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

Opinion

on the results of the Risk Assessment of:

Methyl tertiary-Butyl Ether (MTBE)

CAS N°: 1634-04-4

EINECS N°: 216-653-1

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

expressed at the 23rd CSTEE plenary meeting

Brussels, 24 April 2001

[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

Methyl tertiary-Butyl Ether (MTBE) is a high production volume chemical (more than $3x10^6$ tonnes produced in EU in 1997) mainly used (more than 98%) as a fuel additive. Minor amounts are used as solvent or as an intermediate in chemical industry.

The main sources of MTBE release to the environment are air emissions from fuel use. Other releases, not negligible at least at local level, may occur during the life cycle of the chemical (production, formulation, processing).

MTBE is highly volatile, with very high affinity for the atmospheric compartment. Nevertheless, due to its high solubility, exposure in the aquatic environment, as well as in groundwater, should not be overlooked. An additional reason for concern is the relatively high persistence in soil and water.

GENERAL COMMENTS

The assessment is comprehensive and is of good quality. There are some inconsistencies between the draft version on human health and that done for the environmental risk assessment and some minor mistakes, which have to be avoided in the final versions. The references in the text and the reference list also need improvement.

The CSTEE agrees only partially with the overall conclusion of the RAR, particularly referring to the environmental part.

It is the opinion of the CSTEE that an additional source of local exposure is leakage from intermediate storage tanks, and this is not adequately addressed in the report.

Moreover, the conclusion on risk characterisation for the atmospheric compartment is not supported by adequate information about the effects on terrestrial organisms through atmospheric exposure (data are completely lacking in the environmental part, inhalation data on mammals are reported in the human part). Taking into account that atmosphere is the most exposed compartment, there is a need for more information on the effects of MTBE on terrestrial plants and animals through air exposure.

The organoleptic/odour threshold at levels clearly below health concerns, can also be considered as a useful property for detecting groundwater contaminated by petrol spills. In that sense, MTBE could be used as a potential marker for detecting contamination events including not only MTBE but also other petrol constituents which can represent higher concern for human and/or environmental risk.

SPECIFIC COMMENTS

ENVIRONMENT

Exposure assessment

The description of release scenarios is, in general, detailed and exhaustive and environmental distribution and fate are correctly assessed. Nevertheless, more attention should be addressed to leakage from intermediate storage tanks. This may produce groundwater contamination and could be more relevant for human than for environmental risk.

Air is the most exposed compartment and volatilisation may be expected from water and soil. However, due to the high solubility (42 g/L) emissions in water may produce significant contamination, at least at local level. Moreover, soil contamination may produce leaching to groundwater.

The chemical is not readily biodegradable in aquatic environment and degradation in soil is very slow.

MTBE is poorly photodegraded and under atmospheric conditions react essentially solely with OH radicals.

Due to its low lipophilicity, bioaccumulation of MTBE is not likely to occur.

The PECs for various compartments are correctly calculated according to TGD procedures.

Local PECs in water for production were calculated using EUSES approach and using site-specific data for a number of production sites. The results are in complete disagreement, the EUSES calculation being several orders of magnitude higher in comparison with site-specific data.

This disagreement is not surprising, due to the more detailed site-specific information in comparison with the default worst-case scenario of EUSES. Nevertheless, some more explanation could be useful supporting the unlikelihood of higher concentrations in production sites. This is particularly relevant, taking into account that, at least for one production site (site 10, see table 3053, page 116) the PEC/PNEC ratio is close to 1.

A better agreement was found between EUSES and site-specific calculation for the atmospheric environment (values in table 3.26 are expressed as $\mu g/m^3$ and not mg/ m^3).

Monitoring data in the aquatic environment are rather scarce, but they are in reasonable agreement with regional PEC. A reasonable agreement was also found with monitoring data for the atmosphere.

Groundwater contamination has been frequently recorded. MTBE has high water solubility, low potential for binding in soil and sediment and thus high potential for leakage to groundwater. Furthermore, MTBE is generally resistant to biodegradation in groundwater and accumulation is possible over time.

Effects assessment

MTBE is a non-polar narcotic, with a non-specific mode of action.

For the aquatic environment, toxicological information is rather comprehensive. Short and long term reliable data are available for algae, invertebrates and fish. Experimental data are in good agreement with calculated QSAR data. Therefore a reliable PNEC for the aquatic environment has been calculated.

No data are available for soil organisms and a PNEC has been calculated using the equilibrium partitioning method. Due to the low concern for the soil compartment, the approach may be assumed as acceptable.

No data on effects of MTBE to terrestrial plants and animals through atmospheric exposure are reported in the environmental part. Inhalation toxicity data are reported in the human part, indicating a NOAEL for rat of 800 ppm. Nevertheless, due to the relevance of the atmospheric compartment, this aspect needs to be better investigated, with tests on organisms belonging to other taxonomic groups.

The statement that secondary poisoning is not likely to occur is well supported by the properties of the chemical.

Risk characterisation

In spite of its relatively low toxicity, MTBE is a chemical of concern due to its high production volume and relatively high persistence.

High concentrations are likely to occur at least at local level and PEC/PNEC ratios may be close or higher than 1 in the aquatic environment.

Due to the lack of toxicological data, risk characterisation for the atmospheric compartment cannot be performed.

HUMAN HEALTH

Exposure assessment

The exposure assessment is well performed and based on a rather solid base of measured data. The EASE model predictions of inhalatory exposure gave results much higher than the measured data, and this is discussed in the report. However, no exact reason for this difference could be identified.

It is mentioned (p 12) that MTBE is present in petrol at 2 - 11.5 %, but figures down to 0.5 % are mentioned in the environmental assessment.

The calculation of RWC 8h for the distribution of petrol containing 11 and 2.8 % MTBE, respectively, gives a difference of just about 50% higher (p 34). If there were no other differences between the two scenarios a larger difference would have been expected, especially as a difference of almost an order of magnitude is calculated for the refuelling of the 2.8 and 11 % products (p 57).

To assess the exposure of service station attendants three data sets were seemingly available (p 41). Two of these seem to be from industry (Giaccomello et al. and CONCAWE) while the third, with higher results reported, is not referenced. The conclusion seems to be based on the two referenced reports, and the exclusion of the third data set should have been better justified.

The reasonably worst case scenario for MTBE in drinking water is based on an organoleptic/odour threshold of 15 µg/L. This may be an overestimation as the environmental assessment gives a reference to a Danish study where the odour detection limit was determined to 7.4 and the taste detection threshold to 7.3 µg/L.

The measured values for MTBE in ground water and drinking water is compared to the EUSES calculated value for $PEC_{continental}$ (p 67). The latter is said to be 0.36 µg/L, but in the environmental assessment is found to be 0.1 µg/L, which is more consistent with the measured data. There are also discrepancies between the two reports regarding EUSES predictions for $PEC_{air\ regional}$ and $PEC_{air\ continental}$ (p 73).

Effects assessment

The effects assessment is well done, and partly based on human data. The clinical trials using high doses of MTBE to dissolve gallstones have been utilised to observe short-term effects of high doses of the compound. Generally, mild reversible systemic effects such as drowsiness, sedation and nausea were common. Two cases of intravascular haemolysis were reported, with one case resulting in acute renal failure.

Irritation/sensitisation

MTBE is a skin irritant, but not an eye irritant in experimental animals. Results from animal studies and experience in human volunteers do not indicate that MTBE is a respiratory irritant. There are no indications of a sensitising potential. MTBE has low taste and odour thresholds.

Repeated dose toxicity
In repeated dose studies, kidney and liver are the principal target organs for MTBE. In the kidney, degenerative changes and protein droplet nephropathy with accumulation of alpha2u-globulin. Liver effects are increased organ weight, proliferation of the smooth endoplasmic reticulum and slight transaminase increases. A NOAEC of 800 ppm (3000 mg/m^3) was determined from mild effects on the liver in rat inhalation studies. Based on liver effects, a NOAEL of 300 mg/kg bw/day from a 90-day oral study was set.

MTBE has been shown to produce a number of effects on the endocrine system attributable to a slight antioestrogen-like activity at 8000 ppm. Oral administration of MTBE to Sprague-Dawley rats for 28 days results in decreased serum triiodothyronine levels at 1000 and 1500 mg/kg bw/day and a decrease in serum luteinising hormone and dihydrotestosterone at 1500 mg/kg bw/day (Williams et al., 2000). Since these endocrine effects occur at dosage levels much higher than the inhalation NOAC (8000 ppm vs. 800 ppm) and the oral NOAEL (1000 mg/kg bw/day vs. 300 mg/kg bw/day), these effects are judged not to be critical.

Mutagenicity/Genotoxicity
MTBE was negative in most bacterial and mammalian cell gene mutation and chromosomal aberration assays *in vitro*. A weak positive effect was found after metabolic activation in *Salmonella typhimurium* TA102, a strain that is particularly sensitive to formaldehyde and in a mouse lymphoma test. Conflicting results have been observed in *in vitro* liver UDS assays. The positive findings in these tests, however, are attributed to the MTBE metabolite formaldehyde and not considered relevant for the *in vivo* situation.

Adequately performed standard *in vivo* tests were all negative. A negative result was also observed in the *in vivo* UDS test. Recently a genotoxic effect was reported in a comet assay with lymphocytes from rats treated orally for 28 days with 800 mg/kg; the biological significance of this finding in a non-validated test system is unclear.

The CSTEE agree with the assessor that MTBE is not considered a mutagen.

Carcinogenicity
After inhalation of toxic concentrations (3000 ppm) MTBE induced renal tubular adenoma and carcinoma in male F344 rats, presumably in response to a alpha2u-globulin associated nephropathy, and an increase in Leydig cell tumours (Bird et al., 1997). An increase in Leydig cell tumours was also seen in Sprague-Dawley rats after chronic oral administration of 1000 mg/kg (Belpoggi et al., 1995; Belpoggi et al., 1997).

An increase in lymphoma/leukaemia was found in female rats in a chronic gavage study at doses of 250 and 1000 mg/kg (Belpoggi et al., 1995; Belpoggi et al., 1997). Lack of historical control data and inadequate reporting of this study, together with the lack of these findings in other studies make its interpretation difficult.

Inhalation exposure of 8000 ppm induced liver adenoma and liver carcinoma in female CD-1 mice (Bird et al., 1997). MTBE did not show promoter activity in mouse liver after initiation with DEN (Moser et al., 1998).

Though human relevance of the tumours observed in animals after chronic administration of high and mostly toxic doses remains somewhat unclear it can be assumed that the carcinogenic mechanism is involving non-genotoxic processes. Furthermore, it is considered

unlikely that the compound is mutagenic. At present, the CSTEE considers that MTBE is not classifiable as to its carcinogenicity to humans. This is in line with the recent IARC (1999) classification of MTBE in Group 3.

Reproductive toxicity
MTBE induced cleft palate in an inhalation experiment with CD-1 mice, however, this effect was noted first at 8000 ppm (and not 4000 ppm) where there also was significant maternal pathology. Other embryotoxic effects (post-implantation loss, late resorption and dead foetuses) were also noted at 8000 ppm. No significant developmental effects were seen in inhalation studies with rats or rabbits. MTBE has been tested by inhalation in one 1-generation and one 2-generation reproduction study in Sprague-Dawley rats. The CSTEE agrees with the conclusion of the RAR report that MTBE does not cause significant toxicity to reproduction.

Risk characterisation

Workers
Although MTBE is a skin irritant in experimental animals, occupational experience does not support the notion that the potential dermal irritation is a significant risk for workers. However, conclusion iii) for local effects is given in the RAR for repeated exposure for maintenance and car repair scenarios based on risk of defatting and toxic eczema. The CSTEE supports this conclusion. In the maintenance scenario a Margin of Safety (MOS) value of 24 was calculated with respect to systemic effects after repeated exposure. The CSTEE supports the RAR view that this margin is acceptable given that the NOAEL can be seen as being based on adaptive responses in the liver. In transportation, distribution and maintenance operations, margins between calculated inhalation exposures and NOAEC for Leydig cell tumour formation (1450 mg/m^3) are 15-24. Relatively low MOS values are also calculated for combined inhalation and dermal exposures (maintenance 18, transporting 37). The RAR point to the considerable uncertainty when the relevance of Leydig cell tumour formation to man is assessed. At present, there is no clear understanding of the underlying mechanism for induction of Leydig cell tumours by MTBE. The CSTEE also points to certain limitations in the conducting and reporting of the carcinogenicity studies showing increased incidences in the Leydig cell tumours. The CSTEE therefore concludes that the lower MOS values for certain occupational exposure situations do not give rise to concern and that a conclusion ii) for systemic exposure is warranted.

Consumers
The CSTEE agrees with the RAR conclusion ii) for all toxicological endpoints.

Indirect exposure
The CSTEE agrees with the RAR conclusion ii) for all toxicological endpoints. Spills from petrol stations leading to contamination of groundwater can result in unacceptable organoleptic/aesthetic properties, making groundwater completely useless as a source of drinking water, whereby a conclusion iii) may be drawn.

References

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