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

CONCERNING

FURFURAL

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, regulation 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 of 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 substances classified in category 3 may be used in cosmetics if the substances has been evaluated by the SCCNFP and found acceptable for use in cosmetic products."*

Furfural is classified as a category 3 carcinogen. 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 supporting the safe use of Furfural as a fragrance ingredient.

1.2 Request to SCCNFP

The SCCNFP is requested to answer the following questions:

* *Is Furfural 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 Furfural 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

Furfural

2.1.1. Primary name and/or INCI name

Furfural

2.1.2. Chemical names

IUPAC name : 2-Furaldehyde
Synonyms : 2-Furancarboxaldehyde, 2-formylfuran, furancarbonal, artificial ant oil.

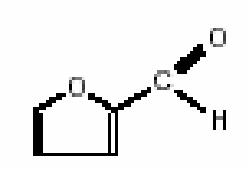
2.1.3. Trade names and abbreviations

None

2.1.4. CAS / EINECS number

CAS : 98-01-1
EINECS : 202-627-7

2.1.5. Structural formula



2.1.6. Empirical formula

Emp. Formula : $C_5H_4O_2$
Mol weight : 96.09

2.1.7. Purity, composition and substance codes

Furfural is available commercially at a purity > 98%

2.1.8. Physical properties

Appearance	:	Clear, colourless oily liquid with a benzaldehyde-like odour
Melting point	:	-38.7°C
Boiling point	:	161.7°C
Vapour Pressure	:	1 mm Hg at 20 °C (0.13 kPa)
Flash Point	:	127 °C
Log K_{ow}	:	0.83 (calculated)
Specific gravity	:	1.156

2.1.9. Solubility

In water: moderate soluble (83 g/l)

3. Function and Uses

Large quantities of Furfural are used in solvent extraction in the petroleum refining industry. It is also used as a solvent (for nitrated cotton, cellulose acetate and gums), to accelerate vulcanization, as an ingredient of phenolic resins (Durite), as an intermediate in the synthesis of furan derivatives, as a weed killer, as a fungicide and as a flavouring agent.

Furfural has been identified in 150 foods, including fruits, vegetables, beverages, bread and bread products. The highest reported concentrations were found in wheat bread (0.8–14 ppm) [mg/kg], cognac (0.6–33 ppm), rum (22 ppm), malt whisky (10–37 ppm), port wine (2–34 ppm) and coffee (55–255 ppm). The concentrations of Furfural in juices were 0.01–4.93 ppm.

Furfural is an ingredient contained in many fragrances and flavours. 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.

Furfural in the in the fragrance compound is reported to be 0.036% or less.

4. Toxicological Evaluation

As Furfural has been classified as a carcinogen category 3, the major emphasizes in the toxicological evaluation will be placed on its carcinogenic properties.

The sections **4.6 Mutagenicity / genotoxicity, 4.7 Carcinogenicity** and **4.9 Toxicokinetics** are copied directly from IARC, 1995.

4.1. Acute toxicity

Oral LD50 for Furfural in rats is between 50 and 100 mg/kg bw.

4.2. Irritation and corrosivity

In a review, the main effect of Furfural in humans was reported to be skin and mucous membrane irritation. Irritant dermatitis has in some cases led to eczema, and there have been reports of allergic skin sensitization and photosensitization (Mishra, 1992).

4.3. Skin sensitisation

Humans
A maximization test (Kligman, 1966; Kligman and Epstein, 1975) was carried out with 2% Furfural in petrolatum on 25 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. Patch sites were pretreated for 24 hours with 2.5 to 5% aqueous sodium lauryl sulphate under occlusion. Reactions were read at patch removal and again 24 hours after patch removal. No sensitisation reactions were produced (RIFM, 1975).

Animal studies
A group of 3 male Hartley guinea pigs weighing 300-400 grams were tested in a guinea pig intradermal injection test. The induction period consisted of 7 daily intradermal injections of a 0.1 ml suspension of 1.0% Furfural in saline containing 1% Tween 80 on both sides of the abdomen. Prior to the elicitation injections, the abdomen of each animal was depilated with a hair remover. Three weeks after the final induction injection, an intradermal challenge injection with a 0.1 ml dose of a freshly prepared suspension of 0.25, 0.5 and 1.0% Furfural in saline containing 1% Tween 80 was administered. Control animals received saline-1% Tween 80 for both the induction and elicitation phases. Reactions were read 24 hours after injections. A positive skin reaction was observed in 1 of the 3 guinea pigs treated with Furfural (Watanabe et al, 2001).

4.4. Dermal / percutaneous absorption

No data

4.5. Repeated dose toxicity

Useful studies of oral exposure are restricted to 13-week gavage experiments with F-344 rats and B6C3F1 mice (NTP, 1981), which indicate that the liver is the target organ of Furfural in these species. In groups of 10 male and 10 female rats treated with 11, 22, 45, 90 or 180 mg/kg, 5 days/week, mortality was associated with greater than or equal to 90 mg/kg and cytoplasmic vacuolization was seen in all treated groups. The lesions were described as mild to moderate, and the low dose level of 11 mg/kg may be considered a LOAEL in rats.

4.6. Mutagenicity / genotoxicity

Humans
Six workers exposed to Furfural and furfuryl alcohol in a furoic resin plant showed no significant difference in sister chromatid exchange frequency in peripheral blood lymphocytes in comparison with six control individuals (Gomez-Arroyo & Souza, 1985). [The Working Group noted the small number of individuals studied and the presence of both smokers and non-smokers. Moreover, the Furfural concentrations in the atmosphere of the plant were not reported.]

Experimental systems (see also Table 1. For references see IARC, 1995)
Furfural reacts with DNA *in vitro*, primarily at AT base pairs, leading to destabilization of the secondary structure of DNA and to single-strand breaks.

Furfural did not induce *umu c'* gene expression, a function related to SOS DNA repair, in *Salmonella typhimurium* TA1535/pSK1002. It was reported to be mutagenic to *S. typhimurium* TA100 in the presence and absence of metabolic activation in one study, but this result was not confirmed in three subsequent studies, which gave equivocal or negative results. Furfural was also reported to be non-mutagenic in *S. typhimurium* strains G46, TA100, TA1535, C3076, TA1537, D3052, TA1538 and TA98 and in *Escherichia coli* strains WP2 and WP2 *uvr*A with a concentration gradient protocol (MacMahon *et al.*, 1979).

Injection, but not feeding Furfural to adult flies *Drosophila melanogaster* induced sex-linked recessive lethal mutation. Furfural did not induce heritable reciprocal translocations in *D. melanogaster.*

Furfural induced gene mutation at the thymidine kinase locus of L5178Y mouse lymphoma cells in the absence of metabolic activation. It induced sister chromatid exchange in Chinese hamster ovary cells and human lymphocytes and chromosomal aberrations in Chinese hamster ovary and V79 lung cells in the absence of metabolic activation.

The frequencies of sister chromatid exchange and chromosomal aberrations were not increased in the bone-marrow cells of B6C3F1 male mice injected intraperitoneally with single doses of Furfural up to 200 mg/kg bw.

Mutation of proto-oncogenes in tumours induced by Furfural
ras Proto-oncogene activation was studied in liver adenomas and carcinomas of B6C3F1 mice treated with Furfural. The frequency of activated H-*ras* and K-*ras* oncogenes in hepatocellular tumours was no different in Furfural-treated (10/16) and vehicle-treated (15/27) mice; however, the spectrum of activating mutations in the H-*ras* gene in tumours from the furfural treated mice differed significantly from that in tumours of untreated animals. Mutations at codon 61 occurred in tumours from both Furfural-treated and untreated animals, but mutations (G→T and G→C transversions) were observed at codons 13 and 117 only in Furfural-treated animals. The authors interpreted their findings as suggesting that novel mutations in *ras* genes could have resulted from a genotoxic effect of Furfural (Reynolds *et al.*, 1987).

Table 1: *Genetic and related effects of furfural (See IARC, 1995 for references)*

Table 3. Genetic and related effects of furfural

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
***, Destabilization of DNA secondary structure *in vitro*	+		1:2	Uddin (1993)
***, DNA strand breaks, calf thymus DNA *in vitro*	+		1:4	Uddin *et al.* (1991)
***, DNA strand breaks, calf thymus DNA *in vitro*	+		1:1	Hadi *et al.* (1989)
PRB, SOS repair, *Salmonella typhimurium* umu	–	–	1932	Nakamura *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	2200	Zdzienicka *et al.* (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2100	Loquet *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1280	US National Toxicology Program (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.00	Dillon *et al.* (1992) (Abstract)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	–	0.00	Dillon *et al.* (1992) (Abstract)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	–	0.00	Dillon *et al.* (1992) (Abstract)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1800	Loquet *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1280	US National Toxicology Program (1990)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1280	US National Toxicology Program (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	4400	Zdzienicka *et al.* (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1800	Loquet *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1280	US National Toxicology Program (1990)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	–		1000 feed	Woodruff *et al.* (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+		100 inj	Woodruff *et al.* (1985)
DMH, *Drosophila melanogaster*, heritable translocation	–		100 inj	Woodruff *et al.* (1985)
GST, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	0	200	McGregor *et al.* (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	+	+	12	US National Toxicology Program (1990)
CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro*	+	+	240	Stich *et al.* (1981)
CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro*	+	+	400	US National Toxicology Program (1990)
CIC, Chromosomal aberrations, Chinese hamster V79 cells *in vitro*	+	0	1000	Nishi *et al.* (1989)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	7	Gomez-Arroyo & Souza (1985)
SVA, Sister chromatid exchange, mouse bone-marrow cells *in vivo*	–		200.0 ip × 1	US National Toxicology Program (1990)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	–		200.0 ip × 1	US National Toxicology Program (1990)

[a] +, considered to be positive; –, considered to be negative; 0, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; *in vitro* tests, µg/ml; *in vivo* tests, mg/kg bw; 0.00, dose not reported; ip, intraperitoneally
***, Not included on the profile

4.7. Carcinogenicity

4.7.1. Animal studies

Oral administration

Mouse

Groups of 50 male and 50 female B6C3F1 mice, aged nine weeks, were administered 0, 50, 100 or 175 mg/kg bw Furfural (purity, 99%) dissolved in corn oil by gavage on five days a week for 103 weeks. Survival at the end of the study was 35/50 male controls, 28/50 at the low dose, 24/50 at the middle dose and 27/50 at the high dose; and 33/50 female controls, 28/50 at the low dose, 29/50 at the middle dose and 32/50 at the high dose. There was a dose-related increase in the incidence of chronic inflammation of the liver. In males, the incidences of hepatocellular

adenomas were 9/50 controls, 13/50 at the low dose, 11/49 at the middle dose and 19/50 at the high dose (p = 0.008, logistic regression analysis); the incidences of hepatocellular carcinoma were 7/50 controls, 12/50 at the low dose, 6/49 at the middle dose and 21/50 at the high dose (p = 0.001). Female mice also had a higher incidence of hepatocellular adenomas, with 1/50 in controls, 3/50 at the low dose, 5/50 at the middle dose and 8/50 at the high dose (p = 0.017); the incidences of hepatocellular carcinoma (4/50, 0/50, 2/50, 4/50) were not increased. The combined incidences of hepatocellular adenomas and carcinomas were: 16/50 male controls, 22/50 at the low dose, 17/49 at the middle dose and 32/50 at the high dose ($p < 0.001$); and 5/50 female controls, 3/50 at the low dose, 7/50 at the middle dose and 12/50 at the high dose (p = 0.051). There was a marginal increase in the incidence of forestomach papillomas in females at the high dose: 6/50 in comparison with 1/50 in controls (p = 0.058) (United States National Toxicology Program, 1990).

Rat
Groups of 50 male and 50 female Fischer 344 rats, seven to eight weeks of age, were administered 0, 30 or 60 mg/kg bw Furfural (purity, 99%) dissolved in corn oil by gavage on five days per week for 103 weeks. Survival at the end of the study was: 31/50 male controls, 28/50 at the low dose and 24/50 at the high dose; and 28/50 female controls, 32/50 at the low dose and 18/50 at the high dose (not significant). A dose-related increase in the frequency of centrilobular necrosis of the liver was seen in males: 3/50 controls, 9/50 at the low dose and 12/50 at the high dose. Two of 50 males given the high dose had bile-duct dysplasia, and two had rarely occurring cholangiocarcinomas. No such lesions were found in the other groups of males or among female rats. There were no other treatment-related lesions in the liver or other organs. The historical incidence of cholangiocarcinoma in control rats at the testing laboratory was 1/449 (United States National Toxicology Program, 1990).

In a study of enzyme-altered foci in the liver, six groups of six male Wistar rats, five weeks of age, were administered Furfural [purity unspecified] in the diet at a concentration of 20 ml/kg of diet for 15–30 days and then at 30 ml/kg of diet for up to 150 days. The exposure of the six groups ceased on days 15, 30, 60, 90, 120 and 150, respectively. Six groups of four male controls were available. The rats were sacrificed 15 days after the end of exposure. Fibrosis was seen in the liver after 30 days of treatment and progressed with the length of exposure, resulting in pseudolobule formation after 150 days of treatment. Foci positive for glutathione *S*-transferase placental form were seen in 4/6 rats after 30 days of treatment and in 6/6 after 150 days. No such foci were seen in the controls. No cancers or neoplastic nodules occurred in any of the groups (Shimizu *et al.*, 1989).

Skin application

Mouse
Groups of 20 female CD-1 mice, seven weeks of age, received topical applications of 50 µmol [4.8 mg] Furfural dissolved in 0.1 ml dimethyl sulfoxide on the back twice a week for five weeks. One week after the last treatment, the mice were treated twice a week with 2.5 µg of the promoter 12-*O*-tetradecanoylphorbol 13-acetate (TPA) in 0.1 ml acetone for 47 weeks. One control group was treated with Furfural and acetone, a second with dimethyl sulfoxide (vehicle control) and TPA, a third with dimethyl sulfoxide and acetone and a fourth with a total dose of 100 µg 7,12-dimethylbenz[*a*]anthracene (DMBA) and TPA (positive control). Five of 19 mice given Furfural and TPA developed seven skin papillomas and one squamous-cell cancer, whereas only one of 20 mice given DMSO and TPA had a papilloma [p = 0.08, Fisher's exact

test]. None of the other negative controls developed tumours, but all 20 mice in the positive control group developed skin tumours (Miyakawa *et al.*, 1991).

Administration with known carcinogens

Hamster
The co-carcinogenic effect of Furfural and the known carcinogens benzo[*a*]pyrene and *N*-nitrosodiethylamine on the respiratory tract of hamsters was studied in two experiments. In one study, long-term exposure to Furfural vapour and repeated intratracheal instillations of benzo[*a*]pyrene or *N*-nitrosodiethylamine did not significantly affect the tumour incidence in hamster respiratory tissues (Feron & Kruysse, 1978). In the other study, repeated, simultaneous intratracheal instillations of Furfural and benzo[*a*]pyrene solutions had a slight co-carcinogenic effect in the respiratory tract (Feron, 1972).

4.7.2. Human studies

No data

IARC has concluded:
There is *inadequate evidence* in humans for the carcinogenicity of Furfural.
There is *limited evidence* in experimental animals for the carcinogenicity of Furfural.

Overall evaluation
Furfural *is not classifiable as to its carcinogenicity to humans (Group 3)*.

4.8. Reproductive toxicity

No data available

4.9. Toxicokinetics

After [carbonyl-^{14}C]Furfural (specific activity, 4.1 mCi/mmol; radiochemical purity, 95%) was administered by gavage to male Fischer 344 rats at single doses of 0.127, 1.15 or 12.5 mg/kg bw in corn oil, 86–89% of the dose was absorbed, and more than 60% was excreted after 12 h, reaching a plateau after 24 h. After 72 h, high concentrations of radiolabel were found in liver and kidney; brain had the lowest concentration. The concentrations in liver and kidney were approximately proportional to the dose. The major route of excretion was urine, which contained 83–88% of the dose; about 7% of a dose of 12.5 mg/kg bw was exhaled as 14C-carbon dioxide, and 2–4% of the dose was detected in the faeces. Furoylglycine was the major urinary metabolite (73–80% of dose), and furanacrylic acid (3–8%) and furoic acid (1–6%) were minor metabolites. The extent and rate of excretion of Furfural metabolites were unaffected by dose. Furoic acid is an oxidation product of Furfural, which may be excreted unchanged or conjugated with glycine. Furanacrylic acid is presumably formed *via* condensation with acetyl coenzyme A (Nomeir *et al.*, 1992).
When the volunteers were exposed dermally to Furfural while breathing pure air, there was considerable but variable absorption. After volunteers submerged their hands up to the wrist in a vessel containing liquid Furfural for 15 min, the total amount of ‘total furoic acid’ excreted

indicated that about 27 mg Furfural had been absorbed through the hand surface. Recalculation of this amount indicated that 1 cm^2 skin absorbed approximately 3 µg Furfural per min (Flek and Šedivec, 1978).

Furfural is extensively absorbed and rapidly eliminated in humans after inhalation and in rats after oral administration. The pattern of metabolites appears to be qualitatively similar, involving oxidation of Furfural to furanoic acid with subsequent conjugation, primarily with glycine. Because of limitations in the reporting of the study of humans (Flek & Šedivec, 1978), a closer, quantitative comparison of the toxicokinetic profiles of humans and rats is not possible.

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 Furfural 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 Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, 5th revision.

Table 2 *Calculation of Exposure to Furfural 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] (%)	Furfural in fragrance compound [f] (%)	Furfural in product (ppm)	Exposure to Furfural (µg/day)	Exposure to Furfural for 60 kg person (µg/kg/day)
Body lotion	8	1	100	0.4	0.036	1.44	11.52	0.192
Face cream [a]	0.8	2	100	0.3	0.036	1.08	1.728	0.029
Eau de toilette [b]	0.75	1	100	8.0	0.036	28.8	21.6	0.36
Fragrance cream	5	0.29	100	4.0	0.036	14.4	20.8	0.348
Anti-perspirant /deodorant	0.5	1	100	1.0	0.036	3.6	1.8	0.03
Shampoo	8	1	1	0.5	0.036	1.8	0.14	0.002
Bath products	17	0.29	1	2.0	0.036	7.2	0.355	0.006
Shower gel	5	2	1	1.2	0.036	4.3	0.432	0.007
Toilet soap	0.8	6	1	1.5	0.036	5.4	0.259	0.004
Hair spray	5	2	1	0.5	0.036	0.13	0.18	0.003
Toothpaste	1.4	2	17	1.0	0.002	0.2	0.095	0.002
						Total [g]		**0.983**

[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.

On the basis of Table 2 it is estimated that the maximum dermal exposures of Furfural is 1 µg/kg bw/d, and it is assumed that 100% of the applied Furfural is absorbed.

Risk assessment

Furfural is classified as a Category 3 carcinogen. Furfural is genotoxic *in vitro,* while no effects were found *in vivo.* On the other hand it has been found that the mutations of proto-oncogenes in mouse liver tumours induced with Furfural differed from that found in liver tumours of control mice. Thus, 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).

Mice gavage study described in section 4.7.1

Male mice hepatocellular carcinomas, high dose

Control	7/50
175 mg/kg bw	21/50
Net:	32.6%

Exposure time:	5 d/week for 103 weeks
Duration of experiment:	103 weeks
Conversion factor:	$(60/0.03)^{0.25} = 6.7$

Dose: 175 x 5/7 = 125 mg/kg

T25 = 125 x 25/32.6 = 95.9 mg/kg
HT25 = 95.9/ 6.7 = 14.3 mg/kg

Maximum exposure 1 µg/kg bw/d

LCR = 0.001/(14.3/0.25) = 1.7 $x10^{-5}$

Conclusion: The maximum exposure stated by RIFM does not represent any significant cancer risk. However, the exposure should not be increased.

4.14. Conclusions

Furfural is a natural occurring substance. The predominant pathway of metabolism of Furfural in humans is oxidation of the aldehyde to yield furoic acid, which may either conjugate with amino acids or condense with acetyl coenzyme A to produce the furanacrylic acid.

In a review, the main effect of Furfural in humans was reported to be skin and mucous membrane irritation. Irritant dermatitis has in some cases led to eczema, and there have been reports of allergic skin sensitization and photosensitization.

In oral subchronic studies in rodents, dose levels of Furfural greater than 50 mg/kg bw/d are primarily associated with hepatic effects. 11 mg/kg may be considered a LOAEL in rats.

Gene mutation (in a single study), sister chromatid exchange and chromosomal aberrations were induced in mammalian cells *in vitro*. Sex-linked recessive lethal mutations were induced in insects. Furfural induced weak or no mutagenicity in bacteria but damaged DNA *in vitro*. Neither chromosomal aberrations nor sister chromatid exchanges were observed in rodents treated with Furfural *in vivo* in a single study.

Furfural is a carcinogen classified in EU as a Category 3 carcinogen. Furfural was tested for carcinogenicity by oral administration in one study in mice and one study in rats. In mice, it increased the incidence of hepatocellular adenomas and carcinomas in males and of hepatocellular adenomas and forestomach papillomas in females. Male rats had a low incidence of cholangiocarcinomas, which occur rarely. In a two-stage assay on mouse skin, Furfural had weak initiating activity.

On the basis of quantitative risk assessment it is concluded that Furfural at the maximum exposure stated by RIFM does not represent any significant cancer risk. However, the exposure should not be increased.

4.15. References

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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 furfural can be safely used as a fragrance/flavour ingredient at a maximum concentration of 0.036% in the fragrance compound. The maximum concentration of furfural that can be safely used as a fragrance/flavour ingredient in toothpaste is 0.002% in the fragrance compound.

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

6. Other Considerations

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7. Minority opinions

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