Health Council of the Netherlands

Acetaldehyde

Evaluation of the carcinogenicity and genotoxicity

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Acetaldehyde*
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Geachte staatssecretaris,

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

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

Acetaldehyde

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. 2012/22, 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 aceetaldehyde onder de loep. Aceetaldehyde wordt vooral gebruikt als intermediair bij de synthese van diverse producten, waaronder de synthese van azijnzuur. Het wordt verder onder meer gebruikt als oplosmiddel bij de productie van diverse chemische stoffen en als bewaarmiddel voor bijvoorbeeld vis en fruit.

De commissie concludeert dat aceetaldehyde beschouwd moet worden als kankerverwekkend voor de mens, en beveelt aan de stof in categorie 1B te classificeren.* Aceetaldehyde heeft een stochastisch genotoxisch werkingsmechanisme.

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

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 acetaldehyde. Acetaldehyde is mainly used as intermediate, for instance in the production of acetic acid. It, furthermore, is used for instance as a solvent in the production of various chemical compounds, and as a fish and fruit preservative.

The Committee concludes that acetaldehyde is presumed to be carcinogenic to man, and recommends classifying the compound in category 1B.* Based on the available data, acetaldehyde acts by a stochastic genotoxic mechanism.

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

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 F)

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

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 acetaldehyde, such an IARC-monograph is available, of which the summary and conclusion of IARC is inserted in annex E.

Additional data were obtained from the online databases Toxline, Medline and Chemical Abstracts, covering the period 1997 to October 2012, using acetaldehyde and CAS no 75-07-0 as key words in combination with key words representative for carcinogenesis and mutagenesis.

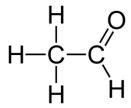
Chapter 2

General information

2.1 Identity, and physico-chemical properties

Acetaldehyde is an aldehyde, occurring widely in nature. For instance, it occurs naturally in coffee, bread, and ripe fruit, and is produced by plants as part of their normal metabolism. It is also a metabolite during the breakdown of ethanol in the body, and is present in tobacco smoke. Acetaldehyde is produced on a large industrial scale for many purposes and uses.[1] For instance, it is used as an intermediate in the production of acetic acid, but also in the production to for instance cellulose acetate, and pyridine derivates. It is furthermore used: in the production of perfumes, paints (aniline dyes), plastics and synthetic rubber; in leather tanning and silvering mirrors; as a denaturant for alcohol; in fuel mixtures; as a hardener for gelatine fibres; in glue and casein products; as a preservative for fish and fruit; in the paper industry; and, as a flavouring agent. The identity, and its properties are shown below. [1-4]

CAS registry number	:	75-07-0
EINECS number	:	200-836-8
Synonyms	:	Ethanal, acetic aldehyde, ethylaldehyde, acetic aldehyde
Appearance	:	Colourless volatile liquid

Chemical and structure formula	:	C_2H_4O 
Molecular weight	:	44.05
Boiling/melting point	:	29°C and -123.5°C
Vapour pressure	:	2.5 kPa at -50°C; 44.0 kPa at 0°C; 101.3 kPa at 20.16°C
Vapour density	:	1.52 (air=1)
Solubility	:	Miscible in water and most common solvents
Conversion factor	:	1 ppm = 1.8 mg/m³; 1mg/m³ = 0.56 ppm (at 25°C, 101.3 kPa)
EU Classification	:	Carc. 2; H224 (extremely flammable liquid and vapour), H319 (causes serious eye irritation), H335 (may cause respiratory irritation), and H351 (suspected of causing cancer).

2.2 IARC classification

In 1999, IARC concluded that there was inadequate evidence in humans for the carci-nogenicity of acetaldehyde, and that there was sufficient evidence in experimental animals.[5] Therefore, IARC classified the compound in Group 2B ('possible carcinogenic to humans'). In 2010, IARC evaluated the risk of cancer due to alcohol consumption, including acetaldehyde. It confirmed that there was sufficient evidence in animal experiments for the carcinogenicity of acetaldehyde.[6] More importantly, in 2012 IARC concluded that 'acetaldehyde associated with alcohol consumption' is carcinogenic to humans.[7]

Chapter 3

Carcinogenicity

3.1 Observations in humans

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

In East-Germany, nine cancer cases were found in a factory where the main process was dimerization of acetaldehyde, and where the main exposures were to acetaldol, acetaldehyde, butyraldehyde, crotonaldehyde and other higher, condensed aldehydes, as well as to traces of acrolein.[8,9] Of these cancer cases, five were bronchial tumours and two were carcinomas of the oral cavity. All nine patients were smokers. The relative frequencies of these tumours were reported to be higher than those observed in the population of East-Germany. A matched control group was not included. The Committee noted the combined exposure with other potential carcinogenic compounds, the small number of cases, and the poorly defined exposed population.

Regarding the general population, some investigators suggest a role for acetaldehyde in cancer development (and other disorders) in humans after alcohol consumption, in particular in people with a genetic predisposition of one of the enzymes that are involved in ethanol metabolism.[5,6,10-16] Acetaldehyde is the major metabolite of ethanol (ethyl alcohol).[5,13,17-19] First, ethanol is oxidized by alcohol dehydrogenase (ADH) to acetaldehyde, and subsequently acetaldehyde

is converted by aldehyde dehydrogenase (ALDH2) to acetate. Both enzymes show genetic polymorphisms. This means that depending on the genotype, the enzymes may lead to a faster breakdown of ethanol to acetaldehyde, and/or to a slower breakdown of acetaldehyde to acetate. Thus, people having unfavourable genotypes of these enzymes are likely to be exposed internally to higher levels of acetaldehyde after alcohol consumption than would be the case when not having one of these isoenzymes. This would increase the susceptibility to cancer development after alcohol consumption, since it is suggested that acetaldehyde possesses carcinogenic properties (see also Chapter 4).

Several studies reported on the association between genetic polymorphism and ethanol-related cancer development, all suggesting a role for acetaldehyde. As a result, a few meta-analysis have been performed to get more clarity. For instance, Chang et al. (2012) performed a meta-analysis to study the association between ADH1B* and ADH1C genotypes in head and neck cancer risk.[20] The analysis included twenty-nine studies. According to the authors, having at least one of the fast alleles ADH1B*2 or ADH1C*1 reduced the risk for head and neck cancer (odds ratios: 0.50 (95% confidence interval (CI), 0.37-0.68) for ADH1B*2; 0.87 (95%CI, 0.76-0.99).

Wang et al. (2012) performed a meta-analysis to derive a more precise estimate of the relationship between ADH1C genotypes, and breast cancer risk.[21] Twelve case-control studies were included in the analysis, covering 6,159 cases and 5,732 controls (all Caucasians). The investigators did not found any significantly increased breast cancer risk that could be related to any ADH1C genotype.

Boccia et al. (2009) reported on a meta-analysis to study the relationship between ALDH2 homozygous and heterozygous genotypes, alcohol consumption, and head and neck cancer.[22] The analysis included six case-control studies, covering 945 Japanese cases and 2,917 controls. For the analysis, the investigators used a Mendelian randomization approach. The homozygous genotype ALDH2*2*2 (unable to metabolize acetaldehyde) reduced the risk of head and neck cancer, whereas the heterozygous genotype ALDH2*1*2 (partly able to metabolize acetaldehyde) did significantly increase the risk compared to

* ADH has seven isoenzymes, which are divided into five classes. Most relevant for alcohol metabolism in the liver of adults are the class one isoenzymes ADH1B and ADH1C (formerly known as ADH2 and ADH3 isoenzymes).[20] For each isoenzyme two or three different alleles are known, leading to different genotypes and thus to functional polymorphism. The genotypes of the isoenzyme ADH1B are expressed as ADH1B*1, ADH1B*2 and ADH1B*3; those for the isoenzyme ADH1C are expressed as ADH1C*1 and ADH1C*2. The metabolic speed is highest for homozygote genotypes ADH1B*2, ADH1B*3 and ADH1C*1. ADH1B*1 and ADH1C*2 are considered slow metabolisers.

the homozygous ALDH2*1*1 genotype (able to metabolize acetaldehyde). According to the authors, the reduction of cancer risk in ALDH2*2*2 was most likely explained by the fact that people having this genotype consumed markedly lower levels of alcohol compared to the other genotypes, probably due to discomfort. Therefore, the authors conclude that their study supports the hypothesis that alcohol increases head and neck cancer risk through the carcinogenic action of acetaldehyde.

The same results were obtained by Fang et al. (2011), who carried out a meta-analysis of ALDH2 genotypes and esophageal cancer development.[23] Data from sixteen studies (hospital- or population-based, one multicenter study) were analysed, covering 2,697 Asian cases and 6,344 controls. The analysis showed that the heterozygous ALDH2*1*2 genotype increased the risk of esophageal cancer, whereas the homozygous ALDH2*2*2 genotype reduced the risk.

Yokoyama and Omori (2005) reviewed a number of case-control studies (including those performed by themselves) on the relationship of genetic polymorphism of ADH1B, ADH1C and ALDH2 genotypes and esophageal, and head and neck cancer risk.[24] They found positive associations between the less-active ADH1B*1 genotype and inactive heterozygous ALDH2*1*2 genotype, and the risk for esophageal cancer in East Asian heavy drinkers. Light-to-moderate drinkers showed a higher vulnerability. According to the authors, some studies suggest similar associations for the risk for head and neck cancer in moderate-to-heavy-drinking Japanese. Data on ADH1C genotype were controversial.

The Committee emphasizes that in none of the studies on genetic polymorphism and alcohol-related cancer risk, direct evidence was found that acetaldehyde had caused cancer, although the data indirectly are suggestive for this.

3.2 Carcinogenicity studies in animals

3.2.1 Inhalation

In a Dutch carcinogenicity study, Wistar rats (105 animals/sex/group) inhaled acetaldehyde at a concentration of 0, 750, 1,500 or 3,000 ppm (0, 1,350, 2,700 or 5,400 mg/m^3) for six hours a day, five days per week for a maximum of 28 months.[25] The highest exposure level was reduced progressively over a period of eleven months to 1,000 ppm (1,800 mg/m^3) due to toxicity.

In general, animals exposed to acetaldehyde showed lower survival rates and body weights compared to controls. This was most pronounced in males exposed

to the highest concentration of acetaldehyde. Gross examination at autopsy did not reveal acetaldehyde-related lesions, except for decolourisation of the fur and nasal swellings in all exposed groups. Microscopic examination revealed several non-neoplastic lesions in the respiratory tract of males and females, such as: hyperplasia in the respiratory nasal and olfactory epithelium; squamous metaplasia in the respiratory nasal epithelium; and, squamous metaplasia/ hyperplasia in the larynx. These lesions were mainly noted in the mid and/or high exposure groups, and were statistically significantly increased compared to controls. No lesions were found in the lungs.

In the nose, also exposure-related neoplastic lesions were observed (see Table 1). It concerned squamous cell carcinoma in the respiratory epithelium of the nose, and adenocarcinomas in the olfactory epithelium. The relative lower tumour incidences in the high exposure groups were explained by the investigators by early mortality due to other causes than cancer. According to the authors, the observations support the hypothesis that nasal tumours arise from degeneration of the nasal epithelium. The same research group reported earlier on degeneration of the olfactory epithelium in rats inhaling acetaldehyde for four weeks, under comparable experimental conditions.[26]

Table 1 Tumour incidences in rats, which were exposed by inhalation to acetaldehyde for 28 months.[25]

Exposure level (ppm)	0	750	1,500	3,000-1,000
Male animals				
Nose:				
Papilloma	0/49	0/52	0/53	0/49
Squamous cell carcinoma	1/49	1/52	10/53*	15/49***
Carcinoma in situ	0/49	0/52	0/53	1/49
Adenocarcinoma	0/49	16/52***	31/53***	21/49***
Larynx: carcinoma in situ	0/50	0/50	0/51	0/47
Lungs: poorly differentiated adenocarcinoma	0/55	0/54	0/55	0/52
Female animals				
Nose:				
Papilloma	0/50	1/48	0/53	0/53
Squamous cell carcinoma	0/50	0/48	5/53	17/53***
Carcinoma in situ	0/50	0/48	3/53	5/53
Adenocarcinoma	0/50	6/48*	26/53***	21/53***
Larynx: carcinoma in situ	0/51	0/46	1/47	0/49
Lungs: poorly differentiated adenocarcinoma	0/53	1/52	0/54	0/54

Fischer exact test: * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

In another study, Syrian golden hamsters (n=36/sex/group) inhaled decreasing concentrations of acetaldehyde (2,500 ppm to 1,650 ppm, equal to 4,500 to 2,970 mg/m^3) or clean room air, for seven hours a day, five days per week for 52 weeks.[27] The concentrations were reduced during the study because of considerable growth retardation and to avoid early death. Acetaldehyde induced rhinitis, hyperplasia and metaplasia of the nasal, laryngeal and tracheal epithelium. The exposed animals also developed laryngeal carcinomas with a few laryngeal polyps, and nasal polyps and carcinomas. The incidences of respiratory tract tumours were 0/30 (males, control), 8/29 (males, exposed), 0/29 (females, control) and 5/29 (females, exposed).

Male Syrian golden hamsters (n=35/group) were exposed to 1,500 ppm (2,700 mg/m^3) acetaldehyde combined with weekly intratracheal instillations of benzo[a]pyrene (0.0625, 0.125, 0.25, 0,5 or 1 mg/kg bw).[28] The exposure was for seven hours a day, five days per week for 52 weeks. No tumours were found in hamsters exposed to acetaldehyde alone, whereas in animals treated with benzo[a]pyrene alone, or with a combination of acetaldehyde and benzo[a]pyrene, a dose-related increase in respiratory-tract tumours were found.

3.2.2 Oral intake

Male and female Sprague-Dawley rats (50 animals/sex/group) were exposed to 0, 50, 250, 500, 1,500 and 2,500 mg/L acetaldehyde in drinking water (dose in kg bw not given), beginning at six weeks of age.[29] Animals were kept under observation until spontaneous death. In various organs and tissues neoplastic lesions were observed. However, no clear increase in number of tumour-bearing animals was found in any of the exposed groups compared to the control group. The investigators reported a significantly increased total number of tumours (per 100 animals) in groups exposed to 50 mg/L (females only), and 2,500 mg/L (males; females). The Committee noted the lack of statistical analysis, and the limited examination of non-neoplastic end-points. Furthermore, the European Food Safety Authority (EFSA) has evaluated the studies performed by the European Ramazzi Foundation of Oncology and Environmental Sciences, who performed this study, and noted that the animals used by this foundation, may have been infected with *Mycoplasma pulmonis*,. This may have resulted in chronic inflammatory changes.[30] For these reasons, the Committee considers the findings of the study of questionable relevance.

Homann et al. (1997) have given male Wistar rats (N=10/group) either water containing acetaldehyde (120 mM) or tap water to drink for eight months. Animals were then sacrificed, and of each animal tissue samples were taken from

the tongue, epiglottis, and forestomach. No tumours were observed. However, in these organs, microscopic examination revealed statistically significant hyperplasia of the basal layers of squamous epithelia in rats receiving acetaldehyde (compared to controls). Furthermore, in the three organs of the treated animals, cell proliferation was significantly increased, and the epithelia were significantly more hyperplastic, than in control animals.[31]

3.2.3 Dermal exposure

Watanabe et al. (1956) reported on the induction of sarcomas in rats given acetaldehyde by subcutaneous injections.[32] The Committee noted the limited study design, such as the small number of animals and the lack of a control group.

3.2.4 Other routes of exposure

No tumours were found in Syrian golden hamsters (n=35/sex/dose), which were given acetaldehyde by intratracheal installations, weekly or biweekly, for 52 weeks, followed by a recovery period for another 52 weeks.[28] Doses applied were 0.2 mL of 2% or 4% solutions. In positive controls, which were given benzo[a]pyrene and N-nitrosodiethylamine, a variety of tumours in the respiratory tract were found.

3.3 Cell transformation tests

Koivisto and Salaspuro (1998) reported on a transformation test in which human colon adenocarcinoma cell line Caco-2 were used to study changes in cell proliferation, cell differentiation, and adhesion due to exposure to acetaldehyde.[33] In the absence of cell cytotoxicity, on acute exposure (for 72 hours), acetaldehyde (500 or 1,000 μM) inhibited the cell proliferation rate, but on chronic exposure (for five weeks) it stimulated cell proliferation. Furthermore, acetaldehyde clearly disturbed the cell differentiation (concentration applied was 1,000 μM for 7, 14 or 21 days); and, a clear decrease of adhesion of Caco-2 cells to collagens was observed when acetaldehyde was applied to the cells at a concentration of 500 or 1,000 μM for four days. According to the authors, the increased proliferation rate, disturbed differentiation, and reduced adhesion, would in vivo predict more aggressive and invasive tumour behaviour.

Eker and Sanner (1986) used a rat kidney cell line in a two-stage cell transformation assay.[34] Acetaldehyde (up to 3,000 μM) did not affect cytotoxicity

nor did it induce colony formation of the cells. When acetaldehyde treatment (3,000 μM) was followed by a tumour promoter 12-O-tetradecanoylphorbol-13-acetate, the ability of the cells to form colonies was increased.

Chapter 4

Mode of action

4.1 Genotoxic mode of action

4.1.1 Gene mutation tests

In vitro

Vapours of acetaldehyde were not mutagenic to *S. typhimurium* or *E.coli WP2 uvrA*, with or without metabolic activation.[35-38] In addition, it did not induce mutations (dose range 0.1 -1.0 mL) in *S. typhimurium* tester strains TA97a, TA100, TA102 and TA104, in the presence and absence of a exogenous metabolic activation system, although the results on strain TA102 were equivocal.[39]

Without an exogenous metabolic activation system, acetaldehyde induced gene mutations in mouse lymphoma L5178T cells.[40] Also in human lymphocytes it induced mutations.[41]

Using a shuttle vector plasmid, acetaldehyde (doses applied: 0.25, 0.5, 1.0, and 2.0 M) increased the frequency of mutations on the *supF* gene. Furthermore, after the plasmid was replicated in human fibrobast cell lines, it was observed that the majority of the mutations were specific tandem base substitutions (GG to TT).[42]

In another study, acetaldehyde induced 1,N^2-propano-dG adducts in a DNA vector that next was introduced into human xeroderma pigmentosum A (XPA)

cells to allow replication.[43] Analysis of the DNA of these cells showed major miscoding events, such as G->T and G->C transversions.

4.1.2 *Cytogenetic tests*

In vitro

Acetaldehyde increased the frequency of sister chromatid exchanges in Chinese Hamster Ovary cells (without an exogenous metabolic activation system), and in human lymphocytes.[41,44-48,48-56]

It furthermore induced chromosomal aberrations in human lymphocytes;[46,48,57] positive- and negative-centromere-staining micronuclei in human lymphocytes;[58] aneuploidy in embryonic Chinese hamster diploid fibroblasts (without exogenous metabolic activation);[59] chromosomal malsegregation in *Aspergillus nidulans*.[60]

In vivo

Acetaldehyde, when given to animals, increased the frequency of sister chromatid exchanges in Chinese hamster bone-marrow cells;[61] chromosomal aberrations in rat embryos;[62] and, chromosomal aberrations in mouse bone-marrow cells.[46,62]

Furthermore, sister-chromatid exchanges in spermatogonial mouse cells were determined after intraperitoneal injection with acetaldehyde (0.4, 4.0, 40.0, and 400 mg/kg bw). All four doses tested produced a positive response, although no clear exposure-response relationship was found. The lowest dose had an increase of sister chromatid exchange of a factor of 1.1 compared to the background value; the highest dose had an increase of a factor of 3.2.[63]

In male mice, which were given an intraperitoneal injection of acetaldehyde, no abnormal sperm morphology or spermocyte micronuclei were observed.[64]

Mice with an inactive ALDH2 gene were generated by gene targeting knockout as a model of ALDH2-deficient humans.[65] The mice and a control group of wild-type ALDH2 mice (able to metabolize acetaldehyde), were continuously exposed to 125 and 500 ppm of acetaldehyde vapour for two weeks. Another group (knock-out and wild-type mice) was orally administered 100 mg acetaldehyde/kg bw, daily, once a day for two weeks. The animals were killed at the end of the exposure period. The frequency of micronucleated reticulocytes induced by acetaldehyde was significantly increased in mice having the inactive ALDH2 gene, but not in the wild-type mice. The T-cell receptor (TCR) mutant frequency was also associated with the acetaldehyde exposure in

mice having an inactive ALDH2 gene, especially after oral administration; however, it was not associated with acetaldehyde exposure in wild-type mice.[65]

4.1.3 *DNA-adducts*

In vitro

Acetaldehyde-DNA adducts have been found in calf thymus DNA, in 2'-deoxyguanosine-3'-monophosphate.[54,66,67] In another study, also using calf thymus DNA, mainly N^2-ethylidene-deoxiguanosine DNA-adducts were found.[68] In that study, three more stable adducts were detected, namely 1,N-propano-deoxiguanosine, N^2-dimethyldioxane-deoxiguanosine, and a cross-link adduct. These three adducts were formed in substantially lower yield (less than 10%) than the major adduct, but they were stable at the nucleoside level, and so may be more stable in DNA.

Acetaldehyde-specific DNA adducts were also found in the DNA of: primary human liver cells, isolated from normal liver tissue (N^2-ethyl-deoxiguanosine adducts);[69] normal and SV40T antigen-immortalized human buccal epithelial cells (N^2-ethyl-3'-dG-monophosphate adducts, dose-dependent, and at relatively non-toxic concentrations);[70] and, in human embryonic kidney cell line 293 (N^2-ethyl-deoxiguanosine adducts).[71]

In vivo

In humans, acetaldehyde induced statistically significantly higher levels of DNA-adducts in granulocytes and lymphocytes of twenty four alcohol abusers ($p<0.001$) compared to controls.[66] The average adduct levels were 3.4±3.8 and 2.1±0.8 adducts/10^7 nucleotides, respectively. In another study, investigators reported on a decrease in the number of acetaldehyde-specific DNA adducts (N^2-ethylidene-deoxiguanosine) in leucocytes after smoking cessation.[72] It is well known that cigarette smoke contains acetaldehyde (but also other potential carcinogens).

Acetaldehyde-derived DNA-adducts were also found in blood samples taken from 44 cancer-free male Japanese alcoholic patients. The levels of these DNA-adducts were significantly higher in alcoholics with the ALDH2*1*2 genotype than in alcoholics with the ALDH2*1*1 genotype.[73]

4.1.4 *Miscellaneous*

Acetaldehyde did not cause differential killing of repair-deficient *Escherichia coli* K-12 *uvrB/recA* cells.[74]

Acetaldehyde induced DNA strand breaks and cross-links in human lymphocytes (without metabolic activation).[75,76] However, acetaldehyde did not induce DNA strand breaks and cross-links in primary human bronchial epithelial cells or human leukocytes.[75,76]

4.2 Non-genotoxic mode of action

In animal carcinogenicity studies using rats and hamsters, exposed animals showed signs of inflammation in the respiratory and olfactory epithelium of the nose.[25,27] When inflammation becomes chronic and permanent, this can end in the development of cancer.

Chapter 5

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

No epidemiological studies have been performed investigating cancer development due to exposure to acetaldehyde alone. In the literature, it is suggested that acetaldehyde may play a role in cancer development in humans after alcohol consumption, in particular in combination with a genetic predisposition for enzymes that convert ethanol in acetaldehyde, and for enzymes that convert acetaldehyde in acetate. The Committee emphasizes that in none of the studies on genetic polymorphism and alcohol-related cancer risk, direct evidence was found that acetaldehyde had caused cancer, although the data indirectly are suggestive for this. Overall, the Committee is of the opinion that human data are insufficient to make a final conclusion on the carcinogenic potential of acetaldehyde in humans.

Regarding animal carcinogenicity studies, chronic inhalation of acetaldehyde induced squamous cell carcinomas and adenocarcinomas in the nose of male and female rats. In hamsters, inhaling the compound, one study showed the presence of laryngeal and nasal tumours, whereas in another study – using a lower exposure concentration – no tumours were observed at all. Based on these findings, the Committee concludes that there is sufficient evidence of carcinogenicity from animal experiments.

Acetaldehyde is a reactive compound with stochastic genotoxic properties that induces stable DNA-adducts (mainly N^2-ethylidene-dG), mutations, genome

and chromosome aberrations in cultured mammalian (and human) cells. Genome and chromosomal aberrations, and DNA-adducts were also induced by acetaldehyde in vivo.

5.2 Recommendation for classification

The Committee concludes that acetaldehyde is presumed to be carcinogenic to man, and recommends classifying the compound in category 1B.* Based on the available data, acetaldehyde acts by a stochastic genotoxic mechanism.

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

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A	Request for advice
B	The Committee
C	The submission letter
D	Comments on the public review draft
E	IARC evaluation and conclusion
F	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
- J.M. Rijnkels, *scientific secretary*
  Health Council, 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 *Acetaldehyde*
Your Reference	: DGV/MBO/U-932342
Our reference	: U-7438/JR/fs/246-H17
Enclosed	: 1
Date	: November 23, 2012

Dear State Secretary,

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

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. 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)
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 organisations and persons have commented on the draft document:

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

Annex **E**

IARC evaluation and conclusion

Acetaldehyde (Group 2B)
VOL.: 71 (1999) (p. 319)

Summary of Data Reported and Evaluation

Exposure data

Exposure to acetaldehyde may occur in its production, and in the production of acetic acid and various other chemical agents. It is a metabolite of sugars and ethanol in humans and has been detected in plant extracts, tobacco smoke, engine exhaust, ambient and indoor air, and in water.

Human carcinogenicity data

An increased relative frequency of bronchial and oral cavity tumours was found among nine cancer cases in one study of chemical workers exposed to various aldehydes. Oesophageal tumours have been associated with genetically determined, high metabolic levels of acetaldehyde after drinking alcohol.

Three case–control studies assessed the risk of oral, pharyngeal, laryngeal and oesophageal cancer following heavy alcohol intake, according to genetic polymorphism of enzymes involved in the metabolism of ethanol to acetaldehyde (alcohol dehydrogenase 3) and in the further metabolism of

acetaldehyde (aldehyde dehydrogenase 2 and glutathione S-transferase M1). Despite limitations in the study design and the small size of most of the studies, these studies consistently showed an increased risk of alcohol-related cancers among subjects with the genetic polymorphisms leading to higher internal doses of acetaldehyde following heavy alcohol intake as compared to subjects with other genetic polymorphisms.

Animal carcinogenicity data

Acetaldehyde was tested for carcinogenicity in rats by inhalation exposure and in hamsters by inhalation exposure and by intratracheal instillation. It produced tumours of the respiratory tract following inhalation, particularly adenocarcinomas and squamous-cell carcinomas of the nasal mucosa in rats and laryngeal carcinomas in hamsters. In hamsters, it did not cause an increased incidence of tumours following intratracheal instillation. Inhalation of acetaldehyde enhanced the incidence of respiratory-tract tumours produced by intratracheal instillation of benzo[a]pyrene.

Other relevant data

Acetaldehyde is metabolized to acetic acid. During inhalation exposure of rats, degeneration of nasal epithelium occurs and leads to hyperplasia and proliferation.

Acetaldehyde causes gene mutations in bacteria and gene mutations, sister chromatid exchanges, micronuclei and aneuploidy in cultured mammalian cells, without metabolic activation. In vivo, it causes mutations in Drosophila melanogaster but not micronuclei in mouse germ cells. It causes DNA damage in cultured mammalian cells and in mice in vivo. Acetaldehyde–DNA adducts have been found in white blood cells from human alcohol abusers.

Evaluation

There is inadequate evidence in humans for the carcinogenicity of acetaldehyde. There is sufficient evidence in experimental animals for the carcinogenicity of acetaldehyde.

Overall evaluation

Acetaldehyde is possibly carcinogenic to humans (Group 2B).

Previous evaluations: Vol. 36 (1985); Suppl. 7 (1987)
Synonyms: Acetic aldehyde; ‘Aldehyde’; Ethanal; Ethylaldehyde

Annex **F**

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	
		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 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 is presumed to be 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: 2010; publication no. A10/07E.[77]