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Directorate C - Public Health and Risk Assessment
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SCIENTIFIC COMMITTEE ON HEALTH AND ENVIRONMENTAL RISKS

SCHER

Opinion on

Risk Assessment Report on 2,4,4-Trimethylpentene

Human Health part

CAS N°: 25167-70-8

EINECS N°: 246-690-9

Adopted by the SCHER
during the 11 plenary of 4 May 2006

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1. BACKGROUND

Council Regulation 793/93 provides the framework for the evaluation and control of the risk of existing substances. Member States prepare Risk Assessment Reports on priority substances. The Reports are then examined by the Technical Committee under the Regulation and, when appropriate, the Commission invites the Scientific Committee on Health and Environmental Risks (SCHER) to give its opinion.

2. TERMS OF REFERENCE

On the basis of the examination of the Risk Assessment Report the SCHER is invited to examine the following issues:

(1) Does the SCHER agree with the conclusions of the Risk Assessment Report?

(2) If the SCHER disagrees with such conclusions, it is invited to elaborate on the reasons.

(3) If the SCHER disagrees with the approaches or methods used to assess the risks, it is invited to suggest possible alternatives.

3. OPINION

3.1 General Comments

The document is written in accordance with the requirements of the TGD and addresses all relevant endpoints in sufficient detail. However, the RAR would benefit from a thorough editing (for instance, there should be consistency in the use of units, English spelling should be used throughout the document, and several references need to be corrected in the text). The SCHER also notes that the term “sub-acute” should not be used and be replaced by information on the study duration. The SCHER further notes that, throughout the document, the term “α2μ globulin” should be replaced by the correct term, i.e., “α2u globulin”. Moreover, the procedure described for risk estimation of 2,4,4-trimethypentene shows considerable weaknesses and needs to be amended.

3.2 Specific comments

2,4,4-Trimethylpentene is a liquid with a vapour pressure of 58 hPa at 25°C. The substance is generally produced and processed in closed systems, and mainly used as intermediate in the chemical synthesis of aldehydes, alkyl phenols and polymers. A small quantity is used as stabilising agent in degreasers for the metal industry. Occupational exposure may occur through the respiratory and the dermal routes with highest exposures occurring during production and processing. Other scenarios, such as exposure through degreasing agents and residues in polymers were considered to be of minor relevance. Consumer exposure is not known to occur.

No toxicokinetic, metabolism or distribution studies in animals were available for 2,4,4-trimethylpentene.

The substance is of low acute oral, dermal and inhalation toxicity in animals (LD_{50} values of greater than 2000 mg/kg bw for the oral and dermal routes with no specific signs of toxicity; LC_{50} values of ca. 30 mg/L/4 hrs in rats), but aspiration was considered a significant hazard for C6-C14 olefins.

2,4,4-Trimethylpentene is slightly irritating to the skin and eyes of rabbits, and has been shown to irritate human nasal mucosa and throat at a concentration of 0.47 mg/L. Three out of 20 test animals were tested positive in a skin sensitisation test according to OECD TG 406 (maximisation test according to Magnusson and Kligman). Data on the sensitisation potential in humans were not available.

Liver and kidneys are the main target organs after repeated exposure of rats to 2,4,4-trimethylpentene. In a modern 28-day oral guideline study, increased absolute and relative liver weights (in both sexes) and kidney weights (in males only) were found at 1000 mg/kg bw/day. The NOAEL in this study was at 300 mg/kg bw/day, whilst the LOAEL for male rats in an oral screening study according to OECD TG 421 was at 100 mg/kg bw/day based on increased kidney weights and α2u globulin nephropathy. No reliable studies were available for the respiratory and dermal routes of exposure.

No data was available on the genotoxicity of 2,4,4-trimethylpentene in humans.. 2,4,4-Trimethylpentene was tested negative in an Ames test which was performed according to current guidelines with and without a metabolic activation system. For completeness, the results of an earlier study by Henschler *et al.* (1977) should be incorporated in the RAR. In this study, 2,4,4-trimethylpentene (erroneously also called 2,2,4-trimethylpentene-1 in the publication) showed a “very low activity”. Due to limitations in reporting, this result is, however, difficult to interpret. No clastogenic activity was found in an *in vitro* cytogenetic test performed on human lymphocytes according to current guidelines. However, these negative findings have to be evaluated with caution. As described in the RAR the compound may be epoxidized by liver microsomal enzyme activity. This renders the slightly positive results of the study by Henschler et al (1977) plausible. Thus, the negative results in the more recent *in vitro* genotoxicity tests may be false negatives and need to be repeated because it nis not clear whether these tests have been performed under conditions that avoid evaporation of the volatile test compound. There were no *in vivo* studies available to corroborate these negative findings.

There were no epidemiology data or data from animal carcinogenicity studies with 2,4,4-trimethylpentene available. However, 2,4,4-Trimethylpentene induced α2u-globulin nephropathy in male rats, similarly to the structural analogue 2,2,4-trimethylpentane, which was shown to be a renal tumour promoter specifically in male rats.

A reproductive toxicity screening test was performed according to OECD TG 421 with oral administration of 2,4,4-trimethylpentene to CD rats during pre-mating, mating, gestation and until lactation day 4. There were no indications for an adverse effect on reproductive performance, peri- and post-natal viability and performance of offspring (NOAEL: 1000 mg/kg bw/day).

3.3 Risk Characterisation

Whilst the most relevant human exposure routes are the dermal and the respiratory routes, the available repeated dose toxicity data is limited to the oral route. Hence, route-to-route extrapolation is necessary. For dermal and oral absorption a default value of 100% was assumed; for the respiratory route, only a 10% absorption was assumed based on data with a similar compound (2,2,4-trimethylpentane). The SCHER notes that, in the absence of substance-specific absorption data, the default for absorption by inhalation should generally also be 100%, although this would not alter the outcome of the risk characterization. The 10% assumed by the authors are based on uptake data from Dahl et al (1988) obtained in rats at 100 ppm exclusively and with another compound (2,4,4-trimethypentane). It is not appropriate to assume, that a most likely wrong value is applicable for another compound at another concentration in another species.

With regard to other aspects of uncertainty, the SCHER questions the use of different adjustment factors. The uncertainty factor of 6 for duration adjustment of repeated dose toxicity data should have been evaluated and possibly been adjusted by considering data from other repeated dose studies like the OECD TG 421 assay.

A reasonable procedure for estimating a limit for occupational exposure from an oral repeated dose animal study is as follows, in case no metabolism and no kinetic data are available: Considering the allometric relationship (body weight)$^{2/3}$ (see Davidson et al 1986, US FDA 2002) a NOEL of 300 mg/kg/d in the rat is equivalent to 300 / 6.54 = 46 mg/kg/d in man. For a worker of 70 kg this amounts to a total daily exposure of 46 x 70 = 3220; inhaling 10 m^3 per shift this is equivalent to 322 m^3 per hour. This value might be adjusted by appropriate uncertainty factors.

Overall, the SCHER agrees with conclusion (ii) for all scenarios (occupational and consumer exposure) and all endpoints. As α2u-globulin nephropathy is a gender- and species specific disease which has no relevance for humans. However, because SCHER assumes that the negative tests for mutagenicity and chromosomal aberrations may be false, SCHER proposes conclusion (i) for mutagenicity (need for further information/testing).

The SCHER notes that the risk characterisation for man exposed via the environment has yet to be completed.

4. LIST OF ABBREVIATIONS

NOEC	No Observed Effect Concentration
PEC	Predicted Environmental Concentration
PNEC	Predicted No Effect Concentration
RAR	Risk Assessment Report
TGD	Technical Guidance Document

5. REFERENCES

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6. ACKNOWLEDGEMENTS

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