Health Council of the Netherlands

Tetrahydrofuran

Evaluation of the carcinogenicity and genotoxicity

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Tetrahydrofuran*
Uw kenmerk : DGV/MBO/U-932342
Ons kenmerk : U-7437/JR/fs/246-G17
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Geachte staatssecretaris,

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

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

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
E-mail: jolanda.rijnkels@gr.nl
Telefoon (070) 340 66 31

Postadres
Postbus 16052
2500 BB Den Haag
www.gr.nl

Tetrahydrofuran

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. 2012/23, The Hague, November 23, 2012

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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Samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid evalueert en beoordeelt de Gezondheidsraad de kankerverwekkende eigenschappen van stoffen waaraan mensen tijdens het uitoefenen van hun beroep kunnen worden blootgesteld. De evaluatie en beoordeling worden verricht door de subcommissie Classificatie van Carcinogene Stoffen van de Commissie Gezondheid en Beroepsmatige blootstelling aan stoffen van de raad, hierna kortweg aangeduid als de commissie. In het voorliggende advies neemt de commissie tetrahydrofuraan onder de loep. De stof wordt onder andere gebruikt: bij de fabricage van artikelen voor verpakkingen, transport en opslag van voedsel; als oplosmiddel; en als chemisch intermediair bij polymerisatie reacties.

Naar het oordeel van de commissie zijn de gegevens niet voldoende om de kankerverwekkende eigenschappen van tetrahydrofuraan 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 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 evaluates tetrahydrofuran. The substance is used: in the manufacture of articles for packaging, transporting, and storing foods; as a solvent; and, as an intermediate in polymerisation processes.

According to the judgement of the Committee, the available data are insufficient to evaluate the carcinogenic properties of tetrahydrofuran (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 (see 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 a classification are expressed in the form of standard sentences (see Annex E)

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

1.2 Committee and procedures

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. The members of the Committee are listed in Annex B. The submission letter (in English) can be found in Annex C.

In 2012 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. 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 tetrahydrofuran, such an IARC-monograph is not available.

Published data were retrieved from the online databases Medline, Toxline, and Chemical Abstracts. The last online search was performed in October 2012. The relevant data were included in this report.

Chapter 2

Tetrahydrofuran

2.1 Identity, and physico-chemical properties

Tetrahydrofuran is used: as a medium for Grignard and metal hydride reactions; in the synthesis of butyrolactone, succinic acid, and 1,4-butanediol diacetate; in the manufacture of articles for packaging, transporting, and storing foods; as a solvent for dyes and lacquers; and as chemical intermediate in polymerisation solvent for fat oils, unvulcanised rubber, resins, and plastics. Tetrahydrofuran is also an indirect additive when it is in the contact surface of articles intended for use in food processing.

The identity, and the physico-chemical properties are shown below.

Chemical name	:	Tetrahydrofuran
CAS registry number	:	109-99-9
EINECS number	:	203-726-8
Synonyms	:	Tetramethylene oxide; tetraidrofurano; tetrahydrofuranne; tetrahydrofuraan; oxolane; oxacyclopentane; furanidine; cyclotetramethylene oxide; butylene oxide
Appearance	:	Colourless volatile liquid, with characteristic odour
Chemical formula	:	C_4H_8O

Structure	:	
Molecular weight	:	72.1
Boiling point	:	66ºC
Melting point	:	-108.5ºC
Vapour pressure	:	114 mm Hg at 20ºC; 204 mm Hg at 30ºC
Vapour density (air = 1)	:	2.5
Solubility	:	Soluble in water (30% at 25ºC), ethyl alcohol, and ethyl ether
Conversion factor	:	1mg/m^3 = 0.34 ppm
EU classification	:	Highly flammable (R11) May form explosive peroxides (R19). Irritating to eyes and respiratory system (R36/37).

2.2 IARC conclusion

Tetrahydrofuran has not been evaluated by IARC.

Chapter 3

Carcinogenicity

3.1 Observations in humans

No human studies addressing the carcinogenicity of tetrahydrofuran have been retrieved from public literature.

3.2 Carcinogenicity studies in animals

The National Toxicology Program (NTP) performed carcinogenicity studies using rats and mice.[1,2] So far known this is the only long-term carcinogenicity study reported in the public literature. The results are discussed below.

Rats. Groups of F344/N rats (N=50/group/sex) inhaled tetrahydrofuran at concentrations of 0 (vehicle control), 200, 600, or 1,800 ppm, for six hours per day, five days per week for a total of 105 weeks. Survival and mean body weights of all dosed groups were comparable to that of the vehicle controls. No clinical findings or non-neoplastic lesions related to exposure were observed in male or female rats.

Regarding neoplastic lesions, tumour development was observed in the kidneys of male rats (see Table 1). However, group-wise comparisons revealed a non-significant increase, although a positive trend was observed, and the number of animals with tumours in the two highest exposure groups exceeded the historical range for vehicle controls. Furthermore, all males suffered from

Table 1 Tumour development in the kidneys of male F344 rats (NTP-study).[1,2]

Number of animals with lesion	Control	200 ppm	600 ppm	1,800 ppm
Number of animals examined	50	50	50	50
Renal tubule, adenoma	1	1	4	3
Renal tubule, carcinoma	0	0	0	2
Renal tubule tumours, combined	1	1	4	5
Renal tubule, hyperplasia	5	5	6	7
Chronic progressive nephropathy (CPN)	48	50	50	50

Historical control range reported: 0-4%, with a mean rate of 0.9 ± 1.3%.

chronic progressive nephropathy without any treatment-related differences in severity. No signs of tumour development were observed in female rats, and in other organs in male rats.

Mice. Groups of B6C3F_1 mice (N=50/group/sex) inhaled tetrahydrofuran at concentrations of 0 (vehicle control), 200, 600, or 1,800 ppm, for six hours per day, five days per week for a total of 105 weeks.[1,2] Throughout the study, the mean body weights of all dosed groups were similar to those of vehicle controls. However, after week 36, the survival of male mice in the highest dose group was significantly less compared to the vehicle controls. Also, the same group suffered from a state of narcosis during, and up to one hour after the exposure periods. This resulted in prolonged wetting of the preputial fur, which probably has caused ascending urogenital tract bacterial infection. Finally, this may have led to a moribund state and death. No exposure-related non-neoplastic lesions were observed in male of female mice.

Signs of neoplastic lesions were observed in the liver only. In the highest group of females, the increase of hepatocellular adenomas combined with carcinomas was statistically significantly higher compared to the vehicle controls (see Table 2). Hepatocellular tumours (adenomas and carcinomas) were also found in males (vehicle control, 35/50 (70%); 200 ppm, 31/50; 600 ppm, 30/50; and, 1,800 ppm, 18/50). However, there was a high spontaneous incidence in male controls (historical controls, 37.8 ± 12.5%, range 11 - 60%). Furthermore, the NTP explained the low liver tumour incidence in the group exposed to 1,800 ppm, to a lower survival in this group. These two factors precluded any conclusion on the carcinogenicity in male mice.

Table 2 Tumour development in the liver of female $B6C3F_1$ mice (NTP-study).[1,2]

Number of animals with lesion	control	200 ppm	600 ppm	1,800 ppm
Number of animals examined	50	50	50	48
Adenoma	10	14	13	19
Adenoma, multiple	2	3	5	12
Carcinoma	4	6	9	10
Carcinoma, multiple	2	4	1	6
Adenoma or carcinoma combined[aa]	17	24	26	41
Eosinophilic focus	7	9	7	11
Necrosis	3	0	0	7

[a] Historical control range incidence: 21.3 ± 11.9%, range 3-54%.

Chapter 4

Mode of action

4.1 Genotoxic mode of action

4.1.1 Gene mutation tests

In vitro

In two independent Ames assays, tetrahydrofuran was tested in concentrations of up to 10,000 µg/plate in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, with and without a metabolic activation system. In both assays, tetrahydrofuran was not mutagenic.[2]

In vivo

No induction of sex-linked recessive lethal mutations was noted in male germ cells of *Drosophila melanogaster*. The flies were administered tetrahydrofuran by feeding or injection doses of 10,000, 40,000, or 125,000 ppm.[2]

4.1.2 *Gytogenetic tests*

In vitro

At doses up to 5 mg/mL with and without a metabolic activation system, tetrahydrofuran did not induce sister chromatid exchanges or chromosome aberrations in cultured Chinese hamster ovary cells.[2]

In vivo

Tetrahydrofuran did not induce sister chromatid exchanges in bone marrow cells of mice given a single intraperitoneal injection of 500 to 2,500 mg/kg bw (23-hour exposure), and 500 to 2,000 mg/kg bw (42-hour exposure).[2] In addition, in mice given 500, 1,000 or 2,000 mg tetrahydrofuran/kg bw, the compound did not induce chromosome aberrations in mouse bone marrow cells (sample times 17- or 36-hours).[2]

In male and female mice, the frequency of tetrahydrofuran-induced micronucleated polychromatic, and normochromatic erythrocytes, was investigated (at the end of a 14-week period; exposure was for six hours a day, five days per week).[2] In female mice, inhalation of doses of 600, 1,800 or 5,000 ppm, did not significantly increase the number of micronucleated erythrocytes. In male mice, a small increase of micronucle-ated normochromatic erythrocytes was noted at the mid dose only. The Committee considers the outcome of this study inconclusive, because the test was not performed according to the current guidelines.

4.1.3 *DNA-adduct formation*

Hermida et al. (2006) showed that tetrahydrofuran has the potential to form adducts with 2'-deoxyguanosine, in the presence of a metabolic activation system, and NADPH.[3] To the Committee, the relevance of the finding is unclear, because the conditions were biologically not relevant.

4.2 Non-genotoxic mode of action

Three short-term animal studies have been performed to elucidate possible non-genotoxic mechanisms of action of tetrahydrofuran in the kidneys of male rats,

and in the liver of female mice. The studies described below all used the same experimental design, and animal species, as was carried out by the NTP.

NTP performed fourteen-week duration studies in rats and mice, with a same design as in the two-year duration study.[2] The animals (N=10/group/sex/species) were exposed to tetrahydrofuran at air concentrations of 0 (control), 66, 200, 600 or 5,000 ppm, for six hours per day, five days per week, for fourteen weeks.

Histopathology on kidney tissue of male and female rats did not reveal signs of tissue degeneration or pre-neoplastic lesions. In female rats, absolute and relative liver weights were significantly increased in rats exposed to 5,000 ppm compared to controls. No other effects were observed in the kidneys or liver.

Significant increases in absolute and relative liver weights were observed in male mice exposed to 600 ppm and greater, and in female mice exposed to 1,800 ppm and greater. In male and female mice exposed to 5,000 ppm, a significant increase in incidence of minimal to mild centrilobular cytomegaly of the liver was observed compared to controls. No such significant effects were observed in the other exposure groups. Also no other effects in the liver were observed, nor any effect in the kidneys.

Gamer et al. (2002) reported on tetrahydrofuran-induced cell proliferation and enzyme induction in male rat kidney and female mouse liver.[4] Male F344 rats (N=6/group), and female $B6C3F_1$ mice (N=10/group) inhaled tetrahydrofuran at concentrations of 0 (vehicle control), 600, 1,800 or 5,400 mg/m^3 (0, 200, 600 and 1,800 ppm, respectively) for six hours a day, for five consecutive days, either for one week (five treatments) or for four weeks (twenty treatments). Also, the reversibility of treatment-related changes was studied in both animal species, which were exposed for five days, and then sacrificed three weeks after the last exposure. Male rat kidney tissue, and female mouse liver tissue were sampled for analyses on α2-microglobulin accumulation (rat kidney tissue only), cell proliferation, apoptosis and metabolic enzyme determination.

After five and twenty treatments, the rats showed a statistically significant dose-related α2-microglobulin accumulation in the renal cortex. No signs of reversibility were observed after the three-week recovery period. In rats exposed to 1,800 ppm for five treatments (without recovery), the α2-microglobulin accumulation in the renal cortex was accompanied with increased apoptosis and cell proliferation. No exposure-related apoptosis and cell proliferation was observed in rats exposed to 1,800 ppm for twenty treatments, five treatments with recovery, or in rats exposed to lower exposure levels. Morphological examination did reveal degeneration or necrosis. A slight increase in hyaline droplet accumulation was observed in males exposed to 1,800 ppm for twenty

treatments, but not in other groups. Tetrahydrofuran did not induce metabolic enzymes.

In female $B6C3F_1$ mice, a statistically significant increase in cell proliferation was observed only in mice inhaling 1,800 ppm for five treatments (all zones), and in zone 3 (central vein region) after twenty treatments. This was accompanied with an increased mitotic index, but not with increased apoptosis. There were no morphological signs of cell degeneration or necrosis. The level and activity of metabolic enzymes were statistically significantly increased in mice exposed to 1,800 ppm for five treatments, but not in other groups.

Van Ravenzwaay et al. (2003) exposed female $B6C3F_1$ mice (N=18/group) to tetrahydrofuran at air concentrations of 0 (control), 1,800 or 5,000 ppm, for six hours per day for five days.[5] The animals were killed on the day of last exposure. Thereafter, they determined metabolic enzyme amount and activity, and performed histochemical analysis (morphology and cell proliferation) on liver tissues. Treatment with tetrahydrofuran at 5,000 ppm increased significantly the level and activity of metabolic enzymes. Furthermore, at this exposure level, cell proliferation was statistically significantly increased compared to controls. No such effects occurred in the group exposed to 1,800 ppm. Tetrahydrofuran did not affect subcellular morphology. The investigators also pretreated groups with a drug metabolism enzyme inhibitor. The inhibitor clearly blocked enzyme activity, whereas histochemical analysis of tissues in these groups (at 5,000 ppm) revealed the presence of significant cell proliferation. Therefore, the authors suggested that cell proliferation was caused by tetrahydrofuran itself, and not by its (oxidative) metabolites.

4.3 Animal carcinogenicity and its relevance for humans

In the literature, it is under debate whether the tetrahydrofuran-induced tumours in the male rat kidney, and in the female mouse liver, are of relevance for humans.[6-9] The state of the art, and the opinion of the Committee are given below.

4.3.1 Male rat kidney tumours

Alpha-2u globulin accumulation

Renal tumours in male rats, which are associated with alpha-2u globulin accumulation via renal nephropathy, are considered not relevant for humans.[4,6,7]

Humans as well as female rats and mice do not synthesize alpha-2u globulin. Alpha-2u globulin accumulation is characterised by:[6,9]

Hyaline droplets. In the two-year NTP-study, the presence of hyaline droplets in renal proximal tubule cells was observed in the kidneys of control animals, and in rats exposed to 1,800 ppm tetrahydrofuran (by the authors called protein droplets).[2] However the severity did not differ between the groups. The NTP also performed a fourteen-week inhalation study (see Section 4.2).[2] In the highest exposed group (5,000 ppm) a slight increase in hyaline droplets was observed compared to control animals, but again, the severity of these droplets did not differ between the two groups. In a third study, Gamer et al. (2002) found only a slight non-significant increase of hyaline droplets in proximal tubular cells of male rats exposed to 1,800 ppm tetrahydrofuran for twenty treatments compared to control animals (see Section 4.2).[4]

Presence of alpha-2u globulin in hyaline droplets. Immunohistochemical analyses by Gamer et al. (2002) demonstrated a statistically significant exposure-related increase in alpha-2u globulin levels in the renal cortex of male rats, which were exposed to tetrahydrofuran for five or twenty treatments (see Section 4.2).[4] Only in the highest exposed group (1,800 ppm) this was accompanied by a slight increase in hyaline droplets.

Alpha-2u globulin specific nephropathological lesions. No evidence for alpha-2u globulin specific lesions, or cell degeneration, in the kidneys have been found in any of the three studies.[2,4]

In summary, hyaline droplets and the presence of alpha-2u globulin in those droplets have been demonstrated in tetrahydrofuran-exposed animals. For alpha-2u globulin levels, the increase was significant, but differences of hyaline droplet accumulation and severity between exposed and control animals, were minimal. No signs of alpha-2u globulin specific lesions or cell degeneration have been observed.

Chronic Progressive Nephropathy (CPN)

Another suggestion is that the development of renal tumours was preceded by advanced chronic progressive nephropathy (CPN). CPN is considered a spontaneous age-related disease that occurs in high incidences in certain common strains of rats only (including Fischer 344 strains).[8] It is, therefore, considered a rodent-specific entity, having no relevance for humans.

In the two-year NTP-study, both the incidence and the severity of CPN did not differ among the groups, including the control group. Almost all rats were affected. The renal tissues of the NTP-study were re-evaluated by others.[9-12]

Within the CPN affected renal tissue, foci of atypical (focal) tubule hyperplasia were observed. These preneoplastic lesions could have contributed to the development of renal tumours. However the incidence of combined preneoplastic and neoplastic lesions did not differ between the exposed animals and the control animals.[10]

Overall, the Committee considers it clear that the tumours found in exposed and non-exposed male rats could be related to these two mechanisms. Since neither alpha-2u globulin accumulation nor CPN occurs in humans, and no genotoxic or non-genotoxic mode of action(s) could be attributed to the development of renal tumours in male rats, the Committee considers the findings in male rats not relevant in assessing the carcinogenic potential of tetrahydrofuran in humans.

4.3.2 *Female mouse liver tumours*

The relevance of chemically-induced liver tumours in mice has long been questioned.[7,13,14] The reason for this is that mouse cancer models frequently develop spontaneous hepatocellular tumours at high rates. A typical pattern observed is that due to differences in sex hormones, the rates in male mice are higher than in female mice.[14] In particular when a high rate is observed in one sex only, some investigators consider the findings not relevant for humans. On the other hand, the Committee considers liver tumours in mice relevant for humans when the induction of tumours can be explained by a specific carcinogenic mechanism, such as genotoxicity, and/or the promotion of tumour development in early or late stages.[7,9]

In evaluating the mode of action, the two-year NTP-study has a main limitation in that data on male mice cannot be judged, because of the lower survival rate in the highest dosed-group. This was most likely due to the presence of a bacterial infection. So, it cannot be ruled out that tetrahydrofuran might have induced liver tumours in male mice as well, if there was no infection at all. However, the Committee is aware that male and female rats, which were also exposed to tetrahydrofuran in the same study, did not show any sign of the development of liver tumours.

Regarding genotoxicity, genotoxicity assays were negative (see Section 4.1). Also, the principal metabolites of tetrahydrofuran, gamma-butyrolactone and gamma-hydroxybutyric acid, did not show signs of carcinogenicity and genotoxicity.[7,15]

In the literature it is suggested that exposure to tetrahydrofuran may have resulted in liver tumours by inducing cell proliferation, which might have led to

promotion in the growth of pre-initiated cells.[4,7,9] Increased cell proliferation was clearly observed in female mice of the highest-exposed group (1,800 ppm; after five treatments) in the short-term study by Gamer et al. (2002; see Section 4.2).[4,5] However, after twenty treatments the increase was non-significant. Furthermore, in the same study, and in the NTP-studies, no clear signs of increased cell degeneration or necrosis were observed.[2,4] This missing link between cell proliferation and cell degeneration indicates that the induction of cell proliferation cannot be associated with the liver tumours that developed in exposed female mice.

Overall, the Committee concludes that there are strong indications (i.e., species specific susceptibility for liver tumours, and lack of a clear genotoxic mode of action) that the liver tumours found in female mice were of no relevance for humans.

Chapter 5

Classification

5.1 Evaluation and conclusion

No data on the carcinogenicity of tetrahydrofuran in humans are available.

In animals one carcinogenicity inhalation study has been performed using rats and mice. In male rats, a slight but statistically non-significant increase in incidence of renal tubule adenomas and carcinomas (combined) was observed at 1,800 ppm; in female mice exposed to the same exposure level, a clear increase in incidence of liver adenomas and carcinomas (combined) was reported. Tetrahydrofuran did not induce tumours at other sites in the body, nor in the opposite sex.

Regarding the kidney tumours in male rats, the Committee concludes that these are not relevant for humans, since the most likely mechanisms that induced these tumours are sex and species specific (alpha-2u globulin accumulation and chronic progressive nephropathy), which do not occur in humans. Also, the Committee concludes that the liver tumours in female mice are of no relevance for humans, because of the high species susceptibility for this type of tumours, and the absence of tumours at other sites of the body in combination with the lack of genotoxic potential of tetrahydrofuran. Overall, there is little or no animal data supporting an association between exposure to tetrahydrofuran and cancer.

5.2 Recommendation for classification

According to the judgement of the Committee, the available data are insufficient to evaluate the carcinogenic properties of tetrahydrofuran (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	Classification of substances with respect to carcinogenicity

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
- J.M. Rijnkels, *scientific secretary*
  Health Council, The Hague

The first draft of the present advisory report was prepared by K. Jenken, TNO Quality of Life, by contract with the Dutch Health Council.

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 *Tetrahydrofuran*
Your Reference	: DGV/MBO/U-932342
Our reference	: U-7437/JR/fs/246-G17
Enclosed	: 1
Date	: November 23, 2012

Dear State Secretary,

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

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 utch Expert Committee on Occupational Safety. The advisory report as 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)
Professor W.A. van Gool,
President

Annex **D**

Comments on the public review draft

A draft of the present report was released in 2012 for public review. The following organisation has commented on the draft document:

- Mr. T.J. Lentz, National Institute for Occupational Safety and Health, USA.

Annex **E**

Classification of substances with respect to carcinogenicity

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

Category	Judgement of the committee (GR_{GHS})	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. • 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. • 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

Source: Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague: Health Council, 2010; publication no. A10/07E.[16]