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 2-METHOXY-2-METHYLBUTANE (TAME). Human Health Part"

CAS N°: 994-05-8

EINECS N°: 213-611-4

Adopted by the SCHER
during the 9th plenary of 27 January 2006

TABLE OF CONTENTS

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 human health section of the document is of good quality, it is comprehensive and the exposure and effects assessments follow the Technical Guidance Document. The RAR covers most of the studies relevant for the exposure and hazard assessments of TAME.

The RAR proposes the following conclusions:

Workers

Conclusion ii[1]) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already. Conclusion ii) applies to acute toxicity, repeated dose toxicity and reproductive toxicity (development). Other end-points were not assessed because they were not considered relevant.

SCHER disagrees with the last sentence because genotoxicity and carcinogenicity were also evaluated.

Consumers

Conclusion ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already. Conclusion ii) applies to

[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.*

acute toxicity, repeated dose toxicity and reproductive toxicity (development). Other end-points were not assessed because they were not considered relevant.

SCHER disagrees with the last sentence because genotoxicity and carcinogenicity were also evaluated.

Humans exposed via the environment

Risks from indirect exposure via the environment were assessed in the consumer section.

SCHER agrees with this approach.

Human health (physico-chemical properties)

Conclusion iii) There is a need for limiting the risk; risk reduction measures which are already being applied shall be taking into account.

This conclusion iii) applies to overall quality of groundwater. The conclusion is reached due to concern of potability of groundwater with respect to taste and odour as a consequence of exposure from leaking underground storage tanks, tank piping and spillage from overfilling the tanks. This conclusion is not based on ecotoxicological or toxicological endpoints. The conclusion applies to drinking water contamination. The risk reduction measures are taken in the environment section with regard to the ground water contamination.

The SCHER agrees with this conclusion. The conclusion is similar to the one previous adopted for MTBE.

3.1. Specific comments

Currently MTBE is the predominant chemical added to gasoline. Other ether oxygenates used are ETBE and TAME. Rarely TAME is used as the primary oxygenate but frequently it is present along with MTBE.

3.1.1. Exposure assessment

Almost all exposure data available originate from Finish studies or industry reports, which makes it difficult to evaluate the representativeness of the data for other EU-countries. The SCHER agrees with this statement.

In Table 4.9 it would be useful to have a comparison of the odour thresholds for TAME and MTBE in air as well. The value of odour and taste thresholds in water is misleading for MTBE and should be given as a range and with a reference (Vetrano et al. 1993).

On page 57 the reference to the pump area exposure of Vainiotalo is missing.

3.1.2. Effects assessment

The toxicology of TAME is described in detail in the RAR and the conclusions are mainly supported by the toxicology data.

SCHER agrees with the conclusion for repeated dose toxicity and the toxicity for reproduction.

Genotoxicity

No data was available on the genotoxicity of TAME in humans.

TAME was tested negative in several Ames test with and without metabolic activation systems and in a forward mutation test (HGPRT test) in CHO cells. A positive result has been reported for chromosomal aberration in CHO cells in the presence of S-9 mix.

This finding was attributed to the formation of formaldehyde in the cell culture system, and assessed to be of limited relevance for the *in vivo* situation because formaldehyde would rapidly be detoxified in the body. *In vivo*, TAME did not induce micronuclei in bone marrow cells of mice treated by single ip. injections of up to 750 mg/kg bw.

SCHER agrees with the interpretation of the genotoxicity results by the rapporteur that TAME should not be considered mutagenic. In Table 4.18, the typographical errors related to the dose unit should be corrected.

Carcinogenicity

It could be mentioned in the RAR that epidemiology data were not available.

TAME was tested in a recent, oral carcinogenicity study on rats (Belpoggi et al. 2002). Sprague-Dawley rats received 0, 250 or 750 mg/kg bw (in olive oil) by gavage on 4 days/week for 78 weeks, and were maintained until natural death. Increased incidences were reported for ear duct carcinomas (3/200, 8/200, 9/200, 1/100, 4/100, 5/100 in males and 2/100, 4/100 and 4/100 in females in control, low and high dose groups, respectively) interstitial cell tumours of the testes (0/100, 3/100, and 4/100), oligodendrogliomas of the brain (males: 0/100, 4/100, 3/100), and in lymphomas and leukaemia (combined, statistically significant) in females (7/100, 14/100, 27/100) in males the frequency was 17/100, 7/100 and 21/100. The rapporteur pointed to the fact that only limited study details were reported by the authors (e.g. no historical control data, no mortality data, and no toxicological findings were presented in the publication), which makes the interpretation of the reported findings difficult.

SCHER therefore agrees with the rapporteur that, on the basis of the limited data available, a risk characterisation should not be conducted for this endpoint. In the result section, it should be added that the carcinogenicity endpoint was not assessed because of inadequate data (it presently reads “other endpoints were not assessed because they were not considered relevant”, which may give the wrong impression that there is no concern for carcinogenicity).

3.1.3. Risk characterisation.

Workers

Because ingestion is not likely, a characterisation of risk of acute toxicity via oral route is not considered relevant for the worker risk assessment. Occupational risk assessment for acute toxicity is summarised in table 4. 21.

SCHER agrees with the conclusion ii) for this endpoint.

The smallest MOSs for acute toxicity was seen for service station and fuel pump repair. Although the MOS appears quite low it is not considered to be a concern based on the low severity of the effect.

Irritation

SCHER agrees with the conclusion ii) of the RAR.

Occupational risk assessment for repeated dose toxicity for uses in service station, car motor repair, fuel pump repair and other work groups show high MOSs and the rapporteur concludes ii). For the combined inhalation and dermal route MOSs are more 100.

SCHER agrees with these conclusions.

Mutagenicity

SCHER agrees with the conclusion ii) of the RAR.

Consumers

For consumers none of the scenarios assessed resulted in a margin of safety less than 2120 and the RAR concludes ii).

SCHER agrees with this conclusion.

4. LIST OF ABBREVIATIONS

CHO	Chinese hamster ovary cells
ETBE	Ethyl *tert* butyl ether
MOS	Margin of Safety
MTBE	Methyl *tert* Butyl ether
RAR	Risk Assessment Report
TAME	2- methoxy-2-methylbutane

5. ACKNOWLEDGEMENTS

Dr. O Ladefoged (rapporteur) is acknowledged for his valuable contribution to this opinion.