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

Opinion on the non-food aspects of

"Assessment of the risks 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."

REPORT VERSION:
Final Report 19 July 2002

Adopted by the CSTEE during the 38th plenary meeting of 12 June 2003

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Questions to the CSTEE

The SCTEE is requested:

1. To assess the overall scientific quality of the study. In considering this, the Committee is asked to comment on the methodology, the assumptions used, the sensitivity analyses carried out for particular aspects (e.g. PVC manufacturing sites) and the conclusions of the study.

2. To comment and pronounce itself on the health risks (if any) to consumers that may be associated with exposure to organostannic compounds from non-food consumer products or from environmental sources as reported in the study.

3. Taking into account the exposures of humans to organostannic materials from foods and food contact materials, to assess and quantify (if possible) the total (food and non food) exposures and risks of humans to organostannic materials.

4. To comment and pronounce itself on the risks to the environment that may be associated with organostannic compounds as identified in this study.

5. To comment on the organotin industry plans to measure emissions of organostannic compounds at PVC processing plants, and possibly also timber treatment plants, which might justify the use of lower emission values than those used as worst case in the study.

Comments on the report

Background

Trialkyl- and triaryltin compounds have been used as biocides for many years. Special attention has been paid to the pollution of the marine environment, estuaries and freshwater from the use in paint on boat bottoms (antifouling paint). After the discovery of their endocrine effects (imposex) on marine snails, the use of these

substances on small boats has been restricted in many countries, and there is now an international agreement to stop their use also on large ships.

There are, however, other uses of these and other organotin compounds, and the reviewed report assesses some of these for seven different groups of substances:

- monomethyltins (MMT)
- dimethyltins (DMT)
- monobutyltins (MBT)
- dibutyltins (DBT)
- tributyltins (TBT)
- monooctyltins (MOT)
- dioctyltins (DOT)

The picture is complicated by the fact that the chemicals used can have different counter-ions, such as chloride, oxide, laurate, maleate, naphthenate and mercaptoacetate. As it is assumed that it is the cation (containing tin) that is active, amounts and/or concentrations have been recalculated to tin, or as in this report also to the tinchlorides.

In the report no explanation is given why certain organotins, e.g. triphenyltins (TPT) that are used as pesticide in crop protection, are not included in the risk assessment. There are also other alkyltin compounds in use, e.g. diisodecyltin that are not taken into account.

The main non-biocidal applications of organotin compounds are as stabilisers in polymers, especially PVC, or catalysts in the production of polymers. The final materials often appear in consumer products. There have recently been several reports on the appearance of organotins in food, clothes, shoes and other items in close contact with humans. The CSTEE has therefore with great interest reviewed the risk assessment part of this report, but is not able to comment on the economic part of it.

The literature coverage in the report is not comprehensive.

The CSTEE is unhappy with parts of the remit of the report, especially the exclusion of the use of organotin compounds as an antifouling agent, as this remains a major source of these substances in the environment.

Environmental exposure

Tributyltins are, in addition to antifouling paint, used as wood preservatives. The mono- and dialkyltins are used as stabilisers in PVC, as catalysts in the production of silicones and esters, plus for electrodeposition. All data on volumes used for the different applications have been submitted by industry and/or industry related organisations. In several cases the data does not specify exactly which compounds the data relates to and it is therefore difficult to follow the recalculations to amounts of chlorides or tin.

The information on compounds produced by the eight producers of organotins in the EU given in table 4.2 does not seem to match that in table 3.1. There is also

information in table 4.2 that seems to be inconsequent. A manufacturer with 9 kg emission to water declares 10 tonnes waste per year, while another with 20 kg to water gives 0 for the waste. Information like "Not detectable", "Negligible" and "All data below MAC" in the same table is not very useful for the assessment.

The major source of TBT is wood preservation (mainly to waste water) and emissions from the treated wood (to air, water and mainly soil). The leaching from wood in use is based on an estimated lifetime of 10 years, but this figure is not supported. An underestimation of the lifetime of the wood will give an underestimation of the exposure.

Site specific local PECs for production of organotins are in the range of 0.2 – 0.4 µg/L for MBTC, DBTC, MOTC and DOTC, but only up to 0.015 for TBTC.

For PVC processing local PECs have been estimated using emission factors from BRE (2001), where three different groups are specified depending on the vapour pressure of the substances. For the assessment of organotins factors for the "low volatility group" was used. Vapour pressures for the assessed organotins used in the report are between 0.15 and 33 Pa (except for DOTC, which is much lower). These are much higher than that of DIDP ($3.3x10^{-6}$ Pa) which is the reference for compounds of low volatility in the BRE report. Reference compounds for the "high volatility group" are DEHA ($6.6x10^{-5}$ Pa) and BBP ($6.5x10^{-4}$ Pa). Even if there are uncertainties in the vapour pressures reported for the organotin substances, **the CSTEE cannot see the rationale for using emission factors developed for the "low volatility group" of compounds**.

The application of the low emission factors for the processing predicts **local** environmental concentrations of up to 3 µg/L for the mono- and dialkyl compounds. Again the TBTC is about three orders of magnitude lower. The results for sites using organotins as catalyst are almost identical. Only wood treatment gives higher local PECs for TBTC, and both TGD equations and EUSES give values of about 0.16 µg/L.

As this risk assessment does not include the marine environment, there are few measured data to compare with. Older **regional** data indicate concentrations of up to 2 and 16 µg/L of MBT and DBT, respectively, in fresh water. A more recent investigation found 0.076, 0.81 and 3.6 µg/L of MBT, DBT and TBT, respectively. There is an obvious discrepancy between predicted and measured values for TBT, which may be explained by a heavy earlier use of this substance as a biocide.

Environmental effects and risk characterisation

The focus of the environmental effects assessment of the report is on the freshwater environment. **The risks from the use of organotin compounds, when acting as a biocide in antifouling paints used in marine applications, is excluded as a purpose of the study other than to compare the relative risks from this source against those covered in this study. However, no comparison is made with the results of toxicity studies in algae, daphnia and fish further to the application of anti-fouling paints. Data on the development of imposex are indeed not considered at all. In addition, masculinization (imposex) is not only an issue of**

the marine environment and estuaries but has also been demonstrated to occur in freshwater snails. Not less than 120 marine, 18 estuarine and 17 freshwater snail species were described as imposex-affected (Horiguchi *et al*., 1997; deFur *et al*., 1999; Schulte-Oehlmann *et al.,* 2000; Oehlmann and Schulte-Oehlmann, 2002). For the environmental risk assessment of TBT, in the report the chronic NOEC of 60 ng Sn/litre on *Daphnia magna* is used as the critical concentration. However, laboratory studies show that imposex development occurs at TBT exposure concentrations that are orders of magnitude lower: 1 ng TBT /litre in the dog-whelk (Gibbs *et al*., 1987) and a threshold concentration of 0.1 ng TBT-Sn/litre in *Ocinebrina aciculata* (Oehlmann *et al*., 1996). Recently, masculinization has also been observed in fish following TBT exposure: sex reversal and suppression of the P450arom gene occurred in flounder following exposure to 0.1 mg TBTO/kg diet (Shimasaki *et al*., 2003). In addition there is concern that short-term exposure to endocrine disrupting chemicals may lead to long-term effects.

The data on ecotoxicity especially for MMT, DMT and MBT are scarce, which is unsatisfactory and surprising for substances used in such high volumes. For MMT and DMT only acute data are available, and for MBT there are no daphnid or fish long-term studies, and uncertainty factors of 1000 have to be used. Both MMT and DMT give PEC/PNEC ratios higher than 1. The use of emission factors for compounds of higher volatility would increase these ratios.

The report identifies that PEC/PNEC ratios over 1 are also found for DBT and TBT. For DBT it is the PVC processing emission that is the major problem, while the TBT problem is related to wood treatment, with a PEC/PNEC of over 10. **The CSTEE considers this to be serious as the measured values for TBT indicate that the actual concentrations may be 100 times higher.**

As discussed under the human health assessment below, there is a similar mode of action of TBT, DBT, DOT and TPT regarding immunotoxicity, therefore an additive action seems rationale also for wildlife mammalian species. No data are available for non-mammalian species in this regard.

Human exposure

In the report, a number of exposures to organotin compounds from consumer goods have been investigated in addition to the indirect exposure via the environment. For the latter the PECs are calculated according to the TGD, but comparisons with measured data are only done for water and sediment. At least one of the referenced documents (BgVV, 2000) indicate that the predicted concentrations in seafood are much lower than measured concentrations. Food wrapped in organotin stabilised PVC is another route that may add to the total exposure. Organotin compounds are also used in other types of consumer products, e.g. adhesives and glues, not taken into account in the report.

There seems to be a mistake in the report calculation of TBT uptake from cycling shorts padding. The mass of TBT in the area exposed should be 5 times higher (0.1 m^2 x 1.2 kg/m^2 x 45 mg Sn/kg = 5.4 mg Sn) and consequently the uptake could be estimated to 0.09 μg/kg bw/day.

The exposure from indoor air is neglected in the report. The CSTEE made an attempt to look at this (Annex 1). Different data on concentrations of the organotin compounds in final products from the report were used, complemented with the loss factor given in the BRE (1998) report. **This factor is mainly used for compounds with much lower vapour pressure than DBT, and if this is compensated for by increasing the loss factor, the inhalation exposure becomes unacceptable**.

The other assumptions used in the exposure calculations seem to be reasonable. The exposure to butyltins from cookies prepared using baking paper impregnated with silicones may be a problem. The report says that only octyltins are used in the EU, but as there are no measurements of the exposure to these compounds, it may not mean a better situation. The Scientific Committee on Food have given an opinion on the potential risks from this exposure (SCF, 2003). They conclude that the estimated migration level exceeds the specific migration limit of dioctyltin compounds by a factor of 10 and is therefore not in compliance with the consolidated Plastics Directive 2002/72/EC. The SCF concluded however that "taking into account the ongoing phasing out of the particular baking paper in European production, and given that the group TDI incorporates a safety factor of 100 on the NOAEL, the occasional consumption of foods baked on such paper is unlikely to pose a risk". Food issues may however have consequences for other exposure routes, and the CSTEE notes, that it would be interesting to know what happens with the organotin compounds not absorbed by the cookies; are those emitted to the indoor air?

The report also contains a special assessment of exposure of children. Again the cookies seem to pose a problem. The highest value, 15.9 µg/kg bw/day, is fortunately a miscalculation as it should be 2 µg/kg bw/day (total daily intake is 50 g x 318 µg Sn/kg = 15.9 µg Sn which gives 2 µg/kg bw/day for a 8 kg child). **The assumption that a child eats the same amount per kg bw as an adult can be disputed**. The food intake of a 1-6 year old per kg bodyweight is indeed more than twice that of an adult and for an infant it is approximately 4 times as much (ILSI, 1992).

In the calculation of exposure from a paddling pool made of PVC, a 20-day exposure is converted to an annual average. **The CSTEE does not support this approach, as some critical effects were found in short-term studies.** The daily exposure over the 20 days the pool is used would then be 0.21 µg/kg bw for an 8 kg child (5.1 µg Sn/L x 0.33 L / 8 kg bw). The exposure from toys has not been assessed.

The oral intake of diisononyl phthtalate from a doll by a 7.5 month baby can be calculated to about 20 µg/kg bw/day (Bremmer and van Veen, 2002). If the concentration of DBT is about 1 % of that of DINP, and the release factor is the same for the two substances, the oral intake would be about 0.2 µg/kg bw/day. DBT has, however, much higher water solubility than DINP, and can therefore be expected to be more effectively released. The migration of MBT, DBT and TBT from PVC toys (a bath ball and a pool) to synthetic skin lipids and saliva, as well as to tap water has been investigated (Miljøstyrelsen, 2000). The highest migration was seen for MBT to saliva, while TBT migration was highest into the skin lipid. **The CSTEE is concerned that these exposure routes for children have not been assessed.**

Children may also be more exposed than adults to substances in e.g. flooring material through oral intake of dust containing abrasion particles. The only study of organotin compounds in dust available is on samples from parliament buildings (Santillo *et al*., 2001).

Compound	Concentration range (µg/kg)
MBT	182 - 2390
DBT	172 – 890
TBT	4 – 47
MOT	62 - 832
DOT	4 -116

These or higher levels of organotins can be expected also in dust from home environments.

Human health assessment

Dioctyltin, dibutyltin, tributyltin and triphenyltin cause lymphocyte depletion in the thymus and peripheral lymphoid tissues. The mechanism of toxicity at the level of the thymus appears to be selective inhibition of the proliferation of immature thymocytes (Snoeij *et al*., 1988; Pieters *et al*., 1994; Gennari *et al*., 1997). As a result the thymus-dependent immunity is suppressed. In the report a TDI of 0.27 µg/kg per day TBT as chloride is used (WHO, 1999) which has been established on a NOAEL of 0.5 mg TBTO/kg diet in the chronic immunotoxicity study in rats: reduced resistance to *Trichinella spiralis*. Based on 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 (US EPA 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 a similar concentration level of these compounds, the CSTEE proposes to adopt the TDI value of TBT for DBT and DOT, and even also for TPT. In the absence of contradictory data, this assumption of a similar mode of action supports that the effects of these chemicals can be considered as additive.** The latter is in line with the assessment of the National Chemicals Inspectorate in Sweden (KEMI, 2000). **This approach leads the CSTEE to the conclusion that total exposure to organotin compounds for humans, but especially for children, in view of the sensitivity of the developing immune system, is cause of concern**. However, in the report TDI values for DBT and DOT are based on the individual data sets regarding immunotoxicity and are higher than the TDI for TBT, whereas TPT is not evaluated in the report.

Immunotoxicity studies of triphenyltin

That TPT has similar immunotoxicity as that seen with TBT, DBT and DOT appears from the following. Immunotoxicity studies have been conducted with TPT in guinea pigs and rats. In a guinea pig study of 15 ppm triphenyltinacetate (TPTA) in the diet, decrease in thymus weight and in the number of plasma cells of the spleen and lymph nodes were seen. In addition, the immunological reaction against tetanus toxoid was

inhibited. The dosed group had a lower serum antibody level count and fewer antitoxoid-producing cells in the popliteal lymph nodes than the controls when examined immunohistologically (Verschuuren *et al*., 1970).

Vos *et al*. (1983; 1984) studied immune parameters in male Wistar rats fed 5, 25 or 100 ppm triphenyltinhydroxide (TPTH) for 3 weeks. Even at the lowest concentration tested blood lymphocytes and eosinophils were significantly decreased. At 25 ppm also the thymus weight was reduced, delayed type hypersensitivity was reduced, as was the mitogen response in spleen cells. Thus the LOAEL in this study was 5 ppm.

Snoeij *et al*. (1985, see reference in report) studied male Wistar rats exposed to 0, 15, 50 and 150 mg TPTCl /kg diet for two weeks. Thymus weight was reduced at all doses, and spleen weight was decreased in a dose dependent fashion, while signs of general toxicity were observed only at 150 mg/kg. This leads to a LOAEL of 15 ppm.

Endocrine disruption in mammals

In the report, the WHO publication (1999, cited in the report) quoted that TBT does not cause endocrine effects in mammals although the compound is an aromatase inhibitor which may explain the masculinization of certain snail species. However, *in vivo* studies, not discussed in the report, indicate that endocrine disruption occurs, for example results of a two-generation reproductive toxicity study in rats using dietary concentrations of 5, 25, and 125 ppm of tributyltin chloride (TBTCl) (Ogata *et al*., 2001; Omura *et al*., 2001). In the female offspring a delay in vaginal opening and impaired oestrous cyclicity were observed in the 125 ppm group. However, an increase in anogenital distance was found in all TBTCl groups on postnatal day 1. A dose-effect relationship was observed in TBTCl-induced changes in anogenital distance. These results indicate that the whole-life exposure to TBTCl affects the sexual development and reproductive function of female rats. In addition, the TBTCl-induced increase in anogenital distance seems to suggest a masculinizing effect on female neonates. In the male offspring the weights of the testis and epididymis were decreased and homogenization-resistant spermatid and sperm count were reduced mainly in the 125 ppm TBTCl group. Histopathologic changes were also observed in the testis of this group and included vacuolisation of the seminiferous epithelium, spermatid retention, and delayed spermiation. However, the changes were minor in nature. The weight of the ventral prostate was decreased to 84% of the control value in the 125 ppm group in the F1 generation and decreased to 84 and 69% of the control value in the 25 ppm and 125 ppm TBTCl groups, respectively, in the F2 generation. The serum 17beta-estradiol concentration was also decreased to 55% of the control value in the 125 ppm group in the F1 generation and decreased to 78 and 57% of the control value in the 25 ppm and 125 ppm TBTCl groups, respectively, in the F2 generation. However, the serum concentrations of luteinizing hormone (LH) and testosterone were not decreased in these groups. These changes corresponded with those caused by aromatase inhibition and therefore TBTCl might be a weak aromatase inhibitor in male rats. Inhibition of human aromatase activity *in vitro* has been shown by Heidrich *et al*. (2001) with both TBT and DBT and by Cooke (2002) with TBT. These latter studies are quoted in the report, but nevertheless it is stated that TBT does not cause endocrine effects *in vivo* in mammals. **The CSTEE disagrees with this conclusion in the report.**

Answers to the questions

Question 1. To assess the overall scientific quality of the study. In considering this, the Committee is asked to comment on the methodology, the assumptions used, the sensitivity analyses carried out for particular aspects (e.g. PVC manufacturing sites) and the conclusions of the study.

The quality is judged on the information given in the report. The remit of the report was to investigate uses and use concentrations of organotin compounds in wood preservation, heavy industrial textiles, and consumer products. The risks from use of organotins as biocide in marine antifouling paint were excluded in the remit. This is not a suitable approach, as it is the total exposure to a chemical that gives the effect, and one source can not be assessed in isolation.

The study addresses most of the relevant organotin compounds, but there are some that should have been added. One group that may be of importance is the phenyltin substances, but there are also others with long alkyl chains, such as isodecyltin compounds. The inclusion of all relevant compounds becomes even more important if their effects are additive. This possibility is not discussed in the report, but as TBT, DBT, DOT and TPT seem to act through a common mechanism (i.e. thymus atrophy) additivity can be expected.

For most of these substances there are only very few measured concentrations in the environment, and environmental exposures have to be predicted using emission factors. **In the study, factors developed for compounds with much lower vapour pressures were used, which may lead to underestimations of exposure. The environmental risk assessment does not take the imposex effect into account. This is not acceptable, as this effect has been observed at low levels also in freshwater and estuarine snails**.

The assessment of human exposure is complicated as the organotin compounds are used in materials that come in contact with food and in many consumer products. Several of these pathways have been well assessed in the report, but vapours and dust in the indoor environment is not taken into account. Especially if the emission factors for the stabilised PVC are underestimated, the air concentrations could be a significant exposure route. Children's exposure from toys and indoor dust should also have been addressed.

Question 2. To comment and pronounce itself on the health risks (if any) to consumers that may be associated with exposure to organostannic compounds from non-food consumer products or from environmental sources as reported in the study.

Assuming zero exposure from food, the report covers most exposure pathways, but some potentially important ones have not been assessed. These include: inhalation of indoor air and children's exposure from toys and household dust. Most of the exposure estimates are based on loss factors developed for substances with lower water solubility and vapour pressure than the organotin substances, and this may lead

to underestimations. Measurements to verify the applicability of these loss factors are needed.

In the report a TDI for TBT is based on the reduced resistance to *Trichinella spiralis* following chronic TBT exposure of rats. TBT is more extensively studied than DBT, DOT and TPT.Consequently several endpoints, notably the resistance to infectious disease, have not been examined for these latter compounds, and although the common endpoint of thymus atrophy occurs at a similar concentration level. **The CSTEE proposes adoption of the low TDI value of TBT for DBT, DOT, and also for TPT. As TBT, DBT, DOT and TPT can be assumed to provoke thymus atrophy through a similar mode of action and in the absence of data that contradict it, the effects of these chemicals can consequently be taken as additive. This approach leads the CSTEE to the conclusion that total exposure for humans and especially for children is cause of concern. The additional concern for children is due to the sensitivity of the developing immune system.**

The CSTEE does not agree with the conclusion in the report that TBT does not cause endocrine effects *in vivo* in mammals. However, critical effects for TBT are on the immune system and are used to set up TDI.

Question 3. Taking into account the exposures of humans to organostannic materials from foods and food contact materials, to assess and quantify (if possible) the total (food and non-food) exposures and risks of humans to organostannic materials.

This opinion deals only with non-food aspects of organotins, while EFSA is looking into the food issues. The CSTEE will give an overarching opinion when the EFSA report is available.

Question 4. To comment and pronounce itself on the risks to the environment that may be associated with organostannic compounds as identified in this study.

The emission calculations are based on factors developed for compounds with very low vapour pressure. The actual volatility for the organotin compounds is much higher and the exposures may thus be serious underestimates. Measurements of actual concentrations in the environment are needed.

In the report no data are mentioned regarding the development of imposex and no comparison is made of the results of laboratory studies with TBT with the results of toxicity studies in algae, daphnia and fish (imposex is not only an issue of the marine environment but has also been demonstrated to occur in freshwater snail species; masculinization has also been observed in fish exposed experimentally).

The CSTEE deems that due to the limited measured data on environmental concentrations it is difficult at present to quantitatively assess the risk; but due to too low exposure data and because additivity is not taken into account, the report probably underestimates the risks.

Question 5. To comment on the organotin industry plans to measure emissions of organostannic compounds at PVC processing plants, and possibly also timber treatment plants, which might justify the use of lower emission values than those used as worst case in the study.

The outcome of the assessment shows local PEC/PNEC ratios for the aquatic compartment higher than 1 for PVC processing plants using MMTC, DMTC and DBTC. Wood treatment plants using TBTC gave ratios of over 10 in the assessment.

The exposure assessment is based on emission/loss factors developed for chemicals that are quite different from the organotins now assessed. The uncertainty is thus big, and measurements to verify the outcome of the assessment are needed. The plans to do such measurements are therefore supported, but there are certainly a number of data gaps that are more important to make a reliable risk assessment possible for consumers and the general environment.

Information gaps identified by the CSTEE in the report:

- **antifouling issues not considered**
- **some organotins not considered, e.g. triphenyltin and isodecyltin**
- **measured emission factors for organotin compounds, both for industrial processes and consumer products were not used**
- **various products containing organotins are not mentioned in the report, e.g. adhesives and glues**
- **various exposure routes not mentioned, e.g. related to indoor air, toys, dust**
- **levels in the food chain and in wildlife species not taken into account**
- **additive effects for compounds with similar mode of action not considered**
- **immunotoxic endpoint not addressed for wildlife**
- **comprehensive literature survey on organotins needed.**

The emissions during service life are also estimated with crude models. As this may more directly influence on the assessment of human exposure, **the CSTEE strongly recommends further studies on these emissions.**

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Annex 1

Calculations of DBT in indoor air

Case A: Measured data from the report (Annex 9) is used for the concentrations in the materials. The loss factor is taken from "Use category document, Plastic additives", BRE, 1998.

Case B: Concentration in the materials is taken from table A4.5 in the report.

Case C: Measured concentrations are used in this case. The loss factors in the BRE report were developed for substances with orders of magnitude lower vapour pressure than DBT, and in this case an increase of the loss factor by a factor of ten is tested.

Case D: As C, but concentrations from Table A4.5 in the report.

Room: 3 x 3.3 x 2.5 m; 50 % air exchange per hour
Flooring: 10 m3 x 2 mm x 2.8 kg/dm3 = 56 kg
Wall covering: 25 m2 x 1 mm x 1.4 kg/dm3 = 35 kg
Human exposure: 20 m3/day; 70 kg

	Unit	A	B	C	D
DBT in flooring	mg/kg	500	3588	500	3588
DBT in wall paper	mg/kg	270	3588	270	3588
Loss factor	%	0.05	0.05	0.5	0.5
Emission fr floor	µg/day	38	275	384	2752
Emission fr wall	µg/day	13	172	129	1720
Air conc	µg/m3	0.17	1.49	1.71	14.91
Daily dose	µg/kg bw/day	0.05	0.3	0.49	4.26