Health Council of the Netherlands

Acetone

Evaluation of the carcinogenicity and genotoxicity

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Acetone*
Uw kenmerk : DGV/MBO/U-932342
Ons kenmerk : U-6819/JR/bp/246-H15
Bijlagen : 1
Datum : 15 november 2011

Geachte staatssecretaris,

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

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 aceton 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

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Acetone

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. 2011/27, 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, aceton onder de loep. Aceton wordt gebruikt als oplosmiddel voor verscheidene doeleinden.

Op basis van de beschikbare gegevens is de commissie van mening dat de gegevens over aceton 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 acetone. Acetone is extensively used as solvent for various purposes.

The Committee is of the opinion that the available data are insufficient to evaluate the carcinogenic properties of acetone (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 acetone.

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 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 acetone no such an IARC-monograph is available.

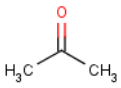
More recently published data were retrieved from the online databases Medline, Toxline, Chemical Abstracts, and RTECS. The last updated online search was in June 2011. The new relevant data were included in this report.

Chapter 2

General information

2.1 Identity and physico-chemical properties

Acetone is manufactured and also found naturally in the environment. It is used as a feedstock to prepare methyl methacrylate or methacrylic acid, and bisphenol A. Furthermore, it is used as a formulating solvent for various commercial products (*i.e.*, plastic, fibres, drugs), and as a industrial process solvent. Below is given the identity and some of its physico-chemical properties.

Chemical name	:	Acetone
CAS registry number	:	67-64-1
EINECS number	:	200-662-2
Synonyms	:	2-Propanone, dimethylformaldehyde, dimethyl ketone, pyroacetic acid, Pyroacetic ether
Appearance	:	Clear colourless liquid
Chemical formula	:	C_3H_6O
Structure	:	
Molecular weight	:	58.08
Boiling point	:	56.1 ºC
Melting point	:	- 94.6 ºC
Vapour pressure	:	24 kPa at 20 ºC
Relative vapour density	:	2.0 (air = 1)

Octanol/water partition coefficient as log Pow	:	-0.24
Solubility	:	Completely miscible in water, soluble in benzene and ethanol
Conversion factor	:	1 mg/m^3= 0.42 ppm 2.38 mg/m^3 = 1 ppm
EU Classification (100% solution)	:	H225: Highly flammable liquid and vapour. H319: Causes serious eye irritation. H336: May cause drowsiness and dizziness. (Based on regulation (EC) No 1272/2008 of the European Parliament and of the Council on Classification, labelling and packaging of substances and mixtures; 16 December 2008)

2.2 IARC classification

Acetone has not been evaluated by IARC.

Chapter 3

Carcinogenicity

3.1 Observations in humans

Ott *et al*. (1983) reported of a retrospective cohort mortality study of employees in a US cellulose fibre plant.[19] The cohort included 948 employees who were exposed to acetone at a time-weighted-average concentration of between 100 and 1,000 ppm. The investigators did not find a significant excess risk of death from any cause, including malignant neoplasms, compared to the general population.

No other data were available to evaluate the carcinogenicity of acetone in humans.

3.2 Carcinogenicity studies in animals

The available data on animal carcinogenicity studies, which are related to acetone exposure, is limited to dermal exposure studies performed in mice. In all these studies, acetone was used as a solvent vehicle, and no dose-response relationships have been assessed. In none of the studies was there found to be an exposure-related increase in tumour development. A summary of the findings is given in Table 1. In general, acetone is not considered carcinogenic when applied to the skin.[27] However, comprehensive examinations of tissues other then dermal tissue are not routine in these studies.

Table 1 Data on tumour development by acetone, used as vehicle controls in carcinogenicity studies.

Animal species	Experimental design	Acetone-induced tumour development	Reference
Cancer prone CB6F1-TgrasH2 (rasH2) mice; N=15/sex	1 mL acetone per kg bw, percutaneously into the back, after depilation; daily for 26 weeks.	No exposure-related local or systemic tumours observed.	22
CF1 mice; N= 100/sex	0.2 mL acetone to the shaved dorsal skin; 2x/week for 103 weeks.	No exposure-related local and systemic tumours observed.	20
CD-1 mice; N=10 to 25 (sex not given)	Pre-promotion application (40 or 80 µL of acetone applied 1-2 minutes, 1 hour or 1 day before application with tumour promoter).	No enhancement of tumours by acetone pre-treatment observed.	25
SENCAR mice; N=30	0.2 mL acetone to the back; 2x/week for 92 weeks.	No exposure-related local or systemic tumours observed.	24
ICR/Ha Swiss mice; N=30 females	0.1 mL acetone to the dorsal skin; 3x/week for the duration of the test (median survival time 478 days; for untreated controls, 484 days).	No exposure-related local and systemic tumours observed.	23

Chapter 4

Genotoxicity

4.1 *In vitro* assays

Regarding mutagenicity testing using *Salmonella typhimurium* strains (TA92, TA94, TA97, TA98, TA100, TA1535, and TA1537), acetone (up to 10 mg/plate) did not induce mutations, with or without the presence of a metabolic activation system (S9 mixes).[1,4,10,11,14,16,17,28] Also in the yeast *Schizosaccharomyces pombe*, acetone (5% solution) did not induce mutations.[1] Negative results were also obtained using an SOS chromotest with *Escherichia coli* PQ37.[16] In addition, negative results were obtained in a mammalian gene mutation assay using L5178Y mouse lymphoma cells.[3] The cells were treated with acetone at a concentration of up to 0.5 M for three hours.

In cultured Chinese hamster ovary cells, and human lymphocytes, acetone did not induce chromosomal aberrations or sister chromatid exchanges, with or without the presence of metabolic activation system (concentrations tested: up to 5 mg/mL in hamster cells; 10 to 21 mM in lymphocytes).[15,18]

Induction of aneuploidy in the yeast strain *Saccharomyces cerevisiae* D61.M was observed, but no other types of genetic effects were noted with 5 to 8% solutions of acetone.[29,30] The aneuploidy was enhanced by cold storage (this was attributed to weakening and interference of microtubule formation). The positive findings with a cold treatment protocol have later been confirmed in a re-evalua-

tion study using the same yeast strain.[2] However, the Committee does not know the significance of this study.

A transformation study using a AKR leukaemia virus-infected NIH Swiss mouse-embryo (AKR-NIH-ME) cell line was reported. In that study, cells were treated with a panel of chemical carcinogens for seven days, and were allowed to grow colonies for another fourteen days. Acetone (0.01% solution) was tested as solvent control, and did not show any transforming activity.[21]

4.2 *In vivo* assays

A 5% solution of acetone was used as solvent for testing dental bonding agents in a somatic mutation and recombination test in *Drosophila melanogaster*.[5] Acetone itself did not induce mutations.

Two micronucleus assays have been performed using mice and hamsters, respectively. No increased number of micronuclei in peripheral erythrocytes have been observed in B6C3F1 mice of both sexes, which were exposed to up to 2 mg acetone/kg bw for thirteen weeks.[26] In hamsters of both sexes, also no increase in number of polychromatic erythrocytes was observed compared to non-treated controls.[6] The animals (N=10/time point) were given acetone intraperitoneally at a dose of 865 mg/kg bw. Blood samples were taken 12, 24, 48 and 72 hours after administration.

The effect of acetone on several parameters for tumour promotion has been studied on the epidermis of hairless mice.[13] Acetone was applied twice weekly in a volume of 100 µL to the skin of hr/hr Oslo mice of both sexes (N=25/group) for 18 weeks. Morphologic and cell kinetic studies were performed weekly on four mice. Treatment with acetone alone led to a moderate hyperplasia and a slight increase in the mitotic rate, which persisted during the ten weeks of subsequent observation. The same authors reported on another study, in which a short stimulation of DNA synthesis, followed by a short-lasting tendency (basal levels reached within 24 hours) to hyperplasia after a single exposure to acetone, was observed.[12]

4.3 Carcinogenic mechanism of action

Acetone is one of the three naturally occurring ketone bodies that occur throughout the body as an intermediary metabolism product.[27] The compound can be enzymatically converted via acetol into methylglyoxal, or into (L-)1,2-propane-

diol.[7,9,27] Methylglyoxal can be converted in D-glucose, forming an energy source for the body. 1,2-Propanediol can be degraded in the liver into acetate and formate; both acetate and formate may enter the glucogenesis pathway.[7,9,27] Up to now there are no indications that for instance 1,2-propanediol has shown genotoxic properties.[9]

There are no human or animal studies available suggesting an association between chronic acetone inhalation and the development of preneoplastic lesions, or other (irreversible) long-term health effects.[8,9,27] In general, occupational inhalation of acetone is mainly associated to irritation of the upper and lower respiratory tract, and of the eyes, and to slight, acute neurological effects (*e.g.*, mood swings, lethargy).[8,9,27]

Chapter 5

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

No data on the carcinogenicity of acetone in humans were available. In animals, data were limited to dermal exposure studies performed in mice. No acetone-related increase in local and systemic tumours were found in these animals. In all these studies acetone solutions were used as a vehicle solvent. Overall, based on these studies, acetone does not appear carcinogenic after dermal exposure, at least in mice. However, data on lifetime inhalation exposure (a relevant route of exposure in the occupational environment), and dose-response relationship studies are missing.

Acetone is and has been widely used as a solvent in genotoxicity testing. There are no indications that acetone interacts with other chemicals to alter their genotoxic potential, nor did acetone show genotoxic activity by itself.

5.2 Recommendation for classification

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

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

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A Request for advice

B The Committee

C Comments on the public review draft

D 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 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 organisations and persons have commented on the draft document:

- Mr. M. Korteweg Maris, Vereniging van de Nederlandse Chemische Industrie, The Netherlands
- Mr. T.J. Lentz, National Institute of Occupational Health and Safety, the USA
- Mr. C. Verge, Phenol&Acetone Producers Sector Group, Spain

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.