EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Health and Environmental Risks

SCHER

# Risk Assessment Report on HEXABROMOCYCLODODECANE (HBCDD)

## Human Health Part

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Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risks

The SCHER adopted this opinion at its 21st plenary on 15 January 2008

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Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) and are made up of external experts.

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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

### 3.1 General comments

Hexabromocyclododecane (HBCDD) is a widely used flame retardant in polymer and textile industry, and the sources of human exposure include production, industrial use, use of consumer products and indirect environmental exposure. The compound is not readily biodegradable and may accumulate in biota.

The health part of the RAR is of good quality, it is comprehensive, and the exposure and effects assessment follow the Technical Guidance Document. The RAR covers all available studies relevant for exposure and hazard assessment of HBCDD. In addition, as acknowledged in the RAR, further relevant information on health effects of HBCDD will be published in the near future.

### 3.2 Specific comments

#### 3.2.1 Exposure assessment

Humans are exposed to HBCDD mainly by inhalation of airborne dust or by dermal contact. Inhalation exposure to HBCDD vapour is insignificant due to low vapour pressure of HBCDD. Exposure via the environment takes place via the oral route. There is also a risk for prenatal and neonatal exposure *in utero* or via breast feeding.

Occupational exposure assessment of HBCDD was carried out without considering personal protective equipment and is based on three scenarios: (1) filling of bags at the manufacture of HBCDD, (2) charging HBCDD to processes for producing end-products or semi-products, and (3) sewing (textile work). The RAR uses both measured data and EASE modelled data with the weight on measured data in order to establish reasonable worst case (RWC) exposure levels. Measured data are available from sites producing HBCDD and from sites using HBCDD as fine powder, standard grade, granules and masterbatch. For industrial end-uses of HBCDD containing semi-products or end-products not enough representative measured data were available. For dermal exposure estimates EASE modelling was used due to the lack of measured data.

The SCHER agrees with these approaches.

Consumer exposure takes place mainly via inhalation or ingestion of airborne dust, or from direct contact with treated textiles and other materials. All these scenarios typically result in insignificant exposures. Indirect exposure via the environment was estimated using EUSES calculations based on available measured HBCDD level data in biota and

food. Highest estimated exposure was related to consumption of fish and root crops. Human exposure to HBCDD from the use of consumer products or via the environment is substantially lower than occupational exposure.

### 3.2.2 Effect assessment

Limited amount of data is available on the toxicokinetics of HBCDD, and there is no data on systemic bioavailability of HBCDD after inhalational exposure. Gastrointestinal absorption of 100% is assumed for dissolved HBCDD. Because oil suspended HBCDD particles were used in one 90-day oral toxicity study in rats the RAR utilises a read-across approach and estimates that the bioavailability of HBCDD particles after peroral administration is of the order of 10-20%. This estimate is based on a kinetic study carried out on felodipine in dogs. The particle size of HBCDD used in the 90-day study and that of felodipine were similar. Felodipine is a calcium channel blocker of dihydropyridine class, and it resembles HBCDD to some extent in terms of lipophilicity and poor water solubility.

The SCHER has reservations for using the read-across approach for comparing compounds with dissimilar chemical structure and somewhat different physico-chemical properties, as well as comparing data from different animal species, but considers this relatively conservative estimate acceptable in this particular case. In the lack of data the absorption of inhaled HBCDD is estimated at 100%. Based upon a percutaneous absorption study using human skin *in vitro* the RAR uses a dermal uptake value of 4%. It is derived after exclusion of the contribution of tape stripping for 10 times.

The SCHER agrees with these approaches.

The RAR concludes that the acute toxicity of HBCDD is low; the compound is not corrosive, irritating or sensitizing to the skin. The SCHER agrees with these conclusions. No repeated dose studies with inhalational or dermal exposure are available. Repeated dose studies with oral exposure identified liver, thyroid and prostate as the target organs of toxicity. The RAR identifies the repeated dose NOAEL/BMD-L value of 22.9 mg/kg/day based upon an increased liver weight. This value was derived from a 28-day oral study in rats that used a study design supporting the Benchmark dose (BMD) modelling, and covers also thyroid effects and increased pituitary weight. This value was used for risk characterization instead of the more uncertain LOAEL of 10-20 mg/kg/day (increased liver weight, thyroid effects) derived from a 90-day rat study after read-across based adjustment for systemic bioavailability of particulate HBCDD (see above).

The SCHER disagrees with this approach, because due to the bioaccumulating properties of HBCDD the use of data from a 28-day study potentially underestimates effects. This is evident when comparing the LOAEL value of 10-20 mg/kg/day for increased liver weight from the 90-day study with the NOAEL/BMD-L value of 22.9 mg/kg/day for the same endpoint from the 28-day study. Moreover, this effect was observed in both genders in the 90-day study, but only in females in the 28-day study.

The SCHER supports the conclusions that HBCDD lacks genotoxic potential *in vitro* and *in vivo*. Carcinogenicity of HBCDD has been assessed in an 18-month bioassay in mice. This inadequately reported study found and increased frequency of liver carcinomas in females at the intermediate dose level, but not at the other dose levels. Based on these reported data and the absence of mutagenicity the RAR concludes that there is no reason to study the carcinogenic effect of HBCDD further.

The SCHER agrees with this conclusion.

Ordinary developmental toxicity studies did not demonstrate fetotoxicity or developmental toxicity, but no fertility studies are available. Due to the high bioaccumulation potential of HBCDD, potential for lactational transfer and potential

effects of life-time exposure the RAR proposes conclusion i)[1] with regard to a properly designed multi-generation reproduction study in rodents. Furthermore, the RAR lists three additional studies that could potentially influence the conclusion.

First, a developmental neurotoxicity study that utilised a non-standard method on neonatal mice (Eriksson *et al.*, 2006) resulted in an indicative LOAEL of 0.9 mg/kg (a single dose). It has been previously agreed that because of inconclusive relevance of this method, findings on chemicals tested using this test system need to be confirmed by other laboratories before they can be considered acceptable for risk characterisation.

Second, a preliminary report of a developmental neurotoxicity study carried out according to the OECD guideline 415 revealed BMD-L values for different types of neurobehavioral effects in the offspring at maternal dose-levels within the range of 0.2–40 mg/kg (Lilienthal *et al.*, 2006). The RAR concludes that the relevance of these data cannot be adequately evaluated before the final report of the study is available.

Third, referring to information from industry the RAR reports that a 2-generation reproduction toxicity study is going on in Japan. Therefore the RAR proposes that the conclusion i) is kept on hold until these data will be available. Conclusion i) on hold is also proposed for developmental neurotoxicity.

The SCHER agrees with this approach and recommends a new risk assessment after completing the database.

### 3.2.3 Risk characterisation

Risk characterization uses the margin-of-safety (MOS) approach and the reference MOS of 20 for occupational exposures. It is composed of an assessment factor of 5 for intraspecies differences in the worker population and a factor of 4 for interspecies differences, which represents the difference in caloric demand between rats and humans. Assuming that enzyme induction explains the liver and the thyroid effects, humans are not expected to be more sensitive to these effects than rats. A factor of 1 is used for differences between the experimental 28-day exposure and chronic exposure, because there is no indication about increasing the liver weight effect with more time.

The SCHER disagrees with the use of reduced reference MOS value due to insufficient justification.

Occupational exposure occurs primarily by dermal and respiratory routes, and the RAR considers these two routes and combined exposure for the three scenarios: (1) manufacture (filling operations with HBCDD powder or granules), (2) industrial use (production of fire-proofed products, adding HBCDD powder or granules to formulation), and (3) end use of HBCDD during sewing textiles. The RAR proposes conclusion ii) for workers during filling of HBCDD powder and granules in the production, adding of HBCDD fine powder, powder and granules in industrial use, and sewing of HBCDD fine powder, powder and granules in industrial end-use. Conclusion iii) is proposed for workers during filling of HBCDD fine grade powder in production. As there is currently no occupational limit values for HBCDD the RAR also concludes that there is a need to establish occupational exposure limit values for this compound.

The SCHER recommends reconsideration of these conclusions after establishing the sufficiently justified reference MOS value.

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[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.*

Risk characterisation for consumer exposure as well as for indirect exposure via the environment uses the reference MOS of 40, which results from a factor of 10 for intraspecies differences in the whole human population and the factor of 4 for interspecies differences (see above). The RAR proposes conclusion ii) for all scenarios for consumers. Similarly, the RAR proposes conclusion ii) and for humans exposed via the environment from local and regional sources, as well as for breast feeding infants. The SCHER disagrees with the use of reduced reference MOS value due to insufficient justification.

For illustrative purposes the RAR presents also a calculation based on the indicative LOAEL of 0.9 mg/kg/day for developmental neurotoxicity and the worst case average daily uptake of a breast-feeding infant. This calculation results a MOS of 60 000. Conclusion ii) is also proposed for physico-chemical properties (flammability, explosive and oxidising properties).

The SCHER agrees with this conclusion.

## 4. LIST OF ABBREVIATIONS

| | |
|---|---|
| BMD | Benchmark dose |
| BMD-L | Lower bound 95% confidence interval of BMD |
| EASE | Estimation and Assessment of Substance Exposure |
| EUSES | EU System for the Evaluation of Substances |
| HBCDD | Hexabromocyclododecane |
| LOAEL | Lowest Observed Adverse Effect Level |
| MOS | Margin of Safety |
| NOAEL | No Observed Adverse Effect Level |
| RAR | Risk Assessment Report |
| TGD | Technical Guidance Document |

## 5. REFERENCES

Eriksson P, Fisher C, Wallin M, Jakobsson E and Fredriksson A. Impaired behaviour, learning and memory, in adult mice neonatally exposed to hexabromocyclododecane (HBCDD). Environ Toxicol Pharmacol 2006; 21: (3): 317-322.

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