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Scientific Committee on Toxicity, Ecotoxicity and the Environment

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

Opinion on the results of the Risk Assessment of:

Methyl acetate

CAS No.: 79-20-9
EINECS No.: 201-185-2

REPORT VERSION (Human Health)

Draft of 18.07.2001

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 30th CSTEE plenary meeting

Brussels, 22 February 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

There are currently four companies producing methyl acetate within the EU, with a reported production of 30 000 t/a in 1993. Methyl acetate is used as a solvent in adhesives, paint systems, cosmetic agents and cleaning products (approx. 70%) and as a chemical intermediate in the production of methanol, acetic acid, plant protection products and vitamins (10%), the rest (20%) is exported.

GENERAL COMMENTS

The database on methyl acetate on which to perform a human effect assessment is very limited. However, it is possible to make a proper evaluation based on the studies with methyl acetate and on those of its metabolites, since methyl acetate is rapidly converted to methanol and acetic acid in the body. The CSTEE disagrees with several of the risk characterisations in the RAR.

SPECIFIC COMMENTS

Exposure assessment

Production and further processing of methyl acetate in the large-scale chemical industry are mainly performed in closed systems. Exposure may occur during certain activities (*e.g.* during filling). Formulation of the substance to paints, lacquers, adhesives and cleansers may also lead to exposure. These formulations are used in different industrial and skilled trade areas, such as for spraying and coating. The highest inhalation exposure levels were obtained during flooring works. Dermal exposures are limited because of the very high vapour pressure of methyl acetate.

Consumers may be exposed to methyl acetate from all-purpose and floor covering adhesives, as well as from nail varnish removers. Methyl acetate is present in food as a natural flavouring substance. Indirect exposure to methyl acetate via the environment is calculated to be very low.

Effects assessment

Methyl acetate is rapidly hydrolysed to methanol and acetic acid, both *in vitro* and after inhalation and oral exposure. With human blood, 60% of methyl acetate was converted to methanol in 2 hours. There are no data on interindividual variation in *in vivo* hydrolysis of methyl acetate in humans.

High inhalation concentrations of methyl acetate elicit headache, vertigo and somnolence.

Methyl acetate is strongly irritating for the rabbit eye; no or very little dermal irritation is observed. Exposure to methyl acetate vapours causes irritation to eyes and the respiratory tract in humans.

There are no studies of dermal sensitisation in animals. Long experience with human dermal exposure to the agent (ingredient in cosmetic nail lacquers) does not indicate skin sensitising potential.

Assessment of the toxicity of methyl acetate after repeated dose administration is limited to results from a inhalation study in rats lasting 28 days to 0, 75, 350 or 2000 ppm corresponding to concentrations of 0, 227, 1057 or 5040 mg/m^3. Degeneration/necrosis of the olfactory mucosa was seen in the highest dose group. Minimal systemic toxicity was also noted (liver cell dysfunction, adrenal weight increase, reduced serum cholesterol). Thus, the NOAC for local and systemic effects was both 1057 mg/m^3.

Methyl acetate was negative in a bacterial mutation test and in a rat bone marrow micronucleus test. Given this and that its metabolites methanol and acetic acid are not genotoxic, there is no concern for mutagenicity.

There are no long-term studies with methyl acetate. A summary report on testing of methanol in inhalation carcinogenicity studies in mice and rats did not reveal any significant effects. Given the lack of indication of mutagenicity and apparent lack of carcinogenic effect of methanol, there is no concern for carcinogenic effects from methyl acetate.

There are no available studies on fertility impairment and developmental toxicity of methyl acetate. Limited data indicate that acetic acid is not teratogenic. Methanol has been tested in a number of studies with respect to developmental toxicity and in one 2-generation fertility study. With methanol there are some indications of embryotoxic/foetotoxic effects at maternally toxic exposure concentrations, as well as structural abnormalities after daily intermittent exposure at very high concentrations without significantly affecting bodyweights of the dams. The rapporteur presents data on blood concentrations in developmental studies of methanol that show NOAELs for mice to be in the range of 63 to 130 µg methanol/ml which correspond to an external concentration of about 1000 ppm. It was further demonstrated that 500 µg/ml is a LOAEC corresponding to 2000 ppm (Rogers *et al.* 1993). For rats a blood methanol concentration of about 1500 µg/ml corresponding to 5000 ppm is a NOAEC and 2000 µg/ml corresponding to 10000 ppm is the LOAEC (Nelson *et al.* 1985). This figure is not given in the RAR, instead the results of a different study with rats (NEDO 1987) with blood methanol measurements at 1000 ppm are mentioned (53 to 99 µg/ml). However, this study used continuous exposure and not intermittent. Therefore the NOAEC cannot be compared with the other studies.

Regarding the developmental studies with intermittent exposure, there is an obvious species difference between mice and rats in sensitivity. Mice are more sensitive than rats having a tenfold lower NOAEC in terms of blood methanol concentrations. According to a PBPK model for methanol (Perkins *et al.*, Env Health Perspect 103, 726-733, 1995), which is not included in the RAR, blood methanol concentrations in humans are far less than those in mice. *E.g.* at 1000 ml methanol/m^3 for mice blood concentrations from 132-268 µg/ml are predicted, for humans only 38.5 µg/ml. Thus there is a large difference in the internal dose between mice and humans. This is not taken into account in the risk assessment. The calculated MOS and the conclusions of the RAR for this endpoint are therefore invalid because the effective concentrations are underestimated.

The study of NEDO (1987) with rats is used for deriving a NOAEC of 1000 ppm for fertility, however, this was continuous exposure and also the highest concentration tested, therefore the real NAEC could have been higher. This should at least be mentioned in the RAR.

For developmental toxicity, again the study of NEDO (1987) with continuous exposure was used for deriving a NOAEC in rats of 1000 ppm. However, the study of Nelson *et al.* (1985) showed 5000 ppm to be the NOAEC for intermittent exposure. This should be mentioned in the RAR.

Risk characterisation

General aspects
Methyl acetate is no longer in the MAK-pregnancy group „D“, but in pregnancy group „C“ as is methanol.

Workers

Irritation
There are uncertainties regarding the NOAEC for degeneration of olfactory epithelium due to the large gap between the mid (350 ppm) and the high (2000 ppm) concentration tested in the 28-day study. Additionally the NOAEC after 5 exposures was 500 ppm. Regarding the data on vinyl acetate (NOAEC of 200 ppm for olfactory epithelium degeneration after 1, 5 and 20 exposures, *i.e.* no decrease of NOAEC with time up to 28 days) it can be concluded that also for methyl acetate the NOAEC in the 28-day study would have been higher, as 500 ppm in the 5-day study did produce no effect. As starting point for MOS calculations 500 ppm (1500 mg/m^3), and not 350 ppm (1057 mg/m^3) should therefore be used.

According to the rapporteur *a direct MOS below 3 is considered to be of concern*. This is not explained further. There is no reason to assume a higher sensitivity of humans regarding this endpoint after acute exposure. The rapporteur states that a species extrapolation factor of 1 is used. This means that the factor of 3 should represent intraspecies differences. There is no scientific basis that such an intraspecies difference for local degenerative effects due to the presence of acid exists for man. However, there could be interindividual differences in the rate of methyl acetate hydrolysis in humans. Taken together, conclusion iii), for the scenario 11 (recalculated MOS 2.0) is supported.

Repeated dose toxicity, local effects

The same argumentation holds true also for repeated dose toxicity. The starting point for calculation should be 1500 mg/m^3. The duration adjustment factor 1/3 for extrapolation from 28-days to chronic exposure is justified, based on the data for vinyl acetate. Again the intraspecies factor of 3 is supported. Therefore, conclusion iii), for the scenarios 2, 5, 12 is not warranted (recalculated MOS values of 3.3, 3.7 and 3.8, respectively). Conclusion iii) for scenarios 4, 9, 11 are, however, justified (recalculated MOS values of 1.7, 2.4 and 0.7, respectively).

Repeated dose, systemic effects

In the 28-day study only minimal effects (reduced food consumption, diuresis in females, increased ALAT in females, increased adrenal weight, decreased serum cholesterol) without histopathological changes in any organ were seen at 2000 ppm. The rapporteur states that *a considerable decrease of the NAEC with time* is not expected. Therefore, a duration adjustment factor of 1/3 instead of 1/6 is used. However, due to the minimal effects and because there is a large gap between LOAEC and NOAEC in the 28-day study a duration adjustment factor seems to be questionable. MOS values should be calculated with 1057 mg/m^3 as NOAEC, and therefore conclusion iii) for the scenarios 4, 5 and 9 are not warranted. Conclusion iii) for scenario 11 is, however, justified.

Reproductive toxicity (developmental toxicity)

As stated above and also in this part of the RAR, the human blood methanol levels are lower than those in mice at the same external concentration. This has been addressed in the RAR but not in a quantitative way: A PBPK model (Perkins *et al.* 1995) indicates that at 1000 ml/m^3 (NOAEC for mouse) the blood methanol level in humans is one third of that in the mouse. Thus, the NOAEC for humans regarding this endpoint should be about 3000 ppm (9000 mg/m^3) and not 1000 ppm, which results in a MOS > 10 for scenario 11. Therefore, for this scenario conclusion ii) is reached instead of conclusion iii).