-3} for 40 years of exposure to 90 µg/m^3.

2.6 Existing occupational exposure limits

Table 2 summarizes the occupational exposure limits established by the regulatory authorities of United Kingdom, and by the USA-ACGIH. No occupational exposure limits have been established in The Netherlands, Germany (TRK value) and Sweden. The lowest occupational exposure limit (HBR-OEL) set by these countries amounts to 0.88 mg/m^3. This concentration is about a factor 10 higher than the concentration leading to an additional cancer risk of 4 x 10^{-3} (i.e., 90 µg/m^3).

Table 2 Occupational exposure limits for aziridine.

country	level		time realtion	notations	ref.
	ppm	mg/m^3			
The Netherlands[a]	-	-	-	-	
Germany[b]	(0.5)	(0.9)	8-h TWA	-	DFG96
UK[c]	-	-	8-h TWA	-	HSE95
Sweden[d]	-	-	-	-	NBO93
USA-ACGIH[e]	0.5	0.88	8-h TWA	skin	ACG96

[a] Aziridine is listed as a carcinogen

[b] The DFG classifies aziridine as a category A2 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 technical means. TRK-values are given in brackets.

[c] In the UK, aziridine has been included in the list of substances defined as carcinogens for the purpose of the COSHH regulations. Aziridine has been assigned the risk phrase “R45” (may cause cancer), and an OEL does not exist anymore.

[d] In Sweden, aziridine is placed under section 9 (carcinogen) and may only be handled by permission of the Labour Inspectorate.

[e] Classified as A3 carcinogen: animal carcinogen.

For the committee,
The Hague, 6 September 2000

dr ASAM van der Burght,
scientific secretary

Prof. dr GJ Mulder,
chairman

References

ACG91 American Conference of Governmental Industrial Hygienists (ACGIH). Ethylenimine. In: Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati OH, USA: ACGIH, 1991: 628-30.

ACG96 American Conference of Governmental Industrial Hygienists (ACGIH).1996. TLVs(R) and BEIs(R). Threshold Limit Valuesfor chemical substances and physical agents.Biological Exposure Indices. Cincinnati OH, USA: ACGIH, 1996: 22.

DEC95 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 Verlagsgesellschaft mbH, 1996: 57, 108, 128 (Mitteilung 32).

Gre95 Greim H, ed. Deutsche Forschungsgemeinschaft (DFG). Äthylenimin/Ethylenimin. In: Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werte (Maximale Arbeitsplatz-Konzentrationen). 1st-21th ed. Weinheim, FRG: VCH Verlagsgesellschaft mbH, 1995.

HSE95 Health and Safety Executive (HSE). Occupational exposure limits 1995. Sudbury (Suffolk), UK: HSE Books, 1995: 18, 49 (Guidance note 40/95).

IARC75 International Agency for Research on Can[illegible]-, S-, O-mustards and selenium. Lyon, France: IARC, 1975: 37-4[illegible]n of carcinogenic risk of chemicals to man, Vol 9.

IARC99 International Agency for Research on Cancer (IARC). Re-evalualtion of some organic chemicals, hydrazine and hydrogen peroxide (part two). Lyon, France: IARC, 1999: 337-344. In: IARC monographs on the evaluation of carcinogenic risk of chemicals to man, Vol 71.

Inn69 Innes JRM, Ulland BM, Valerio MG, *et al*. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. J Natl Cancer Inst 1969; 42: 1101-14.

ISZW95 Inspectiedienst van het Ministerie van Sociale Zaken en Werkgelegenheid (ISZW). De Nationale MAC-lijst 1995. The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1995: 21, 63 (pub no P145).

NBO93 National Board of Occupational Safety and Health (NBOSH). Occupational exposure limits. Solna, Sweden: NBOSH, 1993: 74 (Ordinance AFS 1993/9).

A Request for advice

B The committee

C Comments on the public draft

D Animal studies

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)
- 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: J Toet.
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 organisations and persons have commented on the draft document:

- WF ten Berge, DSM, Heerlen

Annex **D**

Animal studies

See table on the next page.

Table 1 Carcinogenicity studies with aziridine.

authors	species	exposure characteristics	dose	exposure and experimental period	findings	remark
Inn69	mouse[a]	gavage/ diet	4.6 mg/kg bw/day by gavage daily from the 7th to 28th day of age. Subsequently for 78 (male) or 77 (female) weeks at a concentration of 13 mg/kg of diet.	Xpo and Xpe 78 weeks for male and 77 weeks for female.	*male*: number of mice with tumours 16/17 [control 22/79] (15 with hepatomas [control 8/79], 15 with pulmonary tumours [control 5/79]). *female*: number of mice with tumours 15/15 [control 8/87] (11 with hepatomas [control 0/87), 15 with pulmonary tumours [control 3/87]).	
Inn69	mouse[b]	gavage/ diet	4.64 mg/kg bw/day by gavage daily from the 7th to 28th day of age. Subsequently for 77 weeks at a concentration of 13 mg/kg of diet.	Xpo and Xpe 77 weeks for male and female.	*male*: number of mice with tumours 16/16 (9 with hepatomas [control 5/90], 12 with pulmonary tumours [control 10/90]). *female*: number of mice with tumours 11/11 (2 with hepatomas [control 1/82], 10 with pulmonary tumours [control 3/82], 2 with lymphomas).	
IARC75	mouse[a]	subcutaneous injection	1 x 4.64 mg/kg bw on the 7th day of age.	Xpe: 80 weeks	*male*: number of mice with tumours 7/18 (2 hepatomas, 5 pulmonary tumours, 2 lymphomas). *female*: number of mice with tumours 1/18 (1 lung tumour)	number of tumours in treated males significantly higher than in control males (P = 0.01). control data not available
IARC75	mouse[b]	subcutaneous injection	4.64 mg/kg bw on the 7th day of age.	Xpe: 80 weeks	*male*: number of mice with tumours 6/18 (6 pulmonary tumours). *female*: number of mice with tumours 1/18 (1 lung tumour)	number of tumours in treated males significantly higher than in control males (P = 0.01). control data not available
IARC75	rat	subcutaneous injection	twice weekly (total 67 injections); total dose 20 mg/kg bw.	Xpo 33.5 weeks; Xpe 73 weeks	sarcomas at the injection site 5/6 male (control 1/10) and 1/6 female (control 0/9)	

Xpo = exposure period, Xpe = experimental period.

[a] $(C57Bl/6xC3H/Anf)F_1$

[b] $(C57Bl/6xAKR)F_1$