REVISED ASSESSMENT OF THE RISKS TO HEALTH AND THE ENVIRONMENT ASSOCIATED WITH THE USE OF THE FOUR ORGANOTIN COMPOUNDS TBT, DBT, DOT AND TPT

Opinion adopted by the SCHER during the 14th plenary of 30 November 2006

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1. BACKGROUND

During its 43rd plenary meeting of 28 May 2004, the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) issued an opinion entitled "Revised assessment of the risks to health and the environment associated with the use of organotin compounds" based on a revised report produced by the consultant "Risk & Policy Analysts" (RPA). The SCTEE concluded that the report suffered from data gaps that undermined the reliability of the conclusions on risks. DG ENTR has therefore requested RPA to update its report by taking into consideration the CSTEE recommendations, in particular to use the concept of a group TDI for 4 substances with similar endpoints. The 2005 revision of the RPA report has now been completed.

2. TERMS OF REFERENCE

(1) The Scientific Committee on Health and Environmental Risks (SCHER) is invited to comment on whether the recommendations made by the SCTEE in its former opinion on the same topic dated 28 May 2004 have adequately been taken into consideration by RPA.

(2) SCHER is requested to assess whether the 2005 revision of the RPA report has adequately addressed the risks posed by the four organotin compounds TBT, DBT, DOT and TPT, both for human health and the environment. Content from the previous RPA reports carried out from 2002 and 2003 as well as the opinion of the relevant EFSA panels on additives, flavourings and materials in contact with food (EFSA 2005) and on contaminants in the food chain (EFSA 2004) should also be taken into account.

(3) SCHER is requested to assess the overall scientific quality of the 2005 revision of the RPA report. SCHER is specifically requested to comment on the methodology and the assumptions used, e.g. exposure and emissions calculations, and on the conclusions given in the report.

(4) The SCHER is requested to comment and give an opinion on the health risks to consumers that result from exposure to organotin compounds from the various non-food consumer product sources of exposure, or from environmental sources as reported in the studies (tables 3 and 4 of the executive summary, and on each specific exposure scenario of the 2005 RPA report).

(5) In collaboration with the EFSA panels and taking into account the exposures of humans to organotin materials from foods, food contact materials, and non-foods as presented in the RPA reports and EFSA panel opinions, the SCHER is requested to assess and quantify (if possible) the total integrated (food and non-food) risks of humans from organotin compounds. SCHER is in particular requested:

5A - to comment, on whether conclusion (ii*) risk sources should be considered separately (on an exposure by exposure case basis) to estimate the real level of risk to adults and children, or whether conclusion (ii*) risks sources should be considered collectively, taking into consideration the fact that TBT, DBT, DOT and TPT shall be viewed as additive both for the target organs and for the mode of actions.

5B - If the answer to 5A is that risk (ii*) sources should be considered collectively: SCHER is requested to comment on whether it is realistic to conclude that the risks for 25% of adults and 70% of children are likely to exceed 100% group TDI taking into consideration that it is likely that a consumer will be exposed to more than one

exposure route i.e. that a consumer may be exposed to several conclusion (ii*) risks sources.

5C - SCHER is requested to comment whether it is realistic to conclude that, even if a consumer is exposed to several conclusion (ii) risks sources (< 20% TDI), the corresponding risks from these conclusion (ii) sources combined would be below 100 % TDI (for a group TDI both for adult and children), and therefore lead to a negligible risk.

(6) In preparing this integrated assessment, the SCHER is requested to comment as to whether the total ban of organotin compounds in anti-fouling paint (2003), and the ban of the presence of these compounds in EU waters by 2008 will, by itself, reduce the risks (from a conclusion (iii) to (ii)) associated with the consumption of fish/seafood contaminated with the organotin compounds under consideration within a reasonably short period? Should other organotin compounds be taken into consideration when considering the possible establishment of a maximum threshold limit concentration in fish?

(7) SCHER is requested to comment on whether risk conclusion (iii) predicted for child consumers due to organotin-based fish products intake > 100 % TDI is reliable, both at local, regional and continental levels.

(8) SCHER is requested to comment on whether significant additional risk may be posed to consumers and environment by the additional exposure to organotin compounds such as MBTO, DBTO, etc in addition to the targeted group TBT, DBT, DOT and TPT.

(9) SCHER is requested to give its opinion on whether emission of the targeted group TBT, DBT, DOT from plant processing and recycling PVC (flexible and rigid) or at landfill pose a significant risk for adults or children via environment, at local, regional or continental levels.

3. OPINION

The SCHER, supported by external experts including representatives from EFSA Scientific Panels has reviewed the new RPA report (September 2005) on organotin compounds (OTs). First the comments on the report and, to some extent, the OTs in general will be presented, and then the specific questions forwarded to the committee will be addressed.

The assessment of environmental and human health risks caused by the OTs is difficult. The large number of compounds with very different properties in the group makes it difficult to make general conclusions. An unknown fraction of the added substances are also changed to new compounds in some of their functions (e.g. as stabilisers) and in the environment. There are not measured data available for the physical and chemical properties for all these substances. Properties like water solubility, dissociation and octanol-water distribution are also dependent on a number of conditions like temperature, pH and salinity (Laughlin et al, 1986b; Inaba et al, 1995; Arnold et al, 1997), which makes it difficult to estimate these properties. The picture is further complicated by the wide use of the OTs for very different purposes, including applications in consumer products, and the assessment has to be based on a number of assumptions.

Environmental exposure

The environmental exposures have been estimated using the procedures described in the TGD and complemented with measured data where such were available. The uncertainties in the assessment are large due to the limited amount of data available for the OTs, and that their physical and chemical properties make the well established model calculations less useful (e.g. logKow for dioctyltin ethylhexylmercaptoacetate (DOT- EHMA) is calculated to more than 15 by the KOWWIN program). The authors also point at the uncertainties at several places in the report.

One of the EHMA ligands in OTs added to PVC is partly exchanged with a chloride ligand during the processing of the material, and the remaining EHMA ligands are immediately exchanged with other groups (mainly chloride) after emission to water or soil. The environmental assessment should therefore be focussed on the formed substances, but it has to be kept in mind that it is mainly the EHMA derivatives that are emitted.

The OTs usage data are converted to corresponding alkyltin chlorides volumes (RPA Report, Annex 3). For the PVC stabilisers it is then assumed that "there is a 50:50 split between mono- and di-substitutes", and as the mono-substituted compounds do not contribute to the critical effect this will reduce the critical emissions. All of the stabilisers are also given as EHMA compounds, which further reduces the exposure to tin. The SCHER would have preferred to see some arguments for these assumptions.

The 50:50 split mentioned above is also used for the plant losses (RPA Report, Annex 4). In the case of air emissions this would not be applicable as the vapour pressure of the mono-alkyl compounds is much lower than that of the poly-alkylated, and thus the correction factor of 0.6 is doubtful. In this Annex also air emission factors are calculated, and the result is that DOT has two times higher factor than DBT, which in turn has a 3 times higher factor than TBT. If the compounds produced are EHMA esters the reversed order would have been expected.

The amount of remaining OTs catalysts in polyurethane (PU) varies between 0.01% and 0.2% (RPA Report, Table 2.12) and the total production of PU is claimed to be 3352 kt/y (Table 2.13). The total volume of OTs in PU is estimated to be 400 t/y (Table 2.14) and this corresponds to an average concentration of 0.012%, which seems to be a best rather than worst case estimate.

The emission factor for DOTC is claimed to be almost 5 times that of TBTC (RPA Report, Table 3.4). This is not in line with the vapour pressures given, where the value for TBTC (1 Pa, Table 3.26) is more than 1000 times higher than that of DOTC (2.6E-04 Pa, Table 3.27).

The emissions from extrusion and calendering of PVC stabilised with OTs has been estimated using an ESD from OECD. That document identifies two groups of additives with different vapour pressure, and the DOT-EHMA and degradation products all belong to the group with high volatility. The predicted emission is reduced by 80% with a reference to "some limited monitoring data". More recent analyses of grass samples taken around a large PVC calendering plant (processing nearly 100,000 ton PVC annually) shows concentrations of up to 5 µg DOTC / kg ww 300 m from the emission (de Wolf, 2006). This is considerably lower than the 422 µg DOTC / kg ww predicted by EUSES and support a reduced estimate.

Some OTs have been used as plant protection products, in particular as acaricides and fungicides. These include azocyclotin, cyhexatin and fenbutatin oxide used as acaricides on fruit and vegetables plus fentin acetate and fentin hydroxide used as fungicides on potato, sugar beet and beans. Now their use is strongly reduced, and the use of fentin and cyhexatin is not authorised since 2002.

Environmental fate

OTs are mainly used as stabilisers in PVC and as has been mentioned above in this function they will partly be transformed to new substances during use and after release. The EUSES2 modelling described in the report is done for the dialkyltindichlorides and dialkyltinoxides.

Several constants for distribution between media have been calculated with equations developed for non-dissociated compounds, but the OTs are partly dissociated. There is a special section (Appendix XI, Part II) in the TGD describing this problem. This may explain some of the questionable data obtained, e.g. for DOT-EHMA the solubility in water is given as 8.5 mg/L (Table 3.31) and the log Kow as 15.3, two values that seem to be incompatible. The leaf – air distribution has a significant influence on the predicted value for the indirect human exposure. As the calculation of this parameter involves several factors that are connected to a high uncertainty the outcome will be highly uncertain as well. The water solubility demonstrates the difficulties as that of DOT-EHMA is given to be more than six orders of magnitude larger than that of DOT-Cl-EHMA (Table 3.31). The chlorine ligand in the latter will probably make that compound more soluble than the first.

From the registration dossiers for TPTH and fentin acetate several data are available like the sorption constants to organic matter and the degradation rates in soil. For TPTH also information on the photo-degradation is available. The mean half life of TPTH in soil is about 26 days (n=4), whilst the photo-degradation half life has been determined to be about 14 days in natural sunlight. The sorption constant to organic carbon are established around 2200 dm^3/kg (median of 3 values) for TPTH. (RIVM, 1992 and RIVM, 1993)

Environmental effects

PNECs for the freshwater environment are derived from a large database on several organisms not including molluscs and have been calculated from long term toxicity data on *Daphnia magna* that is mentioned as the most sensitive freshwater organism, and a PNEC of 6 ng Sn/L has been calculated for TBT. The SCHER is of the opinion that the proposed value cannot be assumed enough protective for the aquatic environment without taking into account data on freshwater molluscs. Imposex was observed in freshwater gastropods at a concentration of TBT of about 40 ng/L as Sn (Schulte-Oelmann et al, 1995). Taking into account that this value is not a NOEC but a LOEC, a PNEC should be below 4 ng Sn/L, lower than those calculated for *Daphnia*. A careful search of the recent literature is needed to assess if additional data on freshwater molluscs are available.

As suggested in the literature, a PNEC for the marine environment of 0.1 ng/L for TBT seems the most suitable (not explicitly proposed by the report). For other OTs no PNECs are proposed, except an indicative value ("perhaps" 10 ng/L) for DBT.

Classification

Classification of TBT and TPT as PBT and vPvB is appropriate. For DBT, the classification of T must definitely be applied (NOEC *Daphnia* = 4.1 µg/L, T threshold < 10 µg/L) instead of indicated a "probable" (Table 4.3 in the RPA report). A careful BCF assessment for DBT is needed for the classification of B. The same is needed for DOT.

Justifications must be provided for the inconsistencies between observed and EUSES predicted BCF values. Many papers found in the literature, not mentioned in the RPA report, indicate high bioaccumulation and bio-magnification potential for OTs (see for example Iwata et al., 1995; Kannan et al., 1997, 1998; Tanabe et al., 1998; Hu et al., 2006). Laughlin et al. (1986b) found BCF values in marine animals for TBT higher than those predictable from Kow. The authors hypothesize a conjugation mechanism to biological molecules, increasing the simple process of partition on lipids. A more careful literature search on bio-accumulation and bio-magnification processes is needed.

Risk characterisation

The comments given above regarding both hazard and exposure assessments also have implications on the risk assessment. As most of the comments indicate an underestimate of at least the exposure, the conclusion must be that the risk estimates may not represent realistic worst case situations.

Human health

Human exposure via food

Several food items contain organotin compounds, especially those from the aquatic environment due to the use of such compounds as antifouling agents on boat hulls. In a recent opinion from EFSA (2004) the possible risks connected to consumption of food containing these substances have been assessed. The EFSA Panel on Contaminants in the Food Chain focused on TBT, DBT and TPT, primarily found in fish and fishery products. Based on SCOOP data (SCOOP, 2003) the panel estimated the median intake in Norway to 0.007 µg Sn/kg bw/day and the corresponding value based on mean data was 0.033. High consumers were exposed to 0.015 (median) and 0.070 (mean) µg Sn/kg bw/day.

Children are generally, because of their lower body weight, considered as a group at risk for food chemicals when the dietary exposure is compared with a tolerable daily intake expressed in µg/kg bw. Based on this fact, a factor 3 is commonly used to estimate children dietary exposure when only data on adult consumption are available, i.e. the daily exposure for adults is multiplied by a factor 3. On the other hand children are expected to eat less in absolute value than adults in particular certain food categories like fish. In a recent study (Verger, 2006) focusing on the long term frequency of fish consumption on a population of consumers of fish located on the western coast of France, it was observed that the frequency of fish consumption is similar for adults, children between 6 and 15 years old and children below 6 years old with respectively 2.9 ± 1.4, 2.1 ± 1.1 and 2.1 ± 1.2 servings per week. On a quantitative point of view, based on the French national food consumption survey (Volatier, 2000), the average fish consumption (consumers only) for adults is 249 grams per week when the average consumption for children below 15 years old is 185 grams per week. Consequently for the current opinion, the SCHER can assume on a long term basis that the consumption of fish by children corresponds at least to 75% of the consumption of adults. In other EU Member States this percentage can even be higher. Considering both the difference in body weight and food consumption, a factor 3 can be used to estimate the exposure of children from the one of adults.

Several investigations of organotin compounds in food have been reported since the EFSA opinion. A recent study (CALIPSO, 2006) analysed the contamination by OTC of fish on the French market. It consists in sampling the fish and seafood mainly consumed by the population studied, taking into account the form of purchase (fresh, frozen, canned, etc.) and provisioning (bought or self-procured). The list of sampled food is based on an analysis of the individual dietary consumptions of the respondents. The final list included 138 products from which 95 fish and 43 molluscs and crustaceans. The sum of DBT, TBT, DOT and TPT was about 0.004 µg/g fresh weight for fish and sea food. For a hypothetical portion of 100 g/day, the total dietary exposure from fish would be 0.4 µg OTC.

In another study (Rantakokko et al, 2006) the average intake of organotin compounds from foodstuffs was estimated in a Finnish market basket. The study was conducted by collecting 13 market baskets from supermarkets and market places in the city of Kuopio, eastern Finland. Altogether 115 different food items were bought. In each basket, foodstuffs were mixed in proportion to their consumption and analysed for seven organic tin compounds (mono-, di-, and tributyltin, mono-, di-, and triphenyltin, and dioctyltin). Organotin compounds were detected in only four baskets, with the fish basket containing the largest number of different organotin compounds. OTs were not detected in cereals, peas and nuts,

milk and milk products, fats and oils, sugar, juices and soft drinks. On the contrary OTs were quantified in fish and sea foods, potatoes, vegetables and fruits. In potatoes, vegetables and fruits, the predominant compound was MBT at a concentration up to 0.57 ng/g fresh weight. In fish and sea foods, the predominant compounds were TBT, MBT, TPT, DBT and DPT measured at levels up to respectively 2.53, 1.52, 1.11, 0.25 and 0.14 ng/g fresh weight. Overall results of this study are reinsuring and show dietary exposure corresponding to a limited fraction of the Tolerable Daily Intake established by EFSA. However, it should be mentioned that the methodology used in the Finnish study combines average contamination levels with average food consumption and for consumers eating fish from contaminated areas the intake may be much higher. Moreover the exposure assessment is based on an average fish consumption of 39.5 grams per day representing 1.8 % of the total food consumption. High consumers of fish can also be highly exposed to OTs even considering an average level of contamination.

A monitoring project (Sternbeck et al, 2006) that analysed fish samples from Swedish waters found higher concentrations than those reported from Finland. The values for fish were nd – 2.8 (DBT), nd – 7.8 (TBT) and 2.2 – 12 (TPT) ng/g fresh weight for background areas. Fish from Stockholm had even higher concentrations and values up to 14 (DBT), 71 (TBT) and 171 (TPT) ng/g fresh weight were measured.

Human exposure via the local environment

The RPA report identifies high intake of TBT (mainly from wood preservation) and DOT (mainly from PVC processing) via the local environment (Tables 5.1, 5.2 and 5.4). For DOT, however, the picture is complicated by the fact that it may be mainly DOT-EHMA that is emitted and then converted to the chloride in the environment. The daily intake was therefore also predicted for the compounds containing one or two EHMA ligands. DOT-EHMA and DOTC gave a similar result, but the DOT-Cl-EHMA gave three orders of magnitude lower intake. It is then assumed that 80% of the emission is in the form of DOT-Cl-EHMA and 10% each of the other two compounds and the predicted intake is reduced dramatically. This is not in line with the information from industry that approximately 10 to 15% of the DOT-EHMA is reacted in the PVC during processing. It is also mentioned at several places in the report that DOT-Cl-EHMA is effectively degraded to DOTC in the environment, and if that is the case the exposure via the local environment would have been 0.61 µg Sn/kg bw/day.

Individual consumers can be exposed to OTC via local environment including crops, vegetables, meat and milk. Such an exposure can occur in the case of food produced at home or of local purchases in rural areas. The French National Institute of Statistics (Bertrand, 1991) described the home production of food as the major component of local consumption and estimated its importance as a function of various food groups and for various populations of consumers. For farmers the consumption of home produced food represents on the average 25 % of the total food consumption (ranging from 0.2 % for bread to 89 % for rabbits) when for non-farmers it represents 9.5 % (0.2 to 66 %) and 4.6 % (0.1 to 36 %) of the total consumption respectively for consumers living or not in a rural area. For the current opinion, considering the worst case assumptions made on the food contamination, assuming the regular consumption of food produced locally to 20 % of the total food consumption seems reasonable.

Consumer exposure assessment

PVC is probably one of the most common materials in consumer goods and we are exposed to the additives used in this material via a number of pathways. Some of them have been assessed by RPA and some worst case exposures were calculated. The assessors have made some wide ranging assumptions in this work, but as our knowledge is so limited in this field that is probably the only way to do it.

The intake via PVC food packaging has been estimated based on a study by Piringer et al. (2005), in which the values for aqueous food simulants in the primary table (µg/dm^2) disappears and are reported as non detects in the following table (µg/kg food) and furthermore the wrong factor seem to have been used for the remaining values. The values used by RPA were for fatty food and those seem to be right (104 and 417% of the TDI for adults and children, respectively, in Table 5.35 in the report). RPA also used a report from CSL (2005) for a refined assessment, which is based on the results of the Piringer (2005) study. Fortunately the original (µg/dm^2) were used, but there are also data on a Simulant A that the SCHER is not able to locate in the original study and one result from Simulant D is tabled as a Simulant B result.

The RPA report claims that the level of OTs in indoor air is below the detection limit (but there is no reference to either a report or even a value for the limit of detection). Air levels are therefore estimated with loss factors and reduced by a factor of 100 under the assumption that 1% is going to air and 99% to water based on migration measured to air and water, respectively (Piringer et al., 2000). If there is no water present evaporation is the only possible emission pathway, and if the data for emission to air is used, the investigated material would give an adult exposure of about 0.1 µg/kg bw, day of each of DBT and TBT. The ventilation rate used in the example was 0.5 exchanges/h, which probably is too high in many regions. Furthermore, the results presented by Piringer et al. (2000) indicate that it is not the diffusion of the organotin compounds within the PVC matrix that determines the emission rate, but rather the removal from the surface. This is well demonstrated by the relative concentrations of MBT, DBT, TBT and TeBT in the octane, water and air extracts from the same PVC matrix. Thus the calculations of loss factors based on diffusion rates can be questioned. A recent paper (Xu and Little, 2006) also shows that the emissions of semi volatile compounds from polymeric materials are subject to "external" control, e.g. partitioning into the gas phase and the convective mass transfer coefficient.

The exposure to DBT from the domestic use of silicone moulds is calculated to be close to the TDI, but it is assumed that the catalyst is pure dibutyltin laurate. As the melting point of that compound is over 200°C this is probably used in a solution, and may thus give a lower exposure than that calculated in the report. Another type of silicone moulds could, however, be of interest from the human exposure point of view. This is the moulds used to bake cookies, where the high oven temperature will favour emission both to the cold cookies and the kitchen air. This may thus be a more serious source than the baking papers now being phased out.

It is surprising that the assessor did not look at the use of OTs in medical devices. There is a debate on the exposure to DEHP from PVC materials, but if OTs are used as stabilisers the emission of those may also constitute a risk. OTs may also be used as catalysts in the production of silicones for medical devices. A couple of breast implants can probably contain a kg of silicone, and if that contains 0.1% OTs it would correspond to 1 gram. An emission factor as low as 0.000007 would thus give a 70 kg person the TDI. Silicones are also used in many other medical devices, such as tubes and bags, and a further look into this should have been done.

The SCHER would also have liked to see some information on the possible levels of catalysts remaining in esters used as plasticizers, e.g. DEHP. That volume may add to the exposures now calculated from the volume used as stabilisers in PVC. Also other esters used for e.g. food packaging may be important exposure pathways for the consumers and should have been included in the assessment.

The exposure to DBT and TBT from non-allergenic pillows also has an inhalation component in addition to the dermal route assessed in the report. If the sleeping person is inhaling 10 m^3 saturated with TBTC (Vp=1Pa @ 25 C) that would be 100 mL of pure TBTC gas, which is more than 1 g and corresponding to more than 10,000,000% of the TDI. If only 1% of the

inhaled air comes from the pillow and it is only saturated to 1% the inhaled dose would still correspond to 1000% of the TDI. This is an application where further studies of the exposure are needed.

The SCHER recommends that measurements of OTs are included in some future bio-monitoring programs in order to get better information on the total body burden of the OTs.

Effect assessment

The RPA report follows the CSTEE recommendation to use a group TDI for the four OTs based upon the immunotoxicity and assuming that the effect of the compounds are additive. A similar approach has been taken by the EFSA opinion on organotin compounds in foodstuff (EFSA, 2004). The group TDI, corresponding to 0.1 µg Sn/kg bw/day, is assuming the same molecular mechanism of the four compounds and the same potency (per µg Sn), but the mechanism of these compounds has not been investigated in a systematic way.

The new RPA report does not give any further information on human health effects of OTs compared to the earlier versions of this report. The SCHER has therefore done a review of the present knowledge to see if there is reason to change the earlier adopted TDI.

There are no epidemiological studies on chronic low level exposure to OTs available for human risk assessment, following either oral, dermal or inhalation exposure. Several experimental studies in vitro and in vivo have demonstrated various effects after multiple exposures at low dose levels, but most of the positive studies are based upon oral administration.

Inhalation studies

Humans can be exposed to OTs by inhalation of dust particles or to the compounds themselves. Death has been reported in workers accidentally exposed to OTs. There are no quantitative studies regarding absorption of OTs following inhalation exposure, but several case studies report adverse health effects following exposure to e.g. paint containing TBTO and carpet sprays. However, the level of exposure was not estimated. No studies regarding immunological effects in humans and animals after inhalation exposure to OTs have been reported.

Persistent neurological changes have been observed in humans following accidental exposure for methyltin compounds, but no neurological effects have been observed in animals. No histopathological changes were observed in the brain of mice following 6 days of exposure to TBT (ATSDR, 2005).

Dermal exposure studies

No studies regarding absorption in humans or animals after dermal exposure have been reported, but the OECD *in vitro* model (OECD 2004) has been used to compare the effect of different OTs and species differences in uptake. The uptake of OTs was significantly lower in human skin than in rat skin, e.g. DOTC 0.01 and 1.5% respectively over a 24 hrs period (dose 1000 µg/cm^2). The uptake did depend on the ligand, e.g., DBT dichloride was more easily taken up than DBT-EHMA, 6.58% and 0.004%, respectively. The relevance of some of these results can, however, be questioned as the dose used in the tests have been in the mg/cm^2 range while the worst exposure scenarios identified in the RPA report are in the ng/cm^2 range. The OECD guideline specifically states that the tested dose shall span the realistic range of potential human exposures. As a comparison, 2.2% TBTO was taken upon within 24 hrs. Trialkyltin compounds were well absorbed in contact with the rat skin, whereas triphenyltin acetate did not penetrate. Thus, using the total amount of the OTs and a fixed uptake rate may give overrun erroneous estimate of exposure. The SCHER therefore support the relatively conservative approach taken in the RPA report. The information from

industry that the EHMA ligands are effectively substituted to chlorides after emission indicates that the values for the latter have to be used.

Except for direct dermal effects, no adverse health effect was observed in either humans or experimental animals following dermal exposure to OTs. These compounds are skin irritants in humans, e.g., TPT produced irritant contact folliculitis and in workers using paint containing TBTO, which is also a severe irritant to the skin in rabbits, whereas TBT and TPT only produced minimal skin irritation. TBTO induced contact sensitization in mice exposed for the test material for 3 days.

Oral exposure studies

In contrast to the limited information on OTs toxicity following inhalation and dermal exposure more data are available for oral exposure. OTs are readily hydrolyzed in human gastric juice and may be converted to the corresponding chlorides, which will be absorbed. No quantitative estimates of absorption of OTs in humans have been published. In experimental animals, absorption from the intestinal tract of tin compounds with short alkyl chains depends on the chemical compound and shows considerable compound differences, e.g. TBT>DBT>MBT. TBTO was absorbed incompletely and slowly, and depends on the vehicle. Toxicity related to oral exposure has been presented in an EFSA opinion (EFSA, 2004).

The NOAEL used in the RPA is base upon the immunotoxicity of OTs. For TBTO a NOAEL of 0.025 mg/kg bw/day (0.01 mg Sn/kg bw/day) was established based upon resistance to T. spiralis and a similar NOAEL was established for TBTC (0.00869 mg Sn/kg bw/day). A NOAEL for TPT was estimated to be equivalent to 0.75 mg/kg bw (0.22 mg Sn/kg bw/day) while for DOT no NOAEL could be established, but the LOAEL was equivalent to 2.5 mg /kg bw/day (0.68 mg Sn/kg bw/day).

Mechanism of immunotoxicity

Thymus atrophy produced by certain OTs, e.g. TPT, TBT, DBT and DOT involves a decrease in the number of cortical thymocytes. With prolonged exposure T-cell mediated immune responses are suppressed due to both suppression of proliferation of immature thymocytes and apoptosis of mature thymocytes.

Genotoxicity and reprotoxicity

No carcinogenic effect was observed following dermal exposure, but hyperplastic skin changes were observed in mouse skin following 6 weeks exposure TBT.

Recent studies show that peripubertal exposure to TPT influence female sexual developments in rat (Grote et al., 2006). The effect is mediated indirectly by influencing the expression and activities of 17beta-HSD1 and 11beta-HSD2, thus influencing the glucocorticoid concentration.

After the completion of the RPA report a completely new type of toxic effect was described as low doses of OTs were shown to induce adipogenesis in mice (Grün et al., 2006). Using a comprehensive set of receptor binding studies, transfection assays, cell culture studies and *in vivo* experiments this report showed that TBT activates genes promoting adipogenesis, induces differentiation of adipocytes and increases the mass of adipose tissue *in vivo*. The adipogenic activity was observed in offspring of mice exposed to TBT during gestation days 12-18 at maternal dose of 0.5 mg/kg bw/day (and to a lesser extent at 0.05 mg/kg bw/day). This effect seems to be associated with high affinity and specific binding of TBT to the human retinoid X receptor α (RXRα) and to the human peroxisome proliferator activated receptor γ (PPARγ) at nanomolar concentrations. Comparison of relative potencies based on receptor binding and transactivation studies indicated that trisubstituted compounds (TBT

and TPT) are most potent, TeBT and DBT moderately potent, whereas monobutyltin lacks the activity.

These findings have three implications for the risk assessment of OTs. First, they confirm the validity of the currently used TDI value, because they were observed at dose-levels similar with (or even slightly lower than) those causing immunotoxicity after chronic administration, the most sensitive set of endpoints that form the basis of current organotin risk assessment. Therefore, there is no need to adjust the current TDI value. Second, they indicate that in addition to immunotoxicity, also a previously uncharacterized type of toxic effect is possible after exposure to low doses of organotin compounds. Third, they provide scientific justification for the future use of endpoint specific relative potency factors for different organotin compounds.

Risk characterisation

The comments given above, especially on the exposure assessment also have implications on the risk characterisation. As most of the comments indicate an underestimate of the exposure, the conclusion must be that the risk estimates may not represent realistic worst case situations.

3.1 Question 1

The Scientific Committee on Health and Environmental Risks (SCHER) is invited to comment on whether the recommendations made by the SCTEE in its former opinion on the same topic dated 28 May 2004 have adequately been taken into consideration by RPA.

Response to question 1

In the present RPA report on organotin compounds the reaction on the comments from CSTEE on the former report is described in an annex. Generally the comments have been accepted and the present document has been improved compared to the previous version. There are, however, a few points where RPA and the Scientific Committee still disagree.

Freshwater toxicity

In the report the availability of data on freshwater molluscs is not mentioned. This information is essential in this case as the freshwater species are also sensitive. It was already observed in the previous CSTEE Opinion that imposex was observed in freshwater gastropods a 125 ng/L of TBT (corresponding to about 40 ng/L as Sn). This figure (not a NOEC but a LOEC) is a little bit lower than those on *Daphnia magna*. On this point, the new report does not give satisfying answers to the criticisms of the previous CSTEE Opinion. Moreover, it is the opinion of the SCHER that recent literature has not been adequately taken into account.

Human exposure

As described in the review above the SCHER does not support the reduction of emissions of OTs to indoor air from PVC. The use of the air concentrations measured by Piringer et al. (2000) indicates that the inhaled amounts are much higher than the "worst case" described in the report.

3.2 Question 2

SCHER is requested to assess whether the 2005 revision of the RPA report has adequately addressed the risks posed by the four organotin compounds TBT, DBT,

DOT and TPT, both for human health and the environment. Content from the previous RPA reports carried out from 2002 and 2003 as well as the opinion of the relevant EFSA panels on additives, flavourings and materials in contact with food (AFC) and on contaminants in the food chain (CONTAM) should also be taken into account.

Response to question 2

The assessments of several exposure pathways, important for both environmental and human health, have been found to have shortcomings. In most cases it is possible that the estimated exposure does not represent a worst case as it is stated in the report. There are also several additional pathways (such as via moulds for baking, medical devices, via esters (used as e.g. plasticizers) produced with OT catalysts and inhalation of OTs from non-allergenic pillows) that should have seen assessed. SCHER also have comments on some environmental effects that need to be reviewed. The conclusion must be that the risk may be even larger than that described in the RPA report

3.3 Question 3

SCHER is requested to assess the overall scientific quality of the 2005 revision of the RPA report. SCHER is specifically requested to comment on the methodology and the assumptions used (e.g. exposure and emissions calculations) and on the conclusions given in the report.

Response to question 3

The assessment in the RPA report is based on the methodology described in the TGD and is the recommended for risk assessment of chemicals in the EU. A central role is therefore the prediction of both exposure and no-effect concentrations, which is based on properties for the investigated substances. If data for those properties are missing, which is the case for many OTs, there are also ways to estimate several of those. Some of the values for properties essential for exposure assessment, mainly delivered by industry, seem unreliable and thus the assessment will have a high uncertainty.

In absence of data the assessor has to make assumptions to be able to do the risk assessment. Some of the disputable assumptions made in the present report have been highlighted in the review above. Examples are

- The assumption of the relative amounts of different OTs being produced and emitted;
- 80% of the OT emission from manufacturing of PVC products is assumed to be in the form of DOT-Cl-EHMA;
- The emission from PVC is assumed to be 1% to air and 99% to water.

The basis for the assumptions made to estimate the exposure of the typical consumer (section 6.4 in the RPA report).

3.4 Question 4

The SCHER is requested to comment and give an opinion on the health risks to consumers that result from exposure to organotin compounds from the various non-food consumer product sources of exposure, or from environmental sources as reported in the studies (tables 3 and 4 of the executive summary, and on each specific exposure scenario of the 2005 RPA report).

Response to question 4

The SCHER supports the group TDI for DBT, TBT, DOT and TPT corresponding to 0.1 µg Sn/kg bw/day. The health risk is therefore determined by the total exposure to substances containing any of these four groups.

The exposure is very complex due to the many applications of the OTs, and the wide use of the materials containing them. There are several possible pathways other than those described in the RPA report, e.g. via medical devices and products containing esters produced with organotin catalysts.

In Tables 3 and 4 all results except those for dietary intake are related to point estimates of the exposure. Many of those are based on assumptions and are trying to describe worst case exposures. As have been discussed above some of these assumptions may be questioned and make the estimated exposure considerably lower than real worst cases. Indoor air is an example of an important exposure pathway for the OTs that is underestimated in the RPA report.

The Tables 3 and 4 don't give a correct description of the risks connected to the OTs. Many individuals are exposed via several of the pathways described in the Tables and those have to be combined to get the total exposure. This will be addressed further under question 5.

Some of the sources are classified as "Eliminated", but it has to be remembered that products already in use may be there for a considerable time and will still contribute to the total exposure of the individual. Sources like old wood treatment plants is also known to act as important sources long after the use of a chemical is ceased.

There may also be a couple of pathways that need be added to the list. The exposure from OTs in both silicones (e.g. in medical devices and cookie moulds) and esters (e.g. used as plasticizers) need to be further assessed, as well as the possible inhalation exposure from non-allergenic pillows.

3.5 Question 5

In collaboration with the EFSA panels and taking into account the exposures of humans to organotin materials from foods, food contact materials, and non-foods as presented in the RPA reports and EFSA panel opinions, the SCHER is requested to assess and quantify (if possible) the total integrated (food and non-food) risks of humans from organotin compounds. SCHER is in particular requested:

5A - to comment, on whether conclusion (ii*) risk sources should be considered separately (on an exposure by exposure case basis) to estimate the real level of risk to adults and children, or whether conclusion (ii*) risks sources should be considered collectively, taking into consideration the fact that TBT, DBT, DOT and TPT shall be viewed as additive both for the target organs and for the mode of actions.

Response to question 5A

The SCHER is of the opinion that it is the total exposure that should be used in the risk assessment. That includes all identified pathways also those estimated to contribute with less than 20% of the TDI. The consumer risks estimated in section 6.2 for the different exposure pathways are regarded as worst cases and the probability that one person experiences worst case situations via all pathways on a long term basis is very small (see further under 5B)

5B - If the answer to 5A is that risk (ii*) sources should be considered collectively: SCHER is requested to comment on whether it is realistic to conclude that the risks for 25% of adults and 70% of children are likely to exceed 100% group TDI taking into consideration that it is likely that a consumer will be exposed to more than one exposure route i.e. that a consumer may be exposed to several conclusion (ii*) risks sources.

Response to question 5B

It is obvious that consumers are exposed to OTs via more than one pathway. The use of probabilistic methods would be a way to estimate the overall risk, but to do that a lot of information on use pattern and concentration distributions would be needed. This information is only available for the dietary intakes, and not easy to obtain for the other pathways. The RPA assessor therefore assumed, without presenting the motivations in the report, intake distributions by setting the ratio between median and high. It is also unclear how the fact that only a rather limited part of the population is exposed to the local environmental levels has been dealt with. In the RPA report the description of the whole process would need to be more detailed.

SCHER believes that the most important exposure pathways are food, indoor air, household dust and via dermal contact with different polymer materials. A large fraction of the population is exposed via several of the following pathways:

- EFSA (2004) assessed the OTs in food and concluded that fish and seafood give about 7% of the TDI based on median concentrations and about 33% based on the mean concentrations. For high consumers the corresponding fractions were 15 and 70%, respectively. The EFSA opinion does not say anything about children, but as they consume more per kg bw (a factor of four is used in the RPA report, a factor of three suggested in this opinion) it can be assumed that some children's dietary intake exceeds the TDI.

- The indoor air levels were in the RPA report calculated for a room with both floor and walls covered with PVC, but the ventilation rate was rather high, and it may therefore be regarded as a realistic worst case. It was also assumed that the persons stayed 24h/d in the room; 12h/d may make it even more realistic. The 99% reduction of the OT emission is not appropriate and the air concentrations may thus be up to 100 times higher. That would give exposure to 600% of the TDI for an adult and 1500% for a child, and there is an obvious need for further measurements.

- The RPA estimate of the exposure to OTs via dust is based on a 200 mg/d intake and on maximum reported concentrations. Dust intake data in the literature span over a wide range, and 200 mg seems reasonable for children, while it is probably lower for adults. The use of maximum concentrations is justified by the fact that several samples were pooled. A reasonable conclusion would be that adults are exposed to less than 10% of the ADI via dust, while children may be in the region of 100%. The uncertainty of this estimate is high due to both the limited information on dust intakes and the bioavailability of the OTs.

- The dermal exposure pathways (T-shirts, gloves, sandals, hygiene products etc.) have to be assessed based on default values for the uptake fractions. Values between 10 and 100% are normally used and the 10% chosen by RPA can be supported by the SCHER. The different pathways contribute, according to the RPA report, each with up to 62% for adults and 189% of the TDI for children.

In the SCHER review of the RPA report above a number of further possibly very important OTs exposure pathways have been identified. Massive doses of OTs may be obtained from medical devices of PVC and silicones, as well as inhalation of the vapours from anti-allergenic pillows.

SCHER concludes that the probability for an individual of the general population, especially a child, to exceed the TDI for OTs is high, and that some people may be exposed to doses much higher than the TDI.

People living in regions where industries are producing or using OTs may also get an extra high exposure via locally produced food. The highest value in the RPA report is describing the situation around a timber treatment plant. Assuming this will be decreased in the future the major source would be the processing of stabilised PVC. As there is no support for the assumption that 80% of that emission is as DOT-Cl-EHMA, a worst case has to be calculated as if the total emission is DOT-EHMA. This corresponds to 0.73 µg Sn/kg bw/day from locally produced food. An assumption that only 20% of the food is locally produced will reduce this to 0.15 µg Sn/kg bw/day which is 150% of the TDI for an adult. In view of the physico-chemical characteristics of the organotin compounds the model EUSES2 is not fully applicable as the log Kow is outside the valid range. In addition EUSES2 is not able to handle ionisable substances correctly. Therefore the results calculated with EUSES2 should be interpreted with great care. The recent measurements (de Wolf, 2006) also indicate that the intake via locally produced food may be overestimated.

5C - SCHER is requested to comment whether it is realistic to conclude that, even if a consumer is exposed to several conclusion (ii) risks sources (< 20% TDI), the corresponding risks from these conclusion (ii) sources combined would be below 100 % TDI (for a group TDI both for adult and children), and therefore lead to a negligible risk.

Response to question 5C

If the total exposure exceeds the TDI there is reason for concern regardless of whether this exposure comes via one or a large number of pathways. The uncertainty of the exposure assessment will be larger if many pathways are involved, but as the amount of data available for the assessment of exposure to OTs is very limited it is very difficult also to estimate the uncertainty in those exposure predictions

3.6 Question 6

In preparing this integrated assessment, the SCHER is requested to comment as to whether the total ban of organotin compounds in anti-fouling paint (2003), and the ban of the presence of these compounds in EU waters by 2008 will, by itself, reduce the risks (from a conclusion (iii) to (ii)) associated with the consumption of fish/seafood contaminated with the organotin compounds under consideration within a reasonably short period? Should other organotin compounds be taken into consideration when considering the possible establishment of a maximum threshold limit concentration in fish?

Response to question 6

The major source of OTs in the marine environment is antifouling paints. Additionally these substances may be used as antifouling agents is the application in cooling-water pipes for electric power plants or industries (UNEP, 1989). This use is not taken into account in the RPA report and is not included in Regulation EC 782/2003, but seems to be regulated by Directive 2002/62/EC, even if this Directive is not very explicit to this specific use.

Moreover, this use will in the future be regulated by the biocides directive 98/8/EC once it fully enters into effect. Finally, for this kind of use, treatment with chlorine is usually preferred. Thus emissions due to cleaning of cooling-water pipes do not seem to be of high concern.

At present no recent data are available to assess the effects of the total ban of organotin compounds in anti-fouling paint. A French survey, performed in 1999 along the coasts of Corsica, demonstrates concentrations of high concern for TBT and DBT, not only in harbours and marinas, but also in two Natural Reserves (Michel et al., 2001). The authors underline that, although past measures were effective in reducing organotin concentrations, they were not sufficient for a complete solution of the problem. More recent data for the same sites are not available.

A survey on shellfish in 2004 along the coasts of England (Vazquez, 2005) indicates a large variability of total concentrations of OTs in molluscs. Maximum concentrations may indicate a potential risk for high consumers, but as no data are reported for the past it is not possible to evaluate the temporal trend.

A Swedish study (Tesfalidet, 2004) reports data on water, sediments and biota from selected sampling sites at the Swedish west coast. Water samples were collected in 2001-02 (before the total ban) and in some cases a comparison with data from 1987 is possible, indicating a concentration decrease of more than two orders of magnitude. The use of TBT on boats shorter than 25 m was banned in Sweden 1989. On the other hand, a recent monitoring project found high concentrations of TBT in fish from Stockholm area and even higher (around 0.1 µg/g ww) of TPT (Sternbeck, 2006).

In a recent OSPAR document (OSPAR, 2005a) the results of some studies performed in Denmark, Norway and UK are reported. The studies measured the content of TBT and the occurrence of sexual disorder (imposex/intersex) in different mollusc species. In all studies a large spatial variability was recorded, with levels of concern, mainly in the proximity of harbours. The UK study covers all national shoreline during a period from early 1990s up to 2003. In spite of the extension of the survey, the results cannot be used to assess a temporal trend, since different areas were sampled in different years. The Norwegian study is less extensive but more systematic, covering 9 stations from 1997 to 2003, but does not show a statistically significant trend. In the Danish study a statistically significant decrease from 1998 to 2003 was observed in a few sampling stations (3 of 25). All studies were performed before the total TBT ban.

Experimental evidence seems to indicate that control measures before the total ban have been effective in reducing OTs concentrations in the marine environment, at least in some European coastal areas, but situations of concern were still present before 2003. The few data available need to be confirmed with more information. As a consequence of the total ban in 2003, emissions have not been immediately reduced. Emissions from ships painted before the ban will continue for some time. Daily OTs emissions from painted ships are initially in the order of some µg/cm^2. A large ship (hull area 6900 m^2) would then release around 2-300 g TBT per day, but the leaching rate is rapidly decreasing with time (UNEP, 1989; EC, 1998).

Most OTs are accumulated in sediments. The degradation rate and pathways in sediments is still controversial. Values used in the RPA report (that need to be supported by more information) indicate half-lives in the range 120-150 days for DBT, TBT, DOT and TPT. From a rough calculation, it derives that reduction will be of about one order of magnitude in a couple of years. This should indicate that, if emissions will be reduced and stopped in a relatively short time, sediment cleaning will occur in a few years. Michel and Averty (1999) hypothesize that in oligotrophic sediments of open coastal areas, the half-lives may be substantially higher, so the cleaning time for indirectly polluted sites could be longer. This process will be improved and accelerated by the cleaning of harbour sediments.

Most OTs have bio-concentration and bio-magnification potential. Nevertheless, if exposure stops, complete clearance will take place in a reasonably short time (Laughlin et al., 1986a). More experimental evidence is however needed to quantify the length of the period and to better describe differences in clearance patterns in harbours and in open coasts. The SCHER therefore fully support the need for regular monitoring performed according with suitable protocols. The guidelines proposed by OSPAR (OSPAR, 2005b) are perfectly adequate to this goal.

The data on toxicity of other organotin compounds is relatively sparse and described in the answer to Question 8.

3.7 Question 7

SCHER is requested to comment on whether risk conclusion (iii) predicted for child consumers due to organotin-based fish products intake > 100 % TDI is reliable, both at local, regional and continental levels.

Response to question 7

The SCHER is not aware of any facts that reduce the estimated dietary intake of OTs for children. Possible reasons for lower exposure could include that children eat other fish species or less shellfish than adults, but it has not been possible to find data to support that this is the case. The opinions from EFSA have triggered further studies in member states and more information on dietary intake of OTs can be expected in the near future. The SCHER also again underlines the importance to assess the total exposure to describe the risk connected to OTs, and taking that into account the number of children at risk may be considerably higher.

3.8 Question 8

SCHER is requested to comment on whether significant additional risk may be posed to consumers and environment by the additional exposure to organotin compounds such as MBTO, DBTO, etc in addition to the targeted group TBT, DBT, DOT and TPT.

Response to question 8

The data on the toxicity of mono- and dibutyltin oxide are limited and only few studies addressing the toxicity of these compounds have been located. Unfortunately, none of these studies investigates endpoints related to the major health effects of tributyl tins (immunotoxicity) in detail. However, since alkyl tin oxides are rapidly transformed to the respective alkyltin chlorides in the human stomach, data on the different alkyltin species may be used for an assessment.

Monobutyltin has limited application and the toxicology data are scarce, indicating low toxicity, and an oral LD50 in rats of 2140 mg/kg bw has been reported (HSDB, 2006). In a comparative toxicity study in rats using TBTC, DBTC, and MBTC no effect on body weight and relative organ weights of thymus, spleen, liver and adrenals were noted when a single oral dose of 180 mg/kg bw was applied, while toxic effects, notably thymus atrophy, was seen from 10 mg TBTC and 5 mg DBTC onwards (Snoeij 1987). Therefore the contribution of MBT which occurs mainly as a metabolite of TBT and DBT is considered of no importance when the group TDI is considered.

MOT stabilisers are normally used as a mixture with DOT. This mixture causes thymus atrophy

but further research has pointed out that this was exclusively due to DOT. For DOT a group TDI of 0.6 µg Sn/kg bw was established, for MOT 20 µg Sn/kg BW (SCF, 1999). Target organ for MOT is the kidney, and the effect appears at much higher doses.

Dibutyltin oxide caused reproductive toxicity (craniofacial and musculoskeletal abnormalities) when given in a single dose of approx. 20 mg/kg bw on day 8 of pregnancy. Moreover, other studies have also shown embryo-toxicity of dibutyltins in dose ranges > 10 mg/kg bw/day when administered during pregnancy. There also seems to be a 90-day oral study with a NOAEL of 2 mg/kg (no further information on effects).

In vitro, dialkyltins have been shown to be as or even more potent regarding induction of cell death as compared to trialkyltins. Regarding the mode of action for toxicity responsible for cell death and ensuing toxicities (specific interactions of organotin compounds with sulhydryl containing proteins of the plasma membrane and the cytoskeleton), dialkyltins also have a high affinity binding site at the plasma membrane of cells. A high reactivity of DBTO with SH-containing proteins is also supported by chemistry of this compound. Dialkyltin oxide is present as an oligomer and retains a high reactivity with SH-groups. Based on these considerations, DBTO may have a similar potency as compared to tributyltins in vivo and the SCHER therefore recommends including dibutyltin oxide in the risk assessment approach and the group TDI.

Regarding MBTO, results from a 90-day oral study suggest that this compound has a lower potential for toxicity with a NOAEL of 96 mg/kg bw/day based on effects on the liver (immunotoxicity unknown). MBTC also seems to have a lower potential for reproductive toxicity since administration of up to 685 mg/kg bw of that compound during pregnancy and up to post natal day 4 did not cause effects. As a general observation, monoalkyl tins have a lower potential for toxicity as compared to di- and trialkyltins. For example, MBTO, in a developmental neurotoxicity study using maternal doses of up to 25, respectively 94 mg/kg bw per day (with drinking water) during gestation and lactation did not induce developmental neurotoxicity. However, monomethyltin oxide caused a low incidence of specific brain lesions in the high dose off-spring, but the available data are too limited to make a conclusion regarding inclusion into the group TDI.

Neurotoxicity is an endpoint of toxicological relevance for OTs. The best-known organotin compounds with neurotoxic potential are trimethyltin and triethyltin, but also TBT and TPT have been shown to be neurotoxic. Recent studies have identified DBT as a relatively potent developmental neurotoxicant in rats (Jenkins et al., 2004). In addition, monomethyltin was shown to induce vacuolization in cerebral cortex of rats (Moser et al., 2006). Due to lack of systematic *in vivo* data the significance of neurotoxicity for organotin risk assessment remains uncertain, but based on available data neurotoxicity is not likely to be the critical endpoint for setting organotin TDI, because neurotoxic effects are observed at higher dose levels than immunotoxicity. Due to differences in the mechanisms of neurotoxicity among different organotin compounds there seem to be no scientific basis for using a group TDI for this endpoint.

3.9 Question 9

SCHER is requested to give its opinion on whether emission of the targeted group TBT, DBT, DOT from plant processing and recycling PVC (flexible and rigid) or at landfill pose a significant risk for adults or children via environment, at local, regional or continental levels.

Response to question 9

The outcome of the RPA assessment indicates that the local environment around industries producing and using OTs is exposed to levels that make human intake exceeds the TDI.

This result is also produced under an assumption that 50% of the produced/used OTs are mono-alkylated which is not proven, and the actual exposure could be even higher. However, the uncertainties in the exposure assessment are considerable, mainly due to uncertainties in the data for the properties of the compounds. The regional and continental levels of these substances are mainly influenced by more diffuse sources.

Regarding recycling of PVC the information available to the SCHER is limited, but it is assumed that the processing of the recycled material is similar to that of new PVC. If that is the case the similar human exposure can be expected from both types of industries, and it is also expected that some industries are using both new and recycled PVC.

Most landfills in Europe receive a mixture of solid waste of different origin. Common are the deposit of household waste, commercial waste, construction and demolition waste and in the 70-ties and 80-ties of the last century sometimes sewage sludge and hazardous wastes.

Some PVC products contain organotin compounds as stabilizers. In particular mono– and dioctyltin compounds can be assumed to originate from PVC products (Mersiowsky et al. 1999). Methyl– and butyltin compounds may also emanate from a number of other sources put onto the landfill. An X-ray survey of waste material show that PVC articles contained tin and/or lead and tin levels up to 0.68 % were found (Bilitewski, personal communication).

TBT is used as a biocide in water based vanishes (amount unknown) and heavy textiles like tents and lorries (only until 1999 in Germany), disinfectants, wood fungicides (only until 1990 in Germany) and other preservations like silicon for the sanitary area (until 1999 in Germany) and roof linings (until 1994 in Germany).

Another relevant source of OT compounds is sewage sludge and Table 1 gives some examples of data levels found in Germany. Kuballa et al. (1998) indicated 100 mg/kg dw to be a conservative estimate of the contents of organotin compounds.

Organotin	No. of samples	Minimum	Average	Median	90. percentile	Maximum
Dibutyltin	156	0.008	0.22	0.13	0.35	4.8
Dioctyltin	156	0.0025	0.056	0.021	0.05	3.0
Monobutyltin	156	0.009	0.17	0.12	0.32	2.7
Monooctyltin	156	0.0025	0.031	0.019	0.043	1.3
Tetrabutyltin	156	0.0025	0.0067	0.0025	0.0025	0.4
Tributyltin	156	0.0025	0.033	0.027	0.065	0.3

Table 1: Concentration (mg/kg dw) of OTs in sewage sludge from North Rhein-Westfalia in Germany (MUNLV 2005).

The possible fate of organotin compounds in landfills has been summarized by Mersiowsky et al. (2001). The OTs may be retained in the solid waste matrix, either being included in e.g. rigid PVC products or being adsorbed on organic matrix surfaces. Parts of the substances are transported in the leachate, either as solute or adsorbed to colloids or suspended solids. The relative relevance of the latter route seems to be comparatively low. A third possibility is that the compounds may be volatilized into the landfill gas. A screening investigation of the occurrence of OTs in leachate samples of landfills from Sweden, Germany and Italy indicate that monobutyltin is the most widely detectable species. Findings of all target compounds (MMT, DMT, MBT, DBT, TBT, MOT and DOT) range between not detectable (< 0.1 mg/L) and maximum levels of 1 mg/L (2-4 mg/L in the case of MBT and MOT) (Mersiowsky et al. 2001). The high levels of monobutyl– and monooctyltin were found in a German landfill with fresh not older than 2 years material. Landfills undergo

a pH value drop in the first 1 to 2 years, so this might be a possible explanation of the high values. The highest value of TBT (0.9 µg/L) was found in a sample in Germany of an old already closed landfill (Mersiowsky et al. 2001).

Sanjay et al. (2005) reported about the identification and quantification of alkylated tin compounds in landfill gas from three landfills in Germany and one in Scotland.

Landfill	A	B	C	D
	µg Sn/m^3			
Me_4Sn	1050	12.6	14.8	14-17
$BuSnH_3$	0.06	0.06	N.d.	N.d.
$EtSnMe_3$	55	1.1.	1.2	0.89
Et_2Me_2Sn	13	0.45	0.50	0.20
n-$PrSnMe_3$	117	2.8	1.1	0.21

Table 2: Concentrations (µg Sn/m^3) of selected OTs in landfill gas (Sanjay et al. 2005)

The concentrations of the different tin species were two orders of magnitude higher in one landfill than in the other three studied sites. The relative species distribution is however site independent indicating that this formation is a general process (Sanjay 2005). So far sources of airborne organotin compounds have not been established, but Feldmann (2003) also reported that landfill gas contains volatile tin compounds in concentrations up to 100 µg Sn/m^3. A cubic meter of waste gives about 240 m^3 gas emissions, containing some 10 to 100 mg of volatile OTs. The fate and effect of these substances are not known to the SCHER.

4. LIST OF ABBREVIATIONS

11beta-HSD2	11beta-hydroxysteroid dehydrogenase type 2
17beta-HSD1	17beta-hydroxysteroid dehydrogenase type 1
AFC	EFSA Panel on Additives, Flavourings and Contact materials
B	Bioaccumulation
BCF	Bioconcentration factor
bw	Body weight
CONTAM	EFSA Panel on Contaminants in the food chain
CSTEE	Scientific Committee on Toxicity, Ecotoxicity and the Environment
DBT	Dibutyltin
DBT-EHMA	Dibutyltin ethylhexylmercaptoacetate
DBTL	Dibutyltin laurate
DBTO	Dibutyltin oxide
DEHP	Di(2-ethylhexyl)phthalate
DMT	Dimethyltin
DOT	Dioctyltin
DOT-Cl-EHMA	Dioctyltin ethylhexylmercaptoacetate chloride
DOT-EHMA	Dioctyltin ethylhexylmercaptoacetate
DOTC	Dioctyltin chloride
dw	Dry weight
EFSA	European Food Safety Authority
ESD	Emission scenario document
Kow	Partitioning factor between octanol and water
LD50	Median lethal dose
LOEAL	Lowest observed adverse effect level
LOEC	Lowest observed effect concentration
MBT	Monobutyltin
MBTC	Monobutyltin chloride
MBTO	Monobutyltin oxide
MMT	Monomethyltin
MOT	Monooctyltin
nd	Not detected
NOAEL	No observed adverse effect level
NOEC	No observed effect concentration
OECD	Organisation for Economic Co-operation and Development
OSPAR	OSPAR Commission for the protection of the marine environment of the North-East Atlantic
OT	Organotin compound
PBT	Persistent, bioaccumulative and toxic substances
PNEC	Predicted no-effect concentration
PPARγ	Peroxisome proliferator-activated receptor γ
PU	Polyurethane
PVC	Polyvinylchloride
RAR	Risk assessment report
RPA	Risk & Policy Analysts
RXRα	Retinoid X receptor α
T	Toxicity
TBT	Tributyltin
TBTC	Tributyltin chloride
TBTO	Tributyltin oxide
TDI	Tolerable Daily Intake
TeBT	Tetrabutyltin
TGD	Technical Guidance Document
TPT	Triphenyltin
TPTH	Triphenyltin hydrid

UK-FSA	United Kingdom Food Standards Agency
UNEP	United Nations Environment Programme
Vp	Vapour pressure
vPvB	Very persistent and very bioaccumulative substances

5. REFERENCES

Arnold CG, Weidenhaupt A, David MM, Muller SR, Haderlein SB, Schwarzenbach RP. Aqueous speciation and 1-octanol-water partitioning of tributyl- and triphenyltin: Effect of pH and ion composition. Environ. Sci. Technol. 1997;31:2596-602.

ATSDR, Agency for Toxic Substances and Disease Registry. Toxicological profile for tin and tin compounds. US Department of Health and Human Services; 2005 http://www.atsdr.cdc.gov/toxprofiles/tp55.pdf

Bertrand M. Consommation et lieux d'achats des produits alimentaires en French. National Institute of Statistics; 1991.

CALIPSO. Tec & Doc Lavoisier, editions. Analyse des risques alimentaires Collection Sciences et techniques alimentaires; 2006.
http://metarisk.inapg.inra.fr/content/view/full/113

CSL. Tin Stabilised Rigid PVC Films Exposure Assessment. UK Central Science Laboratory; 2005.

CSTEE, Scientific Committee on Toxicity, Ecotoxicity and the Environment. Opinion on Revised assessment of the risk to health and the environment associated with the use of organotin compounds (excluding use in antifouling paints). 2004.

De Wolf JM. Determination of dioctyltin residues in grass samples taken near a large PVC calendering plant, including validation of the analytical method. TNO Report; 2006 (V7143 Final).

EFSA, Scientific Panel on Contaminants in the Food Chain. Opinion on the health risks assessment to consumers associated with the exposure to organotins in foodstuff. The EFSA Journal 2004;102:1-119.

EFSA, Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials with Food. Statement on some octyltin compounds authorised to be used in food contact materials. 23 February 2005.

Feldmann J. Volatilization of metals from a landfill site – Generation and immobilization of volatile species of tin, antimony, bismuth, mercury, arsenic, and tellurium on a municipal waste deposit in Delta, British Columbia. ACS Sym Ser 2003;835:128–40

Grote K, Andrade AJM, Grande SW, Kuriyama SN, Talsness CE, Appel K, Chahoud I. Effects of peripubertal exposure to triphenyltin on female sexual development of the rat. Toxicology 2006;222:17-24.

Grün F, Watanabe H, Zamanian Z, Maeda L, Arima K, et al. Endocrine disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. Mol. Endocrinol. 2006;20: 2141-55

HSDB, Hazardous Substances Data Bank. US National Library of Medicine. 2006 http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~kLWQJD:1

Hu H, Zhen H, Wan Y, Gao J, An W, et al., Trophic magnification of triphenyltin in a marine food web of Bohai Bay, North China: comparison with tributhil tin. Environ. Sci. Technol. 2006; (in press).

Inaba K, Shiraishi H, Soma Y. Effects of salinity, pH and temperature on aqueous solubility of four organotin compounds. Wat. Res. 1995;29:1415-17.

Iwata H, Tanabe S, Mizuno T, Tastsukawa R. High accumulation of toxic buthyltins in marine mammals from Japanese coastal waters. Environ. Sci. Technol. 1995;29: 2959-62.

Jenkins SM, Ehman K Barone SJr. Structure-activity comparison of organotin species: dibutyltin is a developmental neurotoxicant in vitro and in vivo. Devel. Brain Res. 2004; 151:1-12.

Kannan K, Senthilkumar K, Loganathan BG, Takahashi S, Odell DK, Tanabe S. Elevated accumulation of tributyltin and its breakdown products in bottlenose dolphins (*Tursiops truncatus*) found stranded along the U.S. Atlantic and Gulf Coasts. Environ. Sci. Technol. 1997;31:296-01.

Kannan K, Guruge KS, Thomas NJ, Loganathan BG, Tanabe S, Giesy JP. Butyltin residues in southern sea otter (*Enhydra lutris nereis*) found dead along California coastal waters. Environ. Sci. Technol. 1998;32:1169-75.

Kuballa J, Jantzen E, Steffen D. Endocrine disrupters in municipal sewage sludge – The example of organotin compounds. Wasser und Boden 1998:50:30-2.

Laughlin RB, French W, Guard HE. Accumulation of Bis (tributhyltin) Oxide by the marine mussel *Mytilus edulis.* Environ. Sci. Technol. 1986a;20:844-90.

Laughlin RB, Guard HE, Coleman WM. Tributyltin in seawater: Speciation and octanol-water partition coefficient. Environ. Sci. Technol. 1986b;20: 201-4.

Mersiowsky I, Ejlertsson J, Stegmann R, Svensson BH. Long-term behaviour of PVC products under soil-buried and landfill conditions, Report for Norsk Hydro ASA, ECVM, ECPI, ESPA, and ORTEP. Hamburg (DE);1999

Mersiowsky I, Brandsch R, Ejlertsson J. Screening for Organotin Compounds in European Landfill Leachate, J. Environ. Qual. 2001;30:1604-11

Michel P, Averty B. Distribution and fate of Tributyltin in surface and deep waters of the North-western Mediterranean. Environ. Sci. Technol. 1999;33:2524-8.

Michel P, Averty B, Andral B, Chiffoleau JF, Galgani F, Tributyltin along the Coasts of Corsica (Western Mediterranean) : a persistent problem. Mar. Poll. Bull. 2001:42:1128-32.

Moser VC, Barone S Jr, Phillips PM, McDaniel KL, Ehman KD. Evaluation of developmental neurotoxicity of organotin compounds via drinking water in rats: Monomethyl tin. Neurotoxicology. 2006;27:409-420.

MULNV. Abfälle aus Kläranlagen in Nordrhein-Westfalen, Teil E. Organische Schadstoffe in Klärschlämmen – Bewertung und Ableitung von Anforderungen an die landwirtschaftliche Verwertung, Ministerium für Umwelt- und Naturschutz; 2005

OECD Guideline for the Testing of Chemicals; Skin absorption: *in vitro* method. 2004 (428)

OSPAR Co-ordinated Environmental Monitoring Programme (CEMP). 2005a. (Commission reference 2005-5).

OSPAR Assessment of data collected under the Co-ordinated Environmental Monitoring Programme (CEMP). 2005b. (Commission reference 2005-235).

Piringer O, Brandsch J, Benz H. Migration von Organozinnverbindungen aus PVC_Bodenbelägen. FABES Forschungs-GmbH fur Analytik und bewertung von Stoffübergängen 2000;.

Piringer O, Steiner K. 2005, Migration study of organotin compounds from octyltin stabilized PVC. FABES Forschungs-GMBH fur Analytik und Bewertung von Stoffubergängen, 2005.

Rantakokko P, Kuningas T, Saastamoinen K, Vartiainen T,. Dietary intake of organotin compounds in Finland: A market-basket study. Food Add. and Contam. 2006;23:749–56

RIVM. Advisory report on fentin acetate. Bilthoven, The Netherlands; 1992 (92/670104/006)

RIVM. Advisory report on fentin hydroxide. Bilthoven, The Netherlands; 1993. (92/670104/005)

Sanjay KM, Kijeung J, Haas K, Feldmann, J. Municipal landfills exhale newly formed organotins. J. Environ. Monit. 2005;7:1066-8

SCF, Scientific Committee on Food. Opinion on additional list of monomers and additives for food contact materials. 1999 http://ec.europa.eu/food/fs/sc/scf/out41_en.pdf

SCOOP. Assessment of the dietary exposure to organotin compounds of the population of the EU Member States, Report on tasks for scientific cooperation. 2003.

Schulte-Oehlmann U, Bettin C, Fioroni P, Oehlmann J, Stroben E. *Marisa cornuarietis (Gastropoda Prosobranchia)*: A potential TBT bioindicator for freshwater environments. Ecotoxicology 1995;4:372-84.

Snoeij NJ. Triorganotin Compounds in Immunotoxicology and Biochemistry. PhD thesis 1987; University of Utrecht.

Sternbeck J, Fäldt J, Österås AH. Screening of organotin compounds in the Swedish environment.2006
http://www.naturvardsverket.se/dokument/mo/modok/export/Screening%20tennorganiska.pdf

Tanabe S, Prudente M, Mizuno T, Hasegawa J, Iwata H, Miyazaki N. Butyltin contamination in marine mammals from North Pacific and Asian coastal waters. Environ. Sci. Technol. 1998;32:193-8.

Tesfalidet S. Screening of organotin compounds in the Swedish environment. Report to Swedish Environmental Protection Agency; 2004 (Contract 2190102)

UNEP, Assessment of organotin compounds as marine pollutants in the Mediterranean. UNEP, Athens;1989. MAP Technical Reports Series, No. 33.

Vazquez I, Survey of organotins in shellfish, Food Standards Agency. 2005.

Verger P. Consumer Risk Advisory Inquiry Survey. 2006. Personal communication.

Volatier JL. TEC et DOC Editors. Enquête INCA individuelle et nationale sur les consommations alimentaires. 2000.

Xu Y, Little JC. Predicting emissions of SVOCs from polymeric materials and their interaction with airborne particles. Environ. Sci. Technol. 2006;40:456-61.