N-vinyl-2-pyrrolidone

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-Vinyl-2-pyrrolidone*
Uw kenmerk : DGV/MBO/U-932542
Ons kenmerk : U-1483/JR/pg/246-X11
Bijlagen : 1
Datum : 12 december 2007

Geachte minister,

Graag bied ik u hierbij het advies aan over de kankerverwekkendheid van *N*-vinyl-2-pyrrolidon. 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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N-vinyl-2-pyrrolidone

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. 2007/11OSH, The Hague, December 12, 2007

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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Samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid evalueert en beoordeelt de Gezondheidsraad de kankerverwekkende eigenschappen van stoffen waaraan mensen tijdens de beroepsmatige uitoefening 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 angeduid als de commissie. In het voorliggende advies neemt de commissie *N*-vinyl-2-pyrrolidon onder de loep. *N*-Vinyl-2-pyrrsolidon wordt onder andere gebruikt bij de productie van polyvinylpyrrolidon en copolymeren.

De commissie meent dat *N*-vinyl-2-pyrrolidon 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 de commissie van mening dat waakzaamheid geboden is. De commissie adviseert daarom *N*-vinyl-2-pyrrolidon te classificeren als *verdacht kankerverwekkend voor de mens*. Volgens de richtlijnen van de Europese Unie komt dit overeen met een classificatie in categorie 3. 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*-vinyl-2-pyrrolidone. *N*-Vinyl-2-pyrrolidone is an agent that is used to produce polyvinyl pyrrolidone and copolymers.

The committee concludes that *N*-vinyl-2-pyrrolidone 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 for man*. This recommendation corresponds to EU classification in category 3. This 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 with reference to an EU-directive (see annex A and F). In addition to classifying substances, the Health Council also assesses the genotoxic properties of the substance in question. The assessment and the proposal for a classification are expressed in the form of standard sentences (see annex E). This report contains the evaluation of the carcinogenicity of *N*-vinyl-2-pyrrolidone.

1.2 Committee and procedure

The evaluation is performed by the committee 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 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.

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*-vinyl-2-pyrrolidone, 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 March 2007. The new relevant data were included in this report.

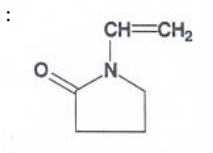
Chapter 2

General information

2.1 Identity and physico-chemical properties

The main use of *N*-vinyl-2-pyrrolidone (N-VP) is in the production of polyvinyl pyrrolidone, which is used in for instance pharmaceuticals, cosmetics and food additives.[1,2] It is also used in the production of copolymers, as a viscosity improver in oils, and in water-borne paints and adhesives. In addition, N-VP is used as a reactive intermediate.

Below is given the identity and some of its physical and chemical properties.[2,3]

Chemical name	:	*N*-vinyl-2-pyrrolidone
CAS registry number	:	88-12-0
EINECS number	:	201-800-4
IUPAC name	:	1-vinyl-2-pyrrolidone
Synonyms	:	1-ethenyl-2-pyrrolidone; vinylbutyrolactam; vinylpyrrolidinone; 1-vinylpyrrolidinone; *N*-vinylpyrrolidinone; 1-vinyl-2-pyrrolidinone; *N*-vinyl-2-pyrrolidinone; vinylpyrrolidone; *N*-vinylpyrrolidone
Description	:	colourless to yellow liquid at room temperature
Molecular formula	:	C_6H_9NO
Structure	:	

Molecular weight	:	111.1
Boiling point	:	193 °C (533 hPa); 96 °C (18.6 hPa)
Melting point	:	13.5 °C
Relative density (air = 1)	:	1.04 at 20 °C
Vapour pressure	:	0.12 hPa at 20 °C
Solubility	:	miscible with water, ether, alcohols, esters, ketones, chlorinated hydrocarbons and aromatic hydrocarbons
Stability	:	flash-point, 98.4 °C; polymerizes readily in the presence of oxygen
Conversion factors (20°C)	:	1 ppm = 4.61 mg/m^3 air 1 mg/m^3 = 0.22 ppm
Risk and safety phrases (annex I of Directive 67/548/EEC)	:	R20/21/22: harmful by inhalation, in contact with skin and if swallowed; R37: irritating to the respiratory tract; R40: limited evidence for a carcinogenic effect; R41: risk of serious damage to the eyes; R48/20: harmful: danger of serious damage to health by prolonged exposure through inhalation; S26: in case of contact with eyes, rinse immediately with plenty of water and seek medical advice; S36/37/39: wear suitable protective clothing, gloves, and eye/face protection Xn: harmful.
EU classification (see annex I of Directive 67/548/EEC)		Carcinogenic categorie 3

2.2 IARC classification

In 1999, IARC summarized that no relevant epidemiological data were available on the carcinogenicity of *N*-vinyl-2-pyrrolidone, and that there was limited evidence in experimental animals.[2] Therefore, it concluded that *N*-vinyl-2-pyrrolidone is *not classifiable as to its carcinogenicity to humans* (Group 3).

Chapter 3

Carcinogenicity studies

3.1 Observations in humans

No data were available to evaluate the carcinogenicity of *N*-vinyl-2-pyrrolidone in humans.

3.2 Carcinogenicity studies in animals

In 1997, Klimisch *et al.* published a paper in which the results of two carcinogenicity studies were reported.[4] In study A, groups of male and female Sprague-Dawley rats inhaled N-VP at air concentrations of 22, 45, or 90 mg/m^3 (5, 10, or 20 ppm) by whole body exposure, for 6 hours a day, 5 days per week for a maximum of two years. The study also included animals that were exposed to clean air alone.

No differences in survival were observed among the groups. Furthermore, no non-carcinogenic haematotoxicity and hepatoxicity was detected in any of the exposed groups, although a significant reduction in body weight gain and increased absolute and relative liver weight was reported. In male and females, a statistically significant increase in number of tumour-bearing animals was observed in the groups exposed to 90 mg N-VP/m^3 compared to controls (see table 3.1). The types of tumours concerned adenomas and adenocarcinomas of the nasal cavity, and hepatocellular carcinomas. In the same groups, a non-significant increase in incidence of squamous carcinomas of the larynx was found.

Table 3.1 Incidence of tumours in Sprague Dawley-rats, after chronic inhalation exposure to *N*-vinyl-2-pyrrolidone for a maximum of two years (study A; Klimisch *et al.* 1997).[4]

	males				females			
exposure (mg/m^3)	0	22	45	90	0	22	45	90
no. of animals	70	60	60	60	70	60	60	60
the nasal cavity	0	8	9	10*	0	2	8	12**
Adenoma adenocarcinoma	0	0	4	6**	0	0	0	4*
the liver	1	6	5	17**	1	3	6	26**
Hepatocelluar carcinoma								
the larynx	0	0	0	4	0	0	0	4
Squamous cell carcinoma								

Peto's analysis for trend: *, $p<0.001$; ** $p<0.0001$

In study B, female Sprague-Dawley rats inhaled N-VP at air concentrations of 0 or 202 mg/m^3 (0 or 45 ppm) by whole body exposure, for 6 hours a day, 5 days per week for a maximum of three months. The animals were sacrificed at 3, 12 or 24 months after the exposure period. No differences between the groups were observed concerning survival rate, body weight gain and clinical signs.

Histopathological analysis was performed in the liver only of rats that died or were killed after one year or longer in study. The number of animals examined was 15 per group. In the exposed animals, a non-significant increase in neoplastic lesions in the liver was observed (2/15, neoplastic nodules; 2/15, well-differentiated hepatocellular carcinomas; no neoplasms in control animals, 0/15). Furthermore, in the control and exposed groups, various non-neoplastic lesions were observed, such as; foci and/or areas of hepatocellular alternations; focal cirrhosis-like metaplasia (in exposed animals only, 2/15); focal telangiectasia; bile-duct proliferation and fibrosis; liver cell enlargement (in exposed animals only, 6/15); focal/multifocal parenchymal necrosis; and, fatty degeneration. The differences between the exposed and the control group were non-significant. The committee noted the small number of animals in the group, and the limited reporting on histopathological analysis.

The same authors also reported on the histopathological findings of a series of animal experiments, using different rat, mice and hamster strains, which were exposed to N-VP by inhalation for various durations (1 week to 12 months).[5] Non-neoplastic and neoplastic lesions were mainly found in the liver and nasal cavity. However, in none of these cases, the lesions could be related to exposure to N-VP.

In the Monograph of 1999, the Working Group of IARC reported also on the carcinogenicity of polyvinyl pyrrolidone.[2] The agent was tested in mice, rats, and

rabbits by several routes of administration, using materials of various molecular weights. Repeated subcutaneous injections of an aqueous solution of polyvinyl pyrrolidone to rats resulted in local sarcomas. Single, or several subcutaneous or intraperitoneal implantations of polyvinyl pyrrolidone powder, resulted in a low incidence of local tumours. After several intravenous injections or after intraperitoneal implantation of polyvinyl pyrrolidone, tumours occurred in rats at distant sites, including the reticuloendothelial system. According to IARC, the results of these experiments do not allow an evaluation of a possible association of these distant tumours with such treatments.

Chapter 4

Mutagenicity and genotoxicity

The committee noted that most of the mutagenicity and genotoxicity studies have not been published in the open literature. In these cases, the committee refers to secondary sources, such as the IARC Monograph (1999), the risk assessment report and the IUCLID dataset of the European Chemicals Bureau (2003, 2000), and the documentation of the German MAK (1994).[1-3,6]

4.1 *In vitro* assays

N-Vinyl-2-pyrrolidone has been extensively tested in various bacterial mutagenicity systems, in the presence and absence of a metabolic activation system. In short, in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, no increased frequencies of reversed mutations could be detected up to cytotoxic levels (European Chemicals Bureau 2003; DFG 1994; IARC 1999; IUCLID 2000; Simmon and Baden 1980, Knaap *et al*. 1985).[1-3,6-8] In addition, no increased frequencies in point mutations were detected, using a fluctuation test in *Klebsiella pneumoniae* (Knaap *et al.* 1985).[8] Overall, the committee noted the limited reporting of the experimental details.

Negative outcomes were also found in mammalian cells. For instance, N-VP did not induce gene mutations at the *hprt* and *tk* loci in L5178Y- mouse lymphoma cells, nor did it induce chromosomal aberrations in human peripheral blood lymphocytes (Knaap *et al*. 1985; Litton Bionetics 1980; BASF 1987; IUCLID 2000).[3,8-10]

Also negative results were reported on unscheduled DNA synthesis and DNA repair in primary rat hepatocytes, and on cell transformation in BALB/3T3 cells (Litton Bionetics 1980b; Litton Bionetics 1980c; IUCLID 2000).[3,11,12]

Norppa and Tursi (1984) reported on a slight *N*-vinyl-2-pyrrolidone-related induction of sister chromatid exchanges in human whole blood and isolated human peripheral lymphocytes.[13] However, no experimental details or actual data were given.

4.2 *In vivo* assays

Knaap *et al.* (1985) reported on negative outcomes from a sex-linked recessive lethal assay in *Drosophila melanogaster*.[8] The assay was performed in a closed system, but no further details were given.

Regarding clastogenic activity, the European Chemicals Bureau reported on unpublished results of a standard genotoxicity test in male and female NMRI mice.[1,3,14] In that study, groups of five male and female mice received a single dose of 150, 300, or 600 mg N-PV/kg bw by gavage. Twenty-four hours later, the animals were sacrificed (some animals in the highest dose group also after 16 and 48 hours). All the treated animals had signs of toxicity, including irregular respiration, piloerection, and a squatting posture; animals exposed to 600 mg/kg bw were in a poor state of health. In none of the treated animals an increase in the number of micronuclei in polychromatic erythrocytes was observed compared to controls, whereas the positive controls showed clear increases.

In an unpublished study, it was reported that N-VP or its metabolites did not bind to rat liver proteins, DNA or RNA.[1,15] In this study, three male rats were given a single intraperitoneal injection of radiolabelled N-VP at a dose of 150 or 300 mg/kg bw, or repeated intraperitoneal injections of the same doses for five consecutive days. Samples were taken one or five hours after (last) treatment. The liver was examined, because it was considered the target organ for N-VP induced carcinogenicity.

4.3 Carcinogenic mechanism

In the literature, there is no information available on the carcinogenic mechanism of *N*-vinyl-2-pyrrolidone. Since in a variety of *in vitro* and *in vivo* mutagenicity and genotoxicity assays N-VP did not produce positive outcomes, the committee

assumes that the agent induced tumours in animals by a nongenotoxic mechanism. An explanation might be conversion of N-VP into acid compounds, which causes cytotoxicity and irriation. Further research is needed to clarify the mode of action.

Chapter 5

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

No data are available on the carcinogenicity in exposed humans. One animal inhalation and carcinogenicity study was available, in which *N*-vinyl-2-pyrrolidone increased the incidence of rats having tumours in the nasal cavity, the liver, and to a lesser extent the larynx. No carcinogenicity studies were performed in other animal species. Overall, there is some evidence for carcinogenicity of the agent, and this finding worries the committee.

Extensive testing in various *in vitro* and *in vivo* assays did not result in mutagenicity or genotoxicity of N-VP. Despite the limited reporting on study details, the findings were consistent. Based on these data, the committee assumes that N-VP is not genotoxic. However, the mechanism underlying tumour-development, as observed in rats, is not clarified yet.

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

The committee concludes that *N*-vinyl-2-pyrrolidone 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 for man*. This recommendation corresponds

to EU classification in category 3. This situation is, furthermore, comparable with subcategory b of this category.

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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 Nutrition and Food Research, 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:

- G. Jonkers, Vereniging van Verf en Drukinktfabrikanten, the Netherlands;
- 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

VOL.: 71 (1999) (p. 1181)[2]

CAS No.: 88-12-0
Chem. Abstr. Name: 1-Ethenyl-2-pyrrolidinone

Summary of Data Reported and Evaluation

Exposure data

Little information was available to the Working Group regarding potential exposures to *N*-vinyl-2-pyrrolidone.

Human carcinogenicity data

No data were available to the Working Group.

Animal carcinogenicity data

N-Vinyl-2-pyrrolidone was tested for carcinogenicity in one experiment in rats by inhalation exposure. It produced adenomas and adenocarcinomas of the nasal cavity, squamous carcinomas of the larynx and hepatocellular carcinomas in both sexes. Another 12-month inhalation experiment in rats of the same strain indi-

cated occurrence of adenomas of the nasal cavity and foci of cellular alteration of the liver.

Other relevant data

N-Vinyl-2-pyrrolidone metabolites and polyvinyl pyrrolidone are excreted mainly in urine. Inhalation of low concentrations of *N*-vinyl-2-pyrrolidone by rats can cause nasal cavity inflammation, atrophy of olfactory epithelium and hyperplasia of the basal cells of the respiratory and olfactory epithelium. There have been no genetic toxicity studies.

Evaluation

No epidemiological data relevant to the carcinogenicity of *N*-vinyl-2-pyrrolidone or polyvinyl pyrrolidone were available.

There is *limited evidence* for the carcinogenicity of *N*-vinyl-2-pyrrolidone in experimental animals.

Overall evaluation

N-Vinyl-2-pyrrolidone is *not classifiable as to its carcinogenicity to humans (Group3).*

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 • It is stochastic or non-stochastic genotoxic • It is non-genotoxic • 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 • It is stochastic or non-stochastic genotoxic • It is non-genotoxic • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether it is genotoxic	2
This compound is a suspected human carcinogen.	3
• 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.	(A)
• 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.	(B)
This compound cannot be classified • There is a lack of carcinogenicity and genotoxicity data. • 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.