# 2-Nitronaphthalene

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 Secreatry of Social Affairs & Employment

No. 2005/02OSH, The Hague, 19 April 2005

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 21, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

This report can be downloaded from www.healthcouncil.nl.

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# Contents

# Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid, schat de Commissie WGD van de Gezondheidsraad het extra kankerrisico bij beroepsmatige blootstelling aan stoffen, die door de Europese Unie of door de Commissie WGD als genotoxisch kankerverwekkend zijn aangemerkt. In dit rapport maakt zij zo'n schatting voor 2-nitronafthaleen, een nitro-polycyclische aromatisch koolwaterstof dat wordt gevormd door incomplete verbranding van organisch materiaal. Voor de schatting heeft de commissie gebruik gemaakt van de methode die beschreven is in het rapport 'Berekening van het risico op kanker' (Hea95).

De commissie is echter van mening dat wegens gebrek aan voldoende gegevens het niet mogelijk is om het extra kankerrisico voor 2-nitronafthaleen te berekenen.

# 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 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-nitronaphthalene. This carcinogen is a nitro-polycyclic aromatic hydrocarbon (nitroPAH) that is formed by incomplete combustion of organic material. For the estimation, the committee used the method described in the report 'Calculating cancer risk due to occupational exposure to genotoxic carcinogens' (Hea95).

The committee is of the opinion that due to insufficient data it is not possible to estimate the additional lifetime cancer risk for 2-nitronaphthalene.

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, at 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 that case, an exposure-response relationship is recommended for use in regulatory standard setting, *i.e.,* 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 committee.

For the establishment of the HBC-OCRVs, 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' (Hea95). The linear model 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

This document contains the derivation of HBC-OCRV's by the committee for 2-nitronaphthalene. The members of the committee are listed in Annex B. The first draft of this report was prepared by Ms MI Willems of the TNO Nutrition and Food Research, Zeist, The Netherlands, for the Ministry of Social Affairs and Employment.

In 2004, 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.

## 1.3 Data

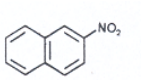
The evaluation of the carcinogenicity and other toxic effects of 2-nitronaphthalene has been based on reviews by IARC (IAR89), IPCS (IPC03) and Berlin *et al*. (Ber89). Where relevant, the original publications were reviewed and evaluated as indicated in the text. In addition, literature has been retrieved from the online databases Chemical Abstracts, Toxline, and Medline, covering the period 1985 to May 2004.

Chapter 2

# 2-Nitronaphthalene

## 2.1 General information

2-Nitronaphthalene is a nitro-polycyclic aromatic hydrocarbon (nitroPAH) containing two fused aromatic rings (IPC03). The compound is formed by incomplete combustion of organic material. 2-Nitronaphthalene occurs in the environment as a mixture of other (nitro)PAH and non-(nitro)PAH compounds. The chemical and physical properties of 2-nitronaphthalene are shown below (data obtained from IAR89, IPC03 and Ric94).

| | | |
|---|---|---|
| Chemical name | : | Naphthalene, 2-nitro- |
| CAS registry number | : | 581-89-5 |
| EINECS number | : | 209-474-5 |
| IUPAC name | : | 2-nitronaphthalene |
| Synonyms | : | β-nitronaphthalene |
| Description | : | Yellow needles or plates from ethanol |
| Occurrence | : | In vehicle exhaust, industrial emission, wood burning some batches of carbon black |
| Molecular weight | : | 173.2 |
| Molecular formula | : | $C_{10}H_7NO_2$ |
| Structure | : |  |
| Boiling point | : | 165°C (at 15°C); 304°C (at 101.3 kPa) |
| Melting point | : | 79°C |

| | | |
|---|---|---|
| Partition coefficient log $P_{ow}$ | : | 3.24 |
| Solubility | : | Insoluble in water; Soluble in organic solvents, such as ethanol and diethyl ether |
| EC classification | : | Carc. Cat. 2; T; R45 (may cause cancer) |

## 2.2 Carcinogenicity studies

### *2.2.1 Overall conclusion*

In 1989, IARC (IAR89) concluded that there was inadequate evidence for the carcinogenicity of 2-nitronaphthalene in experimental animals and that 2-nitronaphthalene was not classifiable as to its carcinogenicity in humans (Group 3). More recently, The European Union listed 2-nitronaphthalene in Category 2, indicating that the substance should be regarded as if it is carcinogenic to man (76/769/EEC-I and 23rd Amendment of Annex I of Directive 67/548/EEC (dated December 5, 1997)).

### *2.2.2 Human data*

No data on the carcinogenicity of 2-nitronaphthalene in humans have been reported.

### *2.2.3 Animal data*

No data were available to the committee on carcinogenic effects by inhalation exposure. In addition, the number of animal studies on other routes of exposure is very limited. A summary of these studies is given below.

#### Oral administration

[Cited from Finklea (Fin77)] In a study conducted by Allied Chemical, four female mongrel dogs were daily fed 100 mg of 2-nitronaphthalene for 8 months. After 10.5 years, bladder papillomas were observed in various stages of malignancy in the 3 dogs for which autopsy results were available. Allied concluded from this study that 2-nitronaphthalene is an active carcinogen in the female dog. In this study, no concurrent control animals were included. Other details on the study were not presented.

Conzelman *et al*. (Con70) administered 2-nitronaphthalene by gavage to three rhesus monkeys (*Macaca mulatta*) that had been cured from a *Plasmodium cynomolgi* infection 12 weeks earlier. No concurrent controls were used. The animals received doses of 121 mg/kg bw (gelatin capsules) twice a day for 6 days per week. Two of the

animals were sacrificed one month after starting the treatment. Urine collected from these animals showed the presence of 2-amino-1-naphthyl sulphate and 2-acetamido-6-naphthyl glucuronide, two metabolites of 2-nitronaphthalene. In this report no details were given on the health effects of these two animals. However, gross and histological examination was performed on the third animal (female), that was kept alive and treated with the compound for 54 months before it was sacrificed. These examinations revealed numerous papillomas of the urinary bladder. However, no malignancies were observed. Moreover, no gross pathologic lesions were noted in other organs than the urinary bladder.

### Implantation into the urinary bladder

Using a mouse model, Bryan and his colleagues (Bry64) reported on chemically induced bladder cancer. In the urinary bladder of mice (specifications not given) one cholesterol pellet containing 2-nitronaphthalene was implanted by surgery. Also two control groups were included in the experiment, one sham control group and one group implanted with the cholesterol pellet only. The experiments was repeated three times. The authors did not report on the dose and purity of 2-nitronaphthalene. Tumour incidence data were recorded for mice surviving at least 175 days up to 490 days. The incidences of carcinomas in the urinary bladder were 7/80 (8.7%), 2/76 (2.6%) and 2/41 (4.9%) for the three experiments separately. For comparison reasons, the incidences in the cholesterol pellet control groups were 1/82 (1.2%), 2/140 (1.4%) and 4/72 (5.6%) for the respective three experiments. In the sham control group (n=38) no tumours were observed. Furthermore, no effects on survival were observed.

## 2.3 Conclusion

The animal studies described in the previous section indicate that 2-nitronaphthalene may induce tumours or other neoplastic changes in the urinary bladder. However, the database is very limited and does not meet the criteria for calculating the cancer risk of 2-nitronaphthalene under occupational conditions of exposure. Furthermore, no data were available on exposure routes which are relevant for the occupational situation.

In conclusion, the committee is of the opinion that it is not possible to estimate additional lifetime cancer risk for 2-nitronaphthalene.

## 2.4 Existing occupational exposure limits

No occupational exposure limits have been established for 2-nitronaphthalene in the Netherlands (SZW04), Germany (Bun03, DFG03), the United Kingdom (HSE02),

Scandinavian countries (Arb02, NBO00), the United States of America (ACGIH, OSHA, NIOSH (ACG04) and by the SCOEL of the European Union (Hun97). Instead, the Netherlands, the United Kingdom, Denmark, American NIOSH and Germany (DFG) have classified the compound as a carcinogen. Concerning Germany, because 2-nitronaphthalene is considered a carcinogen (class 2), a Technical Exposure Limits (TRK*) was established of 0.25 mg/m$^3$ (0.035 ppm; 8-h TWA) instead of a MAK-value (DFG03).

## 2.5 Toxicity profile (Gre98, IAR89, IPC03)

### *2.5.1 Observations in humans*

No data were available to the committee on the non-carcinogenic effects of 2-nitronaphthalene in humans.

### *2.5.2 Observations in animals*

No animal data were available on the acute and chronic non-carcinogenic effects of 2-nitronaphthalene after inhalation, dermal or oral exposure.

The oral $LD_{50}$ of 2-nitronaphthalene in mice, rats, and rabbits amount to 1,300, 4,400, and 2,650 mg/kg bw, respectively.

Johnson *et al*. (Joh84) found no lung or liver toxicity in male Sprague-Dawley rats, after the animals were treated with a single intraperitoneal injection of 2-nitronaphthalene of a dose of 100 mg/kg bw.

Sauer and Sipes (Sau95) treated male Sprague-Dawley rats with 2-nitronaphthalene by a single intraperitoneal injection of 200 mg/kg bw. The animals were sacrificed 3 to 24 hours after the injection and then prepared for morphological evaluation of lung and liver injury. The treated animals showed no signs of respiratory distress syndrome. Pulmonary lesions were restricted to the bronchioles and included: Clara and ciliated cell necrosis; mild interstitial oedema; and moderate pneumonitis. In addition, clinical chemistry showed some hepatotoxicity.

Rasmussen *et al*. (Ras86) exposed male Swiss-Webster mice (n=2/group) to 2-nitronaphthalene by a single intraperitoneal injection of 0.5 to 3.0 mmol/kg bw (≈ 87 to 520 mg/kg bw). The animals were then sacrificed twenty-four hours up to 14 days after the injection. Treatment with the compound evoked slight cytotoxicity in the Clara cells

* TRK (Technische Richtkonzentrationen) defines that concentrations of gas, vapour or airborne particulates which is the minimum possible with current technology and which serves as a guide for necessary protective measures and monitoring at the workplace. TRK values are assigned only for hazardous materials for which MAK values based on toxicological or occupational-medical data cannot be established at the present time.

of the bronchiolar epithelium of the lungs, and slight necrosis in small areas of the centrizonal part in the liver. No discernible effects in the kidneys were observed.

### 2.5.3 *Metabolism and genotoxicity*

2-Nitronaphthalene is, like all other nitroPAH, metabolized by various metabolic activation pathways. Some of these metabolites, such as N-hydroxy-2-naphthylamine, 2-naphthylamine (*β*-naphthylamine) and 2-amino-1-naphthyl sulphate, are known bladder carcinogens, and are found in the urine of monkeys and rats after oral administration of 2-nitronaphthalene (Joh76).

Concerning genotoxicity, 2-nitronaphthalene (two aromatic rings) showed low mutagenic potency in *Salmonella typhimurium* microsome assay with or without a metabolic activation system in comparison with nitroPAH with three or more rings. Mixed results on gene mutations were reported when using human metabolically competent lymphoblastoid cells *in vitro*. In addition, 2-nitronaphthalene scored positive in the host-mediated reverse gene mutation assay in Swiss-Webster mice when given a dose of 125 mg/kg bw by intramuscular injection, but negative when given a dose of 1,300 mg/kg bw by gavage.

# References


Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Danmark: Arbejdstilsynet, Oktober 2002. [In Danish]

Ber89 Berlin A, Draper M, Krug E, Rol R and Van der Venne MT. 2-Nitronaphthalene. In: The toxicology of chemicals - 1. Carcinogenicity, Volume 1 - summary reviews of the scientific evidence. Office for Official Publications of the European Communities, Luxembourg 1989: pp 131-133.

Bry64 Bryan GT, Brown RR, Price JM. Mouse bladder carcinogenicity of certain tryptophan metabolites and other aromatic nitrogen compounds suspended in cholesterol. Cancer Res 1964; 24: 596-602.

Bun03 Bundesministerium für Arbeit und Sozialordnung. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe; TRGS 900. FRG: Verlag W. Kolhammer, Ausgabe: Okotber 2000, zuletzt geändert BarbBI. Heft 9/2003. [In German]

Con70 Conzelman GM, Moulton JE, Flanders LE. III Tumors in urinary bladder of a monkey: induction with 2-nitronaphthalene. Gann 1970; 61: 79-80.

DFG03 Deutsche Forschungsgemeinschaft (DFG): Commission for the investigation of health hazards of chemical compounds in the work area. List of MAK and BAT Values 2003. Maximum concentrations and biological tolerance values at the workplace. Weinheim: Wiley-VCH Verlagsgesellschaft mbH, 2003; Report no. 39.

Fin77 Finklea JF. Metabolic precursors of a known human carcinogen, beta-naphthylamine. Am Ind Hyg Assoc J 1977; 38: A21-A23.

Gre98 Greim H, ed. Mononitronaphthaline (alle Isomeren). In: Gesundheidsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werte (Maximale Arbeitsplatz-Konzentrationen). 1st-27th ed. Weinheim, FRG: Wiley-VCH, 1998.

Hea95 Health Council of The Netherlands: Dutch Expert Committee on Occupational Standards (DECOS). Calculating cancer risk due to occupational exposure to genotoxic carcinogens'. The Hague, The Netherlands: Health Council of the Netherlands, 1995; pub no 1995/06WGD.

HSE02 Health and Safety Executive (HSE). EH 40/02. Occupational Exposure Limits 2002. Sudbury (Suffolk), UK: HSE Books, 2002.

Hun97 Hunter WJ, Aresini G, Haigh R, *et al*. Occupational exposure limits for chemicals in the European Union. Occup Environ Med 1997; 54: 217-22.

IAR89 International Agency for Research on Cancer (IARC). 2-Nitronaphthalene. In: Diesel and gasoline engine exhausts and some nitroarenes. Lyon, France: IARC, 1989: 303-12 (IARC monographs on the evaluation of carcinogenic risks to humans; Vol 46).

IPC03 International Programme on Chemical Safety. Selected nitro- and nitro-oxy-polycyclic aromatic hydrocarbons. Environmental Health Criteria 229. World Health Organization, Geneva, 2003.

Joh76 Johnson DE and Cornish HH. *In vivo* nitroreduction of the nitronaphthalenes. Toxicol Appl Pharmacol 1976; 37: 182.

Joh84 Johnson DE, Riley MG and Cornish HH. Acute target organ toxicity of 1-nitronaphthalene in the rat. J Appl Toxicol 1984; 4: 253-257.

NBO00 National Board of Occupational Safety and Health (NBOSH). Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000 (Ordinance AFS 2000:3).

Ras86 Rasmussen RE, Do DH, Kim TS. Comparative cytotoxicity of naphthalene and its monomethyl- and mononitro-derivatives in the mouse lung. J Appl Toxicol 1986; 6: 13-20.

Ric94 Richardson ML, Gangolli S, ed. N126. 2-Nitronaphthalene. In: The dictionary of substances and their effects. Cambridge, UK: Royal Society of Chemistry, 1994: 193-4 (Vol 6).

Sau95 Sauer J-M and Sipes G. Modulation of chemical-induced lung and liver toxicity by all-trans-retinol in the male Sprague-Dawley rat. Toxicology 1995; 105: 237-249.

SZW04 Ministerie van Sociale Zaken en Werkgelegenheid (SZW) De Nationale MAC-lijst 2004, The Hague, The Netherlands: Servicecentrum Sdu Uitgevers, 2004. [In Dutch]

A Request for advice

B The Committee

C Comments on the public review draft

# 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
- LJNGM Bloemen
  epidemiologist; Environ, the Netherlands
- PJ Boogaard
  toxicologist; SHELL International BV, The Hague
- PJ Borm
  professor of inhalation toxicology; Heinrich Heine Universität, Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- DJJ Heederik
  professor of risk assessment in occupational epidemiology; IRAS, University of Utrecht, Utrecht
- TM Pal
  occupational physician; Dutch Centre for Occupational Diseases, Amsterdam
- IM Rietjens
  professor of toxicology; Wageningen University, Wageningen.

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol; and, professor of working conditions; Free University, Amsterdam
- GMH Swaen
  epidemiologist; DOW Benelux NV, Terneuzen
- AA Vijlbrief, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- RA Woutersen
  toxicologic pathologist; TNO Nutrition and Food Research, Zeist
- P Wulp
  occupational physician; Labour Inspectorate, Groningen
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- JM Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

The first draft of the this report was prepared by Ms MI Willems, from the Department of Occupational Toxicology of the TNO Nutrition and Food Research, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: Ms F Smith.
Lay-out: Ms M Javanmardi.

Annex **C**

# Comments on the public review draft

A draft of the present report was released in 2004 for public review. The following organisation and person have commented on the draft document:

- R Zumwalde, National Institute for Occupational Safety and Health, the USA