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

Opinion on the results of the Risk Assessment of:

TRICHLOROETHYLENE

CAS NO: 79- 01- 6
EINECS NO: 201-167- 4

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

Trichloroethene is a widely used industrial chemical, which has been in use for over 100 years. Due to its widespread application and long-term use, an extensive database on the toxicology of trichloroethene in experimental animals and in humans is available. Trichlorethene is mainly used as an inert solvent for degreasing operations, as a solvent in adhesives, and as chemical intermediate.

General comments

The document follows the recommendations of the TGD and is comprehensive and well written. The CSTEE agrees with the conclusion iii) for most exposure scenarios since trichloroethene may be regarded as a weak mutagen and a weak carcinogen. Conclusion ii) is supported for irritation since trichloroethene has only a low potential for skin and eye irritation.

Specific comments

1. Exposure assessment

Due to the high volatility of trichloroethene and its low toxicity, inhalation and dermal contact are expected to be major pathways of exposure both to workers and consumers. Occupational exposure may occur during the manufacture of trichloroethene, recycling of degreasing baths, during metal cleaning and during the manufacture of adhesives. Measured exposure data (8hr TWAs) range from 0.2 to up to 600 ppm, with geometric means in the range between 0.1 and 9 ppm. The occupational exposure data used in the document are mainly based on measured data generated by companies in the United Kingdom. The available data from other EU countries are not reported in the document, it is only mentioned that exposures under less strict occupational hygiene may be substantially higher.

Consumer exposures to trichloroethene are estimated by modelling (use of trichloroethene as spot cleaner) and by using measured data on the concentration of trichloroethene in air, drinking water and biota. Use of trichloroethene in spot cleaners (commercially available in some EU countries) is predicted to result in a potential inhalation exposure of up to 1.9 g trichloroethene/day by inhalation and of up to 2,5 g trichloroethene by dermal contact.

2. Effects assessment

Acute toxicity
The acute toxicity of trichloroethene after oral uptake, inhalation and skin contact is low. Signs of CNS-depression are the major toxic effects observed after single exposures to trichloroethene both in laboratory animals and also in humans after accidents or use of trichloroethene as inhalation anaesthetic. Under several of the exposure scenarios developed in the RAR, the MOS between the NOAEL and estimated exposures are low, conclusion iii) is therefore supported by the CSTEE.

Toxicokinetics
The RAR comprehensively describes the toxicokinetics of trichloroethene in rodents and in studies with controlled human exposure. Trichloroethene is rapidly absorbed and distributed in the organism, elimination of trichloroethene occurs by exhalation of the unchanged parent compound and by biotransformation. The extent of trichloroethene metabolised is highly dose and species specific with the highest rates of biotransformation observed in mice. Metabolites (glutathione conjugate-derived) assumed to be responsible for nephrotoxicity and renal tumour induction by trichloroethene are only excreted in very low concentrations as a very minor fraction of total metabolism. Qualitatively, trichloroethene biotransformation is identical in all species studied so far.

Irritation and corrosivity
Although no appropriate experimental studies are available, the human experience and the available animal data indicate that, due to its defatting properties on the skin, trichloroethene is a skin and eye irritant. However, trichloroethene is not corrosive to skin.

Sensitising properties
Results of animal experiments on sensitising properties for trichloroethene are not available. However, despite widespread use of trichloroethene, there are very few reports on skin sensitisation in humans and no reports on respiratory sensitisation. The CSTEE agrees that trichloroethene should not be classified as a skin and respiratory sensitiser.

Repeated dose toxicity
After repeated administration, the main target organs for trichloroethene toxicity are the liver in mice and the kidney in rats. A NOAEL of 500 mg/kg/day is derived for liver toxicity in mice and a NOAEL of 50 mg/kg/day for kidney toxicity in rats. The NOAEL for neurotoxicity in rats is derived from a well conducted 13 week study and is 250 ppm.

Genotoxicity
Trichloroethene genotoxicity has been studied both *in vivo* and *in vitro* using many different endpoints. The interpretation of many of the older studies is hampered by impurities in the trichloroethene used or by mutagenic stabilisers added. Purified trichloroethene, in *Salmonella typhimurium*, is a weak mutagen. The results of other studies also provide evidence that trichloroethene is a weak mutagen *in vitro*. The RAR should also summarise the studies on the bacterial mutagenicity of trichloroethene metabolites such as DCVC, since these studies are important in the context of discussions on mutagenicity and carcinogenicity of trichloroethene.

The conclusion of the *rapporteur* (p. 211) that trichloroethene is not a mutagen in vivo is contradicted by the recent EU classification in category M3 (see p. 214). It is not helpful for the reader if this opinion of the *rapporteur* is expressed. It would be better to only describe the discussion and final outcome of the Specialised Experts decision as stated on p. 214.

Carcinogenicity
The carcinogenicity section of the RAR is extensive and comprehensively summarises the available data on carcinogenicity of trichloroethene in rodents.

Trichloroethene carcinogenicity has been studied in more than 20 bioassays after inhalation or oral administration in rats and mice. Oral administration and inhalation of trichloroethene in mice resulted in an increased incidence of hepatocellular carcinoma. In addition, trichloroethene inhalation also caused lung tumours in mice. In rats, trichloroethene inhalation caused nephrotoxicity; oral administration resulted in a consistent increase of the incidence of rare renal tubular adenomas and adenocarcinomas in association with pathological changes.

Renal tumours induced in inhalation experiments of Maltoni (1986) are called “tubular adenocarcinomas” in the description of the study (page 215) and those found in excess in the gavage experiment are described as “renal tubular cell adenomas and adenocarcinomas” (pages 216-217). Nevertheless, these renal tumours in rats treated with trichloroethene become “renal tubular adenomas” in the summary of animal carcinogenicity (page 219). This discrepancy between terms alluding respectively to malignant and benign tumours should be clarified. If the *rapporteur* has doubts on reliability of diagnosis of renal tumours, he should spell these doubts out.

The document also extensively discusses the presumed mechanisms of target organ specific carcinogenicity of trichloroethene in rodents. Mouse liver tumours are thought to be induced by trichlorethene through peroxisome proliferation induced by the metabolite trichloroacetic acid. Trichloroacetic acid is formed in mice at much higher rates as compared to rats and humans. Since there are major species differences in the peroxisome-proliferation mediated effects of trichloroethene, the hepatotoxic effects of trichloroethene in mice are judged of little relevance to humans.

The species selective toxicity of trichloroethene to mouse lung is likely to be due to a highly efficient biotransformation of trichloroethene chloral hydrate in mouse lung. The available data suggest that trichloroethene biotransformation in human lung is much less efficient as compared to mouse lung; therefore, mouse lung tumours observed after trichloroethene inhalation are considered of little relevance for human hazard assessment at low exposure conditions.

A proposed mechanism to explain nephrotoxicity and renal tumour induction by trichloroethene is based on the observation that a minor trichloroethene metabolite causes selective nephrotoxicity in rodents. Trichloroethene is conjugated to give DCVG, a precursor of DCVC, at very low rates in rats, and formed DCVC is bioactivated by ß-lyase in the kidney.

Glutathione conjugation of trichloroethene and metabolism by the mercapturic acid pathway have been proposed to be involved in the renal carcinogenicity of trichloroethene. Studies have shown that DCVC and other trichloroethene metabolites are toxic to rat renal tubular cells in culture and are mutagenic, however, the relative contribution of genotoxic and non-

genotoxic events (chronic renal toxicity) to trichloroethene induced renal tumour formation in male rats is not defined.

While the CSTEE supports the conclusions on relevance of lung and liver tumours, the section on mechanism of action could be shortened since a defined mechanism for the induction of kidney tumours cannot be presented and genotoxic metabolites seem to be involved (p. 232); thus, a genotoxic mechanism of action may be assumed for hazard identification.

The RAR also contains a detailed description of the epidemiology of cancer in trichloroethene exposed populations. In general, cohort studies in trichloroethene-exposed populations did not detect an increase in overall cancer mortality or, when investigated, cancer incidence. Breakdown of cancer mortality or cancer incidence by anatomical sites gave inconsistent results. Cancer incidence or mortality was decreased for some target organs and increased for some others in the exposed groups. In individual studies, the liver cancer incidence in the exposed group in one study was significantly increased, the increase occurred in the highest exposure group with the longest exposure duration. However, an increase in liver cancer mortality was not seen in much larger studies with comparable exposures.

One cohort study reported an association between trichloroethene exposure and kidney cancer. The exposed group in the study was specifically exposed to high concentrations of trichloroethene by inhalation for more than 20 years and had an almost fourfold excess of kidney cancer incidence. The results of this study are supported by results from a case-control study showing an association between trichloroethene exposure and renal cancer. The authors found a greater than ten-fold increased risk for kidney cancer associated with occupational exposure to high concentrations of trichloroethene for a prolonged time. The RAR seems to downplay these findings on kidney cancer in workers and the overall assessment gives too little weight to the corroborative kidney tumour findings in rats and the possible genotoxic mechanism.

The design of these studies is criticised and several shortcomings are noted in the RAR and also in the scientific literature. However, the epidemiological studies of Henschler *et al.* and Vamvakas *et al.* have, despite their weaknesses, also advantages compared to the other epidemiological studies. In both studies, exposure has been exceptionally high whereas the other studies with measured exposure report only low exposure levels (Antilla *et al.* 1995; Axelson *et al.* 1994; Tola *et al.* 1980). This issue is not addressed sufficiently in the RAR.

The results of both of these studies have been discussed repeatedly at hearings with the authors, members of the scientific community and German authorities. In these hearings, the weaknesses of the studies were identified and in most of the cases a sufficient explanation of the study authors was given to come to the final conclusion that there is convincing evidence from these studies that trichloroethene, under extremely high exposure concentrations likely exceeding by far the allowable exposure levels, can cause kidney tumours in man. This conclusion is also based on the identical target organs in carcinogenicity studies with rats.

The M. State *rapporteur* argues that:

- *"The interview of the cases and controls were carried out by physicians who were aware of case status and would have had knowledge of the hypothesis being investigated*"
  - this assumption is not true, the interviewer was blinded to the case status.

- *"there is a strong possibility that cases´ physicians would probe more deeply"*
  - see comment above

- *" and cases would overreport their exposure"*
  - the overreporting of exposure of cases can never be excluded, however, the semiquantitative exposure data point to a dose-response relationship.

- *"it is not clear…that the control subjects were from the exactly the same catchment area as the cases"*
  - in the hearings, the authors provided full evidence that the cases were indeed from the same catchment area.

- "*The cases were on average 11 years older than the controls and therefore the cases would have had more opportunity for trichloroethylene exposure"*
  - the age difference of 11 years can hardly explain an odds ratio of 10.8.

The conclusion that trichloroethene can cause kidney cancer in man is biologically consistent with the animal data. This consistency outweighs the possible flaws of the Henschler and Vamvakas studies. Therefore, for hazard assessment, trichloroethylene should be regarded as a human carcinogen.

Other points:
The assessor should specify whether there was an overlap in the databases used for the Henschler and Vamvakas studies. If two studies are using independent databases, this would strengthen causality.

p 237, para 2, last sentence: "…because supporting evidence is not available from other human studies…", this statement is not correct as the study of Vamvakas et al. gives supporting evidence.

p 236, line 6: it should read "…association between trichloroethylene exposure and cancer .

The RAR also does not discuss the community-based studies on an association between drinking-water contamination with trichloroethene and cancer outcomes and case-control studies on an association between trichloroethene exposure and risk of lymphoma. The RAR should at least explain why the observations made in the studies were not used in the risk assessment.

3. Risk characterisation

4.1.3.1 General aspects
p 256, para 1, last sentence:
The possibility that the kidney tumours are caused via a genotoxic action of DCVC should also be mentioned, as this possibility was also discussed by the Specialised Experts (see p 242).

4.1.3.2 Workers

Conclusion iii) concerning carcinogenicity for the various applications is supported. Due to low MOS, conclusion iii) is supported for all endpoints except irritation. P. 266, table 4.17, why is conclusion ii) applied to a MOS of 0.5 ?

4.1.3.3 Consumers

p 269: Conclusion iii) concerning carcinogenicity is supported. However, as already stated by the *rapporteur*, the exposure estimates are unrealistically high. The use of 50 ml trichloroethene for 10 minutes will result in a body burden of 62 mg/kg bw for this exposure scenario. This is higher than the body burden resulting from 8 hour occupational exposure to 50 ppm, an occupational exposure standard valid in many countries. Moreover, consumers would use trichloroethene rarely and not daily.

4.1.3.4 Humans exposed indirectly via the environment

p 270: Conclusion iii) concerning carcinogenicity is supported. Conclusion ii) is supported for all other endpoints.