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Scientific Committee on Toxicity, Ecotoxicity and the Environment

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

Opinion on the results of the Risk Assessment of:

Diphenyl ether, octabromo derivative

Environmental and Human Health Part

CAS No.: 32536-52-0

EINECS No.: 251-087-9

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

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 provided by the European Chemicals Bureau, The CSTEE is invited to examine the following issues.

RISK TO THE ENVIRONMENT

The risk assessment report concludes that:

- 1 There is a need for limiting the risks with regard to secondary poisoning concerns for the hexabromodiphenyl ether (hexa-BDE) component that is present in the commercial octa-BDE product.
2. As concerns secondary poisoning concerning octa-BDE and its debromination products, there is a need for further information and/or testing, although risk reduction measures should be considered in the absence of adequate scientific knowledge.

With regard to point (2) above, the question to the CSTEE is:

Is the risk assessment sufficient to draw the conclusion that risk reduction measures are necessary, if not, the Committee is requested to characterise the hazards and risks and indicate the information which would be necessary to complete the risk assessment?

RISK TO HUMANS

1. Is the risk with respect to human health effects from octa-BDE and its debrominated products sufficient to draw the conclusion that risk reduction measures are necessary, and if not, the Committee is requested to characterise the hazards and risks and indicate the information which would be necessary to complete the risk assessment?

BACKGROUND

Octabromodiphenyl ether is a member of the group of polybrominated diphenyl ethers that are mainly used as fire retardants. These fire retardants are added to plastics and textiles to reduce flammability and improve fire safety. Flame retardants are present in some materials in concentrations of up to 30% by weight. The brominated biphenyl ethers are not chemically bound into the products and therefore have the potential for release.

The technical product octabromodiphenyl ether is a mixture that contains diphenyl ethers with six to ten bromine atoms. For most bromination degrees there are in addition a number of isomers. All of these compounds are very lipophilic. Although they have similar structures they have different properties in biological systems, for example the uptake in biological organisms varies greatly between homologues. Many of the components of technical octabromodiphenyl ether are likely to be very poorly metabolised. Some biotransformation will occur however and some of the debrominated products may cause increased toxicity. As a consequence of the differences in uptake and metabolism, the composition of PBDEs both in the human body and in the environment can differ from that in the commercial products. Ideally every congener should be assessed individually, but the present knowledge of these

substances does not allow this. The exposure assessment is further complicated by the fact that the commercial product pentabromo diphenyl ether also contains a number of the congeners contained in the octabromo product.

GENERAL COMMENTS ON THE RISKS TO THE ENVIRONMENT

The CSTEE gave its Opinion on a previous draft of the environmental section of this report in June 2000. The present version of the RAR is an update of this earlier draft, which includes recent published data. The assessors have appropriately tried to conduct a separate estimation of the risk posed by the compounds containing six bromine atoms, as these have the highest bioavailability. There are several problems connected to this:

- as these compounds are also present in the commercial pentabromodiphenyl ether products and it is difficult to identify exposure data due to the octabromodiphenyl ether.
- The 2,2',3,4,4',5',6-heptabromodiphenyl ether (BDE-183) is the major component in octabromodiphenyl ether products and should also have been a candidate for a separate assessment (the technical product is named octa-BDE because of the average bromine content).
- Octa-BDE is the least studied of the PBDE products, and a number of assumptions and estimations have to be used, which make the final outcome of the assessment uncertain.

The CSTEE considers the separate assessment of the contribution from the hexa-BDE isomers to be unreliable. Thus the resulting calculated PEC/PNEC ratio of 1.2 for secondary poisoning is based on a number of assumptions and uncertainties in the data. It is noted that the assessment has not taken into account that the hexa-BDEs have higher vapour pressure than the octa-BDE product, and thus the PEC/PNEC could be higher.

The CSTEE therefore agree with the conclusion iii) because of the risk for secondary poisoning from the hexa-BDEs and from debromination products from the octa-BDE. The CSTEE is concerned too about the persistence of octabromodiphenyl ether related materials, and about the possibility that octa-BDE may be contaminated with PBDDs/PBDFs, compounds that also can be formed during heating and incineration.

SPECIFIC COMMENTS

Exposure assessment

There are only very few reported measurements of concentrations of octa-BDE in the environment, and the assessors had therefore to use the EUSES model to estimate the exposure. The technical mixture contains hexa- hepta- octa- nona and deca-BDEs and the availability of measured data for the individual substances is very limited. Measurements based on the complex product are difficult to interpret, as the values may depend principally on one or two compounds in the product. Studies on the penta- and deca-BDE products are used to estimate the properties of the low and high brominated components in the octa-BDE product. In the light of the limited data available the CSTEE fully support this approach.

In an appendix the outcome of the exposure estimates due to the uncertainty of the parameters used in the assessment is shown. It is found that the predicted concentrations in water, soil and sediment are relatively insensitive to these uncertainties. The indirect exposure is, however, very dependent on the log Kow value chosen for the prediction. This, together with the uncertainties in uptake efficiency in organisms, is a major problem in the risk assessment of these substances.

Measured concentrations of octa-BDE in water, sediment and fish are of the same order as the predicted values. There are no data for the levels of this substance in air.

As the lower brominated isomers are more readily accumulated in biological organisms, a special interest has been paid to the hexa-BDEs in the octa-BDE products. A problem of this approach is that these isomers are also present in the penta-BDE products, and it is not possible to say how much of the hexa-BDE compounds in the environment is emanating from which product. 2,2',3,4,4',5',6-Heptabromodiphenyl ether (BDE-183) is a much better indicator substance for the octa-BDE product, as it is the major component of the commercial mixture (the concentration is almost an order of magnitude higher than the hexa-BDEs). There is a need for further studies on BDE-183, especially as it is found in several bird species and humans.

Not discussed in the RAR is the possibility that octa-BDE may be contaminated with PBDDs/PBDFs, compounds that also can be formed during combustion. These substances are regarded as equally toxic as the chlorinated counterparts (IPCS, 1998). In addition, incineration may also form dioxins and furans containing both chlorine and bromine.

Effects assessment

Many of the detailed comments are provided in the earlier opinion of the CSTEE and are not repeated here.

There are data on effects in invertebrates and fish available for the octa-BDE product, but not for algae. The assessors try to extrapolate results from studies of penta- and deca-BDE to compensate for this. The CSTEE finds that unwise, as the data on water solubility for all these substances are connected with large uncertainties and the studies have been performed in saturated solutions. A test with a sediment organism showed low toxicity of octa-BDE, as well as a study with microorganisms.

The effect of octa-BDE on six plant species indicated a low toxicity. In another study the effects on earthworms was investigated, and no effect could be seen at the highest dose of 1,470 mg/kg dw in the soil. If this result is recalculated for the hexa-BDE isomers in the product it gives a NOEC of ≥ 81 mg/kg dw.

In mammalian test systems developmental and reproductive effects of the octa-BDE have been found at 2mg/kg bw/day, or 67 mg/kg in the animal diet. If an assessment factor of ten is used it gives a PNEC for secondary poisoning of 6.7 mg/kg food. It is assumed that this effect is caused by the hexa-BDE in the product it corresponds to a PNEC of 0.58 mg/kg food for these isomers (PNEC for the penta-BDE product was 1 mg/kg food).

Risk characterisation

The PEC/PNEC ratios for the octa-BDE products are below 1 in all compartment, except water where the result is <1.4. The CSTEE agrees that this is not of great concern as the PNEC_{water} was >0.2 microg/L, which is close to the expected water solubility of 0.5 microg/L.

The assessment of the hexa-BDE components in the technical product is more difficult to perform. The report concludes that the PEC/PNEC is 1.2 for secondary poisoning. This result is based on many assumptions and uncertainties in the data. The PEC value is based on an EUSES estimation, where the emissions during the service life of flame retarded products is the major source. This is supposed to be due to evaporation to air, and is calculated for the whole product. The emission of hexa-BDE is then obtained from this result by a multiplication with the concentration of those isomers in the product. The CSTEE would expect a higher concentration of the hexa-BDEs in the air due to their higher vapour pressure, and the exposure may therefore be underestimated.

The PNEC used in the calculation of the risk for secondary poisoning is based on a study of the octa-BDE product. For the assessment of the hexa-BDE isomers it is assumed that the whole effect is due to the presence of these isomers in the product. This may be an overestimation of the risk connected with these substances. On the other hand, the lower brominated substances are much more effectively taken up by the animals, and may therefore be responsible for most of the effect.

The CSTEE agrees with the conclusion iii) due to the risk for secondary poisoning from the hexa-BDE isomers in the octa-BDE products.

Necessary information to complete/improve the environmental risk assessment

1. There is a need for further studies on BDE-183, especially as this compound is found in several bird species and humans.
2. The most critical parameter in the exposure assessment is the uptake of these large, very lipophilic molecules in biota. Monitoring data indicate substantial species differences, and there are indications that the uptake process is slow for the more heavily brominated molecules. Further studies in this field are essential, also for the assessment of other substances in this category, such as deca-BDE.
3. There are several information requirements in order to improve the environmental exposure assessment. These include determination of bioaccumulation in algae and aquatic invertebrates. When more mammalian toxicokinetic data become available, some of these can also be used for environmental assessments. There is also a need to address the biomagnification potential using proper models.
4. The contribution of PBBDDs/PBDDFs to the total risk should be addressed.

HUMAN HEALTH RISK ASSESSMENT

GENERAL COMMENTS

The health part of the document is of good quality and follows the TGD. However, some parts of the document should be written in a more concise way and would profit from the presentation of risk assessment results in tabular form. Descriptions of the results of a published study should not simply be repeated in identical words in the document.

The CSTEE is concerned about the absence of information on the debromination products, and about the possibility that octa-BDE may be contaminated with PBDDs/PBDFs, compounds that also can be formed during heating and incineration.

The CSTEE agrees with most of the conclusions for most exposure scenarios that there is a need either for further information, conclusion (i) or need for risk reduction (iii).

Although the CSTEE supports the conclusion (i) for indirect exposure via the environment, CSTEE wishes to express its concerns with the potential risks with this compound if future use is continued or increased. It is true that octa-BDE production and use today is limited as compared to the corresponding deca-BDE commercial product. Available data on octa-BDE are scarce and there has been very limited monitoring of this compound in humans and the environment. However, on the whole, human data demonstrate systemic absorption of the octa-BDE in humans and accumulation in adipose tissues and lipid. A recent mass balance feeding study of a commercial octa-BDE mixture in rats confirms these data (Huwe et al., 2002). Furthermore, the presence of 2,2',4,4',5,5'-hexabromodiphenylether, which is a component of a commercial octa-BDE product plus tetra-BDE and penta-BDE, confirms this distribution with the consequence of appearance in breast milk. Using historical evidence (read-across) from substances with comparable persistent and bioaccumulating properties, it can be anticipated that octa-BDE will have the same toxicokinetics. Hexa-BDE (BDE 153) has also recently been found to biomagnify in marine food chains (Boon et al., 2002). Thus, there may be a risk to top-predators including humans at the continental scale and the CSTEE will therefore suggest conclusions (i) and (iii).

SPECIFIC COMMENTS

Despite the high production volumes and the widespread use and potential for human exposure, the database on octabromodiphenyl ether toxicity is limited. In addition, some of the information on toxicity has been obtained using technical mixtures of polybrominated diphenylethers containing varying amounts of octabromodiphenyl ether.

Exposure assessment

In the RAR, exposures to man via environmental routes has been estimated using EUSES and show no increase for octa-BDE from 1994 to 1999. However, PBDEs have been steadily increasing over the last decades in biota including humans. Consequently, the question rises to which extent these brominated flame retardants (BFRs) pose a risk to species higher in the food chain, in particular top predators and humans. Human exposure probably occurs mainly via food in analogy to PCBs and related compounds, but occupational exposure, e.g. through handling electronic equipment, may also play a significant role.

An important observation mentioned in the RAR is that in contrast to e.g. PCBs and DDT, the levels of PBDEs are increasing in human milk: a study in Sweden showed a doubling in concentration every five year over the period 1972 to 1997, BDE-47 being the predominant congener. From 1998 to 2000 a decrease in PBDE levels was noticed, which can be a consequence of the phase out of the commercial pentaBDE in Sweden (Guvenius Meironyté, 2002). The temporal trends and influence of age and gender on six BDE congeners was investigated on archived serum samples from Norway (Thomsen et al., 2002). The sum of the BDEs increased from 0.44 ng/g lipids in 1977 to 3.3 ng/g in 1999, with BDE-47 being the most abundant congener. BFR levels in the different age groups were relatively similar, except for the age group of 0-4 years, which had 1.6-3.5 times higher serum concentrations; breast milk being considered the main source. Recent data from the USA indicate that PBDE levels in mothers milk are much higher than the values reported from Sweden and Norway as levels of approx. 200 ng/g lipid were reported in a pooled sample of mothers milk from the U.S (levels of 132, 27 and 15 ng/g lipid of BDE-47, BDE-99 and BDE-153, respectively) (Päpke et al., 2001). The latter data are not included in the RAR.

Not discussed in the RAR is the possibility that octa-BDE may be contaminated with PBDDs/PBDFs, compounds that also can be formed during combustion. These substances are regarded as equally toxic as the chlorinated counterparts (IPCS, 1998). In addition, incineration may also form dioxins and furans containing both chlorine and bromine.

There is a lack of information on the potential exposure of consumers; assessment therefore depends on predicted levels

Effects assessment

Acute toxicity

The acute oral, inhalation and dermal toxicity of octabromodiphenyl ether have been studied in rats and rabbits. The available data show that the acute oral toxicity of octabromodiphenyl ether is low with LD₅₀-values > 5 000 mg/kg. The acute inhalation of octabromodiphenyl ether (respirable particles) resulted in LC₅₀-values > 50 mg/L (this should be given in mg/m³).

Irritation and corrosivity

Skin and eye irritation by octabromodiphenyl ether was studied in rabbits according to accepted protocols and the available data do not suggest that octabromodiphenyl ether is a dermal or ocular irritant.

Sensitizing properties

A guinea pig maximization test on octabromodiphenyl ether did not indicate a potential for octabromodiphenyl ether to act as sensitizer.

Toxicokinetics

Almost no data on the toxicokinetics of octabromodiphenyl ether are available and the assessors make conclusions based on very limited data. Increased bromine concentration after repeated administration of octabromodiphenyl ether suggests a potential for bioaccumulation. However, the available information does not give any qualitative information on extent of absorption, biotransformation and kinetics of excretion. The human data discussed provide only very limited information on toxicokinetics suggesting that an unspecified amount of

octabromodiphenyl ether taken up by unspecified routes is stored in adipose tissue. The studies discussed are more appropriately mentioned in the exposure section since none of them addresses aspects of toxicokinetics. The CSTEE suggests to change the sentence on page 110 "Limited data on human toxicokinetics are available" to "Very limited data.....".

Repeated dose toxicity

Octabromodiphenyl ether was administered orally to rats for 28 and 90 days. The liver was found to be the most sensitive target organ for the toxicity of octabromodiphenyl ether but NOAELs could not be established because of improper dosage selection. The CSTEE agrees with the LOAEL of 7.2 mg/kg/day based on liver histopathology and the occasionally increased liver weights. The toxicity of octabromodiphenyl ether was also studied after inhalation exposure for 14 days using particles of respirable sizes. Again, the liver was identified as the most sensitive target organ and a NOAEC of 1 mg/m³ was derived for effects on the liver. Regarding local toxicity to the respiratory tract, a LOAEC of 1 mg/m³ was defined. The CSTEE agrees with both values.

Minor point: In table 4.6, the inhalation studies should be addressed using a different heading giving route of exposure since air concentrations are not equivalent to doses received.

Genotoxicity

The data on the genotoxicity of octabromodiphenyl ether are limited. Octabromodiphenyl ether was studied for mutagenicity in bacteria either as the pure compound or as component in a mixture with other polybrominated diphenyl ethers. Usually, mutagenicity was not observed using metabolic activation and in different strains of *Salmonella typhimurium*.

Octabromodiphenyl ether did also not induce unscheduled DNA-synthesis and sister chromatid exchanges in cultured cells or cytogenetic changes in human lymphocytes. Despite the limitations of the testing conditions using these type of materials, the CSTEE agrees that there is no concern for mutagenicity.

Carcinogenicity

No experimental data are available on the carcinogenicity of octabromodiphenyl ether. However, based on the low toxicity, structural similarity to other weak carcinogens such as PCBs and the effect on thyroid hormones and enzyme induction, it could indicate a potential for non-genotoxic carcinogenicity.

Reproductive toxicity

Toxic effects of octabromodiphenyl ether to reproductive organs were studied in a recent well reported inhalation study. No treatment related effects on male reproductive organs were seen after exposure of rats up to 250 mg octabromodiphenyl ether/m³. In females, absence of corpora lutea was observed in a recent well conducted inhalation study, and a NOAEC of 16 mg/m³ is identified for reproductive effects in female rats. The CSTEE agrees with these conclusions.

Developmental toxicity

The developmental toxicity of commercial octabromodiphenyl ether was studied in two rat and in one rabbit study. In rats, dose-dependent effects on the conceptus were seen after administration of doses > 10 mg/kg/day. In rabbits, slight toxicity to the foetus, represented by decreased body weight gains, was observed after 5 mg/kg/day. For the risk characterisation, the RAR uses a NOAEL of 2 mg/kg/day. The CSTEE agrees with this and with the

classification 'Toxic for Reproduction'.

Regarding developmental neurotoxicity, only the Viberg et al., 2001 study (available as abstract only) with hexabromo-diphenylether is mentioned in the RAR indicating neurotoxic effects in the adult following neonatal exposure. However, similar toxicity was published earlier following treatment of mice with tetrabromo- and pentabromo-diphenylether (Eriksson et al., 1998; 2001).

Risk characterisation

Genotoxicity

The CSTEE agrees with the view that there are no concerns for genotoxicity and with the overall conclusion (ii) for this endpoint for all scenarios

Carcinogenicity

No conclusion can be drawn since no studies are available.

Workers

Due to very small or non-existing MOS, the CSTEE agrees with conclusion (iii) regarding all endpoints for worker exposure. Regarding risk characterisation, due to insufficient information available and potential effects due to the accumulation of octabromodiphenyl ether, the CSTEE also agrees with conclusion (i) for some endpoints regarding worker exposure.

Consumers

The CSTEE agrees with the overall results of the risk assessment report that there is at present no need for further information and/or testing and for risk reduction measures regarding liver toxicity since the relevant MOS are sufficiently high and are based on adequately performed animal studies. Regarding developmental toxicity, a MOS of > 100 is estimated, but conclusion (i) is reached. The authors should, however, provide the rationale for conclusion (i). If insufficient information on human exposure to octabromodiphenyl ether is the driving force for conclusion (i), this conclusion should also apply to the other exposure scenarios. Conclusion (i) is also indicated by the time-related increase in the levels in humans and environment of lower brominated diphenylethers: this information is currently lacking for octa-bromodiphenylether. The CSTEE supports conclusion (i) for all other endpoints due to the lack of information on toxic effects or potential exposures to octabromodiphenyl ether.

Minor point: A table listing MOS and estimated exposures for the different scenarios would be helpful to the reader

Necessary information to complete the human risk assessment

Since potential bioaccumulation is one the major concerns with octabromodiphenyl ether due to the structural similarity with other bioaccumulative chemicals, a detailed study on the toxicokinetics of octabromodiphenyl ether in rodents including lactational transfer is one the the main pieces of information needed to conclude the risk assessment. An extrapolation of existing data on decabromodiphenyl ether and pentabromodiphenyl ether may not be applicable since the toxicity profile of these compounds and the available data on their toxicokinetics suggest major differences between these chemicals and octabromodiphenyl

ether. In addition, the potential effect of octabromodiphenyl ether on thyroid function in rodents should be examined in more detail. - Further information regarding the endocrine disruption potential is also required on the possibility of Ah-receptor mediated effects (either agonist or antagonist as described for lower brominated diphenylethers: Meerts et al., 1998 and Zhou et al., 2001).

There is an absence of information on the mammalian toxicity of the debrominated diphenyl ethers and other metabolites.

N.B.

Before considering any substitution of octabromodiphenyl ether with alternative flame retardants, due consideration should be given to the potential human and environmental risks such substitutes could pose.

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