1,2-Dibromoethane

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. 1999/07OSH, The Hague, 20 December 1999

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Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid schat de Commissie WGD van de Gezondheidsraad het extra kankerrisico bij beroepsmatige blootstelling aan stoffen die door de Europese Unie of door de Commissie WGD als genotoxisch kankerverwekkend zijn aangemerkt. In dit rapport maakt zij zo'n schatting voor 1,2-dibroomethaan. 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 1,2-dibroomethaan:

- 4×10^{-5} bij 40 jaar beroepsmatige blootstelling aan 0.002 mg/m^3
- 4×10^{-3} bij 40 jaar beroepsmatige blootstelling aan 0.2 mg/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 1,2-dibromoethane. 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 1,2-dibromoethane amounts to:

- 4×10^{-5} for 40 years of occupational exposure to 0.002 mg/m^3
- 4×10^{-3} for 40 years of occupational exposure to 0.2 mg/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 1,2-dibromoethane 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

1,2-Dibromoethane

2.1 Introduction

1,2-Dibromoethane has been classified as a genotoxic carcinogen by the Dutch Expert Committee on Occupational Standards (WGD87).

This evaluation of the carcinogenicity and other toxic effects of 1,2-dibromoethane has been based on evaluations by the International Agency for research on Cancer — IARC (IARC77, IARC87), American Conference of Governmental Industrial Hygienists — ACGIH (ACG91), Deutsche Forschungsgemeinschaft — DFG (Gre95), Gold *et al*. (Gol84) and a previous document of the present committee (DECOS) (WGD87)*. In the latter document, the committee concluded that there was sufficient evidence for carcinogenicity to animals, but inadequate evidence for carcinogenicity to humans (WGD87). In addition, literature was retrieved from online databases Medline, Toxline and Chemical Abstracts covering the period 1966 to January 1996.

1,2-Dibromoethane (cas no. 106-93-4) is a colourless, non-flammable liquid, which decomposes in air. It is used as a fumigant.

* After completion of the report, IARC concluded in 1999 that 1,2-dibromoethane was a IARC-group 2A-compound (IARC99).

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

The available epidemiological data do not allow a quantitative risk assessment for 1,2-dibromoethane. Table 1 (Annex D) summarizes the carcinogenicity studies with experimental animals.

The committee selected the NTP rat inhalation study for calculation of the carcinogenic activity. In the NTP-inhalation study, in which 50 male and female rats were exposed to different concentrations of 1,2-dibromoethane, the total incidences of rats with a mixture of different tumors were 7/100 (0 mg/m^3), 87/100 (77 mg/m^3) and 93/100 (307 mg/m^3). Since the publication of this study was not available, the data summarized by Gold *et al* (Gol84) i.e. the number of animals being at risk showing a mixture of different tumours, were used to calculate the potential risk of cancer at the workplace.

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 the incidence per unit 1,2-dibromoethane concentration in air, the observed number of animals (rat) showing a mixture of different tumours is used. In addition, the committee assumes that the exposure was 8 hours per day for 5 days per week.

The incidence of tumour bearing animals per mg/m^3 (lifespan conditions, assuming a linear dose response relationship), $I_{concentration}$, is calculated as follows:

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

$$= \frac{87/100 - 7/100}{77\ [\text{mg/m3}] \times 721/1000 \times 721/1000 \times 8/24 \times 5/7} = 8.4 \times 10^{-2}\ [\text{mg/m}^3]^{-1}$$

* $I_{concentration}$ 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 per m^3
Ie and *Ic* are the tumour incidences in exposed and control animals, respectively
C is the concentration to which the animals are exposed, usually expressed in mg/m^3
X_{po} and X_{pe} are the exposure and experimental periods, respectively
L is the standard lifespan for animal species in question

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 of 8.4 x 10^{-2} per mg/m^3, the additional lifetime cancer risk per mg/m^3 under occupational conditions, the HBC-OCRV, amounts to:

$$\text{HBC-OCRV} = 8.4x10^{-2}\ x\frac{40y}{75y}x\frac{48w}{52w}x\frac{5d}{7d}x\frac{10m^3}{18m^3} = 1.64x10^{-2}[\text{mg/m}^3]^{-1}$$

Based on the HBC-OCRV of 1.64 x 10^{-2} per mg/m^3 the reference additional lifetime cancer risk* corresponds to:

- 4 x 10^{-5} for 40 years of exposure to 0.002 mg/m^3
- 4 x 10^{-3} for 40 years of exposure to 0.2 mg/m^3

2.6 Existing occupational exposure limits

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

The lowest occupational exposure limit set amounts to 4 mg/m^3. This concentration is about a factor 16 higher than the concentration leading to an additional cancer risk of 4 x 10^{-3} (i.e., 0.2 mg/m^3).

* The additional lifetime incidences of 4 x 10^{-3} and 4 x 10^{-5} for 40 years of occupational exposure are used by the Ministry of Social Affairs and Employment as reference values in deciding on occupational exposure limits.

Table 2 Occupational exposure limits for 1,2-dibromoethane.

country	level		time relation	skin notation
	ppm	mg/m^3		
The Netherlands[a]	-	-	-	-
Germany[b]	(0.1)	(0.8)	8-h TWA	+
UK[c]	0,5	4	8-h TWA	+
Sweden[d]	-	-	-	-
USA-ACGIH[e]	-	-	-	+

[a] The substance is classified as a carcinogen

[b] The DFG classifies 1,2-dibromoethane 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] Maximum exposure limit (8-h TWA reference period).

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

[e] Classified as A3 carcinogen: animal carcinogen.

2.7 Toxicity profile of 1,2-dibromoethane

Animal experiments indicate that 1,2-dibromoethane irritates the eyes, skin and respiratory tract. At long respiratory exposure, the nose is considered to be the target organ. Exposure to 115 mg/m^3, 6 h/d, 5 d/w, for 13 weeks results in nasal metaplasia, while no such effects were seen following exposure to 23 mg/m^3. Systemic effects (liver) occur at higher levels (NOAEL: 115 mg/m^3, 6 h/d, 5 d/w, 13 w) (WGD87).

The committee believes that a health based occupational exposure limit for 1,2-dibromoethane derived from non-genotoxicity and non-carcinogenicity data would in all likelihood 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

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7Chu81 Chu C, Milman HA. Review of experimental carcinogenesis by compounds related to vinyl chloride. Environ Health Persp 1981; 41: 211-20.

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 Verlagsgesellschaft mbH, 1996: 43, 107, 127 (Mitteilung 32).

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Duu79 Van Duuren BL, Goldschmidt BM, Loewengart G, *et al*. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J Natl Cancer Inst 1979; 63: 1433-9.

Gol84 Gold LS, Sawyer CB, Magaw R, *et al*. A carcinogenic potency database of the standarized results of animal bioassays. Environ Health Persp 1984; 58: 9-319.

Gre95 Greim H, ed. 1,2-Dibromäthan. In: Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werte (Maximale Arbeitsplatzkonzentrationen). 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, 27 (Guidance note EH 40/95).

IARC77 International Agency for Research on Cancer (IARC). Ethylene dibromide. Some fumigants, the herbicides 2,4-D and 2,4,5-T chlorinated dibenzodioxins and miscellaneous industrial chemicals. Lyon, France: IARC, 1979: 195-209. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to man, Vol 15.

IARC87 International Agency for Research on Cancer (IARC). Ethylene dibromide. Overall evaluations of carcinogenicity: an updating of IARC monographs. Lyon, France: IARC, 1987: 204-5. In: IARC monographs on the evaluation of carcinogenic risks to humans, Volumes 1 to 42; Suppl 7.

IARC99 International Agency for Research on Cancer (IARC). Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (part two) 1999; 71: 641-69.

ISZW95 Inspectiedienst van het Ministerie van Sociale Zaken en Werkgelegenheid (ISZW). De Nationale MAC-lijst 1995. The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1995: 28, 63, 65 (pub no P145).

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

Ols73 Olson WA, Haberman RT, Weisburger EK, *et al*. Brief communication: Induction of stomach cancer in rats and mice by halogenated aliphatic fumigants. J Natl Cancer Inst 1973; 51: 1993-5.

Plo78 Plotnik HB. Carcinogenesis in rats of combined ethylene dibromide and disulfiram. J Am Med Assoc 1978; 239: 1609.

Sti81 Stinson SF, Reznik G, Ward JM. Characteristics of proliferative lesions in the nasal cavities of mice following chronic inhalation of 1,2-dibromoethane. Cancer Lett 1981; 12: 121-9.

Wei75 Weisburger K, Kraybill HF. Carcinogenicity of ethylene dibromide (EDB) and 1,2-dibromo-3-chloropropane (DBCP) after oral administration in rats and mice. Toxicol Appl Pharmacol 1975; 33: 171-2.

WGD87 Werkgroep van Deskundigen (WGD). Rapport inzake grenswaarde dibroomethaan. The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1987; rep no RA 5/87.

Won82 Wong LCK, Winston JM, Hong CB, *et al.* Carcinogenicity and toxicity of 1,2-dibromoethane in the rat. Toxicol Appl Pharmacol 1982; 63: 155-65.

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

See next pages.

Table 1 Carcinogenicity studies with 1,2-dibromoethane.

authors	species	exposure characteristics	dose	exposure and experimental period	findings	remark
Olson *et al* (Ols73); Weisburger /Kraybill (Wei75)	rat[a] male and female (50) Osborne - Mendel	gavage, 5 x per week, corn oil	0, 40, 80 mg/kg bw/day	Xpo/Xpe[b]: 54 w (interim results)	at 40 mg/kg bw, 73/91 had squamous cell carcinomas of the forestomach. at 80 mg/kg bw, 45/91 had squamous cell carcinomas of the forestomach. control: 1/20 females had mammary adenoma; no carcinomas in 20 control males	after 16 w, the higher dose level was discontinued for 14 w due to toxic effects. from week 30 all rats received 40 mg/kg bw/d
Chu, Milman (Chu81)	rat[0] male and female (50) Osborne - Mendel	gavage, ? x per week, corn oil	male : 0, 38, 41 mg/kg bw female : 0, 37, 39 mg/kg bw	37 mg: Xpo 57 w, Xpe 63 w. 38 mg: Xpo 47 w, Xpe 63 w. 39 mg: Xpo 44 w, Xpe 61 w, 41 mg: Xpo 34 w, Xpe 49 w.	tumour incidences: forestomach: male 0/20, 45/50, 33/50; female 0/20, 40/50, 29/50. hemangiosarcoma: male 0/20, 11/50, 4/50. liver (hepatocellular): female 0/20, 1/47, 5/48	complete results can be found in NCI-CG-TR-86 DHEW/Pub/NIH-78-1336, 1978
Chu, Milman (Chu81)	mouse male and female (50) $B6C3F_1$	gavage, ? x per week, corn oil	0, 62, 107 mg/kg bw	Xpo: 53 w, Xpe: 78 w (male) and 90 w (female)	tumour incidences: forestomach: male 0/20, 45/50, 29/49; female 0/20, 46/49, 28/50. lung: male 0/20, 4/45, 10/47; female 0/20, 11/43, 6/46	complete results can be found in NCI-CG-TR-86 DHEW/Pub/NIH-78-1336, 1978
Olson *et al* (Ols73)	mouse male and female (50) (57 BLx (3H)F_1	gavage, 5 x per week, corn oil	0, 60, 120 mg/kg bw/d	Xpo/Xpe: 42 w (interim results)	at 60 mg/kg bw, 5/12 had squamous-cell carcinomas of the forestomach. at 120 mg/kg bw, 2/42 had squamous-cell carcinomas of the forestoamch. no tumours in 20 male and 20 female controls	the dose levels were increased to 100 and 200 mg/kg bw/day between weeks 13 and 15
Van Duuren (Duu79)	mouse male and female (30) non-imbred Ha:ICR	skin application, 3 x per week	50 mg per application 25 mg per application	Xpo/Xpe: 440-594 d.	8/30 skin papillomas; 26/30 lung tumours (benign papillomas); 3/30 stomach tumour 2/30 skin papillomas; 24/30 lung tumours (benign papillomas); 3/30 stomach tumour	

[a] Number between parenthesis represents the number of animals exposed per sex per group.

[b] X_{po}: exposure period; X_{pe}: experimental/ observation period

Table 1 Carcinogenicity studies with 1,2-dibromoethane, Continued.

authors	species	exposure characteristics	dose	exposure and experimental period	findings	remark
Chu, Milman (Chu81)	mouse male and female (50) $B6C3F_1$	inhalation, ? h/d, ? d/w	0, 10 ppm (77 mg/m^3), 40 ppm (307 mg/m^3)	Xpo/Xpe: 103 w	tumour incidences: lung: male 0/41, 3/48, 19/46; female 1/49, 5/49, 37/50. nasal Cavity: female 0/50, 0/50, 6/50. mammary gland: female 2/50, 14/50, 8/50	full details can be found in the NTP study (1982)
Stinson *et al* (Sti81)	mouse male and female (50) $B6C3F_1$	inhalation, 6 h/d, 5 d/w	0, 10 ppm (77 mg/m^3), 40 ppm (307 mg/m^3)	Xpo/Xpe: 103 w (10 ppm) , 90 w (40 ppm)	lesions induced in the nasal cavities: focal epithelial hyperlasia: fale 0/45, 1/44, 10/46; female 0/50, 3/49, 11/49 (0, 10, 40 ppm, respectively). squamous papillomas in the 40 ppm group: male 3/46, female 7/49. squamous adeno-, or mixed carcinomas in the 40 ppm group: female 7/49	
Wong *et al* (Won82). Preliminary results were published by Plotnik (Plo78)	rat male and female (48) Sprague-Dawley	inhalation, 7 h/d, 5 d/w	0, 20 ppm (154 mg/m^3).	Xpo/Xpe: 18 mo	mortality after 18 mo: control male 5/48, female 6/48; treatment male 43/46, female 37/48. tumours: mammary tumours: control female 2/48; treatment female 25/48. spleen (haemangiosarcoma): male 0/48, female 0/48; treatment male 10/46, female 6/48. adrenal: control male 2/48, female 1/48; treatment male 11/46, female 6/48. subcutaneous tissue (mesenchymal tumour): control male 3/48, female 0/48; treatment male 11/46, female 1/48	
Chu, Milman (Chu81); Gold *et al*. (Gol84)	rat male and female (50) F344	inhalation, ? h/d, ? d/ w	0, 10 ppm (77 mg/m^3), 40 ppm (307 mg/m^3)	Xpo/Xpe: 78- 103 w	tumour incidences: nasal cavity: male 0/50, 20/50, 28/50; female 0/50, 20/50, 29/50. mesothelioma: male 1/50, 7/50, 25/50. mammary gland: female 4/50, 29/50, 24/50. mixture of different tumours (adenomas and carcinomas of the nasal cavity, haemangiosarcomas of the spleen, mammary tumours): male + female 7/100, 87/100, 93/100	full details can be found in the NTP study (1982) (NTP-TR-210; PB82-181710). exposure assumed to be 8 h/d, 5 d/w

[1] Number between parenthesis represents the number of animals exposed per sex per group.

[2] X_{po}: exposure period; X_{pe}: experimental/ observation period