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Institute for Health and Consumer Protection
European Chemicals Bureau
I-21020 Ispra (VA) Italy

4'-TERT-BUTYL-2',6'-DIMETHYL-3',5'-DINITROACETOPHENONE (MUSK KETONE)

CAS No: 81-14-1

EINECS No: 201-328-9

Summary Risk Assessment Report

2005 **Special Publication I.05.14**

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SUMMARY RISK ASSESSMENT REPORT

Final report, 2005

The Netherlands

Rapporteur for the risk assessment of 4’-tert-butyl-2’,6’-dimethyl-3’,5’-dinitroacetophenone (musk ketone) is the Ministry of Housing, Spatial Planning and the Environment (VROM) in consultation with the Ministry of Social Affairs and Employment (SZW) and the Ministry of Public Health, Welfare and Sport (VWS). Responsible for the risk evaluation and subsequently for the contents of this report, is the rapporteur.

The scientific work on this report has been prepared by the Netherlands Organisation for Applied Scientific Research (TNO) and the National Institute for Public Health and the Environment (RIVM), by order of the rapporteur.

Contact point:
Chemical Substances Bureau
P.O. Box 1
3720 BA Bilthoven
The Netherlands

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Final report:	**2005**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance 4'-tert-butyl-2'6'-dimethyl-3',5'-dinitroacetophenone (musk ketone) that has been prepared by The Netherlands in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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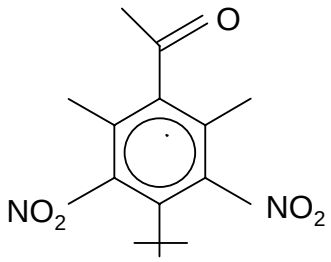
1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 81-14-1
EINECS Number: 201-328-9
IUPAC Name: 4'-tert-butyl-2',6'-dimethyl-3',5'-dinitroacetophenone
Synonyms: [4-(1,1-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl] ethanone,musk ketone
Molecular weight: 294.3
Molecular formula: $C_{14}H_{18}N_2O_5$
Structural formula:



1.2 PURITY/IMPURITIES, ADDITIVES

Purity: >98.5%
Impurities: musk xylene, <1.5%
Additives: none

1.3 PHYSICO-CHEMICAL PROPERTIES

In **Table 1.1** the physico-chemical properties of musk ketone are summarised.

Table 1.1 Summary of physico-chemical properties

Property	Result	Comment
Physical state	solid, powder	
Melting point	135-137°C	*
Boiling point	not applicable	**
Relative density	0.73 g/cm^3	*
Vapour pressure	0.27 Pa at 50°C, 7.6 Pa at 80°C 0.00004 Pa (calculated) at 20°C Recommended: 0.00004 Pa at 20°C	*
Surface tension	not applicable	&
Water solubility	0.46 mg/l (measured) 1.9 mg/l (calculated) Recommended: 0.46 mg/l	*
Solubility in other solvents	-	
Partition coefficient n-octanol/water (log value)	4.3, 3.8, 3.2 (measured) 3.78, 4.3 (calculated) Recommended: 4.3	* #
Flash point	>168°C	*
Flammability	not flammable	*
Autoflammability temperature	not applicable	***
Explosive properties	not explosive	*
Oxidising properties	not oxidising	***
Granulometry	100% v/v < 200 μm 22.1% v/v < 10 μm 13.5% v/v < 4 μm	*

* One or several values found in literature, all in the same range, not all methods are specified.
** Not applicable, decomposition starts at 250°C.
*** Conclusion based on theoretical, and/or structural considerations.
& The low water solubility renders further determinations as superfluous.
# Recommended value based on test report.

Data on boiling point, surface tension, and oxidising properties were not provided. In view of the nature of the substance, determination of these parameters is considered to be irrelevant. All other required physico-chemical data were submitted. Most of these data are based on information from databases, material safety data sheets, or general published information. Only the particle size distribution, the relative density and one measured value for the water/octanol coefficient are based on test reports.

All data are considered as sufficiently reliable to fulfill the Annex VIIA requirements. The substance propagates burning but may be considered not flammable on account of the high flashpoint and the limited effect in the explosive burning test.

1.4 CLASSIFICATION AND LABELLING

Current classification according to Annex 1

No classification.

Decision of the TC C&L

The Meeting of the Technical Committee C&L on the Classification and Labelling of Dangerous Substances in June 2002 (environment) and January 2003 (human health) recommended the following classification and labelling:

Classification

Carc. Cat. 3, R40
N;R50-53

Labelling

Xn; N
S(2)-36/37-46-60-61
R40-50/53

Explanation:

Carc. Cat. 3, R40	Limited evidence of carcinogenic effect.
N;R50-53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Xn; N	Harmful; Very toxic to aquatic organisms.
S(2)-36/37-46-60-61	Keep out of the reach of children-Wear suitable protective clothing and gloves-If swallowed, seek medical advice immediately and show this container or label-This material and its container must be disposed of as hazardous waste-Avoid release to the environment. Refer to special instructions/Safety data sheets.

2 GENERAL INFORMATION ON EXPOSURE

Production

There is no production of musk ketone in the European Union (EU). Several European companies have terminated their productions in the last decade. Producers in China are now the most important source for the European imports.

Uses

The imported crystalline solid is used as an ingredient in fragrance compositions. Fragrances are complex mixtures, prepared by blending many fragrance ingredients in varying concentrations. They are nearly always liquids, in which musk ketone has to be dissolved. Musk ketone is partly used in cosmetic products and partly in detergents, fabric softeners, household cleaning products and other fragranced products.

The EU import volume for musk ketone amounts to 35 tonnes/year (year 2000).

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General

Musk ketone may be released into the environment during its compounding into the fragrance, the formulating of the fragrance into end products and the use of those end products (private use).

General characteristics of musk ketone which are relevant for the exposure assessment are given below.

Abiotic degradation

Studies on hydrolysis of musk ketone are not available. Based on the structure of the compound it is assumed that hydrolysis does not take place.

Photolysis of musk ketone was studied under experimental conditions. Based on these data and on structural grounds it can be concluded that photolysis of musk ketone occurs. However, extrapolation of these results to a field situation is difficult, e.g. UV radiation intensity decreases with the depth of the water. In addition, in eutrophic surface waters algae and humic substances will adsorb most of the UV radiation. The estimated DT50 for photodegradation for reaction with OH-radicals also indicates that this is not a major degradation route. Therefore, in the environmental risk assessment no photodegradation will be assumed.

Biotic degradation

Based on the experimental test results a biodegradation rate constant of 0 hr^{-1} could be assumed as musk ketone is not inherently biodegradable. The use of the BIOWIN model for estimating aerobic biodegradability also points to the lack of biodegradation of musk ketone. However, the amino reaction products have been measured in substantial amounts in effluents showing that primary degradation of musk ketone occurs in an STP. As the formation of these metabolites has not yet been shown in laboratory experiments and there are no quantitative data on biodegradation kinetics, the PECs for musk ketone will be calculated assuming a biodegradation rate constant of 0 hr^{-1}.

Distribution

Using a vapour pressure of $0.04 \cdot 10^{-3}$ Pa and a water solubility of 0.46 mg/l a Henry's law constant of 0.026 $Pa.m^3/mol$ is calculated.

Using the measured log K_{ow} of 4.3 a log Koc of 3.58 L/kg can be estimated using the TGD equation for predominantly hydrophobics. This results in the following partition coefficients:

- $K_{soil\text{-}water}$: 115 m^3/m^3;
- $K_{susp\text{-}water}$: 96 m^3/m^3;
- $K_{sed\text{-}water}$: 96 m^3/m^3.

The calculated solids-water partition coefficient for suspended matter is 383 l/kg (organic carbon content: 10%).

EUSES (SimpleTreat) estimates the following default distribution for musk ketone in a STP: air: 0%, water: 68% and sludge: 32%.

Bioaccumulation

The BCF fish can be calculated using the QSAR mentioned in the TGD. Using a log K_{ow} of 4.3 a BCF of 920 L/kg is obtained. In addition to the calculated BCF a number of experimental data are available for musk ketone. An experimental BCF value of 1,380 l/kg will be used in the risk assessment.

No experimental data are available on accumulation in earthworms. Therefore, the BCF earthworm is estimated according to the TGD QSAR: 3.6 kg/kg.

3.1.2 PECs at processing and private use

The environmental exposure assessment of musk ketone will be based on the expected releases of the substance during the following life cycle stages:

I Fragrance compounding (five compounding sites)
II Formulation into end products
III Private use

Local PECs for the above-mentioned scenarios were calculated based on the TGD principles using both default information and site-specific data.

For calculating the PECs at the regional scale only the emissions due to private use are taken into account. At such scale emissions from compounding sites and end product formulation are negligible compared to those from private use.

In addition to these estimated PECs also a number of local and regional monitoring data are available for musk ketone in various environmental compartments (mainly water and fish). The monitoring data set comprises various EU regions (esp. musk ketone levels in biota) and that the set also contains data from before 1994. Such 'old' data may be representative for those EU regions where at present no legal restrictions on the use of nitromusks have been taken.

3.2 EFFECTS ASSESSMENT

Aquatic compartment (incl. sediment)

For the determination of the PNEC both short and long-term toxicity test results studies are available. The 72 hour-growth test with algae and the 21-day-reproduction test for *Daphnia magna* are considered long term tests. The 21-day-fish growth test for musk ketone is considered to be a test on chronic effects as well. An assessment factor of 10 is applied to the lowest of three NOECs leading to a $PNEC_{water}$ of 6.3 µg/l (A tentative PNEC of 1 µg/l could be derived on the basis of the Acartia and Nitocra studies).

No experimental data are available for sediment organisms. Via the equilibrium partitioning theory, a $PNEC_{sed}$ of 0.5 mg/kg ww is calculated

For micro-organisms one test was available with bacteria where no effects were observed at the highest test concentration of 0.37 mg/l. However, according to the TGD these tests with photoluminescent bacteria can not be used for deriving a $PNEC_{STP}$. From the test on inherent biodegradability a NOEC of > 39 mg/l could be derived. Applying an assessment factor of 10 leads to a $PNEC_{STP}$ of >3.9 mg/l. It is realised that this PNEC is higher than the water solubility of musk ketone of 0.46 mg/l.

Terrestrial compartment

For musk ketone two long-term toxicity tests are available: for a shredder (4 weeks, springtail) and a detritivorous species (8 weeks, earthworm), allowing an assessment factor of 50 to be applied to the lowest NOEC. This lowest NOEC should first be normalised to the standard soil defined in the TGD. This leads to a value of 11 mg/kg dw. Subsequently, applying the assessment factor of 50 gives a $PNEC_{soil}$ of 0.22 mg/kg dw.

Atmosphere

No data available.

Non compartment specific effects relevant to the food chain

No toxicological data are available for (top-) predators. The PNEC for secondary poisoning will therefore be based on mammalian toxicity data for musk ketone. The oral NOAEL of 2.5 mg/kg bw/day for postnatal toxicity in rats is used for this purpose. An AF of 150 is subsequently used as a reasonable 'compromise' between 90 and 300. The $PNEC_{oral}$ then becomes: $2.5 \cdot 20/150 = 0.3$ mg/kg food.

3.3 RISK CHARACTERISATION

3.3.1 General

Table 3.1 presents the local PEC/PNEC ratios for the various relevant life cycle stages of musk ketone. Details will be discussed in the following sections.

Table 3.1 Local PEC/PNEC ratios

	STP	Surface water	Soil	Soil alternative*	Fish	Worm	Worm alternative*
Site 1	< 0.01	0.02-0.03	<0.01-0.01	<0.01	0.5	<0.1	<0.1
Site 2	< 0.01	0.02	<0.01	<0.01	0.5	<0.1	<0.1
Site 3	n.r	0.02	<0.01	<0.01	0.5	<0.1	<0.1
Site 4	< 0.01	0.02	0.06	0.06	0.5	0.15	<0.1
Site 5	< 0.01	0.02	<0.01	<0.01	0.5	<0.1	<0.1
end product formulation	<0.01	0.08	0.29	0.29	1	0.41	0.35
private use	< 0.01	0.1	0.5	0.1	1.8	0.65	0.16

* Based on maximum sludge concentration of 2 mg/kg dwt

Aquatic compartment (incl. sediment)

From **Table 3.1** it can be seen that all aquatic PEC/PNEC ratios are below 1: **conclusion (ii)**. This conclusion is confirmed by measured data as all the available aquatic monitoring data are below the calculated PEC. This conclusion holds also for the regional assessment. The same conclusion would be true if the tentative PNEC water of 1 µg/l would be used.

PEC/PNEC ratios for sediment based on calculated PECs are similar to those for surface water. In addition, however, also measured concentrations are available. Sediment levels in the rivers Elbe, Rhine and Meuse, being comparable to a regional scale, lead to a PEC/PNEC

less than one: **conclusion (ii)**. For fragrance compounding (formulation), end product formulation (local scale) and private use (local scale) no aquatic monitoring data were available. Terrestrial compartment

Atmosphere

A risk characterisation for the atmosphere is not considered relevant for this purpose as there are no experimental data and also no indications of either biotic or abiotic effects.

Terrestrial compartment

For the compounding sites 1-5, end product formulation scenario, private use and the regional scenario the PEC/PNEC for soil is ≤ 1, both in the default and alternative scenario:
conclusion (ii).

Non compartment specific effects relevant to the food chain

All PEC/PNEC ratios for fish eating predators are found to be below 1, except for the private use scenario (**Table 3.1**). The calculated PEC/PNECs for the private use scenario can be overruled, however, by using the rather large regional monitoring data set for fish from a number of different EU regions. All these measured values are much lower than the maximum calculated value of 600 µg/kg dwt (private use). The set also contains data from before 1994 which may represent those regions in which reduction measures were (possibly) not yet taken for this compound. Several data are also available for which both the sampling year (before 1994) and the location (effluent pond) reflect a worst case situation. Therefore a **conclusion (ii)** is considered most appropriate for the private use, the five compounding and the end product formulation scenarios.

For worm-eating animals the PEC/PNEC ratios are <1: **conclusion (ii)**.

Metabolites of musk ketone

A limited risk assessment has been carried out for the major metabolites of musk ketone. Overall, a **conclusion (ii)** is considered most relevant for musk ketone metabolites in the environment.

PBT assessment

Musk ketone is considered not to be a PBT candidate substance. Although the Persistence criterion seems to be fulfilled (one experimental biodegradation test clearly showing no (ready) biodegradability, accompanied by some inconclusive influent/effluent studies and the BIOWIN model results), the Bioaccumulation criterion is not met as the experimental BCF is below 2000. The Toxicity-criterion would be a borderline case for ecotoxicity with the tentative NOECs of 10 µg/l for Acartia and Nitocra. The T-criterion in the TGD is that long-term NOECs should be less than 10 µg/l. For human health toxicity, the situation around musk ketone fulfilling the T-criterion is not clear yet. This is because the CMR group has decided that more information should/could be provided about the potential carcinogenicity (R40?). The outcome of this discussion on carcinogenicity has no influence on the final PBT assessment for musk ketone, as the B-criterion is not met.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

Occupational exposure

Musk ketone is widely used in consumer products like toiletries, colognes, shampoos, laundry detergents and cleaning agents. The concentration of musks in these end products varies largely and may be up to 1%.

The substance is not produced within the EU, but imported from China. Inside the EU the pure substance is used in fragrance compounding.

The substance, a crystalline material, is imported in plastic bags in 50 kg cardboard drums and added to other compounds on an 'as needed' basis to form a liquid fragrance compound. Musk ketone is added to the fragrance mixture in closed vessels, in relative small quantities. The batches are typically less than 1,000 kg of which less than 10% is musk ketone (Company A, 1998a). Per facility usually one batch per day is made. Batches are made in vessels with local exhaust systems. Exposure of workers to dust can not be excluded in the process of manual weighing and filling the vessels through dumping the substance from the drums. The end product is a liquid which is drummed and used in the cosmetic industry for the production of consumer products like toiletries or cleaning products. It is assumed that the major part of the liquid in which it is mixed, and in which it will dissolve, are fragrance oils. In the cosmetic industry, it is assumed that dosing to consumer products will be highly automated and exposure may be possible when the liquid fragrance is poured.

Scenario 1: The production of fragrance compounds

Musk ketone is imported as a crystalline powder. At room temperature the substance has a very low vapour pressure, so inhalation exposure to the vapour is probably negligible, but exposure to dust may be possible. The fragrance compounds are probably mixed on costumers demand and the amount of ketone musk added may vary from batch to batch. Exposure may occur during weighing and adding of the solid to the (liquid) mixture.

After production, the drums containing the (liquid) compounded musk will be used in the cosmetic industry for the production of toiletries and household detergents etc. Exposure will occur when the drums are opened and poured.

When evaporating, the fragrance oil may probably serve as a vehicle for evaporation of the musk. It is therefore assumed that, with a maximum of 10% in the liquid, the maximum concentration in the vapour may also be 10%.

Fragrance compounding

For risk assessment, the results of the estimation with the EASE model and the analogue substances were used. The quantities of musk ketone that are used are relatively small. Per facility usually one batch per day of less than 1,000 kg is made, with less than 10% musk ketone. In this case, it seems reasonable to consider the value of the analogue substance as a short term value and the ranges of the EASE model as typical and worst case values.

Dermal exposure was estimated with the EASE model for dumping only one or two bags per day.

Drumming of liquid fragrance

For inhalation exposure, the estimate of the USEPA model was used for the risk evaluation.

For dermal exposure the result of the EASE model was used.

Scenario 2 The use of liquid fragrance compounds

The drummed liquid fragrance is used in the cosmetic industry for production of toiletries, shampoos etc. Exposure may be possible during the handling of the drums, and during cleaning and maintenance. It is assumed that the rest of the production is a highly automated process, with little of no exposure to musks.

For the risk characterisation, the values estimated with the EASE model were used.

Scenario 3 The use of cleaning agents by professional cleaners.

The use of musks in consumer products is subject to changes. The general trend in detergents and cleaning products is to replace musks by other fragrances. One of the end products which may (still) contain musks, are household cleaning agents. Professional cleaners may be exposed to some extent. It is assumed that no special high pressure spraying equipment is used, so that no aerosol formation takes place, and that the products are diluted before use.

The values estimated by the EASE model were taken forward to the risk characterisation.

Results of the estimates are presented in **Table 4.1**.

Table 4.1 Conclusions of the occupational exposure assessment

Scenario	Exposure		Estimated inhalation exposure level (musk ketone; mg/m3)						Estimated skin exposure level (musk ketone; mg/day)
			Full shift (8 hour time weighted average)				Short-term		
	Duration (hr/day)	Frequency (day/year)	Typical	Method	Reasonable worst case	Method	Level	Method	
1. The production of fragrance compounds	0-1	225	0.1	EASE	0.3	EASE	10	Analogy	42
2. The use of liquid fragrance compounds:									
-addition	0-1	225	negl.	EASE	negl.	EASE	negl.	Expert	4
-cleaning and maintenance	0-1	20-50	negl.	EASE	negl.	EASE	negl.	Expert	6.5
3. The use of cleaning agents by professional cleaners	4-6	225	negl.	EASE	negl.	EASE	negl.	Expert	2.5

EASE Calculation with the EASE model
Analogy Based on measured data for other substances used in similar exposure situations
Expert Expert judgement
Negl. Negligible

Consumer exposure

Consumer exposure occurs from consumer products to which musk ketone is added intentionally. Musk ketone is used as fragrance and fragrance enhancer in cosmetics, detergents and air fresheners. The main exposure of consumers is via cosmetics via the dermal route. According to the EU Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) this dermal exposure amounts to 200 µg/kg bw/day. As the SCCNFP based their calculation on a range of cosmetic products likely to be used in any one weekly period, and all products were assumed to be perfumed with the upper 97.5th percentile level of the fragrance ingredient, this value must be regarded as conservative. Compared to cosmetics, the exposure of consumers to musk ketone in detergents and air fresheners is negligible. Therefore only the figure of 200 µg/kg bw/day is taken forward to the risk characterisation. It should be noted that in 1999 the SCCNFP recommended that the exposure of consumers due to the cosmetic use of musk ketone should be reduced by 50%. This because musk ketone is retained in human fat and is excreted in human milk (see Section 4.1.3). If this measure comes into effect, the exposure would drop to 100 µg/kg bw/day.

Humans exposed via the environment

Local emissions of musk ketone to the environment may occur at formulation (fragrance compounding and end product formulation) and from private use. For both the local and regional scale, human intake via air is negligible compared to other uptake routes (especially root crops and fish). Hence, the main exposure route is oral. On a local scale, private use showed the highest total daily intake of all life cycle steps (3.31e-3 mg/kg bw/day). For the regional scale, the total daily intake was calculated to be 4.55e-4 mg/kg bw/day.

Musk ketone is retained in human adipose tissue and is excreted in human breast milk. The levels of musk ketone in human breast milk seem to have declined in the last decade, given that the mean and maximum levels found in 1999/2000 were considerably lower than those found in the early nineties. The exposure (worst-case estimate) via mother's milk for infants varies between 0.17 and 1 µg musk ketone/kg bw/day.

Combined exposure

Local emissions of musk ketone to the environment may occur at formulation (fragrance compounding and end product formulation) and from private use. For both the local and regional scale, human intake via air is negligible compared to other uptake routes (especially root crops and fish). Hence, the main exposure route is oral. On a local scale, private use showed the highest total daily intake of all life cycle steps (3.31e-3 mg/kg bw/day). For the regional scale, the total daily intake was calculated to be 4.55e-4 mg/kg bw/day.

Musk ketone is retained in human adipose tissue and is excreted in human breast milk. The levels of musk ketone in human breast milk seem to have declined in the last decade, given that the mean and maximum levels found in 1999/2000 were considerably lower than those found in the early nineties. The exposure (worst-case estimate) via mother's milk for infants varies between 0.17 and 1 µg musk ketone/kg bw/day.

4.1.2 Effects assessment

The human population may be exposed by the oral, dermal and inhalatory route.

In the data set for musk ketone animal studies as well as human studies are available.

There are no data available on the toxicokinetics of musk ketone after oral and inhalation exposure. For the related compound musk xylene some toxicokinetic data were available after oral exposure, on the basis of which for both rats and humans a percentage of 50% for oral absorption is taken forward to the risk characterisation of musk xylene. Musk ketone is quite comparable to musk xylene with respect to physico-chemical properties. Dermal uptake and penetration rates do not indicate a major difference for the two substances either. Based on these similarities between musk ketone and musk xylene, for musk ketone a percentage of 50% for oral absorption will be taken forward to the risk characterisation in concordance with musk xylene.

After a 6 hour dermal application of ^{14}C-labelled musk ketone (under occlusion) to rats, a total of about 40% of the applied dose was absorbed within 48 hours, with 2-3.5% remaining in the skin. Between 6 and 48 hours, the skin acted as a reservoir from which musk ketone continued to be absorbed. Excretion via urine and faeces (predominantly via bile) was highest during the first 48 hours, with small amounts additionally excreted between 48 and 120 hours. After 120 hours, about 7-11% of the applied dose was excreted in urine, and 17-27% in faeces. Radioactivity was detected in nearly all tissues, with highest levels at 6 hours in gastrointestinal tract, followed by liver, adipose tissue, adrenals, thyroid, fat, and kidneys.

^{14}C-labelled musk ketone was poorly absorbed from human skin during a 6 hour application, as only 0.5% of the applied dose was excreted in urine and faeces within 120 hours, and >86% of the applied dose was recovered from the site of application.

In vitro experiments with unoccluded rat skin indicate that the percutaneous absorption of musk ketone is poor, and that the skin acts as a depot from which musk ketone can be absorbed.

Metabolism of musk ketone in rats and humans involves glucuronide conjugation.

For dermal absorption of musk ketone in rats and humans, values of 40% and 14%, respectively, are taken forward to the risk characterisation.

The plasma elimination half-life in rats after intravenous administration of musk ketone is approximately 60 hours. No data on plasma half-life in humans are available for musk ketone.

When administered orally to rats from day 14 of gestation up to 7 days post-parturition, musk ketone appeared in milk and milk fat. Musk ketone is also found in human milk fat and in adipose tissue.

Although the available studies for acute toxicity testing of musk ketone have not been performed according to OECD guidelines, it can be concluded that the oral LD_{50} for rats and the dermal LD_{50} for rabbits are both greater than 2,000 mg/kg bw. Data for acute inhalation toxicity are not available.

According to EC criteria musk ketone needs not to be classified for acute oral and dermal toxicity based on the reported LD_{50} values.

Base set requirements for testing of skin irritation have not been met as adequate skin irritation studies are lacking. However, a request for a skin irritation study performed according to current guidelines is not deemed appropriate because:

- the available data on musk ketone do not point to a skin irritating potential: upon single treatment very high doses of musk ketone (as a 40% suspension in corn oil) are not irritating to the rabbit skin when applied for 24 hours under occlusion. After repeated

dosing no signs of skin irritation were seen in rats, while in rabbits slight irritation was observed at high doses which partly could be attributed to the vehicle used. In sensitisation studies no irritation was observed in guinea pigs and in humans when applied at concentrations up to 75% and 5%, respectively.

- the test conditions used in a guideline study on rabbits (0.5 g for 4 hours under occlusion) are not expected to result in skin irritation given the results of the acute dermal study at much higher doses and longer duration.

From a well performed experiment it can be concluded that musk ketone is not eye irritating. According to EC criteria musk ketone needs not to be classified for skin and eye irritating properties.

No data on respiratory tract irritation are available.

Based on the results of a recently performed guinea pig maximisation study it can be concluded that musk ketone has weak sensitising properties. From two maximisation studies with human volunteers it can only be concluded that musk ketone up to a concentration of 5% is not skin sensitising in humans. There is no need for classification according to EU guidelines.

Data on respiratory tract sensitisation or occupational asthma are not available.

The available oral repeated dose toxicity studies with musk ketone are limited to special studies into biotransformation enzyme induction of comparatively short duration. In these studies (apart from enzyme induction) the only toxic responses reported were liver enlargement at dose levels greater than 20 mg/kg bw/day for 7 days in mice (NOEL) and at 20 mg/kg bw/day and above in the rat (LOEL). In mice, musk ketone also caused histological changes in the liver (primarily centrilobular hepatocellular hypertrophy and at 200 mg/kg bw/day panlobular hepatocellular hypertrophy). Details as to the dose-response relationship for the histological effects on the liver were not available. In rats liver histology was not studied. These studies are too limited to derive an NOAEL for oral repeated dose toxicity.

In a well performed dermal 90-days toxicity study with rats effects at the highest dose of 240 mg musk ketone/kg bw included a decreased body weight gain without a concomitant decrease in food consumption, decreases in red blood cell parameters and an increase in absolute and relative liver weight without a histopathological correlation. The decrease in body weight gain was also seen in females at the lower dose of 75 mg/kg bw. In the experiment no neuropathological effects and no effects on the reproductive organs were seen. The NOEL of 24 mg/kg bw/day in this study can be considered as a NOAEL, although the extent of the body weight changes at the next higher dose level was only marginal and of questionable biological significance. The value of 24 mg/kg bw/day is taken forward to the risk characterisation.

In dermal experiments with rabbits doses up to 750 mg musk ketone/kg bw for 20 days, microscopic pathology revealed hepatocyte vacuolisation and decreased bone marrow haematogenic activity, but these may have been caused, at least in part, by the vehicle (dimethyl phthalate).

When administered as part of a fragrance mixture, inhalatory exposure to musk ketone up to a maximum tested dose of 170.5 $\mu g/m^3$ for 4 h per day, 5 days per week for 13 weeks did not result in any toxicity. This study is of limited value because the animals were not exposed to musk ketone alone, and musk ketone was only present at rather low levels in the mixtures.

In special studies for enzyme induction, 7 consecutive daily oral musk ketone doses of up to 500 mg/kg bw for mice and up to 200 mg/kg bw for rats resulted in general hepatic effects consistent with those associated with PB-like microsomal enzyme inducers. In mice, musk ketone treatment resulted in a markedly increased CYP2B enzyme activity, together with increases in CYP2B protein and mRNA levels. Small changes in CYP1A and CYP3A enzyme activities were also observed, with concomitant increases in protein and mRNA levels. Although to a smaller degree, musk ketone treatment in rats resulted in identical effects on CYP2B. In contrast to mice, however, musk ketone induced CYP1A enzyme activities even more than CYP2B enzyme activity, while it reduced CYP3A enzyme activity. In both mice and rats, 20 mg/kg bw was the LOEL for enzyme induction.

In mice, three oral doses of 20 mg musk ketone have also been shown to induce GST enzyme activity in liver, small intestinal mucosa and colon. Intraperitoneal doses of 10 to 40 mg musk ketone/kg bw proved to be strong inducers of biotransformation enzymes in rat liver.

From information on the related compound musk xylene (see RAR musk xylene, 2003) it is clear that musk ketone is quite similar to musk xylene with respect to enzyme induction properties, musk xylene being the more potent one, with a NOEL of 10 mg/kg bw in mice and a LOEL of 10 mg/kg bw in rats. However, although musk xylene CYP2B enzyme induction is characterised by large increases in mRNA and immunoreactive protein for the CYP2B enzymes, in contrast to musk ketone there is no commensurate increase in CYP2B enzyme activity with musk xylene. This inhibition of induced CYP2B enzyme activity is caused by the *p*-NH_2-metabolite of musk xylene which is formed by nitroreduction. Musk ketone possesses an acetyl rather than a nitro group para to the t-butyl substitution, and therefore musk ketone lacks the appropriate nitro reduction needed to inactivate the CYP2B enzymes.

In the absence of any other indication of liver toxicity the slight changes in levels of biotransformation enzyme activities are considered to be of an adaptive nature rather than adverse. Therefore this effect as such and the LOEL for it will not be taken forward to the risk characterisation.

Musk ketone was negative in several *in vitro* tests (bacterial gene mutation tests, SOS chromotests, a mammalian gene mutation test, tests for micronuclei induction and SCEs in mammalian cells, and an UDS test). A chromosome aberration test in mammalian cells *in vitro* provided an equivocal result, but as an *in vivo* mouse micronucleus test was negative, it can be concluded that musk ketone is a non-genotoxic substance. Due to its enzyme-inducing properties, musk ketone can exhibit cogenotoxic activity.

There are no carcinogenicity data for musk ketone. However, the related compound musk xylene was tested for carcinogenicity in mice. It was concluded (see RAR musk xylene, 2003) that musk xylene is carcinogenic in mice, that it acts by a non-genotoxic mode of action, and that the most serious type of tumour for which the incidence was statistically significantly increased (i.e. liver carcinomas in male mice) is mechanistically related to microsomal enzyme induction. Therefore, for the characterisation of the carcinogenic risk of musk xylene to humans a threshold approach was taken, in which the (oral) LOAEL of 70 mg/kg bw/day for tumour development (liver tumours in particular) served as starting point and in which the NOEL for enzyme induction was taken into account in the interpretation of the MOS.

Given that:

- musk ketone is quite comparable to musk xylene with respect to physico-chemical and toxicokinetic properties, and in particular

- both musk ketone and musk xylene are phenobarbital-like inducers of liver enzymes in both rats and mice (with a LOEL of 20 mg/kg bw for musk ketone in both species, while for musk xylene 10 mg/kg bw is a NOEL in mice and a LOEL in rats),

there is a concern that musk ketone may be hepatocarcinogenic in mice as well. Just like musk xylene, musk ketone is a phenobarbital-like inducer of liver enzymes, but as such it is somewhat less potent than musk xylene. In concurrence with the risk characterisation for musk xylene, for the characterisation of the carcinogenic risk of musk ketone to humans a threshold approach would thus seem justified, also because musk ketone is a non-genotoxic substance. Given all this, it is concluded that, despite the lack of data on the carcinogenicity of musk ketone itself, there is no need for further testing because from the information above it is felt that the data available on musk xylene can be safely used for the risk characterisation of musk ketone.

As to classification: realising that it is a borderline case (musk xylene was not tested for carcinogenicity in rats, and the strain of mice used in the carcinogenicity study is particularly prone to develop certain types of tumours, especially liver tumours), it was nevertheless concluded (see RAR musk xylene, 2003) that the non-genotoxic compound musk xylene should be classified as a carcinogen category 3 (R40). In addition, the liver effects induced by musk xylene resemble those that can be seen after dosing rats and mice with phenobarbital, a (liver) carcinogenic substance in rodents which was classified by IARC as a group 2B substance ("possibly carcinogenic to humans") in 2001. The case is even more borderline for musk ketone as no carcinogenicity data on musk ketone are available. However, on the basis of its similarity to musk xylene, musk ketone should be classified as a carcinogen category 3 (R40).

With respect to fertility no multi-generation reproductive toxicity study was available for either route. In the 90-day dermal toxicity study with rats, musk ketone caused no effects on the reproductive organs, whereas the structurally related compound musk ambrette caused testicular atrophy in the same study.

In an oral peri/postnatal toxicity study slight toxicity (decreased body weight gain and food consumption) was seen at the highest dose level of 25 mg/kg bw in the dams (NOAEL for maternal toxicity is 7.5 mg/kg bw/day). Pup toxicity at this dose included a lower weight (at birth and through to weaning) and a later day of attainment for surface and air righting and fluxual maturation. Lower body weight gains up to post-natal week 20 were seen in F_1 males from F_0 dams receiving 7.5 and 25 mg/kg b/w/day. It is to be noted that exposure of the F_1-generation to musk ketone was only *in utero* during the peri-natal phase or through any transfer in the milk of the lactating dams. Next to a direct effect of the substance, reduced milk production or wasting cannot be excluded as (alternative) causes of the effect on body weight gain. Dosing up to 25 mg/kg bw did not result in behavioural changes or in reduced reproductive capacity. The lowest dose tested, 2.5 mg/kg bw/day, can be considered the NOAEL in this study. Realising that this is a conservative approach, the fact that the effect at the next higher dose is very small and that it is limited to males and of uncertain biological significance has to be taken into account in the interpretation of the MOS values for this endpoint.

In a well performed oral developmental toxicity study with rats, maternal toxicity occurred in a dose-related way at 45 and 150 mg/kg bw/day. This toxicity included reduced body weight gain and reduced food consumption. Developmental toxicity, including increased post implantation loss and reduced fetal body weight, was only seen at 150 mg/kg bw/day. There was no indication for teratogenicity. The NOAEL for maternal toxicity can be established at

15 mg/kg bw, and the NOAEL for developmental toxicity can be established at 45 mg/kg bw. No developmental toxicity studies are available for the dermal and inhalatory route.

The available data obtained from the peri/postnatal toxicity study indicate that musk ketone needs not to be classified for reproductive toxicity. Given the marginal effects elicited in the offspring in that study and the fact that these effects are of uncertain biological significance, there is also no need to label musk ketone with R64 ("May cause harm to breast fed babies").

In a 90-day dermal toxicity study with rats no indications for a neurotoxic potential was found for musk ketone, in contrast to the structurally related compound musk ambrette.

4.1.3 Risk characterisation

Workers

For the purpose of risk characterisation, it is assumed that inhalation of dust and skin contact is the main routes of exposure. Oral exposure is not considered to be a significant route of exposure under normal working practices. If applicable, quantitative risk assessment is performed by calculation of the MOS (the ratio between NOAEL/LOAEL and exposure levels) and comparison of this value with the minimal MOS. This minimal MOS is established via assessment factors, taking into account inter- and intraspecies differences, differences between experimental conditions and the exposure pattern of the worker, type of critical effects, dose-response relationship, confidence in the database, and correction for route-to-route extrapolation. A risk is indicated when the MOS is lower than the minimal MOS. In case of combined exposure the calculations are based on internal NOAELs and systemic exposure levels.

Acute toxicity

Given the absence of lethality or other systemic effects in the acute dermal study, and the anticipated occupational exposure levels, it is concluded that musk ketone is of no concern for workers with regard to acute dermal effects: **conclusion (ii)**. There are no data on acute inhalation toxicity, however given the estimated inhalation exposure levels and the low acute toxicity after oral and dermal administration; there are no indications for concern with respect to acute toxicity by inhalation exposure: **conclusion (ii)**.

Irritation and corrosivity

The occupational risks for local effects is characterised for exposure via the skin, the respiratory tract and the eyes.

Acute dermal irritation

Adequate skin irritation studies are lacking. Based on the available data it is not possible to classify musk ketone for skin irritation properties. However, exposure to musk ketone is not expected to result in skin irritation since musk ketone is not irritating to rabbit skin after single exposure, musk ketone is not irritating to rat skin after repeated exposure and only slight irritation was observed at rabbit skin after exposure to high doses which partly could be attributed to the vehicle used: **conclusion (ii)**.

Dermal irritation after repeated exposure

Repeated dermal exposure may induce local skin effects. The NOAEL for local effects of the 90-day dermal toxicity study with rats (1.7 mg/cm^2)[2] is used as starting point for the risk characterisation. Comparison of the calculated MOSs (17-567) between this NOAEL and the dermal exposure levels (0.003-0.1 mg/cm^2) with the minimal MOS (9)[3], indicates that there is no concern for local effects due to repeated dermal exposure: **conclusion (ii)**.

Eye irritation

Exposure to the eyes is possible via vapours or accidentally by splashing. Given the effects observed in the acute eye irritation study in rabbits, it is concluded that musk ketone is of no concern for workers with regard to acute eye irritation: **conclusion (ii)**.

Respiratory irritation

No data are available on the local respiratory tract effects of musk ketone after acute or repeated respiratory exposure. The risk for local effects after respiratory exposure cannot be derived from oral or dermal toxicity studies, so a quantitative risk characterisation is not possible. Musk ketone administered for 13 weeks by the inhalatory route as part of fragrance mixture did not result in any toxicity up to a dose of 0.17 mg/m^3. Based on this inhalation study and given the low or negligible estimated inhalation exposure there are no indications for concern for respiratory irritation: **conclusion** (**ii)**.

Sensitisation

Based on the dermal sensitisation study in guinea pigs it can be concluded that musk ketone only has weak sensitising properties. In humans, musk ketone is not a skin sensitiser in concentrations up to 5%. Therefore musk ketone is of no concern for workers with regard to skin sensitisation: **conclusion (ii)**.

Repeated-dose toxicity

Risk characterisation for local skin effects after repeated exposure to musk xylene is described in the paragraph 'Irritation and corrosivity'. This paragraph is limited to the systemic effects due to repeated exposure to musk ketone.

The NOAEL for systemic effects from the dermal 90-day rat study (24 mg/kg bw/day) is used as starting point for the risk characterisation. Assuming a dermal absorption value of 40% for rats, this NOAEL corresponds to an internal level of 9.6 mg/kg bw/day. The minimal MOSs required for chronic occupational exposure using this NOAEL, the actual exposure levels and the MOSs calculated between the NOAEL and the exposure levels are given in **Table 4.2**.

[2] Based on a NOAEL of 240 mg/kg bw/day assuming a body weight of the rat of 0.3 kg and an exposed dermal area of the rat of 42.5 cm^2 (which is 10% of the total body surface area)

[3] Minimal MOS local effects dermal (9): 3 (interspecies) x 3 (intraspecies)

Table 4.2 Occupational risk assessment for repeated-dose toxicity of musk ketone

	Scenario 1			Scenario 2			Scenario 3		
	Derm	Resp	Comb	Derm	Resp	Comb	Derm	Resp	Comb
NOAEL (in mg/kg bw/day)	24	24	9.6	24	24	9.6	24	24	9.6
Exposure (in mg/kg bw/day)	0.6	0.04	0.12#	0.06-0.09	negl	0.008-0.013#	0.04	negl	0.005#
calculated MOS	40	600	80	267-400	high	739-1200	600	high	1920
minimal MOS	126[a]	900[b]	360[c]	126[a]	900[b]	360[c]	126[a]	900[b]	360[c]

Derm: Dermal exposure;
Resp: Respiratory exposure; comb: combined exposure; negl: negligible exposure
The total systemic exposure, based on 14% dermal absorption and 100% inhalatory absorption
a 126 = 12 (interspecies) · 3 (intraspecies) · 10 (exposure duration) · 0.35 (absorption differences; 14% human/ 40% animal)
b 900 = 12 (interspecies) · 3 (intraspecies) · 10 (exposure duration) · 2.5 (absorption differences; 100% inhalatory/40% dermal)
c 360 = 12 (interspecies) · 3 (intraspecies) · 10 (exposure duration)

Comparison of the minimal MOSs and the calculated MOSs indicates no concern for systemic effects due to repeated dermal, inhalatory, or combined exposure in scenarios 2 and 3 **conclusion (ii)** and a concern for all routes in scenario 1. However, due to the crystalline nature of the substance, the repeated dermal and combined exposure for scenario 1 is substantially overestimated. Moreover, the strong odour of the substance will urge workers to wear protective clothing, thus further reducing the exposure. Based on these considerations **conclusion (ii)** is drawn for systemic effects due to dermal and combined exposure in scenario 1 as well. Furthermore, in view of the worst case character of the minimal MOS for inhalation exposure (caused by multiplication of different assessment factors) **conclusion (ii)** is also considered justified for systemic effects due to inhalatory exposure in Scenario 1.

Mutagenicity

Given the results from the mutagenicity studies, it is concluded that musk ketone is of no concern for workers with regard to mutagenicity: **conclusion (ii)**.

Carcinogenicity

There are no carcinogenicity studies available. However, for the related compound musk xylene there is information available on the carcinogenic properties (the observed LOAEL for carcinogenic effects in mice was 70 mg/kg bw/day). For musk xylene it was concluded that there is no concern for workers with regard to systemic carcinogenicity after dermal, inhalation, and combined exposure for all scenarios. Since musk ketone and musk xylene are comparable with regard to their toxicokinetic and toxicodynamic properties and given the comparable results observed in the enzyme induction studies, and because the exposure levels for both substances are the same, it is assumed that the same conclusions are applicable for musk ketone: **conclusion (ii)**.

Reproductive toxicity

Reproduction toxicity studies by inhalation or dermal exposure are lacking. There are no indications for effects on fertility in the dermal 90-day toxicity study with rats, although in this study investigations were limited to histological examination of the reproductive organs: **conclusion (ii).** In an oral developmental toxicity study, developmental toxicity only occurred

at maternal toxic dose levels ($NOAEL_{developmental\ toxicity}$ 45 mg/kg bw/day, $NOAEL_{maternal\ toxicity}$ 15 mg/kg bw/day).

In an oral peri/postnatal toxicity study in rats a NOAEL of 2.5 mg/kg bw/day was observed based on a slightly but significantly and dose-related decreased growth of male pups from the next higher dose level (7.5 mg/kg bw/day). This NOAEL is used for risk characterisation for off spring effects by route-to-route extrapolation. By use of this NOAEL as starting point for the risk assessment, it is assumed that the pre-natal effects as observed in the developmental toxicity study (NOAEL 45 mg/kg bw/day) are covered. Assuming 50% oral absorption, this NOAEL corresponds to an internal no-effect dose of 1.25 mg/kg bw/day. The MOSs calculated between this NOAEL and the actual exposure levels and the minimal MOSs required using this NOAEL for chronic occupational exposure are given in **Table 4.3**.

Table 4.3 Occupational risk assessment for off spring effects of musk ketone

	Scenario 1			Scenario 2			Scenario 3		
	Derm	Resp	Comb	Derm	Resp	Comb	Derm	Resp	Comb
NOAEL (in mg/kg bw/day)	2.5	2.5	1.25	2.5	2.5	1.25	2.5	2.5	1.25
Exposure (in mg/kg bw/day)	0.6	0.04	0.12#	0.06-0.09	negl	0.008-0.013#	0.04	negl	0.005#
calculated MOS	4	63	10	28-42	high	96-156	63	high	250
minimal MOS	10a	72b	36c	10a	72b	36c	10a	72b	36c

Derm: Dermal exposure;
Resp: Respiratory exposure; comb: combined exposure; negl: negligible exposure
The total systemic exposure, based on 14% dermal absorption and 100% inhalatory absorption
a 10 = 12 (interspecies) · 3 (intraspecies) · 0.28 (absorption differences; 14% dermal/50% oral)
b 72 = 12 (interspecies) · 3 (intraspecies) · 2 (absorption differences; 100% inhalatory/50% oral)
c 36 = 12 (interspecies) · 3 (intraspecies)

Comparison of the minimal MOSs and the calculated MOSs indicates no concern for systemic effects due to repeated dermal, inhalatory, or combined exposure in Scenarios 2 and 3 **conclusion (ii)** and a concern for all routes in scenario 1. However, taking into account the small effect limited to males (at the LOAEL) and the considerations for dermal and combined exposure in scenario 1 as put forward in the risk characterisation for repeated-dose toxicity, it is concluded that based upon the present information there seems to be no reason for concern with regard to effects on the offspring in scenario 1 as well: **conclusion (ii)**.

Occupational limit values

At the moment, occupational limit values for musk ketone have not been established.

Consumers

Starting point for the risk characterisation is the (frequent) dermal exposure of consumers to musk ketone in cosmetic products, for which an external exposure level of 200 μg/kg bw/day was calculated. Because the absorption of musk ketone through human skin is at maximum 14%, this external exposure level results in an internal exposure level of 28 μg/kg bw/day.

Musk ketone has only weak skin sensitising properties in animals, whereas in humans it is not skin sensitising in concentrations up to 5%. As higher concentrations of musk ketone do not occur in consumer cosmetic articles, there is no concern for consumers for skin sensitisation :

conclusion (ii). There is also no concern for consumers for skin and eye irritation: **conclusion (ii)**.

Starting point for the risk assessment for repeated dose toxicity is the dermal NOAEL of 24 mg/kg bw/day from the 90-day toxicity study with rats. Assuming a dermal absorption value of 40% for rats, this NOAEL corresponds to an internal no-effect dose of 9.6 mg/kg w/day. Comparing the latter with the calculated human systemic exposure level of 28 μg/kg bw/day results in a MOS of 343. This MOS indicates no concern for consumers, taking into account intra- and interspecies differences, the use of a NOAEL from a semi-chronic study but also the worst-case character of the exposure estimate and the marginal effects observed at the LOAEL: **conclusion (ii)**.

Musk ketone is a non-genotoxic substance: **conclusion (ii)**. There are no data on the carcinogenic potential of musk ketone. However, the related compound musk xylene appeared to be carcinogenic in mice, acting by a non-genotoxic mode of action that, at least for the observed liver tumours, involved microsomal enzyme induction. For the characterisation of the carcinogenic risk of musk xylene to humans a threshold approach was taken, in which the (oral) LOAEL of 70 mg/kg bw/day for tumour development (liver tumours in particular) served as starting point and in which the NOEL for enzyme induction was taken into account in the interpretation of the MOS. It is assumed that the information available on musk xylene can be used for the risk characterisation of musk ketone, because:

- musk ketone is quite comparable to musk xylene with respect to physico-chemical and toxicokinetic properties, and
- both musk ketone and musk xylene are non-genotoxic substances, and
- both musk ketone and musk xylene are phenobarbital-like inducers of liver enzymes in both rats and mice, with musk ketone being somewhat less potent than musk xylene.

For musk xylene, the risk characterisation did not indicate concern for consumers for carcinogenicity after dermal exposure: **conclusion (ii)**. It is assumed that the same conclusion for carcinogenicity **conclusion (ii)** is applicable for consumers after dermal exposure to musk ketone, because the human systemic exposure level for musk ketone and musk xylene is comparable.

There are no indications for effects on fertility in the dermal 90-day toxicity study with rats and in the oral peri/postnatal study in which rats were exposed to musk ketone *in utero* and during lactation. Developmental effects have been observed in an oral developmental toxicity study with rats (but only at maternal toxic dose levels; NOAEL for developmental toxicity 45 mg/kg bw/day) and in the oral peri/postnatal study with rats (NOAEL for pup toxicity 2.5 mg/kg bw/day). In the absence of dermal developmental toxicity studies, these oral NOAELs are used as starting point for the risk characterisation for the progeny of pregnant consumers. Assuming 50% oral absorption, these NOAELs correspond to internal no-effect doses of 22.5 and 1.25 mg/kg bw/day, respectively. Comparing these internal no-effect doses with the calculated human systemic exposure level of 28 μg/kg bw/day, the MOSs are 804 and 45, respectively. Taking into account intra- and interspecies differences the MOS of 804 indicates no concern for developmental effects to the progeny of consumers: **conclusion (ii)**. As to peri/postnatal effects, a MOS of 45 also indicates no concern for the progeny of consumers: **conclusion (ii)**. This is because the peri/postnatal study was directed towards this specific subpopulation, and that for any subpopulation the intraspecies differences in sensitivity will be smaller than for the population in total. Hence, it is reasonable to apply a smaller intraspecies factor for the progeny than 10, which is in concurrence with the risk characterisation for the progeny of workers. A MOS of 45 would then lead to a

conclusion (ii), also because the effect seen at the LOAEL in the peri/postnatal study only occurred in males and was marginal in nature and of uncertain biological significance.

Humans exposed via the environment

For man exposed via the environment inhalation exposure is negligible (**conclusion (ii)** for all relevant endpoints). The main exposure route for man indirectly exposed is oral. Starting point for the risk characterisation for the local scale is private use, which shows the highest total daily intake of 3.31e-3 mg/kg bw/day. For the regional scale the total daily intake is 4.55e-4 mg/kg bw/day. Assuming an oral absorption of 50% for humans, these external exposures correspond to internal exposures of 1.66e-3 and 2.28e-4 mg/kg bw/day, respectively. Only for repeated dose toxicity the internal exposure is necessary for route-to-route extrapolation. Because of the occurrence of musk ketone in mother's milk, a separate risk characterisation is necessary for breast-fed babies (highest exposure value 1 μg/kg bw/day).

Total daily intake

In the absence of oral repeated dose toxicity studies, the dermal NOAEL of 24 mg/kg bw/day from the 90-day toxicity study with rats is used as starting point for the risk assessment. Assuming a dermal absorption value of 40% for rats, this NOAEL corresponds to an internal no-effect dose of 9.6 mg/kg bw/day. Comparing the latter with the estimated internal total human daily intake levels, the MOSs for both local and regional scale are >>1,000. These MOSs indicate no concern for man repeatedly exposed indirectly via the environment, taking into account intra- and interspecies differences, the use of a NOAEL from a semi-chronic study but also the marginal effects observed at the LOAEL: **conclusion (ii)**.

Musk ketone is a non-genotoxic substance: **conclusion (ii)**. There are no data on the carcinogenic potential of musk ketone. However, the related compound musk xylene appeared to be carcinogenic in mice, acting by a non-genotoxic mode of action that, at least for the observed liver tumours, involved microsomal enzyme induction. For the characterisation of the carcinogenic risk of musk xylene to humans a threshold approach was taken, in which the (oral) LOAEL of 70 mg/kg bw/day for tumour development (liver tumours in particular) served as starting point and in which the NOEL for enzyme induction was taken into account in the interpretation of the MOS. It is assumed that the information available on musk xylene can be used for the risk characterisation of musk ketone, because:

- musk ketone is quite comparable to musk xylene with respect to physico-chemical and toxicokinetic properties, and
- both musk ketone and musk xylene are non-genotoxic substances, and
- both musk ketone and musk xylene are phenobarbital-like inducers of liver enzymes in both rats and mice, with musk ketone being somewhat less potent than musk xylene.

For musk xylene, the risk characterisation did not indicate concern for carcinogenicity for man exposed indirectly via the environment: **conclusion (ii)**. It is assumed that the same conclusion for carcinogenicity **conclusion (ii)** is applicable for man exposed indirectly via the environment to musk ketone, because the human total daily intake levels for musk ketone and musk xylene are comparable.

There are no indications for effects on fertility in the dermal 90-day toxicity study with rats and in the oral peri/postnatal study in which rats were exposed to musk ketone *in utero* and during lactation. Developmental effects have been observed in an oral developmental toxicity study with rats (but only at maternal toxic dose levels; NOAEL for developmental toxicity

45 mg/kg bw/day) and in the oral peri/postnatal study with rats (NOAEL for pup toxicity 2.5 mg/kg bw/day). These oral NOAELs are used as starting point for the risk characterisation for the progeny of pregnant women indirectly exposed via the environment. Comparing these no-effect doses with the estimated total human daily intake levels, the MOSs for both local and regional scale are >700. Taking into account intra- and interspecies differences and the fact that the effect seen at the LOAEL in the peri/postnatal study only occurred in males and was marginal in nature and of uncertain biological significance, the MOSs indicate no concern for the progeny of women exposed indirectly via the environment for peri/postnatal and developmental effects: **conclusion (ii)**.

Exposure via mother's milk

The highest exposure of musk ketone via mother's milk was calculated to be 1 μg/kg bw/day. Data from a peri/postnatal toxicity study would be the most suitable to characterise the risk for babies exposed via mother's milk. For musk ketone, the NOAEL for peri/postnatal effects is 2.5 mg/kg bw/day. Comparing this no-effect dose with the maximum exposure level via mother's milk, a MOS of 2,500 is derived. Taking into account intra- and interspecies differences, and the fact that the effect seen at the LOAEL in the peri/postnatal study only occurred in males and was marginal in nature and of uncertain biological significance, this MOS indicates no concern for breast-fed babies: **conclusion (ii)**.

Combined exposure

A worst case estimate for the combined (external) exposure to musk ketone would be the sum of the worst case estimates for the three individual populations, i.e. 0.6 mg/kg bw/day (dermal, workplace) + 0.043 mg/kg bw/day (inhalation, workplace) + 0.20 mg/kg bw/day (dermal, consumers) + 3.31e-3 mg/kg bw/day (oral, locally via the environment). Assuming figures of 14%, 100% and 50% for dermal, inhalation and oral absorption, respectively, an internal exposure of 0.15 mg/kg bw/day (i.e. 0.08 mg/kg bw/day (dermal, workplace) + 0.043 mg/kg bw/day (inhalation, workplace) + 0.028 mg/kg bw/day (dermal, consumers) + 1.66e-3 mg/kg bw/day (oral, locally via the environment)) can be calculated. Note that approximately 80% of the combined internal exposure estimate originates from occupational sources.

Acute toxicity / Irritation / Sensitisation / Genotoxicity

Given that musk ketone is not acutely toxic, eye irritating and genotoxic, and musk ketone has no skin irritating and only weak, if any, skin sensitising potential, there is no concern for these endpoints after combined exposure to musk ketone: **conclusion (ii)**.

Repeated dose toxicity

Starting point for the risk assessment for repeated dose toxicity is the dermal NOAEL of 24 mg/kg bw/day from the 90-day toxicity study with rats. Assuming a dermal absorption value of 40% for rats, this NOAEL corresponds to an internal no-effect dose of 9.6 mg/kg bw/day. Comparing the latter with the calculated combined human systemic exposure level of 0.15 mg/kg bw/day results in a MOS of 64. This MOS indicates no concern for repeated combined exposure, taking into account intra- and interspecies differences, the use of a NOAEL from a semi-chronic study but also the worst case character of the combined exposure estimate and the marginal effects observed at the LOAEL: **conclusion (ii)**.

Carcinogenicity

There are no data available on the carcinogenic potential of musk ketone. However, as stated in earlier sections on carcinogenicity (see Section 4.1.3) it is assumed that the information available on musk xylene can be used for the risk characterisation of musk ketone.

For musk xylene, the risk characterisation indicated no concern for carcinogenicity after combined exposure: **conclusion (ii)**.

Reproductive toxicity

There are no indications for effects on fertility in the dermal 90-day toxicity study with rats and in the oral peri/postnatal study in which rats were exposed to musk ketone *in utero* and during lactation. Developmental effects have been observed in an oral developmental toxicity study with rats (but only at maternal toxic dose levels; NOAEL for developmental toxicity 45 mg/kg bw/day) and in the oral peri/postnatal study with rats (NOAEL for pup toxicity 2.5 mg/kg bw/day). These oral NOAELs are used as starting point for the risk characterisation for the progeny of pregnant women. Assuming 50% oral absorption, these NOAELs correspond to internal no-effect doses of 22.5 and 1.25 mg/kg bw/day, respectively. Comparing these internal no-effect doses with the calculated combined human systemic exposure level of 0.15 mg/kg bw/day, the MOSs are 150 and 8, respectively.

Taking into account intra- and interspecies differences and the worst case character of the combined exposure estimate, the MOS of 150 indicates no concern for developmental effects to the progeny of pregnant women after combined exposure: **conclusion (ii)**. As the peri/postnatal study was directed towards this specific subpopulation, and that for any subpopulation the intraspecies differences in sensitivity will be smaller than for the population in total, it is reasonable to apply a smaller intraspecies factor for the progeny than 10 (which is in concurrence with the risk characterisation for the progeny of workers). Given also the worst case character of the combined exposure estimate and the fact that the effect seen at the LOAEL in the peri/postnatal study only occurred in males and was marginal in nature and of uncertain biological significance, it is concluded that also for peri/postnatal effects the MOS of 8 represents no concern **conclusion (ii)** for the progeny of pregnant women after combined exposure.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

Given the physico-chemical data, musk ketone is considered not to form a risk with respect to flammability, and explosive and oxidising properties: **conclusion (ii)**.

5 RESULTS

5.1 ENVIRONMENT

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Combined exposure

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5.2.2 Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Given the physico-chemical data, musk ketone is considered not to form a risk with respect to flammability, and explosive and oxidising properties: **conclusion (ii)**.