EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Public Health and Risk Assessment
C7 - Risk assessment

Brussels, C7/VR/csteeop/musk xyl hh/080104 D(04)

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

Opinion on the results of the Risk Assessment of:

MUSK XYLENE
HUMAN HEALTH PART

CAS N°: 81-15-2

EINECS N°: 201-329-4

Carried out in the framework of Council Regulation (EEC) 793/93 on the evaluation and control of the risks of existing substances[1]

Adopted by the CSTEE during the 41st plenary meeting of 8 January 2004

[1] 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.

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

Opinion on the results of the Risk Assessment of:

MUSK XYLENE
HUMAN HEALTH PART

CAS N°: 81-15-2
EINECS N°: 201-329-4

Adopted by the CSTEE during the 41st plenary meeting of 8 January 2004

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 xylene is an aromatic nitro compound used as a synthetic fragrance. It is not produced in Europe but imported in amounts of < 100 tonnes per year. Musk xylene is used as fragrance in a variety of consumer products such as body care products and household detergents. The concentration of musk xylene in these products is usually < 1%. Human exposure to musk xylene 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 very large, when a MOS of < 100 is derived, the RAR adequately justifies conclusion ii) due to a very conservative exposure and effects assessment for many endpoints. CSTEE agrees with conclusion ii) for all exposure scenarios.

SPECIFIC COMMENTS

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

1. Exposure assessment

Human exposure to musk xylene may occur during occupational scenarios and due to skin contact with musk xylene containing products. Since measured data on occupational exposure are limited, the RAR uses physico-chemical data and data on production processes 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 risk characterisation. For the three scenarios, inhalation exposure is considered negligible due to the low vapor pressure of musk xylene. The major pathways of exposure predicted is skin contact which may reach up to 42 mg musk xylene/person/day for the scenario "production of fragrance compounds". Regarding direct consumer exposure due to the presence of musk xylene in cosmetics, the RAR relies on an evaluation by the SCCNFP (1999) which estimated a dermal exposure of up to 210 µg/kg bw per day due to use of cosmetics. Other routes of exposure are considered negligible (handling of powdered detergents and inhalation exposures). Indirect exposure via the environment is based on EUSES calculations and predicts only low human exposure through the indirect pathway.

2. Effects assessment

Toxicokinetics

Information on the toxicokinetics of musk xylene are only available regarding the dermal and oral route both in animals and in humans. The obtained results suggest that uptake from the skin amounts to app. 40 % of dose in animals and less than 20 % in humans. Using a conservative approach, a 50% absorption after oral uptake and a 20 % (rats) resp. 10 % (humans) dermal absorption are carried forward to risk characterisation. The CSTEE supports the approach performed by the evaluators.

Acute toxicity

Musk xylene only has a low acute toxicity after oral and dermal application with LD_{50}-values > 2000 mg/kg, data on acute toxicity after inhalation are not available.

Irritation and corrosivity

Musk xylene is not a potent irritant to skin in humans, it is not an eye irritant when using a standard protocol, and is not corrosive. The required base set data for assessment 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 xylene were applied to the skin of rabbits and guinea pigs. Skin irritation was also not observed after repeated dermal application in humans and in skin sensitisation studies. The CSTEE accepts this conclusion.

Sensitising properties

A number of studies are available to assess the skin sensitising and photo allergenic potential of musk xylene both in animals and in humans. The RAR concludes that the animal studies are inadequate for a conclusion on skin sensitising properties of musk xylene. Musk xylene did not show skin sensitisation in humans when applied in concentrations of up to 5 %. Based on this observation, the RAR concluded that musk xylene is not a skin sensitiser in humans.

Repeated dose toxicity

A number of repeated dose toxicty studies after oral and dermal applications are available, the only adequately reported study is a 90-day dermal study. Based on the results of this study, a conservative NOEL of 24 mg/kg bw per day is derived. Adequate data to establish an oral NOAEL are not available. Regarding the determination of a MOS for repeated oral exposure, the RAR uses a LOAEL for liver tumor induction in mice (the mechanistic information available demonstrates absence of genotoxicity and a thresholded mechanism of action) and the mouse NOEL for enzyme induction concluding that this is a conservative approach. The CSTEE agrees with these conclusions since musk xylene is consistently non-genotoxic and a plausible mechanism for liver tumor induction in a strain of mice prone to develop liver tumors has been characterized.

Genotoxicity

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

Carcinogenicity

Musk xylene has been studied for carcinogenicity in mice only and induced liver tumors after dietary administration of 750 and 1 500 mg/kg bw. In addition, a significant increase in the incidence of Harderian gland adenoma was observed in male mice. The absence of genotoxicity and mechanistic studies on enzyme induction support the conclusion that the liver 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. The RAR uses a threshold approach for musk xylene risk characterisation regarding carcinogenicity and applies the NOEL for enzyme induction in mice 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 repeated-dose studies and the results of an oral developmental toxicity study, the RAR derives a NOAEL for developmental toxicity of 60 mg/kg bw In a peri/postnatal toxicity study, only marginal effects were seen at the highest dose levels of 25 mg/kg bw and a NOAEL for pups is derived as 7.5 mg/kg bw using a conservative approach since only marginal effects (small reduction in weight gain) were seen at the higher dose level.

3. Risk characterisation

Genotoxicity/Mutagenicity

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

Carcinogenicity

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 xylene 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 xylene for many exposure scenarios result in large MOS and therefore in conclusion ii). The RAR derives minimal MOS for different endpoints using an 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 17 resp. 13 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.

Consumers

Regarding consumer exposure, most of the MOS derived are very large and conclusion ii) is supported by the CSTEE. Some of the MOS derived are < 100, but 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 very conservative exposure assessment. The CSTEE agrees with this approach.

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