Health Council of the Netherlands

4-Methoxyphenol

Evaluation of the carcinogenicity and genotoxicity

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *4-Methoxyphenol*
Uw kenmerk : DGV/MBO/U-932342
Ons kenmerk : U-6820/JR/bp/246-I15
Bijlagen : 1
Datum : 15 november 2011

Geachte staatssecretaris,

Graag bied ik u hierbij het advies aan over de gevolgen van beroepsmatige blootstelling aan 4-methoxyfenol.

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. Daarbij heeft de subcommissie op verzoek van uw ministerie de formulering van de categorie waarin 4-methoxyfenol valt, aangepast; niet een numerieke aanduiding maar een standaardzin vormt de hoofdformulering. 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. L.J. Gunning-Schepers,
voorzitter

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

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

4-Methoxyphenol

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. 2011/28, The Hague, November 15, 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.

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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 de beroepsmatige uitoefening kunnen worden blootgesteld. In het voorliggende advies neemt de Subcommissie Classificatie van Carcinogene Stoffen van de Commissie Gezondheid en Beroepsmatige Blootstelling aan Stoffen van de Raad, die deze evaluatie en beoordeling verricht, 4-methoxyfenol onder de loep. 4-Methoxyfenol wordt onder andere gebruikt als stabiliserend agens en chemisch intermediair voor het maken van verschillende producten.

Op basis van de beschikbare gegevens is de commissie van mening dat de gegevens over 4-methoxyfenol niet voldoende zijn om de kankerverwekkende eigenschappen te evalueren (categorie 3)*.

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

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 the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council. In this report, the Committee evaluated 4-methoxyphenol. The compound is used, for instance as a stabilizer, and chemical intermediary for various products.

The Committee is of the opinion that the available data are insufficient to evaluate the carcinogenic properties of 4-methoxyphenol (category 3)*.

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

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 D).

This report contains the evaluation of the carcinogenicity of 4-methoxyphenol.

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.

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 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 4-methoxyphenol no such an IARC-monograph is available.

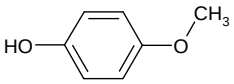
More recently published data were retrieved from the online databases Medline, Toxline, Chemical Abstracts, and RTECS. The last updated online search was in June 2011. The new relevant data were included in this report.

Chapter 2

General information

2.1 Identity and physico-chemical properties

4-Methoxyphenol is used for the manufacturing of antioxidants, pharmaceuticals, plasticisers, dyestuffs; as UV inhibitor; as stabiliser for chlorinated hydrocarbons, textile lubricating oils, and ethyl cellulose; and, as an inhibitor for acrylic monomers and acrylonitriles.

Chemical name	:	4-methoxyphenol
CAS registry number	:	150-76-5
EINECS number	:	205-769-8
Synonyms	:	Mequinol; 4-hydroxyanisole; hydroquinone monomethyl ether; para-methoxyphenol; para-hydroxyanisole.
Appearance	:	Plates from water, white waxy solid, white to tan flaky crystalline substance, colourless to white waxy solid
Chemical formula	:	$C_7H_8O_2$
Structural formula	:	
Molecular weight	:	124.14
Boiling point	:	243 ºC at 766 mm Hg
Melting point	:	57 ºC
Vapour pressure	:	3.2 – 4.9 mm Hg at 20 ºC
Vapour density (air = 1)	:	4.3
Log P (octanol – water)	:	1.58 (log K_{ow})

Solubility	:	Soluble in benzene, acetone, ethanol and ethyl acetate. Water solubility is 40 g/L at 25 ºC
EU Classification (100% solution)		H302: Harmful if swallowed H317: May cause an allergic skin reaction H319: Causes serious eye irritation (Based on regulation (EC) No. 1272/2008 of the European Parliament and the Council on Classification, labelling and packaging of substances and mixtures; 16 December 2008)

2.2 IARC classification

4-Methoxyphenol has not been evaluated by IARC.

Chapter 3

Carcinogenicity studies

3.1 Observations in humans

No data were available to evaluate the carcinogenicity of 4-methoxyphenol in humans.

3.2 Carcinogenicity studies in animals

No animal studies have been performed on inhalatory or dermal exposure. Regarding oral intake, a summary of the individual studies is given in Table 1. They were all performed in F344 rats. Furthermore, most observations concerned abnormalities in the forestomach.

Table 1 Summary of 4-methoxyphenol-induced abnormalities in F344 rats.

Dose applied and experimental design[A]	Tumour development		Ref.
	Forestomach	Other organs	
2% (≈ 800 and 1,000 mg/kg bw in males and females, respectively); applied in basal diet; daily for 104 weeks; included controls fed basal diet only. F344 rats, N=30/sex/group	Hyperplasia: 30/30 (M), 30/30 (F); atypical hyperplasia: 20/30 (M), 11/30 (F); papilloma: 15/30 (M), 7/30 (F); squamous cell carcinoma: 23/30 (M), 6/30 (F). In controls no abnormalities found, except for one case of papillomas.	No exposure-related increase in tumour development observed, including glandular stomach. Relative kidney and liver weights in exposed animals were increased significantly compared to control; final body weights were significantly decreased.	1
0.4% (≈ 160 mg/kg bw); applied in basal diet; daily for 104 weeks; included controls fed basal diet only. F344 rats (males only); N=30-31/group	Papillary and nodular hyperplasia: 8/26 (M), 1/25 (C); papilloma: 3/26 (M), 0/25 (C); carcinoma: 0/26 (M), 0/25 (C).	No exposure-related increase in tumour development observed, including glandular stomach. Final body weight of treated animals was significantly decreased compared to controls.	4
1.5% (≈ 600 mg/kg bw); applied in basal diet for 51 weeks; included controls fed basal diet only. F344 rats (males only); N=15	Hyperplasia: 15/15 (M), 0/10 (C); atypical hyperplasia: 1/15 (M), 0/10 (C); carcinoma in situ: 0/15 (M), 0/10 (C); squamous cell carcinoma: 0/15 (M), 0/10 (C).	Organs investigated were: the glandular stomach, liver, kidneys, esophagus, and intestines. Relative kidney and liver weights were significantly increased compared to control. No other abnormalities observed.	3
0.25, 0.5, 1.0, 2.0% (≈ 100, 200, 400 and 800 mg/kg bw, respectively); applied in diet for 51 weeks; included controls fed basal diet only. F344 rats (males only); N=10-11/group	Hyperplasia (mild): 1/11 (0.25%), 7/11 (0.5%), 11/11 (1%), 11/11 (2%); hyperplasia (moderate): 8/11 (1%), 11/11 (2%), 0/11 (other groups); hyperplasia (severe): not found in any group; papilloma: not found in any group; carcinoma: not found in any group.	Organs investigated were: the stomach, esophagus, liver, kidneys, and intestines. Glandular stomach: *erosion/ ulceration*: 7/11 (1%), 8/11 (2%), 0/11 (other groups); *submucosal hyperplasia*: 2/11 (2%), 0/11 (other groups). No other abnormalities observed in any of the organs investigated. A dose-related reduction of body weight, and increases in relative liver and kidney weight were noted.	8
2% (≈ 800 mg/kg bw); applied in the diet. Group A, daily intake for 24 weeks, than killed; Group B, daily intake for 24 weeks, than 24 weeks on basal diet; Group C: daily intake for 48 weeks. Study included controls fed basal diet only. F344 rats (males only); N=10/group	Group A: simple/papillary hyperplasia (mild, moderate, severe): 10/10, 10/10, 10/10; basal cell hyperplasia (mild, moderate, severe): 7/10, 1/10, 0/10; atypical hyperplasia: 0/10. Group B: simple/papillary hyperplasia (mild, moderate, severe): 7/10, 0/10, 0/10; basal cell hyperplasia (mild, moderate, severe): 6/10, 0/10, 0/10; atypical hyperplasia: 1/10. Group C: simple/papillary hyperplasia (mild, moderate, severe): 11/11, 10/11, 1/11; basal cell hyperplasia (mild, moderate, severe): 11/11, 11/11, 0/11; atypical hyperplasia: 0/11. Control animals: only three cases of mild simple/papillary hyperplasia were observed. In none of the groups papillomas or carcinomas were observed.	No exposure-related abnormalities in other organs found, including the glandular stomach. Final body weights of treated animals were lower than controls; body weight was regained after cessation of exposure.	5

[A] Recalculation to mg/kg bw was performed using default values.[6]
M, male; F, female; C, control.

Chapter 4

Genotoxicity

4.1 *In vitro* assays

4-Methoxyphenol was tested for mutagenicity in a *Salmonella typhimurium* plate incorporation assay, using strains TA100 and TA1530, in the presence of a metabolic activation system.[2] No mutagenic activity of the compound was found. The concentration tested was up to 500 µg/plate.

No other data on *in vitro* genotoxicity studies were found.

4.2 *In vivo* assays

No data found.

4.3 Mechanism of carcinogenic action

Although the oral route of exposure in animals could be of relevance in occupational exposure, the Committee doubts whether the findings in rats are relevant for humans. Humans do not have a homologue for the forestomach; the most potential risk for humans being than the mouth, the pharynx and the esophagus, because these organs have squamous epithelium at the surface, like the forestomach. Although the food retention time may be significant in the human stomach, like the forestomach in rodents, the epithelial layer of the stomach in humans is protected by mucous secretions, whereas the forestomach is not.[7]

The mechanisms by which 4-methoxyphenol induces carcinomas in the forestomach of rats are not fully understood. Since no systemic effects are observed, genotoxic mechanisms probably do not play a role. The most likely explanation is site-specific tissue irritation due to chronic and prolonged exposure, which results in hyperplasia and subsequent tumour development. Prolonged exposure could explain why in rats hyperplasia and squamous cell carcinomas were observed only in the forestomach; the forestomach functions as a reservoir in which the retention time may be significant, whereas other parts of the upper gastro-intestinal tract, such as the mouth, pharynx, esophagus and the glandular stomach, function mainly as conduction organs with negligible retention times.

Chapter 5

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

No data on the carcinogenicity of 4-methoxyphenol in humans are available. In animals, carcinogenicity studies were performed in rats only, and were restricted to oral intake. Overall, the outcomes showed preneoplastic and neoplastic abnormalities (*i.e.*, hyperplasia and squamous cell carcinomas) that were found only in the forestomach of the animals. No neoplastic lesions were reported in other organs.

There is a lack of information on the genotoxic properties of 4-methoxyphenol. However, since lesions were observed to be site-specific, tissue irritation may be the likely explanation for the observed effects.

In conclusion, based on the data presented in this report, the Committee is of the opinion that the observations in animals are not relevant to humans. The reasons being that humans do not have a homologue for the forestomach, and the effects appeared to be site and function specific for this organ.

5.2 Recommendation for classification

The Committee is of the opinion that the available data are insufficient to evaluate the carcinogenic properties of 4-methoxyphenol (category 3)*.

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

References

1 Asakawa E, Hirose M, Hagiwara A, Takahashi S, Ito N. Carcinogenicity of 4-methoxyphenol and 4-methylcatechol in F344 rats. Int J Cancer 1994; 56(1): 146-152.

2 Bartsch H, Malaveille C, Camus AM, Martel-Planche G, Brun G, Hautefeuille A *et al*. Validation and comparative studies on 180 chemicals with S. typhimurium strains and V79 Chinese hamster cells in the presence of various metabolizing systems. Mutat Res 1980; 76(1): 1-50.

3 Hirose M, Fukushima S, Kurata Y, Tsuda H, Tatematsu M, Ito N. Modification of N-methyl-N'-nitro-N-nitrosoguanidine-induced forestomach and glandular stomach carcinogenesis by phenolic antioxidants in rats. Cancer Res 1988; 48(18): 5310-5315.

4 Hirose M, Takesada Y, Tanaka H, Tamano S, Kato T, Shirai T. Carcinogenicity of antioxidants BHA, caffeic acid, sesamol, 4-methoxyphenol and catechol at low doses, either alone or in combination, and modulation of their effects in a rat medium-term multi-organ carcinogenesis model. Carcinogenesis 1998; 19(1): 207-212.

5 Kagawa M, Hakoi K, Yamamoto A, Futakuchi M, Hirose M. Comparison of reversibility of rat forestomach lesions induced by genotoxic and non-genotoxic carcinogens. Jpn J Cancer Res 1993; 84(11): 1120-1129.

6 Paulussen JJC, Mahieu CM, Bos PMJ. Default values in occupational risk assessment. The Netherlands Organization for Applied Scientific Research (TNO) Quality for Life, Zeist, The Netherlands, Report No. V98.390; 1998.

7 Proctor DM, Gatto NM, Hong SJ, Allamneni KP. Mode-of-action framework for evaluating the relevance of rodent forestomach tumors in cancer risk assessment. Toxicol Sci 2007; 98(2): 313-326.

8 Wada S, Hirose M, Takahashi S, Okazaki S, Ito N. Para-methoxyphenol strongly stimulates cell proliferation in the rat forestomach but is not a promoter of rat forestomach carcinogenesis. Carcinogenesis 1990; 11(10): 1891-1894.

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 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 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 Quality of Life, Zeist; Professor of Translational Toxicology, Wageningen University and Research Centre, Wageningen
- J. Van Benthem
  Genetic Toxicologist, National Health 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 Benelux NV, Terneuzen
- E.J.J. van Zoelen
  Professor of Cell Biology, Radboud University Nijmegen, Nijmegen
- J.M. Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

The 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 inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Comments on the public review draft

A draft of the present report was released in 2010 for public review. The following organisation and person has commented on the draft document:

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

Annex **D**

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. • 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. Guidline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.