2-Nitropropane

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. 1999/13OSH, 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 2-nitropropaan. 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 2-nitropropaan:

- 4×10^{-5} bij 40 jaar beroepsmatige blootstelling aan 0.036 mg/m^3
- 4×10^{-3} bij 40 jaar beroepsmatige blootstelling aan 3.6 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 2-nitropropane. 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 2-nitropropane amounts to:

- 4×10^{-5} for 40 years of occupational exposure to 0.036 mg/m^3
- 4×10^{-3} for 40 years of occupational exposure to 3.6 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 by the committee for 2-nitropropane. 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

2-Nitropropane

2.1 Introduction

2-Nitropropane has been classified as a genotoxic carcinogen by the European Union (ISZW99).

This evaluation of the carcinogenicity and other toxic effects of 2-nitropropane has been based on reviews by IARC (IARC82), the Dutch Expert Committee on Occupational Standards (DECOS; WGD85), the Deutsche Forschungsgemeinschaft (DFG; Gre95), the American Conference of Governmental Industrial Hygienists (ACGIH; ACG91), and the UK Health and Safety Executive (HSE96a). In addition, literature was retrieved from the online data bases Medline, Toxline, and Chemical Abstracts, covering the period 1966 to December 1995/January 1996. Where relevant, the original publications were reviewed and evaluated as indicated in the text.

2.2 Identity and physical and chemical properties*

Chemical name	:	2-nitropropane
CAS registry number	:	79-46-9
EEC number	:	609-002-00-1
EINECS number	:	201-209-1
Synonyms	:	β-nitropropane; dimethylnitromethane; isonitropropane; nitroisopropane; sec-nitropropane
Description	:	2-nitropropane is a colourless, oily liquid with a pleasant odour (detectable at 5-25 ppm)
Molecular formula	:	$C_3H_7NO_2$
Structure	:	

Molecular weight	:	89.1
Boiling point (101.3 kPa)	:	120.25 ºC
Melting point	:	-93 ºC

Density of the fluid (20 ºC)	:	0.998 g/ml
Vapour density (air = 1; 101.3 kPa)	:	3.06
Vapour pressure (20 ºC)	:	2.3 kPa
Relative density of saturated vapour/air mixture (air = 1; 20 ºC)	:	1.04
Saturated vapour concentration	:	17,100 ppm
Flash point	:	39 ºC (open cup)
Explosive limits, vol% in air	:	2.6%
Solubility in water	:	170 g/l
Solubility in organic solvents	:	soluble in ethanol and diethylether
Log $P_{oct/w}$	:	0.554
Conversion factors (25 ºC, 101.3 kPa)	:	1 mg/m^3 = 0.28 ppm 1 ppm = 3.6 mg/m^3
EEC labeling	:	R: 45-10-20/22; S: 53-45
EEC classification	:	R 10/ Carc cat 2; R45/ Xn; R 20/22

* CEG93; HSE96a; IARC82; WGD85

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

The carcinogenicity of 2-nitropropane has been evaluated by IARC (IARC82), DECOS (WGD85), DFG (DFG89), ACGIH (ACG91), and WHO (WHO92). IARC concluded that there was sufficient evidence for carcinogenicity to rats but that there were no adequate epidemiological data available (IARC82); the DFG concluded that 2-nitropropane was unmistakably carcinogenic in animal experimentation only (Gre95), while ACGIH concluded that 2-nitropropane is a suspect human carcinogen. However, the available epidemiological data do not allow quantitative risk assessment for 2-nitropropane.

The ACGIH evaluated a retrospective mortality study of a group of 1481 employees and former employees of a 2-nitropropane production facility in Sterlington, Louisiana, with up to 27 years of exposure (Mil79). In 1983, an update of this study up to January 1982 was published (Bol83). The ACGIH concludes that lack of individual exposure data, the limited number of workers with long exposures (15 years), and the small number of deaths among the group studied prohibit the conclusion from these data that 2-nitropropane is without carcinogenic activity in humans (ACG91).

Tables 1 and 2 (Annex D) summarize the carcinogenicity studies in experimental animals. The chronic toxicity of 2-nitropropane was examined in mice exposed by inhalation and in rats exposed orally (gavage) or by inhalation. Exposure by inhalation resulted in hepatocellular carcinomas and hepatocellular nodules in rats and in an increased incidence of nodular hyperplasia in the liver of mice. Male animals appeared more susceptible than females. Oral exposure of rats for 16 weeks resulted in hepatocarcinomas in all exposed animals in week 77.

The series of studies reported by Griffin *et al*. is used for calculation of the potential cancer risk of 2-nitropropane under workplace conditions. Griffin *et al*. examined in 3 separate experiments the long term toxicity of 25, 100 and 200 ppm 2-nitropropane in male and female SD-rats exposed by inhalation, 7 hr/day, 5 days per week for 6 months (200 ppm), 18 months (100 ppm) and 22 months (25 ppm) (Gri78, Gri80, Gri81). At 100 ppm, hepatocellular carcinomas in males occurred after 12 months of exposure, and in females after 18 months; at 200 ppm, hepatocellular carcinomas in males occurred after 6 months of exposure (Gri80, p.280). Except for a short note in the discussion part of Gri80, no information is given on the number of tumour-bearing animals in the 100 and 200 ppm groups (Gri78, Gri80, Gri81). At 25 ppm, focal areas of hepatic cellular nodules were reported to occur in 3 of 250 control animals and 13 of 249 exposed animals (Gri80). Despite a number of shortcomings, e.g. limited reporting, lack of information on the number of tumours and tumour-bearing animals in the 100 and 200

ppm groups, and, moreover, inconsistencies in the reporting, the studies of Griffin *et al*. are considered to be the most appropriate to estimate the carcinogenic activity of 2-nitropropane in view of their experimental set up, namely duration time up to 22 months and data of different exposure levels. In the absence of reliable data on the numbers of tumour bearing animals in the 100 and 200 ppm exposure groups and the incidence of tumour-bearing animals in the control groups, the incidence of hepatic cellular nodules in the 25 ppm group is used as starting point to calculate the carcinogenic activity of 2-nitropropane. At this exposure level, the combined incidence (male and female) of hepatic cellular nodules amounted to 13/249.

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

To calculate the carcinogenic activity expressed as the incidence per mg 2-nitropropane per m^3, the lowest concentration (25 ppm*, ie 78 mg/m^3) resulting in the induction of hepatocellular nodules in the study of Griffin is used as starting point (Gri80, Gri81). 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/kg bw/day (lifespan conditions, assuming a linear dose-response relationship), $I_{concentration}$, is calculated as follows:

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

$$\frac{13/249 - 3/250}{(78\ mg/m^3) \times (665^d/1000^d) \times (665^d/1000^d) \times 7/24 \times 5/7} = 5.6*10^{-3}\ [mg/m^3]^{-1}$$

2.5 Health risk to humans, lifetime low-dose exposure

To estimate the additional lifetime risk of cancer in humans under lifespan conditions un 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

* Conversion of 25 ppm into 78 mg/m^3 is taken over from Griffin *et al* and is based on daily measurements of temperature and atmospheric pressure.

** $I_{concentration}$ = 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)

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.

2.6 Health risk to workers, establishment 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 during 5 days per week, 48 weeks per year, for 40 years, and inhales 10 m^3 air per 8-hour-working day.

Using as starting point the estimated incidence of 5.6 x 10^{-3} per mg/m^3, the additional lifetime cancer risk per mg/m^3 under occupational conditions (=HBC-OCRV) amounts to:

$$\text{HBC-OCRV} = 5.6 \times 10^{-3} x \frac{40y}{75y} x \frac{48w}{52w} x \frac{5d}{7d} x \frac{10m^3}{18m^3} = 1.1 \times 10^{-3} [\text{mg/m}^3]^{-1}$$

Based on the HBC-OCRV the additional lifetime cancer risk amounts to:

- 4 x 10^{-5} for 40 years of exposure to 0.036 mg/m^3
- 4 x 10^{-3} for 40 years of exposure to 3.6 mg/m^3

2.7 Existing occupational exposure limits

Table 1 summarizes the occupational exposure limits settled by regulatory authorities of the Netherlands, Germany, Sweden, and the UK and by the USA-ACGIH.

The Netherlands have a limit of 3.6 mg/m^3 being comparable with the concentration leading to an additional cancer risk of 4 x 10^{-3}. Sweden and the UK have a limit of 18 mg/m^3, being about a factor 4 higher than the concentration leading to an additional cancer risk of 4 x 10^{-3}.

Table 1 Occupational exposure limits for 2-nitropropane.

	level		time relation	ref.
	ppm	mg/m^3		
The Netherlands	1	3.6	8-h TWA	ISZW99
Germany[a] (TRK)	(5)	(18)	-	DFG99
Sweden[b]	5	18	8-h TWA	NBO93
UK[c]	5	19	8-h TWA	HSE99
USA-ACGIH[d]	10	36	8-h TWA	ACG99

[a] The DFG classifies 2-nitropropane 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

[b] With the following designation: C, the substance is carcinogenic

[c] Maximum Exposure Limit (MEL). 2-Nitropropane belongs to a group substances with risk phrase R45 (may cause cancer)

[d] Classified as a category A3 carcinogen: confirmed animal carcinogen with unknown relevance to humans

2.8 Toxicity profile

The toxicity of 2-nitropropane has been reviewed by the IARC (IARC82), the ACGIH (ACG91), the HSE (HSE96), and WHO (WHO92).

2-Nitropropane has moderate acute toxicity in mammals, although sensitivity differs widely among species tested. For rats, the 6-hour LC_{50} amounted to 400 ppm (1456 mg/m^3) in males and 720 ppm (2621 mg/m^3) in females. The acute oral LD_{50}-value in rats was reported to be 720 mg/kg (ACG91, HSE96a).

Skin application daily for 5 days did neither result in local irritation, nor in signs of systemic disease (IARC82). The review documents did not give data on sensitization or eye irritation.

In repeated-dose toxicity studies the liver appeared the main target organ upon exposure by inhalation and in orally exposed animals. In rats treated with oral doses of 0.002, 0.01, 0.05, and 0.25 g/kg, 5 times per week for 4 weeks by gavage, treatment-related effects were seen at 0.05 and 0.25 g/kg bw; the two lowest dose levels 0.002 and 0.01 g/kg bw were without obvious harmful effects (Wester *et al*. 1989 in WHO92).

Tests for mutagenicity in mammals and mammalian cell lines were generally negative, although strongly positive results were obtained in assays for DNA repair synthesis in rat hepatocytes following dosing of 2-nitropropane both *in vitro* and *in vivo*.

Apart from an ip teratogenicity study in rats, no reproduction and/or other teratogenicity studies were available.

Studies of humans accidently exposed to 2-nitropropane show that exposure to high concentrations (unspecified) induces liver damage and may cause death (ACG91). Daily occupational exposure to 20 - 45 ppm (72 - 162 mg/m^3) induced headache, nausea and anorexia which persisted for several hours after leaving the workplace, whereas 10 to 30 ppm ((36 - 108 mg/m^3, 4 hrs/day for 3 or fewerdays/week) produced no noticeable effects.

Based on the NOAEL of 0.01 g/kg bw found in the oral 4-wk experiment with rats and the findings in humans it is concluded that a health-based occupational exposure limit for 2-nitropropane derived from data other than on genotoxicity/carcinogenicity would in all likelihood be expected to be in between the concentration levels associated with the referential cancer risk levels.

The Hague, 20 December 1999,
for the committee

dr ASAM van der Burght, Prof. dr GJ Mulder,

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scientific secretary chairman

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A Request for advice

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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 2-nitropropane, oral experiments.

authors	species	experimental	findings, tumours	remark
Fiala *et al.* (Fia87)	Sprague-Dawley rat (22 males)	Xpo: three times/week for 16 weeks Xpe: 77 weeks Dl: 0, 89 mg/kg bw (gavage)	hepatocarcinomas: 0/22 controls, 22/22 test animals, of which 4 with lung metastases	Xpo less than 1/4 lifespan

Xpo = exposure period; Xpe = experimental period

Table 2 Carcinogenicity studies with 2-nitropropane, inhalation experiments.

authors	species	experimental	findings, tumours	remark
Griffin *et al*, 1980,1981 (Gri80; Gri81)	Sprague-Dawley rat (125/sex/group)	Xpo: 7 hr/day, 5 days/week, 22 months (95 weeks). Concentration 0, 25 ppm (78 mg/m^3)[a] Xpe = Xpo	Focal areas of hepatocellular nodules were noted in 3/250 control animals (2/125 males, 1/125 females) and 13/249 exposed animals (10/125 males, 3/124 females)	I per mg/m^3 (lifespan exposure conditions) = 5.6 x 10^{-3}
Angus Chemical Co., 1985 in EPA95 Gri78, Gri80, WHO90	Sprague-Dawley rat (125/sex/group)	Xpo: 7 hr/day, 5 days/week for 18 months. Concentrations: 0, 100 ppm (312 mg/m^3)[a] Xpe = Xpo	Hepatocellular carcinomas in males at 12 months of exposure and in females at 18 months	Very limited reporting, a.o. numbers of tumour-bearing animals not reported
Gri78, Angus Chemical Co., 1985 in IRI95, Gri78, Gri80, WHO90	Sprague-Dawley rat (125/sex/group)	Xpo: 7 hr/day, 5 days/week for 6 months. Concentrations: 0, 200 ppm (624 mg/m^3)[a] Xpe variable, up to 12 months	Xpe 6 m: hyperplastic areas, hyperplastic nodules and preneoplastic foci in 6/10 males; Xpe 12 m: metastasizing tumours in 9/10 males	Very limited reporting
Griffin *et al* (Gri87)	TEX:(ICR)AM mice 60/sex/group	Xpo: 7 hr/day, 5 days/week for 18 months. Concentrations: 0, 100 ppm (360 mg/m^3). Xpe = Xpo	Liver: nodular hyperplasia males: 10/60, 15/60 females: 4/60, 13/60 Hepatocellular carcinoma: males: 1/60, 4/60 females: 1/60, 1/60	
Lewis *et al* (Lew79)	Sprague-Dawley rat (10/group)	Xpo: 7 hr/day, 5 days/week for 6 months (24 weeks). Concentrations: 0, 27 ppm (98 mg/m^3), 207 ppm (754 mg/m^3) Xpe = Xpo	Multiple hepatocellular carcinomas or hepatic adenomas: 0/10, 0/10, 10/10 in control, low and high dose group, resp.	Short study duration Xpo < 1/4 lifespan
Lewis *et al* (Lew79)	New Zealand white rabbits (5/group)	Xpo: 7 hr/day, 5 days/week for 6 months (24 weeks). Concentrations: 0, 27 ppm (98 mg/m^3), 207 ppm (754 mg/m^3) Xpe = Xpo	No treatment-related neoplastic lesions were found	Short study duration and a small number of animals. Xpo < 1/4 lifespan Xpe too short for carcinogenicity study

[a] authors conversion based on daily measurements of temperature and atmospheric pressure