N-Nitrosodimethylamine (NDMA)

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. 1999/12OSH, The Hague, 20 December 1999

Preferred citation:
Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards (DECOS). *N*-Nitrosodimethylamine (NDMA). The Hague: Health Council of the Netherlands, 1999; publication no. 1999/12OSH.

ISBN: 90-5549-298-1

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 N-nitrosodimethylamine (NDMA). Zij heeft daarbij gebruik gemaakt van de methode die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06WGD) (Hea95).

Naar schatting van de commissie is de extra kans op kanker voor N-nitrosodimethylamine (NDMA):

- 4×10^{-5} bij 40 jaar beroepsmatige blootstelling aan 0.002 $\mu g/m^3$
- 4×10^{-3} bij 40 jaar beroepsmatige blootstelling aan 0.2 $\mu g/m^3$

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 *N*-nitrosodimethylamine (NDMA). It has used the method described in the report 'Calculating cancer risks due to occupational exposure to genotoxic carcinogens' (1995/06WGD) (Hea95).

The committee estimated that the additional lifetime cancer risk for *N*-nitrosodimethylamine (NDMA) amounts to:

- 4×10^{-5} for 40 years of occupational exposure to 0.002 μg/m^3
- 4×10^{-3} for 40 years of occupational exposure to 0.2 μg/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-OCRV's by the committee for *N*-nitrosodimethylamine. The members of the committee are listed in Annex B. The first draft of this report was prepared by H Stouten and MI Willems, from the TNO Nutrition and Food Research Institute in Zeist, by contract with the Ministry of Social Affairs and Employment. .

Chapter 2

N-Nitrosodimethylamine (NDMA)

2.1 Introduction

NDMA has been classified as a genotoxic carcinogen by the European Union (ISZW99).

The carcinogenicity of NDMA has been evaluated by DFG (Gre95), and IARC (IARC7; IARC78). NDMA is carcinogenic in all animal species tested: mice, rats, hamsters, guinea pigs, rabbits, ducks, mastomys, various fishes, newts and frogs. It induces benign and malignant tumours following administration by various routes, including ingestion and inhalation, in a wide variety of organs, but mainly in the liver, kidneys and respiratory tract. It is carcinogenic following prenatal administration and in single doses (IARC78).

This evaluation is based on literature retrieved from online databases covering the period up to 1994.

2.2 Identity and physical and chemical properties

Chemical name	:	*N*-nitrosodimethylamine
CAS registry number	:	62-75-9
Synonyms	:	*N*-methyl-*N*-nitrosomethanamine; *N*-nitrosodimethylamine; DMN; DMNA; dimethylnitrosoamine; nitrosodimethylamine; methanamine, *N*-methyl-*N*-nitroso-; dimethylamine, *N*-nitroso-
Description	:	yellow, oily liquid
Molecular formula	:	$C_2H_6N_2O$
Structure	:	

Molecular weight	:	74.08
Boiling point (100 kPa)	:	151-153°C
Density of the liquid (20°C)		
(water = 4°C)	:	1.0048
Flash point	:	61°C
Solubility	:	soluble in water, organic solvents and lipids
Conversion factors	:	1 ppm = 3 mg/m^3 air
(20°C, 100 kPa)	:	1 mg/m^3 air = 0.333 ppm

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

No information was found on the possible carcinogenicity in humans. However, similarities in metabolism between human and rodent tissues have been demonstrated.

Tables 1 and 2 (Annex D) summarize the main oral and inhalatory carcinogenicity studies in experimental animals. Besides the studies tabulated, a number of other studies has been conducted including studies in which the test substance was administered by the subcutaneous, intramuscular or intraperitoneal route. These latter studies were not tabulated, since they are considered to be less relevant for estimation of long-term cancer risk under workplace exposure conditions than dermal, inhalation and oral studies. No dermal studies were found.

NDMA has been tested in rats by oral administration via drinking water, gavage and diet (Table 1). The main target organ upon long-term oral administration is the liver, although also tumours in lungs and kidneys have been reported. A comprehensive oral long-term carcinogenicity study has been conducted by Peto *et al*. (Pet91a, Pet91b), who examined in detail the dose-response relationship for the effects of NDMA and NDEA on esophageal cancer (NDEA) or on various types of liver cancer (NDEA and NDMA). Each of the nitrosamines was given at 16 different doses in drinking water for lifetime. The dose range varied between 0, 0.033 and 16.896 ppm in drinking water*. The main target organ for tumour formation by NDMA was the liver, although NDMA also caused a few tumours of the lung (Pet91a; Pet91b). The authors concluded that the linear relationship observed at low doses (below 1 ppm) suggests that, among rats which were allowed to live their natural life span (median survival about 2.5 years), a dose of 1 ppm NDMA in drinking water (corresponding to an oral intake of 50 µg NDMA/kg bw/day), will cause about 25% of the animals to develop a liver neoplasm (Pet91a). In other words the additional lifetime cancer risk in rats for NDMA orally dosed in drinking water amounts to 5×10^{-3} per µg/kg bw/day (life span conditions) or 1.3×10^{-3} ($= 5 \times 10^{-3} \times 18/70$) per µg/m^3 (life span conditions).

Several of the inhalation studies summarized in Table 2 (Annex D) allow an estimation of the additional life-time cancer risk under life span conditions of exposure.

An inhalation experiment with rats published by Klein *et al*. appears to be the most sensitive and most reliable study for estimation of the potential risk of cancer at the workplace. Klein *et al*. exposed female rats to atmospheres containing 0, 0.04, 0.2 or 1.0 ppm NDMA in air (corresponding to 120, 600 and 3000 µg/m^3) four times per week, 4-5 hours per day, for 207 days. The median survival time of animals exposed to 1 ppm NDMA was nine months less than that of untreated controls owing to toxicity. The median survival of animals given 0.04 ppm was two months longer than that of control rats (see Table 1, annex D). Tumours occurred mainly in the nasal cavity, with the highest incidences in the groups receiving 1.0 and 0.2 ppm NDMA (19/36 and 31/36 tumour-bearing animals); in the lowest exposure group in 13 out of 36 animals nasal tumours were observed. No nasal or respiratory tract tumours were seen in control animals. At 1 ppm 47% of the tumours were aesthesioneuroblastomas, whereas only 6% and 15% of this tumour type was observed following inhalation of 0.2 and 0.04 ppm NDMA, respectively. In the 0.2 and 0.04 ppm group mucoepidermoid tumours represented the greatest proportion (Kle91).

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* The dose in mg/kg bw/day may be obtained by dividing ppm by a factor of 20 (see Pet91.

2.4 Carcinogenic activity in experimental animals, life-time low-dose exposure

The lowest concentration (120 µg/m^3) resulting in the induction of the tumour of interest i.e. tumours of the nasal mucosa in the study of Klein was used as starting point to calculate the incidence per µg NDMA per m^3 (Kle91). 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 per µg/m^3 (life span conditions assuming a linear dose-response relationship) is calculated as follows:

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

Since it is not clear from the paper of Klein *et al*. (Kle91), whether the animals were exposed 4 times a week for a total exposure period of 207 days, or 4 times a week with a total of 207 exposure days (total exposure period 207/4 x 7 days = 362 days) the estimated incidence per µg/m^3 amounts either to:

- $\frac{13/36-0/36}{120x4.5/24x4/7x207/795x860/795} = 1 \times 10^{-1}\ [\mu g/m^3]^{-1}$

or to

- $\frac{13/36-0/36}{120x4.5/24x4/7x362/795x860/795} = 5.7 \times 10^{-2}\ [\mu g/m^3]^{-1}$

2.5 Health risk to humans

To estimate the additional lifetime risk of cancer in humans under life span conditions on the basis of results from animal experiments, it is assumed that no difference exists between experimental animals and man with respect to toxicokinetics, mechanism of

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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, usually expressed per mg/m^3 or per mg/kg bw/day.
I_e and I_c = incidence of tumour bearing animals or tumours in exposed and control animals, respectively,
X_{po} = exposure period, X_{pe} = experimental period
L = standard lifespan for the animals in question (L rat is assumed to be 1000 days)

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, weighs 70 kg, and is exposed 24 hours per day, 7 days per week, 52 weeks per year, for life-time.

2.6 Health risk to workers, calculation of the HBC-OCRV

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, five days a week, for 40 years, and inhales 10 m^3/8 hour-working day.

Using as starting point the estimated incidence of 1 x 10^{-1} per µg/m^3, the additional life-time cancer risk per µg/m^3 under occupational exposure conditions (=HBC-OCRV) amounts to:

$$\text{HBC-OCRV} = 0.1\ x\frac{40y}{75y}x\frac{48w}{52w}x\frac{5d}{7d}x\frac{10m^3}{18m^3} = 1.9 \times 10^{-2}[x10^{-3}mg/m^3]^{-1}$$

Based on the HBC-OCRV of 1.9x10^{-2} per µg/m^3 the additional life-time cancer risk amounts to:

- 4 x 10^{-5}, for 40 years of exposure to 0.2 x 10^{-2} µg/m^3
- 4 x 10^{-3}, for 40 years of exposure to 0.2 µg/m^3

2.7 Existing occupational exposure limits

The regulatory authorities of The Netherlands, have not established an occupational exposure limits for NDMA (ISZW99). The regulatory authorities of Germany and the UK, have classified NDMA as a suspected human carcinogen (DFG99; HSE99). ACGIH has classified NDMA as an A3 carcinogen, ie a confirmed animal carcinogen with unknown relevance to human (ACG99). Occupational exposure limits have not been established (ACG99, Arb96, DFG99, HSE99, Hun97, NBO93, ISZW99). NDMA has been given a skin notation by ACGIH (ACG99).

2.8 Toxicity profile of NDMA

The toxicology of NDMA has been reviewed by IARC (IARC78), and EPA cited in ACG91. NDMA is a highly toxic compound by several routes of administration. The acute oral LD_{50} in adult male rats ranges from 27 to 41 mg/kg bw. Administration of NDMA is hepatotoxic, and it induces centrilobular necrosis with hemorrhage within 24 hours, followed by ascites and jaundice.

The LC_{50} from a 4-hour exposure was 78 ppm for rats (234 mg/m^3) and 57 ppm (171 mg/m^3) for mice. Of three dogs exposed 4 hours at 16 ppm (48 mg/m^3), only one survived but with liver damage. A NOAEL for repeated dose studies was not available for any of the exposure routes.

Conclusion

Due to a lack of toxicity data the concentration levels associated with the referential cancer risk levels cannot be compared with a tentatively estimated health-based occupational exposure limit derived from data other than those on genotoxicity/carcinogenicity.

The Hague, 20 December 1999,
for the committee

dr ASAM van der Burght,
scientific secretary

Prof. dr GJ Mulder,
chairman

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ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). 1999. TLVs® and BEIs®. Guide to Occupational Exposure Values, Cincinnati OH, USA: ACGIH, 1999: 126.

Arb96 Arbejdstilsynet. Exposure Limit value for substances and materials. Copenhagen, Danmark: Arbejdstilsynet, 1996:10.

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Lij91 Lijinsky W, Thomas BJ, Kovatch RM. Local and systemic carcinogenic effects of alkylating carcinogens in rats treated by intravesicular administration. Jpn J Cancer Res 1991; 82: 980-6.

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Tan88 Tanaka A, Hisanaga A, Inamasu T et al. A comparison of the carcinogenicity and *N*-nitrosodiethylamine or *N*-nitrosodimethylamine after intratracheal instillation into Syrian golden hamsters. Food Chem Toxicol 1988; 26: 847-50.

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 H Stouten and M Willems, from the Department of Occupational Toxicology of the TNO Nutrition and Food Research Institute, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: E Vandenbussche-Parméus.
Lay-out: J van Kan.

Annex **C**

Comments on the public draft

A draft of the present report was released in 1999 for public review. The following organizations and persons have commented on the draft document:

- mr P Ridgeway, Health and Safety Executive, United Kingdom
- mr A Aalto, Tampere, Finland

Annex **D**

Animal studies

Table 1 Carcinogenicity studies with NDMA, oral experiments.

authors	species	experimental	findings, tumours	remark
Peto *et al.* (Pet91a; Pet91b)	rat Colworth 60 males + 60 females/group 120 males, 120 females controls	dose levels: 0, 0.033, 0.066 ... 17.896 ppm in drinking water (15 different doses of NDMA), interim sacrifices at 12 (N = 6) and 18 (N = 6) months Xpo = 3.5 yrs, N = 48	liver lung	I (life span) = 2.5 x 10^{-3} per µg/kg bw/day for details see description in text
Crampton. (in Gre95)	rat male/female 120/group drinking water	33 ppb: 2 µg/kg bw/day, total 2 mg/kg bw 132 ppb: 8 µg/kg bw/day, total 8 mg/kg bw Xpo = Xpe , life span	33 ppb: hyperplastic liver modules in male 132 ppb: carcinogenic in male	no details reported
Keefer *et al.* (in Gre95; IARC78)	rat males 30/group drinking water	Xpo = 5 mg/l drinking water, 5 times a week for 30 weeks (total dose 45 mg/kg bw) Xpe = 2 years	controls: 0%? NDMA group: 27% TBA (liver) Gold	I (life span) = 8.2 x 10^{-3} per µg/kg bw/day
Magee and Barnes (in Gre95; IARC78)	rat male/female diet	dose levels, mg/kg diet: 0, 5 (total 250 mg/kg bw), 10 (total 500 mg/kg bw), 20 (total 1000 mg/kg bw) Xpo = Xpe, life span	Percentage of animals with a liver tumour amounted to 0% in controls, 0% in 5 mg group, 33% in 10 mg group, 83% in 20 mg group	I (life span) = 6.6 x 10^{-4} per µg/kg bw/day
Terracini (in Gre95; IARC78)	rat male/female diet	dose groups, mg/kg diet: 0 (N = 41), 2 (N= 37), 5 (N = 68), 10 (N = 5), 20 (N = 23), 50 (N = 12) Xpo = Xpe = 120 weeks	number of animals with a tumour of the liver amounted to 0/41, 1/37, 5/68, 2/5, 15/23, 10/12 in the resp. groups.	I (life span) = 1.2 x 10^{-3} per µg/kg bw/day

Continuation *table 1*

authors	species	experimental	findings, tumours	remark
Anderson (in Gre95)	mouse male/female drinking water	10 ppb in drinking water total dose ± 10 mg/kg bw Xpo = 28 weeks (in utero ± 25 weeks)	TBA, lungtumours male test 8/25 (32%), control 1/23 (4,3%) female test 6/36 (17%), control 4/38 (10%) male/female test 14/61(23%), control 5/61 (8.2%)	no details reported
Lijinksi and Kovatch (in Lij91)	rat gavage	Xpo = 4 mg weekly for 30 weeks Xpe = life span Total dose: 0.8 mmol	% rats with tumours of kidney 83, lung 75, liver 42 Median week of death 59	no details reported

Table 2 Carcinogenicity studies with NDMA, inhalation and intratracheal experiments.

authors	species	experimental	findings, tumours	remark
Moiseev and Benemanskij (in Gre95; IARC78)	rat males and females Wistar inhalation	*Experimental groups:* 0, N = ? 0.05 mg/m^3, N = 87, 1.5 mg/kg total 0.2 mg/m^3, N = 61, 40 mg/kg total Xpo = 25 months, hours/day? days/week? Xpe = ? Assumptions for incidence calculation: Xpo 8hrs/d, 7 d/wk, Xpe = Xpo	***0.05 mg/m***^{3}, no increased carcinogenicity *0.2 mg/m*^{3}, 12/61 lung (control 5/77) 12/61 liver (control 3/77) 32/61 kidneys (control 2/77)	Not given: - total number of TBA with tumours of interest - exposure characteristics - experimental period I (kidneys, life span) > 1.3 x 10^{-2} per mg/m^3
Moiseev and Benemanskij (in Gre95; IARC78)	mouse males and females Balb/C inhalation	*Experimental groups:* 0, N = ? 0.05 mg/m3, 2 mg/kg total, N = 77, 0.2 mg/m^3, 100 mg/kg total, N = 101 Xpo = 17 months, daily, hours/day? Xpe = ? Assumptions for incidence calculation: Xpo 8hrs/d, 7 d/wk, Xpe = Xpo	*0.05 mg/m*^{3}, no increased carcinogenicity *0.2 mg/m*^{3} 19/101 lung (control 3/81) 6/101 liver (control 0/81) 4/101 kidneys (control 0/81)	Not given: - total number of TBA with tumours of interest - exposure characteristics - experimental period I (lung, life span) > 4.8 x 10^{-3} per mg/m^3
Druckrey *et al*. (Dru67)	rats BD inhalation	twice weekly 30 min. 50 ppm (150 mg/m^3) and 100 ppm (300 mg/m^3), Xpe = life span, Xpo?	*2 mg/kg bw* 8/12 nasal tumours (olfactory region) *4 mg/kg bw* 4/6 nasal tumours	
Klein *et al*. (Kle91)	rats Sprague-Dawley 36 males/group inhalation	*Experimental groups:* 0 ppm 0.04 ppm (120 µg/m^3)[a] 0.2 ppm (600 µg/m^3) 1.0 ppm (3000 µg/m^3) Xpo = 4 times per week, 4-5 h/day, 207 days Xpe = life span	TBA nasal cavity[b] *0 ppm* 0/36 (795) *0.04 ppm* 13/36 (860) ***0.2 ppm*** 31/36 (772) ***1.0 ppm*** 19/36 (524)	see description in text I (life span) = 5.7 a 10 x 10^{-2} per µg/m^3
Tanaka *et al*. (Tan88)	Syrian golden hamsters intratracheal	Xpo = once a week for 15 weeks Vehicle control: N = 39 0.05 mg/animal/wk, N = 20 0.1 mg/animal/wk, N = 20 Xpe = life span	TBA liver: Vehicle control: 1/26 *0.05 mg*: 1/18 *0.1 mg*: 3/16	Exposure period < 1/4 natural life span

[a] Estimation of mean daily uptake on the basis of actual [NDMA] and the mean breathing volume of all rats in each group amounted to 10 µg, 40 µg and 180 µg/kw bw/day for the 0.04, 0.2 and 1.0 ppm group, respectively.

[b] In brackets the mean survival time in days is given