Urethane (ethyl carbamate)

Health based calculated occupational cancer risk values

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

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

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

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

w.g.
prof. dr JJ Sixma

Urethane (ethyl carbamate)

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Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of the Netherlands

to

the Minister and State Secretary of Social Affairs and Employment

No. 2000/12OSH, The Hague, 6 September 2000

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Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid schat de Commissie WGD van de Gezondheidsraad het extra kankerrisico bij beroepsmatige blootstelling aan stoffen die door de Europese Unie of door de Commissie WGD als genotoxisch kankerverwekkend zijn aangemerkt. In dit rapport maakt zij zo'n schatting voor urethaan. Zij heeft daarbij gebruik gemaakt van de methode die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06WGD) (Dec95).

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

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

The committee estimated that the additional lifetime cancer risk for urethane 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 urethane by the committee. The members of the committee are listed in Annex B. The first draft of this report was prepared by MI Willems, from the TNO Nutrition and Food Research Institute in Zeist, by contract with the Ministry of Social Affairs and Employment.

In 1998, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in annex C. The committee has taken these comments into account in deciding on the final version of the report.

Chapter 2

Urethane (ethyl carbamate)

2.1 Introduction

Urethane (CAS no. 51-79-6) has been classified as a category 2 carcinogen by the European Union. This evaluation of the carcinogenicity was based on a review by IARC (IARC74). In addition, literature was retrieved from online databases Medline, Toxline and Cancerlit covering the period 1975 to 1996.

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

Human data either case reports or epidemiological reports were not available (IARC74).

Urethane, an *in vivo* and *in vitro* genotoxicant, has been studied extensively for carcinogenicity in experimental animals. Urethane has been shown to be carcinogenic in mice, rats and hamsters following administration by the oral, inhalation, subcutaneous or intraperitoneal routes, producing, among others, lung tumours, lymphomas, hepatomas, melanomas and vascular tumours. When urethane is administered orally or topically, it is an initiator for skin carcinogenesis in mice. It was also shown to enhance the leukaemogenic effect of X-irradiation. The compound is carcinogenic in single dose experiments and following prenatal exposure. Neonatal and infant mice are more susceptible to cancer induction by urethane than are adult mice (IARC74).

Table 1 (Annex D) summarizes the available oral and inhalation carcinogenicity studies with experimental animals. Experiments using skin application, and intraperitoneal or subcutaneous administration are not included in this table.

For cancer risk assessment in humans, the committee selected the rat and mouse experiments conducted by Port and Schmähl (Por76, Schm77, Schl90). One reason to select the study of Port and Schmähl is that they used doses in the lower mg/kg body weight range, while in most of the other studies high dose levels in the order of 100-1000 mg urethane/kg body weight per day were used. Other criteria for selection of studies suitable for cancer risk assessment in humans included the length of exposure and experimental period, the presence of a control group, adequate reporting of experimental design and results etc.

In the studies of Port and Schmähl mice and rats were exposed to 0, 0.1, 0.5, 2.5 or 12.5 mg urethane per kg body weight/day in the drinking water for up to 2 years. Table 2 (Annex D) lists the tumour incidences in the various organs and tissues, the total numbers of tumour-bearing animals, and mean survival times for male and female rats and mice, separately. Treatment-related increases in tumour incidences were seen in female rats from dose levels of 2.5 mg (mammary tumours and total number of females with a malignant tumour) and in mice, males and females, from dose levels of 0.5 mg/kg body weight/day (lung tumours, mammary tumours and total number of mice with a malignant tumour).

To calculate the risk of cancer at the workplace we have used the total number of male and female mice with (a) malignant tumour(s) observed after exposure to 0.5 mg/kg bw per day. 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 mg urethane, the total number of mice with a malignant tumour per number of animals examined was used.

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

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

* I_{dose} = the carcinogenic activity attributable to the exposure to the substance per unit daily dose under lifespan conditions assuming a linear dose response relationship
Ie and Ic = incidence of tumour bearing animals or tumours in exposed and control amnimals, respectively,
Xpo = exposure period, Xpe = experimental period

$$\frac{\frac{17}{69} - \frac{6}{74}}{0.5 \times \frac{730}{750} \times \frac{730}{750} \times \frac{24}{24} \times \frac{7}{7}} = 3.5 \times 10^{-1} \text{ [mg/kg/d]}^{-1}$$

2.4 Health risk to humans

To estimate the additional lifetime risk of cancer in humans under lifespan conditions on the basis of results in animal experiments, it is assumed that no difference exists between experimental animals and man with respect to toxicokinetics, mechanism of tumour induction, target, susceptibility etc, unless specific information is available which justifies a different approach. Furthermore, it is assumed that the average man lives 75 years, weights 70 kg and is exposed 24 hours per day 7 days/week, 52 weeks per year for lifetime.

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

$$\text{HBC-OCRV} = 3.5x10^{-1} \; x\frac{40y}{75y}x\frac{48w}{52w}x\frac{5d}{7d}x\frac{10m^3}{70kg} = 1.8 \text{ x } 10\text{-}2 \text{ [mg/m}^3\text{]}^{-1}$$

Based on the HBC-OCRV of 1.8 x 10^{-2} per mg/m^3 the reference additional lifetime cancer risks amount 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

The regulatory authorities of Sweden, Germany, and the UK have classified urethane as a carcinogen and the compound is being reviewed in the Netherlands.

No occupational exposure limits have been established in The Netherlands, Germany, Sweden, United Kingdom or USA (ACG95, ISZW95, DFG95, HSE95, NBO93), see table 3.

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and L = standard lifespan for the animals in question (L rat is assumed to be 1000 days)

Table 3 Occupational exposure limits for urethane.

country	level		time relation	remark	ref.
	ppm	mg/m^3			
The Netherlands[a]	-	-	-	reviewed	ISZW95
Germany[b]	-	-	-	-	DFG96
Sweden[c]	-	-	-	-	NBO93
UK[d]	-	-	-	-	HSE95
USA-ACGIH	-	-	-	not listed	ACG95

[a] the substance is classified as a carcinogen

[b] The DFG classifies urethane as a category A2 carcinogen.

[c] In Sweden, urethane is placed under section 9 as a group B carcinogen and may only be handled by permission of the Labour Inspectorate.

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

2.7 Toxicity profile of urethane

The toxicity profile of urethane has been taken over from the data compiled by Lewis (Lew96). Urethane is moderately toxic by ingestion, intraperitoneal, subcutaneous, intramuscular, parenteral and intravenous routes. The oral LD_{50}s amounting to 1809 and 2500 mg/kg bw in rat and mice, respectively. Urethane is an experimental teratogen and gives reproductive effects in laboratory animals. It causes depression of bone marrow and occasional focal degeneration in the brain. It can also produce central nervous system depression, nausea and vomiting. Dose levels or concentrations are not given. With respect to irritation no animal or human data were available. Urethane has been found in over 1000 beverages sold in the US (Lew96).

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.

For the committee,
The Hague, 6 September 2000

dr ASAM van der Burght,
scientific secretary

Prof. dr GJ Mulder,
chairman

References

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

DEC95 Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards (DECOS). Calculating cancer risk. The Hague: Health Council of the Netherlands, 1995 publication no 1995/06WGD.

DFG96 Deutsche Forschungsgemeinschaft (DFG): Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. MAK- und BAT-Werte-Liste 1996. Maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleranzwerte. Weinheim, FRG: VCH Verlagsgesellschaft mbH, 1996: 56, 108 (Mitteilung 32).

HSE95 Health and Safety Executive (HSE). Occupational exposure limits 1995. Sudbury (Suffolk), UK: HSE Books, 1995: 26, 50 (Guidance note 40/95).

IARC74 International Agency for Research on Cancer (IARC). Urethane. Some anti-thyroid and related substances, nitrofurans and industrial chemicals Lyon, France: IARC, 1974: 111-40. In: IARC monographs on the evaluation of carcinogenic risk of chemicals to man: Vol 7.

Ina91 Inai K, Arihiro K, Takeshima Y, *et al*. Quantitative risk assessment of carcinogenicity of urethane (ethyl carbamate) on the basis of long-term oral administration to B6C3F_1 mice. Jpn J Cancer Res 1991; 82: 380-5.

ISZW95 Inspectiedienst van het Ministerie van Sociale Zaken en Werkgelegenheid (I-SZW). De Nationale MAC-lijst 1995. The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1995: 51, 63 (pub no P145).

Lew96 Lewis RJ Sr, ed.. Urethane. In: Sax's dangerous properties of industrial materials. 9th ed. New York, USA: Van Nostrand Reinhold, 1996: 3353-4.

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

Por76 Port R, Schmähl D, Wahrendorf J. Some examples of dose-response studies in chemical carcinogenesis. Oncology 1976; 33: 66-71.

Schl90 Schlatter J, Lutz WK. The carcinogenic potential of ethyl carbamate (urethane): risk assessment at human dietary exposure levels. Food Chem Toxicol 1990; 28: 205-11.

Schm77 Schmähl D, Port R, Wahrendorf J. A dose-response study on urethane carcinogenesis in rats and mice. Int J Cancer 1977; 19: 77-80.

A Request for advice

B The committee

C Comments on the public draft

D Animal studies

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in

the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Annex **B**

The Committee

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- PJ Borm
  toxicologist; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- VJ Feron,
  professor of toxicology; TNO Nutrition and Food Research Institute, Zeist
- DJJ Heederik
  epidemiologist; Wageningen University, Wageningen
- LCMP Hontelez, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- G de Jong
  occupational physician; Shell International Petroleum Maatschappij, The Hague
- J Molier-Bloot
  occupational physician; BMD Akers bv, Amsterdam
- IM Rietjens
  professor in Biochemical toxicology; Wageningen University, Wageningen

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, Den Haag
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- HG Verschuuren
  toxicologist; DOW Europe, Horgen (Switzerland)
- F de Wit
  occupational physician; Labour Inspectorate, Arnhem
- CA Bouwman, *scientific secretary*
  Health Council of the Netherlands, Den Haag
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, Den Haag

The first draft of the present advisory report was prepared by M Willems, from the Department of Occupational Toxicology of the TNO Nutrition and Food Research Institute, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: J Toet.
Lay-out: J van Kan.

Annex **C**

Comments on the public draft

A draft of the present report was relased in 1998 for public review. The following organisations and persons have commented on the draft document:

- WF ten Berge, DSM, Heerlen

Annex **D**

Animal studies

See tables on the next pages.

Table 1 Carcinogenicity studies with urethane.[a]

authors	species	exposure characteristics	findings	remark
Otto and Plötz (1966) (see IARC74)	mouse/3 strains BLH NMRI C57 BL	inhalation, aerosol concentrations: 0.5, 10, 15, 20% Xpo: 20-60 min/day ? days/week, 3.5 - 14.5 weeks Xpe: ?	at 20% an increase in lung tumours (adenomas and solid tumours of a squamous type) was observed	duration of the exposure was less than one-fourth the standard lifespan
Toth *et al*. (1961) (see IARC74)	mouse, Swiss albino 100/sex/group	p.o. drinking water concentration: 0, 0.4% Xpo: two 10-day treatment periods Xpe: 42 weeks	treatment group: lymphomas (mainly lymphosarcomas) 15/100 male, 28/100 female; papillomas 3/100 male, 2/100 female. control group: lymphomas 4/100 male, 16/100 female	duration of the exposure was less than one-fourth the standard lifespan
Della Porta *et al*. (1963) (see IARC74)	mouse, CTM albino 100/sex/group	p.o. drinking water concentration: 0, 0.4% Xpo: varying between 5 and 35 days Xpe: 60-80 weeks	two 10-day treatments: lung adenomas 80-84%; lymphosarcomas 33% male, 27% female. control group: lung adenomas 2-7%; lymphosarcomas 4.5% male, 5% female	duration of the exposure was less than one-fourth the standard lifespan
Tannenbaum & Maltoni (1962) (see IARC74)	mouse, C3H, 36 female	p.o. drinking water concentration: 0, 0.1% Xpo: 13 weeks Xpe: 76 weeks	treatment group: pulmonary adenomas 15/32; leukaemia 8/36. control group: pulmonary adenomas 2/36	duration of the exposure was less than one-fourth the standard lifespan.
Tannenbaum & Maltoni (1962) (see IARC74)	mouse, DBA 54-62/sex/group	p.o. drinking water concentration: 0, 0.1% Xpo: 31 weeks Xpe: 45 weeks	treatment group: pulmonary adenomatosis 20/54 male, 20/52 female; pulmonary adenomas 10/54 male, 11/52 female; squamous-cell tumours 11/54 male, 6/52 female. control group: pulmonary adenomatosis 1/59 male, 2/56 female	animals were 53-week old at the start of the treatment
Por76 Schm77 Schl90	mouse, NMRI	p.o. drinking water dose levels: 0, 0.1, 0.5, 2.5, 12.5 mg/kg bw/day Xpo = Xpe[b]	the number of animals (both sexes combined) with a malignant tumour were 6/74 (control), 11/65 (0.1 mg), 17/69 (0.5 mg), 20/59 (2.5 mg) and 32/65 (12.5 mg). difference statistically significant at 0.5 mg/kg bw/day and higher	$I = 3.5 \times 10^{-1}$ per mg/kg bw/day (TBA males + females)
Por76 Schm77 Schl90	rat, Sprague - Dawley	p.o. drinking water dose levels: 0, 0.1, 0.5, 2.5, 12.5 mg/kg bw/day Xpo = Xpe[c]	the number of females with a malignant tumour were 2/36 (control), 1/37 (0.1 mg), 2/34 (0.5 mg), 6/39 (2.5 mg) and 12/38 (12.5 mg)	$I = 8 \times 10^{-2}$ per mg/kg bw/day (females TBA). for details see Table 2
Adenis et al. (1968) (see IARC74)	rat, Sprague-Dawley, 50 female	p.o. drinking water concentration: 0.1% Xpo = Xpe = lifespan	33/40 developed tumours (7 malignant lymphomas, 11 haemangiomas or haemangiosarcomas of the liver, spleen or uterus, 7 heptomas, 10 adrenal cortex adenomas and 4 fibrosarcomas of the mesentery uterus	there was no control group

Table 1 Continued.

authors	species	exposure characteristics	findings	remark
Toth *et al.* (1961), Toth & Boreisha 1969 (see IARC74)	hamster, Syrian golden	p.o. drinking water concentration: 0, 0.2, 0.4% Xpo: 20 weeks 0.2% followed by 22 weeks 0.4% total 42 weeks. Xpe: 80 weeks	tumours were found in 22/27 male and 21/25 female survivors, compared with 9/54 in male and 3/47 female controls. tumours included melanotic tumours of the skin, papillomas and squamous-cell carcinomas of the forestomach, malignant lymphomas, mammary tumours, hepatomas, haemangiomas, haemangiosarcomas, pulmonary adenomatosis and adenomatous polyps of the caecum. very few of these tumours occurred in 13 tumour-bearing controls	
Pietra & Shubik (1960) (see IARC74)	hamster, Syrian golden	p.o. drinking water concentration: 0.2% Xpo = Xpe = lifespan	melanotic tumours of the skin in 8/20 animals, compared to 1/63 in controls	
Ina91	B6C3F_1 mice 50 males/ group	p.o. drinking water, concentrations: 0, 0.6, 3, 6, 60, 600 ppm (0, 0.095, 0.58, 1.0, 10, 100 mg/kg bw/day) Xpo = Xpe = 70 weeks	exposure-related tumours were found in liver and lungs. the lung tumourincidence amounted to 9/49, 4/49, 7/48, 8/50, 34/50 ($P<0.01$), and 42/44 ($p<0.01$) in the successive exposure groups	I per mg/kg bw based on lung tumour incidence in the 100 mg group amounted to 1.2×10^{-1} (lifespan exposure conditions)

[a] References with respect to treatment of suckling animals or skin application are not summarized.

[b] Xpe in mice amounted to 760, 730, 730, 730 and 660 for the 0, 0.1, 0.5, 2.5 and 12.5 mg/kg bw groups, respectively (Schm76).

[c] X_{pe} in rats amounted to 680, 730, 670 and 670 for the 0, 0.1, 0.5, 2.5 and 12.5 mg/kg bw groups, respectively (Schm76).

Table 2[a] Tumour incidence in SD rats and NMRI mice treated for their lifetime with ethyl carbamate (urethane) in the drinking water. Summary data of this study have been published by Schmähl et al. (Sch77). Protocols were kindly provided by the authors.

	males				females		
dose of ethyl carbamate (µg/kg body weight/day)	no. of animals evaluated	no. with malignant (benign[b]) tumours	site of carcinoma or type of other malignant tumour[c]		no. of animals evaluated	no. with malignant (benign) tumours	site of carcinoma or type of other malignant tumour
0	38	0 (1)	--	*Rats*	36	2 (0)	ovaries (1), fibrosarcoma (1)
100	33	1 (0)	lymphoma/leukaemia (1)		37	1 (3)	lymphoma/leukaemia (1)
500	31	2 (0)	fibrosarcoma (2)		34	2 (2)	mammary gland (1), sarcoma (1)
2500	31	1 (1)	lymphoma/leukaemia (1)		39	6 (4)	mammary gland (2), mixed (4)
12 500	36	3 (0)	mixed (3)		38	12 (8)	mammary gland (9), mixed (3)
				Mice			
0	36	4 (0)	sarcoma (3), lymphoma/leukaemia (1)		38	2 (2)	lymphoma/leukaemia (2)
100	32	6 (2)	lymphoma/leukaemia (3), mixed (3)		33	5 (9)	lymphosarcoma (2), mixed (3)
500	33	3 (7)	mixed (3)		36	14 (5)	mammary gland (2), lung (2), lymphosarcoma (4), lymphoma/leukaemia (4), mixed (3)
2.500	28	10 (10)	lung (4), blood vessels (2), mixed (4)		31	10 (11)	Mammary gland (2), lymphoma/leukaemia (4), lymphosarcoma (3), mixed (3)
12 500	32	14 (15)	lung (5), lymphoma/keukaemia (3), blood vessels (3), mixed (3)		33	18 (15)	mammary gland (6), lung (10), blood vessels (4), mixed (3)

[a] This table has been taken over from the paper published by Schlatter and Lutz (Schl90, Table 1 page 208).

[b] The benign tumours were, in the rats, predominantly in the mammary glands, and in the mice, mainly adenomas of the lung (males and females).

[c] Mixed = more than one site and/or tumour type.