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

CONCERNING

MUSK XYLENE AND MUSK KETONE

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

1. Terms of Reference

1.1. Context of the question

The SCCNFP adopted by its plenary session of 8 December 1999 opinions concerning Musk xylene (SCCNFP/0163/99) and Musk ketone (SCCNFP/0162/99). Based on these opinions Musk ketone and Musk xylene were proposed to be regulated within the 26th Commission Directive.

In the meeting of the Committee for Adaptation to Technical Progress of Directive 76/768/EEC on Cosmetic Products (CAPT) in July 2001 it was decided to include the two substances in Annex III, part 2 with a time limit of 18 months until a full risk assessment of these substances in the framework of Council Regulation (EEC) No 793/93 on evaluation and control of the risks of existing substances has been finalised.

Commission Directive 2003/16/EC of 19 February 2003 postponed the deadline from 28.02.2003 to 30.09.2004 as the risk assessment (monitored by European Chemicals Bureau DG JRC) had not been finalized by 28.02.2003.

At the same time Enterprise DG asked industry whether new data on Musk ketone and Musk xylene were available.

Meanwhile Enterprise DG received a literature review on nitromusks containing full copies of all publications on nitromusks between the last submission to the SCCNFP in 1999 and November 2003.

During the 41st plenary meeting of 8 January 2004 the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) adopted an opinion on the results of the Risk Assessment of MUSK XYLENE HUMAN HEALTH PART and ENVIRONMENTAL PART as well as MUSK KETONE HUMAN HEALTH PART and ENVIRONMENTAL PART that were carried out in the framework of Council Regulation (EEC) 793/93 on the evaluation and control of the risks of existing substances.

1.2. Request to SCCNFP

The SCCNFP is requested to answer the following questions:

* Does the SCCNFP consider that Musk ketone and Musk xylene can be used safely in cosmetic products taking into account recent scientific literature and the risk assessment carried out in the framework of Council Regulation 793/93?

* If yes, does the SCCNFP propose any restrictions or conditions for its use in cosmetic products?

* So does the SCCNFP confirm its previous opinion of 8 December 1999 or does it consider necessary to change it?

1.3. Statement on the toxicological evaluation

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

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

2. Chemical and Physical Specifications

2.1. Chemical identity

Musk xylene

2.1.1. Primary name and/or INCI name

Musk xylene

2.1.2. Chemical names

IUPAC name : 1-tert-butyl-3,5-dimethyl-2,4,6-trinitrobenzene
Synonyms : 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitrobenzene
5-tert-butyl-2,4,6-trinitroxylene

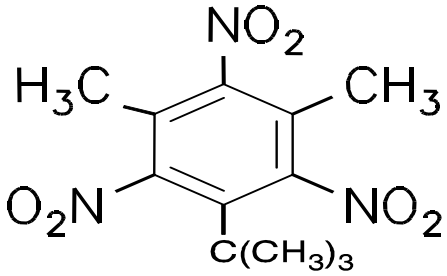
2.1.3. Trade names and abbreviations

None

2.1.4. CAS / EINECS number

CAS : 81-15-2
EINECS : 201-329-4

2.1.5. Structural formula



2.1.6.	Empirical formula

Emp. Formula : $C_{12}H_{15}N_3O_6$
Mol weight : 297.27

2.1.7.	Purity, composition and substance codes

No data

2.1.8.	Physical properties

Appearance : pale yellow crystals or fine crystalline powder
Melting point : 114°C
Vapour pressure : <0.1 mm Hg at 20 °C (< 10 Pa)
Flash point : > 100 °C

2.1.9.	Solubility

In water: practically insoluble

Musk ketone

2.2.1.	Primary name

Musk ketone

2.2.2.	Chemical names

IUPAC name : 4-tert-butyl-3,5-dinitro-2,6-dimethylacetophenone
Synonyms : 3,5-Dinitro-2,6-dimethyl-4-tert-butylacetophenone
Ethanone, 1-[4-(1,1-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]

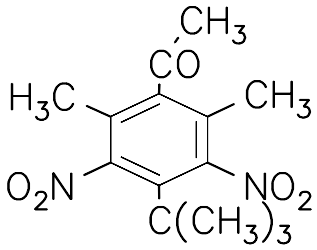
2.2.3.	Trade names and abbreviations

None

2.2.4. CAS / EINECS number

CAS : 81-14-1
EINECS : 201-328-9

2.2.5. Structural formula



2.2.6. Empirical formula

Emp. Formula : $C_{14}H_{18}N_2O_5$
Mol weight : 294.3

2.2.7. Purity, composition and substance codes

No data

2.2.8. Physical properties

Appearance : pale yellow crystals
Melting point : 137°C
Vapour pressure : <0.001 mm Hg at 20 °C
Flash point : > 100 °C

2.2.9. Solubility

In water: practically insoluble

3. Function and Uses

Musk xylene is provisionally allowed to be used up to 1.0 % in fine fragrance, up to 0.4 % in eau de toilette and up to 0.03 % in other cosmetic products, Musk ketone provisionally allowed to be

used up to 1.4 % in fine fragrance, up to 0.56 % in eau de toilette and up to 0.042 % in other cosmetic products (26th Commission Directive 2002/34/EC of 15 April 2002 and Commission Directive 2003/14/EC of 19 February 2003).

Musk xylene and Musk ketone are also found in non-cosmetic products such as household cleaners and detergents.

4. Toxicological Evaluation

Since SCCNFP adopted at its plenary session of 8 December 1999 opinions concerning Musk xylene (SCCNFP/0163/99) and Musk ketone (SCCNFP/0162/99), two reports have been published indicating that amines formed by reduction of musk xylene and musk ketone are weak estrogens and are persistent in the environment (discussed in section 4.8. Reproductive toxicity). Other new relevant reports that would influence the toxicological characterisation have not been found.

Risk Assessment Reports (RAR) on the two substances has been prepared in accordance with Council Regulation (EEC) 793/93. The Commission Working Group on the Classification and Labelling of Dangerous Substances has later concluded that the substances should be classified as carcinogens category 3.

In the RARs the risk characterisations in relation to the carcinogenic effect have been performed assuming that a threshold exist for the carcinogenic effect. SCCNFP does not consider that the evidence for establishing a threshold is sufficient for using this approach.

Only the risk characterisation in relation to carcinogenicity and the two new reports concerning possible estrogenic effects will be discussed in the toxicological evaluation. Otherwise it is referred to the Opinions from 1999.

4.1. Acute toxicity

No new data

4.2. Irritation and corrosivity

No new data

4.3. Skin sensitisation

No new data

4.4. Dermal / percutaneous absorption

No new data

4.5. Repeated dose toxicity

No new data

4.6. Mutagenicity / genotoxicity

No new data

4.7. Carcinogenicity

4.7.1. Animal studies

The data below was included in the Opinion from 1999, but is repeated as they are used in the final risk characterization (the old reference numbers are used):

- In a carcinogenicity study performed in 1990, Musk xylene (purity >60%) was fed ad lib to groups of 50 male and 50 female SPF B6C3 F1 mice at concentration doses of 0, 0.075% or 0.15% for 80 weeks. Afterwards the animals were maintained on basal diet until week 90 when all survivors were killed. Dietary intakes were on the average 91 and 170 mg/kg bw/d for males and on the average 101 and 192 mg/kg bw/d for females in low and high dose groups, respectively. The overall tumour incidence in all treated groups of both sexes were significantly higher than those in the corresponding control group. Malignant and benign liver cell tumours were clearly increased. In males, the incidence of Harderian gland tumours was also significantly greater in both treated groups than in controls.

Musk xylene intake had a significant inhibitory effect on growth in high dose males and this was apparent from week 4 to week 80. In female, no significant difference in growth occurred throughout the experiment. There was no significant difference in cumulative mortality between controls and treated males and females. Complete histopathological examination was carried out on all animals. Increased tumour incidences were observed in the liver and Harderian gland.

Table 1: Summary of main neoplastic lesions in B6C3F1 mice given Musk xylene in the diet for 80 weeks

Tumour site and type	Number of male mice with tumours			Number of female mice with tumours		
Dose	0 %	0.075 %	0.15 %	0 %	0.075 %	0.15 %
Effective number of mice	49	50	47	46	50	49
Liver						
Adenoma	9	19*	20**	1	14***	13***
Carcinoma	2	8*	13**	0	1	2
Adenoma/carcinoma	11	27**	33***	1	15***	15***
Harderian gland						
Adenoma	2	9*	10*	3	3	5
Carcinoma	1	1	0	0	0	0
Adenoma/carcinoma	3	10*	10*	3	3	5

* $p < 0.05$, **$p < 0.01$, ***$p< 0.001$

Ref.: 1/16

4.7.2. Special investigations

One study of special relevance in the discussion whether a threshold exists in tumour induction is retained from the Opinion of 1999.

- Musk xylene was dosed by gavage in 1997 to male B6C3F1 mice for 7 days at 0, 1, 5, 10, 20, 50, 100, and 200 mg/kg after which microsomes were prepared. Mice were treated with phenobarbital (0.05% in drinking water for 5 days), and then given a single dosage of corn oil or Musk xylene (200 mg/kg) at 2 or 18 hr before necropsy. In a separate group phenobarbital-induced mice were orally dosed with a regimen of broad spectrum antibiotics. Musk xylene is a phenobarbital-like inducer of cytochrome P-450 enzymes and may cause liver tumours in a manner analogous to phenobarbital. No increase in CYP2B enzyme activity was observed. When the intestinal flora was eliminated, Musk xylene no longer inhibited the CYP2B enzymes.

Ref.: 34/50

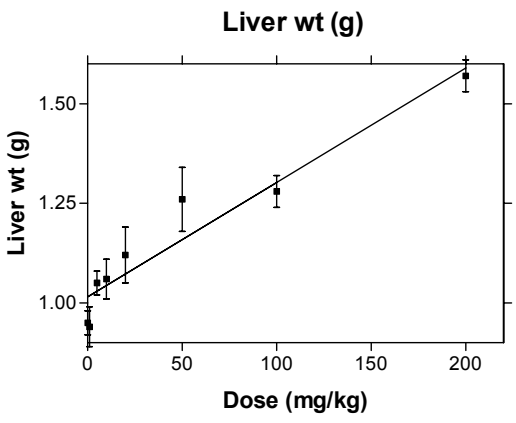
Comment
Table 2 is taken from the above reference. On the basis of these data, the RAR on Musk xylene and Musk ketone uses a threshold approach for risk characterisation regarding carcinogenicity. On the basis of the carcinogenicity study a LOAEL of 70 mg/kg/d is used. Assuming 50% oral absorption, an internal low-effect dose of 35 mg/kg/d is used for LOAEL.

Table 2: General hepatic effects of Musk xylene treatment (Ref.: 34/50)

Dose (mg/kg)	**Liver wt.** (g)	***L/BW*** (%)[a]	**Microsomal protein** (mg/g liver)	**Total cytochrome P-450** (nmol/mg protein)
0	0.95 ± 0.03	3.85 ± 0.06	7.00 ± 0.41	1.09 ± 0.04
1	0.94 ± 0.05	3.90 ± 0.07	7.54 ± 0.53	1.01 ± 0.05
5	1.05 ± 0.03	4.06 ± 0.15	7.55 ± 0.49	1.12 ± 0.07
10	1.06 ± 0.05	4.47 ± 0.23	6.76 ± 0.56	1.11 ± 0.13
20	1.12 ± 0.07*	4.38 ± 0.15	8.70 ± 0.51	1.56 ± 0.11*
50	1.26 ± 0.08*	4.81 ± 0.18*	10.10 ± 0.48*	1.88 ± 0.14*
100	1.28 ± 0.04*	5.13 ± 0.14*	14.37 ± 1.11*	2.16 ± 0.14*
200	1.57 ± 0.04*	6.35 ± 0.14*	17.05 ± 3.06*	2.24 ± 0.23*

[a] Liver to body weight ratio, with liver weight expressed as a percentage of total body weight.
* Statistically different from control ($p < 0.05$).

The results show that the lowest doses giving a significant increase in the hepatic effects vary between 20 and 50 mg/kg/d.



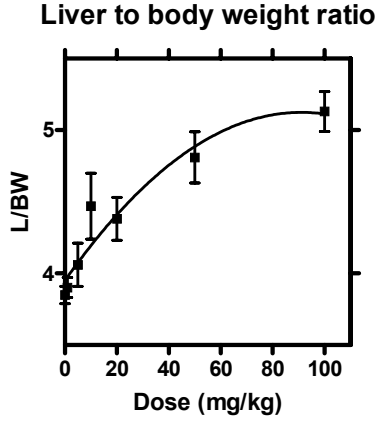
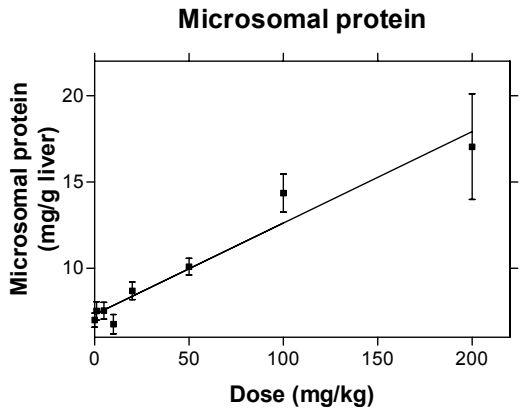


Fig. 1 *Liver weight versus dose.*

Fig. 2 *Liver to body weight versus dose.*



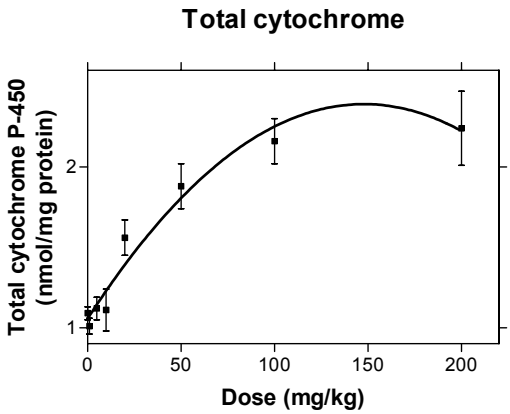


Fig. 3 *Microsomal protein versus dose.*

Fig. 4 *Total cytochrome versus dose.*

In figs 1 – 4 the data in Table 2 have been plotted. It is seen that a threshold cannot be identified with certainty for any of the parameters. However, from the biochemical data in Table 2, 10 mg/kg/d may be considered as a NOAEL. Thus, the risk characterization in the present opinion will be based both on MOS considerations and on the assumption of non-threshold by the T25 method.

4.8. Reproductive toxicity

No new data

4.9. Toxicokinetics

No new data

4.10. Photo-induced toxicity

No new data

4.11. Human data

No new data

4.12. Special investigations

Two articles have been published suggesting that Musk xylene and Musk ketone may be able to act as endocrine disrupters.

The competitive binding capability of Musk xylene, 4-aminomusk xylene, 2-aminomusk xylene and 2-aminomusk ketone to the oestrogen receptors in rainbow trout and xenopus was investigated. No binding of Musk xylene or Musk ketone to the oestrogen receptors of either species was observed. In contrast, binding to the oestrogen receptors was observed for the three amino metabolites in both species.

Ref.: A

Musk xylene, Musk ketone, 2-aminomusk xylene, 4-aminomusk xylene and 2-aminomusk ketone have been tested in the E-screen assay using human MCF-7 cells. A statistical significant increase in proliferation rate of human MCF-7 breast cancer cells were detected for Musk xylene and Musk ketone as well as for 4-aminomusk xylene. This indicates that these substances do demonstrate estrogenic activity *in vitro*. Co-incubation with the anti-oestrogen tamoxifen shows that the increase in proliferation rate by the musk fragrances is oestrogen receptor-mediated. It should be noted that the effective estrogenic strength and estrogenic potency were low compared to 17β-estradiol. 2-Aminomusk xylene and 2-aminomusk ketone were not estrogenically active.

Ref.: B

4.13. Safety evaluation

Musk xylene

Industry provided a table (Table 3), which has been reproduced from Opinion 163/99 with the exception, that the "Application frequency per day" has been changed according to the SCCNFP's Notes of guidance for the testing of cosmetic ingredients and their safety evaluation, 5th revision (SCCNFP/0690/03 Final). As a consequence, the calculated total exposure is about 10% higher than given in Opinion 163/99. This does not change the Opinion.

It is considered that the range of cosmetic products selected covers all those that are likely to be used in any one weekly period.

Table 3: *Calculation of Exposure to Musk xylene in Cosmetic Products*

Type of	Application	Application	Retention	Fragrance	Musk xylene	Musk xylene	Exposure to	Exposure to

cosmetic product	quantity in grams per application	frequency per day [c]	factor [d] (%)	compound in product [e] (%)	in fragrance compound [f] (%)	in product (%)	Musk xylene (mg/day)	Musk xylene for 60 kg person (µg/kg/day)
Body lotion	8	1	100	0.4	7.1	0.028	2.27	37.9
Face cream [a]	0.8	2	100	0.3	7.1	0.021	0.34	5.7
Eau de toilette [b]	0.75	1	100	8.0	7.1	0.568	4.26	71.0
Fragrance cream	5	0.29	100	4.0	7.1	0.284	4.12	68.6
Anti-perspirant /deodorant	0.5	1	100	1.0	7.1	0.071	0.36	5.9
Shampoo	8	1	10	0.5	7.1	0.036	0.29	4.8
Bath products	17	0.29	1	2.0	7.1	0.142	0.07	1.2
Shower gel	5	2	10	1.2	7.1	0.085	0.85	14.2
Toilet soap	0.8	6	10	1.5	7.1	0.107	0.51	8.6
Hair spray	5	2	10	0.5	7.1	0.036	0.36	6.0
						Total [g]		**223.9**

[a] Including make up and foundation

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

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

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

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

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

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

Risk assessment

MOS approach

$$MoS = \frac{NO(A)EL}{SED}$$

NOAEL = 10 mg/kg/d (see page 9)

Exposure dose 223.9 µg/kg/d. Absorption 10%

SED = 22 µg/kg/d.

MOS = 10/0.022 = 455

Lifetime cancer risk (T25 method)
The tumours induced in the mice may be caused by a non-genotoxic mechanism indicating the presence of a threshold dose below which no tumours are induced. However, it is not possible from the available data to identify NOAELs for tumour induction or for the underlying mechanisms.

Quantitative risk characterisation has been carried out on the basis of the T25 method.

Ref.: C

Male mice, liver carcinomas
Control 2/49
91 mg/kg/d 8/50
net 12.4% (Harderian gland 15%)

Dosed 80 weeks, killed after 90 weeks

T25 = 91 x 25/12.4 x 80/104 x 90/104 = 122 mg/kg/d

HT25 = 122/6.7 = 18.2 mg/kg/d

$HT10^{-4}$ = 18.2/0.25 $x10^{-4}$ = 7.3 µg/kg/d

Lifetime exposure dose representing a lifetime cancer risk of 10^{-4} was about 7.3 µg/kg bw/d both when based on the liver carcinomas or the Harderian gland tumours in male mice. As the worst case daily intake of Musk xylene is about 22 µg/kg bw/day, it follows that this intake could represent a lifetime cancer risk of about 3 x 10^{-4}. Taken into consideration that only one animal carcinogenicity study in one species is available, that it is likely that the tumours are induced by a non-genotoxic mechanism and that a threshold may be present, the calculated risk is considered tolerable.

Musk ketone

Industry provided a table (Table 4), which has been reproduced from Opinion 162/99 with the exception, that the "Application frequency per day" has been changed according to the SCCNFP's Notes of guidance for the testing of cosmetic ingredients and their safety evaluation, 5th revision (SCCNFP/0690/03 Final). As a consequence, the calculated total exposure is about 10% higher than given in Opinion 162/99. This does not change the Opinion.

It is considered that the range of cosmetic products selected covers all those that are likely to be used in any one weekly period.

Table 4: *Calculation of Exposure to Musk ketone in Cosmetic Products*

Type of cosmetic product	Application quantity in grams per application	Application frequency per day [c]	Retention factor [d] (%)	Fragrance compound in product [e] (%)	Musk ketone in fragrance compound [f] (%)	Musk ketone in product (%)	Exposure to Musk ketone (mg/day)	Exposure to Musk ketone for 60 kg person (µg/kg/d)
Body lotion	8	1	100	0.4	6.9	0.028	2.21	36.8
Face cream [a]	0.8	2	100	0.3	6.9	0.021	0.33	5.5
Eau de toilette [b]	0.75	1	100	8.0	6.9	0.552	4.14	69.0
Fragrance cream	5	0.29	100	4.0	6.9	0.276	4.00	66.7
Anti-perspirant /deodorant	0.5	1	100	1.0	6.9	0.069	0.35	5.8
Shampoo	8	1	10	0.5	6.9	0.035	0.28	4.7
Bath products	17	0.29	1	2.0	6.9	0.138	0.07	1.1
Shower gel	5	2	10	1.2	6.9	0.083	0.83	13.8
Toilet soap	0.8	6	10	1.5	6.9	0.104	0.50	8.3
Hair spray	5	2	10	0.5	6.9	0.035	0.35	5.8
						Total [g]	**12.03**	**217.5**

[a] Including make up and foundation

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

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

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

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

[f] The concentration of a fragrance ingredient in a fragrance mixture is based on data obtained by the fragrance industry from the examination of commercialized formulations containing the fragrance ingredient. The concentration used corresponds to the upper 97.5th percentile concentration of the fragrance ingredient in fragrance mixtures, a concentration which is in itself

maximized because the products not containing the fragrance ingredient were not included as zero values in the distribution of samples.
[g] Total consumer exposure to the fragrance ingredient is determined by adding figures for the different product types expressed as mg/kg body weight/day. In view of all the above assumptions, this figure has to be regarded as conservative; it is most unlikely that a consumer will consistently use a number of different cosmetic products which are all perfumed with the upper 97.5th percentile level of the fragrance ingredient.

Risk assessment

The risk assessment for Musk ketone is based on the same experiments as for Musk xylene.

NOAEL = 10 mg/kg/d

$HT10^{-4}$ = 7.3 µg/kg/d

MOS approach

Exposure dose 217.5 µg/kg/d. Absorption 14%

SED = 30 µg/kg/d.

MOS = 10/0.030 = 333

Lifetime cancer risk (T25 method)

$HT10^{-4}$ = 7.3 µg/kg/d

Lifetime exposure dose representing a lifetime cancer risk of 10^{-4} was about 7.3 µg/kg bw/d both when based on the liver carcinomas or the Harderian gland tumours in male mice exposed to Musk xylene. As the worst case daily intake of Musk ketone is about 30 µg/kg bw/day, it follows that this intake could represent a lifetime cancer risk of about 4 x 10^{-4}. Taken into consideration that only one animal carcinogenicity study in one species is available, that it is likely that the tumours are induced by a non-genotoxic mechanism and that a threshold may be present, the calculated risk is considered tolerable.

4.14. Conclusions

Musk xylene and Musk ketone have low acute and subchronic toxicity. Musk xylene is mildly irritating under occlusion on human skin. Musk xylene and Musk ketone is not irritating on rabbit skin and eye. Musk ketone has weak photoirritating potential in the guinea-pig skin.
Musk xylene and Musk ketone have a sensitising potential in the guinea-pig. Musk xylene has a weak photoallergic effect. Human experience is limited with both substances.

Musk xylene and Musk ketone have been tested for genotoxicity. All assays developed according to international protocols have produced results that demonstrate the absence of genotoxicity potential.

Musk xylene (purity >96%) was carcinogenic in B6C3F1 mice when given at dose levels of 0.075% and 0.15% in the diet for 80 weeks. The overall tumours incidence in all treated groups of both sexes were significantly higher than those in the corresponding control group: malignant and benign liver cell tumours were clearly increased; in males the incidence of Harderian gland tumours was also significantly greater in both treated groups than in the controls. No carcinogenic effect was observed in other organs. In the absence of genotoxicity, the induction of CYP2B enzymes could possibly explain the increased formation of the liver tumours. No thresholds for tumour induction in mice have been identified. Biochemical *in vivo* studies on mice with Musk xylene suggest a NOAEL of 10 mg/kg/d.

No carcinogenicity study is available for Musk ketone. It has been found, however, that Musk ketone like Musk xylene induced CYP2B enzymes. Consequently, Musk ketone might be a mice carcinogen.

Absorption, distribution, and excretion of Musk xylene and Musk ketone have been investigated *in vitro* and *in vivo*, in animals and in human skin. Based on *in vivo* studies in human under simulated exposure conditions less than 0.3% and 0.5% was absorbed of Musk xylene and Musk ketone, repectively, but 10% of Musk xylene and 14% of Musk ketone were unaccounted. Considering these variations an estimate of 10% absorption of Musk xylene and 14% absorption of Musk ketone is retained for the safety evaluation

Musk xylene and musk ketone may have a weak endocrine disruptor activity *in vitro*.

Musk xylene and Musk ketone are present in human fat and excreted in human milk. The available data indicate that the levels have decreased since 1993, probably due to reduced exposure.

4.15. References

List of references from the SCCNFP/0163/99

Titles of studies relative to Musk Xylene Dossier.
The first number corresponds to the order where documents are quoted in the report
The second number refers to the COLIPA submission

Ref 1/16 : MAEKAWA et al : Long-term toxicity/carcinogenicity of Musk Xylol in B6C3F$_1$ mice. Fd.Chem.Toxicol. **28** 581 - 586 (1990).

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5. Opinion of the SCCNFP

On review of the information presently available, it is the opinion of the SCCNFP that Musk xylene can be safely used in cosmetic products, excluding oral care products, up to a maximum concentration in the final product of 1% in fine fragrances, 0.4% in eau de toilette and 0.03% in other products and Musk ketone can be safely used in cosmetic products, excluding oral care products, up to a maximum concentration in the final product of 1.4 % in fine fragrances, 0.56% in eau de toilette and 0.042 % in other products.

The above has been formulated only on review of the cosmetic use of Musk xylene and Musk ketone. For the full safety assessment of Musk xylene and Musk ketone, it is necessary to consider other sources of consumer exposure from non-food products e.g., laundry products. Exposure from other sources is described in the RAR of the two substances that were carried out in the framework of Council Regulation (EEC) 793/93.

SCCNFP confirm its previous opinions 99/162 and 99/163 of 8 December 1999 and does not consider it necessary to change it.

6. Other Considerations

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7. Minority opinions

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