Concise International Chemical Assessment Document 73

MONO- AND DISUBSTITUTED METHYLTIN, BUTYLTIN, AND OCTYLTIN COMPOUNDS

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are published by the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs have been developed from the Environmental Health Criteria documents (EHCs), more than 200 of which have been published since 1976 as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are usually based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170.[1]

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Coordinator, IPCS, on the selection of chemicals for an IPCS risk assessment based on the following criteria:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that:

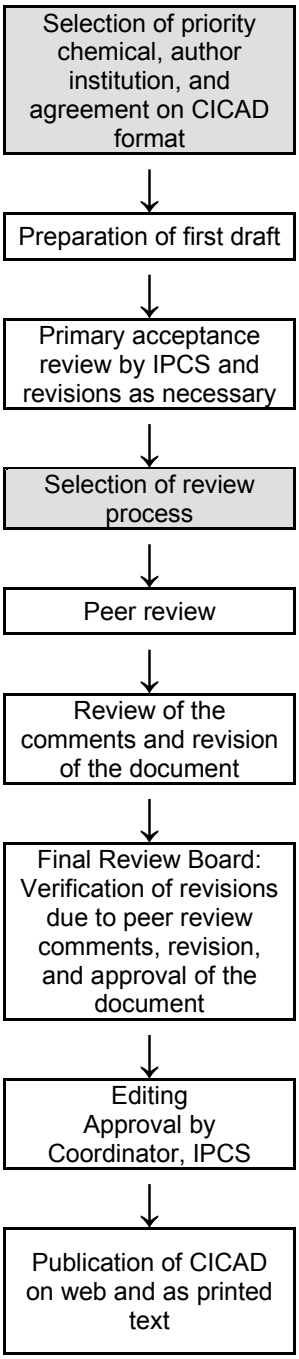
- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- it has high production volume;
- it has dispersive use.

The Steering Group will also advise IPCS on the appropriate form of the document (i.e. a standard CICAD or a de novo CICAD) and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is usually based on an existing national, regional, or international review. When no appropriate source document is available, a CICAD may be produced de novo. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170) (also available at http://www.who.int/pcs/).

CICAD PREPARATION FLOW CHART



Advice from Risk Assessment Steering Group

Criteria of priority:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that:

- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- the production volume is high;
- the use is dispersive.

Special emphasis is placed on avoiding duplication of effort by WHO and other international organizations.

A usual prerequisite of the production of a CICAD is the availability of a recent high-quality national/regional risk assessment document = source document. The source document and the CICAD may be produced in parallel. If the source document does not contain an environmental section, this may be produced de novo, provided it is not controversial. If no source document is available, IPCS may produce a de novo risk assessment document if the cost is justified.

Depending on the complexity and extent of controversy of the issues involved, the steering group may advise on different levels of peer review:

- standard IPCS Contact Points;
- above + specialized experts;
- above + consultative group.

first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments. At any stage in the international review process, a consultative group may be necessary to address specific areas of the science. When a CICAD is prepared de novo, a consultative group is normally convened.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD[1] on mono- and disubstituted methyltin, butyltin, and octyltin compounds was prepared by the United Kingdom's Centre for Ecology & Hydrology and by Risk & Policy Analysts Limited of the United Kingdom and was based on an assessment report of the risks to health and the environment associated with the use of organotin compounds (excluding use as a biocide in antifouling paints) submitted to the European Commission (Enterprise Directorate-General). To address literature not included in this source report, a comprehensive literature search of several online databases was conducted in April 2005. Information on the source document and its peer review is presented in Appendix 2. Information on the peer review of this CICAD is presented in Appendix 3. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Nagpur, India, on 31 October – 3 November 2005. Participants at the Final Review Board meeting are presented in Appendix 4. The IPCS International Chemical Safety Cards for dibutyltin oxide and dibutyltin dilaurate are reproduced in this CICAD (IPCS, 1999c, 2005). Previous CICADs have reviewed triphenyltin compounds and tributyltin oxide (IPCS, 1999a,b).

Organotin compounds are characterized by a tin–carbon bond and have the general formula $R_xSn(L)_{(4-x)}$, where R is an organic alkyl or aryl group and L is an organic (or sometimes inorganic) ligand. The organotin moiety is significant toxicologically. The anionic ligand influences physicochemical properties but generally has little or no effect on the toxicology.

Because of the influence of the ligand, physicochemical properties and environmental fate modelling derived from them are often uncertain for the organotins.

Water solubility across the group is low; however, hydrolysis of the reactive ligands and/or ligand exchange in the environment or tissues of organisms could lead to the formation of species that are more soluble, casting doubt on the relevance of some of the modelled data.

Methyltins are less likely than the butyl- and octyltins to partition to sediments, soils, and organic carbon. Modelled data for K_{oc} suggest much lower capacity for binding to organic carbon than do measured values, often by several orders of magnitude. Measured data have been used in preference to model environmental fate of the compounds. The compounds also bind strongly to clay minerals, montmorillonite in particular.

[1] For a list of acronyms and abbreviations used in this report, please refer to Appendix 1.

The organotins have a wide range of uses, which are largely specific for the different organotins. Thus, mono- and disubstituted organotin compounds are not suitable as biocides, and trisubstituted organotin compounds are not suitable as PVC stabilizers.

The mono- and disubstituted organotins considered here are used as stabilizers in PVC or as catalysts for the production of electrodeposited coatings (mainly in motor vehicle primers), silicone rubbers, esterification and powder coatings, and polyurethanes, as well as for coating glass.

Standard tests using the organotin compounds show ready biodegradation. However, there is some doubt as to whether this reflects full degradation or dissociation of the ligand. For the purposes of fate modelling and risk assessment, the compounds have been assumed to be "inherently" biodegradable, giving a default half-life of 150 days. Measured half-lives in soils for dialkyltins are around 120–150 days in laboratory tests. Methyltins and butyltins in forest soils showed half-lives ranging from 6 months to 15 years.

There are few measured concentrations of organotins in the environment. Measured values for butyltins (where widespread use of tributyltin has led to levels in the environment of dibutyltin as a breakdown product not related to the manufacture or use of dibutyltin as a stabilizer or catalyst) and methyltins (which are produced in the environment by bacterial action) are not reliable indicators of current industrial use of the substances. Despite quite substantial monitoring effort, octyltins have never been measured in the wider environment. Data are available on measured octyltin concentrations in wastewater treatment plants, to a maximum of 715 and 560 µg/kg dry weight for monooctyltin trichloride and dioctyltin dichloride, respectively, in sludge and 0.12 and 0.008 µg/l for monooctyltin trichloride and dioctyltin, respectively, in effluent. Maximum concentrations of mono- and dibutyltins in water and sediment are 76 and 810 ng/l and 3360 and 8510 µg/kg dry weight, respectively, both expressed as tin. Similar maxima for mono- and dimethyltins are 1200 and 400 ng/l and 170 and 0.27 µg/kg dry weight, respectively, both expressed as tin. Two studies have looked at leaching of PVC additives from landfill sites; both showed some organotins in leachate, at concentrations up to 2 µg/l as tin.

PECs have been calculated for various scenarios (production, formulation, and use) as a means to conduct a risk assessment.

Organotins have been detected in a wide range of consumer products; these measured values have been used to calculate worst-case exposure of human consumers (adults and children).

There are very limited data on the kinetics and metabolism of organotins in laboratory mammals. A widespread distribution of organotins throughout body tissues has been observed. Transplacental transfer seems to occur, whereas transfer across the blood–brain barrier is limited, since brain levels are usually low. The only compound for which data are available on metabolites is dibutyltin, which has butyl(3-hydroxybutyl)tin as its major metabolite. Limited information suggests quite rapid metabolism and elimination, with half-lives of several days. Much of an oral dose of dioctyltin was eliminated in the faeces, with the remainder in urine.

The organotins covered in this assessment have low acute toxicity to laboratory mammals, with most studies indicating LD_{50}s above 100 mg/kg body weight, and many above 1000 mg/kg body weight; this may reflect low absorption from the gut. Studies on irritation are highly variable, with reports ranging from non-irritating to severely irritating for the same compound. The compounds should be regarded as irritating to skin and eyes. Similar variation occurs in sensitization tests, and the database should be regarded as inadequate to draw firm conclusions; however, a number of organotin compounds have shown strong sensitization in some tests, and it would be precautionary to regard the group as sensitizing.

Short- to medium-term exposures have shown neurotoxicity, developmental toxicity, immunotoxicity, and endocrine disruption to be relevant end-points, although the degree of each of these toxic end-points differs across the group as a whole.

Neurotoxicity is the major end-point for the methyltins, with a NOAEL of approximately 0.6 mg/kg body weight based on neuropathology for dimethyltin; limited data for monomethyltin preclude the derivation of a NOAEL. No neurotoxicity was found with dibutyltin or mono- and dioctyltins; no information is available for monobutyltin.

Developmental toxicity is shown by the disubstituted methyl-, butyl-, and octyltins, but not by the corresponding monosubstituted compounds. The major reported effect is teratogenicity, with effects on fetuses shown at doses close to maternally toxic ones in most cases. NOAELs for dimethyltin, dibutyltin, and dioctyltin are 10 (10), 2.5 (1.0), and 45 (30) mg/kg body weight per day for teratogenicity (maternal toxicity NOAELs in parentheses).

Immunotoxicity, consistently effects on thymus weight but also measures of functional immunotoxicity, is demonstrated for dibutyltin and mono- and dioctylins. A NOAEL could not be determined for dibutyltin, but the lowest dose reported as causing effects was 2.5 mg/kg body weight per day (as dibutyltin dichloride). NOAELs for mono- and dioctyltin have been determined to be 0.87 and 0.23 mg/kg body weight per day, respectively, although the value for monooctyltin is an estimate, because the study was performed using a mixture. Other information suggests that dioctyltin is the more immunotoxic of the two compounds.

Tributyltin is well established as an aromatase inhibitor, and dibutyltin appears to have some potency also (exact characterization of the endocrine disrupting capacity of dibutyltin alone is difficult because of the presence of tributyltin as an impurity). Monobutyltin and mono- and dioctyltins have no aromatase inhibiting capacity in in vitro tests. No data are available for this end-point for the methyltins.

The vast majority of in vivo tests show no genotoxicity of mono- and dialkyltins. Results from in vitro tests are variable, with little indication of DNA reactivity. There are, however, indications of clastogenicity and effects on spindle formation in mitosis in vitro.

Brief summaries were available for unpublished long-term studies for some of the organotins under consideration. These showed no carcinogenicity for mixtures of mono- and dimethyltins in rats and mono- or dioctyltins in rats or dogs except for a single study on a mixture of mono- and dioctyltin chlorides. This showed significantly increased frequency of thymic lymphomas in female rats only at the 150 mg/kg diet dose. Significant increases were seen in the incidence of generalized malignant lymphomas in males of the 50 and 150 mg/kg groups, but only in females at the highest dose.

Very few data are available on the effects of organotins in humans. Of the reported unintentional occupational exposures, none has an estimate of exposure concentration. Exposure was largely via the inhalation route, with some possibility of dermal exposure. Neurological effects were the most commonly reported, and these can persist for long periods.

Reliable lifetime TDI values cannot be derived, since long-term studies at the appropriate doses and in the appropriate species are not available. Medium-term exposure TDIs for the estimation of risk were estimated (as the chlorides) as 0.0012 mg/kg body weight for monomethyltin and dimethyltin based on neurotoxicity, 0.003 mg/kg body weight for dibutyltin based on immunotoxicity, and 0.002 mg/kg body weight for dioctyltin, also based on immunotoxicity. No reliable TDI could be derived for monobutyltin or monooctyltin.

Comparison of estimated worst-case exposure of human consumers (adults and children) indicates a cause for concern from the use of organotins in silicone baking papers, although information from industry indicates that this use of organotins has been discontinued worldwide.

Calculation of human exposure via the environment indicates cause for concern from exposure to dioctyltin deriving from consumption of locally produced food near PVC processing plants, where it is used as a stabilizer. The concern is greater for children, for whom the TDI is exceeded by a factor of 3.6, than for adults. Much of the exposure estimates is based on modelling, which is highly dependent on physicochemical properties of the compounds; actual monitoring is minimal in most cases.

Data sets on toxicity of organotins vary considerably from compound to compound, with dibutyltin being by far the best studied. Critical end-points and species are as follows: 0.007 mg/l chronic NOEC for *Scenedesmus subspicatus* for monomethyltin (growth rate), 0.2 mg/l chronic NOEC for *Daphnia* for dimethyltin (reproduction), 25 mg/l acute EC_{50} for *Daphnia* for monobutyltin (immobilization), 0.015 mg/l chronic NOEC for *Daphnia* for dibutyltin (reproduction), 0.003 mg/l chronic NOEC for *Scenedesmus subspicatus* for monooctyltin (growth rate), and 0.02 mg/l chronic NOEC for *Scenedesmus subspicatus* for dioctyltin (growth rate). For the purposes of comparability, all values given here have been converted to the chloride salt. The data sets are too small to conduct a probabilistic analysis, and PNECs have been derived by the application of uncertainty factors.

Regional PEC/PNEC ratios are all substantially lower than 1, indicating low risk from general environmental levels of these organotins. Some local PEC/PNEC ratios exceed 1, specifically organotin production with respect to monooctyltin and a large calendering plant for monomethyltin. Both of these values derive from using default worst-case values in the modelling. They indicate that local monitoring of actual concentrations is required to determine risk levels based on real concentrations.

Insufficient information is available to assess risk to the terrestrial environment.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Organotin compounds are characterized by the presence of a carbon–tin bond and have the following general formula:

$$R_xSn(L)_{(4-x)}$$

where R is an organic alkyl or aryl group and L is an organic (or sometimes inorganic) ligand. While the carbon–tin bond is strong, the association with the anionic ligand is less so, and it has a tendency to undergo dissociation both in use and in the environment. Thus, there is a wide range of organotin compounds that can be manufactured and indeed that are placed on the market. The properties of organotin compounds vary significantly, depending upon the number and nature of the R groups in particular, but also upon the type of ligand (L).

Table 1 presents a summary of the key physicochemical properties of the organotins under study. Tributyltin has already been assessed in a previous CICAD (IPCS, 1999b) and is not considered here.

It is of note that there is considerable uncertainty regarding the water solubility of some of the organotin compounds. The substances are generally sparingly soluble in water; however, through hydrolysis of the reactive ligands or ligand exchange, tin compounds of greater solubility may be formed, possibly casting doubt upon some of the data included in the table.

The environmental behaviour of organotins is strongly influenced by partition coefficients. Based upon the water solubility and vapour pressure data, EUSES estimates the dimensionless Henry's law constant (the air/water partition coefficient). As indicated in Table 1, there is a wide variability in the air/water partition coefficients for the six substances.

The EUSES model provides an estimate of the organic carbon/water partition coefficient (K_{oc}) based on the octanol/water partition coefficient (K_{ow}). From these data, it is evident that the methyltins are less likely to partition onto organic carbon (in sediments, soils, biota) than are the butyl- and octyltin compounds due to their lower partition coefficients and higher water solubilities. The K_{oc} value can then be used to derive solids/water partition coefficients in suspended matter, in sediment, and in soil using values of 10%, 5%, and 2% for organic carbon, representing typical organic carbon contents of suspended matter, sediment, and soil, respectively.

As with water solubility data, there is considerable uncertainty associated with some of the log K_{ow} values reported in the IUCLID data sets, with impurities in the substances possibly contributing to increased water solubility and, hence, a lower than expected partition coefficient.

Some measured K_{oc} data are available that are significantly higher than the modelled K_{oc} values derived from the log K_{ow} values (Terytze et al., 2000; Berg et al., 2001). The measured values (as log K_{oc}) plotted against both log K_{ow} and the predicted log K_{oc} values are shown in Figure 1; to facilitate comparison, the organotins are presented in order of increasing log K_{ow}, and tributyltin has been included to complete the series. Measured K_{oc} values are generally orders of magnitude above those

Table 1: Chemical identity of organotins (as chloride).[a]

	Monomethyltin trichloride	Dimethyltin dichloride	Monobutyltin trichloride	Dibutyltin dichloride	Monooctyltin trichloride	Dioctyltin dichloride
Synonyms	MMTC	DMTC	MBTC	DBTC	MOTC	DOTC
Chemical formula	CH_3Cl_3Sn	$(CH_3)_2Cl_2Sn$	$C_4H_9Cl_3Sn$	$(C_4H_9)_2Cl_2Sn$	$C_8H_{17}Cl_3Sn$	$(C_8H_{17})_2Cl_2Sn$
CAS No.	993-16-8	753-73-1	1118-46-3	683-18-1	3091-25-6	3542-36-7
Molecular weight	240.8	219.7	282.2	303.8	338.3	416
Melting point (°C)	47	105	−63	40	10	47
Boiling point (°C)	173	189	250	250	250	250
Solubility (g/l)	1×10^5	1×10^5	8.2	36	0.1	1.0
Vapour pressure at 25 °C (Pa)	33.3	30.0	5.84	0.15	0.55	1.35×10^{-4}
Log K_{ow}	−2.15	−2.18 to −3.1	0.18	1.89	2.14	5.82
K_{oc} (l/kg)	0.2	0.2; 21 537[b]	1.76; 75 354[c]	42.8; 61 664[b]; 223 867[c]	68.2	65 200; 292 556[b]
Henry's law constant ($Pa \cdot m^3/mol$)	0.08	0.066	201	1.27	1420	0.056
Air/water partition coefficient	3.38×10^{-5}	2.78×10^{-5}	8.48×10^{-2}	5.34×10^{-4}	5.98×10^{-1}	2.37×10^{-5}

[a] As most organotins decompose, boiling points of 250 °C were assumed in the absence of a "true" boiling point. The values for Henry's law constant and organic carbon/water partition coefficient were all derived from EUSES unless otherwise indicated. The chlorides were chosen as soluble salts in this table; toxicity is independent of salt (see section 8), and soluble salts maximize likely environmental exposure, giving worst case in modelling environmental fate.

[b] Terytze et al. (2000) undertook various tests on soils; the values in the table are not presented in their report but have been provided by the authors.

[c] Berg et al. (2001) derived K_{oc} values from measurements in sediments.

predicted using EUSES, which reinforces doubts over the log K_{ow} values. Although clearly uncertain, the measured values have been used in preference for further modelling; for monomethyltin trichloride and monooctyltin trichloride, where no measured data were available, a K_{oc} value of 10 000 (log K_{oc} = 4) has been assumed. Where more than one measured value was available, the geometric mean was used in further modelling.

3. ANALYTICAL METHODS

Analysis of organotin compounds usually consists of four steps: extraction, formation of volatile derivatives, separation, and detection/quantification. The preferred separation technique is gas chromatography owing to its high resolution and detector versatility. For biological materials, a cleanup step is required. Derivatization methods include formation of alkyl (methyl or pentyl) derivatives using a Grignard reagent, formation of ethyl derivatives using sodium tetraethylborate, or formation of hydrides using sodium borohydride. Detection and quantification can be performed using a flame photometric detector, atomic absorption spectrometry, or mass spectrometry (IPCS, 1990; Prange & Jantzen, 1995; Jiang et al., 1999; Takeuchi et al., 2000; Liu et al., 2001; Boraiko et al., 2004) or microwave-induced and inductively coupled plasma atomic emission spectrometry (Tutschku et al., 1994; Minganti et al., 1995).

Inductively coupled plasma mass spectrometry was applied to the analysis of six organotin compounds (chlorides of dimethyl-, dibutyl-, trimethyl-, tributyl-, diphenyl-, and triphenyltin). Detection limits for the six organotins ranged from 24 to 51 pg as tin; the dynamic range was over 10^4, from 1 µg/l to 10 mg/l (Inoue & Kawabata, 1993).

High-performance liquid chromatography has also been used, the advantage being that no derivatization step is required. Most separations are based on ion exchange or reversed-phase gradient elutions. Atomic absorption spectrometry, inductively coupled plasma mass spectrometry, and fluorometric detection can be used. High-performance liquid chromatography coupled with atomic absorption spectrometry is commonly used for speciation of organotin compounds (Takeuchi et al., 2000).

A more thorough review of analytical methods can be found in ATSDR (2003). Sample detection limits for biological material are typically in the range of 1–5

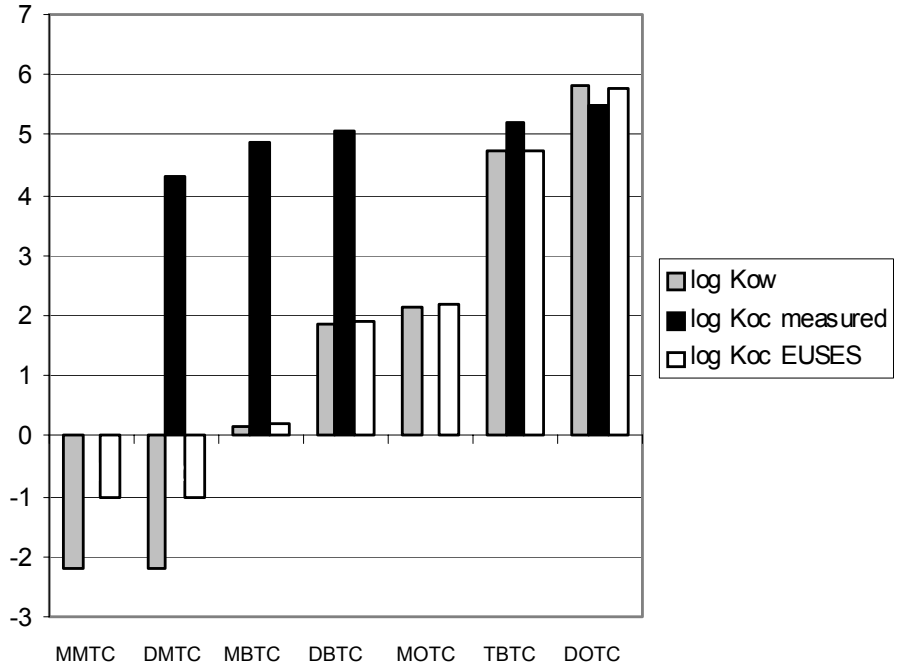


Fig. 1: Plot of measured/predicted partition coefficients.
(TBTC = tributyltin chloride)

µg/kg and for environmental samples typically less than 1 µg/l (0.1 µg/l in water).

At present, it is reported that there is no analytical technique capable of quantifying the entire organotin compound with its associated ligand in dilute solutions in water (Parametrix, 2002g), although experimental procedures are under development that may allow for determination of the entire organotin compound in water (e.g. Yoder, 2003).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

In the EU, a total of 12 779 tonnes of inorganic tin in 2001 was used in the production of the various organotin compounds, as well as in the production of inorganic tin compounds. It should be further noted that the above tonnage applies only to butyltin and octyltin compounds; methyltin compounds, while used in the EU, are produced only outside the EU and are imported.

A wide range of organotin compounds can be manufactured and placed on the market. Commercially used organotins are characterized by the number of organic groups in the compound. Tetrasubstituted compounds are used only as intermediates in the synthesis of other organic chemicals; they are not considered in this CICAD. Trisubstituted organotins are used as pesticides and biocides (i.e. pesticides used non-agriculturally) and as intermediates in the production of other chemicals (tributyl- and triphenyltins have been discussed in separate CICADs). Mono- and disubstituted organotins are generally considered together and are used as PVC stabilizers, as catalysts, and in glass coating.

Methods of manufacture of organotin compounds usually comprise two principal steps: the first consists of making direct tin–carbon bonds in compounds such as R_4Sn by reaction of tin tetrachloride with suitable reagents to form various tetraalkyltin compounds; the second stage is one of co-proportionation (Kocheshkov redistribution), in which R_4 is reacted with tin tetrachloride to produce compounds of the type R_3SnCl, R_2SnCl_2, and $RSnCl_3$. Other derivatives may then be simply produced from these chlorides for industrial end uses. Organotins can also be made by direct synthesis: $Sn + 2RI \rightarrow R_2SnI_2$ (where R is the alkyl group and I is the anion). Methyltin stabilizers are produced by direct synthesis in the United States. Dibutyltin dichloride is manufactured from crude tetrabutyltin and tin tetrachloride and is usually catalysed with aluminium trichloride (Blunden & Evans, 1989; Gaver, 1997; Thoonen et al., 2001).

Table 2 outlines the key uses for organotins in the EU and the quantities sold to the EU market in 2002.

Table 2: Organotin uses and quantities sold in the EU (estimates for 2002).[a]

Organotin	Applications	Quantity (tonnes/year)
Tetrasubstituted	Intermediate in synthesis	N/A
Trisubstituted	Biocide[b]	<100
	Pesticide	100
	Synthesis	<150
Mono- and disubstituted	PVC stabilizers	15 610
	Catalysts	1300–1650
	Glass coating	760–800
Total (maximum)	**All uses (except tetrasubstituted)**	**18 410**

[a] Data from ORTEPA (2002) (biocides, pesticides, synthesis, and glass coating), ESPA (2002) (PVC stabilizers), and ETICA (2002) (catalysts), as updated by ETINSA (2003).
[b] Excludes use as a biocide in antifouling paints, which was estimated at over 1250 tonnes per year (but is rapidly declining as the international ban is implemented).

The production figure for organotin PVC stabilizer in 1996–1998 in Japan was 6983–8649 tonnes per year (Chemical Daily Co., Ltd, 1999, as communicated to the Final Review Board by Dr J. Sekizawa).

It should be noted that uses of the trisubstituted organotins and uses of the mono- and disubstituted compounds do not overlap. Thus, for example, mono- and disubstituted compounds are not suitable for use as biocides, and trisubstituted compounds are not suitable as PVC stabilizers.

Within a commercial organotin product, there will always be some quantity of related substances in addition to the substance itself. In some cases, the performance of these products relies upon the presence of more than one related substance (e.g. mono- and disubstituted octyltin stabilizers), whereas in others, the related substances are present as an inevitable impurity. For example, tributyltin chloride will contain impurities of mono-, di-, and tetrabutyltins, as well as tin tetrachloride (Parametrix, 2002a,b).

Similarly, while the main products used as stabilizers in PVC are mono- and disubstituted compounds, owing to the chemistry involved in their production, trisubstituted organotin compounds will comprise a small fraction of the total amount. This could be significant in assessing the toxicity of the compounds (see below).

However, it should be noted that the R (alkyl or aryl) groups in most impurities of organotin compounds are the same as the major component; thus, tributyltin will contain other butyltins, but not, for example, octyltins.

4.1 Use of mono- and disubstituted organotins in PVC

The largest use for tin compounds is in the stabilization of PVC. Stabilizers are used in all PVC products in order to avoid decomposition while heating during processing and also to reduce deterioration through exposure to ultraviolet light and weathering (EVC, 1996). The consumption of tin stabilizers in Europe is about 15 000 tonnes per year, of which about 60% is used for food (and medical) packaging and 40% for technical applications (ESPA, 2002). Tin systems are used for almost all rigid PVC applications in North America, whereas the main use in Europe is for rigid, transparent applications where rigorous processing conditions require enhanced stabilization. These consumption levels have remained fairly constant over recent years. The substances concerned include methyl-, butyl-, and octyltins, all of which are used in both flexible and rigid PVC products.

Tin stabilizers are divided into two main categories: tin carboxylates (stabilizers with tin–oxygen bonds) and tin mercaptides (stabilizers with tin–sulfur bonds). Tin carboxylate stabilizers are typically used in outdoor applications owing to their ability to provide light and weathering stability. Examples include transparent panels and translucent doublewall panels for greenhouses. Tin mercaptide stabilizers allow the production of clear, rigid vinyl commodities even under high-demanding processing conditions. The most common stabilizers are produced by reaction of mono- and dialkyltin chlorides with mercaptoesters.

PVC is generally classified as either “rigid” (unplasticized PVC) or “flexible”, with the latter softened by incorporation of plasticizers such as phthalates and adipates. About one third of the PVC used in the EU is “flexible”. PVC is processed by techniques such as calendering, injection moulding, and extrusion. *Calendering* involves processing a mass of material through successive pairs of parallel rolls to form a sheet or a film. This process is generally used in the thermoplastics, rubber, textile, paper, and non-woven fabrics industries. The process of *injection moulding* allows the conversion of thermoplastic and thermosetting materials into final products. This process permits the manufacture of small PVC parts. Finally, the process of *extrusion* consists of forcing a heat-softened plastic through a die, which determines the cross-section of the profile after cooling.

Additionally, plastisol ("paste") type PVC compounds are in the form of a thick paste that can be applied by techniques such as coating, dipping, or rotational moulding.

Over 90% of organotin stabilizers are used in rigid PVC. Table 3 provides details of the estimated quantities of methyl-, butyl-, and octyltin stabilizers used in rigid and flexible PVC applications, whereas Table 4 details the types of applications in which the PVC products are used.

Table 3: Use of organotin stabilizer types in rigid and flexible PVC in Europe (2001).[a]

Organotin	Rigid PVC	Flexible PVC	Total
Methyltin	1 141	91	1 232
Butyltin	4 105	729	4 834
Octyltin	9 275	273	9 548
Total	**14 521**	**1 093**	**15 614**

[a] From ESPA (2002).

Table 4: Applications for rigid and flexible PVC containing organotin stabilizers.[a]

Applications	Tonnage
Rigid	
Packaging, including food contact; credit cards	12 343
Rigid construction, including formed sheeting	1 016
Thin rigid film	290
Bottles	290
Pipes and mouldings	290
Profile extrusions (e.g. windows)	290
Flexible	
Flooring	312
Wall coverings	312
Steel coating	312
Miscellaneous (e.g. T-shirt printing)	156

[a] From ESPA (2002). Note that figures are based on percentages and have not been rounded.

Industry estimates suggest that, for the two major uses — packaging and rigid construction, accounting for over 85% of use — the products in question are produced at 55 PVC processing plants across the EU. For all uses, there are estimated to be 130 major plants and a further 250 smaller users, spread fairly evenly across the EU (ESPA, 2002).

PVC is the only plastic in which organotin stabilizers are used. The total European market for PVC is slightly more than 5.5 million tonnes of PVC resin or 8.3 million tonnes of finished product.

Levels of organotins in rigid PVC are 1–1.5%. The minor use in flexible PVC is probably more in the range of 0.8–1.2% due to the plasticizer present (personal communication to IPCS, 2006).

4.2 Use of mono- and disubstituted organotins as catalysts

The concentration of tin catalysts is between 0.001% and 0.5% of the finished polymer. Following production, the catalyst is retained within the polymer (they are homogeneous catalysts) and hence within the finished product (ETICA, 2002), although in some cases the organotin may be partially degraded by the high temperatures used in the production processes.

There are several key areas of use for organotins as catalysts, and a separate discussion, including that for downstream markets, is provided for each of these in the following sections.

4.2.1 Electrodeposition

Dibutyltin oxide is used as a catalyst for the curing of cathodically applied electrodeposition coatings; it is the only organotin used for this purpose in the EU. The main use for electrodeposition coatings containing dibutyltin oxide is as a primer applied for corrosion protection on motor vehicles. The electrodeposition process involves submerging an uncoated negatively charged vehicle body in a tank containing an aqueous dispersion of the electrodeposition coating resin system. The resin from the electrodeposition medium is deposited on the metal surface, washed, and then baked on in an oven (Environment Agency, 1997; ETICA, 2002). In 2000, between 700 and 800 tonnes of organotin catalysts were used in electrodeposition coatings in the EU. If it is assumed that the concentration of organotin catalyst in the final electrodeposition coating is as high as 0.5%, the maximum recommended, the total quantity of coating produced would be around 160 000 tonnes.

4.2.2 Silicones

Organotins are used as catalysts in "room temperature vulcanization" via a condensation reaction. Dibutyltin laurate is the most commonly used organotin catalyst for this application. It is typically used at between 0.01% and 0.1% by weight. Between 50 and 100 tonnes of organotin catalysts were used in the production of silicones in the EU in 2000 (ETICA, 2002).

Typical uses for silicones that employ organotin catalysts include:

- one-component sealants for consumer (do-it-yourself) sealant application;
- two-component systems for industrial application; and
- condensation cross-linking of silicone-grafted polyolefins, such as polyethylene cable insulation (ETICA, 2002).

There is a wide range of silicone products on the EU market, some of which will contain organotin compounds as catalysts. These include gaskets, adhesives, lubricants, fuel additives, paints, sealants, protective coatings, shampoos/conditioners, deodorants, creams and gels, water repellents for sports clothing, textile finishes, paper finishes, domestic appliances, and computers (CES, 2002a). However, some of the above uses do not contain organotin catalysts in the EU. The European Tin Stabilisers Association has advised that, in general terms, manufacturers have worked to minimize the use of organotin catalysts in products that are likely to come into contact with consumers — although this is not entirely borne out by other catalyst uses. Personal care products, textiles, and sports goods contain no organotin-catalysed silicones in the EU (ETICA, 2003).

In relation to consumer uses of possible concern for this CICAD, data from the Women's Environmental Network indicate that butyltin stabilizers have been detected in the non-woven polypropylene topsheet of babies' nappies (diapers). It is possible that this could relate to the last of the three key uses described above, in that the topsheet could be of silicone-grafted polypropylene (or, as discussed below, the butyltin may be present because of its use as a catalyst in the production of an antioxidant in polyolefin films).

Additionally, organotin-catalysed silicones have been used in products such as coatings on baking paper (for use in food preparation), and this use is considered in more detail in the consumer exposure assessment (section 6). Information provided by the Centre Européen des Silicones (CES, 2002b) indicated that organotin-catalysed silicones are used in only a small proportion of baking paper produced in the EU:

- The European baking paper market is composed of around 95% greaseproof paper, of which around half is uncoated, 10% is chromium stearate-coated, and the remainder is silicone-coated.
- Of the silicone-coated baking paper, only around 1.5% is related to silicones catalysed with organotin compounds.

The associated baking paper is supplied by two companies, which use dioctyltin-based stabilizers exclusively. Thus, dioctyltin-catalysed silicone-coated baking paper represents only 0.6% of the total baking paper market in the EU. However, the Centre Européen des Silicones has now advised that the supply of tin-catalysed silicone-coated baking paper ceased at the end of 2002 (CES, 2003); import of silicones for use in baking paper production from outside the EU is thought to be unlikely. In non-EU countries, other organotin catalysts, such as butyltin compounds, may also be used in silicones for baking paper. These are understood to represent around 5–10% of the silicone-coated baking paper market in the United States (where their use is regulated by the Food and Drug Administration). In Japan, butyltin-catalysed silicone baking papers have been used in the past (Kannan et al., 1999); however, it is understood that no organotin-catalysed products are now used.

4.2.3 Esterification and powder coating

Organotin compounds such as monobutyltin oxide, the main substance used, accounting for 70% of consumption, dibutyltin oxide, monooctyltin oxide, and dioctyltin oxide are used in certain esterification and transesterification reactions, at concentrations between 0.001% and 0.5% by weight. They are used in the production of substances such as phthalates, polyesters, alkyd resins, fatty acid esters, and adipates and in transesterifications. These substances are in turn used as plasticizers, synthetic lubricants, and coatings. Organotins are used as catalysts to reduce the formation of unwanted by-products and also provide the required colour properties (ETICA, 2002).

Organotins are used at a concentration of around 0.3% in the production of polyester resins that are used for powder coating (which accounts for over 50% of the organotins used in this area). This process also involves an esterification reaction, typically using mono- or dibutyltin oxide as the catalyst. The final coatings consist of the polyester resin with a curing agent and other additives. They are applied as a dry powder via an electrostatic spray gun, followed by heating of the coating layer to cause formation of the cured coating. Typical applications include:

- household appliances (washing machines, refrigerators, etc.);
- office furniture;
- architectural uses (e.g. aluminium window frames);
- automotive components (e.g. trim parts, body primers, wheels);
- lawn and garden equipment; and
- heating and air conditioning systems (ETICA, 2002).

4.2.4 Polyurethanes

Organotin catalysts are used in a wide variety of urethane applications, aiding formation of the urethane bond in applications such as:

- urethane-modified resins (e.g. alkyd, acrylic, and acrylate) for printing inks, adhesives, and surface coatings;
- two-component polyurethane elastomers for a variety of applications;
- industrial and automotive two-component coatings; and
- flexible cushioning and rigid insulation foams (the main applications of polyurethanes) (ETICA, 2002).

The catalyst is reported to be highly compatible with the final polyurethane product and may become chemically bound into the polymer backbone where used in polyester-based urethanes.

4.3 Use of monobutyltin trichloride in glass coating

Approximately 700 tonnes per year of monobutyltin trichloride are used in hot-end coating of glass bottles, and a further 60–100 tonnes per year are used in the coating of flat glass. This technique was developed as an alternative to coating with tin tetrachloride. Hot glass products are exposed to hot air containing monobutyltin trichloride liquid and vapour. On the glass surface, the atomized liquid and vapour react to form tin oxide, which strengthens the glass, filling any "micro-cracks" in the glass (Atofina, 2002).

The above process is well established, having been introduced around 35 years ago, and is reported to be universally applied in the glass industry. It produces a surface that is more resistant to scratching and splintering (Pechiney, 2002). It should be noted that this process does not leave any residue of organic tin on the glass surface, since it is all converted to tin oxide through heating to over 400 °C.

Industry has indicated that the number of production lines undertaking coating of glass bottles with monobutyltin trichloride is around 500, with an estimated 2000 production lines worldwide. Sites in the EU could be expected to use a little over 1 tonne of monobutyltin trichloride per year on average.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

As discussed in section 2, the alkyltin component of organotin compounds is relatively stable to environmental degradation processes such as hydrolysis, compared with the association with the relative ligand (such as an isooctyl mercaptoacetate group). Thus, in water, most of the derivatives are reported to dissociate to the constituent alkyltin (usually as the chloride or the oxide) and the relevant anion (KemI, 2000).

Huang & Matzner (2004a) studied the adsorption and desorption of methyltins and butyltins in organic and mineral soils in batch experiments in the laboratory. Strength of sorption correlated well with organic carbon content and cation exchange capacity of the soils; sorption was in the order mono- ≥ di- > trisubstituted organotins, and butyltins sorbed to a greater extent than methyltins. Adsorption coefficients were much larger in organic soils ($K_d > 10^4$ l/kg) than in mineral soils. Dimethyltin and dibutyltin showed reversible sorption only in mineral soils (4–33% of the adsorbed material). Monosubstituted organotins adsorbed almost irreversibly in all soils.

Studies on aquatic sediments are restricted to butyltins and estuarine environments. Hoch et al. (2003) examined adsorption/desorption of dibutyltin to four natural clay-rich sediments. Strongest affinity was to montmorillonite-rich sediment characterized by the highest specific surface area and cation exchange capacity of all the sediments used. K_d values ranged between 12 and 40 l/kg under simulated marine conditions (pH 8; 32‰ salinity). Sorption increased with decreasing pH and salinity. Desorption (inversely related to the strength of adsorption) occurred over the entire pH range studied (4–8) when the sediments were in contact with butyltin-free water. Montmorillonite also showed strong binding affinity with monobutyltin under simulated estuarine conditions (Hermosin et al., 1993). Dai et al. (2003) found comparable results using sediments from the Haithe River, China. They found sorption constants decreased in the order monobutyltin > dibutyltin > tributyltin and also demonstrated increasing sorption with decreasing pH and decreasing salinity. They concluded that sorption of monobutyltin and dibutyltin was largely controlled by their cationic character.

For the purposes of environmental modelling using the EUSES program, data are available regarding photodegradation of the substances, as summarized in Table 5.

There are data available on biodegradation (for surface water) from tests conducted according to OECD 301F (respiration inhibition). These data are outlined in Table 6.

Table 5: Photodegradation of organotins.[a]

Organo-tin	Photodegradation constant (cm^3/molecule per second at 25 °C)	Half-life (days)
MMTC	2.5×10^{-13}	64
DMTC	1.8×10^{-12}	8.9
MBTC	1.42×10^{-11}	1.1
DBTC	2.84×10^{-11}	0.6
MOTC	1.99×10^{-11}	0.8
DOTC	3.97×10^{-11}	0.4

[a] Data drawn from Parametrix (2002a,c,e,g,i,k).

It is generally accepted that biodegradation half-lives are longer in both seawater and soil/sediment than in fresh water (CEC, 2003).

The measured biodegradation rates reported above are believed to be reflecting the dissociation of the ligand, whereas it is the remaining carbon–tin bond that is of interest from an ecotoxicity point of view. For this reason, in the subsequent modelling, the biodegradation for all the compounds being considered has been set at "inherently biodegradable" (i.e. 150-day half-life assumed).

In addition, data are available for a study on the degradation of dimethyl-, dibutyl-, and dioctyltin chlorides in soil (Terytze et al., 2000). It is of note that the results of the degradation testing indicate that the diorganotin compounds are partially degraded to the corresponding monosubstituted compounds; by way of example, dioctyltin concentrations were observed to decrease from 40 to 12 ng/l over a 3-month period while the monooctyltin concentration stayed relatively constant at around 2 ng/l. It is therefore likely that only a fraction of dioctyltin decayed to monooctyltin and/or the biodegradation rate for monooctyltin is significantly greater than that for dioctyltin. The resultant worst-case half-life values (where these relate to the decay of the alkyl group rather than the anionic ligand), as determined from sampling in the lysimeters over a period of 6 months, are detailed in Table 7.

A more recent field study of methyltins and butyltins in organic and mineral forest soils determined half-lives ranging from 0.5 to 15 years. Degradation rates were generally in the order mono- ≥ di- > trisubstituted organotins. Decomposition rates were higher in organic forest soils than in wetland and mineral soils (Huang & Matzner, 2004b). A comparable half-life was determined for dibutyltin in marine sediments (Almeida et al., 2004).

The categorization as "inherently biodegradable" together with the K_{oc} values and other physical properties enabled estimates of biodegradation half-lives in water, soil, and sediment to be made by EUSES. Those for soil and sediment were then reduced to be more consistent with the results of Terytze et al. (2000), as shown in Table 8.

A study of the degradation of butyltins in activated sludge batch reactors in the laboratory (Stasinakis et al., 2005) found half-lives for dibutyltin to be 5.1 days and 3.6 days for non-acclimatized and acclimatized sludge, respectively. Samples of sewage treatment influent and sludges collected monthly from five Canadian cities over the period from July 1990 to January 1991 revealed that monobutyltin was found in all influent samples, dibutyltin and tributyltin were found infrequently, and octyltin species were not found at all. There was a significant reduction (average 40%) in the concentration of monobutyltin by degradation and adsorption to sludge during

Table 6: Results of biodegradation according to respiration inhibition test OECD 301F.

Substance	Biodegradation results	Biodegradation category	Reference
Monomethyltin (EHMA)	95% degradation in 28 days	Readily biodegradable	Parametrix (2002b,d,h,j,l,m)
Dimethyltin (EHMA)	45% degradation in 28 days; 58% in 39 days	Readily, but failing 10-day window	
Monobutyltin (EHMA)	69% degradation in 28 days	Readily biodegradable	
Dibutyltin (EHMA)	35% degradation in 28 days; 56% in 74 days	Readily, but failing 10-day window	
Monooctyltin (EHMA)	37% degradation in 28 days; 55% in 39 days	Readily, but failing 10-day window	
Dioctyltin (EHMA)	36% degradation in 28 days; 49% in 74 days	Readily, but failing 10-day window	
Monomethyltin trichloride	7% degradation in 35 days	Not readily biodegradable	Hanstveit (2003a,b,c,d,e,f, g)
Dimethyltin dichloride	3% degradation in 35 days	Not readily biodegradable	
Dibutyltin laurate	23% degradation in 39 days	Not readily biodegradable	
Dibutyltin oxide	0% degradation in 28 days	No biodegradation observed	
Monooctyltin chloride	0.2% degradation in 39 days	Not readily biodegradable	
Dioctyltin dichloride	0% degradation in 39 days	No biodegradation observed	
Dioctyltin oxide	2% degradation in 31 days	Not readily biodegradable	

Table 7: Measured half-lives of dialkyltin compounds in soils.[a]

Organotin	Half-life (days)
Dimethyltin	152
Dibutyltin	122
Dioctyltin	152

[a] From Terytze et al. (2000).

passage through the sewage treatment plant. The monobutyltin found in the effluent was believed to have originated from its use as PVC stabilizer as well as from the degradation of tributyltin, which is used as a slimicide. No butyltin or octyltin species were found in five landfill leachate samples in southern Ontario, Canada, during the same period (Chau et al., 1992).

In a recent Swedish survey on effluents from sewage treatment plants, small amounts of dioctyltin substances were occasionally found in the sewage sludge, but no dioctyltin substances were detected in the water phase (Walterson et al., 1993).

There are limited data on measured BCFs in freshwater fish. The results are summarized in Table 9, together with predicted values from EUSES.

The observed BCFs for dibutyltin dichloride in round crucian carp (*Carassius carassius grandoculis*) muscle, vertebra, liver, and kidney tissue were 12, 46, 135, and 61, respectively (Tsuda et al., 1986).

Predictions of bioaccumulation assume a standard model of dissolution in fat and are based on partition between water and organic solvent. The better studied tributyltin has been shown to partition based on binding to protein rather than dissolution in fat; this might account for discrepancies between observed and predicted BCFs.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

6.1.1 Measured concentrations

For the octyltin compounds, the only source of these substances relates to their use as stabilizer compounds in PVC products (including other relevant life cycle stages such as production). Thus, it can be safely assumed that measured levels in the environment relate to this application.

Butyltin compounds, in contrast, are produced only anthropogenically. Besides the applications covered in this CICAD, there exist other applications of butyltin compounds that may represent a significant source of these substances in the environment. In particular, the use of tributyltin compounds in antifouling coatings represents a significant source of these substances in the marine and freshwater environments. Hence, many of the measured concentrations reported will relate predominantly to this use.

Methyltin compounds, in addition to being used as stabilizers in PVC products, can also be produced via natural processes in the environment. Thus, as with butyltin compounds, it is not possible to exactly attribute the source of methyltin compounds in the environment.

A number of extensive reviews have concluded that there are no data suggesting the presence of octyltin compounds in water or in sediment in the environment, despite numerous monitoring studies for organotin compounds (GC, 1993; KemI, 2000; Summer et al., 2003). No additional data have been found.

A screening test for organotin compounds in European landfill leachates (Mersiowsky et al., 2001) indicated maximum levels of approximately 4 µg/l of monooctyltin.

Table 8: Biodegradation half-lives in fresh water, soils, and sediments.

Parameter	MMTC	DMTC	MBTC	DBTC	TBTC	MOTC	DOTC
EUSES prediction of half-life (days):							
- fresh water	150	150	150	150	150	150	150
- soil	3 000	3 000	30 000	30 000	30 000	3 000	30 000
- sediment	3 000	30 000	30 000	30 000	30 000	3 000	300 000
Measured half-life in soil (days)		~150		~120			~150
Half-life values used for soil and sediment in EUSES modelling (days)	150	150	150	120	150	150	150

Table 9: Bioconcentration factors.[a]

Organotin	BCF measured	BCF predicted by EUSES
MMTC	No data	1.41
DMTC	No data	1.41
MBTC	126	1.41
DBTC	136	8.06
MOTC	No data	13.2
DOTC	1	18 000

[a] Value for dioctyltin dichloride drawn from Japanese Ministry of International Trade and Industry (1992); values for butyltins are from Tsuda et al. (1986, 1988).

A number of studies have detected octyltin compounds in sewage sludge resulting from wastewater treatment. A report by KemI (2000) details concentrations found in sewage sludge and effluent at Swedish, Danish, and Canadian wastewater treatment plants, as summarized in Table 10.

Table 10: Measured concentrations of octyltins at wastewater treatment plants.[a]

Survey	Measured concentrations
Sweden (1993)	Maximum 0.6 mg/kg dry weight (0.2 mg/kg as tin)
Sweden (1996–1998)	Up to 0.49 mg monooctyltin/kg; 0.14 mg dioctyltin/kg (0.25 and 0.05 mg/kg as tin) in sludge
	<10–80 ng monooctyltin/l in effluent (<5–40 ng/l as tin)
Denmark (1993–1994)	Up to 1.3 mg/kg dry weight as tin
Canada (1997)	89 µg tin/kg (for monooctyltin); 82 µg tin/kg (for dioctyltin)
	8 ng dioctyltin/l in effluent (4 ng/l as tin)

[a] From KemI (2000).

Data supplied by industry provide further information on the sampling of six Swedish wastewater treatment plants in 1997 and 1998, as reported in Table 11.

A higher concentration of dioctyltin in sewage sludge of 0.56 mg/kg as the chloride is reported by Summer et al. (2003). Thus, the maximum reported concentrations for the individual compounds are as follows:

- 715 and 560 µg/kg dry weight for monooctyltin trichloride and dioctyltin dichloride, respectively, in sludge; and
- 0.12 and 0.008 µg/l for monooctyltin trichloride and dioctyltin, respectively, in effluent.

It can be seen that the measured concentration in sewage sludge for monooctyltin is consistently higher than that for dioctyltin. By comparison, the values calculated by the EUSES model indicate that, for the same life cycle stages, the concentration of dioctyltin dichloride is about twice that of monooctyltin trichloride. Concentrations of monooctyltin trichloride and dioctyltin dichloride in dry sewage sludge calculated by EUSES were 43 and 116 µg/kg, respectively, for production; 2740 and 5080 µg/kg, respectively, for "formulation" involving catalysts; and 1190 and 2200 µg/kg, respectively, for processing of products with catalysts. This is likely to be the consequence of the uncertainties associated with some of the physicochemical input parameters (such as K_{oc}) used in the model.

Summer et al. (2003), in their review of the available data, refer to measured concentrations of mono- and dibutyltin compounds with maximum values of:

- 1.9 and 15.7 µg/l (as tin) for monobutyltin and dibutyltin, respectively, in fresh water (but also up to 2600 µg/l in freshwater surface microlayer in Canada);

Table 11: Sampling in Swedish wastewater treatment plant water and sludge.[a]

	Results from 1997				Results from 1998			
	Water (µg/l)		Sludge (µg/kg)		Water (µg/l)		Sludge (µg/kg)	
Location	MOTC	DOTC	MOTC	DOTC	MOTC	DOTC	MOTC	DOTC
Björklinge	<0.015	<0.012	394	181	<0.015	<0.012	540	<12
Kungsängen	<0.015	<0.012	423	157	<0.015	<0.012	292	76
Kungsängen	0.029	<0.012	496	<12	<0.015	<0.012	335	99
Gässlösa	0.12	<0.012	656	<12	<0.015	<0.012	350	89
Linköping	<0.015	<0.012	715	<12	<0.015	<0.012	350	<12
Storvreta	<0.015	<0.012	598	133	<0.015	<0.012	467	111

[a] Data from Nowak (1998). All values converted to chlorides.

- 2.8 and 1.3 µg/l (as tin) for monobutyltin and dibutyltin, respectively, in coastal waters; and
- 6.8 and 9.6 mg/kg for monobutyltin and dibutyltin, respectively, in sediments.

The highest levels of monobutyltin and dibutyltin in water and sediment are thought to relate mainly to degradation of tributyltin from its use on boats as an antifouling paint.

Hoch (2001) provides a review of the concentrations of various organotin compounds found in the environment. A summary of the main results for mono- and dibutyltins is provided in Table 12.

Table 12: Concentrations of butyltins in water and sediment.[a,b]

	Monobutyltin	Dibutyltin
Maximum concentration in water (ng/l as tin)	76	810
Maximum concentration in sediment (µg/kg dry weight as tin)	3360	8510

[a] From Hoch (2001).
[b] Includes river, lake, marine, and harbour sediments.

Concentrations of butyltin compounds in sewage sludge from wastewater treatment plants have also been measured in the environment. Values reported are up to 0.77 and 2.22 mg/kg dry weight, respectively, for mono- and dibutyltins (Summer et al., 2003).

Summer et al. (2003) also reviewed the concentrations of methyltin compounds in the environment (Table 13). No higher values were found in later literature. As indicated above, methyltin compounds can be produced naturally in the environment by microorganisms (Maguire, 1991).

Table 13: Concentrations of methyltins in water and sediment.[a,b]

	Monomethyltin	Dimethyltin
Maximum concentration in water (ng/l as tin)	1200	400
Maximum concentration in sediment (µg/kg dry weight as tin)	170	0.27

[a] Summer et al. (2003).
[b] Includes river, lake, marine, and harbour sediments.

There is some evidence to suggest that methyltin compounds bind to sewage sludge. Concentrations between 11 946 and 92 642 µg/kg were observed in activated sludge slurry in an industrial study to determine the partitioning of methyltin chlorides between activated sludge and water. In contrast, in earlier work, Donard et al. (1993) found that methyltins were progressively removed in a large wastewater treatment plant in Bordeaux, as shown in Table 14 — although the data are reported by the authors as uncertain.

Table 14: Concentrations of mono- and dimethyltins in a wastewater treatment plant.[a,b]

	Monomethyltin	Dimethyltin
Influent concentration (ng/l as tin)	106	132
Activated sludge concentration (ng/l as tin)	30	40
Effluent concentration (ng/l as tin)	70	22

[a] From Donard et al. (1993).
[b] Much lower concentrations of mono- and dimethyltin were also measured.

Some information exists regarding the potential for emissions of organotin compounds from landfills, including laboratory-scale experiments as well as measured concentrations of organotins in landfill leachate.

A study carried out for the European Commission examined the behaviour of PVC products in landfills (ARGUS, 2000). In this study, landfill simulation investigations were carried out using lysimeters, with PVC products including rigid and flexible types as well as short- and long-lifetime products. The study concluded that aerobic thermophilic conditions are the most aggressive in relation to degradation of PVC in landfills. However, a change in the weight distribution of PVC was observed only for thin plasticized PVC within the landfill simulations.

In relation to PVC additives, the study concluded that heavy metal additives are more likely to be released under acidogenic conditions (compared with plasticizers, for example, which are released mainly during the anaerobic and methanogenic phases of landfill development). With respect to landfill emissions, it was concluded that organotin compounds cannot be directly attributed to the presence of PVC in landfills.

Another study (Mersiowsky et al., 1999) also undertook laboratory-scale landfill simulations of PVC products, with leachate and landfill gas as well as PVC degradation analysed. It was found that some of the plasticized PVC products exhibited a partial loss of additives into the leachate. Furthermore, Mersiowsky et al. (2000) also monitored a number of actual landfill

sites for leaching of various additives, including organotin compounds. The maximum concentrations reported are detailed in Table 15.

Table 15: Concentrations of organotins in landfill leachates (Sweden, Germany, and Italy).[a]

Organotin species	Cation (µg/l)	As tin (µg/l)	As chloride (µg/l)
Monomethyltin	0.57	0.33	0.67
Dimethyltin	0.47	0.30	0.56
Monobutyltin	4.11	1.98	4.70
Dibutyltin	0.92	0.41	1.04
Monooctyltin	1.72	0.67	1.92
Dioctyltin	0.8	0.25	0.87

[a] From Mersiowsky et al. (2000).

Concentrations found in leachate do not necessarily represent the concentrations that would be found in the wider environment. Landfill leachate may be treated using on-site water treatment facilities, it may be disposed of directly to the municipal sewer, or, in some cases — for older facilities — it may leach directly out of the landfill into the environment. Even in the latter case, there will be a significant dilution of the landfill leachate upon entering the environment. Resulting environmental concentrations are, therefore, likely to be significantly lower than those reported above.

6.1.2 Estimation of PECs

The EUSES model has been run for each of the organotins under consideration. This involved developing "use patterns" for each compound, together with appropriate emission factors (based on the results presented above) and data on the properties of each of the compounds. The data upon which the analysis is based are the usage of each compound by application. More details on the method can be found in the source document (EC, 2003). Regional PECs for fresh water are summarized in Table 16.

Although these concentrations are lower than some of the values measured in the environment, the absence of extensive monitoring data makes it difficult to draw firm conclusions.

Local PECs for the aquatic environment for each of the organotin groups have been derived for four scenarios:

- close to a major organotin production facility;
- close to a major PVC processing facility using organotin stabilizers;
- close to a major formulator (of paints, sealants, etc.) using organotin catalysts; and
- close to a site of significant application of sealants (or similar).

Local PEC values were derived for two production sites (coded as "V" and "W"), which gave the highest PEC values for all sites for which information was provided by industry, using site-specific data, as follows:

- estimate effluent concentration of specific organotins based on total reported effluent concentration;
- apply a dilution factor (ratio of river flow to effluent flow) to effluent concentration to provide a first-order estimate of the local PEC value; and
- apply correction factors for suspended solids (and associated partition coefficients) using Equation 45 of the revised Technical Guidance Document (CEC, 2003).

Two hypothetical PVC processing sites — a calendering plant and a spread coating plant — have been used to generate local PEC values. Although it is acknowledged that PVC processes are generally regarded as "dry" processes with no liquid effluent, it has been assumed (as a worst case) that 50% of emissions to air find their way into wastewater (e.g. due to rainwater flushing local deposition into surface water drains). Such a scenario might apply where a PVC processing plant is located on an industrial site and the site's drains are connected to a local sewage treatment plant.

Similar calculations have been undertaken for the mono- and dimethyltin compounds and the mono- and dioctyltin compounds. All of the calculations and input data used are the same (in terms of quantities used at a site, losses to air, and percentages lost to wastewater). It is assumed that the stabilizer compounds contained either 50% each of monomethyltin trichloride and dimethyltin dichloride (for the methyltins) or 50% each of monooctyltin trichloride and dioctyltin dichloride (for the octyltin compounds).

Two hypothetical sites, a polyurethane plant using butyltin-based products and a paint formulator using either butyltin- or octyltin-based products, have also been used to generate local PEC values.

For the application of a sealant (or similar product) containing catalysts, an indication of the local PEC value has been determined.

A summary of PEC values derived as above is presented in Table 17. As can be seen, the site-specific

Table 16: Regional PECs (aquatic).

Regional PEC in surface water (ng/l dissolved)					
MMTC	**DMTC**	**MBTC**	**DBTC**	**MOTC**	**DOTC**
0.3	0.4	1.0	2.1	0.1	0.6

Table 17: Local PEC values.[a]

	Local PEC in surface water (ng/l)					
Activity	**MMTC**	**DMTC**	**MBTC**	**DBTC**	**MOTC**	**DOTC**
Organotin production						
Plant V (using TGD)	–	–	49	99	105	125
Plant W (using TGD)	–	–	187	**227**	**241**	**285**
Generic plant (EUSES)	–	–	44	5	0.3	0.9
PVC processing sites (using stabilizers)						
Large calendering plant (using TGD)	**134**	**117**	40	63	29	49
Small spread coating plant (using TGD)	81	71	24	38	14	21
Generic plant (EUSES)	0.3	0.4	1.0	2.1	0.1	0.6
Product manufacture (catalysts)						
Polyurethane plant (using TGD)	–	–	n/a	2.6	n/a	n/a
Paint formulator (using TGD)	–	–	**810**	120	71	76
Generic formulation (EUSES)	–	–	130	33	11	13
Product application (sealant with catalysts)						
Generic application (EUSES)	–	–	4.8	4.7	0.5	1.0
Maximum local PEC	**134**	**117**	**810**	**227**	**241**	**285**

[a] Site-specific modelling used the Technical Guidance Document (CEC, 2003); generic modelling used the EUSES model.

Technical Guidance Document (CEC, 2003) calculations lead to significantly higher results than those derived using EUSES. This is mainly due to the assumption that local air emissions will enter the wastewater stream — which is not applied to the EUSES calculations.

By comparison with the measured data presented above, it can be seen that the local PECs are generally below, or in the order of, the maximum values measured in the aquatic environment. By way of exception, the values reported for methyltins, and in particular dimethyltin dichloride, from stabilizer production using the Technical Guidance Document (CEC, 2003) equations are significantly higher than the maximum measured values reported in the environment.

6.2 Human exposure

Organotins have been detected in a range of consumer products. Table 18 summarizes the maximum values reported within each study tabulated.

These data have been used to model worst-case exposure for an adult consumer and for a child. Details of the methods and assumptions can be found in the source document (EC, 2003). Table 19 gives the exposure estimates for adults, and Table 20 those for children.

In both cases, tributyltin is included in the table for routes of exposure resulting from contamination of commercial dibutyltin; direct exposure from the deliberate use of tributyltin is covered in the appropriate CICAD (IPCS, 1999b).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Gastric hydrolysis was estimated for monomethyltin EHMA, three salts of dibutyltin (maleate, dilaurate, and oxide), and monooctyltin EHMA in 0.07 mol/l hydrochloric acid solution. Half-lives for hydrolysis were 0.27, 3.5, <0.5, <0.5, and 0.3 h, respectively.

There are very limited studies on absorption of organotins. Noland et al. (1983) found maximum blood concentrations of dimethyltin after dosing pregnant rats

Table 18: Organotin compounds in consumer products.

Product	Concentration (mg/kg)							Substance measured	Reference
	MMT	DMT	MBT	DBT	TBT	MOT	DOT		
Sanitary pads							5.2	Organotin cation	RIVM (2000)
Sanitary pantiliners							33.1	Organotin cation	RIVM (2000)
Tampons				1.3				Organotin cation	RIVM (2000)
Maternity sanitary pads							2.2	Organotin cation	RIVM (2000)
Nappies/diapers (tape system)							47	Organotin cation	RIVM (2000)
Pilches (tape system)				20				Organotin cation	RIVM (2000)
Clothing				0.1	9.9		13.3	Organotin cation	RIVM (2000)
Shower curtains			0.26	2.5				Organotin cation	DEPA (2001)
Gloves			18	240	48	65	24	Organotin cation	DEPA (2001)
Vinyl flooring			0.03	0.04	0.56			Organotin cation	DEPA (2001)
Vinyl wallpaper			15	270	2.5	0.004	0.69	Organotin cation	DEPA (2001)
Bags			2.8	6.6				Organotin cation	DEPA (2001)
Nappies/diapers			0.004	0.016	0.003			Organotin cation	DEPA (2002)
Swimming pool/ beach ball			2.3	14	0.1			Organotin cation	DEPA (2002)
Dummies			0.009					Organotin cation	DEPA (2002)
Sponges			0.016	0.016				Organotin cation	DEPA (2002)
Sportsware			0.004	0.009				Organotin cation	DEPA (2002)
Flooring			446	279	3	6.7	5.1	Tin	Fabes (2000)
Flooring			48.8	589	17.94	0.98	10.2	Organotin cation	Greenpeace (2000)
Carpets (treated)			1.14	7.2	47.5			Organotin cation	Greenpeace (2001)
PVC print of soccer jersey			2.7	7.5	0.0021	0.134	1.1	Organotin cation	FRG (2001)
PVC flooring					3.2			Organotin cation	FRG (2001)
Nappies/diapers			0.0057	0.0347	0.0086			Organotin cation	FRG (2001)
Garden hoses					0.737			Organotin cation	FRG (2001)
Indoor wall paints			0.0654	1.85	0.0147			Organotin cation	FRG (2001)
Inflatable whale (toy)				6.253				Organotin cation	DTI (2002)
Inflatable dinosaur (toy)				20.33				Organotin cation	DTI (2002)
Flooring				603				Organotin cation	DTI (2002)
Nappy/diaper covers (polyester)				33.7				Organotin cation	Kannan et al. (1999)
Sanitary napkins (nylon/poly-urethane)				5.5				Organotin cation	Kannan et al. (1999)
Silicone-soaked baking paper			130	140	0.8			Organotin cation	Kannan et al. (1999)
Cookies prepared on above paper			260	720	15			Organotin cation	Kannan et al. (1999)
Nappies/diapers			0.0033	0.0071	0.0086			Organotin cation	PG (2000)
Nappies/diapers				<0.01	0.024			Organotin cation	WEN (2000)
Children's face masks	0.041 –0.23	0.22– 1.45		0.53– 0.99		0.075– 0.92	0.47– 3.96		Ohno et al. (2003)

MMT, monomethyltin; DMT, dimethyltin; MBT, monobutyltin; DBT, dibutyltin; TBT, tributyltin; MOT, monooctyltin; DOT, dioctyltin

Table 19: Worst-case consumer exposure to organotin compounds (adults).

	Exposure (µg/kg body weight per day, as tin)						
	MMT	**DMT**	**MBT**	**DBT**	**TBT**	**MOT**	**DOT**
Food wrapped in PVC	0.07	0.07				0.1	0.06
PVC gloves			0.128	0.033	0.000 44		
Sanitary pantiliners							0.062
Cookies (from baking paper)			0.29	0.61	0.01		
Indoor air[a]	0.004	0.009	0.024	0.008	0.001	0.002	0.004
Dental mouldings				0.046			
Earplugs			0.000 6	0.000 2	<0.000 1		
Via the environment (worst-case local)	0.000 3	0.000 5	0.012	0.003 3		0.000 6	0.53

MMT, monomethyltin; DMT, dimethyltin; MBT, monobutyltin; DBT, dibutyltin; TBT, tributyltin; MOT, monooctyltin; DOT, dioctyltin

[a] Exposure via house dust (which has been measured as containing organotins) was also considered; it is likely that inhalation exposure indoors includes house dust, which picks up leached organotins from vinyl flooring.

Table 20: Worst-case consumer exposure to organotin compounds (children).

	Exposure (µg/kg body weight per day, as tin)						
	MMT	**DMT**	**MBT**	**DBT**	**TBT**	**MOT**	**DOT**
Nappies/diapers			0.0029	0.013	0.007		
Cookies (from baking paper)			1.10	2.29	0.038		
Paddling pool water			0.012	0.003	<0.001		
Food wrapper in PVC	0.28	0.28				0.41	0.23
T-shirt (printed)				0.0019	0.015		0.17
Indoor air	0.010	0.021	0.059	0.019	0.008	0.017	0.010
PVC toys	negligible	negligible	negligible	negligible	negligible	negligible	negligible
Via the environment (worst-case local)[a]	0.0012	0.0018	0.049	0.013		0.0026	2.13

MMT, monomethyltin; DMT, dimethyltin; MBT, monobutyltin; DBT, dibutyltin; TBT, tributyltin; MOT, monooctyltin; DOT, dioctyltin

[a] The uptake via the environment is derived from the adult figures multiplied by four to account for a higher food intake per unit body weight.

intragastrically with dimethyltin dichloride at 0.026 mg/kg body weight; no quantification of blood concentration was given. Maximum concentrations in the blood of fetuses occurred 6 h after dosing of the dam. An industry study dosed rats orally with monooctyltin trichloride at 25 mg/kg body weight. A maximum blood concentration of 62 ng/ml was found 4.3 h after administration; absorption was estimated at 0.03% of the dose. Penninks et al. (1987) administered an oral dose of ^{14}C-labelled dioctyltin dichloride at 6.3 mg/kg body weight to rats and recorded absorption at 20% of the administered dose. The highest amount of radioactivity was found in the liver and kidney, with lesser amounts in the adrenal, pituitary, and thyroid glands; the lowest activity was recovered from blood and brain, and no selective accumulation was observed.

In vitro studies on the absorption of dioctyltin dichloride and dioctyltin EHMA through rat and human epidermis (occluded and unoccluded) were performed by Ward (2003). Doses were equivalent to 1000 µg/cm^2 as dichloride and 17 007 µg/cm^2 as tin, respectively. Of the recovered tin for dioctyltin dichloride, mean amounts absorbed after 24 h were 0.035 µg/cm^2 (unoccluded) and 0.039 µg/cm^2 (occluded) for human skin and 1.04 µg/cm^2 (unoccluded) and 4.14 µg/cm^2 (occluded) for rat skin. Corresponding results for dioctyltin EHMA were 0.010 µg/cm^2 (unoccluded), 0.011 µg/cm^2 (occluded), 0.641 µg/cm^2 (unoccluded), and 0.547 µg/cm^2 (occluded) for human and rat skin, respectively.

After administration of a single oral dose of dibutyltin diacetate of 22 mg/kg body weight to pregnant rats on day 8 of gestation, both dibutyltin and monobutyltin were detected in the embryos, indicating placental transfer (Noda et al., 1994). Nakamura et al. (1993) also detected dibutyltin in embryos after dosing the mother orally on days 7–17 of gestation.

Penninks & Seinen (1980) measured the relative distribution of [^{14}C]dioctyltin dichloride in organs of rats dosed orally at 8 mg/kg body weight; results were liver (3.37%), kidney (0.79%), adrenals (0.69%), pituitary glands (0.51%), spleen (0.37%), lymph nodes (0.26%), thymus (0.12%), blood (0.12%), and brain (0.04%) after 2 days. Results after a single intravenous dose at 2 mg/kg body weight were liver (10.07%), kidney (4.22%), adrenals (2.46%), spleen (1.29%), pituitary glands (1.10%), lymph nodes (0.08%), thymus (0.46%), blood (0.20%), and brain (0.17%). Penninks et al. (1987) conducted a repeat study at doses of 6.3 mg/kg body weight orally and 1.2 mg/kg body weight intravenously. Radioactivity in tissues was about 3–4 times higher after intravenous administration than after oral dosing, but the relative distribution between tissues was the same. Loss of radioactivity from all tissues over the following 7 days was approximately equal for all tissues except kidney, adipose tissue, thymus, and brain, giving a slight increase in relative accumulation indices for these tissues. It should be emphasized that these studies followed distribution of the ^{14}C label and not the organotin moiety as such.

Administration of dibutyltin dichloride intraperitoneally to rats led to the formation of butyl(3-hydroxybutyl)tin, butyl(4-hydroxybutyl)tin, and monobutyltin. The major metabolite (butyl(3-hydroxybutyl)tin) was distributed to the kidney at a relatively high concentration compared with the other metabolites, and its concentration increased with time. Butyl(4-hydroxybutyl)tin was found in urine only. The parent compound and other metabolites were detected in the brain (Ishizaka et al., 1989). Dibutyltin diacetate was destannylated by 14% within 90 h following a single oral dose in mice at 1.1 mg/kg body weight, with several butyltin derivatives found in the liver or faeces (Boyer, 1989).

Arakawa et al. (1983) reported that dibutyltin elimination from kidney, liver, spleen, and thymus, following cessation of dietary dosing with dibutyltin dichloride for 1 week at 100 mg/kg diet, was rapid, with half-lives for each organ at several days. Merkord et al. (1982) suggested active transport of dibutyltin into bile, with a bile:plasma ratio of 151:1.

Penninks et al. (1987) reported that 80% of a single oral dose of dioctyltin dichloride at 2 mg/kg body weight was excreted in the faeces within 2 days. After 3 days, excretion of radioactivity followed first-order kinetics, with a half-life of 8.9 days. After intravenous administration, 66% of the radioactivity was excreted in the faeces, and a half-life value of 8.3 days was obtained, roughly similar to that of oral administration. Percentages of radioactivity excreted in the urine were 11% and 22% following intravenous and oral dosing, respectively.

There are no data on kinetics or metabolism in humans; therefore, no conclusions can be drawn as to the relevance of animal data to human metabolism of these compounds.

Penninks & Seinen (1980) looked at subcellular distribution of dibutyltin in rat liver and thymus cells in vitro. Radioactivity was concentrated in mitochondria and low in cytoplasm in thymus cells, in marked contrast to liver cells, where mitochondrial radioactivity was very low. Differences in cellular distribution have been suggested as a reason for the selective effect on the thymus.

8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

8.1 Single exposure

Selected acute toxicity values for organotin compounds are presented in Table 21.

Symptoms were usually nonspecific and included weakness, hypoactivity, ruffled fur, dyspnoea, tremor, and sedation. Autopsy findings included haemorrhages in the gastrointestinal tract, congested organs, discoloration of the liver, spleen, and kidney, focal peritonitis, and enteritis. After inhalation exposure, additional haemorrhages in the lungs, lung emphysema, and oedema were observed (Summer et al., 2003).

8.2 Irritation and sensitization

Dermal exposure of rats to doses of dimethyltin dichloride at 80 mg/kg body weight produced dermal necrosis with the formation of black scars; the same dose of dibutyltin dichloride produced little surface damage to the skin together with subcutaneous oedema. Dioctyltin dichloride produced no skin lesions (Barnes & Stoner, 1958). A number of unpublished industry studies were summarized by Summer et al. (2003): monomethyltins produced very slight erythema or no effects (even at a lethal dose), whereas dimethyltins and mixtures of mono- and dimethyltins produced minimal to slight (and in one case moderate) irritancy. Monobutyltins gave conflicting results in two studies; one showed slight irritation, and the other severe. Dibutyltins were extremely irritating in most studies, leading to severe necrosis. Mixtures of mono- and dibutyltins were markedly to extremely irritating. Dioctyltins and mixtures of mono- and dioctyltins vary in studies from negative to marked irritancy.

Eye irritancy is also summarized by Summer et al. (2003): a single study showed monomethyltin to be a

Table 21: Acute toxicity of organotin compounds.

Compound	Species	Route	LD_{50}[a]	Reference
Monomethyltin	Rat	Oral	2150 mg/kg body weight	Hill-Top Toxicology (1978)
	Rat	Oral	2300–3300 mg/kg body weight	Cannon Laboratories (1979)
	Rat	Oral	566–1355 mg/kg body weight	Walterson et al. (1993)
	Rat	Oral	1370 mg/kg body weight	Mesch & Kugele (1992)
	Rat	Inhalation	600 mg/l for 1 h (aerosol)	Wells Laboratories (1973)
	Rabbit	Dermal	~200 mg/kg body weight[b]	Ciba-Geigy Ltd (1973)
Dimethyltin	Rat	Oral	73.9 mg/kg body weight	Klimmer (1971)
	Rat	Oral	141.4 mg/kg body weight	AME (1971)
	Rat	Oral	160–190 mg/kg body weight	Cannon Laboratories (1979)
	Rat	Oral	80–160 mg/kg body weight	Figge & Koch (1973)
	Rat	Inhalation	125 mg/l for 1 h (aerosol)	Wells Laboratories (1973)
	Rat	Inhalation	139 µg/l for 4 h (aerosol)	Sterner & Grahwit (1976)
Monobutyltin	Rat	Oral	2200 mg/kg body weight	Schering AG (1969a)
	Rat	Oral	2300 mg/kg body weight	Mesch & Kugele (1992)
	Rat	Oral	2140–3200 mg/kg body weight	Elf Atochem NA (1991)
	Rat	Oral	357–642 mg/kg body weight	Walterson et al. (1993)
	Mouse	Oral	1400 mg/kg body weight	NIOSH (1976)
Dibutyltin	Rat	Oral	58 mg/kg body weight	Klimmer (1971)
	Rat	Oral	219 mg/kg body weight	Schering (1969b)
	Rat	Oral	100 mg/kg body weight	Figge & Koch (1973)
	Rat	Oral	126 mg/kg body weight	Mesch & Kugele (1992)
	Rat	Inhalation	59 mg/m^3 for 4 h (aerosol)	Ciba-Geigy Ltd (1980)
	Rat	Inhalation	2.76 µl/l for 4 h (aerosol)	Sterner & Chibanguza (1976)
Monooctyltin	Rat	Oral	2400 mg/kg body weight	Hess & Schweinfurt (1989)
	Rat	Oral	2200 mg/kg body weight	Witco (1992)
	Rat	Oral	3100 mg/kg body weight	Ciba-Geigy Ltd (1982a)
	Rat	Oral	3800 mg/kg body weight	Mesch & Kugele (1992)
Dioctyltin	Rat	Oral	5.0–6.8 mg/kg body weight	Hill-Top Toxicology (1978)
	Rat	Oral	3300–4700 mg/kg body weight	Cannon Laboratories (1979)
	Rat	Oral	7000 mg/kg body weight	Mesch & Kugele (1992)
	Rat	Oral	>5000 mg/kg body weight	Ciba-Geigy Ltd (1982b)

[a] LC_{50} for inhalation studies.
[b] LD_{100}.

non-irritant, whereas dimethyltins showed moderate to severe irritancy, with erythema, oedema, and conjunctivitis. Mixtures of mono- and dimethyltins had no or minimal effects. Mono- and dibutyltin and their mixtures showed minimal to extreme irritation. Dioctyltins and mixtures of mono- and dioctyltins were minimally to moderately irritating.

In sensitization tests, dimethyltins showed one positive and one negative result; a mixture of mono- and dimethyltins was negative. Dibutyltins were non-sensitizing, but mixtures of mono- and dibutyltins showed slight to strong sensitization (di- and monobutyltin in the mixture as isooctylthioglycolates increased the sensitization response). Mixtures of mono- and dioctyltins showed slight to strong sensitization (higher proportions of dioctyltin as the ethylhexylthioglycolate increased the sensitization rate) (Summer et al., 2003).

In summary, studies on irritation and sensitization are highly variable, with reports ranging from non-irritating to severely irritating for the same compound. The compounds should be regarded as irritating to skin and eyes. Similar variation occurs in sensitization tests, and the database should be regarded as inadequate to draw firm conclusions; however, it would be sensible and precautionary to regard organotins as sensitizing.

8.3 Short- and medium-term exposure

The predominant toxic end-points vary among the different organotins and include neurotoxicity, reproductive and developmental toxicity, immunotoxicity,

and endocrine disruption. Short- and medium-term studies are, therefore, arranged under these headings.

8.3.1 Neurotoxicity

Two 90-day repeat oral toxicity studies (Elf Atochem NA, 1996; Rohm & Haas, 1999) have been reported for a mixture of monomethyltin trichloride and dimethyltin dichloride. The two studies are complementary, and the doses taken together provide indications of medium-term lethality; doses in the drinking-water study fill in the large gap between the highest and next dose in the feeding study in terms of mg/kg body weight, adding confidence to determination of the NOAEL. The studies used mixtures of different proportions; it is anticipated that dimethyltin dichloride is the more potent of the two components (based on a series of older industry studies of mixtures of different proportions of dimethyltin dichloride and monomethyltin trichloride, summarized in Summer et al., 2003).

The Rohm & Haas (1999) study used a mixture of dimethyltin dichloride (90%) and monomethyltin trichloride (10%) in drinking-water for Sprague-Dawley rats (male and female; $n = 60$) daily for 13 weeks; concentrations were 0, 25, 75, and 200 mg/l. For the 200 mg/l group, all showed signs of tremors, convulsions, and aggression/hypersensitivity when handled. Body weight and food intake were significantly lowered at all time intervals of sampling. Similar signs were reported for the 75 mg/l group, but these were less severe. Body weight change was not significant for the 25 mg/l group, and no clear abnormal clinical signs were reported. Water consumption was reduced for all treated groups. Significant findings for the 75 mg/l group were limited to lower body temperature of females and reduced rearing. No treatment-related findings were reported for the 25 mg/l group. Absolute and relative thymus weights were reduced significantly in the 200 mg/l group; other organ effects were transitory or inconclusive. Histopathological changes were clear and treatment related, characterized by slight to mild ventricular dilation, mild to moderate neuronal necrosis, and slight to mild white matter vacuolation. Less frequent and less pronounced effects were seen at 75 mg/l than at 200 mg/l. The NOAEL was considered to be <25 mg/l.

The Elf Atochem NA (1996) study used doses of 0, 1, 6, 15, or 200 mg/kg diet and Wistar rats over a period of 13 weeks following OECD Test Guideline 408. Mean intakes of the test substance (66.5% dimethyltin dichloride:33.5% monomethyltin trichloride) were 0, 0.06, 0.39, 0.98, and 16.81 mg/kg body weight per day in males and 0, 0.07, 0.41, 1.02, and 17.31 mg/kg body weight per day in females. Histopathological examination of a wide range of organs showed treatment-related changes in the brain, kidneys, and thymus of the 200 mg/kg diet group; no such changes were observed at 15 mg/kg diet. Animals in the 200 mg/kg diet group showed signs of convulsions, tremor, blepharospasm, and hunched posture; these signs were not seen in other dose groups. Microscopic examination of the brain showed predominant lesions of the hippocampus and the surrounding cortical regions (e.g. entorhinal and perirhinal cortices), the amygdala, olfactory structures (e.g. olfactory nuclei and piriform cortex), and the tenia tecta. The presence of swollen axons was observed in the spinal cord at the highest dose level. No neuropathology was found in the 15 mg/kg diet group or the controls. The NOAEL was determined to be 15 mg/kg diet, which is equivalent to 0.98 mg/kg body weight per day (males) and 1.02 mg/kg body weight per day (females) for the test mixture or 0.62 mg/kg body weight per day (males) and 0.65 mg/kg body weight per day (females) for the dimethyltin dichloride component of the mixture.

The overall NOAEL for neuropathology is considered to be 0.6 mg/kg body weight for the dimethyltin dichloride component of the mixture (feeding study), with marginal effects seen at 1.4 and 2 mg/kg body weight (for males and females, respectively, in a drinking-water study) and clear effects at 4.6 and 6 mg/kg body weight (for males and females, respectively, in the drinking-water study).

8.3.2 Reproductive and developmental toxicity

In a full gestational exposure developmental study, Wistar rats were dosed daily by gavage on days 7–17 of gestation with dimethyltin dichloride at 0, 5, 10, 15, or 20 mg/kg body weight per day. There was maternal toxicity at 15 and 20 mg/kg body weight per day (maternal death, tremors, reduction in body weight gain, reduction in thymus weight). At 15 mg/kg body weight per day, there was a reduction in fetal body weight, whereas at 20 mg/kg body weight per day, fetal deaths, reduced fetal body weight, and anatomical defects were reported; the latter comprised cleft palate (21 fetuses from 5 out of 7 pregnant rats with living fetuses at day 20 of gestation). There was a dose-dependent reduction in maternal thymus weight, with a significant reduction at 15 and 20 mg/kg body weight per day. The authors concluded that the LOAEL for maternal and fetal effects was 15 mg/kg body weight per day (lower body weight gain, reduced thymus weight in dams, reduced fetal body weights). The maternal and fetal NOAEL for dimethyltin dichloride was 10 mg/kg body weight per day (Noda, 2001). In a second experiment in the same report, Noda (2001) looked at the effect of dosing with dimethyltin dichloride for shorter periods at different stages of gestation. Rats were given 20 or 40 mg/kg body weight per day for 3-day periods at days 7–9, 10–12, 13–15, or 16–17 of gestation. Cleft palate was not seen at either dose level after any of the exposure periods. Numbers of fetuses with skeletal variation, cervical ribs, and/or splitting of the first cervical vertebral arch increased

significantly in the 40 mg/kg body weight per day group dosed on days 7–9 or 13–15 of gestation.

A reproduction/developmental screening study (OECD Test Guideline 421) was conducted using monomethyltin trichloride at doses of 0, 30, 150, and 750 mg/kg diet over 8 weeks. The NOAEL for fertility and developmental effects and maternal toxicity was 150 mg/kg diet (Appel & Waalkens-Berendsen, 2004a). A comparable study using monooctyltin trichloride at doses of 0, 10, 100, and 500 mg/kg diet gave NOAELs of 100 mg/kg diet for fertility and developmental effects and 10 mg/kg diet for maternal toxicity (Appel & Waalkens-Berendsen, 2004b).

The comparative developmental toxicities of monobutyltin trichloride (one of the major metabolites of dibutyltin dichloride) and dibutyltin dichloride were reported in a series of studies by Noda et al. (1992a,b) and Ema et al. (1995), using full gestational and partial gestational exposures. In the full gestational study, Noda et al. (1992a) treated Wistar rats orally with monobutyltin trichloride (0, 50, 100, 200, and 400 mg/kg body weight per day) during days 7–17 of gestation. Caesarean sections were performed on day 20 of gestation. No maternal toxicity or thymic atrophy was reported, and no dose-dependent developmental toxicity was evident. In the partial gestational exposures, Ema et al. (1995) treated Wistar rats with monobutyltin trichloride (0, 1000, 1500, or 2000 mg/kg body weight) via gastric intubation on days 7 and 8 of pregnancy. Maternal deaths were significantly increased at the 1500 and 2000 mg/kg body weight doses, and maternal body weight gain was significantly decreased at the 1000 and 1500 mg/kg body weight doses; however, no external malformations were found in the fetuses. The authors concluded that monobutyltin is not a developmental toxicant, since effects were seen only at maternally toxic doses.

Animal data consistently show dibutyltin dichloride to cause dose-dependent developmental toxicity, such as fetal deaths, birth defects, and reductions in fetal weight.

Ema et al. (1995) dosed pregnant rats at 10 or 15 mg/kg body weight on days 7 and 8 of gestation only; the incidence of external and skeletal abnormalities was increased in both groups, whereas maternal body weight gain was reduced. Ema et al. (1992) investigated the susceptible period of pregnancy for teratogenic effects by dosing with dibutyltin dichloride on groups of days (days 7–9, 10–12, or 13–15; 20 mg/kg body weight via gastric intubation) or specific days (day 6, 7, 8, or 9; 20 or 40 mg/kg body weight by gastric intubation) of gestation. Dibutyltin administered on days 7–9 caused teratogenicity, but no effects were seen when the compound was dosed on days 10–12 or 13–15. Dibutyltin administered on day 7 or day 8 alone, but not on day 6 or day 9, did lead to increases in malformation. In a later study, Ema et al. (1996) dosed rats at a late stage of pregnancy (13–15 days) and demonstrated that dibutyltin, even at maternally toxic doses, was not teratogenic when administered during late organogenesis.

Ema et al. (1991) dosed pregnant rats once daily for 8 days on days 7–15 of gestation with dibutyltin dichloride at 0, 2.5, 5.0, 7.5, or 10 mg/kg body weight by gavage; rats were killed on day 20. Doses of 7.5 and 10 mg/kg body weight caused maternal deaths, and survivors showed reduced weight gain and food consumption; there was no maternal toxicity at lower doses. In the 7.5 mg/kg body weight group, number of resorptions, number of dead fetuses, post-implantation loss, number of live fetuses per litter, body weight of live fetuses, and placental weight were all significantly different from controls. Similar, but less consistent, results were seen in the 10 mg/kg body weight group, but these were not statistically significant; it was thought by the authors that this was due to high maternal toxicity in this group, with reduced litter sizes for statistical analysis. There was a significant dose-related increase in the incidence of fetuses with external and skeletal malformations; no such abnormalities were observed in the 2.5 mg/kg body weight group.

A 20-day study with dosing of pregnant rats on days 6–15 of gestation was conducted with dibutyltin dichloride at 0, 1.0, 2.5, 5.0, and 10 mg/kg body weight (ORTEPA, 1994). Maternal toxicity, as indicated by reduced body weight gain, reduced food consumption, and thymus atrophy, occurred at the 10 mg/kg body weight dose level. Administration of 5.0 mg/kg body weight resulted in minor maternal toxicity (slightly reduced weight gain and possible thymus atrophy), but did not lead to teratogenic effects in fetuses. No developmental toxicity was seen at 2.5 mg/kg body weight.

The NOAEL for maternal toxicity was regarded as 1.0 mg/kg body weight by the authors (ORTEPA, 1994) and 5.0 mg/kg body weight by Ema et al. (1991); the peer reviewers and members of the Final Review Board regarded 5.0 mg/kg to be the NOAEL for both studies, since the effects noted by ORTEPA at 5.0 mg/kg body weight were not considered to be of biological significance. The NOAELs for teratogenicity were 5.0 and 2.5 mg/kg body weight for the ORTEPA (1994) and Ema et al. (1991) studies, respectively.

A study on Wistar rats by Farr et al. (2001) showed no maternal toxicity at doses up to 5 mg/kg body weight for dibutyltin dichloride; signs of maternal toxicity — reduced body weight gain, decreased food consumption, and thymus weight — were observed at 10 mg/kg body weight. No teratogenic effects were seen at 10 mg/kg

body weight except for a slight (4/262 treated compared with 1/269 controls) increase in malformations.

The teratogenic effects of various dibutyltins with different anions have been studied by Noda et al. (1992a,b, 1993). Dibutyltin diacetate has been shown to cause malformations such as cleft mandibles, ankyloglossia, fused ribs, etc. in rat fetuses after oral treatment of maternal rats on day 8 of gestation (Noda et al., 1992b). Noda et al. (1993) gave a single dose of dibutyltin maleate to Wistar rats on day 8 of gestation in a study to compare different anions. Doses by gavage were 0 or ~28 mg/kg body weight. There was no significant difference in maternal body weight gain or food consumption, and no maternal toxicity was observed in the treated group. No difference in resorption or body weight of living fetuses was observed. The incidence of external and skeletal abnormalities was 12.5% and 9.3% for treated and control groups, respectively. Dibutyltin maleate caused a significant increase in mandibular malformations (cleft mandible, cleft lower lip, ankyloglossia, or schistoglossia) and anomalies (mandibular fixation and cranial hypoplasia). Skeletal variations were predominantly cervical rib. In separate experiments, dibutyltin oxide or dibutyltin dilaurate was dosed by gavage at 0 or ~20 and 0 or ~50 mg/kg body weight, respectively, also on day 8 of gestation. No maternal toxicity was reported. The incidence of external and skeletal abnormalities was 20.7% and 26.2% for control and treated groups, respectively, for dibutyltin oxide and 28.1% and 30.6%, respectively, for dibutyltin dilaurate. Malformations, anomalies, and variations were the same as for dibutyltin maleate. Molar concentrations of dibutyltin maleate, dibutyltin oxide, and dibutyltin dilaurate were identical, at 80 µmol/kg body weight.

Ema et al. (2003) and Harazono & Ema (2003) suggest that the embryonic loss seen with dibutyltin compounds results from a suppression of uterine decidual cell response and decreased progesterone levels (progesterone is protective of this aspect of reproductive toxicity in rats). Dibutyltin causes implantation failure in rats exposed to dibutyltin dichloride at 7.6 mg/kg body weight and above on days 0–3 and at 3.8 mg/kg body weight and above on days 4–7 of pregnancy (Harazono & Ema, 2003). The susceptible period for teratogenicity and types of malformations induced by dibutyltin are different from those induced by tetra-, tri-, and monosubstituted organotins. In vitro exposure to dibutyltin dichloride interfered with normal development of embryos during three different stages of organogenesis, and the susceptibility to embryotoxicity, including dismorphogenic potential of dibutyltin dichloride, varies with developmental stages (Hirose et al., 2004).

Faqi et al. (2001) studied the developmental toxicity in NMRI mice of an octyltin stabilizer ZK 30.434, a mixture of 80% dioctyltin diisooctylthioglycolate and 20% monooctyltin triisooctylthioglycolate. Dams were treated with the mixture by gavage once per day for 12 days of gestation (days 6–17) at 0, 20, 30, 45, 67, or 100 mg/kg body weight. There was no reduction in maternal body weight gain or clinical signs of toxicity in the 20, 30, or 45 mg/kg body weight groups, but a significant reduction in maternal weight gain was observed at 100 mg/kg body weight. Mean maternal thymus and liver weights were reduced in the 45 and 100 mg/kg body weight groups. Resorption rate was increased at 67 and 100 mg/kg body weight, and fetal weights were decreased. No external malformations were reported in the 20, 30, or 45 mg/kg body weight groups; a significant increase in incidence of cleft palate in fetuses of dams exposed at 67 and 100 mg/kg body weight was reported. The incidences of bent forelimbs and exencephaly were significantly increased at 100 mg/kg body weight. Skeletal abnormalities were significantly increased at 67 and 100 mg/kg body weight. The authors concluded that the maternally toxic dose was 100 mg/kg body weight per day based on body weight gain and liver weight and 45 mg/kg body weight per day based on thymus weight; a NOAEL for maternal toxicity was determined to be 30 mg/kg body weight per day. A NOAEL for malformation in the fetus was reported at 45 mg/kg body weight per day based on increases in cleft palate in fetuses from dams exposed at 67 mg/kg body weight.

A study in rats dosed on days 6–15 of gestation with the same 80:20 mixture of dioctyltin and monooctyltin showed no effects up to and including 5 mg/kg body weight, but significant embryotoxicity was observed at 25 mg/kg body weight (Schering AG, 1991). A comparable study on rabbits (dosed on days 6–18 of gestation) showed no treatment-related effects at 1 mg/kg body weight, marginal effect on fetal development at 10 mg/kg body weight, and significant embryotoxicity/embryolethality at 100 mg/kg body weight (Schering AG, 1992). Decreasing the dioctyltin in the mixtures reduced the observed effects on fetuses (Summer et al., 2003).

Ciba-Geigy Ltd (1983) found no treatment-related embryotoxic or teratogenic effects after dosing rats by gavage at 0, 20, 60, or 120 mg/kg body weight per day during days 6–15 of gestation with a mixture of mono- and dioctyltin thioglycolates (67:33).

8.3.3 Immunotoxicity

Arakawa & Wada (1993) dosed rats with monomethyltin trichloride or dimethyltin dichloride for 10 days at 5 mg/kg body weight per day and reported no effects on thymus weight; this is the only study examining immunotoxic end-points for the methyltins.

Seinen & Willems (1976) fed male and female Wistar rats for 6 weeks with diets containing dioctyltin dichloride concentrations of 0, 50, or 150 mg/kg diet. Relative thymus weight showed a highly significant dose-dependent decrease for both sexes. Popliteal lymph node weights of males also showed a dose-dependent decrease. The thymal cortex was almost completely depleted of lymphocytes in the 150 mg/kg diet group and, to a lesser extent, in the 50 mg/kg diet group. There was no evidence of lymphocyte destruction. Periarteriolar lymphocyte sheaths in the spleen were smaller and lymphocyte populations were less dense than in controls. Lymphocyte depletion was also evident in the thymus-dependent paracortical areas of peripheral lymph nodes. No treatment-related histopathological changes were seen in the other organs examined. Since effects were seen at both dose levels, no NOAEL can be determined.

Penninks & Seinen (1982) reported reduced weights of thymus and spleen at both dose levels from a 14-day feeding study in rats fed dioctyltin dichloride at concentrations of 50 and 150 mg/kg diet (equivalent to 2.5 and 7.5 mg/kg body weight).

Wistar rats fed diets containing dibutyltin dichloride at a dose of approximately 7 mg/kg body weight per day for 2 weeks showed a 50% reduction in relative thymus weight and lower but significant reductions in relative spleen weight and popliteal lymph nodes. All treated rats showed marked lymphocyte depletion in the thymus, particularly the cortex, but no cell destruction was reported (in marked contrast to the effects of tributyltin). Rats dosed at 23 mg/kg body weight per day showed almost complete depletion of lymphocytes (Seinen et al., 1977a). Similar results were obtained with dioctyltin dichloride. A 4-week dosing period followed by an 8-week period on clean diet showed that effects on the thymus were reversed after about 2 weeks (Seinen et al., 1977a).

In studies with Fischer 344 rats exposed prenatally and postnatally or just postnatally to dioctyltin dichloride by oral gavage of pregnant and/or lactating females at various ages ranging from 3 to 16 weeks, it was found that direct dosing of pups during early postnatal life may be the most effective means of inducing immunosuppression with dioctyltin dichloride. The results also provided evidence for the greater sensitivity of the developing immune system compared with the fully developed immune system to a known immunotoxicant (Smialowicz et al., 1988).

Similar studies on dimethyltin dichloride and monooctyltin trichloride showed no effects on the lymphoid organs (Seinen et al., 1977a).

Rohm & Haas (1976) conducted a 90-day dietary toxicity study on rats fed monooctyltin trichloride at 0, 30, 100, 300, or 1000 mg/kg diet. Relative weights of the thymus showed a dose-related decrease at and above 30 mg/kg diet. Relative weight of the spleen was low for all test groups, but this was not dose related. Appel & Waalkens-Berendsen (2004b) conducted a comparable 90-day study on rats using dioctyltin dichloride at 0, 10, 100, and 300 mg/kg diet. Decreased absolute and relative thymus weights at the 10 mg/kg diet dose meant that a NOAEL could not be determined; the LOAEL was considered to be 10 mg/kg diet, equivalent to 0.7 mg/kg body weight per day.

Functional changes in the immune system have also been reported; following dosing with dibutyltin dichloride for 4–6 weeks, there was depressed humoral response to immunization with sheep red blood cells and a significant delay in allograft response at approximately 2.5 mg/kg body weight per day and a significant delay in allograft response at 7.5 mg/kg body weight per day (Seinen et al., 1977b). The same authors also showed that immune effects were greater in rats exposed during the developmental phase of the immune system. In the same study, rats treated with dioctyltin dichloride at a dose of 5 mg/kg body weight per day exhibited delayed hypersensitivity to tuberculin, a cell-mediated immune response.

Immunotoxicity of organotin compounds is not mediated by stress-induced release of glucocorticoids, since adrenalectomy did not prevent development of thymus atrophy (Seinen & Willems, 1976). Also, adrenal weights were unaffected in these studies.

Mice also show immune responses to dosing with dibutyltin and dioctyltin, but only at levels much higher than rats (around 300 mg/kg diet); guinea-pigs showed no altered immune response at 50 mg/kg diet (Seinen et al., 1977a,b; Miller et al., 1986). Dosing of rats and mice for 78 weeks (up to 6.7 and 19.8 mg/kg body weight per day, respectively) caused no histopathological effects in lymphoid tissues.

Miller & Scott (1985) reported marked reduction in thymus weight in rats fed dioctyltin dichloride for 8 or 12 weeks at a level of 75 mg/kg diet. Numbers of lymphocytes together with T cell subpopulations were reduced in treated rats, but no difference was seen in antibody response to sheep red blood cells in vivo. No evidence was found of in vitro cytocidal effects of dioctyltin dichloride on blood lymphocytes. Evans et al. (1986) dosed pregnant and non-pregnant rats for 3 weeks at 75 mg/kg diet and reported severe thymic atrophy and extensive vacuolation of reticuloendothelial cells in pregnant animals only.

In a 3-month feeding study on rats using a 65:35 mixture of mono- and dioctyltin chlorides at 0, 3, 10, 30, or 100 mg/kg diet, no treatment-related effects on food

intake or growth were seen. A significant reduction in thymus weight was seen in the 100 mg/kg diet group, with a marginal decrease in the 30 mg/kg diet group. No histopathological changes were seen in thymic tissue. The NOAEL was considered to be 3 mg/kg diet, equivalent to 0.87 and 0.23 mg/kg body weight per day, respectively, for mono- and dioctyltin chlorides (Ciba-Geigy Ltd, 1981). A 90-day study feeding rats a mixture (94:6) of mono- and dioctyltin chlorides at levels of 0, 30, 100, 300, and 1000 mg/kg diet showed reduced thymus weights at all doses (TNO, 1976).

Studies of the effects of in vitro exposure to a range of concentrations (encompassing environmentally relevant concentrations of monobutyltin, dibutyltin, and tributyltin) on human natural killer lymphocytes obtained from adult male and female donors revealed the presence of detectable concentrations of the butyltins in all the donors, indicating possible exposure of natural killer cells to butyltins in the blood. It was suggested that the study provided evidence that butyltin compounds significantly inhibit natural killer cell function and possible natural killer cell–mediated potential in humans (Whalen et al., 1999).

8.3.4 Endocrine disruption

No data are available on endocrine-related effects of methyltins.

Tributyltin is well established as an aromatase inhibitor (IPCS, 1990). Quantitative comparisons of potency cannot be defined for other organotins, because a full range of in vitro tests has not been performed.

In recent in vitro studies, an aromatase inhibiting effect on human placental microsomal extracts has been demonstrated with both tributyltin chloride and dibutyltin dichloride (Heidrich et al., 2001; Cooke, 2002). The dibutyltin compound tested seemed to have a slight aromatase inhibiting effect, but at a lower potency than tributyltin (it should be noted that tributyltin was probably present as an impurity). However, the difference in the aromatase inhibiting potency between tributyltin and dibutyltin (approximately a factor of 10) suggests that dibutyltin alone must have a slight inhibiting effect too. Monobutyltin trichloride had no aromatase inhibiting activity.

Investigations of the aromatase inhibiting effects in in vitro assays gave no indication of an endocrine response after incubation with mono-, di-, or trioctyltin (Cooke, 2002).

8.4 Long-term exposure and carcinogenicity

Only one published carcinogenicity study is available for the organotins under consideration; this studied the long-term effects of dibutyltin diacetate in both rats and mice. Male and female Fischer 344 rats were fed dietary doses of dibutyltin diacetate at 0, 3.33, or 6.65 mg/kg body weight per day for 78 weeks, followed by 26 weeks on a clean diet. B6C3F1 mice received doses of 0, 9.9, or 19.8 mg/kg body weight per day also for 78 weeks, followed by a clean diet for 14 weeks (NCI, 1978). There were no statistically significant increases in tumour incidence compared with controls in either study. Uterine tissues from 17 of the high-dose females were accidentally lost; absolute preclusion of neoplasms in uterine tissue cannot, therefore, be made. However, a general conclusion that dibutyltin was not carcinogenic to either rats or mice was made. For non-neoplastic effects, no histopathological effects were found in lung, heart, endocrine glands, lymphoid tissues, gastrointestinal tract, liver, or kidney. There was no significant effect on body weight. No gross or microscopic effects were seen in the brain.

Brief summaries were available for unpublished long-term studies for other organotins. These showed no carcinogenicity for mixtures of mono- and dimethyltins in rats and mono- or dioctyltins in rats or dogs in almost all studies (Summer et al., 2003). One study on a mixture (65:35) of mono- and dioctyltin chlorides at doses of 0, 5, 15, 50, or 150 mg/kg diet for 2 years showed significantly increased frequency of thymic lymphomas (13/55 compared with 2/57) in female rats only at the 150 mg/kg diet dose. Significant increases were seen in the incidence of generalized malignant lymphomas in males of the 50 and 150 mg/kg groups, but in females only at the highest dose (Ciba-Geigy Ltd, 1986).

Antitumour activity has been reported for alkyltins, particularly dibutyltin. The effect in mouse skin initiation/promotion protocols showed dibutyltin inhibiting the promotion stage (Arakawa & Wada, 1993).

Toxicity studies described in sections 8.3 and 8.4 are summarized in Table 22, where studies used to derive medium-term exposure TDIs (see section 11.1.2) are also indicated.

8.5 Genotoxicity and related end-points

The vast majority of in vivo tests show no genotoxicity of mono- and dialkyltins. Results from in vitro tests are variable, with little indication of DNA reactivity. There are, however, indications of clastogenicity and effects on spindle formation in mitosis in vitro.

Table 22: Summary of toxicological data for the critical toxic effects (studies used to derive TDIs in bold type).

Tin compound	Species	Test material	Exposure period and dose	Effects	NOAEL/LOAEL (mg/kg body weight per day)	Reference
Immunotoxicity						
Monomethyltin	Rat	MMTC	10 days at 5 mg/kg body weight	Thymus weight	No effect reported at 5	Arakawa & Wada (1993)
Dimethyltin	Rat	DMTC	10 days at 5 mg/kg body weight	Thymus atrophy	No effect reported at 5	Arakawa & Wada (1993)
Dibutyltin	Rat	DBTC	14 days at 0, 50, and 150 mg/kg diet ≡ 0, 2.5, and 7.5 mg/kg body weight	Decreased weight of thymus	**Lowest dose at which effect was reported = 2.5**	**Penninks & Seinen (1982)**
	Rat	DBTC	4–6 weeks at 0, 50, and 150 mg/kg diet ≡ 0, 2.5, and 7.5 mg/kg body weight	Decrease in cellular and humoral immune response, in haemagglutination and haemolysin titres; suppression of primary antibody response against sheep red blood cells	**Lowest dose at which effects were reported = 2.5**	**Seinen et al. (1977b)**
	Rat	DBTC	Day 2 of pregnancy to 34 days postpartum at 0, 50, or 150 mg/kg diet ≡ 0, 2.5, and 7.5 mg/kg body weight	Decreased number of antibody-producing cells in spleen	**Lowest dose at which effect was reported = 2.5**	**Seinen et al. (1977b)**
				Suppression of primary antibody response against sheep red blood cells	Lowest dose at which effect was reported = 7.5	
	Rat	DBTC	Gestation days 4–7 at 3.8 mg/kg body weight and above	Implantation failure	LOAEL = 3.8	Harazono and Ema (2003)
Dioctyltin	Rat	DOTC	14 days at 0, 50, or 150 mg/kg diet ≡ 0, 2.5, and 7.5 mg/kg body weight	Decreased weight of thymus and spleen	Lowest dose at which effects were reported = 2.5	Penninks & Seinen (1982)
	Rat	DOTC	6 weeks (males), 1–28 days (females) at 0, 50, or 150 mg/kg diet ≡ 0, 2.5, and 7.5 mg/kg body weight	Decreased weight of thymus; lymphocyte depletion in thymus and thymus-dependent areas of spleen and lymph nodes; decrease of number and viability of nucleated thymocytes	Lowest dose at which effects were reported = 2.5	Seinen & Willems (1976)

Table 22 (Contd)

Tin compound	Species	Test material	Exposure period and dose	Effects	NOAEL/LOAEL (mg/kg body weight per day)	Reference
Dioctyltin (contd)	Rat	DOTC	3 weeks at 75 mg/kg diet ≡ 3.75 mg/kg body weight	Severe thymic atrophy; extensive vacuolation of the reticuloepithelial cells in pregnant animals only	Effects reported at 3.75	Evans et al. (1986)
	Rat	DOTC	6 weeks at 0, 50, or 150 mg/kg diet ≡ 0, 2.5, and 7.5 mg/kg body weight	Decreased cellular immune response, decreased haemolysin titres	Lowest dose at which effect was reported = 2.5	Seinen et al. (1977b)
	Rat	DOTC	8 or 12 weeks at 75 mg/kg diet ≡ 3.75 mg/kg body weight	Decreased thymus weight; histopathology of the thymus: depletion of small thymocytes, septal thickness, loss of cortico-medullary boundaries; loss of circulating leukocytes; impaired ability to respond to mitogenic stimulation; depressed responsiveness to alloantigenic stimulation; humoral response to sheep red blood cells not affected	Effects reported at 3.75	Miller & Scott (1985)
Monooctyltin/ dioctyltin	Rat	MOTC: DOTC (65:35)	3 months at 0, 3, 10, 30, and 100 mg/kg diet ≡ 0, 1.5, 5, 15, and 50 mg/kg body weight	Decreased weight of thymus	NOAEL = 0.87 (males), 0.88 (females)	Ciba-Geigy Ltd (1981)
	Rat	MOTC: DOTC (65:35)	2 years at 0, 5, 15, 50, and 150 mg/kg diet ≡ 0, 0.25, 0.75, 2.5, and 7.5 mg/kg body weight	Thymic lymphoma	**NOAEL = 0.75 (0.23 as DOTC)**	**Ciba-Geigy Ltd (1986)**
	Rat	MOTC: DOTC (94:6)	90 days at 0, 30, 100, 300, and 1000 mg/kg diet ≡ 0, 1.5, 5, 15, and 50 mg/kg body weight	Decreased weight of thymus	LOAEL = 1.5 (females); 5 (males)	TNO (1976)
Neurotoxicity						
Monomethyltin/ dimethyltin	Rat	MMTC: DMTC (11:89)	90-day drinking-water at 0, 25, 75, and 200 mg/l ≡ 0, 2, 6, and 16 mg/kg body weight	Neuropathology	**LOAEL = 2 mg/kg body weight = 1.42 (males), 1.96 (females) as DMTC**	**Rohm & Haas (1999)**

Table 22 (Contd)

Tin compound	Species	Test material	Exposure period and dose	Effects	NOAEL/LOAEL (mg/kg body weight per day)	Reference
Monomethyltin/ dimethyltin (contd)	Rat	MMTC: DMTC (33.5:66.5)	90-day feeding at 0, 1, 6, and 15 mg/kg diet ≡ 0, 0.1, 0.6, and 1 mg/kg body weight	Neuropathology	**NOAEL = 1 mg/kg body weight = 0.62 (males), 0.65 (females) as DMTC**	**Elf Atochem NA (1996)**
Developmental toxicity						
Monomethyltin	Rat	MMTC	8 weeks at 0, 30, 150, and 750 mg/kg diet ≡ 0, 1.5, 7.5, and 37.5 mg/kg body weight	Fertility, developmental toxicity, and maternal toxicity (screening)	NOAEL = 7.5	Appel & Waalkens-Berendsen (2004a)
Dimethyltin	Rat	DMTC	Gestation days 7–17 at 0, 5, 10, 15, and 20 mg/kg body weight	Maternal toxicity; reduction in fetal body weight; reduced thymus weight in dams	LOAEL = 15 NOAEL = 10	Noda (2001)
Monobutyltin	Rat	MBTC	Gestation days 7–17 at 0, 50, 100, 200, and 400 mg/kg body weight	Maternal toxicity; thymic atrophy; dose-dependent developmental toxicity; fetuses with visceral or skeletal abnormalities	NOAEL >400	Noda et al. (1992)
	Rat	MBTC	Gestation days 7–8 at 0, 1000, 1500, and 2000 mg/kg body weight	Maternal body weight Fetal body weight reduced Significant incidence of fetal malformations	LOAEL = 1000 LOAEL = 2000 NOAEL = 2000	Ema et al. (1995)
Dibutyltin	Rat	DBTC	Gestation days 7–15 at 0, 2.5, 5, 7.5, and 10 mg/kg body weight	Maternal toxicity: body weight gain Teratogenicity	LOAEL = 7.5 NOAEL = 5 LOAEL = 5 NOAEL = 2.5	Ema et al. (1991)
	Rat	DBTC	Gestation days 6–15 at 0, 1, 2.5, 5, and 10 mg/kg body weight	Slightly increased incidence of maternal thymic atrophy Incidence of fetuses with malformations slightly increased	LOAEL = 2.5 NOAEL = 1 LOAEL = 10 NOAEL = 5	ORTEPA (1994)
	Rat	DBTC	Gestation days 6–17 at 0, 1, 2.5, 5, and 10 mg/kg body weight	Maternal toxicity; embryotoxicity; malformations	NOAEL = 5	Farr et al. (2001)
Monooctyltin/ dioctyltin	Mouse	DOT stabilizer mix (DOT(IOMA): MOT(IOMA) 80:20)	Gestation days 6–17 at 0, 20, 30, 45, 67, and 100 mg/kg body weight	Embryo/fetal malformations Maternal: thymus weight	LOAEL = 67 NOAEL = 45 LOAEL = 45 NOAEL = 30	Faqi et al. (2001)
	Rat	MOT:DOT thio-glycolates (67:33)	Gestation days 6–15 at 0, 20, 60, and 120 mg/kg body weight	No adverse effects	NOAEL = 120	Ciba-Geigy Ltd (1983)

Table 22 (Contd)

Tin compound	Species	Test material	Exposure period and dose	Effects	NOAEL/LOAEL (mg/kg body weight per day)	Reference
Monooctyltin/ dioctyltin (contd)	Rat	DOT stabilizer mix (DOT(IOMA): MOT(IOMA) 80:20)	Gestation days 6–15 at 0, 1, 5, and 25 mg/kg body weight	Marginal maternal toxicity; marginal but significant embryo-fetal lethal effect	LOAEL = 25 NOAEL = 5	Schering AG (1991)
	Rabbit	DOT stabilizer mix (DOT(IOMA): MOT(IOMA) 80:20)	Gestation days 6–18 at 0, 1, 10, and 100 mg/kg body weight	Marginal retardation of fetal development; marginal maternal toxicity at 100 mg/kg body weight per day	LOAEL = 10 NOAEL = 1	Schering AG (1992)
Monooctyltin	Rat	MOTC	8 weeks at 0, 10, 100, and 500 mg/kg diet ≡ 0, 0.5, 5, and 25 mg/kg body weight	Fertility, developmental toxicity, and maternal toxicity (screening)	NOAEL (maternal) = 5 NOAEL (developmental) = 0.5	Appel & Waalkens-Berendsen (2004b)

MMTC, monomethyltin trichloride; DMTC, dimethyltin dichloride; MBTC, monobutyltin trichloride; DBTC, dibutyltin dichloride; MOT, monooctyltin; MOTC, monooctyltin trichloride; MOT(IOMA), monooctyltin bis(isooctyl mercaptoacetate); DOT, dioctyltin; DOTC, dioctyltin dichloride; DOT(IOMA), dioctyltin bis(isooctyl mercaptoacetate)

Hamasaki et al. (1993) tested a range of organotin compounds in two strains of *Salmonella typhimurium* (TA98 and TA100), without metabolic activation. In the TA98 strain, only dibutyltin dichloride gave a positive result. In the TA100 strain, monobutyltin oxide, monobutyltin trichloride, dibutyltin dichloride, and dimethyltin dichloride were positive. Summer et al. (2003) reviewed studies on dibutyltins and octyltins on yeast; with the exception of a single study on dioctyltin dichloride at the highest concentration tested (10 mg/ml), all were negative.

Hamasaki et al. (1992) reported that monobutyltin oxide, monobutyltin trichloride, and dibutyltin dichloride showed high SOS-inducing potency in the SOS chromotest with *Escherichia coli* PQ 37. Dibutyltin dichloride and dimethyltin dichloride were also recognized as producing DNA damage by the rec-assay in *Bacillus subtilis* H 17 Rec^+ and M45 Rec^-. Li et al. (1982) had earlier reported that dibutyltin dichloride was able to induce mutations in Chinese hamster ovary cells.

The direct and indirect assessment of the aneuploidy-inducing potency of a number of organotin compounds was reported by Jensen et al. (1991a). The effects of dimethyltin dichloride, diphenyltin dichloride, trimethyltin chloride, tributyltin chloride, and triphenyltin chloride at 10^{-3}–10^{-9} mol/l on chromosomal contractions in cultures of human peripheral lymphocytes were investigated. Diphenyltin dichloride, trimethyltin chloride, tributyltin chloride, and triphenyltin chloride appeared to be very strong inducers of chromosomal supercontraction, indicating that these compounds induce aneuploidy, probably by affecting spindle function. Additional studies in V79 Chinese hamster cells and on in vitro assembly of bovine brain tubules by di- and trimethyltin chlorides, di- and tributyltin chlorides, and di- and triphenyltin chlorides all demonstrated effects on mitosis and spindle structure, and all compounds showed a concentration-dependent inhibition of microtubule assembly (Jensen et al., 1991b).

Summer et al. (2003) reviewed 16 in vivo studies on gentoxicity in a range of organotins individually or as mixtures. Of 11 micronucleus tests in mice and rats, one using dibutyltin dichloride was positive (Life Sciences Research Ltd, 1991), with a significant increase in the incidence of micronuclei at 50 mg/kg body weight preferentially in females after 48 and 72 h. The remaining tests were negative. Further, recent micronucleus tests on rats using dioctyltin dichloride and oxide were also negative (Krul, 2003a; de Vogel, 2004). One recent micronucleus test using monomethyltin trichloride was positive (Krul, 2003b); statistically significant increases in micronucleated polychromatic erythrocytes were seen at dose levels of 37, 333, and 1000 mg/kg body weight, but not at 111 mg/kg body weight. The linear trend showed weak significant effect. The substance was considered to be weakly genotoxic. Other in vivo tests (unscheduled DNA synthesis, host-mediated assay/ mouse lymphoma cells, sister chromatid exchange, and covalent DNA binding assays) were all negative (Summer et al., 2003).

8.6 Other toxicities

Dibutyltin dichloride induced acute pancreatitis and bile duct lesions in rats, depending on dose (6 and 8 mg/kg body weight intravenously) and time (1–24 weeks) (Merkord & Hennighausen, 1989; Merkord et al., 1997, 1999; Sparmann et al., 2001). The lesions in the pancreas developed into a pancreatic fibrosis, and the lesions in the liver into liver cirrhosis. A single intravenous administration of dibutyltin dichloride at 4 mg/kg body weight induced a mild interstitial pancreatitis after 2–4 days (Merkord et al., 2001). Repeated administration of dibutyltin dichloride (4 mg/kg body weight intravenously) to rats at intervals of 3 weeks induced acute interstitial pancreatitis and, after 9–12 weeks, a pancreatic fibrosis and liver lesions (intrahepatic bile duct hyperplasia) (Merkord et al., 2001).

8.7 Mode of action

Organotins, particularly dibutyltins (Seinen et al., 1977a; Snoeij et al., 1988), dioctyltins (Seinen & Willems, 1976; Seinen et al., 1977b), and tributyltins (IPCS, 1990), cause a reduction of thymus weight and cellularity in small rodents (see section 8.3.3). A number of possible mechanisms involved in organotin-induced thymus atrophy and subsequent suppression of the T cell–dependent immune responses have been suggested (Snoeij et al., 1988; Pieters et al., 1994a,b,c, 1995). Dialkyltins, particularly dibutyltin dichloride, have been shown to display a strong affinity for dithiol groups and may thus interfere with receptor-dependent communication between intrathymic cells (Penninks & Seinen, 1983; Pieters et al., 1994a).

Various findings together suggest that organotins may have an effect at the level of the cell membrane and/or cytoskeleton, resulting in disturbances of inter- and intracellular communication processes, which are of crucial importance to thymocyte maturation (Pieters et al., 1994a).

In vivo and in vitro studies on the differentiation and proliferation of immature rat thymus subsets have shown that dibutyltin dichloride reduces the production of $CD4^{-}CD8^{+}$ and mature single-positive thymocyte proliferation by selectively inhibiting immature $CD4^{-}CD8^{+}$ thymocyte proliferation but without affecting the differentiation capacity of these cells, suggesting that thymocyte proliferation and differentiation are separately regulated processes (Pieters et al., 1993, 1994a,b, 1995).

Additionally, mechanisms of immunosuppression by organotins have also focused on the role of apoptosis versus proliferation arrest. The apoptotic pathway followed by organotin compounds such as dibutyltin dichloride and tributyltin chloride at high doses is initiated by an increase in intracellular Ca^{2+} concentrations, then continues with release of reactive oxygen species and cytochrome c from the mitochondria and activation of caspases in rat thymocytes (in vitro), and finally results in DNA fragmentation (Gennari et al., 2000). Tributyltin chloride is significantly more potent than dibutyltin dichloride in inducing these intracellular changes. Further studies by Gennari et al. (2002) to characterize by a cDNA macroarray the expression of genes involved in dibutyltin dichloride–induced apoptosis found that nur-77 is a transcription factor expressed in response to T cell receptor–mediated apoptosis in immature T cells. Antisense oligonucleotide inhibition of nur-77 expression prevented apoptosis induced by dibutyltin dichloride, supporting a role of nur-77 in organotin-induced apoptotic cell death.

9. EFFECTS ON HUMANS

One of six workers died 12 days after exposure to a mixture of half dimethyltin dichloride and half trimethyltin chloride vapour during cleaning of a cauldron at a chemical plant in Germany in 1981. Maximum exposure time was 1.5 h over a 3-day period; no estimates of exposure concentration were made. Symptoms preceding death included excretion of high levels of tin in the urine, respiratory depression, and coma (Rey et al., 1984). Two of the surviving workers developed neurological disabilities (still in evidence 6 years later), but respiratory problems did not persist. The remaining survivors experienced memory loss. Fortemps et al. (1978) reported symptoms developed by two chemists in a small pilot plant in Belgium for the synthesis of dimethyltin dichloride intermittently exposed to vapours of dimethyltin and trimethyltin chlorides for about 3 months. Both abruptly developed mental confusion with generalized epileptic seizures. Before this episode, both had complained of headaches, pain in various organs, and psychological disturbances, such as memory defects, vigilance loss, insomnia, anorexia, and disorientation. Both became asymptomatic following removal from exposure. Ross et al. (1981) studied 22 male chemical workers exposed to trimethyltin chloride during 1978 in a plant in the United States following a spillage (inhalation and dermal exposure presumed). They compared symptoms between individuals who had experienced high or low exposure. The high exposure group showed significantly higher incidence of non-specific symptoms, such as forgetfulness, fatigue, weakness, and loss of motivation, and specific symptoms, such as bouts of depression and attacks of rage; some symptoms persisted for at least 3 years. Yanofsky et al. (1991) and Feldman et al. (1993) described symptoms of a 23-year-old male university chemistry student accidentally exposed to vapours of trimethyltin. The

symptoms, which developed 72 h after the exposure, included delirium, spatial disorientation, and memory loss. Five months later, the man developed complex partial seizures, which required anticonvulsive medication for 7 years. Tests 4 years after exposure showed persistent memory defects, cognitive dysfunction, and dysphoria. All of these reports of symptomatic effects following spillages relate to trimethyltin, which is known to cause neuropathology in rodents and humans; results may not, therefore, be relevant to other organotins.

A Witco (1994) study involved 83 workers. Clinical abnormalities were noted as slightly decreased ratios of T helper/inducer and T suppressor/cytotoxic cells in 6 of 83 and 9 of 83 samples, respectively. No correlation in the number of T helper and T suppressor cells to the number of years of occupational organotin exposure was found. The organotins were unspecified. Urinary tin in the exposed group was not reported. A study by Atochem (Baaijens, 1992) involving 46 employees working in the production of unspecified organotin compounds and 44 controls showed an increased percentage of T lymphocytes, T helper, and T suppressor cells in the exposed group. No test for significance was presented. Urinary tin in the exposed group was 5.5 µg/ml, significantly higher than in controls (2.8 µg/ml).

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

A substantial volume of information has been reviewed for the environmental effects assessment. Much of this is in the public domain, but various additional unpublished information has been supplied by industry. For the purposes of the environmental effects assessment, the focus is on the freshwater environment.

Data on the toxicity of the various organotin species to aquatic organisms are summarized in Table 23.

10.2 Terrestrial environment

Effects on terrestrial organisms are reported only for mixtures of mono- and dimethyltin compounds (50:50 and 25:75), with 14-day LC_{50} values of 320 and >1000 mg/kg (as chloride), respectively, in the earthworm (*Eisenia foetida*); respective NOECs were 100 and 1000 mg/kg (as chloride) (Wilbury, 1995a,b, 1996).

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

The organotins covered in this assessment have low acute toxicity to laboratory mammals, with most studies indicating LD_{50}s above 100 mg/kg body weight, and many above 1000 mg/kg body weight.

In sensitization tests, dimethyltins showed one positive and one negative result; a mixture of di- and monomethyltins was negative. Dibutyltins were non-sensitizing, but mixtures of mono- and dibutyltins showed slight to strong sensitization (di- and monobutyltin in the mixture as isooctylthioglycolates increased the sensitization response). Mixtures of mono- and dioctyltins showed slight to strong sensitization (higher proportions of dioctyltin as the ethylhexylthioglycolate increased the sensitization rate).

Studies on irritation are highly variable, with reports ranging from non-irritating to severely irritating for the same compound. The compounds should be regarded as irritating to skin and eyes. Similar variation occurs in sensitization tests, and the database should be regarded as inadequate to draw firm conclusions; however, it would be sensible and precautionary to regard the organotins assessed here as sensitizing.

Short- to medium-term exposure has shown neurotoxicity, developmental toxicity, immunotoxicity, and endocrine disruption to be relevant end-points. Table 24 summarizes the critical studies for each compound and identifies NOAELs or LOAELs. The degree of each of the toxic end-points differs across the group as a whole. For example, tributyltin is well established as an aromatase inhibitor, and dibutyltin appears to have some potency also (exact characterization of the endocrine disrupting capacity of dibutyltin alone is difficult because of the presence of tributyltin as an impurity). Monobutyltin and mono- and dioctyltins have no aromatase inhibiting capacity in in vitro tests. No data are available for this end-point for the methyltins.

The vast majority of in vivo tests show no genotoxicity of mono- and dialkyltins. Results from in vitro tests are variable, with little indication of DNA reactivity. There are, however, indications of clastogenicity and effects on spindle formation in mitosis in vitro.

Brief summaries were available for unpublished long-term studies for some of the organotins under consideration. These showed no carcinogenicity for mixtures of mono- and dimethyltins in rats and mono- or

Table 23: Toxicity of organotin compounds to aquatic organisms.

Species	Test compound	End-point	Concentration (mg/l)	Concentration (mg organotin chloride/l)	Reference
Monomethyltin					
Freshwater					
Green alga (*Ankistrodesmus falcatus*)	MMTC	24-h EC_{50} (primary productivity)	46.5	46.5	Wong et al. (1982)
Green alga (*Scenedesmus subspicatus*)	MMTC	72-h EC_{50} (growth rate)	0.03	0.03	Oldersma et al. (2003a)
Green alga (*Scenedesmus subspicatus*)	MMTC	72-h NOEC (growth rate)	0.007	0.007	Oldersma et al. (2003a)
Green alga (*Scenedesmus subspicatus*)	MMT(EHMA)	72-h EC_{50} (growth rate)	>1.84	>0.6	Oldersma et al. (2004a)
Green alga (*Scenedesmus subspicatus*)	MMT(EHMA)	72-h NOEC (growth rate)	0.6	0.19	Oldersma et al. (2004a)
Daphnid (*Daphnia magna*)	MMTC	24-h EC_{50} (immobilization)	90	90	Vighi & Calamari (1985)
Daphnid (*Daphnia magna*)	MMTC	48-h EC_{50} (immobilization)	>101	>101	Hooftman & de Wolf (2003a)
Daphnid (*Daphnia magna*)	MMT(IOMA)	48-h EC_{50} (immobilization)	2.9	0.9	Steinhäuser et al. (1985)
Daphnid (*Daphnia magna*)	MMT(EHMA)	21-day NOEC (reproduction and mortality)	0.14	0.05	de Roode & de Haan (2004a)
Fathead minnow (*Pimephales promelas*)	MMTC	96-h LC_{50}	320	320	Ward et al. (1996a)
Zebrafish (*Brachydanio rerio*)	MMTC	96-h LC_{50}	>102	>102	Hooftman & de Wolf (2003b)
Zebrafish (*Brachydanio rerio*)	MMT(EHMA)	96-h LC_{50}	>6	>1.9	Migchielsen (2004a)
Marine					
Diatom (*Skeletonema costatum*)	MMTC	72-h EC_{50} (growth rate)	0.16	0.16	Walsh et al. (1985)
Diatom (*Skeletonema costatum*)	MMTC	96-h EC_{50} (growth rate)	5.8	5.8	Morton International, Inc. (1996a)
Diatom (*Skeletonema costatum*)	MMTC	96-h NOEC (growth rate)	1.0	1.0	Morton International, Inc. (1996a)
Diatom (*Thalassiosira pseudonana*)	MMTC	72-h EC_{50} (growth rate)	0.69	0.69	Walsh et al. (1985)
Dimethyltin					
Freshwater					
Green alga (*Scenedesmus obliquus*)	DMTC	96-h EC_{50} (growth rate)	1.1	1.1	Huang et al. (1993)
Green alga (*Scenedesmus subspicatus*)	DMTC	96-h EC_{50} (growth rate)	37	37	Oldersma et al. (2003b)
Green alga (*Scenedesmus subspicatus*)	DMTC	96-h NOEC (growth rate)	1.1	1.1	Oldersma et al. (2003b)
Green alga (*Scenedesmus subspicatus*)	DMT(IOMA)	96-h EC_{50} (growth rate)	>0.07	>0.03	Steinhäuser et al. (1985)
Green alga (*Selenastrum capricornutum*)	DMT(EHMA)	96-h EC_{50} (growth rate)	260	103	Ward et al. (1995a)
Green alga (*Selenastrum capricornutum*)	DMT(EHMA)	96-h NOEC (growth rate)	100	39.6	Ward et al. (1995a)
Green alga (*Scenedesmus quadricauda*)	DMTC	24-h EC_{50} (primary productivity)	7.6	7.6	Wong et al. (1982)

Table 23 (Contd)

Species	Test compound	End-point	Concentration (mg/l)	Concentration (mg organotin chloride/l)	Reference
Green alga (*Ankistrodesmus falcatus*)	DMTC	24-h EC_{50} (primary productivity)	38.9	38.9	Wong et al. (1982)
Daphnid (*Daphnia magna*)	DMTC	24-h EC_{50} (immobilization)	88	88	Vighi & Calamari (1985)
Daphnid (*Daphnia magna*)	DMTC	48-h EC_{50} (immobilization)	17	17	Hooftman & de Wolf (2003c)
Daphnid (*Daphnia magna*)	DMT(IOMA)	48-h EC_{50} (immobilization)	>0.13	>0.05	Steinhäuser et al. (1985)
Daphnid (*Daphnia magna*)	DMT(EHMA)	48-h EC_{50} (immobilization)	32	12.1	Ward et al. (1995b)
Daphnid (*Daphnia magna*)	DMT(EHMA)	21-day NOEC (reproduction)	0.5	0.2	de Roode & de Haan (2004a)
Fathead minnow (*Pimephales promelas*)	DMTC	96-h LC_{50}	320	320	Ward et al. (1996a)
Fathead minnow (*Pimephales promelas*)	DMT(EHMA)	96-h LC_{50}	>1000	>1000	Ward et al. (1995c)
Zebrafish (*Brachydanio rerio*)	DMTC	96-h LC_{50}	>100	>100	Hooftman & de Wolf (2003d)
Marine					
Diatom (*Skeletonema costatum*)	DMTC	72-h EC_{50} (growth rate)	>0.93	>0.93	Walsh et al. (1985)
Diatom (*Skeletonema costatum*)	DMTC	96-h EC_{50} (growth rate)	>9.8	>9.8	Morton International, Inc. (1996b)
Diatom (*Skeletonema costatum*)	DMTC	96-h NOEC (growth rate)	4.9	4.9	Morton International, Inc. (1996b)
Diatom (*Thalassiosira pseudonana*)	DMTC	72-h EC_{50} (growth rate)	>0.93	>0.93	Walsh et al. (1985)
Mysid shrimp (*Mysidopsis bahia*)	DMTC	96-h LC_{50}	170	170	Ward et al. (1996b)
Brine shrimp (*Artemia franciscana*)	DMTC	24-h LC_{50}	148	148	Hadjispyrou et al. (2001)
Sheepshead minnow (*Cyprinodon variegates*)	DMTC	96-h LC_{50}	>1000	>1000	Boeri et al. (1995)
Monobutyltin					
Freshwater green alga (*Ankistrodesmus falcatus*)	MBTC	24-h EC_{50} (primary productivity)	59.4	59.4	Wong et al. (1982)
Daphnid (*Daphnia magna*)	MBTC	24-h EC_{50} (immobilization)	49	49	Vighi & Calamari (1985)
Daphnid (*Daphnia magna*)	MBTC	48-h EC_{50} (immobilization)	25	25	ACIMA AG (1992)
Medaka (*Oryzias latipes*)	MBTC	48-h LC_{50}	38	38	Nagase et al. (1991)
Dibutyltin					
Freshwater					
Green alga (*Ankistrodesmus falcatus*)	DBTC	24-h EC_{50} (primary productivity)	17.4	17.4	Wong et al. (1982)
Green alga (*Scenedesmus obliquus*)	DBTC	96-h EC_{50} (growth rate)	0.04	0.04	Huang et al. (1993)
Green alga (*Scenedesmus subspicatus*)	DBTL	72-h EC_{50} (growth rate)	>saturated solution (~3 mg/l)	>saturated solution (~1.4 mg/l)	Schering AG (1999a)

Table 23 (Contd)

Species	Test compound	End-point	Concentration (mg/l)	Concentration (mg organotin chloride/l)	Reference
Green alga (*Scenedesmus subspicatus*)	DBTO	72-h EC_{50} (growth rate)	>saturated solution (~1.6 mg/l)	>saturated solution (~2 mg/l)	Schering AG (1999b)
Green alga (*Scenedesmus subspicatus*)	DBTM	72-h EC_{50} (growth rate)	4.1	3.6	Oldersma et al. (2003c)
Green alga (*Scenedesmus subspicatus*)	DBTM	72-h NOEC (growth rate)	0.9	0.8	Oldersma et al. (2003c)
Daphnid (*Daphnia magna*)	DBTC	48-h EC_{50} (immobilization)	1.4	1.4	ABC (1990a)
Daphnid (*Daphnia magna*)	DBTC	24-h EC_{50} (immobilization)	0.9	0.9	Vighi & Calamari (1985)
Daphnid (*Daphnia magna*)	DBTL	24-h EC_{50} (immobilization)	0.7	0.3	Steinhäuser et al. (1985)
Daphnid (*Daphnia magna*)	DBTL	48-h EC_{50} (immobilization)	<1	<0.5	Schering AG (1999c)
Daphnid (*Daphnia magna*)	DBTO	48-h EC_{50} (immobilization)	1.5	1.8	Schering AG (1998a)
Daphnid (*Daphnia magna*)	DBTM	48-h EC_{50} (immobilization)	0.21	0.18	Hooftman & de Wolf (2003e)
Daphnid (*Daphnia magna*)	DBT(EHMA)	48-h EC_{50} (immobilization)	>saturated solution (~1.5 mg/l)	>saturated solution (~0.7 mg/l)	Schering AG (1998b)
Daphnid (*Daphnia magna*)	DBT(EHMA)	48-h EC_{50} (immobilization)	0.04	0.02	Ciba-Geigy Ltd (1993a)
Daphnid (*Daphnia magna*)	DBTC	21-day NOEC (survival and reproduction)	0.015 = highest concentration tested	0.015	ABC (1990b)
Zebrafish (*Brachydanio rerio*)	DBTL	96-h LC_{50}	>saturated solution (~2 mg/l)	>saturated solution (~1 mg/l)	Schering AG (1998c)
Zebrafish (*Brachydanio rerio*)	DBTO	96-h LC_{50}	>saturated solution (~3 mg/l)	>saturated solution (~3.7 mg/l)	Schering AG (1998d)
Zebrafish (*Brachydanio rerio*)	DBTM	96-h LC_{50}	>5.7	>5.7	Hooftman & de Wolf (2003f)
Zebrafish (*Brachydanio rerio*)	DBT(EHMA)	96-h LC_{50}	>saturated solution (~10 mg/l)	>saturated solution (~5 mg/l)	Schering AG (1998e)
Medaka (*Oryzias latipes*)	DBTC	48-h LC_{50}	5.8	5.8	Nagase et al. (1991)
Medaka (*Oryzias latipes*)	DBTO	48-h LC_{50}	0.8	1.0	Nagase et al. (1991)
Medaka (*Oryzias latipes*)	DBTM	48-h LC_{50}	13	11	Nagase et al. (1991)
Medaka (*Oryzias latipes*)	DBTL	48-h LC_{50}	2	0.9	Nagase et al. (1991)
Golden orfe (*Leuciscus idus*)	DBTC	48-h LC_{50}	0.6	0.6	Steinhäuser et al. (1985)
Golden orfe (*Leuciscus idus*)	DBTL	48-h LC_{50}	2	0.9	Steinhäuser et al. (1985)
Medaka (*Oryzias latipes*)	DBTC	28-day NOEC (mortality, growth, and behaviour)	1.8	1.8	Wester & Canton (1987)
Rainbow trout (*Oncorhynchus mykiss*)	DBTC	110-day NOEC (survival and growth)	0.04	0.04	de Vries et al. (1991)
Marine					
Diatom (*Skeletonema costatum*)	DBTC	72-h EC_{50} (growth rate)	0.1	0.1	Walsh et al. (1985)

Table 23 (Contd)

Species	Test compound	End-point	Concentration (mg/l)	Concentration (mg organotin chloride/l)	Reference
Diatom (*Thalassiosira pseudonana*)	DBTC	72-h EC_{50} (growth rate)	0.46	0.46	Walsh et al. (1985)
Diatom (*Skeletonema costatum*)	DBTA	72-h EC_{50} (growth rate)	0.1	0.09	Walsh et al. (1985)
Diatom (*Thalassiosira pseudonana*)	DBTA	72-h EC_{50} (growth rate)	0.38	0.32	Walsh et al. (1985)
Brine shrimp (*Artemia franciscana*)	DBTA	24-h LC_{50}	264	229	Hadjispyrou et al. (2001)
Sheepshead minnow (*Cyprinodon variegatus*)	DBTC	191-day NOEC (survival, growth, and fecundity)	0.45	0.45	Elf Atochem NA (1992)
Monooctyltin					
Freshwater					
Green alga (*Scenedesmus subspicatus*)	MOTC	72-h EC_{50} (growth rate)	0.22	0.22	Oldersma et al. (2003d)
Green alga (*Scenedesmus subspicatus*)	MOTC	72-h NOEC (growth rate)	0.05	0.05	Oldersma et al. (2003d)
Green alga (*Scenedesmus subspicatus*)	MOT(EHMA)	72-h EC_{50} (growth rate)	>0.5	>0.2	Oldersma et al. (2004b)
Green alga (*Scenedesmus subspicatus*)	MOT(EHMA)	72-h NOEC (growth rate)	0.007	0.003	Oldersma et al. (2004b)
Green alga (*Scenedesmus subspicatus*)	MOT(EHMA)	72-h EC_{50} (growth rate)	0.71	0.3	Ciba-Geigy Ltd (1993b)
Daphnid (*Daphnia magna*)	MOTC	48-h EC_{50} (immobilization)	>solubility limit (0.3 mg/l)	>solubility limit (0.3 mg/l)	Schering AG (1998f)
Daphnid (*Daphnia magna*)	MOT(EHMA)	48-h EC_{50} (immobilization)	1	0.4	Ciba-Geigy Ltd (1993c)
Daphnid (*Daphnia magna*)	MOT(EHMA)	21-day NOEC (reproduction)	0.04	0.016	de Roode & de Haan (2004b)
Zebrafish (*Brachydanio rerio*)	MOTC	96-h LC_{50}	>solubility limit (0.3 mg/l)	>solubility limit (0.3 mg/l)	Schering AG (1998g)
Zebrafish (*Brachydanio rerio*)	MOT(EHMA)	96-h LC_{50}	>2.3	>0.9	Migchielsen (2004b)
Zebrafish (*Brachydanio rerio*)	MOT(EHMA)	96-h LC_{50}	73	29.4	Ciba-Geigy Ltd (1993d)
Dioctyltin					
Freshwater					
Green alga (*Scenedesmus subspicatus*)	DOTC	72-h EC_{50} (growth rate)	>saturated solution (~0.002 mg/l)	>saturated solution (~0.002 mg/l)	Ciba-Geigy Ltd (1988a)
Green alga (*Scenedesmus subspicatus*)	DOTO	72-h EC_{50} (growth rate)	>saturated solution (~0.002 mg/l)	>saturated solution (~0.002 mg/l)	Ciba-Geigy Ltd (1988b)
Green alga (*Scenedesmus subspicatus*)	DOT(EHMA)	72-h EC_{50} (growth rate)	>solubility (~0.07 mg/l)	>solubility (~0.07 mg/l)	Ciba-Geigy Ltd (1988c)
Green alga (*Scenedesmus subspicatus*)	DOT(EHMA)	72-h EC_{50} (growth rate)	0.17	0.09	Ciba-Geigy Ltd (1993e)
Green alga (*Scenedesmus subspicatus*)	DOT(EHMA)	72-h NOEC (growth rate)	0.04	0.02	Ciba-Geigy Ltd (1993e)
Daphnid (*Daphnia magna*)	DOTC	24-h EC_{50} (immobilization)	>saturated solution (~0.0045 mg/l)	>saturated solution (~0.0045 mg/l)	Ciba-Geigy Ltd (1988d)
Daphnid (*Daphnia magna*)	DOTC	48-h EC_{50} (immobilization)	>0.28	>0.28	Hooftman & de Wolf (2003g)

Table 23 (Contd)

Species	Test compound	End-point	Concentration (mg/l)	Concentration (mg organotin chloride/l)	Reference
Daphnid (*Daphnia magna*)	DOTO	24-h EC_{50} (immobilization)	>saturated solution	>saturated solution	Ciba-Geigy Ltd (1988e)
Daphnid (*Daphnia magna*)	DOTO	48-h EC_{50} (immobilization)	>solubility (0.21 mg/l)	>solubility (0.26 mg/l)	Hooftman & de Wolf (2004a)
Daphnid (*Daphnia magna*)	DOT(EHMA)	24-h EC_{50} (immobilization)	>solubility (~0.07 mg/l)	>solubility (~0.04 mg/l)	Ciba-Geigy Ltd (1988f)
Daphnid (*Daphnia magna*)	DOT(EHMA)	48-h EC_{50} (immobilization)	0.17	0.09	Ciba-Geigy Ltd (1993f)
Daphnid (*Daphnia magna*)	DOTC	21-day NOEC (survival and growth)	0.4	0.4	Schering AG (1999d)
Daphnid (*Daphnia magna*)	DOT(EHMA)	21-day NOEC (growth and reproduction)	0.3	0.17	de Roode & de Haan (2004b)
Zebrafish (*Brachydanio rerio*)	DOTC	96-h LC_{50}	>0.24	>0.24	Hooftman & de Wolf (2003h)
Zebrafish (*Brachydanio rerio*)	DOTO	96-h LC_{50}	>0.09	>0.1	Hooftman & de Wolf (2004b)
Zebrafish (*Brachydanio rerio*)	DOT(EHMA)	96-h LC_{50}	>24.8	>13.6	Migchielsen (2004c)
Zebrafish (*Brachydanio rerio*)	DOT(EHMA)	96-h LC_{50}	>5.8	>3.2	Ciba-Geigy Ltd (1993g)

MMTC, monomethyltin trichloride; MMT(EHMA), monomethyltin tris(2-ethylhexylmercaptoacetate); MMT(IOMA), monomethyltin bis(isooctyl mercaptoacetate); DMTC, dimethyltin dichloride; DMT(EHMA), dimethyltin bis(2-ethylhexylmercaptoacetate); DMT(IOMA), dimethyltin bis(isooctyl mercaptoacetate); MBTC, monobutyltin trichloride; DBTC, dibutyltin dichloride; DBTA, dibutyltin diacetate; DBTL, dibutyltin dilaurate; DBTO, dibutyltin oxide; DBTM, dibutyltin maleate; DBT(EHMA), dibutyltin bis(2-ethylhexylmercaptoacetate); MOTC, monooctyltin trichloride; MOT(EHMA), monooctyltin tris(2-ethylhexylmercaptoacetate); DOTC, dioctyltin dichloride; DOTO, dioctyltin oxide; DOT(EHMA), dioctyltin bis(2-ethylhexylmercaptoacetate); DOT(IOMA), dioctyltin bis(isooctyl mercaptoacetate)

dioctyltins in rats or dogs, except for a single study on a mixture of mono- and dioctyltin chlorides. This showed significantly increased frequency of thymic lymphomas in female rats only at the 150 mg/kg diet dose. Significant increases were seen in the incidence of generalized malignant lymphomas in males of the 50 and 150 mg/kg groups, but only in females at the highest dose.

11.1.2 Criteria for setting tolerable intakes and tolerable concentrations

Based upon the review of the toxicological data, reliable lifetime TDI values for the organotin species in question cannot be derived, since long-term studies at the appropriate doses and in the appropriate species are not available. Medium-term exposure results have therefore been used to derive TDIs for preliminary risk characterization. For dimethyltin, there is a reliable NOAEL as a basis for setting a TDI against a neurotoxicity end-point. For the remaining compounds, best estimates of amedium-term exposure TDI for preliminary risk characterization have been derived from the available studies (Table 25).

Uncertainty factors applied are precautionary ones. In addition to an uncertainty factor of 10 for intraspecies and 10 for interspecies variation, an additional factor of 5 has been applied to the methyltins given the lack of, or limited, data available for end-points other than neurotoxicity. A further factor of 10 was applied to dibutyltin on top of the 100 for intra- and interspecies variation because the critical end-point was the same as that for tributyltin, but a substantially smaller immunotoxicity research database was available for the dibutyltin. It should be emphasized that these are working estimates of TDIs for the purposes of calculating provisional risk and the prioritization of possible risk management.

11.1.3 Sample risk characterization

Based upon the various sources of adult consumer exposure to organotin compounds (section 6) and the TDI values derived above, it is possible to estimate the relative exposure from the various organotin compounds expressed as a percentage of the TDI values. The exposure calculations in section 6 were based on a realistic worst-case exposure assessment. Table 26 presents the results of this risk characterization.

Based upon the information in Table 26, it can be seen that the TDI for each organotin is not exceeded for any of the consumer products under investigation. The

Table 24: Summary of critical toxicological data in laboratory mammals.[a]

Organotin	Neurotoxicity	Developmental toxicity	Endocrine disruption	Immunotoxicity
Monomethyltin	Limited information (based on DMTC NOAEL >0.6 mg/kg body weight per day[b])	No data available	No data available	Limited data; thymus weight unaffected at 5 mg/kg body weight per day (as MMTC)
Dimethyltin	Yes. NOAEL = 0.6 (neuropathology) mg/kg body weight per day (as DMTC)	Yes. NOAEL = 10 (maternal and fetal toxicity) mg/kg body weight per day (as DMTC)	No data available	Limited data; thymus weight unaffected at 5 mg/kg body weight per day (as DMTC)
Monobutyltin	No data available	No. NOAELs >400–2000 mg/kg body weight per day (as MBTC)	No aromatase inhibition in vitro	No data available
Dibutyltin	No significant neurotoxicity reported	Yes. NOAEL = 2.5 (teratogenicity) and 1.0/5.0 (maternal toxicity) mg/kg body weight per day (as DBTC)	Aromatase inhibition present (at least 10 times less potent than tributyltin); no imposex in vivo in invertebrates	Yes. NOAEL could not be determined; lowest dose reported to cause immunological effects = 2.5 mg/kg body weight per day (as DBTC)
Monooctyltin	No neurotoxicity reported in 90-day studies	Teratogenicity appears to be low (NOAEL = 120 mg/kg body weight per day) based on one study on a monooctyltin/dioctyltin mixture at 67:33	No aromatase inhibition in vitro	NOAEL = 0.87 (decreased thymus weight) mg/kg body weight per day (as MOTC/DOTC mixture 65:35[c])
Dioctyltin	No neurotoxicity reported in 90-day studies	Yes. NOAEL = 45 (teratogenicity) and 30 (maternal toxicity: thymus weight) mg/kg body weight per day (as dioctyltin diisooctylthioglycolate:monooctyltin triisooctylthioglycolate mixture 80:20)	No aromatase inhibition in vitro	NOAEL = 0.23 (thymus lymphoma) mg/kg body weight per day (as DOTC calculated from MOTC:DOTC mixture)

[a] The individual studies from which these critical NOAELs are derived are indicated in Table 22 in section 8 in bold type.

[b] The database for monomethyltin is not conclusive for neurotoxic effects, and, therefore, a NOAEL could not be determined. However, on the basis of 90-day studies on monomethyltin/dimethyltin mixtures detailing histopathology, dose comparisons between studies on different mixtures suggest that dimethyltin is the predominant active ingredient, and, taking into account structure–activity relationships, it would be expected that the neurotoxicity of monomethyltin is lower than that of dimethyltin.

[c] Since the immunotoxicity of monooctyltin is likely to be lower than that for dioctyltin, it is difficult to extrapolate from this study on a monooctyltin:dioctyltin mixture to a critical end-point concentration for monooctyltin alone. With monooctyltin compounds alone, immunotoxicity appears to play a subordinate role. Significant effects on thymus weight appeared only at 150 mg/kg body weight for monooctyltin tris(2-ethylhexylmercaptoacetate) (20 mg of tin per kilogram body weight) in a subchronic (90-day) toxicity study on rats (Seinen & Penninks, 1979; Boyer, 1989).

results for dibutyltin suggest a cause for concern from its use in baking paper; including the risk factor for tributyltin (a contaminant of commercial dibutyltin) would suggest approaching the TDI (71%) for a combination of all butyltins. It is understood that organotins have been withdrawn from use in baking papers as a result of this concern.

The value for dioctyltin is primarily due to the use of octyltin stabilizers in PVC processing.

Table 27 presents the results of the child consumer exposure scenario in the same manner as for the adult scenario. Again, the exposure from each source is expressed in relation to the TDI.

Based on the information in the tables, it can be seen that the TDI for each organotin is not exceeded for any of the consumer products except for the case of cookies. For cookies, the TDI for dibutyltin is exceeded, but it is noted that this use has been discontinued worldwide (personal communication to IPCS, 2006).

The exceeded value for children via the environment from exposure to dioctyltin (356% of the TDI) relates to the consumption of local produce close to a PVC processing plant and largely derives from default values on release to the environment. Further refinement of this exposure assessment is currently under way. Until this is clarified, dioctyltin remains a compound of concern via this exposure route for children.

Table 25: Estimates of TDI for use in the risk assessment on the basis of medium-term exposure.

Organotin	TDI (µg/kg body weight) as chloride	TDI (µg/kg body weight) as tin	Toxicity	Uncertainty factor
Monomethyltin	1.2	0.6	Neurotoxicity[a]	500
Dimethyltin	1.1	0.6	Neurotoxicity[a]	500
Monobutyltin			No available data	
Dibutyltin	2.6	1.0	Immunotoxicity	1000
Monooctyltin			Insufficient data to establish a TDI; indications that MOT less immunotoxic than DOT	
Dioctyltin	2.1	0.6	Immunotoxicity	100

[a] Dimethyltin/monomethyltin neurotoxicity studies (2 × 90 day; one drinking-water, one food) were performed using mixtures. The NOAEL is based on measured dimethyltin intake. Dimethyltin is assumed to be the more neurotoxic of the two. The suggested TDI for monomethyltin is therefore highly conservative.

Table 26: Worst-case adult consumer risk characterization as percentage of TDI.

	Percentage of TDI				
	Monomethyltin	Dimethyltin	Dibutyltin	Tributyltin[a]	Dioctyltin
Food wrapped in PVC	12	12			9.4
PVC gloves			3.3	0.4	
Sanitary pantiliners					10
Cookies (from baking paper)[b]			61	10	
Indoor air[c]	0.7	1.5	0.8	1.0	0.7
Dental mouldings			4.6		
Earplugs			<0.1	<0.1	
Via the environment (worst-case local)[d]	0.1	0.1	0.3		89

[a] Tributyltin risk calculations are based on a reliable TDI at 0.27 µg/kg body weight per day as chloride (IPCS, 1999a); tributyltin is included here as a contaminant of commercial dibutyltin.
[b] Information from industry indicates that this use of organotins has been discontinued worldwide (personal communication to IPCS, 2006).
[c] Exposure via house dust (which has been measured as containing organotins) was also considered; it is likely that inhalation exposure indoors includes house dust, which picks up leached organotins from vinyl flooring.
[d] "Via the environment" relates to the consumption of local produce close to a PVC processing plant and largely derives from default values on release to the environment

Table 27: Worst-case child consumer risk characterization as percentage of TDI.

	Percentage of TDI				
	Monomethyltin	Dimethyltin	Dibutyltin	Tributyltin[a]	Dioctyltin
Nappies/diapers			1.3	7.4	
Cookies (from baking paper)[b]			229	38	
Paddling pool water			0.3	0	
Food wrapped in PVC	47	47			38
T-shirt (printed)			0.2	15	170
Indoor air[c]	1.6	3.5	1.9	7.8	1.6
PVC toys	negligible	negligible	negligible	negligible	negligible
Via the environment (worst-case local)[d]	0.2	0.3	1.3		356

[a] Tributyltin risk calculations are based on a reliable TDI at 0.27 µg/kg body weight per day as chloride (IPCS, 1999a); tributyltin is included here as a contaminant of commercial dibutyltin.
[b] Information from industry indicates that this use of organotins has been discontinued worldwide (personal communication to IPCS, 2006).
[c] Exposure via house dust (which has been measured as containing organotins) was also considered; it is likely that inhalation exposure indoors includes house dust, which picks up leached organotins from vinyl flooring.
[d] "Via the environment" relates to the consumption of local produce close to a PVC processing plant and largely derives from default values on release to the environment; the uptake via the environment is derived from the adult figures multiplied by four to account for a higher food intake per unit body weight.

11.2 Evaluation of environmental effects

11.2.1 Hazard identification

The organotins are sparingly soluble in water, particularly with the anionic ligands that are present in the commercial products; these tend to hydrolyse in the environment to form the basic organotin moiety, which is the part of the compound of toxicological significance. Modelling tends to overestimate bioaccumulation potential and underestimate binding to organic carbon, sediments, and soils as a result of this initial hydrolysis. Measured binding to organic carbon suggests that this is significant and a major determinant of environmental fate. Measured BCFs confirm a much lower likelihood of accumulation than would be suggested by the K_{ow}. All commercial compounds show ready biodegradability in standard OECD tests; however, there is uncertainty as to how far biodegradation proceeds in the test protocol, and modelling of exposure has been done on the precautionary assumption that the compounds are inherently degradable (half-life set at 150 days).

Data sets on toxicity to aquatic organisms vary considerably from compound to compound, with dibutyltin being the best studied. Results of toxicity tests for all compounds are summarized in Figure 2. Values for all but one test on the octyltins have been set at the solubility of the compounds, since no toxicity was observed below the solubilities; derivation of PNECs for the octyltins are, therefore, more precautionary than for the other compounds.

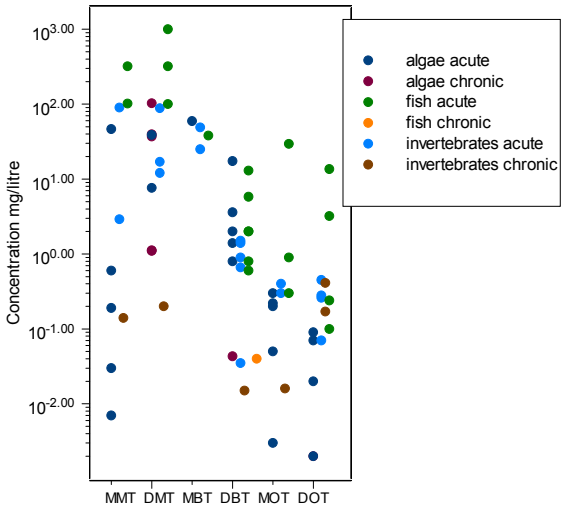


Fig. 2. Acute toxicity of organotin compounds to freshwater aquatic organisms.

11.2.2 Derivation of PNECs in fresh water

Table 28 outlines the critical end-points for the organotin species and the estimated PNECs derived using appropriate uncertainty factors. For the purposes of comparability, all values have been converted to the chloride salt.

There are insufficient data to conduct a probabilistic estimate of no-effect concentrations. For each of the organotins, the following outlines the reasoning for selection of studies and application of uncertainty factors:

- *Monomethyltin*: Acute toxicity studies were identified for monomethyltin for algae, invertebrates, and fish. Chronic NOECs were available for algae and invertebrates. A chronic NOEC of 0.007 mg/l for monomethyltin chloride in *Scenedesmus subspicatus* was the lowest reported result. Since there were no long-term test results available for fish, it was necessary to apply an uncertainty factor of 50 to the critical study.

- *Dimethyltin*: Acute toxicity studies were identified for dimethyltin for algae, invertebrates, and fish. Chronic NOECs were available for algae and invertebrates. A chronic NOEC of 0.2 mg/l for dimethyltin chloride in *Daphnia magna* was the lowest reported result; the result has been corrected to the chloride salt for comparison with the majority of test results. Since there were no long-term test results available for fish, it was necessary to apply an uncertainty factor of 50 to the critical study.

- *Monobutyltin*: Four acute toxicity studies were identified for monobutyltin chloride. The critical study was an acute EC_{50}, based on immobilization, for *Daphnia magna* at a concentration of 25 mg/l. All four tests were acute, and, in the absence of long-term tests, it was decided to apply an uncertainty factor of 1000.

- *Dibutyltin*: A larger data set exists for dibutyltin, including both acute and long-term test results. The lowest concentration identified was a chronic NOEC of 0.015 mg/l for *Daphnia magna* exposure to dibutyltin chloride. Long-term values were available across three trophic levels, and, therefore, an uncertainty factor of 10 was considered appropriate.

- *Monooctyltin*: Acute toxicity studies were identified for monooctyltin for invertebrates and fish. Chronic NOECs were available for algae and invertebrates. A chronic NOEC of 0.003 mg/l for monooctyltin chloride in *Scenedesmus subspicatus* was the lowest reported result; the result has been corrected to the chloride salt for comparison with the majority of

Table 28: Predicted no-effect concentrations (PNECs).

Organotin	End-point	Uncertainty factor	Estimated PNEC (µg/l)
MMTC	0.007 mg/l chronic NOEC for *Scenedesmus subspicatus* (Oldersma et al., 2003a)	50	0.1
DMTC	0.2 mg/l chronic NOEC for *Daphnia* (de Roode & de Haan, 2004a)	50	4
MBTC	25 mg/l acute EC_{50} for *Daphnia* (ACIMA AG, 1992)	1000	25
DBTC	0.015 mg/l chronic NOEC for *Daphnia* (ABC, 1990b)	10	1.5
MOTC	0.003 mg/l chronic NOEC for *Scenedesmus subspicatus* (Oldersma et al., 2004b)	50	0.06
DOTC	0.02 mg/l chronic NOEC for *Scenedesmus subspicatus* (Ciba-Geigy Ltd, 1993a)	50	0.4

test results. Since there were no long-term test results available for fish, it was necessary to apply an uncertainty factor of 50 to the critical study.

- *Dioctyltin*: Acute toxicity studies were identified for dioctyltin for invertebrates and fish. Chronic NOECs were available for algae and invertebrates. A chronic NOEC of 0.02 mg/l for dioctyltin chloride in *Scenedesmus subspicatus* was the lowest reported result; the result has been corrected to the chloride salt for comparison with the majority of test results. Since there were no long-term test results available for fish, it was necessary to apply an uncertainty factor of 50 to the critical study.

11.2.3 Derivation of PNECs for marine organisms

A much more limited data set is available for marine organisms, and this is restricted to three of the organotin compounds being considered here. For monomethyltin, diatoms are the only organisms tested, with the lowest reported EC_{50} for growth at 0.16 mg/l. Applying an uncertainty factor of 10 000 to this value would give a PNEC of 0.016 µg/l; however, this would be extremely unreliable as a guidance value for the substance. Dimethyltin has acute toxicity data for algae, invertebrates, and fish; applying an uncertainty factor of 1000 to the lowest reported test result (4.9 mg/l for a NOEC for growth in a diatom) would give a PNEC of 4.9 µg/l. Dibutyltin has acute toxicity data for algae and invertebrates and a chronic study for fish; applying an uncertainty factor of 1000 to the lowest reported test result (0.09 mg/l for an EC_{50} for growth in a diatom) would give a PNEC of 0.09 µg/l.

11.2.4 Risk characterization

Using the PECs from section 6 and the above PNECs (Table 28), both based on the organotin chlorides, risk ratios (PEC/PNEC) can be derived for each of the identified uses of organotins; these are summarized in Table 29. Regional PEC/PNEC ratios are given in Table 30.

Regional PEC/PNEC ratios are all substantially lower than 1, indicating low risk from general environmental levels of these organotins. Some local PEC/ PNEC ratios exceed 1, specifically organotin production and paint formulator manufacture with respect to monooctyltin and a large calendering plant for monomethyltin. All three of these values derive from using default worst-case values in the modelling. They indicate that local monitoring of actual concentrations is required to determine risk levels based on real concentrations.

Lack of exposure data for most organotins together with limited toxicity information for marine organisms preclude the calculation of risk factors for the marine environment. For dibutyltin, measured concentrations in seawater reflect the use of tributyltin as a marine anti-foulant rather than the use of dibutyltin in plastics. It is therefore not possible to conduct a reliable risk assessment for the current uses of the compound.

11.3 Uncertainties in the risk characterization

Most of the exposure estimates are based on modelling, which is highly dependent on physicochemical properties of the compounds; actual monitoring is minimal in most cases.

The water solubility, capacity to bioaccumulate, and binding to environmental media, such as organic carbon and sediment, are uncertain. These potentially have a large effect on the outcome for environmental fate and thus exposure of both human consumers and organisms in the environment. Sensitivity testing was conducted on the modelling; very little difference was seen when solubility and degradation inputs were varied across the range of reported and modelled values.

Exposure of both consumers and organisms in the environment is highly dependent on accurate values for production and use; results presented here are based on refined information provided by industry following an earlier draft risk characterization. It is believed to be as accurate as possible.

Table 29: Local PEC/PNEC ratios for the various uses of organotins.

Activity	MMTC	DMTC	MBTC	DBTC	MOTC	DOTC
Organotin production						
Plant V (using TGD)	–	–	0.002	0.07	2	0.3
Plant W (using TGD)	–	–	0.007	**0.2**	**4**	**0.7**
Generic plant (EUSES)	–	–	0.002	0.003	0.005	0.002
PVC processing sites (using stabilizers)						
Large calendering plant (using TGD)	**1**	**0.03**	0.002	0.04	0.5	0.1
Small spread coating plant (using TGD)	0.8	0.02	0.001	0.03	0.23	0.05
Generic plant (EUSES)	0.003	0.0001	0.00004	0.001	0.002	0.002
Product manufacture (catalysts)						
Polyurethane plant (using TGD)	–	–	n/a	0.002	n/a	n/a
Paint formulator (using TGD)	–	–	**0.03**	0.08	1	0.2
Generic formulation (EUSES)	–	–	0.005	0.02	0.2	0.03
Product application (sealant with catalysts)						
Generic application (EUSES)	–	–	0.0002	0.003	0.008	0.003
Maximum PEC/PNEC ratio	**1**	**0.03**	**0.03**	**0.2**	**4**	**0.7**

Table 30: Regional PEC/PNEC ratios.

	MMTC	DMTC	MBTC	DBTC	MOTC	DOTC
PEC/PNEC ratio	0.003	0.0001	0.00004	0.001	0.002	0.002

12. PREVIOUS EVALUATIONS BY IOMC BODIES

WHO (2004) concluded that "The mono- and disubstituted compounds that may leach from PVC water pipes for a short time after installation are primarily immunotoxins; although they appear to be of low general toxicity, some are developmental toxins in rodents. The data available are insufficient to permit the proposal of guideline values for individual dialkyltins or the mono derivatives, although the concentrations observed in drinking-water are several orders of magnitude lower than the doses reported to cause developmental effects in rats and mice."

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APPENDIX 1 — ACRONYMS AND ABBREVIATIONS

BCF	bioconcentration factor
CAS	Chemical Abstracts Service
cDNA	complementary deoxyribonucleic acid
CICAD	Concise International Chemical Assessment Document
DBTC	dibutyltin dichloride
DMTC	dimethyltin dichloride
DNA	deoxyribonucleic acid
DOTC	dioctyltin dichloride
EC_{50}	median effective concentration
EHMA	2-ethylhexylmercaptoacetate
EU	European Union
EUSES	European Union System for the Evaluation of Substances
IOMA	isooctyl mercaptoacetate
IOMC	Inter-Organization Programme for the Sound Management of Chemicals
IPCS	International Programme on Chemical Safety
IUCLID	International Uniform Chemical Information Database
K_d	adsorption coefficient
K_{oc}	organic carbon/water partition coefficient
K_{ow}	octanol/water partition coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MBTC	monobutyltin trichloride
MMTC	monomethyltin trichloride
MOTC	monooctyltin trichloride
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
OECD	Organisation for Economic Co-operation and Development
PEC	predicted environmental concentration
PNEC	predicted no-effect concentration
PVC	polyvinyl chloride
TBTC	tributyltin chloride
TDI	tolerable daily intake
TGD	Technical Guidance Document

APPENDIX 2 — SOURCE DOCUMENT

EC (2003)

This final report, entitled *Revised assessment of the risks to health and the environment associated with the use of organostannic compounds (excluding use as a biocide in antifouling paints)* and released in December 2003, is an update of a report submitted to the Enterprise Directorate-General of the European Commission in July 2002 (EC, 2002).

The report was peer-reviewed through the European Commission of Toxicity, Ecotoxicity and the Environment (CSTEE) and by individual expert peer reviewers in EU Member States. The authors of the report were P. Floyd, C. Corden, P. Howe, and S. Dobson.

APPENDIX 3 — CICAD PEER REVIEW

The draft CICAD on mono- and disubstituted methyltin, butyltin, and octyltin compounds was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

M. Baril, Institut de recherche Robert Sauvé en santé et en sécurité du travail (IRSST), Montreal, Quebec, Canada

R. Benson, United States Environmental Protection Agency, Region 8, Denver, CO, USA

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APPENDIX 4 — CICAD FINAL REVIEW BOARD

Nagpur, India
31 October – 3 November 2005

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DI-n-BUTYLTIN OXIDE

ICSC: 0256
April 1994

CAS #	818-08-6	Dibutyltin oxide
RTECS #	WH7175000	Dibutyloxostannane
UN #	3146	Dibutyloxotin
EC ANNEX 1 INDEX #		$C_8H_{18}OSn$ / $(C_4H_9)_2SnO$
EC/EINECS #	212-449-1	Molecular mass: 248.9

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	Water spray. Powder. Carbon dioxide.
EXPLOSION	Finely dispersed particles form explosive mixtures in air.	Prevent deposition of dust; closed system, dust explosion-proof electrical equipment and lighting. Prevent build-up of electrostatic charges (e.g., by grounding).	
EXPOSURE		**PREVENT DISPERSION OF DUST! STRICT HYGIENE! AVOID EXPOSURE OF (PREGNANT) WOMEN!**	**IN ALL CASES CONSULT A DOCTOR!**
Inhalation	Headache. Ringing in the ears, memory loss, disorientation.	Local exhaust or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	MAY BE ABSORBED! Skin burns. Pain. (Further see Inhalation).	Protective gloves.	Remove contaminated clothes. Rinse and then wash skin with water and soap. Refer for medical attention.
Eyes	Redness. Pain.	Face shield or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Headache. Ringing in the ears, memory loss, disorientation.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Give a slurry of activated charcoal in water to drink. Refer for medical attention.

SPILLAGE DISPOSAL

Do NOT wash away into sewer. Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting. Carefully collect remainder, then remove to safe place. Personal protection: P3 filter respirator for toxic particles.

PACKAGING & LABELLING

Unbreakable packaging; put breakable packaging into closed unbreakable container. Do not transport with food and feedstuffs.

EU Classification
Symbol: T, N
R: 21-25-36/38-48/23/25-50/53
S: 1/2-35-36/37/39-45-60-61
Note: A, 1

UN Classification
UN Hazard Class: 6.1

EMERGENCY RESPONSE

Transport Emergency Card: TEC (R)-61GT3-II-S

STORAGE

Separated from food and feedstuffs.

IPCS
International Programme on Chemical Safety

WHO ILO UNEP

Prepared in the context of cooperation between the International Programme on Chemical Safety and the Commission of the European Communities

SEE IMPORTANT INFORMATION ON BACK

DI-n-BUTYLTIN OXIDE

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
WHITE POWDER.

PHYSICAL DANGERS
Dust explosion possible if in powder or granular form, mixed with air. If dry, it can be charged electrostatically by swirling, pneumatic transport, pouring, etc.

CHEMICAL DANGERS
The substance decomposes on heating producing toxic fumes of tin, tin oxides.

OCCUPATIONAL EXPOSURE LIMITS
TLV: (as Sn) 0.1 ppm as TWA, 0.2 ppm as STEL; (skin); A4 (not classifiable as a human carcinogen); (ACGIH 2004).
MAK: (as Sn) (Inhalable fraction) 0.1 mg/m³; Peak limitation category: II (2); skin absorption (H); Pregnancy risk group: D; (DFG 2004).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation, through the skin and by ingestion.

INHALATION RISK
Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quickly when dispersed.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is irritating to the eyes, the skin and the respiratory tract. The substance may cause effects on the central nervous system, resulting in impaired functions. Exposure may result in death. The effects may be delayed. Medical observation is indicated.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
The substance may have effects on the liver, resulting in liver impairment. Animal tests show that this substance possibly causes toxicity to human reproduction or development.

PHYSICAL PROPERTIES

Decomposes below melting point at 210°C (see Notes)
Relative density (water = 1): 1.6
Solubility in water: none

Auto-ignition temperature: 279°C

ENVIRONMENTAL DATA

This substance may be hazardous to the environment; special attention should be given to algae and crustacea.

NOTES

Different values are found in literature. Depending on the degree of exposure, periodic medical examination is suggested. The symptoms of poisoning do not become manifest until days.
Card has been partly updated in October 2005. See sections Occupational Exposure Limits, EU classification, Emergency Response. Card has been partly updated in October 2006. See section Ingestion First Aid.

ADDITIONAL INFORMATION

DIBUTYLTIN DILAURATE

ICSC: 1171
October 1995

CAS #	77-58-7	Dibutylbis((1-oxododecyl)-oxy) stannane
RTECS #	WH7000000	Dibutylbis(lauroyloxy)tin
UN #	2788; 3146	$(C_4H_9)_2Sn(OOC(CH_2)_{10}CH_3)_2/C_{32}H_{64}O_4Sn$
EC ANNEX 1 INDEX #		Molecular mass: 631.6
EC/EINECS #	201-039-8	

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION			
EXPOSURE		**STRICT HYGIENE!**	
Inhalation		Ventilation.	Fresh air, rest.
Skin		Protective gloves.	Remove contaminated clothes. Rinse and then wash skin with water and soap.
Eyes	Redness.	Safety spectacles.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion		Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Give a slurry of activated charcoal in water to drink.

SPILLAGE DISPOSAL

Collect leaking liquid in sealable containers. Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting. Carefully collect remainder, then remove to safe place (extra personal protection: self-contained breathing apparatus).

PACKAGING & LABELLING

UN Classification
UN Hazard Class: 6.1

EMERGENCY RESPONSE

STORAGE

Separated from food and feedstuffs. Ventilation along the floor.

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the Commission of the European Communities

SEE IMPORTANT INFORMATION ON BACK

ICSC: 1171	DIBUTYLTIN DILAURATE

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
YELLOW OILY LIQUID OR WAXY CRYSTALS.

CHEMICAL DANGERS
The substance decomposes on heating or on burning producing toxic and irritating fumes.

OCCUPATIONAL EXPOSURE LIMITS
TLV not established.

ROUTES OF EXPOSURE
The substance can be absorbed into the body by ingestion.

INHALATION RISK
A harmful contamination of the air will not or will only very slowly be reached on evaporation of this substance at 20°C.

EFFECTS OF SHORT-TERM EXPOSURE
The substance irritates the eyes.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
The substance may have effects on the liver, kidneys and gastrointestinal tract.

PHYSICAL PROPERTIES

Boiling point at 1.3 kPa: 205°C
Melting point: 22-24°C
Relative density (water = 1): 1.1
Solubility in water: none
Relative vapour density (air = 1): 21.8

Flash point: 179°C c.c.

ENVIRONMENTAL DATA

NOTES

Insufficient data are available on the effect of this substance on human health, therefore utmost care must be taken. Butinorate, Davainex and Tinostat are trade names. Card has been partially updated in 2006: see section Ingestion First Aid

ADDITIONAL INFORMATION

RÉSUMÉ D'ORIENTATION

Le présent CICAD[1] relatif aux dérivés méthylstanniques, butylstanniques et octylstanniques mono- et disubstitués a été préparé au Royaume-Uni par le Centre d'écologie et d'hydrologie et par Risks and Policy Analysts Limited. Il s'appuie sur un rapport d'évaluation des risques pour la santé et l'environnement liés à l'utilisation de dérivés organostanniques (à l'exclusion de leur emploi comme biocides ou dans les peintures antisalissures) présenté à la Commission européenne (Direction générale des entreprises). Pour prendre en compte les références qui ne figurent pas dans le rapport original, une recherche bibliographique exhaustive a été effectuée en avril 2005 sur plusieurs bases de données en ligne. Des informations sur le document original et sur son examen par des pairs sont données à l'appendice 2. L'appendice 3 donne des indications sur l'examen par des pairs du présent CICAD. Ce CICAD a été approuvé en tant qu'évaluation internationale lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Nagpur (Inde) du 31 octobre au 3 novembre 2005. La liste des participants à cette réunion figure à l'appendice 4. Les fiches internationales sur la sécurité chimique de l'oxyde de dibutylétain et du dilaurate de dibutylétain établies par le Programme international sur la sécurité chimique (IPCS) sont reproduites dans le présent CICAD (IPCS, 1999c, 2005). Des CICAD ont été consacrés précédemment aux dérivés triphénylstanniques et à l'oxyde de tributylétain (IPCS, 1999a,b).

Les composés organostanniques se caractérisent par la présence d'une liaison carbone-étain et ils ont pour formule générale $R_xSn(L)_{(4-x)}$, dans laquelle R représente un groupement alkyle ou aryle et L un ligand organique (ou parfois minéral). Sur le plan toxicologique, c'est le reste organostannique qui est important. Le ligand anionique influe sur les propriétés physico-chimiques mais n'a guère d'effet du point de vue toxicologique.

Du fait de l'influence du ligand, les propriétés physico-chimiques et la modélisation du devenir environnemental des composés organostanniques qui en découle sont souvent entachées d'incertitude.

La solubilité dans l'eau est faible pour l'ensemble des composés de ce groupe mais l'hydrolyse de ligands réactifs ou des échanges de ligands dans l'environnement ou les tissus des êtres vivants pourraient conduire à la formation d'espèces plus solubles, ce qui fait planer un doute sur la valeur de certaines des données obtenues par modélisation.

[1] La liste des acronymes et abréviations utilisés dans le présent rapport se trouve à l'appendice 1.

Les dérivés méthylstanniques ont probablement moins tendance à se répartir entre les sédiments, les sols et le carbone organique que les dérivés butyl- et méthylstanniques. Les valeurs de K_{oc} obtenues par modélisation indiquent une capacité de liaison au carbone organique beaucoup plus faible que celle que donnent les valeurs mesurées, souvent de plusieurs ordres de grandeur. Ces données mesurées sont utilisées de préférence à la modélisation du devenir environnemental de ces composés. Ces derniers se lient également fortement aux minéraux argileux, notamment à la montmorillonite.

Les organostanniques ont des usages aussi divers que spécifiques. Par exemple, les dérivés mono- et disubstitués ne conviennent pas comme biocides et les dérivés trisubstitués ne peuvent pas être utilisés comme agents stabilisateurs du PVC.

Les composés mono- et disubstitués envisagés ici sont utilisés comme agents stabilisateurs du PVC ou comme catalyseurs dans la production de peintures par électrodéposition (enduits pour véhicules automobiles), d'élastomères de silicone, de revêtements en poudre ou de polyuréthanes ou encore comme catalyseurs d'estérification.

Les tests habituels montrent que les organostanniques sont facilement biodégradables mais on peut se demander s'il s'agit d'une décomposition complète ou d'une dissociation du ligand. Pour les besoins de la modélisation de leur devenir et l'évaluation du risque qu'ils représentent, on considère que ces composés sont « intrinsèquement » biodégradables avec une valeur par défaut de la demi-vie égale à 150 jours. Dans le cas des dérivés dialkylstanniques, les mesures en laboratoire donnent, pour la demi-vie dans le sol, une valeur comprise entre 120 et 150 jours. Pour les dérivés méthyl- et butylstanniques, les valeurs de la demi-vie dans les sols forestiers vont de 6 mois à 15 ans.

Il n'existe guère de mesures de la concentration des organostanniques dans l'environnement. En ce qui concerne les dérivés butylstanniques (là où un usage très répandu de composés tributylstanniques conduit, par décomposition, à la présence dans l'environnement de concentrations de dérivés dibutylstanniques qui sont sans rapport avec l'utilisation de ces dérivés comme stabilisateurs ou catalyseurs) et méthylstanniques (dont la présence dans l'environnement est due à l'action des bactéries), les concentrations mesurées ne constituent pas des indicateurs fiables de l'usage actuel de ces substances par l'industrie. Malgré un effort de surveillance tout à fait notable, on n'a jamais procédé à la mesure de la concentration des dérivés octylstanniques dans l'environnement au sens large. On dispose de données au sujet de la concentration de ces composés dans les installations de traitement des eaux usées, les

valeurs maximales étant respectivement égales, pour le trichlorure de mono-octylétain et le dichlorure de dioctylétain, à 715 et 560 µg/kg de poids sec dans les boues et à 0,12 et 0,008 µg/l pour ces mêmes composés dans les effluents. Les concentrations maximales de dérivés mono- et dibutylstanniques (exprimées dans les deux cas en étain) sont respectivement égales à 76 et 810 ng/l dans l'eau et à 3360 et 8510 µg/kg de poids sec dans les sédiments. En ce qui concerne les dérivés mono- et diméthylstanniques les concentrations maximales dans ces mêmes milieux (également exprimées en étain) sont respectivement égales à 1200 et 400 ng/l et à 170 et 0,27 µg/kg de poids sec. Deux études ont été consacrées au lessivage des additifs contenus dans les déchets de PVC présents dans des décharges; toutes deux ont mis en évidence la présence de quelques composés organostanniques dans les eaux de lessivage, à des concentrations pouvant aller jusqu'à 2 µg d'étain par litre.

On a calculé la concentration prévisible dans l'environnement (PEC) dans un certain nombre de situations (production, élaboration et usage de produits à base d'organostanniques) afin de procéder à une évaluation du risque.

On relevé, dans des produits de consommation très divers, la présence d'organostanniques à des concentrations dont on a utilisé les valeurs pour prévoir les cas les plus extrêmes d'exposition humaine (adultes et enfants).

On ne dispose que de données très limitées sur la cinétique et le métabolisme des organostanniques chez les mammifères de laboratoire. Elles permettent de constater que ces composés se distribuent très largement dans les tissus de l'organisme. Il semble qu'il puisse y avoir passage transplacentaire, mais que le passage à travers la barrière hémato-encéphalique soit limité, comme en témoignent les concentrations généralement faibles mesurées dans l'encéphale. En ce qui concerne les métabolites, on ne possède de données qu'au sujet de ceux des composés dibutylstanniques, le principal métabolite étant dans ce cas un dérivé butyl(3-hydroxybutyl)stannique. Selon les données limitées dont on dispose, la métabolisation et l'élimination sont assez rapides, avec une demi-vie de quelques jours. Dans le cas de dérivés dioctylstanniques, on a constaté qu'une dose de ces composés administrée par voie orale était éliminée en majeure partie dans les matières fécales et le reste dans les urines.

Les organostanniques qui font l'objet de la présente évaluation présentent une faible toxicité aiguë pour les mammifères de laboratoire, la plupart des études indiquant des valeurs de la DL_{50} supérieures à 100 mg/kg de poids corporel et dans beaucoup de cas, supérieures à 1000 mg/kg; la raison pourrait en être une faible absorption intestinale. Les résultats des études sur le pouvoir irritant sont très variables, un même composé pouvant être, selon le cas, qualifié de non irritant à fortement irritant. Quoi qu'il en soit, ces composés doivent être considérés comme irritants pour la peau et les yeux. Les tests de sensibilisation donnent également des résultats variables et il faut convenir que les bases de données ne sont pas suffisantes pour que l'on puisse en tirer des conclusions certaines. Cela étant, un certain nombre de dérivés organostanniques font preuve d'un fort pouvoir sensibilisateur dans certains tests et il serait prudent de considérer que le groupe dans son ensemble possède des propriétés sensibilisatrices.

Dans les cas d'exposition de brève à moyenne durée, on a constaté que les points d'aboutissement importants de l'action toxique étaient le système nerveux, le développement, le système immunitaire et le système endocrinien, mais cette action se manifeste à des degrés variables selon les différents composés.

Le système nerveux est le point d'aboutissement principal de l'action toxique des dérivés méthylstanniques avec une NOAEL (dose sans effet nocif observé) d'environ 0,6 mg/kg de poids corporel dans le cas des effets neuropathologiques dus aux dérivés diméthylés. Pour ce qui est des dérivés monométhylés, les données sont trop limitées pour permettre de déterminer la NOAEL. Dans le cas des dérivés dibutylés et mono- ou dioctylés, aucun effet neurotoxique n'a été observé. On ne dispose d'aucune donnée concernant les dérivés monobutylés.

On observe des effets toxiques sur le développement dans le cas dérivés méthyl-, butyl- et octylstanniques disubstitués, mais pas dans le cas des dérivés monosubstitués correspondants. Le principal effet relevé est la tératogénicité, avec, dans la plupart des cas, des effets sur les fœtus à des doses proches des doses toxiques pour la mère. Les NOAEL pour les dérivés diméthylés, dibutylés et dioctylés, sont en ce qui concerne les effets tératogènes, respectivement égales à 10 (10), 2,5 (1,0) et 45 (30) mg/kg de poids corporel par jour (valeurs de la NOAEL pour les effets toxiques sur la mère entre parenthèses).

Les dérivés dibutyl-, mono- et dioctylstanniques se révèlent immunotoxiques, leurs effets se manifestant systématiquement par une modification du poids du thymus avec également des troubles fonctionnels. Il n'a pas été possible de déterminer la valeur de la NOAEL des dérivés dibutylés, mais on a constaté que la plus faible dose de dichlorure de dibutylétain qui produisait des effets était égale à 2,5 mg de composé par kg de poids corporel et par jour. En ce qui concerne les dérivés mono- et dioctylés, on a obtenu pour la NOAEL des valeurs respectivement égales à 0,87 et 0,23 mg/kg de poids corporel par jour, la valeur relative au dérivé monooctylé n'étant qu'une estimation car l'étude a été

effectuée sur un mélange. Selon d'autres données, le dérivé dioctylique serait le plus immunotoxique des deux.

L'action inhibitrice des dérivés tributylstanniques sur l'aromatase est bien connue et il semble que les dérivés dibutylés aient également une certaine activité de ce type (il est difficile de caractériser avec précision l'aptitude des dérivés dibutylés à perturber les fonctions endocrines en raison de la présence d'impuretés tributylstanniques). Les dérivés monobutylés ou mono- et dioctylés n'inhibent pas l'aromatase *in vitro*. On ne dispose pas de données concernant ce point d'aboutissement de l'action toxique dans le cas des dérivés méthylés.

Dans la très grande majorité des tests *in vivo*, les dérivés mono- et dialkylstanniques se révèlent dépourvus de génotoxicité. Les tests *in vitro* donnent des résultats variables, avec peu d'indices d'une réactivité vis-à-vis de l'ADN. En revanche, on a observé, dans les tests *in vitro*, les indices d'une activité clastogène et des effets sur la formation du fuseau pendant la mitose.

Il existe de brefs comptes rendus d'études à long terme non publiées sur quelques-uns des organostanniques examinés ici. A l'exception d'une seule et unique étude portant sur un mélange de chlorures de mono- et de dioctylétain, aucune activité cancérogène n'a pu être imputée à des mélanges de dérivés mono- ou diméthylés chez le rat ou à des dérivés mono- ou dioctylés chez le rat ou le chien. L'effet observé dans l'étude ayant donné des résultats positifs consistait en une augmentation de la fréquence des lymphomes du thymus chez les rattes, mais uniquement à la dose de 150 mg/kg de nourriture. Une augmentation significative de l'incidence des lymphomes malins généralisés a également été relevée chez les rats mâles aux doses de 50 et 150 mg/kg, cet effet ne s'observant que chez les femelles à la dose la plus élevée.

Il existe très peu de données relatives aux effets des organostanniques sur des sujets humains. Dans aucun des cas connus d'exposition accidentelle sur le lieu de travail on ne dispose d'une estimation de la concentration. Dans une large majorité de cas, l'exposition a eu lieu par inhalation, avec une certaine possibilité d'exposition cutanée. Les effets les plus couramment signalés étaient de nature neurologique et pouvaient persister pendant une longue période.

Il n'est pas possible d'obtenir des valeurs fiables pour les doses journalières tolérables (TDI) car on ne dispose pas d'études à long terme avec des doses et des espèces appropriées. En ce qui concerne l'exposition de moyenne durée, les doses journalières tolérables pour l'estimation du risque sont estimées, dans le cas des chlorures, à 0,0012 mg/kg de poids corporel pour les dérivés mono- et diméthylés sur la base des effets neurotoxiques, à 0,003 mg/kg de poids corporel pour les dérivés dibutylés sur la base des effets immunotoxiques et à 0,002 mg/kg de poids corporel pour les dérivés dioctylés, également sur la base de l'immunotoxicité. Aucune valeur fiable de la dose journalière tolérable n'a pu être obtenue pour les dérivés monobutylés et monooctylés.

En comparant les estimations les plus pessimistes d'exposition de consommateurs (adultes et enfants) on peut considérer que l'utilisation d'organostanniques pour la confection de papier de cuisson siliconé pose problème, mais d'un autre côté, les informations données par l'industrie indiquent que ces composés ne sont plus utilisés nulle part à cette fin. L'estimation, par le calcul, de l'exposition humaine d'origine environnementale indique un risque découlant de l'exposition aux dérivés dioctylstanniques en cas de consommation d'aliments produits à proximité d'ateliers qui travaillent le PVC, un plastique dans lequel ces composés sont utilisés comme agents stabilisateurs. Les enfants sont davantage menacés que les adultes car dans leur cas l'exposition risque d'être 3,6 fois supérieure à la dose journalière tolérable. Beaucoup de ces estimations de l'exposition sont obtenues en utilisant un modèle qui dépend pour une très grande part des propriétés physico-chimiques des composés. Dans la plupart des cas, la surveillance effective est minimale.

Les séries de données sur la toxicité des organostanniques varient considérablement d'un composé à l'autre, les dérivés dibutylés étant de loin les mieux étudiés. Les points d'aboutissement de l'action toxique et les espèces concernées sont les suivants : la NOEC (dose sans effet observé) chronique est de 0,007 mg/l chez *Scenedesmus subspicatus* pour les dérivés monométhylés (taux de croissance); elle est de 0,2 mg/l chez la daphnie pour les dérivés diméthylés (reproduction); la CE_{50} aiguë chez la daphnie est égale à 25 mg/l pour les dérivés monométhylés (immobilisation); la NOEC chronique chez la daphnie pour les dérivés dibutylés est égale à 0,015 mg/l (reproduction); elle est égale à 0,003 mg/l chez *Scenedesmus subspicatus* pour les dérivés monooctylés (taux de croissance) et à 0,02 mg/l chez *Scenedesmus subspicatus* pour les dérivés dioctylés (taux de croissance). Pour assurer la comparabilité des valeurs, toutes celles qui sont données ici se rapportent aux chlorures. Les séries de données sont trop limitées pour que l'on puisse effectuer une analyse probabiliste et les valeurs de la concentration prédite sans effet ont été obtenues en appliquant des facteurs d'incertitude.

Les rapports PEC/PNEC sont sensiblement inférieurs à 1, ce qui indique que, compte tenu de leur concentration dans l'environnement, ces organostanniques représentent un risque faible. Localement, le rapport PEC/PNEC peut être parfois supérieur à 1, en

particulier à proximité d'un site de production de dérivés monooctylstanniques ou en présence d'une grande installation de calandrage utilisant un dérivé mono-méthylé. Dans les deux cas, ces valeurs sont tirées de valeurs par défaut obtenues par modélisation. Elles montrent qu'une surveillance locale des concentrations effectives est nécessaire pour déterminer le niveau de risque qu'elles impliquent.

On ne dispose pas d'informations suffisantes pour évaluer le risque que ces composés représentent pour l'environnement terrestre.

RESUMEN DE ORIENTACIÓN

Este CICAD[1] sobre compuestos de metilestaño, butilestaño y octilestaño con una y dos sustituciones, preparado por el Centro de Ecología e Hidrología del Reino Unido y por Risk & Policy Analysts Limited del Reino Unido, está basado en un informe de evaluación de los riesgos para la salud y el medio ambiente asociados con la utilización de compuestos organo-estánnicos (excluido el uso como biocida en las pinturas antiincrustantes) presentado a la Comisión Europea (Dirección General de Empresa). Para abordar la bibliografía no incluida en este informe original, en abril de 2005 se realizó una búsqueda bibliográfica amplia de varias bases de datos en línea. La información sobre el documento original y su examen colegiado se presenta en el apéndice 2. La información sobre el examen colegiado de este CICAD figura en el apéndice 3. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final, celebrada en Nagpur (India) del 31 de octubre al 3 de noviembre de 2005. La lista de participantes en esta reunión figura en el apéndice 4. También se reproducen en este documento las Fichas internacionales de seguridad química para el óxido de dibutilestaño y el dilaurato de dibutilestaño, preparadas por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1999c, 2005). En otros CICAD anteriores se han examinado compuestos de trifeniltina y el óxido de tributiltina (IPCS, 1999a,b).

Los compuestos organoestánnicos se caracterizan por un enlace estaño-carbono y tienen la fórmula general $R_xSn(L)_{(4-x)}$, siendo R un alquilo orgánico o un grupo arilo y L un ligando orgánico (o a veces inorgánico). El grupo organoestánnico es importante desde el punto de vista toxicológico. El ligando aniónico influye en las propiedades fisicoquímicas, pero en general tiene efectos escasos o nulos en la toxicología.

Debido a la influencia del ligando, las propiedades fisicoquímicas y la creación de modelos sobre su destino final en el medio ambiente derivados de ellas son con frecuencia inciertas para este tipo de compuestos.

La solubilidad de todo el grupo en agua es baja; sin embargo, la hidrólisis de los ligandos reactivos y/o el intercambio de ligandos en el medio ambiente o en los tejidos de los organismos puede llevar a la formación de especies que son más solubles, por lo que se plantean dudas acerca de la importancia de algunos de los datos obtenidos de los modelos.

Los metilestaños tienen menor probabilidad de repartición en los sedimentos, el suelo y el carbono

[1] La lista de siglas y abreviaturas utilizadas en este informe figura en el apéndice 1.

orgánico que los butilestaños y los octilestaños. Los datos del coeficiente de reparto carbono orgánico/agua (K_{oc}) obtenidos de modelos indican una capacidad mucho menor para la unión al carbono orgánico de la que se deduce de los valores medidos, con frecuencia de varios órdenes de magnitud. Para los modelos sobre el destino final de los compuestos en el medio ambiente se ha preferido la utilización de los valores medidos. Los compuestos también se unen con fuerza a minerales de la arcilla, en particular la montmorillonita.

Los compuestos organoestánnicos tienen una gran variedad de aplicaciones, que son básicamente específicas para los diferentes compuestos. Así, los compuestos organoestánnicos monosustituidos y disustituidos no son adecuados como biocidas, y los trisustituidos no lo son como estabilizadores del cloruro de polivinilo (PVC).

Los compuestos organoestánnicos monosustituidos y disustituidos examinados en este CICAD se utilizan como estabilizadores en el PVC o como catalizadores para la producción de revestimientos electrodepositados (principalmente en la imprimación de los vehículos de motor), cauchos de silicona, revestimientos por esterificación y de polvo y poliuretanos, así como en el revestimiento de vidrio.

En las pruebas normalizadas utilizando compuestos organoestánnicos se observa una biodegradación fácil. Sin embargo, hay algunas dudas acerca de si esto obedece a una degradación completa o a la disociación del ligando. A efectos de la creación de modelos sobre el destino final y la evaluación del riesgo, se ha supuesto que los compuestos son "inherentemente" biodegradables, con una semivida por defecto de 150 días. Las semividas medidas en el suelo para los compuestos dialquilestánnicos son de alrededor de 120-150 días en las pruebas de laboratorio. Los metilestaños y los butilestaños de suelos forestales mostraron semividas comprendidas entre seis meses y 15 años.

Son escasas las concentraciones de compuestos organoestánnicos medidas en el medio ambiente. Los valores medidos para los butilestaños (habiendo llevado el uso generalizado de tributilestaño a niveles de dibutilestaño en el medio ambiente como producto de degradación no relacionado con la fabricación o el uso de este compuesto como estabilizador o catalizador) y los metilestaños (que se producen en el medio ambiente por la actividad bacteriana) no son indicadores fidedignos de la utilización industrial de estas sustancias en el presente. A pesar de un esfuerzo de vigilancia bastante sustancial, nunca se han medido los octilestaños en el medio ambiente más general. Se dispone de datos sobre concentraciones de octilestaños medidas en instalaciones de tratamiento de aguas residuales, hasta un máximo de 715 y 560 µg/kg de peso seco para el tricloruro de monooctilestaño y el dicloruro de dioctilestaño, respectivamente, en los fangos de alcantarillado, y de 0,12 y 0,008 µg/l para el tricloruro de monooctilestaño y el dioctilestaño, respectivamente, en los efluentes. Las concentraciones máximas de monobutilestaño y dibutilestaño en el agua y los sedimentos son de 76 y 810 ng/l y de 3360 y 8510 µg/kg de peso seco, respectivamente, expresados en ambos casos como estaño. Los valores máximos semejantes para el monometilestaño y el dimetilestaño son de 1200 y 400 ng/l y de 170 y 0,27 µg/kg de peso seco, respectivamente, expresados en ambos casos como estaño. En dos estudios se ha examinado la lixiviación de aditivos del PVC a partir de vertederos; en ambos casos se observaron algunos compuestos organoestánnicos en la filtración, en concentraciones de hasta 2 µg/l como estaño.

Se han calculado las concentraciones previstas en el medio ambiente para diversas situaciones (producción, formulación y utilización) como medio para realizar una evaluación del riesgo.

Se han detectado compuestos organoestánnicos en una gran variedad de productos de consumo; estos valores medidos se han utilizado para calcular la exposición en el peor de los casos de los consumidores humanos (adultos y niños).

Los datos sobre la cinética y el metabolismo de los compuestos organoestánnicos en mamíferos de laboratorio son muy limitados. Se ha observado una distribución generalizada de estos compuestos en todos los tejidos corporales. Parece que se produce transferencia transplacentaria, mientras que atraviesa con dificultad la barrera hematoencefálica, puesto que sus niveles en el cerebro suelen ser bajos. El único compuesto para el cual se dispone de datos sobre los metabolitos es el dibutilestaño, cuyo principal metabolito es el butil(3-hidroxibutil)estaño. Hay información limitada que parece indicar un metabolismo y eliminación bastante rápidos, con semividas de varios días. Gran parte de una dosis oral de dioctilestaño se eliminó en las heces, y el resto en la orina.

Los compuestos organoestánnicos comprendidos en esta evaluación tienen una toxicidad aguda baja para los mamíferos de laboratorio, indicando la mayoría de los estudios una DL_{50} superior a 100 mg/kg de peso corporal y en muchos casos por encima de 1000 mg/kg de peso corporal; esto puede obedecer a una absorción baja a partir del intestino. Los estudios sobre la irritación son muy variables, con informes que van desde su ausencia hasta una irritación grave para el mismo compuesto. Los compuestos se deben considerar como irritantes cutáneos y oculares. Se producen variaciones semejantes en las pruebas de sensibilización y la base de datos se debe considerar como inadecuada para extraer conclusiones

definitivas; sin embargo, varios compuestos organoestánnicos han mostrado un fuerte potencial de sensibilización en algunas pruebas y sería prudente considerar el grupo como sensibilizador.

En las exposiciones entre breves e intermedias se ha observado neurotoxicidad, toxicidad en el desarrollo, inmunotoxicidad y perturbación endocrina para los efectos finales correspondientes, aunque el grado de cada uno de estos efectos finales tóxicos presenta diferencias en el grupo considerado en conjunto.

La neurotoxicidad es el efecto final más importante de los metilestaños, con una NOAEL de unos 0,6 mg/kg de peso corporal basada en la neuropatología del dimetilestaño; los limitados datos disponibles para el monometilestaño impiden la derivación de una NOAEL. No se detectó neurotoxicidad con el dibutilestaño o el monooctilestaño y el dioctilestaño; no se dispone de información sobre el monobutilestaño.

Los metilestaños, butilestaños y octilestaños disustituidos muestran toxicidad en el desarrollo, pero no los compuestos monosustituidos correspondientes. El principal efecto notificado es la teratogenicidad, provocando en la mayor parte de los casos efectos en los fetos con dosis próximas a las que causan toxicidad materna. Las NOAEL para el dimetilestaño, el dibutilestaño y el dioctilestaño son 10 (10), 2,5 (1,0) y 45 (30) mg/kg de peso corporal al día para la teratogenicidad (entre paréntesis figuran las NOAEL para la toxicidad materna).

Para el dibutilestaño, el monooctilestaño y el dioctilestaño se ha demostrado que hay inmunotoxicidad y efectos sistemáticos en el peso del timo, pero también hay medidas de inmunotoxicidad funcional. No se pudo determinar una NOAEL para el dibutilestaño, pero la dosis más baja notificada como causante de efectos fue de 2,5 mg/kg de peso corporal al día (como dicloruro de dibutilestaño). Se ha determinado que las NOAEL para el monooctilestaño y el dioctiestaño son de 0,87 y 0,23 mg/kg de peso corporal al día, respectivamente, aunque el valor para el monooctilestaño es una estimación, porque el estudio se realizó utilizando una mezcla. Otra información parece indicar que el dioctilestaño es el más inmunotóxico de los dos compuestos.

El tributilestaño es bien conocido como inhibidor de la aromatasa, y también parece tener alguna actividad el dibutilestaño (la caracterización exacta de la capacidad de perturbación endocrina debida exclusivamente al dibutilestaño es difícil, debido a la presencia de tributilestaño como impureza). El monobutilestaño, el monooctilestaño y el dioctilestaño no tienen capacidad de inhibición de la aromatasa en las pruebas *in vitro*. No se dispone de datos relativos a este efecto final para las metilestaños.

En la inmensa mayoría de las pruebas *in vivo*, el monoalquilestaño y el dialquilestaño no muestran genotoxicidad. Los resultados de las pruebas *in vitro* son variables, con escasos indicios de reactividad del ADN. Sin embargo, hay indicios *in vitro* de clastogenicidad y efectos en la formación del huso acromático en la mitosis.

Se consultaron resúmenes breves de estudios prolongados inéditos sobre algunos de los compuestos organoestánnicos que se examinan. No se observó carcinogenicidad para mezclas de monometilestaño y dimetilestaño en ratas y de monooctilestaño o dioctilestaño en ratas o perros, excepto en un solo estudio con una mezcla de cloruros de monooctilestaño y dioctilestaño. En él se puso de manifiesto un aumento significativo de la frecuencia de linfomas tímicos en ratas hembra sólo con dosis de 150 mg/kg de alimentos. Se observó un aumento significativo de la incidencia de linfomas malignos generalizados en los machos de los grupos que recibieron dosis de 50 y 150 mg/kg, pero en las hembras sólo se detectaron con la dosis más alta.

Son muy escasos los datos disponibles sobre los efectos de los compuestos organoestánnicos en las personas. De las exposiciones profesionales no intencionales notificadas, no hay ninguna con una estimación de la concentración de la exposición. La exposición se produjo fundamentalmente por inhalación, con alguna posibilidad de exposición cutánea. Los efectos que se notificaron con más frecuencia fueron los neurológicos, que pueden persistir durante largos periodos.

No se pueden derivar valores fidedignos de la ingesta diaria tolerable (IDT) durante toda la vida, puesto que no se dispone de estudios prolongados con las dosis apropiadas en las especies adecuadas. Se calcularon los valores de la IDT en la exposición intermedia para la estimación del riesgo (como cloruros), siendo de 0,0012 mg/kg de peso corporal para el monometilestaño y el dimetilestaño, basándose en la neurotoxicidad, de 0,003 mg/kg de peso corporal para el dibutilestaño, basándose en la inmunotoxicidad, y de 0,002 mg/kg de peso corporal para el dioctilestaño, basándose también en la inmunotoxicidad. No se pudieron derivar valores fidedignos de la IDT para el monobutilestaño o el monooctilestaño.

La comparación de la exposición en el peor de los casos estimada para los consumidores humanos (adultos y niños) indica que hay motivo de preocupación, debido a la utilización de compuestos organoestánnicos en el papel de horno con silicona, aunque la información procedente de la industria señala que esta aplicación de compuestos organoestánnicos se ha interrumpido en todo el mundo. El cálculo de la exposición humana a través del medio ambiente indica que es motivo de preocupación la exposición al dioctilestaño derivado del consumo

de alimentos producidos localmente cerca de instalaciones de elaboración de PVC, donde se utiliza como estabilizador. La preocupación es mayor en el caso de los niños, para los que la IDT supera en un factor de 3,6 la de los adultos. Gran parte de las estimaciones de la exposición se basan en modelos, que tienen una fuerte dependencia de las propiedades fisicoquímicas de los compuestos; la vigilancia real es mínima en la mayoría de los casos.

Las series de datos sobre la toxicidad de los compuestos organoestánnicos varían considerablemente de un compuesto a otro, siendo el dibutilestaño el más estudiado con diferencia. Los efectos finales y las especies que se consideran fundamentales son los siguientes: NOEC crónica de 0,007 mg/l en *Scenedesmus subspicatus* para el monometilestaño (ritmo de crecimiento), NOEC crónica de 0,2 mg/l en *Daphnia* para el dimetilestaño (reproducción), CE_{50} aguda de 25 mg/l en *Daphnia* para el monobutilestaño (inmovilización), NOEC crónica de 0,015 mg/l en *Daphnia* para el dibutilestaño (reproducción), NOEC crónica de 0,003 mg/l en *Scenedesmus subspicatus* para el monooctilestaño (ritmo de crecimiento) y NOEC crónica de 0,02 mg/l en *Scenedesmus subspicatus* para el dioctilestaño (ritmo de crecimiento). A efectos de la posibilidad de establecer comparaciones, todos los valores indicados se han convertido a la sal de cloruro. Las series de datos son demasiado pequeñas para realizar un análisis probabilístico y las PNEC se han derivado mediante la aplicación de factores de incertidumbre.

Las razones PEC/PNEC regionales son todas sustancialmente inferiores a 1, lo que indica un riesgo bajo a partir de los niveles generales de estos compuestos organoestánnicos en el medio ambiente. Algunas razones PEC/PNEC locales fueron superiores a 1, en particular la producción de compuestos organoestánnicos con respecto al monooctilestaño y una gran instalación de calandrias para el monometilestaño. Ambos valores se derivan de la aplicación en los modelos de valores por defecto en el peor de los casos. Indican la necesidad de vigilancia local de las concentraciones efectivas para determinar los niveles de riesgo basándose en las concentraciones reales.

No se dispone de información suficiente a fin de evaluar el riesgo para el medio ambiente terrestre.

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