# n-Butyl glycidyl ether

Evaluation of the carcinogenicity and genotoxicity

**Gezondheidsraad** **Voorzitter**
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies *n-Butyl glycidyl ether*
Uw kenmerk : DGV/MBO/U-932542
Ons kenmerk : U-5132/JR/pg/246-E12
Bijlagen : 1
Datum : 1 april 2008

Geachte minister,

Graag bied ik u hierbij het advies aan over de kankerverwekkendheid van n-butyl glycidyl ether. Het maakt deel uit van een uitgebreide reeks waarin kankerverwekkende stoffen worden geclassificeerd volgens richtlijnen van de Europese Unie. Het gaat om stoffen waaraan mensen tijdens de beroepsmatige uitoefening kunnen worden blootgesteld.

Het advies is opgesteld door een vaste subcommissie van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS), de Subcommissie Classificatie van carcinogene stoffen. Het advies is voorgelegd aan de Commissie GBBS en vervolgens getoetst door de Beraadsgroep Gezondheid en omgeving van de Gezondheidsraad.

Ik heb dit advies vandaag ter kennisname toegezonden aan de minister van Volksgezondheid, Welzijn en Sport en de minister van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer.

Hoogachtend,

prof. dr. J.A. Knottnerus

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Evaluation of the carcinogenicity and genotoxicity

Subcommittee on the classification of carcinogenic substances of the
Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of the Netherlands

to:

the Minister of Social Affairs and Employment

No. 2008/07OSH, The Hague, April 1, 2008

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 22, 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.

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***INAHTA***

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

Preferred citation:
Health Council of the Netherlands. n-Butyl glycidyl ether; Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/07OSH.



ISBN: 978-90-5549-692-4

# Contents

# Samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid evalueert en beoordeelt de Gezondheidsraad de kankerverwekkende eigenschappen van stoffen waaraan mensen tijdens het uitoefenen van hun beroep kunnen worden blootgesteld. De evaluatie en beoordeling worden verricht door de subcommissie Classificatie van Carcinogene Stoffen van de Commissie Gezondheid en Beroepsmatige Blootstelling aan Stoffen van de Raad, hierna kortweg aangeduid als de commissie. In het voorliggende advies neemt de commissie n-butylglycidylether onder de loep. n-Butylglycidylether wordt gebruikt voor vele doeleinden, waaronder de productie van epoxyharsen.

Op basis van de beschikbare gegevens leidt de commissie af dat n-butylglycidylether onvoldoende is onderzocht. Hoewel de gegevens het niet toelaten de stof te classificeren als kankerverwekkend voor de mens of als moet beschouwd worden als kankerverwekkend voor de mens, is waakzaamheid geboden. De commissie adviseert daarom n-butylglycidylether te classificeren als *verdacht kankerverwekkend voor de mens*. Dit is vergelijkbaar met een classificatie in categorie 3 volgens de richtlijnen van de Europese Unie. Binnen deze categorie komt de situatie het meest overeen met subcategorie b.

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# Executive summary

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. In this report, the committee evaluated n-butyl glycidyl ether. The agent has various uses, such as in the production of epoxy resins.

Based on the available information, the committee is of the opinion that n-butyl glycidyl ether has been insufficiently investigated. While the available data do not warrant a classification as carcinogenic to humans or as should be regarded as carcinogenic to humans, they indicate that there is cause for concern. Therefore, the committee recommends classifying n-butyl glycidyl ether as *a suspected human carcinogen*. This recommendation is comparable to the EU classification in category 3. The situation is, furthermore, comparable with subcategory b of this category.

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Chapter 1

# Scope

## 1.1 Background

In the Netherlands a special policy is in force with respect to occupational use and exposure to carcinogenic substances. Regarding this policy, the Minister of Social Affairs and Employment has asked the Health Council of the Netherlands to evaluate the carcinogenic properties of substances, and to propose a classification (see Annex A). The assessment and the proposal for a classification are expressed in the form of standard sentences (see Annex E). The criteria used for classification are partly based on an EU-directive (see Annex F). In addition to classifying substances, the Health Council also assesses the genotoxic properties of the substance in question.

This report contains the evaluation of the carcinogenicity of n-butyl glycidyl ether.

## 1.2 Committee and procedures

The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. The members of the committee are listed in Annex B. The first draft was prepared by I.A. van de Gevel and M.I. Willems, from the Department of Occupational Toxicology of the TNO Nutrition

and Food Research, by contract with the Ministry of Social Affairs and Employment.

In 2007 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 and recommendation of the committee is standardly based on scientific data, which are publicly available. The starting points of the committees' reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which are mentioned in the IARC-monograph, are reviewed only by the committee when these are considered most relevant in assessing the carcinogenicity and genotoxicity of the substance in question. In the case of n-butyl glycidyl ether, such an IARC-monograph is available, of which the summary and conclusion of IARC is inserted in Annex D.

More recently published data were retrieved from the online databases Medline, Toxline, Chemical Abstracts, and RTECS. The last updated online search was in June 2007. The new relevant data were included in this report.

Chapter 2

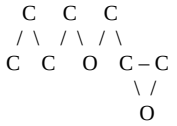
# General information

## 2.1 Identity and physico-chemical properties

n-Butyl glycidyl ether is used: as a reactive diluent in epoxy resins; as a viscosity-reducing agent for easier handling of conventional epoxy resins; as an acid acceptor for stabilizing chlorinated solvents; as a chemical intermediate; as a lubricant antioxidant; in electrical insulating, surface coating and lining, painting, gluing, and fiberglass finishing; in the construction industry, for coating and impregnation of concretes, flooring, and repairing of cracks; and, also it is widely used in the household environment.[1] Occupational exposure may occur during manufacturing and use of these substances.

Below is given the identity and some of its physical and chemical properties.[1]

| | | |
|---|---|---|
| Chemical name | : | *n*-butyl glycidyl ether |
| CAS registry no. | : | 2426-08-6 |
| EINECS no. | : | 219-376-4 |
| Synonyms | : | oxirane, (butoxymethyl)-; 1-butoxy-2,3-epoxypropane; 3-butoxy-1,2-epoxypropane; butyloxymethyl-oxirane; butyl 2,3-epoxypropyl ether; 2,3-epoxypropyl butyl ether |
| Description | : | colourless liquid with a slightly irritative odour |
| Molecular formula | : | $C_7H_{14}O_2$ |

| | | |
|---|---|---|
| Structure | : |  |
| Molecular weight | : | 130.21 |
| Flash point | : | 59 °C |
| Boiling point | : | 163.8 °C |
| Relative density (25°C/4°C) | : | 0.908 |
| Vapour pressure (20°C) | : | 0.4 kPa |
| Partition coefficient ($\log K_{ow}$) | : | 0.63 |
| Solubility | : | slightly soluble (20 g/L at 20°C) |
| Conversion factors (101.3 kPa; 20°C) | : | 1 ppm = 5.4 mg/m$^3$<br>1 mg/m$^3$ = 0.18 ppm |
| Risk and safety phrases | : | R10: flammable<br>R20/22: Harmful by inhalation and if swallowed<br>R37: irritating to respiratory system<br>R40: limited evidence of a carcinogenic effect<br>R52/53: harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment<br>R68: possible risk for irreversible effects<br>S2: keep out of reach of children<br>S24/25: avoid contact with skin and eyes<br>S36/37: wear suitable protective clothing and gloves<br>S61: avoid release to the environment. Refer to special instructions/safety data sheets |
| EU classification | : | carcinogenic category 3<br>mutagenic category 3 |

## 2.2 IARC classification

In 1989, the Working Group of IARC evaluated some glycidyl ethers.[1] However, it did not classify n-butyl glycidyl ether, because of a lack of human and animal carcinogenicity data.

Chapter 3

# Carcinogenicity studies

## 3.1 Observations in humans

No data were available to evaluate the carcinogenicity of n-butyl glycidyl ether in humans.

## 3.2 Carcinogenicity studies in animals

No data were available to evaluate the carcinogenicity of n-butyl glycidyl ether in animals.

Chapter 4

# Mutagenicity and genotoxicity

## 4.1 *In vitro* assays

Several mutagenicity studies have been performed using various strains of the bacteria *Salmonella typhimurium*.[1,2] Overall, in the presence and absence of a metabolic activation system, positive outcomes were reported in strains TA97, TA100, TA1535, and TA1538. Negative outcomes were reported using strains TA98 and TA1537.[1]

In the absence of a metabolic activation system, n-butyl glycidyl ether induced mutations in the *Escherichia coli* WP2uvrA strain.[1]

Furthermore, a dose-related increase in mutation frequency was observed in the L5178Y mouse lymphoma mutagenicity assay.[1,3] In that assay, the agent was tested at a concentration of up to 800 μg/mL, in the presence and absence of a metabolic activation system.

n-Butyl glycidyl ether, at concentrations of 0.3 to 19 mmol/L, caused DNA damage in the SOS-Chromotest, using *E. coli* strain PQ37 and in the absence of metabolic activation system.[4] It also induced DNA damage in cultured human lymphocytes.[1]

Furthermore, slight increases of unscheduled DNA synthesis were reported in human cell line WI38, which was exposed to n-butyl glycidyl ether (0.24 to 8.0 μg/mL) for one hour plus metabolic activation.[2,5] However, since there was no dose-related increase over at least 3 concentrations and since the highest

response was less than twice the control response, the authors considered this to be a negative result. The committee agrees with this conclusion.

At a concentration of 5 mmol/L, and in the absence of metabolic activation system, n-butyl glycidyl ether significantly increased the frequency of sister chromatid exchanges in Chinese hamster V79 cells.[6]

## 4.2 *In vivo* assays

Using the host-mediated assay, mice were given daily intraperitoneal injections of n-butyl glycidyl ether at a dose of 125 up to 1,000 mg/kg bw for five consecutive days.[2] No mutations were observed in the various *S. typhimurium* indicator strains.

n-Butyl glycidyl ether was tested in the mouse dominant lethal assay in three studies, resulting in mixed results. In the first, Pullin (1977) applied the agent at a dose of 1,500 mg/kg bw on the skin of at least 10 male B6D2F1 mice, three times per week for eight weeks.[5] Each male was mated with three untreated virgin females per week, for two weeks. The agent decreased pregnancy rates, increased the number of fetal deaths ($p$=0.04), and decreased the proportion of implants per pregnant female compared to control animals ($p$=0.01). In a repeat study using the same study design, no effects were observed at the same dose level and at 750 mg/kg bw, but an increase in fetal deaths was observed at a dose level of 3,000 mg/kg bw.[7]

In another study, Whorton *et al*. (1983) applied the agent at doses of 375, 750, and 1,500 mg/kg bw on the skin of male BDF hybrid mice (n=15-24 animals/group), three times per week for 8 weeks.[7] Each male was mated with three untreated virgin females per week, for three weeks. No changes in pregnancy rates and number of implants per pregnant female were observed. However, the fetal death rates (7.75%) were significantly increased in the females, which were mated in the first post-treatment week with the highest-dosed males, compared to controls. However, since the increase was comparable to that of controls (death rate, 7.33%) for the same period of time in a second experiment, the results of this study are uncertain.

Regarding clastogenicity, intraperitoneal injections of 225 to 900 mg n-butyl glycidyl ether per kg bw increased the frequency of micronuclei in bone marrow cells of female BDF mice (n=5/group).[1,2,8] However, no treatment-related

increases of micronuclei in female $B_6D_2F_1$ mice was observed after oral administration for five days (200 mg/kg bw, by gavage).[1,2,5,8]

Intraperitoneal administration of 31, 104, and 313 mg/kg bw per day for five consecutive days to Sprague-Dawley rats (n=5/sex/dose) resulted in an increase in the percentage of bone marrow cells with structural chromosomal aberrations on day six.[9] This effect was statistically significant at all dose levels. Comparison with control groups did not show statistically significant differences in mean chromosomal numbers and mean mitotic indices. No distinct adverse effects attributable to n-butyl glycidyl ether were noted in evaluation of in-life animal data (with the exception of one death in the high-dose group).

Chapter 5

# Classification

## 5.1 Evaluation of data on carcinogenicity and genotoxicity

No data on the genotoxicity and carcinogenicity of n-butyl glycidyl ether in humans were available, nor were there any carcinogenicity data available of animals.

The agent showed to be mutagenic and genotoxic in bacterial and mammalian cell systems. Furthermore, it acted as a clastogen when applied by intraperitoneal injections in mice and rats. These findings are a cause for concern to the committee. The outcomes of the mouse dominant lethal assays were uncertain, due to contradictory results.

The committee did not find indications that the observations in animals, and the proposed carcinogenic mechanism would not occur in humans.

## 5.2 Recommendation for classification

Based on the available information, the committee is of the opinion that n-butyl glycidyl ether has been insufficiently investigated. While the available data do not warrant a classification as carcinogenic to humans or as should be regarded as carcinogenic to humans, they indicate that there is cause for concern. Therefore, the committee recommends classifying n-butyl glycidyl ether as *a suspected human carcinogen*. This recommendation is comparable to the EU

classification in category 3. The situation is, furthermore, comparable with sub-category b of this category.

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8 Connor TH, Pullin TG, Meyne J, Frost AF, Legator MS. Evaluation of the mutagenicity of n-BGE and t-BGE in a battery of shortterm assays. Environ Mutagen 1980; 2(2): 284.

9 Piper CE. In vivo bone marrow cytogenetics study in the rat R0065 in the rat. Vienna, Virginia: Hazleton Laboratories America; 1979: Project No. 297-323.

| | |
|---|---|
| A | Request for advice |
| B | The committee |
| C | Comments on the public review draft |
| D | IARC Monograph |
| E | Carcinogenic classification of substances by the committee |
| F | Guideline 93/21/EEG of the European Union |

# 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.

Annex **B**

# The committee

- G.J. Mulder, *chairman*
  emeritus professor of toxicology, Leiden University, Leiden
- P.J. Boogaard
  toxicologist, SHELL International BV, The Hague
- Ms. M.J.M. Nivard
  molecular biologist and genetic toxicologist, Leiden University Medical Center, Leiden
- G.M.H. Swaen
  epidemiologist, Dow Chemicals NV, Terneuzen
- R.A. Woutersen
  toxicologic pathologist, TNO Quality of Life, Zeist
- A.A. van Zeeland
  professor of molecular radiation dosimetry and radiation mutagenesis, University Medical Center, Leiden
- E.J.J. van Zoelen
  professor of cell biology, Radboud University Nijmegen, Nijmegen
- J.M. Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

The committee consulted an additional expert, Prof. dr. G. Mohn, working at Department of Radiation Genetics and Chemical Mutagenesis of the University of Leiden, with respect to the genotoxic data.

## The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

# Comments on the public review draft

A draft of the present report was released in 2007 for public review. The following organisations and persons have commented on the draft document:

- E. González-Fernández, Ministerio de Trabajo y Asuntos Sociales, Spain;
- R.D. Zumwalde, National Institute for Occupational Safety and Health, the USA.

Annex **D**

# IARC Monograph

**Some glycidyl ethers**
**Vol.: 47 (1989) (p. 237)**[1]

Summary of Data Reported and Evaluation

Exposures

Glycidyl ethers are basic components of epoxy resins which have been commercially available since the late 1940s.

Experimental carcinogenicity data

-

Human data

No data were available to the Working Group.

Other relevant data

Some glycidyl ethers have been shown to cause allergic contact dermatitis in humans. Glycidyl ethers generally cause skin sensitization in experimental ani-

mals. Necrosis of the mucous membranes of the nasal cavities was induced in mice exposed to allyl glycidyl ether. Phenyl glycidyl ether, but not *n*-butyl glycidyl ether, induced morphological transformation in mammalian cells *in vitro*. *n*-Butyl glycidyl ether induced micronuclei in mice *in vivo* following intraperitoneal but not oral administration.

### Evaluation

No data were available from studies in humans on the carcinogenicity of glycidyl ethers.

### Overall evaluation

-

Annex **E**

# Carcinogenic classification of substances by the committee

The committee expresses its conclusions in the form of standard phrases:

| *Judgment of the committee* | *Comparable with EU class* |
|---|---|
| This compound is known to be carcinogenic to humans<br>• It is stochastic or non-stochastic genotoxic<br>• It is non-genotoxic<br>• Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether it is genotoxic | 1 |
| This compound should be regarded as carcinogenic to humans<br>• It is stochastic or non-stochastic genotoxic<br>• It is non-genotoxic<br>• Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether it is genotoxic | 2 |
| This compound is a suspected human carcinogen.<br>• This compound has been extensively investigated. Although there is insufficient evidence for a carcinogenic effect to warrant a classification as 'known to be carcinogenic to humans' or as 'should be regarded as carcinogenic to humans', they indicate that there is cause for concern.<br>• This compound has been insufficiently investigated. While the available data do not warrant a classification as 'known to be carcinogenic to humans' or as 'should be regarded as carcinogenic to humans', they indicate that there is a cause for concern. | 3<br>(A)<br>(B) |
| This compound cannot be classified<br>• There is a lack of carcinogenicity and genotoxicity data.<br>• Its carcinogenicity is extensively investigated. The data indicate sufficient evidence suggesting lack of carcinogenicity. | not classifiable |

Annex **F**

# Guideline 93/21/EEG of the European Union

## 4.2 Criteria for classification, indication of danger, choice of risk phrases

### *4.2.1 Carcinogenic substances*

For the purpose of classification and labelling, and having regard to the current state of knowledge, such substances are divided into three categories:

**Category 1:**

*Substances known to be carcinogenic to man.*

There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

**Category 2:**

*Substances which should be regarded as if they are carcinogenic to man.*

There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:

- appropriate long-term animal studies
- other relevant information.

**Category 3:**

*Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment.*

There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2.

*4.2.1.1 The following symbols and specific risk phrases apply:*

**Category 1 and 2:**

T; R45 May cause cancer

However for substances and preparations which present a carcinogenic risk only when inhaled, for example, as dust, vapour or fumes, (other routes of exposure e.g. by swallowing or in contact with skin do not present any carcinogenic risk), the following symbol and specific risk phrase should be used:

T; R49 May cause cancer by inhalation

**Category 3:**

Xn; R40 Possible risk of irreversible effects

*4.2.1.2 Comments regarding the categorisation of carcinogenic substances*

The placing of a substance into Category 1 is done on the basis of epidemiological data; placing into Categories 2 and 3 is based primarily on animal experiments.

For classification as a Category 2 carcinogen either positive results in two animal species should be available or clear positive evidence in one species; together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

*Category 3 actually comprises 2 sub-categories*:

a substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in Category 2. Additional experiments would not be expected to yield further relevant information with respect to classification.

b substances which are insufficiently investigated. The available data are inadequate, but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

For a distinction between Categories 2 and 3 the arguments listed below are relevant which reduce the significance of experimental tumour induction in view of possible human exposure. These arguments, especially in combination, would lead in most cases to classification in Category 3, even though tumours have been induced in animals:

- carcinogenic effects only at very high levels exceeding the 'maximal tolerated dose'. The maximal tolerated dose is characterized by toxic effects which, although not yet reducing lifespan, go along with physical changes such as about 10% retardation in weight gain;
- appearance of tumours, especially at high dose levels, only in particular organs of certain species is known to be susceptible to a high spontaneous tumour formation;
- appearance of tumours, only at the site of application, in very sensitive test systems (e.g. i.p. or s.c. application of certain locally active compounds);
- if the particular target is not relevant to man;
- lack of genotoxicity in short-term tests *in vivo* and *in vitro*;
- existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g. hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation;
- existence of a species - specific mechanism of tumour formation (e.g. by specific metabolic pathways) irrelevant for man.

For a distinction between Category 3 and no classification arguments are relevant which exclude a concern for man:

- a substance should not be classified in any of the categories if the mechanism of experimental tumour formation is clearly identified, with good evidence that this process cannot be extrapolated to man;
- if the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories;
- particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence.