
N,N-dimethylformamide

Evaluation of the carcinogenicity and genotoxicity





Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies N,N-dimethylformamide
Uw kenmerk : DGV/MBO/U-932342
Ons kenmerk : U 6365/AvdB/fs/246-I14
Bijlagen : 1
Datum : 18 februari 2011

Geachte staatssecretaris,

Graag bied ik u hierbij aan het advies over de gevolgen van beroepsmatige blootstelling aan N,N-dimethylformamide.

Dit 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 getoetst door de Beraadsgroep Gezondheid en omgeving van de Gezondheidsraad.

Ik heb dit advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. L.J. Gunning-Schepers,
voorzitter

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
Telefoon (070) 340 70 17
E-mail: a.vander.burght@gr.nl

Postadres
Postbus 16052
2500 BB Den Haag
Telefax (070) 340 75 23
www.gr.nl

N,N-dimethylformamide

Evaluation of the carcinogenicity and genotoxicity

Subcommittee on the Classification of Carcinogenic Substances of
the Dutch Expert Committee on Occupational Safety,
a Committee of the Health Council of the Netherlands

to:

the State Secretary of Social Affairs and Employment

No. 2011/03OSH, The Hague, February 18, 2011

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 and health (services) research...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, Agriculture, & Innovation, and Education, Culture & Science. 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.



The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.



The Health Council of the Netherlands is a member of the International Network of Agencies for Health Technology Assessment (INAHTA), an international collaboration of organisations engaged with *health technology assessment*.

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

Preferred citation:

Health Council of the Netherlands. N,N-dimethylformamide; Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2011; publication no. 2011/03OSH.

all rights reserved

ISBN: 978-90-5549-826-0

Contents

Samenvatting 7

Executive summary 8

1 Scope 9

1.1 Background 9

1.2 Committee and procedures 9

1.3 Data 10

2 General information 11

2.1 Identity and physico-chemical properties 11

2.2 IARC classification 12

3 Carcinogenicity 13

3.1 Observations in humans 13

3.2 Carcinogenicity studies in animals 16

4 Genotoxicity 19

4.1 *In vitro* assays 19

4.2 *In vivo* assays 20

5	Classification	23
5.1	Evaluation of data on carcinogenicity and genotoxicity	23
5.2	Recommendation for classification	24

	References	25
--	------------	----

	Annex	28
A	Request for advice	29
B	The Committee	31
C	Comments on the public review draft	33
D	IARC evaluation and conclusion	34
E	Carcinogenic classification of substances by the Committee	36
F	Regulation (EC) No 1272/2008	37

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 aangeduid als de commissie. In het voorliggende advies neemt de commissie N,N-dimethylformamide onder de loep. N,N-dimethylformamide is een stof die onder andere wordt gebruikt bij zuiveringen en als oplosmiddel, bij de productie van geneesmiddelen en als katalysator en gasdrager bij industriële processen. Hoewel de gegevens over de kankerverwekkende eigenschappen van N,N-dimethylformamide beperkt zijn, is er reden tot zorg met betrekking tot het ontstaan van levertumoren.

Op basis van de beschikbare gegevens leidt de commissie af dat N,N-dimethylformamide verdacht kankerverwekkend voor de mens is, en beveelt zij aan de stof te classificeren in categorie 2*.

* Volgens het nieuwe classificatiesysteem van de Gezondheidsraad (zie bijlage E). Dit systeem is gebaseerd op richtlijn 1272/2008 van de Europese Unie, die op 20 Januari 2009 van kracht werd.

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 Safety of the Health Council, hereafter called the Committee. In this report, the Committee evaluated N,N-dimethylformamide. N,N-dimethylformamide is an agent that is among others used for purification and dissolution purposes, for the production of pharmaceuticals, and as catalyst and as carrier for gases in various industrial processes. Although the data concerning the carcinogenic properties of N,N-dimethylformamide are limited, there is cause for concern with respect to the development of liver tumours.

Based on the available information, the Committee is of the opinion that N,N-dimethylformamide is suspected to be carcinogenic to man, and recommends to classify the substance in category 2*.

* According to the new classification system of the Health Council, which is based on regulation 1272/2008 of the European Union. This regulation entered into force on 20 January 2009.

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,N-dimethylformamide.

1.2 Committee and procedures

The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council, hereafter called the Committee. The members of the Committee are listed in Annex B.

In 2010 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

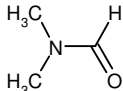
The evaluation and recommendation of the Committee is based on scientific data, which are publicly available. The starting point of the Committees' report is, if possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which 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,N-dimethylformamide, 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, and Chemical Abstracts. The last updated online search was in June 2010. The new relevant data were included in this report.

General information

2.1 Identity and physico-chemical properties

The data have been retrieved from the IARC evaluation³, and from the European Substance Information System (<http://ecb.jrc.it>).

Chemical name	:	N,N-dimethylformamide
CAS registry number	:	68-12-2
EINECS number	:	200-679-5
Synonyms	:	Dimethylformamide, N,N-dimethylformamide
Appearance	:	Colourless to very slightly yellow liquid with a faint amine odour.
Use	:	Used commercially as a solvent, for example, for vinyl resins, adhesives and epoxy formulations; for purification and/or separation of acetylene, 1,3-butadiene, acid gases and aliphatic hydrocarbons; in the production of polyacrylic or cellulose triacetate fibres and pharmaceuticals. It is also used as a catalyst in carboxylation reactions; in organic synthesis, as a quench and cleaner combination for hot-dipped tin parts; as an industrial paint strippers; as a carrier for gases, and in inks and dyes in printing and fibre-dyeing applications.
Chemical formula	:	$N(CH_3)_2COH$
Structural formula	:	
Molecular weight	:	73.09
Boiling point	:	153 °C
Melting point	:	-60.4 °C

Vapour pressure	:	3 kPa at 20 °C
Vapour density (air = 1)	:	2.51
Solubility	:	Miscible with water and most common organic solvents
Conversion factor	:	1 mg/m ³ = 0,3284 ppm 1 ppm = 3.0454 mg/m ³
EU Classification (100% solution)	:	T toxic H312 Harmful by inhalation and in contact with skin. H319 Causes serious eye irritation. H332 Harmful if inhaled. H360D May cause harm to an unborn child. (Based on Regulation (EC) No 1272/2008 of the European Parliament and of the Council on Classification, labelling and packaging of substances and mixtures; 16 December 2008)

2.2 IARC classification

In 1989, IARC initially evaluated the carcinogenicity of N,N-dimethylformamide as Group 2B (“*there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals*”).¹

In 1999, however, IARC concluded that there is inadequate evidence in humans for the carcinogenicity of N,N-dimethylformamide.³ Furthermore, it stated that there is evidence suggesting lack of carcinogenicity of N,N-dimethylformamide in experimental animals. Consequently, IARC concluded that N,N-dimethylformamide is not classifiable as to its carcinogenicity to humans (Group 3, “*the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals*”).

Carcinogenicity

3.1 Observations in humans

3.1.1 IARC data^{1,3}

Three cases of testicular germ-cell tumour were reported to occur during 1981-1983, among 153 white men working at a repair shop for F4 Phantom jet aircraft in the United States (Ducatman *et al.* 1986, cited in IARC). This finding led to surveys of two other repair shops at different locations, one of which repaired F4 Phantom jets, and the other different types of aircraft. Four among 680 white male workers in the F4 Phantom shop had testicular germ-cell cancers (approximately one expected) diagnosed during 1970-1983, while no case of testicular germ-cell cancer was found among 446 white men, who were employed at the other repair shop. Of the seven cases, five were seminomas and two were embryonal cell carcinomas. All seven had long work histories in aircraft repair. There were many common exposures to solvents in the three facilities, but the only exposure identified as unique to the F4 Phantom jet aircraft repair facilities was to a solvent mixture containing 80% N,N-dimethylformamide (20% unspecified). Three of the cases had been exposed to this mixture with certainty, and three cases had probably been exposed.

Levin *et al.* (1987) reported on three cases of embryonic cell carcinoma of the testis in workers at a leather tannery in the United States (cited in IARC). According to the authors, all the tanneries they had surveyed used N,N-dimethyl-

formamide, as well as a wide range of dyes and solvents. No additional cases of testicular cancer were identified in a subsequent screening effort at the same tannery, undertaken in 1989, in which 51 of 83 workers employed at the plant between 1975 and 1989 participated.

The previous reports led to a cohort study of cancer among employees of the Du Pont company (Chen *et al.* 1988a, cited in IARC). Cancer incidence was studied among 2,530 actively employed workers with potential exposure to N,N-dimethylformamide during 1950-1970 in Virginia, and among 1,329 employees with exposure to dimethylformamide and acrylonitrile at an acrylic fibre manufacturing plant in South Carolina, United States. Cancer incidence rates for the company (1956-1984) and national rates (1973-1977) for the United States were used to calculate expected numbers of cases. For all workers exposed to dimethylformamide (alone or with acrylonitrile), the standard incidence ratio (SIR) based on company rates for all cancers combined was 1.1 (95% confidence interval: 0.9-1.4; 88 cases). One case of testicular cancer was found among the 3,859 workers exposed to dimethylformamide (alone or with acrylonitrile), with 1.7 expected based on company rates; and 11 cases of cancer of the buccal cavity and pharynx were found among workers exposed to dimethylformamide. The SIR for cancer of the buccal cavity and pharynx was 3.4 (95% confidence interval: 1.7-6.2). For all workers exposed to N,N-dimethylformamide (alone or with acrylonitrile), the SIR based on company rates for all cancers combined was 1.1 (95% confidence interval: 0.9-1.4). No relationship was found between cancer of the buccal cavity and pharynx and intensity or duration of exposure.

Also, in 1950-1982, mortality was evaluated in the same cohort among both active and pensioned employees (Chen *et al.* 1988b, cited in IARC). For all workers exposed to N,N-dimethylformamide only, the SIR were 2.5 for buccal cavity and pharynx (2 observed *versus* 0.8 expected); 1.4 for lung cancer (19 observed *versus* 13.5 expected); and, 0.9 for all cancers combined (38 observed *versus* 40.1 expected).

In 1989, case-control cancer studies were conducted among workers from four Du Pont plants (Walrath *et al.* 1989, cited in IARC). Two plants had been previously studied for exposure to acrylonitrile and dimethylformamide (Chen *et al.* 1988a/b, cited in IARC). The cancers included: cancers of the buccal cavity and pharynx (39 cases); liver cancer (6 cases); prostate cancer (43 cases); testis cancer (11 cases); and malignant melanoma of the skin (39 cases). The cancers occurring during 1956 to 1985 were identified through the Du Pont Cancer Registry from a combined cohort composed of approximately 8,700 workers per year. For each case, the first two eligible controls from the employment roster were selected, and matched on year of birth, sex, wage/salary class, and plant.

Plants studied were a dimethylformamide production plant; two acrylic fibre plants that used dimethylformamide as a spinning solvent; and; a plant using the chemical as a solvent for inks. Potential exposure to N,N-dimethylformamide was classified as low or moderate (no worker fell in the high category) from job title/work area combinations by a team of two industrial hygienists, and an epidemiologist. Dimethylformamide were available for all plants: geometric means for air measurements ranged from less than 3.0 to 30 mg/m³ (1 to 10 ppm), as low and moderate exposure, respectively. Mantel-Haenszel odds ratios for ever exposed were 0.9 (90% confidence interval: 0.4-2.4; 15 cases); for buccal cavity and pharynx cancers, 1.7 (90% confidence interval: 0.5-5.5; 16 cases); for malignant melanoma, 1.5 (90% confidence interval: 0.7-3.3; 17 cases); for prostate cancer; and, 1.0 (90% confidence interval: 0.2-4.4) for testicular cancer. Odds ratios for malignant melanoma by level of exposure were 1.9 (90% confidence interval: 0.5-7.3) for low, and 3.1 (90% confidence interval: 0.8-11.9) for moderate exposure. Odds ratios for testicular cancer by level of exposure were 0.9 (90% confidence interval: 0.1-8.6) for low, and 11.6 (90% confidence interval: 0.5-286) for moderate exposure.

3.1.2 *Additional data*

Kaefferlein *et al.* (2001) reported on the formation of N-methylcarbamoylated valine of haemoglobin in blood samples from workers, who were exposed to N,N-dimethylformamide in the polyacrylic fiber industry.⁴ N-methylcarbamoylated haemoglobin was suggested to be formed as a result of the reaction of haemoglobin with methyl isocyanate, which in turn is believed to be a reactive intermediate during metabolism of N,N-dimethylformamide in humans. As haemoglobin adducts are accepted biomarkers of potential mutagenic relevance, the authors proposed that the formation of methyl isocyanate directly in the cell, and its possible distribution through the human body, may lead to critical effects after exposure to N,N-dimethylformamide, and may shed some light on its suspected carcinogenicity. However, the haemoglobin adducts, which were found in exposed workers, were determined not to be totally specific for exposure to N,N-dimethylformamide, since an identical adduct was also found in blood samples from the general population. However, concentrations were lower by a factor of about 100. The sources for background adducts are unknown.

3.2 Carcinogenicity studies in animals

3.2.1 IARC data^{1,3}

N,N-dimethylformamide was tested for carcinogenicity by oral administration, and subcutaneous injection in BD-rats (sex and age unspecified). In a study, in which N,N-dimethylformamide was administered by intraperitoneal injection in MRC-rats, a small number of uncommon tumours* was observed in treated rats. However, IARC concluded that all these studies were inadequate for evaluation.

Malley *et al.* (1994, cited in IARC) exposed groups of male and female Crl:CD-1 BR mice (N=78/group/sex; 55 days old) to N,N-dimethylformamide at concentrations of 0, 75, 300 or 1,200 mg/m³ (0, 25, 100 and 400 ppm; purity, 99.9%) in air by whole-body vapour exposure, for 6 hrs/day, 5 days/week, for 18 months. No compound-related effect on survival was evident. At termination, males in the highest two doses, and females in the highest dose, had higher liver weights. In both sexes, at the two highest exposures, centrilobular hepatocellular hypertrophy, and hepatic single-cell necrosis were increased. No increased tumour incidence was observed.

Malley *et al.* (1994, cited in IARC) also exposed groups of male and female Crl:CD BR rats (N=78/group/sex; 55 days old) to N,N-dimethylformamide at concentrations of 0, 75, 300 or 1,200 mg/m³ (0, 25, 100 and 400 ppm; purity, 99.9%) in air by whole-body vapour exposure, for 6 hours per day, five days a week, for two years. Exposure to the highest concentration reduced body weight gain in both sexes, but did not affect survival. The highest concentration also increased liver weights in both sexes. Ten males and ten females per group were killed at 12 months. In both sexes of the two highest concentration groups, incidence of minimal to mild centrilobular hepatocellular hypertrophy, and centrilobular accumulation of lipofuscin/heamosiderin, were increased. No increase in tumours occurred, but a 14.8% incidence of uterine endometrial stromal polyps in high-dose females was observed compared to 1.7% in controls. However, the range of historical control incidence for the laboratory was 2.0-15.0%.

IARC concluded that both studies by Malley *et al.* were adequate for evaluation.

* Uncommon tumours: An embryonic-cell carcinoma of the testis, colon adenomas and squamous cell carcinoma of the rectum.

3.2.2 Additional data

Senoh *et al.* (2004) exposed male and female F344/DuCrj (SPF) rats and Crj: BDF1 (SPF) mice (n=50/group/strain/sex) to airflow containing N,N-dimethylformamide vapour at target concentrations of 609, 1,218, and 2,436 mg/m³ (200, 400 or 800 ppm, respectively) for 6 hours per day, five days a week, for 103 weeks.⁷

Three male and thirteen female rats died of centrilobular necrosis of the liver within the first 13 and 21 weeks, respectively. Survival was not significantly affected for males, but high dose females had a significantly reduced survival from week 9 onwards. Growth rates were dose-related depressed in all treated animals: body weights of animals in groups exposed to 1,218, and 2,436 mg/m³ decreased by more than 10%, without any overt clinical signs. Food consumption was only depressed in high dosed females. Relative liver weights were found significantly increased in all treated groups, while absolute weights were significantly increased only in groups exposed to 609 and 2,436 mg/m³. No other dose-related changes in organ weights were observed.

Exposure of rats to N,N-dimethylformamide vapour significantly increased incidence of hepatocellular adenomas and carcinomas rats of both sexes, in an exposure concentration-related manner. Multiple occurrences of hepatocellular tumours were found in the liver of exposed rats, in contrast to the occurrence of a single tumour in the liver of the control group (see Table 1.1).

Table 1.1 Increased liver tumours incidences in rats and mice treated with N,N-dimethylformamide (6 hours per day, 5 days a week, whole-body vapour exposure for 103 weeks).⁷

Liver tumour type	Control	609 mg/m ³	1,218 mg/m ³	2,436 mg/m ³
<i>Rats, male</i>				
Hepatocellular adenoma and carcinoma, combined	1/50	4/50	13/50 ^a	33/50 ^a
<i>Rats, female</i>				
Hepatocellular adenoma and carcinoma, combined	1/49	1/50	6/50	19/50 ^a
<i>Mice, male</i>				
Hepatocellular adenoma, carcinoma, and hepatoblastoma, combined.	8/50	42/50 ^a	46/50 ^a	44/50 ^a
Hepatoblastoma	(0)	(13)	(7)	(4)
<i>Mice, female</i>				
Hepatocellular adenoma, and carcinoma, combined	3/49	45/50 ^a	49/50 ^a	49/49 ^a

^a *P*<0.01, Statistical analysis by Fischer Exact test.

In mice, there was no significant difference in survival between treated and control animals. Growth rates were dose-related depressed in all treated animals: body weights of all treated males, and females exposed to 2,436 mg/m³ (from 62nd week onwards) were decreased by more than 10% as compared to controls. Food consumption was not affected by treatment, neither were overt clinical signs observed.

The incidence of hepatocellular adenomas and carcinomas had significantly increased in all groups exposed to N,N-dimethylformamide, in an exposure concentration-related manner. Also the incidence of rare hepatoblastomas significantly increased in the male groups exposed to 609, and 1,218 mg/m³ (see Table 1.1).

Genotoxicity

4.1 *In vitro* assays

4.1.1 IARC data^{1,3}

Dimethylformamide was one of 42 chemicals selected for study in the International Collaborative Program for the Evaluation of Short-term Tests for Carcinogens, in which 30 assay systems were included, and more than 50 laboratories contributed data (de Serres and Ashby 1981, cited in IARC). Since then, the database has been expanded.

Most results for gene mutation or mitotic recombination with dimethylformamide were found to be negative. Most *in vitro* assays were performed in both the presence and absence of an exogenous metabolic system. The compound was reported to induce mutation in *Salmonella typhimurium* TA 1538 and TA98 in one test with metabolic activation, but the response occurred at a single, intermediate dose and, in many other studies, dimethylformamide did not induce gene mutation in any strain of *S. typhimurium* or in *E. coli* WP2uvrA, and did not induce differential toxicity indicative of DNA damage in bacteria. It also did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*, in experiments where it was used as a solvent for other substances to be tested. In one study, N,N-dimethylformamide enhanced the mutagenicity of tryptophan-pyrollysate in *S. typhimurium* TA 98 in the presence of an exogenous metabolic system (Arimoto *et al.* 1982, cited in IARC). In the other single study, it induced

aneuploidy in *Saccharomyces cerevisiae* D6 in both the presence and absence of an exogenous metabolic system and gave positive results in another study for mitotic recombination in yeast.

In experiments with mammalian cells, dimethylformamide induced a slight increase in unscheduled DNA synthesis in primary rat hepatocyte cultures in one study, but not in two others, or in studies with mouse and Syrian hamster hepatocytes. It was also not mutagenic in L5178Y tk[±] mouse lymphoma cells in three studies, while an increased mutation frequency of about two-fold was observed at the highest dose level in one experiment. No sister chromatid exchanges were induced in any study with either Chinese hamster or human cells, and no chromosomal aberrations were induced in rodent cells. Also no gene mutations were induced in a single study with human fibroblasts. Chromosomal aberrations were reported to be induced in one study with cultured human lymphocytes at a dose level of 0.007 µg/mL, but not in another study at a dose level of 80,000 µg/mL. N,N-dimethylformamide inhibited intercellular communication between Chinese hamster V79 hprt[±] cells.

4.1.2 Additional data

No additional data found.

4.2 In vivo assays

4.2.1 IARC data^{1,3}

Observations in humans

Chromosomal aberrations in peripheral blood lymphocytes were studied among twenty workers exposed to mono-, di- and trimethylamines, and dimethylformamide in the former German Democratic Republic (Berger *et al.* 1985, cited in IARC). The mean workplace concentration of N,N-dimethylformamide during one year before blood sampling was 12.3 mg/m³ (range 5.6-26.4 mg/m³). The frequency of chromosomal gaps and breaks was 1.4% compared to 0.4% in controls (18 workers of the same factory). A possible effect of smoking was not taken into account.

Chromosomal aberrations in peripheral lymphocytes were also reported in a study of about 40 workers, who were occupationally exposed to trace quantities of methyl ethyl ketone, butyl acetate, toluene, cyclohexanone and xylene, in addition to N,N-dimethylformamide (Koudela and Spazier 1981, cited in IARC).

The frequency of chromosomal aberrations after two four-month intervals, when exposure was to an average of 180 and 150 mg/m³ of N,N-dimethylformamide, were 3.82% and 2.74%, respectively. Subsequent sampling at three six-month intervals, when average dimethylformamide exposures were to 50, 40 and 35 mg/m³, gave lower aberrations frequencies of 1.59%, 1.58% and 1.49%. Aberration frequencies in two control groups were 1.61% and 1.10%.

In a study reported only as an abstract, no evidence for an increased frequency of chromosomal aberrations in peripheral lymphocytes of a group of workers, who were exposed to N,N-dimethylformamide, was found (no details provided) (Šrám *et al.* 1985, cited in IARC).

The effects of occupational exposure to N,N-dimethylformamide on sister chromatid exchange rates in peripheral lymphocytes was also studied in twenty-two women (aged 22-52 years) in comparison with twenty-two sex-, age- and residence-matched controls (Seiji *et al.* 1992, cited in IARC). All subjects were non-smokers and non-drinkers of alcohol. The group was divided into three sub-groups based on the exposure: high (n=8; mean exposure of 17.4 mg/m³); medium (n=5; mean exposure of 2.1 mg/m³; in combination with toluene at 0.9 ppm); and, low (n=9; 0.9 mg/m³). Sister chromatid exchange frequencies per cell were found to be significantly higher in the high- and medium-exposure groups than in matched controls (8.26 ± 1.76 versus 5.63 ± 1.56 , and 7.24 ± 1.53 versus 4.66, respectively), but not in the low-exposure group (5.67 ± 1.35 versus 6.57 ± 1.12). IARC noted the incompleteness of the reported data.

Animal studies

Dimethylformamide did not induce sister chromatid exchanges in mouse bone-marrow cells in a single study or micronuclei in mouse bone-marrow cells in four studies in mouse experiments *in vivo* (intraperitoneal administration up to 2,000 mg/kg bw). In one study, micronuclei were induced at a dose of 1 mg/kg bw. In a study reported as an abstract (Lewis 1979, cited in IARC), no dominant-lethal effect was observed in groups of ten Sprague-Dawley rats, which inhaled 900 mg N,N-dimethylformamide /m³ for 6 hours per day for five consecutive days. No morphologically transformed colonies were observed in Syrian hamster embryo cell cultures, either after treatment *in vitro* or after exposure of the dams to N,N-dimethylformamide (3 mg/kg bw) after a single intraperitoneal injection. Negative results were obtained in several inhalation studies conducted for the United States National Institute of Occupational Health, involving: exposure to 1,200 mg/m³ for 7 hours in a rat bone-marrow cell cytogenetic study; a male rat domi-

nant lethal assay; a mouse sperm morphology assay; and, for 2.25 hours in a *Drosophila melanogaster* sex-linked recessive lethal assay.

4.2.2 Additional data

Observations in humans

Major *et al.* (1998) reported on genotoxicity monitoring of viscose rayon Hungarian plant workers, who were exposed to acrylonitrile, and dimethylformamide.⁵ In peripheral blood lymphocytes of 26 workers, 26 matched controls, and 6 industrial controls (all males), genotoxicity end points were measured, such as: chromosome aberration; sister chromatid exchange; high frequency sister chromatid exchange; cell cycle kinetics; and, UV-induced unscheduled DNA synthesis, for three times (first, second, and twentieth month) during a follow-up period of twenty months. Some subjects left the plant for undisclosed reasons, so that in the twentieth month only 17 exposed subjects, and none of the industrial controls were accessible.

Regarding exposure, the range of peak N,N-dimethylformamide concentrations in the ambient air samples were 0.6-23.0 mg/m³, and 3.5-22.8 mg/m³ in the seventh month; no data for the 20th month were available. As the plant produced viscose rayon for decades, the subjects had been exposed to undefined acrylonitrile and/or N,N-dimethylformamide levels for 3-10 years before the start of the study.

Significant increases in chromosome aberrations, sister chromatid exchange frequencies, and unscheduled DNA synthesis, were found in the peripheral blood lymphocytes of the exposed subjects. The effect of confounding factors (age, alcohol consumption, smoking habits, total leukocyte count, and hematocrit) were also taken into consideration. However, the findings are inconclusive, because of combined exposure to other compounds, and undefined historical exposure.

Major *et al.* (1999) also reported on the induction premature centromere division in peripheral blood lymphocytes of employees of the chemical, petrochemical and pharmaceutical industry, as well as in hospital nurses in Hungary, who were exposed to various substances, such as N,N-dimethylformamide.⁶ For acrylonitrile and/or dimethylformamide exposure, the same subjects as mentioned in the previous paper were investigated; no increase in premature chromosome division yields was found.

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

Several case reports, case control studies and cohort studies have been described concerning the effects of exposure to N,N-dimethylamine. However, the human data are insufficient for the evaluation of the carcinogenic effects.

In addition, using rats and mice, Malley *et al.* (1994) did not find an increase in carcinogenic activity after whole body vapour exposure to N,N-dimethylformamide.^{1,3} On the other hand, Senoh *et al.* (2004) showed that inhalatory exposure of rats and mice increased the incidence of liver tumours of both sexes.⁷ The Committee is of the opinion that the outcomes of the animal studies are conflicting, but might be a result of differences in susceptibility for liver damage between animal strains, in that both studies used different rat and mouse strains; the strains used by Senoh *et al.* are probably more susceptible for liver damage than those used by Malley *et al.* Therefore, the Committee concludes that the available data are limited, but give cause for concern.

Given the co-exposure to acrylonitrile – a known mutagenic and carcinogenic agent² – and the undefined historical exposures, additional genotoxicity data on human blood cells are not reliable. In addition, there is a substantial amount of negative genotoxicity data in experimental animals.

5.2 Recommendation for classification

Based on the available information, the Committee is of the opinion that N,N-dimethylformamide is suspected to be carcinogenic to man, and recommends to classify the substance in category 2*.

* According to the new classification system of the Health Council (see Annex E), which is based on regulation 1272/2008 of the European Union. This regulation entered into force on 20 January 2009.

References

- 1 International Agency for Research on Cancer. Dimethylformamide. IARC Monograph on the evaluation of carcinogenic risks to humans. IARC, World Health Organization, Volume 47, pp-171-197; 1989.
 - 2 International Agency for Research on Cancer. Acrylonitrile. IARC Monograph on the evaluation of carcinogenic risks to humans. IARC, World Health Organization, Volume 71 (Part one), pp 43-108; 1999.
 - 3 International Agency for Research on Cancer. Dimethylformamide. IARC Monograph on the evaluation of carcinogenic risks to humans. IARC, World Health Organization, Volume 71, pp 545-574; 1999.
 - 4 Kafferlein HU, Angerer J. N-methylcarbamoylated valine of hemoglobin in humans after exposure to N,N-dimethylformamide: evidence for the formation of methyl isocyanate? *Chem Res Toxicol* 2001; 14(7): 833-840.
 - 5 Major J, Hudak A, Kiss G, Jakab MG, Szaniszló J, Naray M e.a. Follow-up biological and genotoxicological monitoring of acrylonitrile- and dimethylformamide-exposed viscose rayon plant workers. *Environ Mol Mutagen* 1998; 31(4): 301-310.
 - 6 Major J, Jakab MG, Tompa A. The frequency of induced premature centromere division in human populations occupationally exposed to genotoxic chemicals. *Mutat Res* 1999; 445(2): 241-249.
 - 7 Senoh H, Aiso S, Arito H, Nishizawa T, Nagano K, Yamamoto S e.a. Carcinogenicity and chronic toxicity after inhalation exposure of rats and mice to N,N-dimethylformamide. *J Occup Health* 2004; 46(6): 429-439.
-

References from IARC

Arimoto S, Nakano N, Ohara Y, Tanaka k, Hayatsu H. A solvent effects in the mutagenicity of tryptophan-pyrollysateb mutagen in the *Salmonella*/mammalian microsome assay (1982). *Mutat. Res.* 102, 105-112.

Berger H, Habe I, Wüncher G, Bittersohl G (1985). Epidemiological studies on exposure to dimethylformamide (Ger). *Z.ges.Hyg.* 31,366-368.

Chen JI, Fayerweather WE, Pell S (1988a). Cancer incidence of workers exposed to dimethylformamide and.or acrylonitril. *J.Occup. Med.* 30, 813-818.

Chen JI, Fayerweather WE, Pell S (1988b). Mortality study of workers exposed to dimethylformamide and.or acrylonitril. *J.Occup. Med.* 30, 819-821

De Serres FJ and Ashby J (eds). Evaluation of Short-term Tests for carcinogens. Report of the international Collaborative Program , Amsterdam, Elsevier (1981).

Ducatsman AM, Conwill DE, Crawl J (1986). Germ cell tumours of the testicle among aircraft repairmen. *J. Urol.* 136, 834-836

Koudela K and Spazier K (1981). Results of cytogenetic examination of persons workings in an environment of increased concentration of dimethylformamide vapours in the atmosphere. *Prak. Lek.* 33, 121-123 (in Czech)

Levin SM, Baker DB, Landrigan PJ, Monaghan SV, Frumin E, Braithwaite M, Towne W. (1987) Testicular cancer in leather tanners exposed to dimethylformamide. *Lancet*, ii, 1153

Lewis SC. (1979) Dominant lethal mutagenic boassay of dimethylformamide (DMF). *Environ. Mutagen.* 1, 166

Malley LA, Slone TW, Van Pelt C, Elliott GS, Ross PE< Stadler JC, KEnnedY GL, (1994). Chronic toxicity/oncogenicity of dimethylformamide in rats and mice following inhalation exposure. *Fundam. Appl. Toxicol.* 23, 268-279

Seiji K, Inoue O, Cai S-X, Kawai T, Wanatabe T, Ikeda M (1992). Increase in sister chromatid exchange rates ion association with occupational exposure to N,N-dimethyl;formamide. *Int. Arch.occup. environ. Health*, 64, 65-67

Sram RJ, Landa K, Hola N, Roznickova I, (1985) The use of cytogenetic analysis of periferal lymphocytes as a method for checking the level of MAC in Czechoslovakia. *M utat. Res.* 147, 322

Walrath J, Fayerweather WE, Gliby PG, and Pell S. (1989) A case-control study of cancer among du pont employees with potential for exposure to dimethylformamide. *J. Occup. Med.* 31, 432-438.

-
- A Request for advice
-
- B The Committee
-
- C Comments on the public review draft
-
- D IARC evaluation and conclusion
-
- E Carcinogenic classification of substances by the Committee
-
- F Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling, and packaging of substances and mixtures

Annexes

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 Safety (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 advise 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.

The Committee

-
- G.J. Mulder, *chairman*
Emeritus Professor of toxicology, Leiden University, Leiden
 - J. van Benthem
Genetic toxicologist, National Institute for Public Health and the Environment, Bilthoven
 - 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; Professor of translational toxicology, Wageningen University and Research Centre, Wageningen
 - A.A. van Zeeland
Emeritus Professor of molecular radiation dosimetry and radiation mutagenesis, Leiden University Medical Center, Leiden
 - E.J.J. van Zoelen
Professor of cell biology, Radboud University Nijmegen, Nijmegen
-

- A.S.A.M. van der Burght, *scientific secretary*
Health Council of the Netherlands, The Hague

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.

Comments on the public review draft

A draft of the present report was released in 2010 for public review. The following organisations and persons have commented on the draft document:

- National Institute of Occupational Safety and Health (NIOSH), Cincinnati, USA
- Unidad technical de Evaluaciones Ambientales, CNNT-INSHT, Madrid, Spain

IARC evaluation and conclusion

Vol: 71 (1999) (p. 545)³

CAS No.: 68-12-2

Chem. Abstr. Name: N,N-Dimethylformamide

Summary of Data Reported and Evaluation

Exposure data

Exposures to dimethylformamide occur during its production and during the production of inks, adhesives, resins, fibres, pharmaceuticals, synthetic leather, and its use as a purification or separation solvent in organic synthesis. It has been detected in ambient air and water.

Human carcinogenicity data

Case reports of testicular cancer in aircraft repair and leather tannery facilities suggested possible association with dimethylformamide. Further research has failed to confirm this relationship. A screening effort at a leather tannery, where a cancer cluster had been noted, identified no additional cases. Mortality and cancer incidence studies and nested case-control investigations of testicular cancer and several other anatomical sites at several facilities with exposure to dimethylformamide noted no convincing associations.

Animal carcinogenicity data

Dimethylformamide was adequately tested for carcinogenicity by inhalation in one study in mice and one study in rats. No increase in tumours was found.

Other relevant data

Acute exposure of humans or experimental animals to relatively high concentrations of dimethylformamide causes hepatotoxicity as a major toxic effect. Reports on chromosomal damage in workers exposed to dimethylformamide either failed to take into account smoking as a bias factor or were documented incompletely. Dimethylformamide has been extensively tested in a broad range of in-vitro and in-vivo genotoxicity assays. Results have been consistently negative in well controlled studies.

Evaluation

There is inadequate evidence in humans for the carcinogenicity of dimethylformamide.

There is evidence suggesting lack of carcinogenicity of dimethylformamide in experimental animals.

Overall evaluation

Dimethylformamide is not classifiable as to its carcinogenicity to humans (Group 3).

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 47 (1989)

Synonyms: N,N-dimethylformamide, Last updated: 12 April 1999.

E

Carcinogenic classification of substances by the Committee

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

Category	Judgement of the Committee (GRGHS)	Comparable with EU Category	
		67/584/EEC before 12/16/ 2008	EC No 1272/2008 as from 12/16/ 2008
1A	The compound is known to be carcinogenic to man. <ul style="list-style-type: none"> • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, the mechanism of action is not known. 	1	1A
1B	The compound is presumed to be carcinogenic to man. <ul style="list-style-type: none"> • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, the mechanism of action is not known. 	2	1B
2	The compound is suspected to be carcinogenic to man.	3	2
3	The available data are insufficient to evaluate the carcinogenic properties of the compound.	Not applicable	Not applicable
4	The compound is probably not carcinogenic to man.	Not applicable	Not applicable

Regulation (EC) No 1272/2008

of the European Parliament and of the Council on classification, labelling, and packaging of substances and mixtures

3.6 Carcinogenicity

3.6.1 *Definition*

Carcinogen means a substance or a mixture of substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans.

3.6.2 *Classification criteria for substances*

See Table on the next page.

3.6.2.1 For the purpose of classification for carcinogenicity, substances are allocated to one of two categories based on strength of evidence and additional considerations (weight of evidence). In certain instances, route-specific classification may be warranted, if it can be conclusively proved that no other route of exposure exhibits the hazard.

3.6.2.2 Specific considerations for classification of substances as carcinogens.

3.6.2.2.1 Classification as a carcinogen is made on the basis of evidence from reliable and acceptable studies and is intended to be used for substances which have an intrinsic property to cause can-

Table 3.6.1 Hazard categories for carcinogens.

Categories	Criteria
Category 1:	Known or presumed human carcinogens. A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as:
Category 1A:	Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence, or
Category 1B:	Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence. The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from: human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.
Category 2:	Suspected human carcinogens. The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived either from limited (1) evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

(1) Note: See 3.6.2.2.4.

cer. The evaluations shall be based on all existing data, peer-reviewed published studies and additional acceptable data.

3.6.2.2.2 Classification of a substance as a carcinogen is a process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place substances with human cancer potential into hazard categories.

3.6.2.2.3 Strength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the substance and an increased incidence of tumours. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. The terms 'sufficient' and 'limited' have been used here as they have been defined by the International Agency for Research on Cancer (IARC) and read as follows:

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

- sufficient evidence of carcinogenicity: a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence;
- limited evidence of carcinogenicity: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals. The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

- sufficient evidence of carcinogenicity: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites;
- limited evidence of carcinogenicity: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, *e.g.* (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

3.6.2.2.4 Additional considerations (as part of the weight of evidence approach (see 1.1.1)). Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors need to be considered that influence the overall likelihood that a substance poses a carcinogenic hazard in humans. The full list of factors that influence this determination would be very lengthy, but some of the more important ones are considered here.

3.6.2.2.5 The factors can be viewed as either increasing or decreasing the level of concern for human carcinogenicity. The relative emphasis accorded to each factor depends upon the amount and coherence of evidence bearing on each. Generally there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumour findings and the other factors in a case-by-case manner.

3.6.2.2.6 Some important factors which may be taken into consideration, when assessing the overall level of concern are:

- a tumour type and background incidence;
- b multi-site responses;
- c progression of lesions to malignancy;
- d reduced tumour latency;
- e whether responses are in single or both sexes;
- f whether responses are in a single species or several species;
- g structural similarity to a substance(s) for which there is good evidence of carcinogenicity;
- h routes of exposure;
- i comparison of absorption, distribution, metabolism and excretion between test animals and humans;
- j the possibility of a confounding effect of excessive toxicity at test doses;
- k mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity.

Mutagenicity: it is recognised that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity *in vivo* may indicate that a substance has a potential for carcinogenic effects.

3.6.2.2.7 A substance that has not been tested for carcinogenicity may in certain instances be classified in Category 1A, Category 1B or Category 2 based on tumour data from a structural analogue together with substantial support from consideration of other important factors such as formation of common significant metabolites, *e.g.* for benzidine congener dyes.

3.6.2.2.8 The classification shall take into consideration whether or not the substance is absorbed by a given route(s); or whether there are only local tumours at the site of administration for the tested route(s), and adequate testing by other major route(s) show lack of carcinogenicity.

3.6.2.2.9 It is important that whatever is known of the physico-chemical, toxicokinetic and toxicodynamic properties of the substances, as well as any available relevant information on chemical analogues, i.e. structure activity relationship, is taken into consideration when undertaking classification.

3.6.4 Hazard communication

3.6.4.1 Classification for carcinogenicity:

Category 1A or Category 1B:

Hazard statement H350: May cause cancer *<state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard>*.

Category 2:

Hazard statement H351: Suspected of causing cancer *<state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard>*.