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

Opinion on the results of the Risk Assessment of:

METHYLENEDIPHENYL DIISOCYANATE (MDI)

HUMAN HEALTH PART

CAS N°: 26447-40-5

EINECS N°: 247-714-0

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

Adopted by the CSTEE during the 41st plenary meeting of 8 January 2004

[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 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.

According to the Technical Guidance Document on Risk Assessment – European Communities 2003:

- *conclusion i): There is a need for further information and/or testing;*
- *conclusion ii): There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already;*
- *conclusion iii): There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.*

HUMAN HEALTH

Exposure assessment

Workplace exposure

There were no literature data on the workers inhalation exposure during production of MDI, and the EASE model is not very useful as it does not give any predictions for values below 1 mg/m^3. Industry has submitted a number of measured data of total inhalable MDI (i.e. vapour and aerosol), but the information around these is very limited. There are no measured data available for dermal exposure and the EASE model had to be used. Assuming a 1% dermal absorption gives a combined uptake of 0.10 mg/kg/d. The downstream use of MDI is diverse, and again industry has supported the assessors with a large number of measured data. Using the same technique as for production, the estimated combined uptake in downstream workers comes to 0.19 mg/kg/d for all applications except foam applications, which gives 50.06 mg/kg/d as a worst case estimate. The CSTEE supports these assumptions.

Consumer exposure

MDI is used in a number of consumer products, such as spray foam, adhesives and paint. The available consumer exposure models can not be used due to the reactivity of the substance. The assessors assume that inhalation, but not dermal, exposure will be negligible during outdoor use. Spray foams are used to insulate buildings, and measured levels of MDI during such operations are quite low. Dermal exposure may, on the other hand, be higher due to bad work practices, and the assessors make a worst case estimate of 0.0764 mg/kg/d. Glues for laying a parquet can contain up to 35% MDI, and about 0.5 kg glue is used per m^2. The inhalation is assumed to be low due to the low vapour pressure at room temperature, but the TGD simple algorithms (worst case) gives an estimated dermal uptake of 0.42 mg/kg/d. These assumptions are supported by the CSTEE.

MDI-containing hot melt adhesives are used at temperatures of 140 – 170 °C, and there is a report on inhalation exposure available. Air levels of up to 0.025 mg/m^3 were observed during the use of a heating gun specially designed to minimise the exposure. The CSTEE expects "normal" guns may give higher exposure, and long exposure may give unacceptable uptake of MDI. The dermal uptake was estimated using TGD algorithms, assuming both hands to be covered by the adhesive. Given the temperature of the glue, the CSTEE thinks this situation is very unlikely.

Indirect exposure via the environment

Human exposure to MDI via the environment has been estimated with the use of EUSES. The model predicts intake through air, drinking water, fish, leaf crop, root crop, meat and milk, and those are listed in a table. There is also the total intake given, but this is not the sum of the exposures via the different pathways. Surprisingly, in the RAR, the local exposure is much lower than the regional. This issue will be addressed in the MDI environment opinion. The conclusions would also be that drinking water is the most important source, and not fish as the assessors suggest. As MDI is very reactive, these predictions are probably all overestimates. This does not make any difference in the final assessment as the indirect exposure is so low compared to other pathways.

Effects assessment

Acute toxicity

The information available from animal studies shows that MDI has a very high oral LD50. The available toxicity data following acute exposure to respirable aerosols indicates that MDI toxicity is confined predominantly to the respiratory tract. There is very little information on the effects of acute exposure to MDI in humans. MDI is classified as harmful by inhalation.

Irritation

Based on animal studies and human data MDI can be stated to be a skin and eye irritant. Based on 'regulatory' acute toxicity studies no conclusions can be drawn regarding the respiratory irritating properties of MDI. However, the repeated dose studies, mechanistic studies and human data do indicate that MDI causes irritation of the respiratory tract. The CSTEE agrees with this conclusion.

Sensitisation

In a guinea pig maximization test and in three Mouse Ear Swelling Tests, MDI appeared a strong skin sensitiser, characterized as delayed hypersensitivity. In one of the latter studies MDI-induced sensitivity was transferable with T lymphocytes from lymph nodes. Cross-reactivity to TDI and other isocyanates was also demonstrated. Polymeric MDI was not positive in a modified guinea pig maximisation test. Case reports indicate that MDI is also a skin sensitiser in man causing allergic contact dermatitis as well as IgE-mediated contact urticaria.

In various studies in guinea pigs, monomeric and polymeric MDI appeared to induce respiratory allergic reactions. Positive reactions could be induced by both skin contact as well as following high-level inhalation exposure. Various case reports and epidemiological studies document MDI as a cause of occupational respiratory allergy. MDI-induced allergy is complex as besides immediate-type (IgE-mediated) reactions also late (delayed-type) and dual-phase reactions occur.

Repeated dose toxicity

Following short-term and chronic inhalation exposures in the rat, a NOAEL was found of 0.5 and 0.2 mg/m^3, respectively. Like in the animal studies, human epidemiological data indicate the respiratory tract to be the target organ system. For risk characterization, the RAR uses the NOAEL of 0.2 mg/m^3 for long-term inhalation exposure of workers and the NOAEL of 0.5 mg/m^3 for short-term inhalation exposure of consumers.

Genotoxicity

Monomeric and polymeric MDI dissolved in dimethyl sulfoxide (DMSO) showed both positive and negative results in the Ames test. Negative results were obtained if other solvents were used. Because of the known interaction of DMSO with MDI to yield genotoxic 4,4'-methylenedianiline (MDA) and possibly other reaction products, the positive results are of little relevance. A positive TK$^+$/TK$^-$ mouse lymphoma assay was reported for monomeric MDI (dissolved in DMSO), whilst polymeric MDI showed no evidence of a mutagenic activity in this system.

MDI (dissolved in acetone) induced chromosome aberrations in human lymphocytes at all doses tested (0.54-4.30 µl/ml) after a 24 h treatment in the absence of metabolic activation. In the presence of rat liver S9 mix (1.5 h treatment), an increase was noted only at the highest concentration. MDI marginally increased sister-chromatid exchanges at the highest tested dose with and without S9 mix. There was no evidence that MDI induced double-strand breaks by a genotoxic mechanism in cultured human epithelial lung cells. Aneuploidy was induced by treatment of V79 cells with cysteine and glutathione conjugates of MDI. However, concern has been expressed about the purity of the conjugates synthesized.

In vivo, MDI (in DMSO/corn oil) did not induce micronuclei in erythrocytes of mice after a single intraperitoneal treatment with up to 200 mg/kg bw; the reliability of this study is however limited due to an unusual high number of micronuclei in the solvent control group. The results from a recently performed *in vivo* micronucleus test in rats indicate that aerosolized, inhaled MDI at concentrations that induced signs of respiratory tract irritation and increased lung weights (118 mg/m³ air) did not induce cytogenetic damage. Significant increases in DNA adduct levels have not been found after topical or inhalatory exposure to MDI in animals.

Some human exposure studies have reported on possible alterations in the DNA of lymphocytes (hyperchromicity, cross-linking, acceleration of apoptosis). These data were however obtained with non-validated methodologies and the results are not reliable. In Finnish polyurethane foam workers, MDI exposure was associated with a slightly increased frequency of sister chromatid exchanges, and with an increase in micronuclei in buccal cells (only reported in the form of an abstract, hence the reliability of the information cannot be judged).

The RAR concludes that there is no convincing evidence of a mutagenic or genotoxic potential of MDI.

Carcinogenicity

The carcinogenicity of MDI was investigated in two chronic inhalation toxicity/carcinogenicity studies on Wistar rats. Rats exposed to aerosols of polymeric MDI (containing about 50% monomeric MDI; 0, 0.19, 0.98, or 6.03 mg/m^3) showed changes in the respiratory tract at 0.98 and 6.03 mg/m^3 (basal cell hyperplasia in the olfactory epithelium and alveolar duct epithelialisation), and eight pulmonary adenomas at 6.03 mg/m^3. One single case of pulmonary adenocarcinoma was found in the high dose group. In the other study, rats were exposed to aerosolized monomeric MDI at concentrations of 0, 0.23, 0.70, and 2.05 mg/m^3. One bronchioalveolar adenoma was found in the high-dose group. Dose-dependent signs of irritation, interstitial and peribronchiolar fibrosis, alveolar bronchiolisations and a proliferation of the alveolar epithelium, which was classified as preneoplastic, were also ascertained.

On basis of the available data from toxicokinetic, metabolism, genotoxicity and carcinogenicity studies, no firm conclusion can be drawn with regard to the mechanism of tumor formation. It is possible that tumors were induced by the *in situ* formation of a genotoxic metabolite (e.g. MDA). It is, however, equally possible, that tumors developed through an epigenetic mechanism following irritation, inflammation and increased cell proliferation or through a combined mechanism. The data as presented do not allow for the establishment of a threshold.

There was no evidence for an increased cancer incidence from a cohort study in 4154 workers employed in Swedish polyurethane foam manufacturing plants for at least 1 year. TDI had been used in all the plants and MDI in all but one, so it was impossible to evaluate their individual effects. A retrospective mortality and cancer morbidity study was conducted in 8288 workers from 11 factories in England and Wales to investigate associations between health risk and exposures from polyurethane foam production. TDI was the principal isocyanate, and MDI represented 5% of the amount of TDI used. There was some excess of lung cancer which, according to the authors, was attributed to confounding by cigarette smoking and other factors unrelated to diisocyanate exposure, particularly in females.

There is no adequate evidence for an association between MDI exposure and cancer morbidity from cohort and retrospective studies. The epidemiology studies are, however, limited by co-exposure to other isocyanates. There is limited evidence of carcinogenicity from animal studies, and investigations are ongoing to clarify the mechanism of tumor induction in the respiratory tract of the rat. No data are available for the oral and dermal routes of exposure.

Overall, the RAR concluded that there is inadequate evidence of carcinogenicity in humans and limited evidence in experimental animals. MDI is not classifiable as to its carcinogenicity to humans. The CSTEE agrees with the RAR that continued follow up would allow more definite conclusions to be drawn and more epidemiological surveillance should also be conducted to confirm the lack of carcinogenicity.

Toxicity for reproduction

Neither fertility nor multigeneration animal studies are available for MDI. In the RAR data from (sub)chronic toxicity studies are considered too limited to allow a determination of a NOAEL for fertility (e.g. none of the studies reported ovaries weight).

Developmental inhalation toxicity studies in rats indicated no selective development toxicity at exposure levels that were not associated with maternal toxicity, with a NOAEL of 3 and 4 mg/m^3 for

monomeric and polymeric MDI, respectively. There are no data available in humans on fertility or developmental effects.

Risk characterisation

Based on animal studies and human data MDI is classified in the RAR as an irritant to the skin, the eyes and the respiratory system. Regarding the irritating activity on the skin and the eyes the CSTEE agrees with the conclusion iii) for unprotected workers on building sites as well as for all consumer scenarios. The CSTEE also agrees with the conclusion iii) for respiratory tract irritation for workers for all scenarios and for consumer scenarios 2 and 4.

The CSTEE supports the classification that MDI may cause sensitisation by inhalation and skin contact, and the conclusion iii) for workers and consumers.

The CSTEE agrees with the conclusion of the RAR that at the current stage the weight of evidence based on the experimental data suggests that mutagenicity is of no concern (conclusion ii).

Regarding repeated-dose toxicity, systemic effects, including possible carcinogenicity, the CSTEE is in agreement with conclusion iii) for inhalation exposure and for combined exposure of workers. The CSTEE supports reassessment of carcinogenicity once the studies on the reported *in vivo* conversion of MDI to MDA (or other genotoxic metabolites) have been completed.

As there are no fertility nor multigeneration animal studies available for MDI, and the data from (sub)chronic toxicity studies are too limited to allow a determination of a NOAEL for fertility the CSTEE supports the conclusion i) on hold of the RAR.

Human Health (Physico-chemical properties)

See error on page 3 and 169 (classification of ii) and not of i) and iii)).