



**EUROPEAN COMMISSION**  
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL  
Directorate C - Public Health and Risk Assessment  
**C7 - Risk assessment**

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**SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE  
ENVIRONMENT (CSTEE)**

**Opinion on the results of the Risk Assessment of:**

**MUSK KETONE  
HUMAN HEALTH PART**

**CAS N°: 81-14-1**

**EINECS N°: 201-328-9**

**Carried out in the framework of Council Regulation (EEC) 793/93 on  
the evaluation and control of the risks of existing substances<sup>1</sup>**

**Adopted by the CSTEE during the 41<sup>st</sup> plenary meeting  
of 8 January 2004**

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<sup>1</sup> Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of those substances if they are produced or imported into the Community in volumes above 10 tonnes per year. The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC)1488/94, which is supported by a technical guidance document.

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## Terms of Reference

In the context of Regulation 793/93 (Existing Substances Regulation), and on the basis of the examination of the Risk Assessment Report the CSTEE is invited to examine the following issues:

- (1) Does the CSTEE agree with the conclusions of the Risk Assessment Report?
- (2) If the CSTEE disagrees with such conclusions, the CSTEE is invited to elaborate on the reasons for this divergence of opinion.

*According to the Technical Guidance Document on Risk Assessment – European Communities 2003:*

- conclusion i): *There is a need for further information and/or testing;*
- conclusion ii): *There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already;*
- conclusion iii): *There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.*

## INTRODUCTION

Musk ketone is an aromatic nitro compound used as a synthetic fragrance. It is not produced in Europe but imported in amounts of < 50 tonnes per year. Musk ketone is used as fragrance in a variety of consumer products such as body care products and household detergents. The concentration of musk ketone in these products is usually < 1%. Human exposure to musk ketone may therefore occur during compounding of fragrance materials, by the direct application of these fragrances to the body and, indirectly, through the food chain.

## GENERAL COMMENTS

The health part of the document is of excellent quality, it is comprehensive and exposure and effects assessment follows the TGD. Most of the MOS calculated are large, therefore CSTEE agrees with conclusion ii) for all exposure scenarios.

## SPECIFIC COMMENTS

The available database on human exposure and the toxicity of musk ketone is limited. The document uses published data from peer reviewed journals, industry reports and conclusions based on toxicity data of the closely related musk xylene for the evaluation.

## **1. Exposure assessment**

Human exposure to musk ketone may occur during occupational scenarios and due to direct contact with musk ketone containing materials. Since data on occupational exposure are limited, the RAR uses physico-chemical data, data on production processes and measured data for analogues in combination with model predictions (EASE) for exposure assessment. Three different scenarios (1, the production of fragrance compounds; 2, the use of liquid fragrance compounds; and 3, the use of cleaning agents by professional cleaners) are evaluated. For the three scenarios, inhalation exposure is usually negligible due to the low vapour pressure of musk ketone. The major pathways of exposure predicted is skin contact which may reach up to 42 mg musk ketone/person/day for one scenario. Regarding direct consumer exposure, the RAR relies on an evaluation by the SCCNFP (1999) which estimated a dermal exposure of up to 200 µg/kg b.w. per day due to use of cosmetics. This assessment applied a representative exposure scenario to different cosmetics and used the 97.5<sup>th</sup> percentile of musk ketone concentrations present in these products to determine dermal exposure. This approach most likely overestimates exposures for average cosmetics users since the probability that a combination of all products with high musk ketone content is used by one individual is considered as low. Other routes of exposure for consumers to musk ketone such as inhalation after evaporation from the skin are considered negligible. Indirect exposure via the environment is based on EUSES calculations and predicts only low human exposure through the indirect pathway.

## **2. Effects assessment**

### ***Toxicokinetics***

More detailed information on the toxicokinetics of musk ketone is only available regarding dermal application both in animals and in humans. The obtained results suggest that uptake from the skin amounts to app. 40 % of dose in animals and a dermal absorption of 20 % in humans is carried forward to the risk assessment noting that this may likely overestimate the internal dose from dermal exposures. The conclusions made for musk ketone regarding extent of absorption from the GI-tract are based on data generated for musk xylene, which is closely related in chemical structure and physicochemical properties. For this compound oral uptake amounts to app. 50 % of dose and a 50% absorption after oral uptake is therefore also assumed for musk ketone. The CSTEE accepts the approach performed by the evaluators.

### ***Acute toxicity***

Musk ketone only has a low acute toxicity after oral and dermal application with LD<sub>50</sub>-values > 2000 mg/kg, inhalation data are not available.

### ***Irritation and corrosivity***

Musk ketone is not a potent irritant to the skin and to the eye and is not corrosive. The required base set data for testing of skin irritation are not available. The RAR concludes that further testing for skin irritation is not necessary since skin irritation was not observed when suspensions with a high content of musk ketone were applied to the skin of rabbits and rats and skin irritation was also not observed after repeated dermal application and skin sensitisation studies in humans. The CSTEE accepts this justification.

### ***Sensitising properties***

A number of studies are available to assess the skin sensitising and photo allergenic potential of musk ketone both in animals and in humans. Based on these results, it can be concluded that musk ketone is a weak sensitiser in guinea pigs but did not show skin sensitisation in humans when applied in concentrations of up to 5 %.

### ***Repeated dose toxicity***

Regarding guideline studies, only a well performed dermal 90-day study is available and a NOAEL of 24 mg/kg bw per day is derived.

Most of the oral studies were not performed according to guidelines but were aimed to characterize enzyme induction and therefore used shorter durations. Regarding toxicity after oral administration, the RAR uses the LOEL from one of the enzyme induction studies and a comparison of the musk ketone enzyme induction data with those for the more intensively studied musk xylene for the risk characterisation. The CSTEE supports this approach.

### ***Genotoxicity***

Musk ketone was studied for genotoxicity in bacteria and in mammalian cells using a variety of endpoints. In bacteria, musk ketone was consistently negative in different strains of *S. typhimurium* and in *E. coli* PQ37. Musk ketone was also negative in gene mutation, chromosomal aberration and micronucleus assays in mammalian cells and did not induce unscheduled DNA synthesis in rat hepatocytes. Only a chromosome aberration test according to guidelines gave an equivocal result. In vivo, a mouse micronucleus test with very high doses was negative. Based on this consistent information, the rapporteur concludes that musk ketone is not genotoxic; this conclusion is supported by the CSTEE.

### ***Carcinogenicity***

Musk ketone has not been studied for carcinogenicity. The RAR uses experimental data on the related compound musk xylene for characterisation of this endpoint. Musk xylene causes liver adenoma and carcinoma in male and adenoma in female mice. The absence of genotoxicity and mechanistic studies support the conclusion that the tumors induced by musk xylene are a consequence of the enzyme inducing properties (induction of cytochrome P450 2B) representing a non-genotoxic mechanism for tumor induction. Despite possible differences in the mechanism of enzyme induction between musk xylene and musk ketone, the absence of genotoxicity for both compounds does not support a genotoxic mechanism of action. The RAR uses a threshold approach for musk ketone and applies the NOEL for enzyme induction in the calculation of MOS. No further testing is considered necessary resulting in conclusion ii). The CSTEE supports this approach.

### ***Reproductive and developmental toxicity***

Regarding reproductive toxicity, only a limited amount of studies is available. Based on the absence of effects on reproductive parameters in some of the well-performed subchronic studies and the results of a oral developmental toxicity study, the RAR derives a NOAEL for developmental toxicity of 45 mg/kg bw. In a peri/postnatal toxicity study, only marginal effects (small reduction in body weight gain and food consumption in pups) were seen at the highest dose levels of 7.5 mg/kg bw and a NOAEL for pups is derived as 2.5 mg/kg bw by a highly conservative approach since no effects on reproductive parameters were seen at 25 mg/kg bw.

## **3. Risk characterisation**

### ***Genotoxicity/Mutagenicity***

Because musk ketone is not mutagenic in vivo and in vitro, this endpoint was not considered further in the assessment.

### ***Carcinogenicity***

No carcinogenicity study is available; however, based on data with the closely related musk xylene it has to be assumed that musk ketone may also induce liver tumors in sensitive strains of mice. For musk xylene, enzyme induction after high doses suggests a threshold mechanism for tumor induction in rodents. The RAR concludes that there is no need for further testing of musk ketone and that the data available on musk xylene can be used for the risk characterisation. The CSTEE agrees with this approach and supports conclusion ii).

### ***Workers***

The exposure and effects assessment for musk ketone for many exposure scenarios result in large MOS and therefore in conclusion ii). The RAR derives minimal MOS for different endpoints using a endpoint specific approach which is not in accordance with the TGD. The derived minimal MOS vary with the endpoint considered and range from 10 – 900. This may represent a good approach for the adjustment of magnitude of MOS to the severity of effects observed, uncertainties in extrapolation and general understanding of available information in this specific area of effects.

For one of the occupational scenarios, a minimal MOS of 4 is derived and the RAR comes to conclusion ii) with the justification that the exposure and effects assessment are highly conservative and thus the low MOS provides adequate protection. For combined exposure and the endpoint peri/postnatal effects, a MOS of only 8 is derived in the text on page 91. The text on page 91 and table 5.1 does not indicate a MOS of 8 for combined exposure but gives MOS of 4 for scenario 1 regarding dermal exposure (it seems that the correction for only 50% absorption was not consistently used). Again, the RAR justifies conclusion ii) based on a conservative assessment of the NOAEL used for risk characterisation (the effects seen at the LOAEL were marginal and of uncertain biological significance) and a conservative exposure assessment. The CSTEE agrees with conclusion ii) due to a highly conservative assessment of exposures and a conservative method of determination of the NOAEL.

### ***Consumers***

Regarding consumer exposure, most of the MOS derived are above 100 and conclusion ii) is supported by the CSTEE.

The RAR should mention that the amine formed by reduction from musk ketone is a weak estrogen and is persistent in the environment.