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

Opinion on the results of the Risk Assessment of:

n-PENTANE

Human Health Part

CAS No.: 109-66-0

EINECS No.: 203-692-4

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

Opinion expressed at the 35th CSTEE plenary meeting

Brussels, 17 December 2002

[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.

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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 provided by the European Chemicals Bureau, 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.

Introduction

n-Pentane is a high volume chemical and is mainly obtained from the processing of crude oil or natural gas. n-Pentane is used as a solvent for technical processes requiring highly volatile solvents such as polymer production, generation of aerosols and in adhesives; it is also a component of gasoline and natural gas.

General Comments

The document follows the recommendations of the TGD and is comprehensive, well written and clearly structured.

Specific Comments

HUMAN HEALTH RISK ASSESSMENT

1. Exposure assessment

Due to the high volatility of n-pentane, inhalation is expected as the major pathway of human exposure. In the document, three different scenarios for occupational exposures are developed, the predicted exposures form applying exposure models are supported by measured data. Scenario 1 represents exposure during n-pentane isolation which occurs in closed systems and therefore may result only in inhalation exposure due to high volatility during opening of the reaction vessels for sampling

and discharging. These operations may results in high exposure concentrations (close to current short-term occupational exposure limits) for a short time. In scenario 2, use of n-pentane as solvent in production of polymers and aerosol containers, high inhalation exposures may also occur for a short duration. For the scenario 3, professional end-use of n-pentane containing products, it is concluded that inhalative exposure to n-pentane may occur during the use of aerosol-cans containing n-pentane. The use of hairspray in hair salons is identified as a use with presumably the highest possible inhalation exposures; other applications are also mentioned, but are estimated to result in only low exposure concentrations.
Use of hair spray and car care products may result in intermittent exposure of consumers to low concentrations of n-pentane. Based on exposure assessment methods from the TGD, indirect human exposure to n-pentane is also to be concluded to be low.

2. Effects assessment

Acute toxicity

n-Pentane is of low acute toxicity by inhalation, oral administration and i.v. application. In experimental animals, as typical for solvents, neurobehavioral and neurotoxic effects are major toxic endpoints seen. For neurobehavioural effects in animals after acute exposure, a direct NOAEC or LOAEC is not derived in the RAR, but reasons for this are elaborated later in the document (page 104). The CSTEE agrees with this conclusion.

Irritation, corrosivity and sensitisation

The CSTEE agrees that cyclohexane is not a strong skin or respiratory sensitiser and only a slight irritant to skin and mucous membranes.

Toxicokinetics

Inhaled n-pentane is rapidly absorbed by the lungs and also rapidly eliminated by both exhalation and by biotransformation. Only a minor part of the dose is excreted as metabolites in urine since the initially formed products by a cytochrome P450-dependent oxidation (2- and 3-pentanol) are rapidly converted further to CO_2. Elimination of n-pentane is rapid and potential for accumulation in tissues is correctly assumed to be very low.

Repeated dose toxicity

It is noted that an additional inhalation study with n-pentane has been published in the literature (Stadler JC *et al.*, 2001). The no-observed-adverse-effect level in this study was 1,000 ppm with reversible clinical pathology changes produced at 3,000 and 10,000 ppm.

Genotoxicity

In vitro, n-pentane was not mutagenic in different strains of Salmonella typhimurium, both in the absence and in the presence of a metabolic activation system. n-Pentane

was tested negative, even at cytotoxic concentrations, and modifications to the standard protocol were made to account for the volatility of the test substance. No biologically significant increase in chromosomal aberrations was found in cultured mammalian cells (CHO cells) in a test performed according to current guidelines.

In vivo, n-pentane did not induce an increase in micronuclei or cytotoxicity in bone marrow cells of rats exposed to 5,000, 10,000 or 20,000 mg/m3 for 90 days (6 h/d; 5 d/week). The study was performed according to current standards and is well described in the RAR. It should be mentioned, however, that no clinical signs of toxicity were observed.

There are no data on the genotoxicity of n-pentane in humans.

The CSTEE agrees that, based on the available data, n-pentane can be considered as non-genotoxic.

Carcinogenicity

No human or animal data are available on the carcinogenicity of n-pentane.

Given the results from the mutagenicity and repeated toxicity studies, and the lack of a structural alert, the CSTEE agrees that there is no concern for carcinogenicity, and that there is at present no need for further information and/or testing regarding this endpoint.

Reproductive toxicity

No one or two generation study on reproductive toxicities of n-pentane is available. However, in a 13-week inhalation study in male and female rats, no signs of toxicity to reproduction were noted after exposure to n-pentane concentration up to 20,000 mg/m^3 (6 660 ppm). The CSTEE agrees with the conclusion ii) regarding this endpoint.

Developmental toxicity

Developmental toxicity of n-pentane was not observed in studies in rats performed according to current guidelines. A maternal and developmental NOAEL of $\geq$ 1 000 mg/kg was observed

3. Risk characterisation

Acute and repeated-dose toxicity

Some of the exposure estimates for the occupational scenarios and the derived MOS are < 100, however, the authors of the RAR explain why they selected conclusion ii) based on the likely overestimation of total exposure due to an assumed retention of 100 % after inhalation, unlikely prolonged exposures due to industrial practices and an overestimated dermal uptake of n-pentane in the models used. Therefore, the CSTEE supports conclusions ii) for all endpoints regarding worker and consumer exposure. Very high MOS-values are derived for indirect human

exposures and, therefore, conclusion ii) is also supported.

Genotoxicity

Based on the available negative in vitro and in vivo mutagenicity data, the CSTEE supports the view that there are no concerns for genotoxicity and agrees with the overall conclusion (ii) for this endpoint.

Carcinogenicity

Based on the negative results from mutagenicity studies and results from chronic studies and the lack of a structural alert in the molecule, the CSTEE supports the view that there are no concerns for carcinogenicity and agrees with the overall conclusion (ii) for this endpoint.

Reference:

Stadler JC, O'Neill AJ, Elliott GS, Kennedy GL Jr. (2001): Repeated exposure inhalation study of pentane in rats. Drug Chem Toxicol 24(2):75-86 (Haskell Laboratory for Toxicology and Industrial Medicine, DuPont Co., P.O. Box 50, Newark, DE 19714, USA.)