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

Opinion on the results of the Risk Assessment of:

BENZENE

Human Health part

CAS N°: 71-43-2

EINECS N°: 200-753-7

**Carried out in the framework of Council Regulation (EEC) 793/93 on
the evaluation and control of the risks of existing substances¹**

**Adopted by the CSTEE during the 40th plenary meeting
of 12-13 November 2003**

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.

INTRODUCTION

The annual production of benzene in the EU amounts to about 7247,000 tons, 590,000 tons are imported and 130,000 tons are exported. Benzene occurs naturally in fossil fuels and is also produced in the course of natural processes and human activities that involve the combustion of organic matter such as wood, coal and petroleum products. The main industrial use of benzene is an intermediate for the synthesis of other chemicals.

GENERAL COMMENTS

The human health part of the document is comprehensive and written in accordance with the principles of the Technical Guidance Documents. The CSTEE agrees with the proposed conclusions.

SPECIFIC COMMENTS

Exposure assessment

Benzene is produced and processed at 48 sites in Europe, with a total production volume of about 7247,000 tonnes. It is produced at petroleum refineries or chemical plants by catalytic reforming, steam cracking, and dealkylation. It is also a by-product in the manufacturing of other coal derived chemicals, e.g. xylenes.

Benzene is used as a chemical intermediate, mainly to make ethylbenzene (52%), cumene (20%), cyclohexane (13%), nitrobenzene (9%), alkylbenzene (3%), chlorobenzene (1%), and maleic

anhydride and others (2%). Small amounts are used in chemical laboratories as solvent or reagent.

Eleven occupational exposure scenarios are described in the RAR: two are for the production and further processing, two are for the production of formulations (using solvents containing residual benzene), three are referring to the use of gasoline, and four refer to other uses. Inhalation exposure is highest during production and processing, during production of perfumes and during tank cleaning operations with shift average values between 3.5 and 84 mg/m³. The high exposures occurred during production of perfumes when benzene has been used as a solvent and during cleaning of tanks without protective measures. Highest dermal exposures were identified during production and processing, during production of perfumes, and during tank cleaning operations with an estimated 1 to 3.75 mg/cm² per day as a worst case based on EASE calculations.

Exposure of the general public occurs through the inhalation of air contaminated with benzene from releases of gasoline (containing up to 1% benzene), vehicle exhaust, or through tobacco smoke. Exposure may also occur through the use of contaminated paints, and releases from car interior accessories.

For the exposure via the environment, a local concentration of 890 µg/m³ was determined for the vicinity of a point source, with a regional background concentration of 1.54 µg/m³. Vehicle emissions are a major source of benzene in the environment and measured concentrations in ambient city air were in the range of 1 to 275 µg/m³, with typical concentration levels between 10 and 20 µg/m³.

Exposure scenarios referring to benzene in gasoline were included for illustrative purpose, and are not formal part of the benzene RAR, but will be dealt with in a separate risk assessment on gasoline.

Effects assessment

Toxicokinetics

Benzene is readily absorbed by all routes of exposure, and is rapidly distributed throughout the body. It is metabolised in several organs, including the liver and the bone marrow, and its toxicity has been attributed to its metabolites. The metabolites are mainly excreted with the urine after conjugation reactions. Benzene is also expired unmetabolised. Significant differences in metabolic capacities have been reported for different rodent species, and also for different strains of the same species.

In recent studies (not reported in the RAR), it was shown that reactive metabolites, and DNA and protein adducts were present in liver and bone marrow of mice given ¹⁴C-benzene intraperitoneally at doses from 5 ng/kg to 500 mg/kg bw. The major metabolites found in urine were an unidentified radiolabelled metabolite, phenyl sulfate, phenyl glucuronide, and muconic acid. The major metabolites found in plasma, liver, and bone marrow samples were muconic acid and hydroquinone. Only liver showed a dose response for hydroquinone and muconic acid (Turteltaub and Mani, 2003; Williams et al., 2002).

Acute toxicity

In humans, acute exposure to high concentrations of benzene vapours can cause central nervous system depression, and inhaling benzene at concentrations of 65 mg/l for a few minutes can be fatal. Aspiration of benzene may result in pulmonary oedema and haemorrhage. The acute toxicity of benzene in animals is comparatively low.

Irritation/corrosion

Benzene was irritating to the mucous membranes of eyes, mouth, and respiratory tract, as well as to the skin of laboratory animals.

Sensitisation

There is no indication from human exposure, which indicates that benzene may act as a skin or respiratory tract sensitizer.

Repeated-dose toxicity

In animals and man, the bone marrow and the haematopoietic system are the target organ after repeated exposure to benzene. Chronic exposure can result in bone marrow depression with subsequent reductions in white and red cell counts. The lowest observed adverse effect concentration (LOAEC) in humans is 32 mg/m³ (10 ppm) based on minimal blood count changes.

The LOAEC for haematotoxicity in mice, a species considered more sensitive than the rat, was equally found at 32 mg/m³ (10 ppm). Immunosuppression, probably caused by bone marrow depression, was observed in mice at exposure levels of ≥ 10 ppm (for 6 days) or 40 mg/kg bw/d (orally for 4 weeks). Occasionally, also immune stimulation was observed in studies on mice.

Genotoxicity

In vitro, benzene was not mutagenic in standard bacterial tests, but positive results were seen in some test with mammalian cell cultures, and in chromosomal aberration tests.

In workers exposed to high concentrations of benzene, structural and numerical chromosome aberrations were detected in peripheral blood cells. In animal studies, benzene was mutagenic in somatic cells, while the results of germ cell tests were inconclusive. As benzene can reach the gonads and because there is evidence of a clastogenic effect on spermatogonia, benzene should be considered as a germ cell mutagen.

Carcinogenicity

Benzene is a human carcinogen. Several independent cohort studies have demonstrated an increased incidence of acute myeloid leukaemia, and possibly chronic lymphatic leukaemia in workers exposed to benzene. Although epidemiological evidence indicates that the risk of leukaemia increases with exposure, the available data do not allow the establishment of a safe level of exposure.

In rodents, benzene induced neoplasm at multiple sites in males and females after oral exposure. After exposure to benzene by inhalation, mice showed lymphoid neoplasm, and rats carcinomas at various sites.

New research, using cDNA microarrays to analyze mouse bone marrow tissue both during and after a 2-week exposure to 300 ppm (975 mg/m³) benzene by inhalation, shows that benzene may perturb cell cycling through an effect on the p53 protein, and thus causing blood cell malignancies epigenetically. It was found that benzene caused DNA damage in cells during all phases of the cell cycle. In benzene-exposed wild-type mice, DNA repair genes were activated, but they were suppressed in the p53-knockout mice. Mice in the latter group were therefore susceptible to benzene's direct genotoxic leukaemogenicity, whereas those in the former still experienced epigenetic leukaemogenicity via cell-cycle perturbations despite DNA repair. Besides the p53-mediated pathway, the investigators identified other specific genes that may be involved in G1 cell

cycle arrest and apoptosis following benzene exposure, and confirmed that certain repair genes are also triggered by such exposure. They also found that, during benzene exposure, the production of blood cells was arrested due to alterations in the expression of cell cycle checkpoint genes in the wild-type mice. However, production continued in the p53-knockout mice (Byung-IL et al., 2003).

Toxicity for reproduction

Limitations in epidemiology and human study data do not allow drawing a conclusion on the effect of benzene on fertility and reproduction. In recent studies in petrochemical workers (not reported in the RAR), reductions in mean birth weight and menstrual disturbances were associated with benzene exposures (Chen et al., 2000; Thurston et al., 2000). In the study of Chen et al (2000) benzene exposure of the women ranged from 0.017 ppm (0.055 mg/m³) to 0.191 ppm (0.62 mg/m³), with an overall mean of 0.112 ppm (0.36 mg/m³), whereas Thurston et al (2000) provides information on the number of years continuously exposed to benzene, only.

From animal inhalation studies no observed adverse effect concentrations (NOAEC) of 97 mg/m³ for reproductive, and of 32 mg/m³ for developmental effects were established. After chronic exposure to higher concentrations, degenerative lesions of the gonads were found, and foetal growth retardation was seen at high and maternally toxic exposure levels.

Risk characterisation

Several passages describe the derivation of MOS and “minimal MOS values” on the basis of NOAEC and “critical exposure levels, respectively. For example “critical exposure levels” for acute toxic effects were derived by using the NOAEC as a starting point, an adjustment-factor and an uncertainty factor of 2, the latter to consider “uncertainties”, which however have not been defined. Since the NOAEC used to calculate the MOS is based on a study in workers CSTE does not see the need to consider any uncertainty. Interestingly, the MOS values given in Tables 4.1.3.2.B-F are based on the NOAEC, not on the “critical exposure level”, so that the rationale for applying uncertainty factors remains unclear. Moreover, the term “internal body burden” is used instead of “internal exposure” or “target dose”. Since these are toxicokinetic parameters they should be based on measured data rather than on assumptions.

For carcinogenic risk assessment margins of exposure (MOE) are calculated using the European occupational exposure limit of 1 ppm (3.25 mg/m³).

Workers

The risk characterisation has been performed for the main routes of exposure, i.e. the inhalation and dermal routes.

Acute toxicity

Comparisons of estimated worker exposures with the human inhalation NOAEC values resulted in MOSs of 0.95 and 1.2 for the scenarios production of perfumes and cleaning of tanks, although these scenarios evaluated do no longer seem to reflect the current workplace exposures.

The CSTE agrees with conclusion (iii) for these two scenarios and with conclusion (ii) for the other scenarios.

Irritation/corrosion

Personal protective equipment (gloves, eye protection) is obligatory when handling benzene. The CSTE agrees with conclusion (ii).

Sensitisation

The CSTE agrees that there is no evident concern for skin or respiratory sensitisation and conclusion (ii) for this endpoint.

Repeated-dose toxicity

Conclusion (iii) was reached for 6 scenarios with MOS values below 1. The CSTE is in agreement with these conclusions.

Genotoxicity

Benzene is an *in vivo* mutagen. From the available information it is not possible to deduce a threshold level below which the mutagenic risk would be low. The CSTE therefore agrees with conclusion (iii).

Carcinogenicity

Benzene is an established human carcinogen for which no safe level of exposure has been established. The CSTE agrees with conclusion (iii) for all scenarios.

Toxicity to Reproduction

Conclusion (iii) was reached for 6 scenarios with MOS values below 10. The CSTE is in agreement with these conclusions.

Consumers

Highest exposures are through filling gasoline (1.3 mg/m³), and through tobacco smoking, scenarios that are not formal part of this RAR. Exposures through residues in paints or inside cars through car accessories are 0.017 and 0.012 mg/m³, respectively. The CSTE agrees with conclusion (iii) for mutagenicity and carcinogenicity, and with conclusion (ii) for all other endpoints.

Man exposed indirectly via the environment

The CSTE agrees with conclusion (iii) for mutagenicity and carcinogenicity, and repeated exposure in the vicinity of a point source, and with conclusions (ii) for all other endpoints. It also shares the opinion of the Member States Rapporteur that the MOS with regard to the exposure from road traffic is not sufficient.

References

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