EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Public Health and Risk Assessment
**C7 - Risk assessment**

**SCIENTIFIC COMMITTEE ON HEALTH AND ENVIRONMENTAL RISKS**

**SCHER**

**Opinion on**

# "Risk Assessment Report on 4-methyl-m-phenylenediamine (2,4 TDA) Human Health Part"

## CAS N°: 95-80-7

## EINECS N°: 202-453-1

**Adopted by the SCHER during the 11th plenary meeting of 4 May 2006**

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## 1. BACKGROUND

Council Regulation 793/93 provides the framework for the evaluation and control of the risk of existing substances. Member States prepare Risk Assessment Reports on priority substances. The Reports are then examined by the Technical Committee under the Regulation and, when appropriate, the Commission invites the Scientific Committee on Health and Environmental Risks (SCHER) to give its opinion.

## 2. TERMS OF REFERENCE

On the basis of the examination of the Risk Assessment Report the SCHER is invited to examine the following issues:

(1) Does the SCHER agree with the conclusions of the Risk Assessment Report?

(2) If the SCHER disagrees with such conclusions, it is invited to elaborate on the reasons.

(3) If the SCHER disagrees with the approaches or methods used to assess the risks, it is invited to suggest possible alternatives.

## 3. OPINION

The health part of the document is of good quality, it is comprehensive, and the exposure and effects assessment follow the Technical Guidance Document. The RAR covers all studies relevant for exposure and hazard assessment of toluene-2,4-diamine.

### 3.1. Specific comments

*Exposure assessment*

The occupational exposure assessment regarding inhalation exposure develops three scenarios which are, in part, based on measured data. Potential dermal exposure is modelled using EASE. In the RAR, it is acknowledged that the occupational exposure assessments are conservative. Calculations predict a very low indirect exposure of humans to toluene-2,4-diamine and the absence of any known direct use of toluene-2,4-diamine suggest that consumer exposure is non-existent or very low since toluene-2,4-diamine is below the limit of detection in all end products which involved use of toluene-2,4-diamine in the production process.

*Effects assessment*

SCHER agrees with the conclusion that toluene-2,4-diamine is a sensitizer. The major health effect relevant for risk characterisation observed after repeated exposure to toluene-2,4-diamine are liver and mammary gland tumors in rodents. There is conclusive evidence for a genotoxic mode-of-action of toluene-2,4-diamine based on bacterial mutagenicity, chromosomal aberrations in mammalian cells, DNA-damage and covalent binding of toluene-2,4-diamine to DNA. Carcinogenicity data are only available in rats and mice after oral administration.

Due to the consistent genotoxicity, the SCHER questions the conclusion that the available mutagenicity data are not sufficient to classify toluene-2,4-diamine as a category 2 mutagen.

*Risk characterization*

The risk characterization performed in the RAR uses both the MOS and the MOE approach. The SCHER agrees with conclusion ii)[1] for occupational exposures regarding acute and repeated administration and irritating properties due to the high MOS. Regarding carcinogenicity and mutagenicity, the SCHER supports conclusion iii) due to consistently positive mutagenicity and carcinogenicity data. Due to the genotoxicity, concern remains despite a very high MOE. Conclusion ii) is accepted regarding worker exposure and endpoint reproductive toxicity due to a very high MOS.

Regarding consumer exposure, due to absence of exposure, conclusion ii) is accepted.

The SCHER also supports conclusion ii) for indirect exposure and all endpoints except mutagenicity and carcinogenicity. Regarding these endpoints conclusion iii) is supported despite very high MOS. However, to further define the magnitude of concern regarding indirect human exposure, the MOE approach as performed in the risk characterization for workers should be included in tabular form.

In some parts of the RAR, the language requires improvement, e.g.:

- Page 25, “high-liquid-chromatographically is by HPLC”
- Page 42, first line, “has proven to be toxic”. In this context toxic is used as a classification and is not substance specific.
- Tables, to improve readability number of animals per group and doses applied should be included
- The text on the big blue mice on page 96 should be moved from the carcinogenicity to the mutagenicity section.
- Page 99, “sufficient evidence for the carcinogenicity” is an IARC term used for the level of evidence and should not be used in the context here. However, the SCHER agrees that toluene-2,4-diamine is carcinogenic in rodents.
- Page 103, the SCHER does not think that the available carcinogenicity data are sufficient to justify evaluation of toluene-2,4-diamine as a human carcinogen, since this would require human data. Classification as a category 2 carcinogen is consistent with the available data.
- Page 110, what is a “marginal LOAEL”?
- Table 4.1.3 2A and some following tables, exposure data should be given as a dose in mg/kg/day.

[1] *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.*

## 4. LIST OF ABBREVIATIONS

| | |
|---|---|
| EASE | Estimation and Assessment of Substance Exposure Physico-chemical properties |
| LOAEL | Lowest Observed Adverse Effect Levels |
| MOE | Margin of Exposure |
| MOS | Margin of Safety |
| RAR | Risk Assessment Report |

## 5. ACKNOWLEDGEMENTS

Prof. W. Dekant (rapporteur) is acknowledged for his valuable contribution to this opinion.