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

Opinion on the results of the Risk Assessment of:

CYCLOHEXANE

CAS No.: 110-82-7
EINECS No.: 203-806-2

REPORT VERSION (Human Health)
September 2001

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 29th CSTEE plenary meeting

Brussels, 09 January 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.

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.

Introduction

Cyclohexane is a high volume chemical; approx. 900 000 tonnes are used per year in the EU. Cyclohexane may either be synthesised from benzene or isolated from petroleum hydrocarbons. The majority of the produced Cyclohexane is used as an intermediate in the production of Nylon; minor uses are as a solvent, in glues, adhesives and in printing inks.

General comments

The document follows the recommendations of the TGD and is comprehensive. However, linguistic problems and incorrect use of toxicological terms make the document difficult to read. For example, concentrations of a chemical in air are not equivalent to the dose of the chemical received; several tables do not have annotations or present data which cannot be interpreted as written (*e.g.* tables 4.9, 4.10). For exposure concentrations, sometimes mg/m^3 or ppm or both are used. However, the use is inconsistent. A list of abbreviations is missing.

Specific comments

1. Exposure assessment

Due to the high volatility of Cyclohexane, inhalation is expected as the major pathway of exposure. In the document, four different scenarios for occupational exposures are developed; the predicted exposures in the scenarios are supported by measured data. Scenario 1 represents exposure during Cyclohexane production, which occurs in closed systems and therefore results only in air concentrations well below current threshold limit values. In scenario 2, use as intermediate in the chemical industry, exposures are also assumed to be low. High exposures to Cyclohexane (predicted by modelling to be up to 1 000 ppm, measured data up to 365 ppm, no time of sampling given) occur during formulation and industrial use of Cyclohexane (scenario 3) containing products in industry (main sources of exposure are estimated as evaporation of Cyclohexane from paints and adhesives). Scenario 4 (exposure to Cyclohexane in craft industries) also results in high exposures (estimated in the range of up to 500 ppm in the document). The major source of consumer exposures are

emissions of Cyclohexane from carpet adhesives during carpet laying which are estimated to result in inhalation exposures of up to 1000 ppm. The data on environmental effects indicate a potential for accumulation of Cyclohexane in the food chain. However, the rapid excretion of inhaled or orally administered Cyclohexane in mammals does not suggest a potential for accumulation in mammals (half-life of 10 – 15 hours in plasma and tissues including adipose tissue).

2. Effects assessment

While the CSTEE agrees with the final conclusions of the toxicokinetics chapter, the chapter should be revised using accurate terminology. Moreover, the tables 4-9 and 4-10 should either be omitted or revised to present relevant and interpretable information.

Acute toxicity

Cyclohexane is of low acute and chronic toxicity and, as is typical for solvents, neurobehavioral and neurotoxic effects are major toxic endpoints seen after Cyclohexane inhalation. For neurobehavioral effects in animals after acute exposure, a very conservative NOAEL of 400 ppm is defined. In humans, a NOAEL of 250 ppm can be assumed for neurotoxicity based on experimental data. In the report, extrapolation from a well-designed and performed neurotoxicity study in animals to the human situation using a PBPK-model is described. The use of the model would result in a NOAEL in humans of 1200 ppm Cyclohexane in air. The information to be derived from these data and the validity of the model should be discussed and the information given in the annex should be expanded for a better rationale on why the model data are not used in the risk characterisation. More details of the results of the TNO-study (blood and brain concentrations of Cyclohexane) should be given.

Sensitisation and irritation

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

Repeated dose toxicity

Inhalation exposure to concentrations of Cyclohexane up to 7 000 ppm in rats and mice for 90 days resulted in neurobehavioral effects with a NOAEL of 500 ppm and in increased liver weights with a NOAEL of 2000 ppm. The results of the rat study are adequately described in the report. The description of the results of the mouse study on page 70 is inconclusive.

Mutagenicity

Cyclohexane was tested for genotoxicity in bacteria, in mammalian cells *in vitro* and in animals *in vivo*. In all well evaluated test systems, Cyclohexane did not induce effects indicative of genotoxicity. The CSTEE agrees with the conclusion that the data do not suggest that Cyclohexane has genotoxic properties.

Carcinogenicity

Despite the lack of a carcinogenicity study performed according to current protocols, the available data on genotoxicity do not suggest that Cyclohexane is carcinogenic in animals by a genotoxic mechanism.

3. Risk characterisation

Due to the high exposures in scenarios 3 and 4 for workers, the high potential consumer exposure, and the low (or non-existing) MOS, conclusion iii) is supported by the CSTEE. Since Cyclohexane does not exert genotoxic effects, there is no concern regarding induction of carcinogenicity by genotoxic mechanisms. However, non-genotoxic carcinogenicity cannot be ruled out in the absence of appropriate studies. Taking into account the high worker and consumer exposures which are close to or exceed the NOAEL of the 90-day study, CSTEE does not agree with the RAR statement that there is no need for further testing. On page 95, conclusion iii) is incorrectly expressed as iv).