Health Council of the Netherlands

Dimethylamine

Evaluation of the carcinogenicity and genotoxicity

2013/15

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Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Dimethylamine*
Uw kenmerk : DGV/BMO-U-932542
Ons kenmerk : U-7821/BvdV/fs/246-R18
Bijlagen : 1
Datum : 12 juli 2013

Geachte minister,

Graag bied ik u hierbij het advies aan over de gevolgen van beroepsmatige blootstelling aan dimethylamine.

Dit advies 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.

Dit 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 het 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. W.A. van Gool,
voorzitter

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Dimethylamine

Evaluation of the carcinogenicity and genotoxicity

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

to:

the Minister of Social Affairs and Employment

No. 2013/15, The Hague, July 12, 2013

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, 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.

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INAHTA

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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 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 rapport neemt de commissie dimethylamine onder de loep. Dimethylamine is een stof die onder andere wordt gebruikt als een versneller in de vulkanisatie van rubber, bij het looien, in de vervaardiging van zeep en als intermediair in de synthese van N,N-dimethylformamide, dimethyl-acetamide en andere chemicaliën.

Op basis van de beschikbare gegevens is de commissie van mening dat gegevens over dimethylamine niet voldoende zijn om de kankerverwekkende eigen-schappen te evalueren (categorie 3).*

* Volgens het classificatiesysteem van de Gezondheidsraad (zie bijlage E).

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 accupationally exposed. The evaluation is performed by the Subcommittee on the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee. In this report the Committee evaluated dimethylamine. Dimethylamine is an agent that is among others used as an accelerator in rubber vulcanization, for the manufacture of detergent soaps, and as an intermediate in the synthesis of N,N-dimethylformamide, dimethyl-acedamide and other chemicals.

The Committee is of the opinion that the available data are insufficient to evaluate the carcinogenic properties of dimethylamine (category 3).*

* According to the classification system of the Health Council (see Annex E).

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 (Annex A). In addition to classifying substances, the Health Council also assesses the genotoxic properties of the substance in question. The assessment and the proposal for classification are expressed in the form of standard sentences (see Annex E).

This report contains the evaluation of the carcinogenicity and genotoxicity of dimethylamine.

1.2 Committee and procedures

The evaluation is performed by the Subcommittee on the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee. The members of the committee are listed in Annex B. The submission letter to the Minister can be found in Annex C.

In 2013, 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 D.

1.3 Data

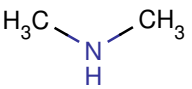
The evaluation and recommendation of the Committee is based on scientific data, which are publicly available. The starting of the Committee's reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). In the case of dimethylamine, however, such an IARC-monograph is not available.

The data were obtained from the online databases Toxline, Medline and Chemical Abstracts, using carcinogenic, cancer, carcinogenicity or mutagenic, mutagenicity, chromosome and CAS no. 124-40-3 as key words. With these searches also papers dealing with co-exposures to dimethylamine and nitrites or nitrates were retrieved. The last search was performed in May 2013.

Chapter 2

General information

2.1 Identity and physico-chemical properties

Chemical name	:	Dimethylamine
CAS registry number	:	124-40-3
EINECS number	:	204-697-4
Synonyms	:	N,N-dimethylamine, N-methylmethamine
Appearance	:	Colourless gas
Use	:	Used as an accelerator in vulcanizing rubber; in tanning and electroplating; in manufacture of detergent soaps; in manufacture of dimethylformamide and dimethylacetamide dyes, textiles and pharmaceuticals; as a flotation agent
Chemical formula	:	$NH(CH_3)_2$
Structural formula		
Molecular weight	:	45.08
Boiling point	:	6.8 °C
Melting point	:	-92.2 °C
Vapour pressure	:	101,3 kPa at 20°C; 202.65 kPa at 25 °C
Vapour density (air = 1)	:	1.6
Solubility	:	Very soluble in water forming a very strong alkaline solution. Soluble in alcohol or ether
Conversion factor	:	1 mg/m^3 = 0,5324 ppm at 20°C 1 ppm = 1,8783 mg/m^3

EU Classification	:	F+	Extremely flammable
	:	Xn	Harmful
	:	C	Corrosive
	:	R12	Extremely flammable
	:	R20/22	Harmful by inhalation and if swallowed
	:	R34	Causes burns

2.2 IARC classification

Dimethylamine has not been evaluated by IARC.

Chapter 3

Carcinogenicity studies

3.1 Observations in humans

No human data on the carcinogenicity of dimethylamine have been recovered from public literature.[1]

3.2 Carcinogenicity studies in animals

3.2.1 Inhalation

Buckley et al. (1985)[2] and Swenberg (1990)[3] studied the toxicity of inhalation exposure of dimethylamine in Fischer 344 rats and B6C3F1 mice. The 4 to 8 weeks old animals were exposed to 0, 10, 50, and 175 ppm (= 0, 18.8, 93.9, 328.7 mg/m^3 respectively) dimethylamine for 6 hr/day, 5 days a week for 2 years. Groups of 9-10 male and female rats and mice were necropsied after 6, 12 and 24 months of exposure (i.e. a total of 95 animals per sex/species). Each animal was examined for gross abnormalities, and 45 tissues and any gross lesions were examined microscopically.

Due to high mortality of male mice in both the control and treatment groups no interim sacrifice in these groups was performed at 12 months of exposure. Therefore, at the end of the study (24 months), the number of male mice in each group, even in the highest dose group, was sufficient.

The highest dose reduced bodyweight with about 10% after 3 weeks of exposure. The only other treatment-related changes were concentration-dependent lesions at two distinct locations in the nasal passages: the anterior respiratory epithelium, and the olfactory epithelium, especially that lining the anterior dorsal meatus. Focal destruction of the anterior nasoturbinate and nasal septum, local inflammation, and focal squamous metaplasia of the respiratory epithelium were observed. Mild goblet cell hyperplasia was only observed in rats. The olfactory epithelium exhibited extensive loss of sensory cells with less damage to sustentacular cells. There was also loss of olfactory nerves, hypertrophy of Bowman's glands, and distention of the ducts of these glands by serocellular debris in regions underlying degenerating olfactory epithelium. At the 175 ppm (= 328.7 mg/ m^3) level, rats had more extensive olfactory lesions than mice, with hyperplasia of small basophilic cells adjacent to the basement membrane being present in rats but not in mice. After 12 months of exposure to 10 ppm dimethylamine, minimal loss of olfactory sensory cells and their axons in olfactory nerve bundles was observed in the nasal passages of a few rats and mice. The mucosal damage in the two species (Fischer 344 rats and B6C3F1 mice) at the end of the study (24-month) was described as focal and mild at 10 ppm (=18.8 mg/m^3), moderate at 50 ppm (= 93.9 mg/m^3) and severe at 175 ppm (=328.7 mg/m^3). No treatment-related increase in the incidence of neoplasms was seen.

3.2.2 Oral exposure

Rubenchik et al. (1980)[4] (study published in Russian) exposed a group of 27 rats to dimethylamine (1.6 g/kg diet) in a diet consisting of a mixture of casein, sunflower oil, carrots, rice and salt mixture. Dimethylamine was administered dissolved in water. Other groups received concurrently dimethylamine and sodium nitrite in the diet, or only sodium nitrite or dimethylnitrosamine. Several animals (on average 5-6 animals) per group were sacrificed after 3.5 and 16.5 months, while the remaining animals were treated for over 2.5 years. The organs of all dead and sacrificed animals were subjected to histological examinations. No neoplastic or preneoplastic changes were found in animals exposed to dimethylamine alone.

Il'nitsky and co-authors (1979)[5] (study published in Russian) exposed groups of male CBA mice to a mixture of dimethylamine, sodium nitrate, and nitrite for one year in drinking water. In this experiment another group of 31 mice received drinking water solely containing 288 mg of dimethylamine hydrochloride, and a group of 30 mice served as untreated controls. After 1 year, treatment was ceased

and the surviving mice received pure water and were allowed to live until 101 weeks after the beginning of the experiment. At this time, the remaining animals were sacrificed and all mice were autopsied and organs were microscopically examined. The main histopathological changes in the experimental animals were liver hepatomas (16/31 in dimethylamine group (no metastases) vs. 8/30 in the control group (no metastases))*. Also 1 case of lung adenoma was found in the dimethylamine group vs. 0 in controls.

3.3 Summary of the carcinogenicity studies

The public literature retrieved by the Committee provided no human data on carcinogenicity of dimethylamine. The effects of long-term (2-year) dimethylamine exposure via inhalation to rats and mice were examined by Buckley et al. (1985)[2] and Swenberg (1990)[3]. Buckley et al.[2] reported that that 12 months of exposure induced dose-related changes at two distinct locations in the nasal passages of rats and mice, the anterior respiratory epithelium, and the olfactory epithelium. Rats had more extensive olfactory lesions than mice. The results reported by Swenberg[3] after 2 years on the same inhalation study gave no evidence of carcinogenicity.

The paper of Rubenchik et al. (1980)[4] states that no increased incidence of tumours was found in Wistar rats exposed orally to only dimethylamine for over 2.5 years. However, the number of animals was limited, and there was only one dose level investigated. Only two very limited oral studies were reported, one in CBA mice showed an increased incidence of liver tumours upon 1 year oral exposure to dimethylamine hydrochloride solution, although not statistically significant.

* The article provides no information on statistical significance for these incidences; no significant difference between groups ($p = 0.08$) was obtained by the Committee by performing the χ^2-test.

Chapter 4

Genotoxicity

4.1 Gene mutation assays

4.1.1 In vitro

Green and Savage (1978)[6] evaluated the mutagenicity of dimethylamine (purity not stated) in an Ames test with and without metabolic activation. Strains tested were Salmonella typhimurium TA1530, TA1531, TA1532 and TA1964. For the assays without S9 1-5 mg dimethylamine was used per plate, and for the assay with S9, bacterial suspensions of 0.05, 0.5, 0.15 and 0.05 M were tested.

The results indicate that dimethylamine was not mutagenic in strains TA1530, TA1531, TA1532 and TA1964 without metabolic activation, but was dose-dependently mutagenic with S9 in TA1530 at 0.5, 0.15 and 0.05 M dimethylamine.

The mutagenic activity of dimethylamine in Ames test was also investigated by Zeiger and co-workers (2009)[7] within the frame of the National Toxicology Program (NTP). Dimethylamine was tested in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, with and without metabolic activation. To determine the appropriate dose range (including a dose that elicited toxicity), a toxicity assay was initially performed on strain TA100. Six different concentrations (33, 100, 333, 1000, 3330 and 4500 µg/plate) were tested in triplicate, with concurrent solvent (water) and positive controls (sodium azide for TA1535

and TA100, 9-aminoacridine for TA1537 and 4-nitro-*o*-phenylenediamine for TA98).

Dimethylamine was found not to be mutagenic either with or without metabolic activation in all tested strains.

Kilkichko et al. (1993)[8] (study published in Russian) studied the mutagenicity of dimethylamine in TA98 and TA100 *Salmonella typhimurium* strains without metabolic activation. The following concentrations of the substance were used: 1.0, 2.5, 5.0, 7.5 and 10.0 mg/plate. Pure distilled water was used as a negative control substance.

The authors stated that no mutagenic activity was detected for dimethylamine.

Galli and co-authors (1993)[9] evaluated the genotoxicity of dimethylamine (tested as a 40% aqueous solution) in the D7 strain of *Saccharomyces cerevisiae.* Dimethylamine was not able to induce mitotic gene conversion and point reverse mutation in the D7 strain in the absence of S9 fraction, when tested up to a maximum concentration of 4 mM. Cell survival was reduced to 25% of the control value at the highest dose examined. A dose-dependent increase in convertants and revertants was observed when the S9 fraction was added to the incubation. Galli and co-authors (1993)[9] postulated that this effect in the D7 strain could have been caused by the presence of formaldehyde obtained upon incubation of dimethylamine with S9 mix, as formaldehyde was detected under these experimental conditions, and can induce revertants and mitotic recombination in yeast (Chanet et al. (1979)[10] [This reference was made in Galli et al.[9]]) At the maximal dose (4 mM), a 3.8-fold increase of convertants and 3.5 fold of revertants were obtained. In the presence of S9 fraction the reduction of cell survival was similar to that seen in the absence of S9. These results demonstrate that the metabolites of dimethylamine are genotoxic in yeast.

4.1.2 In vivo

Green and Savage (1978)[6] evaluated the mutagenicity of dimethylamine (purity not stated) in a host-mediated assay. C3H/HeJ mice were injected intraperitoneally with 2 ml of an overnight growth of one of the *Salmonella typhimurium* strains TA1950, TA1951, TA1952 and TA1534. Each mouse was given 0.1 ml intramuscular injection of the test compound. 3 hours after the intramuscular injection, the mice were sacrificed. Each mouse then received a 1 ml intraperitoneal injection of isotonic saline and as much fluid as possible was aseptically removed from the peritoneum. After two days incubation at 37 ˚C,

mutant frequency was determined. Dimethylamine was not mutagenic in this assay.

Couch and Friedman (1975)[11] studied the mutagenicity of dimethylamine in a host-mediated assay with G46 strain of *Salmonella typhimurium* LT2. Male Swiss (ICR) mice were inoculated with 2.0 ml of a culture of *S. typhimurium* G46 in logarithmic growth phase (2-3x10^7 cells/ml) in tryptone broth by intraperitoneal injection. Immediately prior to inoculation, dimethylamine (2000 mg/kg) was administered by gavage. Animals were killed 3 hours after inoculation, peritoneal fluid was plated on minimal medium and incubated 40 h at 37 ˚C for enumeration of wild-type revertants. Total cell count was obtained from plating dilutions of peritoneal fluid on tryptone agar incubated 18 hours at 37 ˚C. The mutation frequency was calculated as the ratio of total number of mutant cells to total cell count. An appropriate solvent control and a positive control (500 mg/kg dimethylnitrosamine) were run. Two to six mice per group were used and the experiments were performed at least twice and results were pooled: dimethylamine did not significantly alter the mutation frequency.

4.2 Cytogenetic assays

4.2.1 In vitro

No data on in vitro genotoxicity of dimethylamine have been recovered from public literature.

4.2.2 In vivo

The ability of dimethylamine to induce chromosome aberrations and aneuploidy in bone marrow in vivo was evaluated by Isakova and co-workers (1971)[12] (article published in Russian). Groups of 3-8 male Wistar rats were exposed to 0.5 mg/m^3 and 1 mg/m^3 dimethylamine (unspecified purity) 24 hours per day, 7 days/week for either 15 days or 3 months. An untreated group of animals was used as a control group. The incidence of structural chromosome breakages and aneuploidy, recorded in metaphases of marrow cells, was used as the criterion of a mutagenic effect. The results indicated that the frequency of chromosome aberrations remained within the margins of the control group (0-2%). However, at both concentrations the number of aneuploid cells was found to be statistically higher ($p < 0.001$) in the bone marrow of animals exposed to dimethylamine than in the control group: after 3 months 18-24% in comparison to 2% in controls; this

frequency after 3 months was nearly twice as high as after 15 days exposure. The Committee questions the relevance of the observation of aneuploidy in this study.

4.3 Summary of the genotoxicity studies

The data on genotoxicity of dimethylamine are ambiguous. Green and Savage (1978)[6] reported that dimethylamine was not mutagenic in *Salmonella typhimurium* strains TA1530, TA1531, TA1532 and TA1964. Also Zeiger and co-workers (2009)[7] reported that dimethylamine was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, with and without metabolic activation, and Kilkichko et al.[8] either did not observe mutagenic activity in Ames strains TA98 and TA100 without metabolic activation. Dimethylamine was also not mutagenic in D7 strain of *Saccharomyces cerevisiae* without metabolic activation; however, a dose-dependent increase in convertants and revertants was observed when the S9 fraction was added to the latter incubation by Galli et al. (1993)[9]. Also, dimethylamine was found to be mutagenic in the microsomal assay with the base-substitution strain *Salmonella typhimurium* TA1530 (Green and Savage (1978)[6]). Two host-mediated assays with C3H/HeJ mice and *Salmonella typhimurium* strains TA1950, TA1951, TA1952 and TA1534 and Swiss ICR mice with *Salmonella typhimurium* G46 strain were both negative. However, statistically significant increases ($p < 0.001$) in the number of aneuploid cells in bone marrow of rats exposed to 0.5 mg/m^3 and 1.0 mg/m^3 dimethylamine vapours for 3 months in comparison to the control group were found in the study of Isakova and co-workers (1971)[12], although no increase in the number of chromosome aberrations was observed in the treated animals.

In summary, the in vitro and in vivo data show that dimethylamine is not a gene mutagen, but may possess aneugenic activity.

4.4 Role of N,N-dimethylnitrosamine

The reaction of dimethylamine and nitrite at acidic pH results in the formation of the carcinogenic N,N-dimethylnitrosamine (currently classified as Carcinogenic Cat. 2, R45 according to Directive 67/548/EEC). Nitrite may enter the stomach via food, saliva or by intragastric bacterial nitrate reduction. The possibility of in vivo formation of dimethylnitrosamine in the stomach of experimental animals (upon oral uptake of a mixture of dimethylamine and nitrite, or upon oral uptake of dimethylamine and inhalation of nitrous oxide) and the possible resulting carcinogenic and genotoxic effects has been extensively investigated.[4,5,8,11,13-16]

The available data indicate that the formation of dimethylnitrosamine in vivo is possible upon concurrent exposure to dimethylamine and sodium nitrite or nitrogen dioxide. Furthermore, increased incidence of tumours has been reported in experimental animals exposed concurrently to both substances. [The Committee was not able to evaluate the quality of the studies by Rubenchik et al. (1980) and Il'nitsky et al. (1979) (published in Russian)]. In all reported studies focus is on oral exposure to dimethylamine, and dimethylnitrosamine formation is shown to depend on acidic conditions in the stomach or possibly on the presence of micro-organisms in the intestines. Although under experimental conditions increased incidence of tumours may occur, it unclear whether daily oral exposure to nitrite and inhalation exposure to dimethylamine in an occupational setting can result in tumour formation.

The Committee is of the opinion that these studies have no relevance for the classification process.

Chapter 5

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

Dimethylamine was not evaluated by IARC.

The public literature retrieved by the Committee provided no human data on carcinogenicity and genotoxicity of dimethylamine. Two papers examined the effects of long-term dimethylamine exposure via inhalation to rats and mice. In the first one by Buckley et al. (1985)[2] 12 months of exposure induced dose-related changes at two distinct locations in the nasal passages of rats and mice, the anterior respiratory epithelium, and the olfactory epithelium. Rats had more extensive olfactory lesions than mice. After 2 years exposure no evidence of carcinogenicity was observed in the same inhalation study (Swenberg, 1990).[3] The paper of Rubenchik et al.(1980)[4] showed that no increased incidence of tumours was found in Wistar rats exposed orally to only dimethylamine for over 2.5 years. However, the number of animals was limited, and there was only one dose level investigated. Only two very limited oral studies were reported, one in CBA mice showed an increased incidence of liver tumours upon 1 year oral exposure to dimethylamine hydrochloride solution, although not statistically significant. The Committee is of the opinion that the data are insufficient to properly evaluate the carcinogenic properties of the compound.

The data on genotoxicity of dimethylamine are ambiguous. It was reported that dimethylamine was not mutagenic in various bacterial (*Salmonella typhimurium*) strains and in yeast (D7 strain of *Sachharomyces cerevisiae*).[6-9]

Dimethylamine was found to be mutagenic in the microsomal assay with the base-substitution strain *Salmonella typhimurium* TA1530 (Green and Savage (1978).[6] Two host-mediated assays with C3H/HeJ mice and *Salmonella typhimurium* strains and Swiss ICR mice with *Salmonella typhimurium* strain were both negative (Green and Savage, 1978[6]; Couch and Friedman, 1975[11]). However, statistically significant increases ($p < 0.001$) in the number of aneuploid cells in bone marrow of rats exposed to 0.5 mg/m^3 and 1.0 mg/m^3 dimethylamine vapours for 3 months in comparison to the control group were found in the study of Isakova and co-workers (1971)[12], although no increase in the number of chromosome aberrations was observed in the treated animals. In summary, the in vitro and in vivo data show that dimethylamine is not a gene mutagen, but may possess aneugenic activity. The Committee is of the opinion that the data are not sufficient to derive conclusions on the genotoxicity of dimethylamine.

5.2 Recommendation for classification

The Committee is of the opinion that the available data are insufficient to evaluate the carcinogenic properties of dimethylamine (category 3).*

* According to the classification system of the Health Council (see Annex E).

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A	Request for advice
B	The Committee
C	The submission letter
D	Comments on the public review draft
E	Carcinogenic classification of substances by the Committee

Annexes

Annex **A**

Request for advice

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

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

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

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

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request

for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

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

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

Annex **B**

The Committee

- R.A. Woutersen, *chairman*
  Toxicologic Pathologist, TNO Innovation for Life, Zeist; Professor of Translational Toxicology, Wageningen University and Research Centre, Wageningen
- J. van Benthem
  Genetic Toxicologist, National Institute for Public Health and the Environment, Bilthoven
- P.J. Boogaard
  Toxicologist, SHELL International BV, The Hague
- G.J. Mulder
  Emeritus Professor of Toxicology, Leiden University, Leiden
- Ms. M.J.M. Nivard
  Molecular Biologist and Genetic Toxicologist, Leiden University Medical Center, Leiden
- G.M.H. Swaen
  Epidemiologist, Dow Chemicals NV, Terneuzen
- E.J.J. van Zoelen
  Professor of Cell Biology, Radboud University Nijmegen, Nijmegen
- G.B. van der Voet, *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 chairperson 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 inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

The submission letter

Subject : Submission of the advisory report Dimethylamine
Your Reference : DGV/MBO-U-932542
Our reference : U-7821/BvdV/fs/246-R18
Enclosed : 1
Date : July 12, 2013

Dear Minister,

I hereby submit the advisory report on the effects of occupational exposure to Dimethylamine.

This advisory report is part of an extensive series in which carcinogenic substances are classified in accordance with European Union guidelines. This involves substances to which people can be exposed while pursuing their occupation.

The advisory report was prepared by the Subcommittee on the Classification of Carcinogenic Substances, a permanent subcommittee of the Health Council's Dutch Expert Committee on Occupational Safety (DECOS). The advisory report has been assessed by the Health Council's Standing Committee on Health and the Environment.

I have today sent copies of this advisory report to the State Secretary of Infrastructure and the Environment and to the Minister of Health, Welfare and Sport, for their consideration.

Yours sincerely,
(signed)

Prof. dr. W.A. van Gool,
President

Annex **D**

Comments on the public review draft

A draft of the present report was released in February 2013 for public review. No comments were received on the draft document.

Annex **E**

Carcinogenic classification of substances by the Committee

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

Category	Judgement of the Committee (GR_{GHS})	Comparable with EU Category (before 16 December 2008)	Comparable with EU Category (as from 16 December 2008)
1A	The compound is known to be carcinogenic to humans. • 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, it is unclear whether the compound is genotoxic.	1	1A
1B	The compound should be regarded as carcinogenic to humans. • 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, it is unclear whether the compound is genotoxic.	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

Source: Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.[17]

Health Council of the Netherlands

Advisory Reports

The Health Council's task is to advise ministers and parliament on issues in the field of public health. Most of the advisory opinions that the Council produces every year are prepared at the request of one of the ministers.

In addition, the Health Council issues unsolicited advice that has an 'alerting' function. In some cases, such an alerting report leads to a minister requesting further advice on the subject.

Areas of activity

Optimum healthcare
What is the optimum result of cure and care in view of the risks and opportunities?

Prevention
Which forms of prevention can help realise significant health benefits?

Healthy nutrition
Which foods promote good health and which carry certain health risks?

Environmental health
Which environmental influences could have a positive or negative effect on health?

Healthy working conditions
How can employees be protected against working conditions that could harm their health?

Innovation and the knowledge infrastructure
Before we can harvest knowledge in the field of healthcare, we first need to ensure that the right seeds are sown.

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