OPINION OF THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS INTENDED FOR CONSUMERS

CONCERNING

ACETALDEHYDE

Adopted by the SCCNFP during the 28th plenary meeting
of 25 May 2004

1. Terms of Reference

1.1. Context of the question

The SCCNFP stated in its opinion of 25 September 2001 that substances classified pursuant to Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances as carcinogenic (except substances only carcinogenic by inhalation), mutagenic or toxic for reproduction, of category 1 or 2, and substances with similar potential, must not be intentionally added to cosmetic products, and that substances classified pursuant to Directive 67/548/EEC as carcinogenic, mutagenic or toxic for reproduction, of category 3, and substances with similar potential, must not be intentionally added to cosmetic products unless it can be demonstrated that their levels do not pose a threat to the health of the consumer.

Council Directive 2003/15/EEC amended Directive 76/768/EEC introducing Article 4b. It states that *"the use in cosmetic products of substances classified as carcinogenic, mutagenic or toxic for reproduction, of category 1, 2 and 3, under Annex I to Directive 67/548/EEC shall be prohibited. To that end the Commission shall adopt the necessary measures in accordance with the procedure referred to in Article 10(2). A substance classified in category 3 may be used in cosmetics if the substance has been evaluated by the SCCNFP and found acceptable for use in cosmetic products."*

Acetaldehyde is classified as a category 3 carcinogen and mutagen. The substance is not regulated in an Annex to the Cosmetics Directive nor has it been evaluated by the SCC/SCCNFP before.

The European Commission received a submission from the European Flavour & Fragrance Association with data indicating that the potential human exposure to Acetaldehyde from the use of cosmetic products is to be seen as negligible and does not pose a safety risk.

1.2. Request to SCCNFP

The SCCNFP is requested to answer the following questions:

* *Is Acetaldehyde safe when used as a fragrance/flavour ingredient in cosmetic products taking into account the data provided?*

* *And/or does the SCCNFP recommend any further restrictions with regard to the use of Acetaldehyde as a fragrance/flavour ingredient in cosmetic products?*

1.3. Statement on the toxicological evaluation

The SCCNFP is the scientific advisory body to the European Commission in matters of consumer protection with respect to cosmetics and non-food products intended for consumers. The Commission's general policy regarding research on animals supports the development of alternative methods to replace or to reduce animal testing when possible. In this context, the SCCNFP has a specific working group on alternatives to animal testing which, in co-operation

with other Commission services such as ECVAM (European Centre for Validation of Alternative Methods), evaluates these methods.

SCCNFP opinions include evaluations of experiments using laboratory animals; such tests are conducted in accordance with all legal provisions and preferably under chemical law regulations. Only in cases where no alternative method is available will such tests be evaluated and the resulting data accepted, in order to meet the fundamental requirements of the protection of consumer health.

2. Chemical and Physical Specifications

2.1. Chemical identity

Acetaldehyde

2.1.1. Primary name and/or INCI name

Acetaldehyde

2.1.2. Chemical names

IUPAC Name : Acetaldehyde
Synonyms : Acetic aldehyde, ethanal, ethyl aldehyde

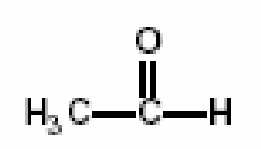
2.1.3. Trade names and abbreviations

None

2.1.4. CAS / EINECS number

CAS : 75-07-0
EINECS : 200-836-6

2.1.5. Structural formula



2.1.6. Empirical formula

Emp. Formula : C_2H_4O
Mol weight : 44.05

2.1.7. Purity, composition and substance codes

No data

2.1.8. Physical properties

Appearance	:	Colourless liquid or gas
Boiling point	:	20.1°C
Melting point	:	-123°C
Vapour Pressure	:	98 kPa at 20 °C
Flash Point	:	-38°C
Log K_{ow}	:	0.45

2.1.9. Solubility

Miscible with water

3. Function and Uses

Acetaldehyde is used as an intermediate in the production of acetic acid, acetic anhydride, cellulose acetate, vinyl acetate resins, acetate esters, pentaerythritol, synthetic pyridine derivatives, terephthalic acid and peracetic acid. Other uses of Acetaldehyde include: in the silvering of mirrors; in leather tanning; as a denaturant for alcohol; in fuel mixtures; as a hardener for gelatin fibres; in glue and casein products; as a preservative for fish and fruit; in the paper industry; as a synthetic flavouring agent; and in the manufacture of cosmetics, aniline dyes, plastics and synthetic rubber.

Acetaldehyde is an ingredient contained used in many fragrance and flavour compounds. It may be found in fragrances used in decorative cosmetics, fine fragrances, shampoos, toilet soaps and other toiletries, in flavours of oral care products as well as in non-cosmetic products such as household cleaners and detergents.

Low levels of Acetaldehyde are reported to occur in several essential oils.

The maximum concentration of Acetaldehyde in fine fragrance products has been reported to be 0.0004%. This is based on the assumption that the fragrance oils used comprised up to 20% of the final cosmetic product (i.e., Acetaldehyde is present at a concentration of 0.002% in the fragrance oil).

4. Toxicological Evaluation

Acetaldehyde is an intermediate product in the metabolism of ethanol and sugars and therefore occurs in small quantities in human blood. It is present in small amounts in all alcoholic beverages, such as beer, wine and spirit and in plant juices and essential oils, roasted coffee and tobacco smoke.

As Acetaldehyde has been classified as a carcinogen category 3, the major emphasis in this toxicological evaluation was be placed on its carcinogenic properties.

The sections **4.6. Mutagenicity / Genotoxicity** and **4.7. Carcinogenicity** were copied directly from IARC, 1999.

4.1. Acute toxicity

Oral LD_{50} values range from greater than 600 to 1,930 mg/kg bodyweight (bw) in rats (summarized in WHO, 1995). In mice, the oral LD_{50} value for Acetaldehyde was reported to be 1,230 mg/kg bw (U.S. NRC, 1977).

By the dermal route of exposure Acetaldehyde is practically non-toxic. A dermal LD_{50} value of greater than 5,000 mg/kg bw has been reported in rabbits on the basis of single death in 10 animals administered 5,000 mg/kg bw (RIFM, 1976).

4.2. Irritation and corrosivity

On the basis of a number of short- and long-term inhalation studies, Acetaldehyde has been shown to be acutely irritating to the skin and eyes, and to produce signs of sensory irritation in rodents (U.S. NRC, 1977).

Concentrations greater than 1% in solution are likely to be irritating to the human skin (RIFM, 2003).

4.3. Skin sensitisation

A maximization test (Kligman, 1966; Kligman and Epstein, 1975) was carried out with 2% Acetaldehyde in petrolatum on 28 healthy, male and female volunteers. Application was under occlusion to the same site on the volar forearms of all subjects for five alternate-day 48-hour periods. The initial patch site was pretreated with 2% aqueous sodium lauryl sulphate (SLS) under occlusion for 24 hours. Following a 10- to 14-day rest period, challenge patches were applied under occlusion to fresh sites for 48 hours. Challenge applications were preceded by 30-minute applications of 2% aqueous SLS under occlusion on the left side of the back whereas the test materials were applied with SLS treatment on the left and petrolatum on the right. Reactions were read at patch removal and again 24 hours after patch removal. No sensitisation reactions were produced (RIFM, 1976).

Fregert et al (1969) assessed the skin sensitisation potential of Acetaldehyde in 4 female patients with eczematous reactions to lower aliphatic alcohols. The individuals were patch tested with 2% Acetaldehyde in water. The study consisted of 48-hour patch tests using A1-test units conducted on the upper backs of the patients. Reactions were read at removal and 24 and 48 hours post-removal. No evidence of skin sensitisation reactions to Acetaldehyde was observed at any time interval.

Following participation in a human repeated insult patch test with ethanol (Stotts and Ely, 1977), one subject became strongly sensitised and was further tested for cross-reactivity. A 0.15 ml 1% aqueous Acetaldehyde was applied to a 12 mm Webril patch. Reactivity to Acetaldehyde was observed (Slotts and Evy, 1977). In the same study the author inadvertently sensitised himself to Acetaldehyde during a test to determine a non-irritant concentration of Acetaldehyde. The

exposure consisted of single applications of 5% and 10% Acetaldehyde for a 3-hour period followed by single sequential applications of 0.5% and 1% for 24 hours, all within an 8-day period. A subsequent application of 2% Acetaldehyde produced a strong allergic response and prompted a flare at the 10% application site that was made 20 days earlier (Stotts and Ely, 1977).

The skin sensitisation potential of Acetaldehyde was tested in a modified Cumulative Contact Enhancement Tests (CCET). Fifteen female albino Dunkin-Hartley guinea pigs were tested. A 0.2 ml aliquot of Acetaldehyde was applied to a 2x4 cm lint cloth and then applied to shaved skin on the upper back for 24 hours under occlusion. Induction applications (15% Acetaldehyde in saline) were administered on days 0, 2, 7 and 9. The animals also received two intradermal injections of 0.1 ml FCA in the same region on day 7. Animals were challenged 14 days after the final induction at doses of 2.5%, 5.0% and 10.0% Acetaldehyde in saline. At challenge, a 0.015 ml aliquot of Acetaldehyde in saline was applied to a Finn Chamber and then applied to a shaved site on the lateral back for 24 hours under occlusion. Reactions were read 48 and 72 hours after start of exposure. Acetaldehyde showed significant sensitising capacity and a clear dose-response relationship was observed. Specifically, at the 48-hour reading, challenge at 2.5% produced 4/15 sensitisation reactions; challenge at 5.0% produced 7/15 sensitisation reactions; challenge at 10.0% produced 13/15 sensitisation reactions. At the 72-hour reading, challenge at 2.5% produced 5/15 sensitisation reactions; challenge at 5.0% produced 9/15 sensitisation reactions; challenge at 10.0% produced 13/15 sensitisation reactions. The animals were rechallenged 78 days after the start of the experiment with Acetaldehyde at concentrations of 0.035 and 2.5%, and no significant reactions were observed (Berg and Karlberg, 1999).

4.4. Dermal / percutaneous absorption

No data

4.5. Repeated dose toxicity

In a 4 weeks study, Acetaldehyde was added to drinking water of rats, providing daily intake levels of 0, 25, 125, or 675 mg/kg bw/d. The only clearly compound-related effect reported was focal hyperkeratosis of the forestomach in the high-dose group (8/10 males and 8/10 females). In the control group, very slight focal hyperkeratosis of the forestomach was noted in 6/20 females and 3/20 males. In the high-dose group, the relative kidney weights were slightly increased in males, and urinary production was decreased. The effects and reported variations in serum biochemistry, were generally attributed to reduced water intake. Acetaldehyde exposure did not affect indices of liver function and produced no evidence of histological change in this organ (Til et al., 1988).

In a group of rats exposed to 0.05% Acetaldehyde in the drinking water (estimated to be about 40 mg/kg bw for 6 months, an increase in collagen synthesis in the liver was reported (Bankowski et al, 1993). Since no other indices of toxicity were reported, the significance of this finding is unknown.

Amirkhanova and Latypova (1967) investigated the potential toxicity of Acetaldehyde administered perorally in aqueous solution to white rats and guinea pigs at dose levels of 0.5, 10, or 100 mg/kg bw/d for periods of 5-6 months. In guinea pigs, indices monitored at every dose

level, with the exception of the high-dose level, included peripheral blood cholinesterase and leukocyte phagocytic activity, as well as the ratio of protein fractions in blood serum. In rats, conditional reflex activity and blood pressure levels were evaluated at every dose level. Rats in the high-dose group were reported to exhibit inhibition of reflex activity, increases in blood pressure, as well as unspecified histological variations in the internal organs. A transient disruption of the conditioned reflex activity also was reported in rats receiving 10 mg Acetaldehyde/kg bw/d at the 2 and 3 month of treatment. Compound-related effects reported in guinea pigs were limited to a statistically significant reduction in eosinophil count in groups treated at 10 mg/kg bw/d. No apparent adverse effects were reported in groups of animals administered 0.5 mg/kg bw/d.

4.6. Mutagenicity / genotoxicity

The toxicity (including genotoxicity) of Acetaldehyde has been reviewed (Dellarco, 1988; Feron *et al*., 1991; WHO, 1995).

Humans
Acetaldehyde–DNA adducts have been observed in granulocytes and lymphocytes of human alcohol abusers (Fang & Vaca, 1997).

Experimental systems (see Table 1. For references see IARC, 1999)
Acetaldehyde did not cause differential killing of repair-deficient *Escherichia coli* K-12 *uvrB*/*recA* cells and was not mutagenic to *Salmonella typhimurium* or *E. coli* WP2 *uvrA* after vapour exposure, with or without metabolic activation. It induced chromosome malsegregation in *Aspergillus nidulans* and was mutagenic in *Drosophila melanogaster* after injection but not after feeding.

In vitro and without exogenous metabolic activation, Acetaldehyde induced gene mutations in mouse lymphoma L5178T cells, sister chromatid exchanges in Chinese hamster ovary cells and aneuploidy in embryonic Chinese hamster diploid fibroblasts. In human lymphocytes it also induced gene mutations and sister chromatid exchanges and, in addition, chromosomal aberrations and both positive- and negative-centromere-staining micronuclei. It did not cause morphological transformation in cultured mammalian cells when tested alone, but positive results were obtained when it was used in combination with the tumour promoter 12-*O*-tetradecanoylphorbol 13-acetate. It did not induce micronuclei in early spermatids of mice.

Acetaldehyde caused DNA strand breaks and cross-links in human lymphocytes *in vitro* without metabolic activation, but not in human bronchial epithelial cells and in human leukocytes. It has been shown to bind covalently to deoxynucleotides *in vitro* and to form DNA–protein cross-links in rat nasal mucosa. Acetaldehyde–DNA adducts have been found *in vitro* in calf thymus DNA, in 22-deoxyguanosine-32-monophosphate and in liver from mice treated with ethanol (Fang & Vaca, 1995). Abnormal sperm morphology or spermatocyte micronuclei were not observed in mice treated with an intraperitoneal injection of Acetaldehyde.

Table 1. *Genetic and related effects of Acetaldehyde (See IARC, 1999 for references).*

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ECD, *Escherichia coli pol*A, differential toxicity (spot test)	–	NT	7800	Rosenkranz (1977)
ERD, *Escherichia coli* K-12 *uvrB/recA*, differential toxicity	–	NT	16317	Hellmér & Bolcsfoldi (1992)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	Mortelmas *et al.* (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.5% in air	JETOC (1997)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	NT	2515	Marnett *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	NT	7800	Rosenkranz (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Mortelmans *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	0.5% in air	JETOC (1997)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.5% in air	JETOC (1997)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	NT	7800	Rosenkranz (1977)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Mortelmans *et al.* (1986)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1% in air	JETOC (1997)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	0.5% in air	JETOC (1997)
SCF, *Saccharomyces cerevisiae*, forward mutation	(+)	NT	23400	Bandas (19892)
ANN, *Aspergillus nidulans*, aneuploidy (chromosome malsegregation)	+	NT	200	Crebelli *et al.* (1989)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		22500 ppm inj × 1	Woodruff *et al.* (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		25000 ppm feed	Woodruff *et al.* (1985)
DIA, DNA–protein cross-links, Fischer 344 rat nasal mucosa cells *in vitro*	+	NT	4410	Lam *et al.* (1986)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	176	Wangenheim & Bolcsfoldi (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	3.9	Obe & Ristow (1977)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	3.9	Obe *et al.* (1978)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	1.9	Obe & Beek (1979)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	+	7.8	De Raat *et al.* (1983)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	1.3	Brambilla *et al.* (1986)
MIA, Micronucleus test, Sprague-Dawley rat primary skin fibroblasts *in vitro*	+	NT	4.4	Bird *et al.* (1982)
CIR, Chromosomal aberrations, Sprague-Dawley rat primary skin fibroblasts *in vitro*	+	NT	44.1	Bird *et al.* (1982)
AIA, Aneuploidy, Chinese hamster embryonic diploid fibroblasts *in vitro*	+	NT	15.6	Dulout & Furnus (1988)
TCM, Cell transformation, C3H 10T½ mouse cells *in vitro*	–	NT	100	Abernathy *et al.* (1982)
TCL, Cell transformation, mammalian cells	–[c]	NT	0.44	Eker & Sanner (1986)
DIH. DNA strand breaks, human leukocytes *in vitro*	–	NT	441	Lambert *et al.* (1985)
DIH, DNA cross-links, human lymphocytes *in vitro*	+	NT	411	Lambert *et al.* (1985)
DIH, DNA strand breaks, human bronchial epithelial cells *in vitro*	–	NT	44	Saladino *et al.* (1985)
DIH, DNA–protein cross-links, human bronchial epithelial cells *in vitro*	–	NT	44	Saladino *et al.* (1985)
DIH, DNA strand breaks, human lymphocytes *in vitro*	+	NT	68.8	Singh & Khan (1995)
GIH, Gene mutation, human lymphocytes, *hprt* locus *in vtro*	+	NT	13	He & Lambert (1990)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	7.8	Obe *et al.* (1978)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	7.8	Ristow & Obe (1978)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	5.8	Jansson (1982)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	8	Bohlke *et al.* (1983)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	4.4	He & Lambert (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	4.4	Knadle (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	11	Norppa *et al.* (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	15.6	Obe *et al.* (1986)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	4.4	Helander & Lindahl-Kiessling (1991)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	11	Sipi *et al.* (1992)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	20	Badr & Hussain (1977)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	(+)	NT	7.8	Obe *et al.* (1978)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	NT	15.6	Obe *et al.* (1979)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	15.9	Böhlke *et al.* (1983)
CIH, Chromosomal aberrations, human Fanconi's anaemia lymphocytes *in vitro*	+	NT	7.8	Obe *et al.* (1979)
MIH, Micronucleus test, human lymphocytes *in vitro*	+[d]		26.5	Migliore *et al.* (1996)
DVA, DNA–protein cross-links, Fischer 344 rat nasal mucosa *in vivo*	+		1000 ppm inh 6 h/d × 5 d	Lam *et al.* (1986)
SVA, Sister chromatid exchange, male C3A mouse bone-marrow cells *in vivo*	+		0.4 µg/mouse ip × 1	Obe *et al.* (1979)
SVA, Sister chromatid exchange, Chinese hamster bone-marrow cells *in vivo*	+		0.5 ip × 1	Korte *et al.* (1981)
MVM, Micronucleus test, C57BL/6J × C3H/He mouse spermatocytes	–		375 ip × 1	Lähdetie (1988)
COE, Chromosomal aberrations, rat embryos *in vivo*	+		7800 iam × 1	Bariliak & Kozachuk (1983)
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	NT	44100	Ristow & Obe (1978)
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	NT	78800	Fang & Vaca (1995)
BID, Binding (covalent) to deoxynucleosides *in vitro*	+	NT	7880	Vaca *et al.* (1995)
SPM, Sperm morphology, C57BL/6J × C3H/He mouse early spermatids *in vivo*	–		250 ip × 5	Lähdetie (1988)

[a] +, positive; (+), weak positive; –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; inj, injection; inh, inhalation; ip, intraperitoneal; iam, intra-amniotic
[c] Positive results when acetaldehyde treatment was followed by exposure of the cells to 12-*O*-tetradecanoylphorbol 13-acetate
[d] A dose-related increase in centromere-positive micronuclei was observed with fluorescence in-situ hybridization but it was not significantly different from the negative control

4.7. Carcinogenicity

4.7.1. Animal studies

Acetaldehyde was tested for carcinogenicity in rats by inhalation exposure and in hamsters by inhalation exposure and intratracheal instillation. Following inhalation exposure, an increased incidence of carcinomas was induced in the nasal mucosa of rats, and laryngeal carcinomas were induced in hamsters. In another inhalation study in hamsters, using a lower exposure level, and in an intratracheal instillation study, no increased incidence of tumours was observed. In hamsters, inhalation of Acetaldehyde enhanced the incidence of respiratory-tract tumours produced by intratracheal instillation of benzo[*a*]pyrene (IARC, 1985).

Inhalation exposure

Rat: In a study summarized from a preliminary report in the previous monograph, four groups of 105 male and 105 female Cpb:WU albino Wistar rats, six weeks of age, were exposed by whole-body inhalation to concentrations of 0, 750, 1500 or 3000 (reduced progressively over a period of 11 months to 1000 ppm due to toxicity) ppm [0, 1350, 2700 or 5400–1800 mg/m^3] Acetaldehyde vapour [purity unspecified] for 6 h per day on five days per week for a maximum of 27 months. Each group comprised five subgroups, three of which were used for interim kills at weeks 13, 26 and 52, respectively. Of the animals killed at these intervals, only one had a tumour of the respiratory tract: a female in the high-dose group killed in week 53, bearing a nasal squamous-cell carcinoma. At day 468, the mortality rate in the high-dose group was 50% (28/55) for males and 42% (23/55) for females. By day 715, all high-dose rats had died and, at termination of the study at day 844, only a few animals were still alive in the mid-dose group. At the end of the study, the incidences of nasal carcinomas (carcinomas *in situ*, squamous-cell carcinomas and adenocarcinomas) were in males: 1/49, 17/52, 41/53 and 37/49 in the control, low-, mid- and high-dose groups, respectively; and in females: 0/50, 6/48, 34/53 and 43/53 in the control, low-, mid- and high-dose groups, respectively. One carcinoma *in situ* of the larynx was found in a female of the mid-dose group and one female of the low-dose group developed a poorly differentiated adenocarcinoma in the lung (Woutersen *et al*., 1986).

4.7.2. Human studies

Case series

In a survey of chemical plants (without prior hypothesis) in the German Democratic Republic, nine cancer cases were found in a factory where the main process was dimerization of Acetaldehyde and where the main exposures were to acetaldol (3-hydroxybutanal), Acetaldehyde, butyraldehyde, crotonaldehyde (IARC, 1995) and other higher, condensed aldehydes, as well as to traces of acrolein (IARC, 1985). Of the 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 expected in the German Democratic Republic. [The Working Group noted the mixed exposure, the small number of cases and the poorly defined exposed population.]

Case–control studies

Acetaldehyde is the main metabolite of ethanol and this reaction is catalysed by alcohol dehydrogenases (ADH). Five ADHs have been characterized in humans, two of which (ADH2 and ADH3), are known to be polymorphic. In particular, polymorphism for ADH3 seems to strongly influence the metabolism of ethanol to Acetaldehyde, with ADH3 1 allele carriers being faster metabolizers than ADH3 2 carriers. Acetaldehyde is metabolized by phase II enzymes, including aldehyde dehydrogenases (ALDH) and glutathione *S*-transferases (GST). ALDH2 is polymorphic; its mutant allele, ALDH2 2, which leads to enzyme inactivity, is prevalent in Asian populations. GSTM1 is also polymorphic, with a null genotype GSTM1 0 present mainly in European populations (Coutelle *et al.*, 1997). Therefore, carriers of ADH3 2, ALDH2 2 and GSTM1 0 alleles are likely to be exposed to higher levels of Acetaldehyde than are other people, following intake of a comparable amount of alcohol.

A Japanese case–control study (Yokoyama *et al*., 1996) of ALDH2-related risk for oesophageal squamous-cell carcinoma in alcoholics (40 cases and 55 controls) and nonalcoholic drinkers (29 cases and 28 controls) during 1991–95 showed a higher risk for oesophageal cancer in those with one ALDH2 2 allele in both alcoholics (crude odds ratio, 7.6; 95% confidence interval (CI), 2.8–20.7) and non-alcoholic drinkers (odds ratio, 12.1; 95% CI, 3.4–42.8). Mantel–Haenszel adjustment for age and daily alcohol consumption had virtually no influence on the risk estimates [adjusted odds ratios not given]. As persons who have the mutant ALDH2 2 allele have a high concentration of blood Acetaldehyde after drinking alcohol, the results of this study were interpreted as strongly suggesting a carcinogenic role of Acetaldehyde in humans.

As part of a population-based study of oral cancer (oral cavity and pharynx) in Puerto Rico in 1992–95, the alcohol dehydrogenase type 3 (ADH3) genotype was determined in 137 patients and 146 controls without cancer by molecular genetic analysis of oral epithelial cell samples (Harty *et al*., 1997). Participation rates were 48% among cases and 57% among controls. After adjustment for tobacco smoking, diet and alcohol drinking, the odds ratio for the ADH3 1-2 genotype was 0.7 (95% CI, 0.4–1.3) and that for the ADH3 2-2 genotype was 0.6 (95% CI, 0.3–1.6), using the ADH3 1-1 genotype as reference category. When non-drinkers with the ADH3 1-1 genotype were used as reference, the risk among drinkers of 57 or more drinks per week was modified by the ADH3 genotype: odds ratios were 40.1 (95% CI, 5.4–296), 7.0 (95% CI, 1.4–35.0) and 4.4 (95% CI, 0.7–33.3) for ADH3 1-1, ADH3 1-2 and ADH3 2-2, respectively. For lower alcohol consumption, the risks were not or only moderately elevated, without a clear pattern according to genotype. [The Working Group noted the low participation rate.]

Coutelle *et al*. (1997) conducted a case–control study in France among male heavy drinkers (more than 100 g of alcohol per day for more than 10 years). They included 21 cases of oral and pharyngeal cancer, 18 cases of laryngeal cancer and 37 heavy drinkers recruited in an alcoholism clinic. As compared to ADH3 1-1 or ADH3 2-2, the ADH3 1-2 genotype was associated with an age-adjusted odds ratio of 2.6 (95% CI, 0.7–10.0) for oropharyngeal cancer and 6.1 (95% CI, 1.3–28.6) for laryngeal cancer. The GSTM1 null genotype had an odds ratio of 1.8 (95% CI, 0.5–6.2) for oropharyngeal cancer and 4.7 (95% CI, 1.0–21.8) for laryngeal cancer. The combination of ADH3 1-1 and GSTM1 null genotypes, as compared to the combination of ADH3 1-2 or ADH3 2-2 and GSTM1 non-null, gave an odds ratio of 4.3 (95% CI, 0.6–28.8) for oropharyngeal cancer and 12.9 (95% CI, 1.8–92.0) for laryngeal cancer.

In an abstract, Freudenheim *et al*. (1997) presented the results of a study conducted in western New York, United States, on 134 premenopausal and 181 postmenopausal cases of breast cancer and 356 population controls. Heavy alcohol intake was associated with an increased risk for premenopausal breast cancer (odds ratio, 3.5; 95% CI, 1.3–9.2) among ADH3 1-1 subjects but not among women with ADH3 1-2 or ADH3 2-2 genotypes. This association was not observed for postmenopausal breast cancer.

IARC has concluded:
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)*.

4.8. Reproductive toxicity

Experimental animal studies on reproductive toxicity have primarily been conducted as part of investigations of the role of Acetaldehyde in ethanol induced reproductive effects. Foetal malformations were found in mice and rats treated with Acetaldehyde, and resorptions were also observed in both species. These studies employed an injection route of exposure.

It is not known whether Acetaldehyde, the primary metabolite of ethanol, is involved in the aetiology of the human foetal alcohol syndrome (IARC, 1985).

4.9. Toxicokinetics

The metabolism of Acetaldehyde is the key to understanding of its toxicological effects, particularly with respect to potential genotoxicity and carcinogenicity. Acetaldehyde is rapidly oxidized to acetate by NAD+-dependent aldehyde dehydrogenase (ALDH) enzymes in the liver and mucosal tissues of the respiratory tract. Acetate then enters the citric acid cycle and is further metabolised to carbon dioxide and water (Asmussen et al, 1948; Lundquist et al, 1962). As a highly reactive electrophile, Acetaldehyde readily reacts with nucleophilic groups, such as amino and sulfhydryl moieties of proteins to form adducts (Tuma and Sorrell, 1985; Feron et al, 1991; Gapstur et al, 1992; Lindahl 1992; Nicholls et al, 1992; Niemelä, 1993; Worrall et al, 1993). The DNA-protein crosslinks are very similar to those reported for formaldehyde. Toxicity associated with the exposure to Acetaldehyde is most likely due to the reaction with cellular macromolecules prior to metabolism (Morris et al, 1996; Environment Canada, 2000).

4.10. Photo-induced toxicity

No data

4.11. Human data

No data

4.12. Special investigations

No data

4.13. Safety evaluation

RIFM provided a table corresponding to the estimated consumer exposure to Acetaldehyde in fragranced cosmetic products. It is considered that the range of cosmetic products selected covers all those that are likely to be used in any one weekly period. In table 2 the data reported by RIFM have been adjusted according to the SCCNFP's Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, 5th revision.

Table 2. *Calculation of Exposure to Acetaldehyde in Cosmetic Products*

Type of cosmetic product	Application quantity in grams per application	Application frequency per day [c]	Retention factor [d] (%)	Fragrance compound in product [e] (%)	Acetalde-hyde in fragrance compound [f] (%)	Acetalde-hyde in product (ppm)	Exposure to Acetalde-hyde (µg/day)	Exposure to Acetaldehyde for 60 kg person (µg/kg/day)
Body lotion	8	1	100	0.4	0.0025	0.10	0.8	0.013
Face cream [a]	0.8	2	100	0.3	0.0025	0.075	0.12	0.002
Eau de toilette [b]	0.75	1	100	8.0	0.0025	2.0	1.5	0.025
Fragrance cream	5	0.29	100	4.0	0.0025	1.0	1.45	0.024
Anti-perspirant /deodorant	0.5	1	100	1.0	0.0025	0.25	0.125	0.002
Shampoo	8	1	1	0.5	0.0025	0.13	0.010	0.0002
Bath products	17	0.29	1	2.0	0.0025	0.50	0.025	0.0004
Shower gel	5	2	1	1.2	0.0025	0.30	0.030	0.0005
Toilet soap	0.8	6	1	1.5	0.0025	0.38	0.018	0.0003
Hair spray	5	2	1	0.5	0.0025	0.13	0.013	0.0002
Toothpaste	1.4	2	17	1.0	0.0040	0.40	0.19	0.003
						Total [g]		**0.071**

[a] Including make up and foundation

[b] The entry for eau de toilette includes all hydroalcoholic products (i.e. parfums, aftershaves, colognes, etc.). These products are not all used on one occasion, the quantity per application being inversely related to the fragrance concentration in the product. The figure for eau de toilette therefore covers all hydroalcoholic fragranced products.

[c] To allow comparison with animal studies, use is expressed as a daily exposure although in fact it is based on weekly figures in order to take account of usage patterns which would not otherwise be evident. For example, a body lotion and a fragranced cream (i.e., a body lotion containing a higher level of fragrance) will not both be used on the same day. It has been estimated therefore that a body lotion may be used on five days per week (i.e., 0.71 times per day) and a fragranced cream on two days per week (i.e., 0.29 times per day). A similar calculation applied to bath products and shower gel.

[d]Retention factors for the skin are taken from "Notes of Guidance for Testing of Ingredients for Their Safety Evaluation".

[e]The concentration of the fragrance mixture in a cosmetic product type has been determined by senior technical representatives of the cosmetic industry.

[f]The concentration of a fragrance ingredient in a fragrance mixture is based on data obtained by the fragrance industry from the examination of commercialized formulations containing the fragrance ingredient. The concentration used corresponds to the upper 97.5th percentile concentration of the fragrance ingredient in fragrance mixtures, a concentration which is in itself maximized because the products not containing the fragrance ingredient were not included as zero values in the distribution of samples.

[g]Total consumer exposure to the fragrance ingredient is determined by adding figures for the different product types. In view of all the above assumptions, this figure has to be regarded as conservative; it is most unlikely that a consumer will consistently use a number of different cosmetic products which are all perfumed with the upper 97.5th percentile level of the fragrance ingredient.

RIFM conclude that based on conservative procedure dermal exposures of Acetaldehyde were estimated to be maximum 0.1 µg/kg bw/day and it is assumed that 100% of the applied Acetaldehyde is absorbed.

Quantitative risk assessment

Acetaldehyde is classified as a Category 3 carcinogen and mutagen. The tumours induced mice may be caused by a genotoxic mechanism indicating a non-threshold mechanism. The quantitative risk assessment has been carried out on the basis of the T25 method (Sanner *et al.,* 2001).

Rat inhalation study describe in section 4.7.1.

Nasal carcinomas in males.

1350 mg/m^3 = 17/52
Control 1/49
Net 31%

Acetaldehyde concentration: 1.35 mg/l
Inhalation rate: 20.5 l/h
Exposure time: 6 h/d, 5 d/week for 27 months
Duration of experiment: 27 months
Conversion factor: $(60/0.5)^{0.25} = 3.3$

D = 1.35 x 20.5 x 6 x 5/7 x 27/24 x 27/24 = 150 mg/kg bw/d

T25 = 150 x 25/31 = 121 mg/kg bw/d
HT25 = 121/3.3 = 36.7 mg/kg bw/d

Maximum exposure 0.1µg/kg bw/d

Lifetime cancer risk: $0.0001/(36.7/0.25) = 7 \times 10^{-7}$

Conclusion: The maximum exposure stated by RIFM does not represent any cancer risk

4.14. Conclusions

Acetaldehyde is a naturally occurring substance, also in human metabolic pathways. It is the main metabolite of ethanol. It has low acute and subchronic toxicity. It is metabolised to acetic acid.

The dermal toxicity data in humans present mixed result. While exposure to high concentrations (i.e., greater than 1% in solution) of Acetaldehyde are likely to be irritating to the skin, there is less compelling evidence to indicate that Acetaldehyde is a skin sensitizer in humans. However, guinea pigs displayed a significant skin sensitisation response to Acetaldehyde in the modified Cumulative Contact Enhancement Test (CCET).

Acetaldehyde is a mutagen classified in EU as a Category 3 mutagen.

Acetaldehyde is a carcinogen classified in EU as a Category 3 carcinogen. 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. IARC concludes that there is *inadequate evidence* in humans for the carcinogenicity of Acetaldehyde.

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. IARC conclude that there is *sufficient evidence* in experimental animals for the carcinogenicity of Acetaldehyde.

On the basis of quantitative risk assessment it is concluded that Acetaldehyde at the maximum exposure stated by RIFM does not represent any cancer risk.

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5. Opinion of the SCCNFP

Based on the information on the amount of fragrance compound present in the finished cosmetic products provided in table 2 of this opinion, the SCCNFP is of the opinion that acetaldehyde can be safely used as a fragrance/flavour ingredient at a maximum concentration of 0.0025% in the fragrance compound.

SCCNFP does not recommend any further restrictions to the use of Acetaldehyde as a fragrance/flavour ingredient in cosmetic products.

6. Other considerations

Not applicable

7. Minority opinions

Not applicable