Scientific Committee on Consumer Safety

SCCS

OPINION ON

Furfural

The SCCS adopted this opinion at its 14th plenary meeting

of 27 March 2012

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.
They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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1. BACKGROUND

Furfural (CAS No 98-01-1 and EC No 202-627-7) has a widespread use in cosmetic products as a perfumery ingredient. Furfural is classified as a CMR carcinogen cat. 2 under the EC Regulation No 1272/2008.

The first scientific opinion (SCCNFP/0822/04) on furfural was adopted by the SCCNFP during its 28th plenary meeting of 25 May 2004 with the following opinion: "*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.*"

At the time of adoption of the opinion by the scientific committee, furfural was considered a non-threshold carcinogenic substance. Meanwhile, new studies have indicated a threshold mechanism and furfural has been evaluated by other scientific committees[1,2] as a threshold carcinogen.

For practical reasons, the stakeholders suggested converting the previously assessed concentration limits for the fragrance compound into a concentration limit in the final product. Based on a realistic content of 0.01% furfural in the fragrance mixture, concentrations in the final products were calculated (see table in annex) and a pragmatic limit of 10 ppm in all cosmetic products was proposed. The use in oral product was excluded from this proposal, but might be intended by other stakeholders and is therefore included in the request.

2. TERMS OF REFERENCE

1. *The SCCS is asked to review the new evidence in relation to the carcinogenicity of furfural and, if necessary, to revise the risk assessment made bythe SCCNPF in 2004*

2. *The SCCS is asked to assess whether furfural can be considered safe for the consumer when used up to the proposed pragmatic concentration limit of 10 ppm in finished cosmetic products (assuming inclusion and exclusion of oral products)*

3. *In the case the SCCS concludes that the pragmatic concentration limit of 10 ppm in finished products results cannot be considered safe, it is asked to revise this concentration limit on the basis of the updated exposure data submitted with this the mandate (assuming inclusion and exclusion of oral products)*

[1] Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to furfural and furfural diethylacetal. The EFSA Journal (2004) 67, 1-27

[2] Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission on Flavouring Group Evaluation 218: alpha-, beta-unsaturated aldehydes and precursors from subgroup 4.2 of FGE.19: Furfural derivatives. The EFSA Journal (2008), 755, 1-23

Supporting document

Table: Proposed level of Furfural in fragrance mixtures and final Cosmetics Products and Calculation of Dermal Exposure

Calculation of exposure based on the real level (concentration) of furfural in the mixture = 0.01 % = 100 ppm in the mixture										
IFRA QRA Cat.	Type of Cosmetic Product	grams applied	Applications Per day	retention factor	fragrance mixture/ product	**Ingredient/ mixture**	Ingredient/ product (%)	Ingredient/ product (ppm)	**Ingredient mg/day**	**Ingredient µg/kg/d**
Cat 2	anti-perspirant	0.50	1.00	1.000	0.010	**0.01**	0.0001	1	0.00050	0.00833
Cat 9	bath products	17.00	0.29	0.001	0.020	**0.01**	0.0002	2	0.00001	0.00016
Cat 4	body lotion	8.00	0.71	1.000	0.004	**0.01**	0.00004	0.4	0.00227	0.03787
Cat 4	eau de toilette	0.75	1.00	1.000	0.080	**0.01**	0.0008	8	0.00600	0.10000
Cat 5	face cream	0.80	2.00	1.000	0.003	**0.01**	0.00003	0.3	0.00048	0.00800
Cat 4	fragrance cream	5.00	0.29	1.000	0.040	**0.01**	0.0004	4	0.00580	0.09667
Cat 4	hair spray	5.00	2.00	0.010	0.005	**0.01**	0.00005	0.5	0.00005	0.00083
Cat 9	shampoo	8.00	1.00	0.010	0.005	**0.01**	0.00005	0.5	0.00004	0.00067
Cat 9	shower gel	5.00	1.07	0.010	0.012	**0.01**	0.00012	1.2	0.00006	0.00107
Cat 9	toilet soap	0.80	6.00	0.010	0.015	**0.01**	0.00015	1.5	0.00007	0.00120
Cat 6	Toothpaste	1.40	2.00	0.017	0.100	**0.01**	0.001	10	0.00048	0.00793
	Total								**0.0158**	**0.2627**

The level of furfural in final product for all applications is well below 10 ppm.

3. OPINION

3.1. Chemical and Physical Specifications

3.1.1. Chemical identity

3.1.1.1. Primary name and/or INCI name

Furfural

3.1.1.2. Chemical names

Furfural (IUPAC)

2-formylfuran, furan-2-aldehyd, 2-furancarboxaldehyde, 2-furyl-methanal, pyromucic aldehyde, 2-furanaldehyde, 2-furancarbonal, carboxylic aldehyde, furan-2-carbaldehyde, furancarbonal

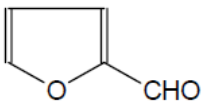
3.1.1.3. Trade names and abbreviations

fural, furale, furole, 2-furole furaldehyde, 2-furaldehyde, furfurol, furfurole, 2-furfural, furfurane, furfuraldehyd, artificial ant oil, bran oil, Quakeral

3.1.1.4. CAS / EC number

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

3.1.1.5. Structural formula



3.1.1.6. Empirical formula

Formula: $C_5H_4O_2$

3.1.2. Physical form

Clear, colourless oily liquid with a benzaldehyde-like odour

3.1.3. Molecular weight

Molecular weight: 96.09 g/mol

3.1.4. Purity, composition and substance codes

Furfural is commercially available at a purity > 98%

3.1.5. Impurities / accompanying contaminants

Impurity < 0.6% 5-methylfurfural

3.1.6. Solubility

In water: 83 g/l

Comment
The method used for solubility determination was not reported

3.1.7. Partition coefficient (Log P_{ow})

Log P_{ow} = 0.41

3.1.8. Additional physical and chemical specifications

Melting point:	-38.7 °C
Boiling point:	161.7 °C
Flash point:	127 °C
Vapour pressure:	1 mm Hg at 20 °C (0.13 kPa)
Density:	1.156
Viscosity:	/
pKa:	/
Refractive index:	/
UV_Vis spectrum (200-800 nm):	/
Conversion factors:	1 ppm = 3.93 mg/m³ 1 mg/m³ = 0.254 ppm

3.1.9. Homogeneity and stability / additional physico-chemical specifications

No data submitted

3.2. Function and uses

Furfural has many use patterns. In the EU, it is primarily used in the production of furan derivatives such as furan and furfuryl alcohol (75% of total volume). Another major application of furfural is as extraction solvent in refineries (13.5% of total volume). 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 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 used as an ingredient in cosmetics and as a flavour in food. It may be found in non-cosmetic products such as household cleaners and detergents.

3.3. Toxicological Evaluation

As furfural has been classified as a CMR carcinogen cat. 2 (CLP), the major emphasis in the toxicological evaluation is placed on its genotoxic and carcinogenic properties.

3.3.1. Acute toxicity

3.3.1.1. Acute oral toxicity

Rat LD50:	65 mg/kg bw
Mouse LD50:	400 mg/kg bw
Guinea pig LD50:	541 mg/kg bw
Rabbit LD50:	800 mg/kg bw
Dog LD50:	950 mg/kg bw

Ref.: 1

3.3.1.2. Acute dermal toxicity

Rabbit LDLo: 620 mg/kg bw

Ref.: 1

3.3.1.3. Acute inhalation toxicity

Rat LC50:	175 ppm/6 h
Mouse LC50:	350 ppm/6 h
Dog LC50:	370 mg/6 h
Human TCLo:	0.31 mg/m³

Ref.: 1

3.3.2. Irritation and corrosivity

3.3.2.1. Skin irritation

No signs of skin irritation were noted in rabbits following a single application of liquid furfural for 12 h, although mild irritation was observed following a 48 h application.

Ref.: 2

Intense but reversible skin irritation was reported in guinea-pigs after repeated application of undiluted liquid furfural.

Ref.: 3, 4

Comment
Because of the limited character of the studies, the relatively high concentrations used, the exposure conditions applied (48 hours, under occlusion or repeated exposure) and the mild nature of the effect, furfural is considered as mildly irritating to the skin.

3.3.2.2. Mucous membrane irritation

A single instillation of liquid furfural produced gross corneal opacities in rabbits.

Ref.: 2

Furfural vapour produced eye irritation in several studies following repeated exposure in different species.

Human data on effects of furfural are extremely limited and of poor quality, although mucous membrane irritation has been identified as the principal effect following exposure to concentrations apparently as low as 12 mg/m³ (3 ppm) (10-min average). However, peak exposure concentrations were not given, and co-exposure with other substances was possible. In another study, exposure to 40 mg/m³ (10 ppm) for 8h or 80 mg/m³ (20 ppm) for 4h apparently did not cause throat or eye irritancy.

Ref.: 6

Comment
Based on human and animal studies furfural is considered irritating to mucous membranes.

3.3.3. Skin sensitisation

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.

Ref.: 7

Humans

A maximisation test 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.

Ref.: 8, 9, 10

Comment
Furfural is not considered a human sensitizer.

Human maximisation tests are considered as unethical.

3.3.4. Dermal / percutaneous absorption

After oral exposure of rats to ^{14}C-furfural, at least 90% is absorbed in the gastro-intestinal tract. After inhalatory exposure to furfural, pulmonary retention in humans was 78%. When humans are exposed to furfural vapours (30 mg/m^3), the dermally absorbed quantity of furfural is about 30% of the amount absorbed through inhalation. After dermal exposure to liquid furfural, about 3 µg furfural per cm^2 skin per minute is absorbed in humans. In the EU Risk Assessment Report, it was concluded that 90% oral and 100% dermal and inhalation absorption were to be used in the risk characterisation.

Ref.: 11

Comment
In the absence of dermal absorption data relevant for the use in cosmetic products, the SCCS will use 100% dermal absorption and 90% for oral absorption for calculation of MoS.

3.3.5. Repeated dose toxicity

3.3.5.1. Repeated Dose (28 days) oral / inhalation toxicity

The subacute oral toxicity of furfural and inhalation toxicity of furfural vapour was studied in F344 rats to investigate whether route-to-route extrapolation could be employed to derive the limit value for inhalation exposure from oral toxicity data.

Groups of 5 rats per sex were treated by gavage daily for 28 days at dose levels of 6-192 mg/kg bw/day, or exposed by inhalation to concentrations of 20-1280 mg/m³ (6 h/day, 5 days/week) or 160-1280 mg/m³ (3 h/day, 5 days/week) for 28 days. Controls received vehicle (corn oil) or were exposed to clean air. Daily oral treatment with the highest dose of furfural (initially 192 mg/kg bw/day, later reduced to 144 mg/kg bw/day and finally to 120 mg/kg bw/day) resulted in mortality, and in increases in absolute and relative kidney and liver weight in surviving females of this group. Exposure of rats by inhalation for 6 h/day, 5 days/week for 28 days induced mortality at concentrations of 640 mg/m³ and above within 1-8 days. At 640 mg/m³ (3 h/day) and at 320 mg/m³ (3 and 6 h/day) and below, however, exposure was tolerated without serious clinical effects. In contrast, histopathological nasal changes were seen even at the lowest concentration of 20 mg/m³. With increasing exposure concentration, the nasal effects increased in incidence and severity and also expanded from the anterior part to the posterior part, including the olfactory epithelium.

It was concluded that the no-observed-adverse-effect level (NOAEL) for oral toxicity was 96 mg/kg bw/day. The NOAEL for systemic inhalation toxicity was comparable, i.e. 92 mg/kg bw/day (corresponding to 320 mg/m³ (6 h/day) or 640 mg/m³ (3 h/day)) assuming 100% absorption. The presence of the histopathological nasal changes at the lowest tested concentration of 20 mg/m³ (corresponding to 6 mg/kg bw/day) proves that for locally acting substances like furfural extrapolation from the oral to the inhalation route is not valid.

Ref.: 12

3.3.5.2. Sub-chronic (90 days) oral / dermal toxicity

Taken from SCCNFP/0822/04

Useful studies of oral exposure are restricted to 13-week gavage experiments with F-344 rats and B6C3F1 mice, 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 bw, 5 days/week, mortality was associated with greater than or equal to 90 mg/kg bw 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 bw/day may be considered a LOAEL in rats.

Ref.: 13

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) pointed out in 1992 and 1999 that because of possible effects of the gavage formulation (corn oil) and dose regimen (bolus dose) a dietary administration studies would be more appropriate for identifying a NOAEL, and requested a new study. SCCS did not have access to the study and the description below is cited from the Opinion of the Scientific Committee on Food on furfural and furfural diethylacetal (2 December 2002).

"In response to a JECFA requirement for the establishment of a NOEL for hepatotoxicity, a 14 day pilot study and a subsequent 90-day study were conducted in F344/N rats in which the animals were given microencapsulated furfural in the diet to provide target dose levels

of 0, 30, 60, 90, 120 and 180 mg/kg bw per day. In the pilot study a NOEL of 120 mg/kg bw/day was established. At the higher dose, there was an increase in liver weight (Jonker, 2000a). In the 90 day study, 10 animals of each sex were used at each dose level. There were no clinical signs of toxicity in any treatment group and food consumption and body weight gain were unaffected. Some haematological changes (decrease in erythrocytes in males in the highest dose group with increased cell volume and mean corpuscular haemoglobin in the top two dose groups males were observed. In females, there was a decrease in serum alkaline phosphatase, an increase in gamma-glutamyltransferase and an increase in plasma albumin in the highest dose group. In males in the high dose group there was a decrease in ALAT, an increase in plasma albumin and albumin/globulin ratio. At necropsy, an increase in liver weight was observed in the top dose group only with no gross pathological changes. Slight histopathological changes occurred in liver of males of the 90 and 180 mg/kg bw dose group in the perilobular region characterised by cells with less coarse cytoplasm with eosinophilic clumps and a less dense periphery and more prominent nucleoli. No such effects were seen in females and there was no sign of hepatotoxic effects such as degeneration, necrosis or inflammation, nor of bile duct proliferation. The NOEL established from this study was 54 mg/kg bw/day (Jonker, 2000b)."

Ref.: 14

Comment
The NOAEL of 54 mg/kg bw/day is the systemic dose calculated from the dose given of 60 mg/kg bw/day and the absorption after oral exposure of 90%.

3.3.5.3. Chronic (> 12 months) toxicity

See Section 3.3.7. Carcinogenicity

General Comment on repeated dose toxicity

The EU Risk Assessment Report on Furfural (ref.: 11) gives the following rationale for choosing the NOAEL from the 13-week dietary study as the relevant effect level for risk assessment:

"Most repeated dose toxicity studies were performed for the oral route of exposure and used gavage as the method of application. NOAELs derived via this methodology varied from 20 down to < 11 mg/kg bw/d. The various studies differed in quality of design and reporting; some were (nearly) according to OECD guidelines, whereas others were clearly not. The lowest NOAEL, i.e. <11 mg/kg bw/d, comes from a subchronic range finding study with rats: at all dose levels, cytoplasmic vacuolization of hepatocytes in the centrilobular region in male rats was found. This effect is considered treatment-related, given the occurrence of mild centrilobular necrosis in male rats in an oral carcinogenicity study with gavage administration.

In more recent studies with rats, furfural was applied via the diet in a microencapsulated form (to prevent loss of the compound due to its volatility). In a 13-week dietary study, effects included minor hepatocellular alterations which were observed in males, but not in females, at doses of 82 and 160 mg/kg bw/d. The NOAEL in this study, therefore, was established at the one lower dose-level of 53 mg/kg bw/d (with corresponding nominal exposure value of 60 mg/kg bw/d), a value clearly higher than the one achieved with gavage application.

Having taken note of the fact that a complementary study showed that furfural was rapidly and completely released from this microencapsulation in an aqueous environment the NOAEL from the 13-week dietary study is selected as the starting point for the risk characterisation for repeated oral exposure for the following reasons: (i) dietary

administration of a test compound is the preferred method of exposure via this route as compared to gavage application; (ii) microencapsulation adequately circumvents loss of furfural due to volatisation and results in an instantaneous release of this substance in the aqueous environment of the GI-tract; (iii) dietary exposure avoids the use of (for this substance) corn oil exposure, that is known to be associated with morphological liver changes upon prolonged exposure; (iv) the alternative key-study NOAEL of <11 mg/kg bw/d has a limited design, being a range-finding study only."

No dermal repeated dose toxicity data are available that can be used for the risk characterisation. Therefore the SCCS will use the oral NOAEL of 54 mg/kg bw/day based on slight histopathological changes in liver of males from the 13-week diet study with rats for calculation of the MOS.

3.3.6. Mutagenicity / Genotoxicity (references are listed separately)

3.3.6.1. Mutagenicity / Genotoxicity *in vitro*

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 (Uddin, 1993, Uddin et al., 1991, Hadi et al. 1989)

Negative or weakly positive results have been obtained for most bacterial tests for genotoxicity. In particular, positive results were obtained in three out of several assays for reverse mutation in Salmonella typhimurium at relatively high concentrations in the absence of metabolic activation. Furfural was found to be clearly genotoxic in cultured mammalian cells at the gene and chromosome level in the absence of metabolic activation. It induced SCE in cultured CHO cells and human lymphocytes.

The results of *in vitro* genotoxicity studies on furfural are summarised in Table 1.

Table 1: *In vitro* mutagenicity/genotoxicity (Taken from EFSA 2004)

End-Point	Test object	Concentration	Result	Reference
Reverse mutation	*S. typhimurium* TA100, TA98, TA1535	0.05-60 µmol/plate	Weakly positive (TA100)[b]	Loquet *et al.,* 1981
	S. typhimurium TA100, TA98, TA102	≤1.2 mmol/plate	Negative[a]	Aeschbacher *et al.,*1989
	S. typhimurium TA100, TA98	0.165-0.660 µmol/plate	Negative[a]	Shinohara *et al.,* 1986
	S. typhimurium TA102, TA104	5-500 µg/plate	Positive (TA104)	Shane *et al.,*1988
	S. typhimurium TA98, TA100,TA1535, TA1537	33.3-6666 µmol/plate	Negative[a]	Mortelmans *et al.,*1986
	S. typhimurium TA98, TA100	1-15 µl/plate	Positive[a] (TA100)	Zdzienicka *et al.,*1978
	S. typhimurium TA98, TA100	7 µl/plate	Negative[a]	Sasaki & Endo, 1978
	S. typhimurium TA100	4.44 µmol/plate	Negative[a]	Osawa & Namiki, 1982
	S. typhimurium TA98, TA100, TA104 *E.coli*WP2uvrA/PKM101	20 µl/plate	Negative[a]	McMahon *et al.,*1979
	S. typhimurium TA104	1 µmol (max. non-toxic dose)	Negative[b]	Marnett *et al.*, 1985
Umu ***gene expression***	*S. typhimurium* TA1535/pSK/002	1932 µg/ml	Negative[a]	Nakamura *et al., 1987*

End-Point	Test object	Concentration	Result	Reference
Rec ***assay***	*B. subtilis* H17, M45 *B. subtilis* H17, M45	1.7-17 mg/disk 1 mg/disk	Positive[a] Negative[a]	Shinohara *et al.,* 1986 Matsui *et al.,* 1989
Forward mutation	L5178Y*tk+/- mouse lymphoma cells*	25-800 µg/ml	Positive[b]	McGregor *et al.,*1988
Chromosomal aberration	Chinese hamster ovary cells Chinese hamster ovary cells Chinese hamster ovary cells Chinese hamster V79 cells	10-40 mM 200-1230 µg/ml 1.5-5000 µg/ml 500-2000 µg/ml	Positive[a] Positive[a] Positive[a] Positive[a]	Stich, 1981a, 1981b Galloway *et al.*, 1985 Gudi & Schadly., 1996 Nishi *et al*., 1989
Sister chromatid exchange	Chinese hamster ovary cells Human peripheral lymphocytes	11.7-3890 µg/ml 3.5-14x10^{-5} M	Positive[a] Positive[b]	Galloway *et al.*, 1985 Gomez-Arroyo & Souza, 1985
Unscheduled DNA synthesis	Human liver slices	0.14 mmol/l 0-25 mmol/l	Negative	Lake *et al.,* 1998

[a] with and without metabolic activation
[b] without metabolic activation

Ref.: 14

3.3.6.2 Mutagenicity/Genotoxicity *in vivo*

Furfural was genotoxic in Drosophila in somatic cells (wing spot test by inhalation) and germ cells (sex-chromosome loss by injection). It did not induce reciprocal translocations and sex-linked recessive lethal mutations, with only a doubtful increase in one study in Drosophila.

Furfural was not genotoxic in any *in vivo* assays for chromosome aberrations, SCE or UDS in experimental animals. The results of *in vivo* genotoxicity studies on furfural are summarised in Table 2.

Table 2: *In vivo* mutagenicity/genotoxicity (Taken from EFSA 2004)

End-Point	Test object	Concentration	Result	Reference
Sex-linked recessive lethal test	*D. melanogaster* *D. melanogaster*	1000 ppm, in diet 100 ppm, by injection	Negative Positive	Woodruff *et al*. 1985
Wing spot test	*D. melanogaster*	3750-7500 ppm by aerial exposure	Positive	Rodriguez-Arnaiz *et al.,* 1989
Sex-chromosome loss	*D. melanogaster*	3750-5000 ppm, in diet and by injection	Positive on injection	Rodriguez-Arnaiz *et al.,* 1989, 1992
Reciprocal translocation	*D. melanogaster*	1000 ppm, in diet	Negative	Woodruff *et al*. 1985
Sister chromatid exchange/chromosomal aberration	B6C3F1 mouse bone marrow cells	50-200 mg/kg bw, once i.p.	Negative	National Toxicology Program 1990
Somatic chromosomal aberration	Swiss albino mouse bone marrow cells	4000 ppm for 5 days, in diet	Negative	Subramanyam *et al*., 1989*
Sperm head abnormalities	Swiss albino mouse	4000 ppm for 5 weeks, in diet	Negative	Subramanyam *et al*., 1989*
Unscheduled DNA synthesis	Fischer 344 rat hepatocytes B6C3F1 mouse hepatocytes	5.0, 16.7 or 50 mg/kg bw, orally 50, 175 or 320 mg/kg bw, orally	Negative Negative	Phillips.*et al*., 1997 Edwards, 1999

*abstract only; no details available

Ref.: 14

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 and Souza, 1985).

Comment
Only a small number of individuals was studied and both smokers and non-smokers were included. The furfural concentrations in the atmosphere of the plant were not reported.

Mutation of proto-oncogenes in tumours induced by furfural.

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 not 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 point out that the "novel mutations in ras genes could have resulted from direct genotoxic effects of furan and furfural. An alternate mechanism is that these mutations were induced by an indirect secondary genotoxic pathway resulting from a cytotoxic event. However, the absence of cytotoxic lesions in the liver, based on histopathological examination after 90 days of administration of the chemical at the carcinogenic dose, argues in favour of direct genotoxic mechanisms" (Reynolds et al., 1987).

Gene mutation by use of λlacZ-transgenic mice with furfural

Guideline:	/
Species/strain:	*λlacZ*-transgenic mice
Group size:	13 male mice, subdivided in 2 groups, Subgroup 1; 3 mice for assessment of hepatotoxicity. Subgroup 2; 10 mice for the main study.
Test substance:	Furfural
Batch:	020220
Purity:	99.88%
Dose level:	0, 37.5, 75, 150, and 300 mg/kg bw; Positive control: 50 mg/kg bw ethylnitrosourea (ENU)
Route:	oral gavage, once daily for 28 consecutive days. ENU administered intraperitoneally for 5 consecutive days (Days 5 – 9).
Vehicle:	Corn oil
Sacrifice times:	Subgroup 1, on day 28; Subgroup 2, on day 62 or 63.
GLP:	In compliance
Study period:	04.04.02 – 06.06.02

As formal technical guidelines for this type of study are not available, the study protocol was designed in conformity with principles for transgenic studies identified by international expert groups (Gorelick and Mirsalis, 1996; Heddle et al. 2000).

The study was conducted with *λlacZ*-transgenic male mice (strain 40.6). *λlacZ*-transgenic mice are CD2F1(BALB/c x DBA/2 mice with *lacZ* genes mutational targets. Every cell of the mouse harbours two concatemers of 40 copies of the *λgt10lacZ*-shuttle vector, located on both homologues of chromosome 3. After treatment of the mice with the test substance and an appropriate treatment-free expression time to allow mutation fixation thereafter,

genomic DNA was isolated from the liver. Then, the *lacZ* genes were excised and single copies of the gene were packaged into infectious phage particles. The phage particles are able to absorb to restriction-deficient *E.coli*-bacteria and every single phage particle can be detected as a phage that forms on a bacterial lawn on an agar surface. Each phage forming a plaque is known as a plaque forming unit (pfu). The use of *E.coli C galE* – strain, deficient for UDP-epimerase, and phenylgalactose as a substrate in the medium, makes it possible to select mutated phages. If a non-functioning (mutated) *lacZ* gene is present in the phage on the positive selection plate, the *lacZ* gene cannot promote the conversion of phenylgalactose to galactose and there is no toxic build-up of UDP-galactose resulting in a normal production and spread of page, visualised as a plaque. The mutant frequency is expressed as the number of mutant phages (positive selection plates) per 10^6 total numbers of pages (standard plates).

The study comprised six groups of mice, one negative control group receiving the vehicle (corn oil) one positive control group receiving EBU for 5 days, and four test groups receiving different levels of furfural (37.5, 75, 150, and 300 mg/kg bw) by oral gavage for 28 consecutive days. The 3 animals per group (subgroup 1) allocated for hepatotoxicity assessment were killed on day 28. The remaining animals (10 per group plus 2 reserve animals) (subgroup 2), allocated to mutation analysis were killed on day 62 or 63.

There were three early deaths in the highest furfural dose group; two during treatment with no clinical signs, and one during the manifestation period. One animal from the low-dose group died during the manifestation period. The cause of death could not be ascertained. Body weights in the furfural-treated groups showed a dose related increase compared to negative controls during the first weeks of treatment. In the post-treatment period the difference between control and two lower dose groups disappeared but the body weight of the group treated with 300 mg furfural/kg bw remained higher.

Evaluation of the clinical chemistry and gross and histopathology of the liver of the treated animals sacrificed at the end of the treatment period (subgroups 1) showed an increase in blood triglycerides, increased liver weight and centrilobular hypertrophy. This was interpreted by the authors as some evidence of hepatotoxicity. These changes did not persist until the end of the manifestation period, 34-35 days after the last dose

Since the protocol only required mutation analysis from three of the four furfural treated groups (to include a toxic dose and a no effect level for toxicity) the low-dose group (37.5 mg/kg bw) was not analysed.

The mutant frequency (MF ± SD per 10^6 colonies) of DNA extracted from the liver cells (subgroups 2) is shown below.

Negative control	mean frequency	61 ± 23
75 mg/kg bw/day	mean frequency	41 ± 7
150 mg/kg bw/day	mean frequency	54 ± 21
300 mg/kg bw/day	mean frequency	37 ± 16
Positive control (ENU)	mean frequency	246 ± 95

The study authors concluded that the mutant frequency of DNA extracted from the liver cells was not increased at any dose level of furfural tested. The negative control group yielded a mutant frequency comparable with laboratory background data and the positive control group yielded the expected increase of mutant frequency, thus confirming the validity of the test (CIVO/TNO 2003).

General comments on mutagenicity/genotoxicity

Furfural reacts with DNA *in vitro*. Although most bacterial mutagenicity tests were negative, positive results were obtained in some experiments *with S. typhimurium* TA100 and TA104 strains. Furfural was found to be genotoxic in cultured mammalian cells at the gene and chromosome level in the absence of metabolic activation. It induced sister chromatid exchange (SCE) in cultured Chinese hamster ovary (CHO) cells and human lymphocytes. Furfural did not induce unscheduled DNA synthesis (UDS) in human liver slices.

Furfural was genotoxic in Drosophila in somatic cells (wing spot test by inhalation) and germ cells (sex-chromosome loss by injection). It did not induce reciprocal translocations and sex-linked recessive lethal mutations, with only a doubtful increase in one study in Drosophila. Furfural was not genotoxic in any *in vivo* assays using experimental animals. The substance was tested for SCE, chromosomal aberration, and sperm head abnormalities in mice and UDS in mouse and rat hepatocytes.

The spectrum of activating mutations in the H-*ras* gene in tumours from the furfural treated mice was found to differ significantly from that in tumours of untreated animals. This finding may suggest that the novel mutations in *ras* genes could have resulted from a genotoxic effect of furfural.

Subsequently, furfural was examined for its potential to induce gene mutations of the *λlacZ*-gene *in vivo* in the liver of male transgenic mice. There was no significant difference in mutant frequency between negative controls and the furfural-treated groups; the positive control group showed a significant increase in mutant frequency. It was concluded that oral administration of furfural in corn oil at levels of up to 300 mg/kg bw/day is not associated with an increase in the induction of mutations in liver cells of *λlacZ* transgenic mice.

In conclusion, furfural is positive in *in vitro* tests using mammalian cells. Although positive results were found in some of the *Drosophila* tests, the positive *in vitro* findings were not confirmed in *in vivo* tests using rodents. Particularly furfural was not genotoxic in tests measuring direct genotoxic endpoints, *i.e.* chromosome aberrations and gene mutations. Consequently, SCCS concludes that the induction of tumours in long term studies of mice and rats (see section 3.3.7.) are likely due to non-genotoxic mechanisms.

3.3.7. Carcinogenicity

3.3.7.1. Animal studies

Taken from SCCNFP/0822/04, modified

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/day 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 (70%) male controls, 28/50 (56%) at the low dose, 24/50 (48%) at the middle dose and 27/50 (54%) at the high dose; and 33/50 (66%) female controls, 28/50 (56%) at the low dose, 29/50 (58%) at the middle dose and 32/50 (64%) 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 (18%) controls, 13/50 (26%) at the low dose, 11/49 (22%) at the middle dose and 19/50 (38%) at the high dose ($p = 0.008$, logistic regression analysis); the incidences of hepatocellular carcinoma were 7/50 (14%) controls, 12/50 (24%) at the low dose, 6/49 (12%) at the middle dose and 21/50 (42%) at the high dose ($p = 0.001$).

Female mice also had a higher incidence of hepatocellular adenomas, with 1/50 (2%) in controls, 3/50 (6%) at the low dose, 5/50 (10%) at the middle dose and 8/50 (16%) at the high dose ($p = 0.017$); the incidences of hepatocellular carcinoma (4/50 (8%), 0/50 (0%), 2/50 (4%), 4/50 (8%)) were not increased. The combined incidences of hepatocellular adenomas and carcinomas were: 16/50 (32%) male controls, 22/50 (44%) at the low dose, 17/49 (35%) at the middle dose and 32/50 (64%) at the high dose ($p < 0.001$); and 5/50 (10%) female controls, 3/50 (6%) at the low dose, 7/50 (14%) at the middle dose and 12/50 (24%) 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 ($p = 0.058$).

Ref.: 13

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 (62%) male controls, 28/50 (56%) at the low dose and 24/50 (48%) at the high dose; and 28/50 (56%) female controls, 32/50 (64%) at the low dose and 18/50 (36%) 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 (6%) controls, 9/50 (18%; not statistically significant) at the low dose and 12/50 (24%) at the high dose. The necrosis was generally minimal to mild in severity in all groups and affected only scattered lobules in the liver sections. Two of 50 (4%) males given the high dose had bileduct dysplasia, and two had rarely occurring cholangiocarcinomas. The lesions diagnosed as biliary dysplasia and fibrosis were similar to the cholangiocarcinomas. The distinction between this lesion and cholangiocarcinoma is based on the relative degree of proliferation of ductular epithelium and the degree of epithelial anaplasia. It is assumed that this lesion can progress to 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 (0.2%).

Ref.: 13

Conclusions of National Toxicology Program

"Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity* of furfural for male F344/N rats, based on the occurrence of uncommon cholangiocarcinomas in two animals and bile duct dysplasia with fibrosis in two other animals. There was *no evidence of carcinogenic activity* for female F344/N rats that received doses of 0, 30 or 60 mg/kg bw furfural.

There was *clear evidence of carcinogenic activity* for male B6C3F1 mice, based on increased incidences of hepatocellular adenomas and hepatocellular carcinomas. There was *some evidence of carcinogenic activity* in female B6C3F1 mice, based on increased incidences of hepatocellular adenomas. Renal cortical adenomas or carcinomas in male mice and squamous cell papillomas of the forestomach in female mice may have been related to exposure to furfural."

Ref.: 13

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 pseudo-lobule 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.

Ref.: 16

Dermal 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 dimethylsulfoxide 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 dimethylsulfoxide (vehicle control) and TPA, a third with dimethylsulfoxide 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.

Ref.: 17

Evaluation by IARC
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).*

Ref.: 18

General comment
Furfural induced liver tumours in mice. A significant increase in both adenomas and carcinomas was found in male mice and in adenomas in female mice. At the lowest dose of furfural (50 mg/kg bw/d), liver carcinomas occurred in 24% compared to 14% in control (not statistically significant). In male rats at the high dose (60 mg/kg bw/d), uncommon cholangiocarcinomas occurred in two animals and bile duct dysplasia with fibrosis in two other animals (may progress to cholangiocarcinomas. No tumours were found at the low dose (30 mg/kg bw/d). The SCCS consider that the tumours are most likely induced by a threshold mechanism although no threshold could be identified.

3.3.8. Reproductive toxicity

Cited from EU Risk Assessment Report (ref. 11)

"In a developmental toxicity study according to OECD 414, 3 groups of 25 bred Sprague-Dawley female rats were exposed to furfural once daily by gavage from gestation day 6 through 15 (Nemec, 1997b). The dose levels used were 50, 100, and 150 mg/kg bw/day; these dose levels were based on the dose-range finding study. A vehicle control group was included. The vehicle was reverse osmosis-treated water. Between gestation day 6 and 15, 3/25 and 16/25 females died in the mid and high dose group. The number of deaths is relatively high. It exceeds the limit of 10% maternal deaths mentioned in OECD 414, limiting the conclusions based on this study. The NOAEL for maternal toxicity was considered to be less than 50 mg/kg bw/day based on clinical observations (exophthalmia during gestation day 6-18) at all dose levels. No treatment-related effects were found at scheduled necropsy in the mother animals. The NOAEL for developmental toxicity is at least 100 mg/kg bw/day. In the 150 mg/kg bw/day dose group a not statistically significant

reduction in mean foetal body weight (one litter) was observed but this dose level could not be evaluated because of the low survival (only 7 gravid females survived at this dose level). It cannot be excluded that this effect is caused by the maternal toxicity."

Ref.: 19

Comment
SCCS has not had access to this study.

3.3.9. Toxicokinetics

After [carbonyl-^{14}C]Furfural (specific activity, 4.1 mCi/mmol; radiochemical purity, 95%) was administered by gavage to male F344 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 12h, reaching a plateau after 24h. After 72h, 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 ^{14}C-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.

Ref.: 20

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 cm² skin absorbed approximately 3 µg Furfural per min.

Ref.: 21

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, a closer, quantitative comparison of the toxicokinetic profiles of humans and rats is not possible.

Ref.: 21

3.3.10. Photo-induced toxicity

No data submitted

3.3.11. Human data

No data submitted

3.3.12. Special investigations

No data submitted

3.3.13. Safety evaluation (including calculation of the MoS)

The MoS calculation below is based on a concentration limit of 10 ppm furfural in finished cosmetic products including oral products.

According to the Notes of Guidance (7th revision, Ref. 22) a global daily exposure value of 17.4 g/day is used (all cosmetic products, including oral products).

Exposure 17.4 g/day, 10 ppm furfural (17.4 x 1000 x $1x10^{-5}$)	=	0.174 mg/day
Maximum absorption 100% (0.174 x 1)	=	0.174 mg/day
Typical body weight of human	=	60 kg
Systemic exposure dose (SED) (0.174/60)	=	0.0029 mg/kg bw/day
NOAEL, 90 day toxicity study, oral	=	54 mg/kg bw/d
Margin of Safety	**NOAEL / SED (54/0.0029) =**	**18 600**

It should be noted that EFSA has established an ADI of 0.5 mg/kg bw/d for furfural (ref.: 15).

3.3.14. Discussion

Furfural is a naturally occurring substance. It has been identified in a number of food products including fruits, vegetables, beverages, and bread products. Furfural is an ingredient contained in many fragrances and flavours.

Furfural is classified as a CMR substance, category 2 carcinogen (CLP).

Physical/chemical properties
Furfural is a colourless oily liquid with a benzaldehyde-like odour. It is commercially available at a purity > 98%. 5-Methylfurfural is the main impurity.

Irritation, sensitisation
Furfural is considered as a mild skin irritant and irritating to mucous membranes. Furfural is not considered a human sensitiser.

Dermal absorption
No adequate dermal absorption studies are available. After dermal exposure to liquid furfural, about 3 µg furfural per cm² skin per minute was absorbed in humans. In the absence of data relevant for use in cosmetic products, 100% absorption is used in calculation of MoS.

Repeated dose toxicity
No dermal repeated dose toxicity data are available that can be used for the risk characterization. Most repeated dose toxicity studies were performed using the oral route, and gavage as the method of application. NOAELs derived via this methodology varied down to 11 mg/kg bw/d. Due to possible effects of the gavage formulation (corn oil) and dose

regimen (bolus dose) effects observed in the gavage studies, the oral NOAEL of 54 mg/kg bw/day based on slight histopathological changes in liver of males from a 13-week dietary study with rats will be used for calculation of MOS.

Reproductive toxicity
In the EU risk assessment report on furfural (ref 11) it is stated that the NOAEL for developmental effects was at least 100 mg/kg bw/d in Sprague-Dawley rats administered furfural by gavage and that the NOAEL for maternal toxicity was less than 50 mg/kg bw/d.

Toxicokinetics
Furfural is extensively absorbed and rapidly eliminated in humans after inhalation and in rats after oral administration.
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 furanacrylic acid.

Mutagenicity / genotoxicity
Furfural reacts with DNA *in vitro*. Although most bacterial mutagenicity tests were negative, positive results were obtained in some experiments in *S. typhimurium* TA100 and TA104 strains. Furfural was genotoxic in cultured mammalian cells at the gene and chromosome level in the absence of metabolic activation. It induced sister chromatid exchange (SCE) in cultured Chinese hamster ovary (CHO) cells and human lymphocytes. Furfural did not induce unscheduled DNA synthesis (UDS) in human liver slices.

Furfural was genotoxic in Drosophila in somatic cells (wing spot test by inhalation) and germ cells (sex-chromosome loss by injection). It did not induce reciprocal translocations and sex-linked recessive lethal mutations, with only a doubtful increase in one study in Drosophila. Furfural was not genotoxic in any in vivo mammalian assays. The substance was tested for SCE, chromosomal aberration, and sperm head abnormalities in mice and UDS in mouse and rat hepatocytes.

The spectrum of activating mutations in the H-ras gene in tumours from the furfural treated mice was found to differ significantly from that in tumours of untreated animals. This finding may suggest that the novel mutations in ras genes could have resulted from a genotoxic effect of furfural.

Furfural has been examined for its potential to induce gene mutations of the λlacZ-gene in vivo in the liver of male transgenic mice. There was no significant difference in mutant frequency between negative controls and the furfural-treated groups; the positive control group showed a significant increase in mutant frequency. It was concluded that oral administration of furfural in corn oil at levels of up to 300 mg/kg bw/day is not associated with an increase in the induction of mutations in liver cells of *λlacZ* transgenic mice.

In conclusion, furfural is positive in *in vitro* tests using mammalian cells. Although positive results were found in some of the *Drosophila* tests, the positive *in vitro* findings were not confirmed in *in vivo* tests using rodents. Particularly furfural was not genotoxic in tests measuring direct genotoxic endpoints, *i.e.* chromosome aberrations and gene mutations. Consequently, SCCS concludes that the induction of tumours in long term studies of mice and rats mice are likely due to non-genotoxic mechanisms.

Carcinogenicity
Furfural has been studied by US NTP in a two year carcinogenicity study after administration by gavage. Furfural induced liver tumours in mice. Thus, a significantly increase in both adenomas and carcinomas were found in male mice and in adenomas in female mice. At the

lowest dose of furfural (50 mg/kg bw/d), liver carcinomas occurred in 24% compared to 14% in control of the male mice (not statistically significant). In male rats at the high dose (60 mg/kg bw/d), uncommon cholangiocarcinomas occurred in two animals and bile duct dysplasia with fibrosis in two other animals (may progress to cholangiocarcinomas). No tumours were found at the low dose (30 mg/kg bw/d). The SCCS consider that the tumours are most likely induced by a threshold mechanism although no threshold could be identified.

4. CONCLUSION

1. *The SCCS is asked to review the new evidence in relation to the carcinogenicity of furfural and, if necessary, to revise the risk assessment made in SCCNFP opinion SCCNFP/0822/04.*

SCCS has reviewed the new evidence on mutagenicity/genotoxicity in relation to the carcinogenicity of furfural and concludes that the tumours in two year carcinogenicity study by US NTP are likely to be induced by a threshold mechanism.

2. *The SCCS is asked to assess whether furfural can be considered safe for the consumer when used up to the proposed pragmatic concentration limit of 10 ppm in finished cosmetic products (assuming inclusion and exclusion of oral products)*

Based on the new data provided, the SCCS is of the opinion that the use of furfural with a maximum concentration limit of 10 ppm in the finished cosmetic product, including oral products, does not pose a risk to the health of the consumer.

3. *In the case the SCCS concludes that the pragmatic concentration limit of 10 ppm in finished products results cannot be considered safe, it is asked to assess the safety on the basis of the concentrations given in the annexed table (assuming inclusion and exclusion of oral products)*

Not applicable

5. MINORITY OPINION

Not applicable

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