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

"Revised assessment of the risks to health and the environment associated with the use of organostannic compounds (excluding use in antifouling paints)."

Report version: Final Report (Draft) December 2003.

Adopted by the CSTEE during the 43rd plenary meeting of 28 May 2004

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Question to the CSTEE

The CSTEE is requested to review the new additional information provided, and consider whether or not it would lead the CSTEE to revise its opinion adopted on 12 June 2003.

Background

In August 2002 the CSTEE was asked by the Commission to comment on "Assessment of the risk to health and the environment posed by the use of organostannic compounds (excluding use as a biocide in antifouling paints) and a description of the economic profile of the industry" published by RPA 19 July 2002. The Committee adopted an opinion on the non-food aspects of the report 12 June 2003 (CSTEE, 2003). The CSTEE had particular concerns on the use of emission factors in the environmental assessment and that the imposex effect was not considered. For the human health assessment the CSTEE commented on the selection of emission factors, food consumption data for children and also the fact that some exposure routes were not considered. The possibility of additive effects from simultaneous exposures to several organotin compounds was also discussed.

After the publication of the CSTEE opinion the report has been revised (RPA, 2002) and the Committee is now asked to review this and see if the information provided change any of the comments on the original report.

General comments

In the new version of this report the exposure data are lower for many routes than in the earlier version. This is due to several changes, such as the selection of lower estimated emission data, a change in the properties chosen for the substances, and lower emission factors. The CSTEE disagree with several of the new data used for the exposure assessment and think that the former version of this report in many cases was closer to the likely true values than the new version.

From the report the possibility remains that human health, especially for children, is at risk due to exposure from organotin compounds.

The CSTEE wishes to underline that it is the total exposure that is important for the assessment of the actual risk. This includes all uses, including antifouling paint

Specific comments

The compounds covered in the report do not include the phenyltin species. This is explained by several restrictions on the use of these substances. Nonetheless in a recent paper (Lo et al., 2003), describing the concentrations of organotin compounds in human serum samples, it was shown that triphenyltin was by far the most common organotin compound in the samples. The CSTEE therefore wishes to stress the importance of including this substance in the assessment.

Environmental exposure

The production/use data are less detailed in the new report than in the first version, and often qualified by terms such as "indicated", "believed", "thought", "estimated" and "information from one company". This gives an overall impression of uncertainty in the basic collection and use of data.

The emission from one of the producers (site X) is in the new report reduced by an order of magnitude, on the basis that the water is sent to WWTP. TBT seems to be the major tin compound in this emission, and this compound may be degraded to mainly DBT in the plant, and consequently the emission of that compound has to be taken into account.

The measurements of loss factors for PVC processing are welcomed, but need to be supported by a sound evaluation before the reduction of the BRE loss factors by a factor of five can be accepted. It must be stressed that the use of this factor will lower all predicted values of PECs where evaporation is playing an important role.

The emission factors for formulation and processing of polymers taken from the BRE document is substances with "high" vapour pressure, which in this document correspond to BBP (some 10^{-3} Pa). The organotin compounds have higher vapour pressures (around 1 Pa) and the loss through evaporation may thus be much bigger.

The loss of organotins to water from PVC during outdoor use has been given an emission factor of 0.15 % per year in the BRE (1998) document. This corresponds to a loss of 3 % over the 20 years, not 0.05 % (see table 3.9). This will change the estimated emissions in Table 3.16 significantly. This comment goes for both versions of this report, but was not identified by the CSTEE before.

The biodegradation categories assigned to the organotin compounds in Table 3.29 are not obvious. MMT is readily biodegradable, but not necessarily MBT and the experimental data seem to classify both DBT and DOT as inherently biodegradable. The BCF value (1) used for the prediction of DOTC distributions is too low, considering that the K_{ow} is over 600,000 according to Table 3.25. More realistic values for both degradability and BCF would have changed the indirect exposure from the environment considerably.

Human exposure

Inhalation

The section on consumer exposure is not transparent in the revised report. In several of the tables it is difficult to see the origin of the used data, especially for loss or emission factors. For example, the estimation of exposure via indoor air is apparently based on diffusion constants derived by Fabes, and the lifetime loss (20 years) obtained in Table 3.14 (not 3.12 as mentioned in the text) was 2.28 % for DBTC. In Table 5.12 the corresponding value is 0.27 % per year, which is 5.4 % over 20 years. This seems to correspond to migration plus abrasion in Table 3.14, but all the

abraded particles will not contribute to the air concentration. The paragraph following Table 5.12 then says that the emission rates used are based on migration to water, and that all values are divided by a factor of 100 to compensate for this. This is not right and the inhalation exposure is underestimated by two orders of magnitude. This indeed may be one of the major sources for human intake of organotin compounds. Several investigations have also shown organotin compounds in household dust (e.g. Al Bitar, 2004), and this is also a possible exposure pathway, especially for children, although it is more difficult to estimate quantitatively.

Oral

It is correct that the exposure from mouthing of toys depend on two factors, mouthing time and leach rate. The CSTEE is aware of the US CPSC study that found mouthing times of about 70 minutes for children between 3 months and 1 year for all objects except pacifiers. The time these children spent mouthing soft plastic items was about 4.5 minutes per day, but this figure is very variable since it is affected by a number of factors, such as the availability of such items. There is also a mouthing study published by the UK Department of Trade and Industry (Norris and Smith, 2002), where the mean daily mouthing of toys for 6 to 9 month children was estimated to be about 39 minutes (maximum 3 hours 47 minutes). It is also correct that the value used by CSTEE for the leaching rate was an assumption, but it is not correct that the result from the Fabes study can be applied. There is a big difference between a passive migration and what is happening in the mouth of a child, where there is a substantial mechanical component. The CSTEE found that the migrations of the phthalates were much higher than could be expected from ordinary leaching data. The fact that the organotin compounds have much higher water solubility may also increase the migration compared to the more lipophilic phthalates. This has been shown in a study of migration of organotin compounds from swimming pools and beach balls, where the migration to artificial saliva and water was about equal as that to artificial skin fat (Miljø-Kemi, 2000).

Total exposure

In the tables (6.7 and 6.8) describing the total consumer exposure, the contributions from insoles, foot spray, cycling shorts and baking paper are described as “eliminated”. This may be true for products produced within the EU, but it gives a false description of the exposure situation as imported products may contain such compounds. A Danish report (Boyd HB, and Höglund L, 2003) has calculated the consumer exposure based on worst case situations and identifies these applications as major contributors. That report is further reviewed in Annex 1.

The total exposure to organotin compounds is very complex including many sources not discussed in this opinion

Effects in the environment

In the revised report, the issue of imposex in gastropods by TBT is mentioned briefly. Nonetheless in setting a threshold level for freshwater species the daphnia NOEC of 60ng Sn/L is used with an uncertainty factor of 10. In marine gastropods a threshold level of 0.1ng/L has been reported. The lowest reported TBT concentration producing imposex in a freshwater gastropod is 125ng/L. The CSTEE considers that the proposed value could be insufficient for covering potential ED effects on freshwater organisms.

Effects in humans

Use of a group exposure standard

The CSTEE considers that a group exposure standard for health protection should be employed if:

i) Exposure to several members of a structurally related series of chemicals is likely to occur frequently.

ii) Several members of the series have been demonstrated to have a common target organ(s)/cell type and the same mode of action.

If these criteria are met individual members of the series for which there is very limited toxicological data should be assumed to make an additive contribution. Toxicological equivalence factors (TEF) should be introduced where the potencies span 3-5 fold or more. If this is not the case the most potent member of the series should be assumed to be representative for the purposes of standard setting;

Application of the group TDI

In the revised report, a group TDI for DOT, DBT, TBT and TPT is not considered, although it is mentioned in the report that a conservative approach has been taken by regarding **all** organotins as immunotoxic, based on their common ability to cause thymus atrophy. The report continues that 'On this basis it is reasonable to consider the effects of the butyl tins as possibly additive but not across the whole group'. The CSTEE does not agree with this conclusion and proposes in line with its earlier opinion (CSTEE, 2003) a group TDI for dioctyltin (DOT), dibutyltin (DBT), tributyltin (TBT) and triphenyltin (TPT) as these compounds have a similar profile of action in terms of immunotoxicity (lymphocyte depletion in the thymus and peripheral lymphoid tissues). In comparative toxicity studies that investigated the structure activity relationship for thymus toxicity in the rat, DBT and DOT were the most potent dialkyltin compounds producing dose-related thymus atrophy at 50 and 150 ppm in the diet (Seinen et al., 1977a). In a subsequent comparative study, DBT and DOT both significantly suppressed the thymus-dependent immunity (retarded rejection of skin transplants) at the 150 ppm dietary level (but no significant effect was found at 50 ppm) (Seinen et al., 1977b). In a later comparative study significant thymus atrophy was noted with TBT and TPT at similar levels (TBT at 50 and 150 ppm; TPT at 15, 50 and 150 ppm) (Snoeij et al., 1985). A function assessment showed that TPT suppressed the thymus-dependent immunity (Vos et al., 1984) like TBT, DBT and DOT. The mechanism of toxicity at the level of the thymus appears to be selective inhibition of the proliferation of immature thymocytes (Penninks et al., 1985; Snoeij et al., 1988; Pieters et al., 1994; Gennari et al., 1997). Regarding TBT, it is likely that the thymus atrophy is produced by the metabolite DBT (Snoeij et al., 1988).

In the report a TDI of 0.27 µg/kg per day TBT as chloride is used (WHO, 1999) based on a NOAEL of 0.5 mg TBTO/kg diet derived from the chronic immunotoxicity study in rats where reduced resistance to *Trichinella spiralis* was noted (Vos et al., 1990). Using this same study the US EPA has calculated a benchmark dose (10% benchmark response, with a 95% confidence limit) at 0.68 ppm, i.e. 0.03 mg.kg BW/day (USEPA Integrated Risk Information System). TBT is more extensively studied than DBT, DOT and TPT and consequently several endpoints, notably the resistance to infectious disease, have not been investigated for these latter compounds. **As the common endpoint of thymus atrophy is affected at similar dietary level of these compounds, the CSTEE again proposes that a group TDI value 0.27µg/kg bw/day for TBT, DBT, DOT and TPT as chloride should be adopted, or 0.1 µg/kg bw/day as Sn. Furthermore, assuming a similar mode of action and in the absence of data that contradict it, it seems rational to consider the effects of these chemicals as additive.**

Finally, the CSTEE considered two recent publications (Cooke et al., 2004; Tryphonas et al., 2004), in which the effect of tributyltin chloride was investigated in rats following in utero, lactational and post-weaning exposure. Regarding thymus toxicity, the study confirmed the thymus as the target organ with a comparable NOAEL as observed in the chronic immunotoxicity study (Vos et al.,

1990). Unfortunately, in the study the *Trichinella spiralis* host resistance model was not used to investigate the thymus-dependent immunity, whereas the current TDI is based on this most sensitive parameter.

Conclusions

The CSTEE has been pleased to receive some additional information on human exposure to various organotin compounds and on their toxicological properties. This has helped with one or two of the issues raised by the CSTEE in its opinion on organotin compounds of the 12th of June 2003.

The CSTEE is concerned however that most of the important information gaps it identified in its opinion of 2003 have not been narrowed by this additional information. The CSTEE therefore considers that there is no scientific reason to change the answers it gave in June 2003 to the five questions raised by the Commission.

The CSTEE wishes to reiterate the importance of taking into account all sources (food and non-food) and routes (oral, inhalation and dermal) of exposure in the assessment of the risks to human health from current exposure to organotin compounds. It also would like to emphasise that the effects of TBT, DBT, DOT and TPT should be viewed as additive since they have common target organs/modes of action.

Completion of the assessment of the total risks from the exposure of the public to organotin compounds must await the conclusions of EFSA on exposure through consumption of fish. This information is expected to be available in the next few months.

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Annex 1

The CSTEE has also been asked to comment on a report from the Danish Toxicology Centre (Boyd HB, and Höglund L, 2003), as it also estimates human exposure to organotin compounds.

The contribution from food wrapped in stabilised PVC has been estimated using the migration data to olive oil described in the original RPA report (2002). The assumption that all food consumed over a day is wrapped in PVC is a worst case situation, but to some extent it may be balanced by the uptake also in food with lower fat content due to the high water solubility of these substances (see e.g. Miljø-Kemi, 2000).

The exposure from dust is based on measurements of organotin compounds in real samples, but as these are taken on the floor, they may not represent the concentrations in the inhaled dust. The floor dust may contain more abraded particles than the dust in the air. The concentration in the air is also a worst case situation, as an occupational threshold limit value is used.

The estimates of organotin compounds emitted to indoor air from PVC flooring and wall papers are based on a loss factor of 0.05 % over lifetime (20 years for flooring and 7 years for wall papers) given in an OECD document. This document has not been accessible to CSTEE, but the factor is the same as is used for annual emission in a BRE emission scenario document (BRE, 1999). These exposure estimates may therefore be underestimations.

In the exposure from baking papers impregnated with silicones containing organotin catalysts the worst case scenario is based on that an adult is consuming 0.5 kg of food prepared in/on such papers. This is probably a gross overestimation, but also a 10-fold reduction will give very high intakes.

Exposure from toys made of PVC has been estimated on data from a Danish study (Miljø-Kemi, 2000). The mouthing and dermal contact scenarios used seem to be realistic worst cases. For the paddling pool scenario the results from the study are used without compensation for the different water/PVC ratio in experiment setup and pool scenario, which results in an overestimate.

The exposures from shoe insoles, cycling pants, and PVC gloves are in agreement with those described in the RTP report (2002), while the foot spray use have not been annualized. The latter could be argued if the use of these products is spread over the whole year.

The CSTEE concludes that although the report calculates worst case scenarios for most of the investigated human exposure pathways, it shows that the ADI recommended for organotin compounds in this opinion may be exceeded especially for children.