Scientific Committee on Consumer Safety

SCCS

SCIENTIFIC OPINION ON

The Report of the ICCR Working Group: Considerations on Acceptable Trace Level of 1,4-Dioxane in Cosmetic Products

The SCCS adopted this Opinion at its 12th Plenary meeting

on 15 December 2015

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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

The International Cooperation on Cosmetics Regulation (ICCR) is an international group of regulatory authorities for cosmetics from Brazil, Canada, the European Union, Japan, and the United States. This multilateral framework seeks to promote regulatory convergence, while maintaining the highest level of global consumer protection and minimising barriers to international trade.

ICCR has identified the responsible handling of traces of banned substances as a topic of international relevance. As a result, it decided to work on this with a view of aligning on best practice among the ICCR regions, while fully respecting their specific regulatory regimes. To this end, a working group was created, which included experts from the jurisdictions' regulators and industry.

The group prepared a general Report for ICCR on Principles for Handling Traces in Cosmetics [1], which was published in 2011. In addition, among the substances of concern, it selected 1,4-dioxane which was assessed individually in order to identify harmonised best practices across the ICCR regions and to give recommendations.

It should be made clear that these documents have no regulatory status. However, the report on 1,4-dioxane could be used as a supporting reference by market surveillance authorities in the EU and beyond, and as a useful starting point for discussion, should any of the ICCR regulators consider it useful to open a regulatory review.

We asked the SCCS to informally review the report on 1,4-dioxane in order to flag any issues it might detect with the two documents or with the general approach used by the ICCR ad-hoc working group. We received an answer on 7 July 2013 (Ares(2013)2570845), which we shared with ICCR partners and used to review the reports.

While the Traces Working Group recommended a two-step approach with a starting acceptable and safe trace level of 1,4-dioxane at 25 ppm, followed by the phasing-in of a 10 ppm level over a short period of time, the SCCS did not support this approach. The SCCS considered that "trace levels of 1,4-dioxane in cosmetic products representing a LCR < 10-5 is considered safe for the consumer. Thus, a trace level of 1,4-dioxane in cosmetic products of < 10 ppm is safe.

SCCS is of the opinion that a target level of less than or equal to 10 ppm of 1,4-dioxane in finished cosmetic products should be phased in over a short transition period."

In order to report the SCCS' position, we have to refer to the formal SCCS assessment in the report and to quote its findings.

2. TERMS OF REFERENCE

Could the SCCS give its scientific opinion on the "Report of the ICCR Working Group: Considerations on Acceptable Trace Level of 1,4-Dioxane in Cosmetic Products"?

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1 http://iccrnet.org/files/5714/0475/3672/2011-04_ICCR_Principles_for_Handling_Traces_in_Cosmetics.pdf

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3. OPINION

In principle the SCCS disagreed with the Report of the ICCR Working Group: Considerations on Acceptable Trace Level of 1,4-Dioxane in Cosmetic Products.

SCCS is of the opinion that a target level of less than or equal to 10 ppm of 1,4-dioxane in finished cosmetic products should be phased in over a short transition period.

INTRODUCTION

1,4-Dioxane is an impurity that may be present in trace amounts in some cosmetic products. 1,4-Dioxane itself is not used as a cosmetic ingredient but can form as a by-product during the manufacturing process of certain ethoxylated cosmetic ingredients. The mandate of the ICCR Traces WG was to establish and recommend appropriate trace levels based on considerations of scientific risk assessment, good manufacturing practices, technical feasibility, and appropriate analytical methods, keeping in mind the ultimate goal of consumer safety.

1,4-Dioxane is a CMR substance classified in EU as carc. 2 (H351). The aim of the ICCR report was that the level of 1,4-dioxane in cosmetics should be sufficiently low to avoid any risk of cancer. In order to achieve this goal, ICCR recommended that the target level of trace 1,4-dioxane in cosmetics is achieved in two phases by industry:

> *Phase 1:* *A target level of less than or equal to 25 ppm in finished products.*

> *Phase 2:* *A target level of less than or equal to 10 ppm in finished cosmetic products should be phased in over a suitable transition period.*

The aim of the present Informal Opinion is to critically evaluate the carcinogenic risk in relation to the presence of traces of 1,4-dioxane in cosmetics.

Chemistry
CAS-No.:   123-91-1
EINECS-No.:   204-661-8
IUPAC name: 1,4-dioxane
Molecular formula: $C_4H_8O_2$
Molecular weight: 88
Structural formula:

Physical form: Liquid
Melting point: 12^oC
Boiling point: 101^oC
Relative density: 1.034
Vapour pressure: 40 hPa at 20^oC
Water solubility: Miscible   in   all   mixtures
Partition coefficient (Log Pow) :   -0.27
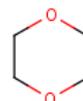
Carcinogenicity

Evidence of Genotoxicity
It is concluded in the EU RAR (EU, 2002) on 1,4-dioxane that *"Although there are some indications that 1,4-dioxane may be weakly genotoxic, 1,4-dioxane is considered a non-genotoxic compound based on the total weight of evidence. This is further supported by the absence of DNA-adducts at hepatotoxic doses."*

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SCCS Comment
SCCS concur with the conclusion in the EU RAR report.

Evidence of Carcinogenicity
1,4-Dioxane has been investigated in a number of long-term carcinogenicity studies on rodents (Table 1).

Table 1. *Carcinogenicity studies with 1,4-dioxane (Taken from EU, 2002)*

Study type	Duration	Result	Reference
Mice 0.5 or 1% in drinking water	90 weeks	liver damage, pneumonia/rhinitis hepatocellular carcinomas	NCI, 1978
Mice 0.05, 0.2 or 0.8% in drinking water	104 weeks	damage to nasal cavity, lungs, kidney hepatocellular carcinomas/adenomas	Yamazaki *et al.*, 1994; Japan Bioassay Research Center, 1998
Rats 1% in drinking water (equivalent to 1g/kg bw/d)	63 weeks	potential for kidney damage and liver tumours	Argus *et al.*, 1965
Rats 0.75, 1.0, 1.4 or 1.8% in drinking water	13 months	kidney damage nasal and liver carcinomas	Hoch-Ligeti *et al.*, 1970; Argus *et al.*, 1973
Rats 0.01, 0.1 or 1.0 % in drinking water	716 days	kidney and liver damage nasal and liver carcinomas	Kociba *et al.*, 1974
Rats 0.5 or 1% in drinking water	110 weeks	damage to liver, kidney, stomach, pneumonia/ rhinitis	NCI, 1978; Goldsworthy *et al.*, 1991
Rats 0.02, 0.10 or 0.50% in drinking water	104 weeks	damage to nose, liver, kidney nasal carcinomas; liver carcinomas/adenomas	Yamazaki *et al.*, 1994; Japan Bioassay Research Center, 1998
Rats 400 mg/m^3 by inhalation	2 years	slight increase in lymphoreticular cell sarcomas in males and mammary gland adenomas in females	Torkelson *et al.*, 1974
Guinea pig 0.5-2% in drinking water	23 months	kidney and lung damage potential for liver and gall bladder tumours	Hoch-Ligeti and Argus, 1970

Mouse studies (oral)

NCI, (1978)
In a drinking water experiment, groups of 50 male and 50 female B6C3F1 mice were exposed to 0, 0.5, and 1% 1,4-dioxane for 90 weeks. The mean doses were 720 and 830 mg/kg bw/day for males and 380 and 860 mg/kg bw/day for females. In both sexes an increased incidence in hepatocellular carcinomas was seen. The incidences were in males 2/49 (4%, control), 18/50 (36%, 720 mg/kg bw/d) and 24/47 (51%, 830 mg/kg bw/d) and in females 0/50 (0, control), 12/48 (25%, 380 mg/kg/d) and 29/37 (78%, 860 mg/kg

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bw/d). The incidences of hepatocellular adenomas plus carcinomas were in males 8/49 (16%, control), 19/50 (38%, 720 mg/kg bw/d) and 28/47 (60%, 860 mg/kg bw/d) and in females 0/50 (0%, control), 21/48 (44% 380 mg/kg bw/d) and 35/37 (95%, 860 mg/kg bw/d).

Yamazaki *et al.* (1994); Japan Bioassay Research Center (1998)[2]
Groups of 50 male and 50 female mice Crj:BDF1 were exposed to 0, 0.05, 0.2, and 0.8% 1,4-dioxane in drinking water for 104 weeks. The mean doses were 0, 66, 250 or 770 mg/kg bw/d for males and 0, 77, 320 or 1070 mg/kg bw/d for females. The animals were sacrificed after 105 weeks.
Necropsy and histopathology were performed on all animals, including dead and moribund animals. The survival of females at the 0.2 and 0.8% groups was significantly lower than those of the controls (17/50 and 5/50 vs 29/50, respectively) due to liver tumours. Mean body weights of females at 0.2 and 0.8% and males at 0.8% were lower than those of controls. In males, effects on haematology, biochemistry or urinalysis parameters were observed at 0.8%, ≥0.2% and 0.8%, respectively. In females, this occurred at ≥0.2%. In males, lesions were also observed in liver (angiectasis) at 0.8% and in testis (decreased mineralisation) at ≥0.2%.
Hepatocellular carcinomas occurred with significantly increased incidences in males at 0.8% and in all treated female groups (incidence in males was 15/50 (30%, control), 20/50 (40%, 0.05%), 23/50 (45%, 0.2%) and 36/50 (72%, 0.8%) and in females 0/50 (control), 6/50 (12%, 0.05%), 30/50 (60%, 0.2%), and 45/50 (90%, 0.8%). Increased incidences of hepatocellular adenomas were also seen in males 7/50 (14%, control) 16/50 (32%, 0.05%), 22/50 (44%, 0.2%), and 8/50 (16%, 0.8%), and females 4/50 (8% control), 30/50 (60%, 0.05%) 20/50 (40%, 0.2%),and 2/50 (4%, 0.8%).

Table 2. *Hepatocellular tumours*

Sex	Results			
Male	0% Control	0.05% 66 mg/kg bw/d	0.2% 250 mg/kg bw/d	0.8% 770 mg/kg bw/d
Adenomas	7/50 (14%)	16/50 (32%)	22/49 (44%)	8/50 (16%)
Carcinomas	15/50 (30%)	20/50 (40%)	23/50 (46%)	36/50 (72%)
Female	0% Control	0.05% 77 mg/kg bw/d	0.2% 320 mg/kg bw/d	0.8% 1070 mg/kg bw/d
Adenomas	4/50 (8%)	30/50 (60%)	20/50 (40%)	2/50 (4%)
Carcinomas	0/50 (0%)	6/50 (12%)	30/50 (60%)	45/50 (90%)

Rat studies (oral)

Argus *et al.* (1965)
In a drinking water study, 26 Wistar rats received 300 mg 1,4-dioxane/animal (equivalent to 1000 mg/kg bw/day) for 63 weeks. A control group of 6 animals was used. There are no data available about the control group. This study was not performed according to current guidelines; however, the results show a potential for kidney damage and liver tumours.

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[2] This study is described in more details as it is used in the LCR calculations. As the original publications have not been available the above text represents a summary of the text from the EU RAR.

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Hoch-Ligeti et al. (1970). Argus et al. (1973)
Groups of 30 male Charles River CD rats were given daily via the drinking water 0, 0.75, 1.0, 1.4 or 1.8% 1,4-dioxane (equal to 0, 750, 1,000, 1,400 or 1,800 mg/kg bw/day) for 13 months. Tumours of the nasal cavity occurred in 0/30, 1/30, 1/30, 2/30 and 2/30 rats of the control, 0.75, 1.0, 1.4 or 1.8% groups, respectively. A dose-dependent increase in liver tumours (nodules and hepatomas) was found. In the control group, 0 nodules were seen, in the 0.75% group, 4, in the 1.0% group, 9, in the 1.4% group, 13 and in the 1.8% group 11 (absolute figures are missing). Hepatomas were seen in the 1.4 and 1.8% group; which amounted to 3 and 12, respectively. Furthermore, marked kidney damage was seen at all dose levels. No data were available about mortality. The study was not performed according to current guidelines.

Kociba *et al*. (1974)
Groups of 60 male and 60 female Sherman rats received via the drinking water 0, 0.01, 0.1 or 1% 1,4-dioxane (equal to 0, 9.6, 94 or 1015 mg/kg bw/day for males and 0, 19, 148 or 1,599 mg/kg bw/day for females) for 716 days. The concentration of 1% 1,4-dioxane led within two to four months to a severe reduction of survival rates in both sexes. The survival rate after four months was essentially the same for all groups. Only in the highest dose group treatment-related tumours were found: in the liver, carcinomas were found in 10/66 (15%) animals surviving at 12 months and cholangiomas in 2/66 (3%) animals, while squamous cell carcinomas of the nasal cavities were found in 3/66 (5%) animals. Histopathological examination revealed variable degrees of renal tubular epithelial and hepatocellular degeneration and necrosis, accompanied by regenerative activities in the liver (hepatocellular hyperplastic nodule formation) and renal tubuli in rats at 0.1 and 1.0% 1,4-dioxane. It is stated that the NOAEL in the study was 0.01% 1,4-dioxane, equal to 9.6 or 19 mg/kg bw/d in males and females, respectively.

NCI (1978)
Groups of 35 male and 35 female Osborne-Mendel rats were exposed via the drinking water to 0, 0.5 and 1% 1,4-dioxane for 110 weeks. The mean dose levels were 0, 240, and 530 mg/kg bw/day for male rats and 0, 350, and 640 mg/kg/bw/day for female rats. Non-neoplastic lesions associated with dioxane treatment were observed in the kidney (tubular degeneration), liver (cytomegaly) and stomach (ulceration). Rats of both sexes developed squamous cell carcinomas in the nasal cavities (0/33 [0%, control], 12/33 [36%, 240 mg/kg bw/d], and 16/34 [47%, 530 mg/kg bw/d] in males and 0/34 [0%, control], 10/35 [29% 350 mg/kg bw/d] and 8/35 [23%, 640 mg/kg bw/d] in females). An increase in hepatocellular adenomas was also seen in females. The incidence was 0/31 (0%, control), 10/33 (30%, 350 mg/kg bw/d) and 11/32 (34%, 640 mg/kg bw/d).

Yamazaki *et al*. (1994), Japan Bioassay Research Center (1998)
In a drinking water study, groups of 50 male and 50 female rats (F344/DuCrj) were administered 1,4-dioxane for 104 weeks. The dose levels were 0, 0.02, 0.1 or 0.5% in drinking water (equal to 0, 16, 81 or 398 mg/kg bw/d for males and 0, 21, 103 or 514 g/kgbw/d for females. After 105 weeks the animals were sacrificed. The survivals of males and females at 0.5% were significantly lower than those of the control group (22/50 vs 40/50 and 24/50 vs 38/50, respectively) due to nasal and liver tumours. Upon histopathology, non-neoplastic lesions were observed in the nasal cavity, liver and kidney of in males at 0.02% or greater groups, and in females at 0.1% or greater groups. Malignant neoplasms of the nasal cavity occurred only in 0.5% males and females, not in controls and 0.02 and 0.1% animals. These tumours included squamous cell carcinoma (3/50 [6%, 398 mg/kg bw/d] for males and 7/50 [14%, 514 mg/kg bw/d] for females). Hepatocellular adenomas and carcinomas occurred with significantly increased incidences in high dose males and females. Hepatocellular adenomas were seen at low incidences in males at 0.02 and 0.1% and in females at 0.1% (see Table 3) The incidence of non-neoplastic lesions in the liver (including spongiosis and hyperplasia) was increased at 0.1 and 0.5% in both males and females. It was considered that 0.02% 1,4-dioxane in drinking water (equal to 16 mg/kg bw/d) represented a LOAEL.

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Table 3. *Hepatocellular tumours*

Sex	Results			
Male	0% Control	0.02% 16 mg/kg bw/d	0.1% 81 mg/kg bw/d	0.5% 398 mg/kg bw/d
Adenomas	0/50 (0%)	2/50 (4%)	4/49 (8%)	24/50 (48%)
Carcinomas	NA	NA	NA	14/50 (28%)
Female	0% Control	0.02% 21 mg/kg bw/d	0.1% 103 mg/kg bw/d	0.5% 514 mg/kg bw/d
Adenomas	1/50 (2%)	0/50 (0%)	5/50 (10%)	38/50 (78%)
Carcinomas	NA	NA	NA	10/50 (20%)

NA; no data available

Rat study (inhalation)

Torkelson *et al*. (1974)
A group of 288 male and 288 female Wistar rats was exposed to air containing 400 mg 1,4-dioxane vapor/m^3 for 7 hours/day, five days a week for a total of 2 years. A dosage of 108 mg/kg bw/day was calculated. A control group of 192 rats/sex was used. Upon gross and microscopic examination, no 1,4-dioxane characteristic nasal and liver tumours were seen. It is however not clear from the text whether or not the nasal cavity was adequately examined. For neoplastic effects, the NOAEL appears to be 400 mg/m^3, as there was no increase in tumour incidence and no gross pathological or histopathological evidence of organ injury.

Guinea pigs, oral

Hoch-Ligeti and Argus (1970)
In a limited study, a group of 22 guinea pigs was exposed for 23 months to drinking water containing 1,4-dioxane in concentrations that ranged from 0.5 to 2.0%. An untreated control group was used. Nine treated animals developed peri- or bronchial and nodular mononuclear infiltration in the lung. In addition 2 guinea pigs developed gall bladder carcinomas, three had early hepatomas and one had an adenoma of the kidney. In the control animals, 4/10 guinea pigs developed peripheral mononuclear cell accumulation and hyperplasia of the bronchial epithelium was observed in one. This study was not performed according to current guidelines; however, the results show some indication for liver and gall bladder tumours.

Kinetics and metabolism in laboratory animals and in humans
(Text taken from WHO 2004)
1,4-Dioxane is well absorbed via the oral and inhalation routes. In rats, more than 95% is taken up from the gastrointestinal tract following administration of up to 1000 mg/kg of body weight. Complete absorption was indicated in rats following exposure by inhalation to 180 mg/m3 for 6 h, compared with a maximum of 80% in humans. Uptake (on a mg/kg of body weight basis) is approximately 5–8 times greater in rats than in humans (Young et al., 1977, 1978).
No data are available on dermal uptake of 1,4-dioxane in humans, although about 3% of applied 1,4-dioxane was absorbed over a 24-h period in non-human primates under non-occluded conditions (Marzulli et al., 1981). *In vitro* human skin studies indicate that 3.2% of

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an applied dose passes through excised skin with occlusion and 0.3% under non-occluded conditions. The high volatility of 1,4-dioxane in air is likely to account for these differences (ECETOC, 1983).

Animal studies have shown that 1,4-dioxane is distributed to the blood, liver, kidney, spleen, lung, colon and skeletal muscle, with selective uptake in liver and kidney (Mikheev et al., 1990; DeRosa et al., 1996). Covalent binding was found to be significantly higher in the liver, spleen and colon than in other tissues. PBPK modelling by Reitz et al. (1990) predicted that the area under the curve liver values for humans would be lower than those for rats or mice continuously exposed to low concentrations of 1,4-dioxane in air or water. Metabolic rate constants developed for rats in a PBPK model were Km = 29.4 mg/litre and Vmax = 13.7 mg/kg of body weight per hour (Reitz et al., 1990). Those for humans were Km = 3.0 mg/litre and Vmax = 6.35 mg/kg of body weight per hour.

The main metabolite in animals and humans is β-hydroxyethoxyacetic acid (HEAA). Other metabolites determined in animal studies include 1,4-dioxan-2-one, β-hydroxyethoxyacetaldehyde, diethylene glycol, oxalic acids and carbon dioxide. Unchanged 1,4-dioxane is excreted in the urine and expired air (DeRosa et al., 1996).

Young et al. (1978) demonstrated the pharmacokinetics of 1,4-dioxane in rats to be dose dependent. Oral doses of 10, 100 and 1000 mg of [14C]1,4-dioxane per kg of body weight administered to rats resulted in about 99%, 85% and 75% of radiolabelled metabolites in urine and approximately 0.5%, 5% and 25% in expired air as 1,4-dioxane, respectively. Excretion in faeces (1–2%) and expired carbon dioxide (2–3%) was not affected by the dosage. With low oral or intravenous doses of 3 and 10 mg/kg of body weight, elimination of 1,4-dioxane from plasma was linear, with a half-time of 1.1 h; above 30 mg/kg of body weight, plasma clearance was characterised by non-linear kinetics. Because pulmonary and renal clearance rates were not significantly different between low and high doses, saturation is thought to be associated with biotransformation rather than elimination. The authors estimated that metabolism of 1,4-dioxane in rats is saturated at plasma levels above 100 mg/ml.

Inhalation exposure of rats to 1,4-dioxane at 180 mg/m3 for 6 h resulted in about 99% being excreted as HEAA. At the end of the exposure, the elimination half-time of 1,4-dioxane from plasma was 59 min. The excretion half-time of HEAA was 2.7 h, and its renal clearance was 121 ml/min. Renal clearance of 1,4-dioxane was 0.34 ml/min, compared with a metabolic clearance of 75 ml/min. Steady-state plasma levels following inhalation at 180 mg/m3 were similar in humans and rats: 10 mg/ml and 7.3 mg/ml, respectively. Simulation of repeated daily exposure to 180 mg/m3 for 8 h per day indicated that 1,4-dioxane would never accumulate to concentrations above those attained after a single 8-h exposure (Young et al., 1977).

In summary, 1,4-dioxane is rapidly absorbed and metabolised and does not accumulate in the body, but metabolism to HEAA is dose dependent, becoming saturated at high doses.

Conclusion

1,4-Dioxane is classified in EU as a carcinogen category 2 (*Suspected of causing cancer),* by IARC as a group 2B carcinogen *(The agent is possibly carcinogenic to humans)* based on *Sufficient evidence of carcinogenicity in animals* and *Inadequate evidence of carcinogenicity in humans* and by US EPA in group B2 *(Probable human carcinogen).* US National Institute for Occupational Safety and Health (NIOSH) consider 1,4-dioxane to be potential occupational carcinogen.

1,4-Dioxane is considered a non-genotoxic compound, and a threshold approach may be justified for risk assessment if a threshold can be identified. The liver tumours are considered to be associated with cytotoxicity, which may be explained by reactive metabolites such as HEAA and its related metabolite, β-hydroxyethoxyacetaldehyde. Whereas toxicokinetics and metabolism in rats (and humans) have been well investigated, corresponding studies in mice are missing. It is therefore not clear whether a similar threshold mechanism in mice based on metabolism can be assumed as it has been suggested for rats. A NOAEL of 9.6 or 10 mg/kg bw/d was used in the ICCR Report based on the considerations from Canada, Europe, Australia and partly Japan. This value is based on the rat study by Kociba *et al.* (1974). They found cytotoxic effects in the liver and kidney

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after exposure to 0.1 and 1.0% 1,4-dioxane in the drinking water, but no effect at 0.01%. (9.6 or 19 mg/kg bw/d in males and females, respectively).

SCCS Comment
SCCS does not concur with the use of a NOAEL of 9.6 or 10 mg/kg bw/d in cancer risk assessment of 1,4-dioxane.
In the rat study by Yamazaki *et al*. (1994) and Japan Bioassay Research Center (1998), non-neoplastic lesions were observed in the nasal cavity, liver and kidney of males receiving 0.02% or more 1,4-dioxane in the drinking water. Moreover, hepatocellular adenomas were seen at low incidences in males receiving 0.02% (16 mg/kg bw/d) of 1,4-dioxane in drinking water (Control 0/50 [0%], 0.02% 2/50 [4%], and 0.1% 4/49 [8%]). The authors considered 16 mg/kg bw/d as a LOAEL. Thus, although a threshold in relation to tumour induction by 1,4-dioxane may be likely, the data do not allow it to be identified.
SCCS notes that in the REACH requirements it is stated that (ECHA, 2012) *"It is to be noted that the decision on a threshold and a non-threshold mode of action may not always be easy to make, especially when, although a biological threshold may be postulated, the data do not allow identification of it. If not clear, the assumption of a non-threshold mode of action would be the prudent choice."*
SCCS will, in agreement with US EPA and EPA of the state of California, calculate life-time cancer risk (LCR). This calculation will, in accordance with REACH (ECHA, 2012), the scientific committees of DG Sanco (SCHER/SCCP/SCENIHR, 2009), and the SCCS's Notes of guidance for testing of cosmetic substances and their safety evaluation (SCCS, 2012a), be made on the basis of T25 and linear extrapolation.

Cancer hazard
The T25 is used as the default dose-descriptor in relation to the determination of LCR by linear extrapolation. It is recognised, though, that linear extrapolation may in some cases result in overestimation of risks at low exposures, but this may be acceptable from a precautionary principle standpoint.
The dose-descriptor T25 is defined as the chronic dose rate that will give 25% of the animals tumours at a specific tissue site after correction for spontaneous incidence, within the standard life time of that species. It is a value calculated from a single observed dose-response and based upon the assumption of a linear dose-response relationship over the dose-range (Dybing *et al*., 1997).
Calculation of LCR is described by ECHA (EU, 2012), SCCS (2012a) and by Sanner *et al*., 2001). The results from the oral mice study of Yamazaki *et al*. (1994), Japan Bioassay Research Center (1998) described above are used.

Calculation of T25

Female mice

Remarks on study:
         species, strain: female mice Crj:BDF1
         route: oral, drinking water
          tumour: hepatocellular carcinomas
Lowest dose with a significant increased tumour incidence:
        Hepatocellular carcinomas
        Control: 0/50 (0%)
        77 mg/kg bw/day: 6/50 (12%) [significant, p<0.03]

        T25 after 104 weeks:
        T25 = 104/104 x 105/104 x 77 x 25/12 mg/kg bw/day = 162 mg/kg bw/d.

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According to Guidelines for setting specific concentration limits for carcinogens in Annex I of Directive 67/548/EEC, 1,4-dioxane can be considered as a low potency carcinogen[3].

Lifetime cancer risk levels

The metabolic scaling factor for mice to humans on the basis of a default body weight of female mice of 25 g and of humans of 60 kg becomes: $(60/0.025)^{0.25} = 7.0$.

$$HT25 = (162/7.0) = 23 \text{ mg/kg bw/day}$$

Lifetime cancer risk (LCR) can be calculated from HT25 if the exposure dose, denoted EXP, is known from the formula:

$$LCR = \frac{Exp}{HT25/0.25}$$

Although there is no EU legislation setting a "virtually safe dose" or an "acceptable" or a "tolerable"' risk level for carcinogens in the society, cancer risk levels have been set and used in different contexts.

WHO (2008) recommends in general that the LCR for exposure to a carcinogenic contaminant in drinking water and air should be 10^{-5} or less. The EU Scientific Committee on Consumer Safety (SCCS, 2012b) has recently considered a LCR of 10^{-5} as a tolerable risk level. This will be at about the same level as that considered to be of little concern on relation to regulation of carcinogens in food (EFSA, 2005) (MoE 10 000 based on BDML10 or 25 000 based on T25, corresponding to a LCR of less than $3 - 7 \times 10^{-5}$).

It should be noted that in a population of 5 million, about 27 500 persons are diagnosed with cancer every year. An LCR of 10^{-5} would result in 1 additional person with cancer per 1½ year in case the whole population is exposed during its whole lifetime assuming an average lifetime of 75 years[4]. On a personal basis, the smoking of 30 cigarettes during the lifetime (1/2 cigarette per year for 60 years [age 16 to age 76]) will theoretically result in a LCR of 10^{-5}. Due to the low sensitivity of epidemiological studies, calculated LCR of less than 10^{-3} can in general not be verified.

In the present Informal Opinion, a LCR of 10^{-5}, will be considered as a tolerable risk in relation to exposure from 1,4-dioxane in cosmetics. It should be noted, however, that the decision of an acceptable/tolerable or less than serious risk is in the end a risk management decision.

Exp = LCR x HT25/0.25

Thus, a LCR = 10^{-5} represents an exposure of (Exp = 10^{-5} x 23/0.25) 9.2×10^{-4} mg/kg bw/d = 0.92 µg/kg bw/d, or assuming a body weight of 60 kg *55 µg 1,4-dioxane per day.*

In the calculations of LCR performed by the EPA of the state of California it was found that a LCR = 10^{-5} was obtained after a lifelong daily dose of *30 µg 1,4-dioxane* (based on a body weight of 70 kg). Their calculations were based on the incidence of squamous cell carcinoma of the nasal cavities in male Osborne-Mendel rats from the study by NCI (1978). The tumours may be related to direct contact with 1,4-dioxane at the site of tumour formation due to inhalation of 1,4-dioxane evaporating from the drinking water and may thus be of less relevance than the liver tumours of the mice.

The small difference between the present calculations of 55 µg 1,4-dioxane per day and the calculations by the Californian EPA of 30 µg 1,4-dioxane per day, although based on different animal species (mice versus rats) and different tumour sites (liver versus nose), lends confidence to the calculations.

Exposure

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[3] EC: *Guidelines for setting specific concentration limits for carcinogens in Annex 1 of directive 67/548/EEC. Inclusion of potency considerations.* Commission working group on the classification and labelling of dangerous substances. Brussel, 1999.
[4] Number of cancer cases = (LCR x Number exposed)/Lifetime = 10^{-5} x 5.10^6 / 75

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Maximum tolerable levels

1,4-Dioxane is rapidly and almost completely absorbed after oral and inhalation exposure by rats. For dermal absorption no quantitative conclusions can be drawn. However, it can be concluded that skin absorption occurs. In an *in vitro* study it was demonstrated that 1,4-dioxane can penetrate human skin when occluded, but evaporates rapidly from human skin when not occluded. In the EU RAR on 1,4-dioxane (EU, 2002) 100% absorption was chosen for the oral and inhalatory route, and 50% for the dermal route for the risk assessment The latter is chosen as default because the limited data available indicate that 100% absorption would also be a worst-case assumption for the volatile compound 1,4-dioxane. A 3.4% dermal absorption was found by Marzulli *et al*. (1981). This study has, however, been seriously criticised (EU, 2002).

1,4-Dioxane can occur as an impurity, as it is formed as a reaction by-product in the manufacture of ethoxylated substances (particularly surfactants and emulsifiers). These substances are used in food, cosmetic, agricultural and veterinary, therapeutic, household and varied industrial applications. A survey undertaken by *National Industrial Chemicals Notification and Assessment Scheme* (NICNAS) in Australia indicated a widespread public exposure to 1,4-dioxane from a variety of consumer products including cosmetics/toiletries, household detergents, pharmaceuticals, foods, agricultural and veterinary products, and ethylene glycol-based antifreeze coolants (NICNAS, 1998).

From the limited quantitative data available on 1,4-dioxane levels in pharmaceuticals (100-380 ppm), agricultural and veterinary products (<<10 ppm), and ethylene glycol-based antifreeze coolants (0.1-22 ppm), and taking into account the use pattern and volatility, it was concluded by NICNAS that consumer exposure from these sources would be negligible (NICNAS, 1998). This is also true for consumer exposure to foods, in which 1,4-dioxane occurs either naturally or as an impurity (<10 ppm) from a number of permitted ethoxylated food additives, such as polysorbates (NICNAS, 1998). 1,4-Dioxane has been identified in a number of natural products including shrimp, chicken, tomatoes, coffee and certain condiments (Hartung, 1989). Although no data are available on the level of 1,4-dioxane in these natural products, it is expected to be low.

The available safety assessments pertaining to 1,4-dioxane by different agencies' / organisations are summarised in Table 4. The daily exposure levels have been calculated by dermal + inhalation exposure (or only exposure) and safety assessed on the basis of NOAEL /LOAEL, or LCR.

Table 4. *Summary of Safety Assessment for 1,4-diaxane (modified from ICCR)*

Agency/Organization	Daily exposure level considered safe*	Comments
Canada – CMP assessment	85 µg/day	Aggregate exposure, 100% inhalation, 3.4% dermal absorption. Based on LOAEL/NOAEL
Europe	217 µg/day	Aggregate exposure, 3 scenarios, 100% inhalation, 50% dermal absorption. Based on NOAEL
Australia	420 µg/day	Aggregate exposure from up to 10 products. Based on NOAEL
Japan	4.3 µg/day	General population exposure estimation using Monte Carlo simulation.Based on MOE from NOAEL

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California (Proposition 65)	30 µg/day	Based on LCR of 10^{-5}
SCCS	55 µg/day	Based on LCR of 10^{-5}

*Based on both cosmetic products and household products

Occurrence of 1,4-dioxane in cosmetic products
The ICCR report includes a section on _Consideration of reasonably achievable levels of 1,4-dioxane in cosmetic products._ In this section analyses of 1,4-dioxane, the contamination of cosmetics has been presented.
FDA (Roderic _et al.,_2001) published a peer-reviewed summary report on their experience analysing cosmetic raw materials and finished products over a period of 16 years using two different methods of analysis. In 1981, 11 products were analysed. 8 products contained 1,4-dioxane (range 2 – 279 ppm) at an average level of 50 ppm. In their analyses from 1997 of 10 products, 6 contained 1,4-dioxane (range 6-34 ppm) and the average level had been reduced to 19 ppm.
The ICCR report does also contain an updated summary were FDA (Hardy _et al.,_ 2010) had analyzed 35 products. 28 of the products (80%) did not contain 1,4-dioxane (detection level 1 ppm). Three products (9%) contained ≥10.1 ppm 1,4-dioxane. The highest level found was 11.6 ppm 1,4-dioxane (it has not been possible to identify the 3 products).
The Organic Consumers Association (2008) analysed 87 cosmetic products. 57 products (66%) contained ≤1 ppm 1,4-dioxane. 6 products product (7%) contained ≥10.1 ppm 1,4-dioxane. One of the six products contained 32.2 ppm 1,4-dioxane, the other 5 products contained between 10.1 and 25.0 ppm dioxane (it has not been possible to identify the 6 products).
The Campaign for Safe Cosmetics (2009) presented the results of analyses of 48 baby and children's products for 1,4-dioxane. 26 products (54%) contained ≤1 ppm 1,4-dioxane. 4 products product (8%) contained ≥10 ppm 1,4-dioxane. One of the four products contained 32.2 ppm 1,4-dioxane (a shower gel), the other 3 products contained between 10.1 and 25.0 ppm dioxane (2 shower gels contained 14 and 18 ppm, respectively, one "bubble bath" contained 11 ppm 1,4-dioxane).
The results of the 170 products are summarised in Table 5.

Table 5. _Consolidation of the data from the 170 cosmetic and household products analysed for 1,4-dioxane (modified from ICCR, 2012)_

Levels Reported	Number of Products	Percent of Total
0.0 – 1.0 ppm	111	65 %
1.1 – 5.0 ppm	32	19 %
5.1 – 10.0 ppm	14	8 %
10.1 – 25.0 ppm	11	6 %
> 25.1 ppm	2 (32.2, 35.0 ppm)	1 %

It appears that 99% of the products contained ≤ 25 ppm 1,4-dioxane. Two products (1%) contained >25.1 ppm 1,4-dioxane. One of these was a shower gel, the other has not been identified. 11 products (6%) contained between 10.1 and 25.0 ppm 1,4-dioxane. Only 2 of these products, have been identified, one shower gel and 1 "bubble bath". It is known that at least 4 of the 11 products contained ≤11 ppm 1,4-dioxane.
Calculation of total exposure if all cosmetic products contained 10 ppm 1,4-dioxane (92% of the products studied contained ≤10 ppm 1,4-dioxane). The aggregate exposure to

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cosmetics is assumed to be 17.4 g per day (SCCS, 2012a). Thus, 10 ppm will represent 174 µg. Assuming 50% dermal absorption this will represent a systemic dose of 87 µg/d. In this calculation, inhalation exposure is not included. However since about 2/3 (65%) of all cosmetic products analysed contained ≤ 1 ppm, the total daily exposure of 1,4-dioxane will probably be considerably less than 87 µg and the lifetime cancer risk from 1,4-dioxane in cosmetics will probably be < 10^{-5} and should be considered tolerable.

It is noted that in Germany, the BUA (Beratergremium für umweltrelevante Altstoffe) suggested already in 1992/94 a residual 1,4-dioxane content in cosmetics/toiletries and household detergents of 10 mg/kg (10 ppm) as a value capable of being attained and a target to be aimed for (BUA, 1992/1994).

SCCS Comment
SCCS is of the opinion that trace levels of 1,4-dioxane in cosmetic products representing a LCR ≤ 10^{-5} is considered safe for the consumer. Thus, a trace level of 1,4-dioxane in cosmetic products of ≤10 ppm is safe.

On the basis of measurements of 1,4-dioxane over time and the more recent measurements discussed above, a level of ≤10 ppm 1,4-dioxane in cosmetic products seems achievable to day.

SCCS do not concur with the considerations of ICCR to regulate the reduction of 1,4-dioxane by two phase targets. SCCS is of the view that "*A target level of less than or equal to 10 ppm in finished cosmetic products should be phased in over a short transition period*".

4. CONCLUSION

SCCS is of the opinion that trace levels of 1,4-dioxane in cosmetic products representing a LCR ≤ 10^{-5} is considered safe for the consumer. Thus, a trace level of 1,4-dioxane in cosmetic products of ≤10 ppm is safe.

SCCS is of the opinion that *a target level of less than or equal to 10 ppm of 1,4-dioxane in finished cosmetic products should be phased in over a short transition period.*

5. MINORITY OPINION

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