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

Opinion on the results of the Risk Assessment of:

1,2,4-Trichlorobenzene

CAS N°: 120-82-1

EINECS N°: 204-428-0

REPORT VERSION: Final version - 20 March 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 25th CSTEE plenary meeting

Brussels, 20 July 2001

[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.

GENERAL COMMENTS

1,2,4-trichlorobenzene (1,2,4-TCB) is an organic chemical strictly of synthetic origin. It is manufactured and used in the chemical industry as an intermediate in closed systems in the processing of herbicides and higher chlorinated benzenes. It is also used as a dye carrier, in sprays as a corrosion inhibitor and in metal working fluids. In the period 1994/1995, 7,000 tonnes have been produced in Europe. Trichlorobenzene may also be formed during combustion of chlorinated organic material or following environmental degradation of hexachlorocyclohexanes and other highly chlorinated benzenes.

The report is of good quality, it follows the recommendations of the TGD and is adequately documented with relevant references.

The CSTEE agrees with most of the proposed classification and labelling and of the conclusions, however, the Committee does not agree with the conclusion of low risk for secondary poisoning.

Environment

The environmental part of the RAR is well written and presents the results in a clear form. The CSTEE acknowledges the efforts to consider special concerns in addition to the standard assessment and in particular the discussion on the potential POP properties of 1,2,4-Trichlorobenzene.

Formation of 1,2,4-TCB as a metabolite resulting from degradation of lindane has not been (on purpose) taken into consideration in the RAR. Although the CSTEE acknowledges that this is a difficult issue especially in the framework of Regulation 793/93, this may lead to underevaluation of some local PEC because of the wide use of lindane in the past and of its persistence in the environment. Due to the long-term adverse effects of 1,2,4-TCB in the aquatic environment and

the possibility of leakage of this substance from contaminated soils, this should be better assessed.

Because the atmosphere is estimated to be the primary recipient of released 1,2,4-TCB, tests should be conducted to assess its effect on organisms living in this compartment. In particular, toxicity data on plants and foliar dwelling invertebrates should be requested and a proper risk assessment should be conducted.

The CSTEE does not agree with the conclusion of low risk for secondary poisoning. The evaluation of the available information indicates a potential risk for fish eating mammals. No information on the toxicity of this chemical to birds is available, but the risk of mammals could be extended to birds assuming a similar toxicity. Therefore, the CSTEE considers that a reproduction study on birds and a new assessment of secondary poisoning is required. Toxicokinetic data suggest a rapid depuration time from fish and mammals, therefore, low risk for biomagnification is expected.

Human Health

Evaluation of the irritating potential of the substance to the eye and the lung should be better evaluated as the available data are not convincing. In addition, the CSTEE draws attention to the need to clarify the issue of adrenal enlargement observed in some toxicity tests

SPECIFIC COMMENTS

Environment

Exposure

The PEC oral, fish reported in Tables 3.33 and 3.47 seems to include erroneous calculations. For a local PEC water of 0.068, assuming 50% of the exposure from the local scenario and a BCF of 2000, the PEC oral fish should be 64mg/kg, while the table reports a value of 1.88 mg/kg.

Effects assessment

Effects of 1,2,4-trichlorobenzene to the aquatic environment are assessed on the basis of a large number of data on algae crustaceans and fish (short and long term). Even if not all toxicity data are produced with methods suitable for this volatile chemical, valid data are enough to calculate a reliable PNEC for the aquatic environment.

Some relevant ecotoxicity tests are available to assess the effects of 1,2,4-TCB on various organisms and with various end points in the terrestrial compartments but not at all in the atmosphere, which is a noticeable lack.

The PNEC soil organisms derivation has been properly addressed and the PNEC derivation is acceptable considering the current data. However, only acute tests are available and chronic toxicity data would refine the real risk.

The PNEC derivation is based on the concentration in food, 100 ppm, corresponding to 6 mg/kg bw day. However, the report does not consider that the daily food intake of the laboratory animals was much lower than that expected for wild mammals. The estimated daily food intake in the test was about 6%, while for risk assessment, worst cases values of 20-25% for mammals and up to 30% for birds should be used. The CSTEE recommends to consider the PNEC oral of 0.6 mg/kg bw/day, and considers the expected food intake in the risk characterisation. The risk characterisation for secondary poisoning should, therefore, considers an exposure level of 12.8 mg/kg bw/day (for a PEC oral fish of 64 mg/kg and a 20% of daily food intake), and a PNEC oral of 0.6 mg/kg bw/day. The PEC/PNEC ratio is about 20 for the worst scenario (D4 dye carrier), and should be also above 1 for the D3 others scenario.

The chemical has potential for bioaccumulation, however, due to the rapid depuration in fish and mammals the potential for biomagnification through the food chain is low.

Risk characterisation

Due to the lack of data, no risk assessment has been conducted for atmospheric exposures. The RAR has addressed the POP potential of this chemical and the CSTEE supports the conclusion to further consider 1,2,4 TCB in relation to the POP issue. In addition, toxicological information on relevant species and by this route should be required. The soil toxicity data suggest the sensibility of terrestrial plants exposed through soil. Therefore, the risk derived from air exposures should be investigated.

The risk for fish eating birds should be estimated and therefore, reproduction toxicity tests on birds are required.

The risk assessment for secondary poisoning is not supported by the CSTEE. Problems have been identified in both, exposure and effect assessment calculations.

The CSTEE agrees with conclusion iii (need for limiting the risk) applied to some site-specific processing conditions.

Human Health

Exposure

The possibility of exposure of farmers to 1,2,4-TCB contained in sewage sludges spread on fields may have been discussed.

Effects assessment

The effects assessment part of the document is comprehensive and of good quality.

Eye irritation

The available results are controversial, in order to clarify this point, further testing is needed.

Lung irritation

Since 1,2,4-TCB is volatile and because the available data are very limited, lung irritation should be better assessed.

Mutagenicity / Genotoxicity

1,2,4-TCB was negative in several standard and one pre-incubation Ames tests both in the absence and in the presence of metabolic activation, and did not induce mitotic recombination in yeast. No cytogenetic effects have been noted *in vitro* in CHO and CHL cell lines. However, metabolic activation was not used in these assays. It was also negative in two *in vitro* UDS assays with rat hepatocytes.

1,2,4-TCB has shown effects on DNA repair in a *Bacillus subtilis* rec assay after metabolic activation and, only in the absence of S-9, in the umu-test.

Two inadequately reported *in vivo* micronucleus tests in mice after intraperitoneal injection of 1,2,4-TCB were positive; a further test, adequately conducted according to current OECD guideline with oral administration of 1,2,4-TCB was negative. In the RAR, there is inconsistency between the text and the information given in Table 4.21 regarding the vehicle used in the micronucleus study of Parrini et al., and the wrong Table number is cited in the Lehn study description.

In summary, there are conflicting results from different genotoxicity tests, but overall the assessor concludes that 1,2,4-TCB is not considered as being genotoxic.

The CSTEE agrees with the assessor that 1,2,4-TCB is not considered a mutagen.

Carcinogenicity

After oral administration in the diet, 1,2,4-TCB induced significant increases in hepatocellular carcinomas in B6C3F1 mice and a not statistically significant increase, without clear dose-response relationship, in the number of tumours of the Zymbal gland in F 344 rats. The liver tumours in mice are not considered to be relevant for humans, as this strain is known to produce a high incidence of hepatocellular carcinomas when exposed to substances, which have a toxic effect on the liver. The Zymbal gland tumours in the rat are of some concern, though their relevance is presently unclear. The CSTEE recommends performing a study of covalent binding to DNA with the Zymbal gland in order to shed more light on the tumour response. For B6C3F1 mice, the NOAEL was 150 ppm (appr. 21-26 mg/kg bw/d).

A rat liver epithelial cell transformation assay was positive at concentrations which caused severe cell toxicity (in the RAR, this assay is described under mutagenicity/genotoxicity, but should be moved to the carcinogenicity chapter).

1,2,4-TCB did not show any promoter activity in rat liver after initiation with diethylnitrosamine.

No carcinogenic effect was seen in Slc:ddy mice after dermal application.

The CSTEE agrees that 1,2,4-TCB is not classifiable as to its carcinogenicity to humans.

Risk characterisation

Mutagenicity

The CSTEE agrees that 1,2,4-TCB cannot be characterised as being genotoxic and agrees with the conclusion (ii) for this endpoint for all scenarios.

Carcinogenicity

The CSTEE agrees that 1,2,4-TCB cannot be considered as carcinogenic. The primary concern for a carcinogenic effect is associated with the potential of 1,2,4-TCB to cause changes in the liver, and a clear NOAEL could be established for the absence of effects on the liver. Thus, the CSTEE agrees with the conclusion (ii) for this endpoint for all scenarios.

Repeated dose toxicity

The CSTEE agrees with the NOAEL of 6mg/kg bw/day that would lead to conclusion iii) for several exposure scenarios for both workers, consumers and man indirectly exposed via the environment.