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

Opinion on the results of the Risk Assessment of:

NAPHTHALENE

CAS No.: 91-20-3
EINECS No.: 202-049-5

REPORT VERSION (Human Health)
Final Report, October 2001

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

Opinion expressed at the 29th CSTEE plenary meeting

Brussels, 09 January 2002

[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

Several companies in the EU produce a total of around 200,000 tonnes of naphthalene per annum and up to 25 per cent of this are exported. Naphthalene is mainly used as an intermediate in the synthesis of other substances and in the manufacture of fumigants, moth repellents (mothballs), pyrotechnics and grinding wheels. It is a constituent in creosote used for timber treatment and in tar used for paints and waterproof membranes. Fuels also contain naphthalene.

Naphthalene is released during the combustion of organic material and releases from vehicle exhausts are a major source of naphthalene in the environment.

GENERAL COMMENTS

The assessment follows the recommendations of the TGD and is comprehensive and properly written except that information on reproductive function is lacking and that the metabolism and genotoxicity of naphthalene has not been described in detail and more recent data need to be considered. All other relevant endpoints are addressed and the CSTEE agrees in general with the overall conclusions of the risk assessment.

SPECIFIC COMMENTS

Exposure assessment

Naphthalene is a solid that sublimes slowly at room temperature. It is mainly used and transported at 90 °C, *i.e.* at temperatures above its melting point. Hence, the major routes to be considered are the dermal and inhalation routes.

Highest occupational exposures occur in mothball manufacture, from the manufacture of grinding wheels and the use of creosote (EASE estimates for combined vapour and particulate exposure: 4.6-21 mg/m³).

Worst-case dermal occupational exposure is estimated to be 0.1 to 1.5 mg/cm²/day (EASE) during mothball manufacture and manufacture of grinding wheels.

Exposure via inhalation may also occur whenever organic material is incompletely combusted (*e.g.* in processing of coal, crude oil and natural gas, metal foundries, and power plants). The levels of human exposure resulting from these sources were considered insignificant.

Exposures via inhalation or dermal contact resulting from fuels should be addressed in the RAR.

The use in pyrotechnics as described under section 2 of the RAR is not included in the human health part. This should be amended.

Consumer exposure to naphthalene may occur through the use of moth repellents, tar shampoos and soaps and through damp proofing operations. A total daily intake from these was estimated to 54.3 mg (0.77 mg/kg/d). A consumer may also infrequently be exposed to naphthalene from creosote or from the laying of a damp proof course. Infants, in particular, may significantly be exposed to textiles (clothing/bedding), which have been in contact with naphthalene mothballs. However, no quantitative exposure data are available for the latter.

Human exposure via the environment is estimated to range from 65 ng/kg/d at the regional level to 0.25 mg/kg/d at the local level with releases from the manufacture of grinding wheels or mothballs contributing most. Environmental airborne levels are 0.14 ug/m³.

Effects assessment

Naphthalene is rapidly absorbed by all exposure routes and is metabolised in rodents by oxidation with subsequent glutathione conjugation as well as metabolism to naphthalene 1,2-dihydrodiol. In humans, naphthalene is metabolised to 1-naphthol, 2-naphthol and 1,2- and 1,4- naphthoquinones. More recent data demonstrate that cytochrome P450-2F2 in cellular systems of rats and mice metabolise naphthalene to 1R,2S-naphthaleneoxide (Schulz *et.al.* 1999) which rearranges to 1-naphthol and forms the 1,2-dihydrodiol by hydratase activity. Oxidation of 1-naphthol forms 1,2- and 1,4-naphthoquinone (Wilson 1996). In Clara cells isolated from the lungs of naphthalene treated mice, Zheng *et.al.* (1997) reported covalent binding of 1,2-naphthoquinone to protein.

In humans, single or repeated exposures to naphthalene may cause severe haemolytic anaemia. In contrast, it is of low acute toxicity in rodents. It may cause slight irritation on contact with the skin and eyes.

Naphthalene was not sensitising in animals. Despite widespread use, the absence of case reports indicates that naphthalene is not a skin or respiratory sensitiser in humans.

Repeated oral administration of naphthalene is known to cause cataract formation in rats and rabbits at doses of 700 mg/kg bw/d and above. Despite its widespread use there are no reliable reports of cataracts in humans suggesting that this finding is not of relevance to humans. Repeated inhalation exposure produces irritation of the nasal epithelium, with mild effects at levels as low as 5 mg/m³ in rats (LOAEL). In mice, signs of chronic respiratory tract inflammation were noted at 50 mg/m³. There was no indication of haemolytic anaemia in rodent studies, but there is sufficient evidence that severe haemolytic anaemia was induced in infants exposed to textiles (clothing/bedding), which have been stored with naphthalene mothballs.

Naphthalene was not mutagenic in bacterial assays and did not induce UDS *in vitro*. It was, however, found to be clastogenic in CHO cells in the presence, but not in the absence of S-9. Sister chromatid exchanges were found *in vitro* in the presence and in the absence of metabolic activation. Other not mentioned in vitro tests (micronuclei in MCL-5 cells (Sasaki *et.al.*, 1997), DNA fragmentation in macrophage (Bagchi *et.al.*, 1998), chromosomal aberrations in mice embryo cultures (Gollahon *et.al.*, 1990, Martin *et.al.*, 1990), indicated genotoxic effects. *In vivo*, it did not induce micronuclei in bone marrow cells of mice or UDS in rat liver cells. Due to the metabolic formation of an epoxide, which may also be formed in the nasal cavity of the exposed rats, the CSTEE points to the possible involvement of a genotoxic mechanism in tumour formation.

In a carcinogenicity study by the inhalational route, naphthalene produced epithelial adenomas and olfactory epithelial neuroblastomas in rats from the lowest exposure concentration (50 mg/m³). Since neuroblastomas are highly malignant and the P450 isozymes that metabolically activate naphthalene in the nasal cavity of rodents are also present in humans the tumours must be considered of high relevance.

Mice showed an increase in the incidence in pulmonary adenomas, which is considered to be due to the particular sensitivity of this species to the toxicity of naphthalene. Since lung tumours were not seen in rats, and due to the experimentally proven unique sensitivity of the mouse lung regarding metabolic activation and inactivation, the pulmonary tumours are seen as of little relevance to humans.

No fertility study with naphthalene has been reported. Changes in the reproductive organs have not been detected in repeated dose studies, but the absence of data on reproductive function indicates the need for a two-generation reproductive study.

Risk characterisation

There are no concerns regarding irritation, sensitisation, mutagenicity and effects on reproduction. The CSTEE therefore agrees with the conclusion ii) for these endpoints for all occupational and consumer scenarios. However, information on reproductive function is lacking.

Overall, the critical health concerns are for haemolytic anaemia and carcinogenicity. Haemolytic anaemia is evidenced in several case reports, however, there is no information as to the dose/concentrations of naphthalene the subjects (mostly neonates and infants) were exposed to. Hence, no NOAEL or dose-response-relationship can be established for this effect and any significant body burden, gives rise to concern [conclusion iii)].

The RAR considers naphthalene as a non-genotoxic respiratory tract carcinogen in rats, chronic inflammation being a key influence in the development of tumours. A NOAEL could not be identified in the rat carcinogenicity study as the tumours occurred at the lowest concentration tested (50 mg/m³). Mild nasal olfactory inflammation was found in a 28-day rat inhalation study at 5 mg/m³. The CSTEE agrees that a secondary genotoxicity due to chronic inflammation is one of naphthalene´s mechanisms to induce tumours. However, formation of an epoxide and the clastogenic effects in vitro also suggest a genotoxic mechanism.

Workers
A significant body burden in the mg/kg bw/d range was estimated from dermal and inhalational exposures for all occupational settings except for the professional use of tar soap and shampoos where exposure was considered to be very low. As it is presently not possible to identify a NOAEL for haemolytic anaemia, it is not possible to derive a toxicologically valid margin of safety for this endpoint and conclusion iii) was reached for this endpoint for all worker scenarios except the professional use of tar soaps and shampoos [conclusion ii)].

In all occupational scenarios (except professional use of tar soaps and shampoos) the predicted exposures are close to concentrations at which local damage to the respiratory tract has occurred in rats and, therefore, give rise to concern [conclusion iii)].

Consumers
Significant body burdens in the mg/kg bw/d range may result from all relevant consumer scenarios (except from the use of coal tar soaps and shampoos where exposure was considered negligible).

At present, a NOAEL for haemolytic anaemia cannot be established, but there is sufficient evidence that severe haemolytic anaemia was induced in infants exposed to textiles (clothing/bedding), which have been stored with naphthalene moth balls. Conclusion iii) was reached for all consumer scenarios for this endpoint.

The predicted exposure levels from the use of mothballs and following dump-proofing are close to concentrations at which local damage to the respiratory tract has occurred in rats and, therefore, give rise to concern [conclusion iii)].

Use of creosote products and damp-proof laying by consumers is considered to be rare events and therefore give no cause for concern relating to inhalation toxicity and carcinogenicity [conclusion ii)].

Humans Exposed Indirectly via the Environment
Very low levels of exposures on a regional scale do not give rise to concern [conclusion ii)]. Much higher intake (0.25 mg/kg/d) than for the regional scenario is estimated in the locality of grinding wheel plants. Since a conclusion iii) was reached for environmental exposure of this use the risk assessment should be reconsidered after measured exposure data have been obtained following environmental risk reduction activity. The CSTEE agrees with this recommendation.

Combined Exposure
The estimate for the body burden from occupational exposure in this section does not correspond to the value given previously (4.1.3.2.2.) and should be amended. The CSTEE agrees with conclusion iii) for combined exposure.

References

(The final NTP report has been published and the reference list should be updated accordingly)

NTP, TR-500: Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in F344/N Rats (Inhalation Studies), December 2000.

Bagchi M et al.: Naphthalene-induced oxidative stress and DNA damage in cultured macrophage J774A.1 cells. Free Radical Biol Med 25, 137-143 (1998).

Gollahon LS et al. : Chromosomal damage to pre-implantation embryos in vitro by naphthalene. Toxicologist 1990 Feb;10(1):274

Martin JE et al. : Development of pre-implantation rodent embryo culture systems for identification of developmentally-toxic chemical agents. In Vitro Cell Dev Biol 1990 Mar;26(3 PART 2):20A

Sasaki JC et al. : Genotoxicity induced in human lymphoblasts by atmospheric reaction products of naphthalene and phenanthrene. Mutat Res. 393, 23-35, 1997

Schulz MA, Choudary PV, Buckpitt AR: Role of murine cytochrome P-450 2F2 in metabolic activation of naphthalene and metabolism of other xenobiotics. J Pharmacol Exp Ther 290, 281-290, 1999

Wilson AS, Davis CD, Williams DP, Buckpitt AR, Pirmohamed M, M, Park BK: Characterisation of the toxic metabolite(s) of naphthalene. Toxicology 114, 233-234, 1996

Zheng J, Cho M, Jones AD, Hammock BD: Evidence of quinone metabolites of naphthalene covalently bound to sulphur nucleophiles of proteins of murine clara cells after exposure to naphthalene. Chem Res Toxicol 10, 1008-1014, 1997