

n-Octyltin Compounds

Supplement 2009

MAK value (2008)	0.004 ml/m³ (ppm) (as Sn) \triangleq 0.02 mg/m³ (as Sn)
Peak limitation (2008)	Category I, excursion factor 1
Absorption through the skin (1964)	H
Sensitization	–
Carcinogenicity (2008)	Category 4
Prenatal toxicity (2009)	Pregnancy risk group B
Germ cell mutagenicity	–
BAT value	

Mono-*n*-octyltin compounds: $\text{CH}_3(\text{CH}_2)_7\text{SnR}$

Compound	CAS No.	R =	Molecular weight [g/mol]	Synonyms	Solubility in water [mg/l]	log K_{ow}
Mono- <i>n</i> -octyltin trichloride (MOTC)	3091-25-6	(-Cl) ₃	338.27	<i>n</i> -octyltin trichloride; tri-chloro- <i>n</i> -octylstannane	107 mg/l at 25°C*	2.14 (calc.)*
1 ml/m³ (ppm) \triangleq 14.036 mg/m³			1 mg/m³ \triangleq 0.071 ml/m³ (ppm)			
Mono- <i>n</i> -octyltin oxide (MOTO)	13356-20-2	=O, -OH	264.9	hydroxy octyl oxostannane	—	—
1 ml/m³ (ppm) \triangleq 10.99 mg/m³			1 mg/m³ \triangleq 0.091 ml/m³ (ppm)			
Mono- <i>n</i> -octyltin tris (2-ethylhexyl mercaptoacetate) (MOT(2-EHMA) ₃)	27107-89-7	(-SCH ₂ COOCH ₂ CH-(C ₂ H ₅)C ₄ H ₉) ₃	841.9	<i>n</i> -octyltin-tris(2-ethylhexyl thioglycolate); <i>n</i> -octyl-tris(2-ethylhexyloxy carbonylmethyl thio)-stannane	1.9 × 10 ⁻¹² (calc.)*	14.42 (calc.)*
1 ml/m³ (ppm) \triangleq 34.036 mg/m³			1 mg/m³ \triangleq 0.029 ml/m³ (ppm)			
Mono- <i>n</i> -octyltin tris (isooctyl-mercaptoacetate) (MOT(IOMA) ₃)	26401-86-5	(-SCH ₂ COO(CH ₂) ₅ -CH(CH ₃) ₂) ₃	841.9	<i>n</i> -octyltin-tris(isooctyl thioglycolate)	1.35 mg/l at 25°C**	14.42 (calc.)**
1 ml/m³ (ppm) \triangleq 34.036 mg/m³			1 mg/m³ \triangleq 0.029 ml/m³ (ppm)			

Compound	CAS No.	R =	Molecular weight [g/mol]	Synonyms	Solubility in water [mg/l]	log K _{ow}
Di-<i>n</i>-octyltin compounds: (CH₃(CH₂)₇)₂SnR₂						
Di- <i>n</i> -octyltin oxide (DOTO)	870-08-6	=O	361.2	di- <i>n</i> -octyloxostannane; dioctyloxostannane	6.6 × 10 ⁻⁵ mg/l (calc.) [*]	9.26 (calc.) [*]
1 ml/m³ (ppm) ≙ 14.985 mg/m³			1 mg/m³ ≙ 0.067 ml/m³ (ppm)			
Di- <i>n</i> -octyltin dichloride (DOIC)	3542-36-7	(-Cl) ₂	416.1	dichlorodioctylstannane; dichlorodioctyltin	0.026 mg/l at 25°C (calc.) [*]	5.82 (calc.) [*]
1 ml/m³ (ppm) ≙ 17.263 mg/m³			1 mg/m³ ≙ 0.579 ml/m³ (ppm)			
Di- <i>n</i> -octyltin bis-(isooctyl maleate)	33568-99-9	(-OOC-CH=CH-COOC ₈ H ₁₇) ₂	799.7	dioctyl-bis(isooctyl maleate)tin; dioctyltin-bis(isooctyl maleate)	4.44 × 10 ⁻¹¹ mg/l at 25°C (calc.) [*]	13.15 (calc.) [*]
1 ml/m³ (ppm) ≙ 33.18 mg/m³			1 mg/m³ ≙ 0.030 ml/m³ (ppm)			
Di- <i>n</i> -octyltin maleate	16091-18-2	(-OOC-CH=CH-COO-)	459.21	dioctyl(maleoyldioxy)-stannane	10 mg/l [*]	6.94 (calc.) [*]
1 ml/m³ (ppm) ≙ 19.05 mg/m³			1 mg/m³ ≙ 0.052 ml/m³ (ppm)			
Di- <i>n</i> -octyltin bismaleate	15571-60-5	(-OOC-CH=CH-COOH) ₂	575.23	disobutyl maleate dioctyltin	0.0185 mg/l at 25°C (calc.) [*]	5.26 (calc.) [*]
1 ml/m³ (ppm) ≙ 23.87 mg/m³			1 mg/m³ ≙ 0.042 ml/m³ (ppm)			

Compound	CAS No.	R =	Molecular weight [g/mol]	Synonyms	Solubility in water [mg/l]	log K _{ow}
Di- <i>n</i> -octyltin-bis (2-ethylhexyl mercap- toacetate) (DOT(2-EHMA) ₂)	15571-58-1	(-SCH ₂ COOCH ₂ CH-(C ₂ H ₅)C ₄ H ₉) ₂	751.8	dioctyltin-bis(2-ethylhexyl thioglycolat)	1.22 × 10 ⁻¹² mg/l at 25°C (calc.) [*]	15.35 (calc.) [*]
	1 ml/m ³ (ppm) ≙ 31.195 mg/m ³		1 mg/m ³ ≙ 0.032 ml/m ³ (ppm)			
Di- <i>n</i> -octyltin- bis(isooctyl mercaptoace- tate) (DOT(IOMA) ₂)	26401-97-8	(-SCH ₂ COO(CH ₂) ₅ -CH(CH ₃) ₂) ₂	751.8	di- <i>n</i> -octyltin-bis(isooctyl thioglycolate)	1.22 × 10 ⁻¹² mg/ l at 25°C (calc.) [*]	15.35 (calc.) [*]
	1 ml/m ³ (ppm) ≙ 31.195 mg/m ³		1 mg/m ³ ≙ 0.032 ml/m ³ (ppm)			
Tetra-<i>n</i>-octyltin: SnR₄						
Tetra- <i>n</i> -octyltin (TOT)	3590-84-9	(-CH ₂ -(CH ₂) ₆ -CH ₃) ₄	571.6	tetra- <i>n</i> -octylstannane	4.77 × 10 ⁻¹³ mg/l at 25°C (calc.) [*]	17.23 (calc.) [*]
	1 ml/m ³ (ppm) ≙ 23.718 mg/m ³		1 mg/m ³ ≙ 0.042 ml/m ³ (ppm)			

calc.: calculated;

*: SRC (2007);

**: OECD Report (2006)

This documentation of data on mono-*n*-octyltin compounds is mainly based on the OECD-ICCA Report on mono-*n*-octyltin compounds (OECD 2006) and the relevant IUCLID data sets (Parametrix Inc 2006 a–c). *n*-Octyltin compounds are used as stabilizers in PVC processing and as catalyst in PVC production.

1 Toxic Effects and Mode of Action

The thymus is the main target organ of *n*-octyltin compounds in studies with repeated administration; rats are particularly sensitive (see also documentation “Di-*n*-octyltin compounds, Mono-*n*-octyltin compounds” 1996, translation of the 1992 German). *n*-Octyltin compounds show no genotoxic potential in vivo and only in some cases in vitro. In an oral carcinogenicity study using a mixture of MOTC (66%) and DOTC (32.5%), a significantly increased incidence of lymphomas of the thymus and benign thymomas occurred in female rats of the highest dose group with a mixture of about 6 mg/kg body weight and day (corresponding to 1.95 mg tin/kg body weight and day). In an oral 90-day study in rats the relative thymus weight was reduced even at the lowest dose of DOTC of 0.7 mg/kg body weight and day (equivalent to a dose of 0.18 mg tin/kg body weight and day). A marked immunotoxic effect occurred especially in young animals. *n*-Octyltin compounds have a slight to moderate irritant effect. There are, however, no studies with repeated inhalation.

n-Octyltin compounds can be absorbed through the skin. They have no sensitizing effect on the skin. However, ligands, for which a sensitizing effect has been demonstrated, can produce a reaction after metabolic cleavage of the organic tin residue. Prenatal and postnatal mortality at about 1.8 mg tin/kg body weight and day and above was observed in rats after administration of DOTC in a screening test. A non-significant increase in delayed ossification was found in rabbits at about 1.55 mg tin/kg body weight and day after prenatal exposure to a mixture of DOT (IOMA)₂ and MOT(IOMA)₃. Relevant ossification disorders occurred in mice in a prenatal developmental toxicity study using a mixture of DOT(IOMA)₂ and MOT(IOMA)₃ at a dose level of 7.1 mg tin/kg body weight and day, which also resulted in reduced maternal thymus weight.

2 Mechanism of Action

No studies are known on possible mechanisms of action for the carcinogenicity of *n*-octyltin compounds. Due to the similarity of their physical chemical properties, it is to be assumed that the biochemical toxicological effects described in detail in the documentation on *n*-butyltin compounds also occur in *n*-octyltin compounds. The marked lipophilic property of alkyltin compounds is of major importance. This is a determinant for their absorption from the gastrointestinal tract and transport into

cells. The ability of alkyltin compounds to bind to proteins and membranes and to change their function is to be emphasized. Such effects include disturbances in Ca^{2+} homeostasis, in signal transduction, in the transport through ion channels as well as the inhibition of oxidative phosphorylation and a number of reactions in the metabolism of xenobiotics (see documentation “*n*-Butyltin Compounds” from 2008).

In the documentation of 1992 (documentation “*Di-n*-octyltin compounds, Mono-*n*-octyltin compounds” 1996, translation of the 1992 German), the thymomas and lymphomas observed in a carcinogenicity study in rats were considered to be age- and species-specific because the animals, at an initial age of four weeks, were younger than usual at the start of the study (according to the OECD test guideline, six week old animals are used) and were thus clearly more sensitive. Although the spontaneous thymus involution starts at sexual maturity in rats, the species retains a lifelong ability for thymus proliferation. In contrast, a restructuring of thymus parenchyma into fatty tissue occurs in humans at and beyond puberty, which is for the most part completed at an age of about 40 years. Here, only a residual lymphoproliferative activity remains (see documentation “*Di-n*-octyltin compounds, Mono-*n*-octyltin compounds” 1996, translation of the 1992 German). But as the ability to form T- and B-lymphocytes is retained in humans for life also without an active thymus, a disturbance of this function could then occur in another organ, and is thus relevant for humans. In animal studies *n*-octyltin compounds not only produced thymomas but also generalized lymphomas. In humans, a carcinogenic effect of *n*-octyltin compounds on the lymphatic system also beyond the age of forty is therefore not to be excluded.

More recent indications of a possible mechanism for the carcinogenicity of *n*-octyltin compounds can be found in the marked organ specificity of this substance group. In animal studies, *n*-octyltin compounds produced specifically lymphomas and thymomas, but no tumours in other organs. As, however, *n*-octyltin compounds do not accumulate preferentially in the thymus, a disturbance in specific thymus functions as cause for the toxicity and carcinogenicity of *n*-octyltin compounds is to be assumed. A disturbance in the repair mechanisms of DNA double strand breaks suggests itself as possible cause for a specific tumour formation in lymphatic tissue. As a constant permutation of gene cassettes takes place during the formation of T- and B-lymphocytes, the DNA strand has to be continuously cut and rejoined. A disturbance during this process could occur during V(D)J recombination, resulting in a genetic instability in the differentiation of T- and B-lymphocytes (Küppers and Dalla-Favera 2001; Kirsch and Lista 1997). Disturbances in V(D)J recombination of this type have been produced by etoposide and related cytostatics in human cell cultures (Chen et al. 1996; Sung et al. 2006). Errors in V(D)J recombination are being discussed as a cause of acute lymphoblastic T-cell leukaemia and non-Hodgkin lymphomas (Marculescu et al. 2006). A disturbance in V(D)J recombination produced by pesticides is being discussed as a cause for lymphoid tumours in agricultural workers (Lipkowitz et al. 1992). Arrestation of the topoisomerase-II DNA complex also represents a disturbance of the DNA repair pro-

cess, and is capable of producing lymphatic leukaemias (Felix et al. 2006; Snyder 2007; Wilstermann and Osheroff 2003).

Consequently, as an association between the disturbed repair mechanism of DNA double strand breaks, for example of V(D)J recombination or of the topoisomerase-II DNA complex, and tumours in the lymphatic tissue is plausible, this effect could be responsible for the high sensitivity of the thymus to exposure with *n*-octyltin compounds.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

In male Wistar rats, the absorption of ^{14}C -DOTC after treatment by oral gavage with 6.3 mg/kg body weight was estimated to be less than 20%. The authors concluded this value from the fact that 79.6% of the administered radioactivity was found in the faeces within the first 48 hours after treatment. The highest amount of radioactivity was found in the liver, followed by the kidney, the adrenal gland, the pituitary gland and the thyroid gland after days one, two, four and seven. Only a small amount of radioactivity was found in the thymus, about 3% in the liver, about 17% in the kidneys and about 25% in the thyroid gland on day one. Whereas radioactivity decreased in all other 19 organs from days one to seven, it increased in the thymus; this was, however, at 110 dpm/mg tissue on day seven, still lower than in the liver at 1092, the kidney at 687 and the adrenal gland at 256 dpm/mg tissue, and about equal to that of the pituitary gland at 112 and the thyroid gland at 122 dpm/mg tissue. The half-life in the plasma was three to four days (Penninks et al. 1987).

Only 0.03% was absorbed after application of MOTC to the skin of rats at 25 mg/kg body weight (no other details) (OECD 2006).

In vitro studies showed that 88% of MOT(2-EHMA)_3 MOTC (half-life 0.28 hours; OECD 2006) and up to 98% of DOT(2-EHMA)_2 DOTC are hydrolysed within 30 minutes under physiological conditions (EFSA 2004; OECD 2006).

Two diffusion cell studies using DOT(2-EHMA)_2 or DOTC with human and rat skin epidermis are available. The epidermal tissue of cadaver skin was removed by heating the skin for 40 to 45 seconds in hot water at 60°C. The rat skin was soaked in 1.5 M sodium bromide for 20 hours and then rinsed with distilled water. Finally, the epidermal tissue was detached. The penetration experiments lasted 24 hours. DOTC was applied at a dose of 1 mg/cm² (tin equivalent 0.284 mg/cm², dissolved in 50% (v/v) aqueous ethanol), and DOT(2-EHMA)_2 undiluted at a volume of 100 µl/cm² skin membrane (tin equivalent 17 mg/cm²). Aqueous ethanol (50%, v/v) was used as receptor liquid in the diffusion cells. Exposure was under occlusive and non-occlusive conditions. The dermal penetration rate (flux) was below the detection limit in the studies with DOT(2-EHMA)_2 and human skin. In the investiga-

tions with epidermal rat skin membranes, the maximum flux calculated under occlusive conditions was $0.035 \mu\text{g tin}/\text{cm}^2$ and hour after 16 up to 24 hours, and without occlusion at $0.033 \mu\text{g tin}/\text{cm}^2$ and hour after 12 up to 24 hours. The flux was also below the detection limit after application of DOTC to epidermal human skin membranes. In the case of the rat skin membranes, the first sample after one hour showed already the highest value. The 24 hour flux averaged across all cells was below the detection limit with occluded rat skin membranes. Without occlusion, this was $0.014 \mu\text{g tin}/\text{cm}^2$ and hour (Tin Stabilizer Association 2003 a, b). As recovery of the substances in these investigations was within a range of 25.2% to 58.9%, whereas the OECD prescribes a recovery of $100\% \pm 10\%$ (OECD 2004) for in vitro tests, these studies are not suitable to quantify penetration.

3.2 Metabolism

Investigations of urine and faeces in rats using gas chromatography with mass selective detection revealed no indications of MOTC or DOTC metabolites. In human gastric fluid DOT(2-EHMA)₂ is rapidly cleaved by hydrolysis. Here, exchange of the thioglycolate residue with chloride probably takes place (see documentation “Di-n-octyltin compounds, Mono-n-octyltin compounds” 1996, translation of the 1992 German).

At concentrations of 1 and $10 \mu\text{g}/\text{ml}$, both MOTC and DOTC showed metabolic stability in in vitro studies using rat and *Cynomolgus* monkey hepatocytes. Also, no metabolites were found with DOTC under conditions of the HPRT test in V79 cells of Chinese hamsters with and without addition of S9 mix. The protein binding of ¹⁴C DOTC was about 50% in the plasma of humans and rats as well as about 60% in a solution of human serum albumin (documentation “Di-n-octyltin compounds, Mono-n-octyltin compounds” 1996, translation of the 1992 German).

Some alkyltin compounds are dealkylated and hydroxylated, and the alkyl residues further oxidized. These reactions occur especially in the liver. They are NADPH-dependent and inhibited by CO, suggesting involvement of cytochrome P450 enzymes (ATSDR 2005).

4 Effects in Humans

There are no new data available.

5 Animal experiments and in vitro studies

5.1 Acute toxicity

5.1.1 Inhalation

In a study with male and female rats (no other details), the LC_{50} for DOTC as aerosol with a particle size of 10 μm after exposure for one hour was unusually high at about 37000 mg/m^3 . No explanation for this is given. In another study with DOTC as aerosol with particle sizes between 2.5 and 3.5 μm , the one-hour LC_{50} in male and female rats was 390 mg/m^3 . In a study with male rats, a four-hour LC_{50} of 439 mg/m^3 was obtained after exposure to DOTC aerosol (no data on particle size; ECB 2003).

5.1.2 Ingestion

The studies on oral acute toxicity with the corresponding LD_{50} values are summarized in Table 1. In rats, they were higher than 2000 mg/kg body weight for MOTC

Table 1 Acute oral toxicity of *n*-octyltin compounds

Substance	Species, strain, sex	LD_{50} [mg/kg body weight]	LD_{50} [$\text{mg tin}/\text{kg}$ body weight]	References
Mono-<i>n</i>-octyltin compounds				
MOTC	Rat	2200–2600	about 772–913	OECD 2006
MOT(2-EHMA) ₃	Rat	1480–3227	about 209–455	OECD 2006, Parametrix Inc 2006 b
	Mouse	1100–2000	about 155–282	Pelikan and Cerny 1970
MOT(IOMA) ₃	Rat, SD	1102–2298	about 155–324	OECD 2006
	Rat, SD	485	about 68	Parametrix Inc 2006 a
	Rat, Wistar	> 4000	> about 564	Parametrix Inc 2006 a
	Rat, Tif RAI	5000	about 705	Parametrix Inc 2006 a
Di-<i>n</i>-octyltin compounds				
DOTC	Rat	5500–8500	about 1567–2422	EFSA 2004
DOTC	Rat	3300–8840	about 941–2519	ECB 2003
DOTC	Rat	> 4000	about 1140	Schering AG 1969

Table 1 (Continued)

Substance	Species, strain, sex	LD ₅₀ [mg/kg body weight]	LD ₅₀ [mg tin/kg body weight]	References
DOTC	Rat	> about 30.3	> about 8.6	Cincinnati Milacron 1978
DOT(IOMA) ₂	Rat	3512	about 555	Ciba-Geigy AG 1980
DOT(IOMA) ₂	Rat, SD	1150–3800	about 182–600	M&T Chemicals Inc 1984
DOT(2-EHMA) ₂	Mouse, H (Czech standard strain)	2010 (1130–3560)	318	Pelikan and Cerny 1970
Di- <i>n</i> -octyltin bismaleate	Rat	2070	about 426	M&T Chemicals Inc 1963
Di- <i>n</i> -octyltin lauryl maleate	Dog	about 1000	about 258	M&T Chemicals Inc 1963
Tetra-<i>n</i>-octyltin				
TOT	Rat, Wistar, ♀	>2000	about 416	Organotin Environmental Programme 2003 c
TOT	Mouse, Swiss ♂/♀ per group	>2000	about 416	Organotin Environmental Programme 2004

and MOT(2-EHMA)₃. Also in rats, a value between 980 (female animals) and 5000 mg/kg body weight (male animals) was obtained for MOT(IOMA)₃. Mainly diarrhoea, ataxia and apathy were observed. With MOTC, lung oedema and haemorrhagic damage to the gastric and intestinal mucosa were seen in addition (OECD 2006).

The oral LD₅₀ values in rats were above 1000 mg/kg body weight (no other details) for di-*n*-octyltin compounds, 5500 or 8500 mg/kg body weight for DOTC (no other details; EFSA 2004) and about 2000 mg/kg body weight for DOT(2-EHMA)₂ (Pelikan and Cerny 1970). The LD₅₀ for TOT (89% purity, dissolved in wheat germ oil) was above 2000 mg/kg body weight in female Wistar rats and male and female Swiss mice. No substance-related toxicity was observed during the 14-day (rat) or 2-day (mouse) observation period and at necropsy (Organotin Environmental Programme 2003 b, c).

5.1.3 Dermal application

There are no studies available.

5.1.4 Intraperitoneal and intravenous injection

The LD₅₀ was between 43 and 500 mg/kg body weight in the rat and 240 mg/kg body weight in the mouse after intraperitoneal injection of DOTC. The LD₅₀ was above 10 mg/kg body weight after intravenous injection of DOTC (see documentation “Di-n-octyltin compounds, Mono-n-octyltin compounds” 1996, translation of the 1992 German).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no studies available.

5.2.2 Ingestion

Table 2 shows the findings after repeated administration of *n*-octyltin compounds to rats and dogs.

In a 90-day study in rats with 85.5% MOTC and 11.1% DOTC carried out in 2004, a NOAEL of about 2.1 or 2.3 mg tin/kg body weight and day for male or female animals was obtained. At about 10.4 or 10.9 mg tin/kg body weight and day, a reduced absolute and relative thymus weight was found and, in the female animals, lymphocyte depletion in the thymus and a reduced absolute liver weight (OECD 2006; Parametrix Inc 2006 c). In an earlier 90-day study, a reduced relative thymus weight was found in the female animals already at the lowest dose of about 1 mg tin/kg body weight and day and in all animals plus a reduced haemoglobin content in the male animals at about 3.5 mg tin/kg body weight and day and above (Cincinnati Milacron Chemicals Inc 1976).

In 90-day studies with male and female rats, a NOAEL of about 2.1 mg tin/kg body weight and day was obtained with MOT(IOMA)₃ and MOT(2-EHMA)₃. This was the highest dose in the study with MOT(2-EHMA)₃. An increased relative kidney weight and a reduced relative liver weight in the male animals was observed at the highest dose at about 7.1 mg tin/kg body weight and day in the study with MOT(IOMA)₃ (OECD 2006).

In a 2-year study with male and female rats with a mixture of MOTC (66%) and DOTC (32%) the NOAEL was about 0.22 or 0.24 mg tin/kg body weight and day. At about 0.72 mg tin/kg body weight and day and above, the absolute thymus weight was increased in the male animals, and an increased incidence of malignant lymphomas in the thymus was found.

Table 2 Studies with repeated oral administration of *n*-octyltin compounds

Species, strain, number per group	Substance	Exposure	Exposure [mg tin/kg body weight and day]	Findings	References
Rat, Wistar, 10 ♂/♀	MOTC (85.5%) + DOTC (11.1%)	90 days, 0, 10, 100, 500 mg/kg diet (♂ about 0, 0.6, 6.4, 31.5 mg/kg body weight and day; ♀ about 0, 0.7, 6.8, 32.9 mg/kg body weight and day)	♂ 0, about 0.2, 2.1, 10.4, ♀ 0, about 0.2, 2.3, 10.9	about 2.1/2.3 mg/kg body weight: NOAEL about 10.4/10.9 mg/kg body weight: alkaline phosphatase activity increased, absolute and relative thymus weight decreased, ♀: absolute liver weight decreased, lymphoid depletion in the thymus	OECD 2006, Parametrix Inc 2006 c
	MOTC (94.4%) + DOTC (5.6%)	90 days, 0, 30, 100, 300, 1000 mg/kg diet (estimated about 0, 3, 10, 30, 100 mg/kg body weight and day)	0, about 1, 3.5, 10.4, 34.7	no NOAEL about 1 mg/kg body weight: ♀: relative thymus weight decreased about 3.5 mg/kg body weight: relative thymus weight decreased, ♂: Hb content decreased	Cincinnati Milacron Chemicals Inc 1976, OECD 2006
Rat, Wistar, 10 ♂/♀				about 10.4 mg/kg body weight: relative thymus weight decreased, glucose concentration decreased, serum alkaline phosphatase activity increased, ♀: lymphocyte count decreased, neutrophil count increased about 34.7 mg/kg body weight: food consumption and body weight decreased, relative thymus weight decreased, relative liver weight increased, Hb content decreased, glucose concentration decreased, serum alkaline	

Table 2 (Continued)

Species, strain, number per group	Substance	Exposure	Exposure [mg tin/kg body weight and day]	Findings referred to tin	References
Rat, F ₃ Hybrid, 60 ♂/ ♀	MOTC (66.3%) + DOTC (32.5%)	2 years, 0.5, 15, 50, 150 mg/kg diet (♂: about 0, 0.24, 0.69, 2.2, 5.5 mg/kg body weight and day; ♀: 0, 0.26, 0.74, 2.3, 6 mg/kg body weight and day)	♂ 0, about 0.08, 0.22, 0.72, 1.79; ♀ 0, about 0.08, 0.24, 0.75, 1.95	phosphatase activity increased, specific urine density decreased, ♀ : lymphocyte count decreased, packed cell volume reduced, neutrophil count increased, protein content decreased (no other details), relative heart weight increased	Ciba-Geigy AG 1986 a
				about 0.22/0.24 mg/kg body weight: NOAEL	
				♂ at and above 0.72 mg/kg body weight: absolute thymus weight increased, malignant lymphomas in the thymus increased ♀ at and above about 0.74 mg/kg body weight: white blood cell count increased ♀ about 1.95 mg/kg body weight: absolute heart weight increased, absolute thymus weight increased, primary tumours in thymus mainly lymphomas increased, malignant lymphomas in thymus increased	
Rat, Wistar, 5 ♂/♀	MOT(IOMA) ₃ , no other details	4 weeks, 0, 50, 150, 450, 1500 mg/kg diet (at 200 g rat and 15 g diet/day: about 0.15, 0.45, 1.35, 4.5 mg/kg body weight and day)	0, about 0.02, 0.06, 0.19, 0.63	about 0.19 mg/kg body weight: NOAEL about 0.63 mg/kg body weight: ♂: food intake decreased, relative liver and kidney weight increased without histopathological correlation	Parametrix Inc 2006 a

Table 2 (Continued)

Species, strain, number per group	Substance	Exposure	Exposure [mg tin/kg body weight and day]	Findings referred to tin	References
Rat , no other details	MOT(IOMA)_{3p} no other details	90 days , 0, 30, 100, 300, 1000 mg/kg diet (about 0, 1.5, 5, 15, 50 mg/kg body weight and day)	0, about 0.2, 0.7, 2.1, 7.1	about 2.1 mg/kg body weight: NOAEL about 7.1 mg/kg body weight: relative kidney weight increased, ♂: relative liver weight decreased, no histopathological changes in liver and thymus	OECD 2006
Rat , no other details	MOT(2-EHMA)_{3p} no other details	90 days , up to 15 mg/kg body weight and day, no other details	about 2.11	about 2.11 mg/kg body weight: NOAEL	OECD 2006
Rat , Wistar, 4 ♂/♀, age: 7 weeks	DOTC , 92% purity	2 weeks , 0, 15, 50, 150, 450 mg/kg diet (about 0, 0.75, 2.5, 7.5, 22.5 mg/kg body weight and day), dose-finding study	0, about 0.2, 0.66, 1.97, 5.9	about 0.2 mg/kg body weight: ♂: absolute liver weight increased, absolute kidney weight increased, ♀: absolute adrenal gland weight increased, relative spleen weight decreased about 0.66 mg/kg body weight: ♀: absolute adrenal gland weight increased about 5.9 mg/kg body weight: food consumption decreased, body weight decreased, ♀: absolute adrenal gland weight decreased, absolute kidney weight decreased, absolute and relative spleen weight decreased, absolute liver weight decreased	Organotin Environmental Programme 2005

Table 2 (Continued)

Species, strain, number per group	Substance	Exposure	Exposure [mg tin/kg body weight and day]	Findings referred to tin	References
Rat, Wistar, 10 ♂/♀ age: 7 weeks	DOTC, 92% purity	90 days, 0, 10, 100, 300 mg/kg diet (♂ about 0, 0.7, 6.5, 19.3 mg/kg body weight and day; ♀ about 0, 0.7, 6.8, 19.8 mg/kg body weight and day), OECD test guideline 408	♂ 0, about 0.18, 1.7, 5.1, ♀ 0, about 0.18, 1.8, 5.2	<p>at about 0.18 mg/kg body weight and above: absolute and relative thymus weight decreased</p> <p>at about 1.7/1.8 mg/kg body weight and above: alkaline phosphatase activity increased, bilirubin increased, lymphoid depletion in the thymus</p> <p>♀: relative adrenal gland weight decreased</p> <p>at about 5.2/5.2 mg/kg body weight and above: food consumption decreased, body weight decreased, haemoglobin decreased, packed cell volume <i>reduced</i>, white blood cell count decreased, lymphocyte count decreased, prothrombin time decreased, total protein decreased, albumin/globulin ratio increased, bile acid increased, calcium decreased, relative liver weight increased,</p> <p>♀: crystals in the urine, absolute spleen weight decreased, relative kidney weight increased, absolute adrenal gland weight decreased,</p> <p>♂: relative testis weight increased</p>	Organotin Environmental Programme 2005

Table 2 (Continued)

Species, strain, number per group	Substance	Exposure	Exposure [mg tin/kg body weight and day]	Findings referred to tin	References
Rat, Wistar, 15 ♂/♀	DOT(2-EHMA)₃ , 97%	90 days , 0, 10, 25, 50, 100, 250, 500,	♂ 0, about 0.08, 0.18, 0.36, 0.71, 1.82, 3.76, 7.27, ♀ 0, about 0.08, 0.23, 0.47, 0.94, 2.35, 4.7, 9.4	about 0.08 mg/kg body weight: NOAEL	Ciba-Geigy AG 1992
	MOT(2-EHMA)₃ , 0.3%	1000 mg/kg diet (♂ 0, about 0.5, 1.15, 2.3, 4.5, 11.5, 23.8,		about 0.18/0.23 mg/kg body weight: relative thymus weight decreased about 0.36/0.47 mg/kg body weight: relative thymus weight decreased about 0.71/0.94 mg/kg	
	TriOT(2-EHMA) , 2.17%	46 mg/kg body weight and day; ♀ 0, about 0.5, 1.48, 2.98, 5.95, 14.86, 29.75, 59.5 mg/kg body weight and day)		body weight: neutrophil count increased, leukocyte count increased, changed urinary parameters, relative thymus weight decreased, relative liver weight increased, relative kidney weight increased, lymphoid depletion and atrophy in the thymus about 1.82/2.35 mg/kg body weight: mortality increased, feed consumption and body weight decreased, haemoglobin decreased, white blood cell count decreased, neutrophilic granulocyte count increased, leukocyte count increased, changed urinary parameters, relative thymus weight decreased, relative liver weight increased, relative kidney weight increased, lymphoid depletion and atrophy in the thymus, mild histological "lesions" in liver and kidneys	

Table 2 (Continued)

Species, strain, number per group	Substance	Exposure	Exposure [mg tin/kg body weight and day]	Findings referred to tin	References
				about 3.76/4.7 mg/kg body weight: mortality increased, feed consumption and body weight decreased, haemoglobin decreased, white blood cell count decreased, neutrophil count increased, leukocyte count increased, changed urinary parameters, relative liver weight increased, relative kidney weight increased, relative thymus weight decreased, relative brain weight increased, lymphoid depletion and atrophy in the thymus, moderate histological lesions in liver and kidneys, ♀ relative heart weight increased, ♂ relative testis weight increased	
				about 7.27/9.4 mg/kg body weight: mortality increased, food consumption and body weight decreased, changed urinary parameters, relative thymus weight decreased, lymphoid depletion and atrophy in the thymus, moderate histological lesions in liver and kidneys	Ciba-Geigy AG 1974
Rat, Sprague Dawley, 10 ♂/♀	DOT(2-EHMA)₂ (70%) MOT(2-EHMA)₃ (30%)	90 days, 0, 25, 50, 100 mg/kg diet (0, about 1.6, 3.3, 6.6 mg/kg body weight and day)	0, about 0.25, 0.51, 1.01	about 0.25 mg/kg body weight: NOAEL about 0.51 mg/kg body weight: relative and absolute thymus weight decreased about 1.01 mg/kg body weight: relative and absolute thymus weight decreased	

Table 2 (Continued)

Species, strain, number per group	Substance	Exposure	Exposure [mg tin/kg body weight and day]	Findings referred to tin	References
Rat , Sprague Dawley, 15 ♂/♀ juveniles	DOT(IOMA)₂ , no data on purity	90 days, 0, 20, 50, 150 mg/kg diet (0, about 0.5–1.8, 1.3–4.3, 3.8–12.8 mg/kg body weight and day)	0, about 0.08–0.13, 0.21–0.68, 0.60–2.02	about 0.6–2.02 mg/kg body weight: NOAEL	Schering AG 1970 a
Dog , beagle, 3 ♂/♀	DOT(IOMA)₂ , no data on purity	14 weeks , 0, 20, 50, 150 mg/kg diet (0, about 0.5, 1.25, 3.75 mg/kg body weight and day), OECD test guideline 409	0, about 0.08, 0.2, 0.59	about 0.59 mg/kg body weight: NOAEL	Schering AG 1970 b
Rat , Long Evans, 25 ♂/♀, controls 50 ♂/♀	di-<i>n</i>-octyltin maleate or DOT(IOMA)₂ , no data on purity	2 years , 0, 20, 125, 375 mg/kg diet (at 200 g body weight and 15 g feed/day: 0, about 1.5, 9.4, 28.1 mg/kg body weight and day)	DOT maleate: 0, about 0.39, 2.43, 7.25, DOT(IOMA) ₂ : 0, about 0.24, 1.48, 4.44	no substance-related increase in tumour incidences, histopathology: ♂/♀: changes in kidneys, lungs ♂: changes in testes, ♀: changes in liver, pituitary gland	M&T Chemicals Inc 1966
Dog , beagle, 4 ♂ per group	di-<i>n</i>-octyltin maleate or DOT(IOMA)₂ , no data on purity	3 and 6 months , 0, 20, 125, 375 mg/kg diet (at 10 kg body weight and 750 g diet/day: 0, about 1.5, 9.4, 28.1 mg/kg body weight and day)	DOT maleate: 0, about 0.39, 2.43, 7.25, DOT (IOMA) ₂ : 0, about 0.24, 1.48, 4.44	no substance-related increase in tumour incidences	M&T Chemicals Inc 1966

Table 2 (Continued)

Species, strain, number per group	Substance	Exposure	Exposure [mg tin/kg body weight and day]	Findings referred to tin	References
Dog , beagle, 3 ♂/♀	di-<i>n</i>-octyltin maleate , DOT(IOMA) ₂ , no data on purity	2 years , controls: per group 5 animals 0, 20, 125, 375 mg/kg diet DOT maleate (at 10 kg body weight and 750 g diet/day: 0, about 1.5, 9.4, 28.1 or 0, 20, 50, 150 mg/kg diet DOT(IOMA), (at 10 kg body weight and 750 g diet/day: 0, about 1.5, 3.75, 11.25)	DOT maleate: 0, about 0.39, 2.43, 7.25 DOT(IOMA) ₂ : 0, about 0.24, 0.59, 1.78	no substance-related increase in tumour incidences	M&T Chemicals Inc 1966
Rat , Wistar, 52 ♂/♀	TOT , purity 90.79%	28 day study , ♂: 33 days, ♀: 2 weeks before mating up to day 5 of lactation, 0, 500, 1500, 7500 mg/kg diet (♂: about 31, 92, 460 mg/kg body weight and day, ♀: about 34, 110, 525 mg/kg body weight and day) OECD test guideline 422	♂: 0, about 6.5, 19.1, 95.7, ♀: 0, about 7.1, 22.9, 109.2	about 19.1/22.9 mg/kg body weight: NOAEL about 95.7/109.2 mg/kg body weight: food consumption decreased, albumin/globulin ratio increased, slight accumulation of macrophages in mesenteric lymph nodes, ♂: absolute thymus weight decreased, ♀: absolute and relative thymus weight decreased, lymphoid depletion in the thymus	Organotin Environmental Programme 2004

Hb: haemoglobin

In the female animals, blood parameters were changed at 0.75 mg tin/kg body weight and above. Changes in the thymus were found at about 1.95 mg/kg body weight and day (Ciba-Geigy AG 1986 a).

No NOAEL was obtained from any of the studies in rats with repeated administration of DOTC alone. In a 2-week study, increased absolute kidney and liver weights occurred in the male animals and increased absolute adrenal gland and reduced relative spleen weights in the female animals at the lowest dose of about 0.2 mg tin/kg body weight and day (Organotin Environmental Programme 2005). In a 90-day study, reduced relative thymus weight and lymphoid depletion in the thymus and thymus-dependent tissues were mainly observed at about 0.18 mg tin/kg body weight and day and above (Organotin Environmental Programme 2005). No lower dose was tested.

In two 90-day studies in rats, a NOAEL of about 0.08 mg tin/kg body weight and day (70% DOT(2-EHMA)₂; Ciba-Geigy AG 1992) was obtained for DOT(2-EHMA)₂ in one of the studies, and a NOAEL of about 0.25 mg tin/kg body weight and day in the other (97% DOT(2-EHMA)₂; Ciba-Geigy AG 1974). Reduced relative thymus weights were found at the next higher dose; at and above about 0.18 or 0.23 mg tin/kg body weight and day in male and female animals in the first study, and at and above about 0.51 mg tin/kg body weight and day in the second.

In a 90-day study with DOT(IOMA)₂ in rats, the NOAEL was at the highest dose of about 0.6 up to 2.02 mg tin/kg body weight and day (Schering AG 1970 a) and in a 14-week study in dogs at the highest dose of about 0.59 mg tin /kg body weight and day (Schering AG 1970b). Other studies with **di-*n*-octyltin maleate** or **DOT (IOMA)₂** in rats and dogs (M&T Chemicals Inc. 1966) are inadequately documented and cannot be included in the evaluation.

In a one-generation study in rats (male animals exposed about five weeks, female animals about six weeks), the NOAEL for TOT was about 19.1 or 22.9 mg tin /kg body weight and day in male animals or female animals. At about 95.7 mg tin/kg body weight and day and above, the absolute thymus weight was reduced. Slight accumulation of macrophages in the lymph nodes and, in the female animals, lymphoid depletion in the thymus were found (Organotin Environmental Programme 2004).

The lowest effect level of one of the *n*-octyltin compounds in studies with repeated oral administration was about 0.18 mg tin/kg body weight and day in two 90-day studies in rats, one with DOTC and one with DOT(2-EHMA)₂. After administration of DOTC, reduced relative thymus weight and lymphoid depletion in the thymus were found. No lower doses were tested. A reduced relative thymus weight was observed with DOT(2-EHMA)₂. In this study, a lower dose of about 0.08 mg tin/kg body weight and day was tested, which was without effect and thus formed the NOAEL for this study.

5.2.3 Dermal absorption

There are no studies available.

5.3 Effects on skin and mucous membranes

5.3.1 Skin

Undiluted MOTC was slightly irritating to the skin of rabbits. Mild to severe oedemas were observed after 24 hours, which had only slightly regressed after 72 hours. As the study is not described in greater detail, this statement is to be evaluated as an indication only (OECD 2006).

Undiluted MOT(2-EHMA)₃ or MOT(IOMA)₃ (0.5 ml, 99% purity) after semiocclusive treatment over a period of four hours was regarded as slightly irritating to the skin of three New Zealand rabbits per group (OECD test guideline 404). The reactions in the skin were reversible within ten days after application (OECD 2006).

In a patch test with three male and female rabbits per group and occlusive application, DOTC (0.5 g in 50% polyethylene glycol) produced mild and well defined erythema and mild oedema on the intact or abraded skin after 24 hours. These were almost completely reversible after 72 hours. The primary irritation index was given as 1.8 (no other details) (ECB 2003).

In a test in accordance with OECD test guideline 404, a mixture of undiluted DOT(2-EHMA)₂ and MOT(2-EHMA)₃ (70:30) was irritating to the skin of three female New Zealand rabbits after occlusive application (application time four hours). The skin reactions were no longer present after ten days (OECD 2006; Parametrix Inc. 2006 b, c). In an earlier test, a mixture of DOT(2-EHMA)₂ and MOT(2-EHMA)₃ (53%:23%) dissolved in 25% castor oil produced mild erythema and mild oedema in the intact or abraded skin of three rabbits per group after 24 hours occlusive application. The substances were classified as slightly irritating (OECD 2006).

No data are available on the effect of TOT on the skin (OECD 2006).

5.3.2 Eyes

MOTC was assessed as being highly irritating to the conjunctiva of rabbits (OECD 2006).

0.1 ml undiluted MOT(IOMA)₃ was slightly irritating to the conjunctiva of three New Zealand rabbits each after 24 hours. The redness was reversible after three days. MOT(IOMA)₃ was evaluated as being not irritant to the eyes (OECD test guideline 405; Parametrix Inc. 2006 a).

Twenty-four hours after application, undiluted DOTC (0.1 ml, about 80 mg) produced mild irritation of the conjunctiva in the unrinsed eyes of six male and six

female rabbits (primary irritation index 7.5; no other details). The symptoms had almost disappeared after 48 hours (primary irritation index 1.3) and were completely gone after 72 hours (no other details; ECB 2003).

There are no data available on the effects of TOT on the mucous membranes (OECD 2006).

The *n*-octyltin compounds investigated were slightly irritating in the skin and conjunctiva of rabbits.

5.4 Allergenic effects

MOT(2-EHMA)₃ was weakly sensitizing in guinea pigs after intradermal injection and occlusive dermal application in accordance with OECD test guideline 406 (OECD 2006; Ciba-Geigy AG 1993 a).

In studies carried out with DOT(2-EHMA)₂ and MOT(2-EHMA)₃ (70:30 mixture) in accordance with OECD test guideline 406, intradermal application in guinea pigs resulted in pronounced skin sensitization. Erythemas were found in > 75% of the animals after 24 hours and in > 80% after 48 hours (Ciba-Geigy AG 1993 b).

No studies are available on the other compounds. As, under physiological conditions, cleavage of at least part of the ligands can be assumed, the pronounced and weak sensitization produced by DOT(2-EHMA)₂ and MOT(2-EHMA)₃, respectively, in guinea pigs is probably due to the sensitizing effects of the ligands found and not to that of the tin compounds.

5.5 Reproductive toxicity

5.5.1 Fertility

The available fertility studies are listed in Table 3.

In a two-generation study, Sprague Dawley rats were given 99.3% pure MOT (IOMA)₃ with their feed (about 3.17 mg tin/kg body weight and day). This was the NOAEL for fertility and toxicity for parent animals and offspring (Schering AG 1996).

In a 90-day toxicity study female Wistar rats were given 0, approx. 0.2, 2.3 or 10.9 mg tin/kg body weight and day as MOTC (85.5%) and DOTC (11.1%) with their diet (see Section 5.2.2). In accordance with OECD test guideline 421 satellite groups consisting of ten male and female animals per dose were mated after two weeks of exposure and the offspring investigated on postnatal day 4. Toxic effects such as thymus atrophy and lymphoid depletion occurred at about 2.3 mg tin/kg body weight and day and above, and a reduced gestation index was obtained at about 10.9 mg tin/kg body weight and day. The NOAEL for parental toxicity was at the lowest dose group, i.e. about 0.2 mg tin/kg body weight and day. The NOAEL

Table 3 Studies on fertility with *n*-octyltin compounds

Species, strain, number per group	Exposure	Exposure [mg tin/kg body weight and day]	Findings referred to tin	References
Rat, Sprague-Dawley, 25 ♂/♀	2-generation study 0, 300 mg/kg diet (F ₀ about 22.5 mg/kg body weight and day; F ₁ about 24 mg/kg body weight and day), MOT (IOMA) ₃ (99.3%) OECD 416	F ₀ : about 3.17, F ₁ : about 3.38	about 3.17 mg/kg body weight: F₀; NOAEL (fertility, toxicity); F ₁ : ♀ body weight gain increased within the range of historical controls; ♂: relative thyroid weight increased, ♀: relative spleen weight increased, relative thymus weight increased; F ₂ : no substance-related changes	Schering AG 1996
Rat, Wistar, 10 ♀/♂	90 days, satellite group OECD 421 0, 10, 100, 500 mg/kg diet (♂ about 0, 0.6, 6.4, 31.5 mg/kg body weight and day; ♀ about 0, 0.7, 6.8, 32.9 mg/kg body weight and day); MOTC (85.5%) + DOTC (11.1%) mating of one satellite group; study of offspring on PND 4	♂: 0, about 0.2, 2.1, 10.4, ♀: 0, about 0.2, 2.3, 10.9	about 0.2 mg/kg body weight: F₀; NOAEL (toxicity) about 2.3 mg/kg body weight: ♀ F₀; NOAEL (fertility); thymus atrophy, lymphoid depletion, alkaline phosphatase activity increased; F ₁ : NOAEL (developmental toxicity) about 10.9 mg/kg body weight: ♀ F₀; severe thymus atrophy, lymphoid depletion, gestation index decreased; F ₁ : postimplantation loss (41%) increased, litter size decreased, number of stillbirths increased, postnatal mortality increased	OECD 2006; Parametrix Inc 2006 c
Rat, Sprague Dawley, 25 ♂/♀	2-generation study 0, 20, 60, 200 mg/kg diet (about 0, 1.5, 4.5, 15 mg/kg body weight and day); DOT(IOMA)₂(78.8%) + MOT(IOMA)₃ (16.9%) OECD test guideline 416	0, about 0.22; 0.67, 2.23	about 0.22 mg/kg body weight: F₀ + F₁; NOAEL (toxicity, developmental toxicity) about 0.67 mg/kg body weight: F ₀ : NOAEL (fertility) ♂: relative thymus weight slightly decreased (not significant); F ₁ : stillbirths slightly increased (not significant), relative thymus weight decreased (not significant in ♀ on postnatal day 22); F ₁ parent animals: relative thymus weight decreased (♂)	Schering AG 1996

Table 3 (Continued)

Species, strain, number per group (wie Tabelle 2?)	Exposure	Exposure [mg tin/kg body weight and day]	Findings referred to tin	References
			about 2.23 mg/kg body weight: F ₀ : food consumption decreased, ♂: thymus involution increased, relative thymus weight decreased, ♀: relative thymus weight decreased; F ₁ : weight at birth decreased, mortality up to postnatal day 4 unchanged, mortality on postnatal days 4 to 21 increased, body weight gain up to postnatal day 21 decreased, delayed vaginal opening, relative thymus weight decreased, ♂:body weight decreased, ♀: relative spleen weight decreased; F ₁ parent animals: ♀: absolute food consumption decreased, ♂: relative thymus weight decreased; thymus involution increased; F ₂ : number of stillbirths increased, mortality up to postnatal day 21 increased, delayed development of external ear, delayed opening of eyes and ears, number of negative acoustic startle reflexes increased	
Rat, Wistar, 10 ♀/♂	90 days, satellite group OECD 421 0, 10, 100, 300 mg/kg diet (about 0, 0.7, 6.8, 19.8 mg/kg body weight and day), DOTC (92%) mating of one satellite group; study of offspring on PND 4	♂: 0, about 0.18, 1.7, 5.1, ♀: 0, about 0.18, 1.8, 5.2	at about 0.18 mg/kg body weight and above: F ₀ : NOAEL (fertility), lymphoid depletion in the thymus; F ₁ : NOAEL (developmental toxicity) at about 1.8 mg/kg body weight and above: F ₀ : gestation index decreased, body weight decreased, food consumption decreased, absolute and relative thymus weight decreased; F ₁ : postimplantation loss increased, number of stillbirths increased,	Organotin Environmental Programme 2005

Table 3 (Continued)

Species, strain, number per group (wie Tabelle 2?)	Exposure	Exposure [mg tin/kg body weight and day]	Findings referred to tin	References
Rat, Long-Evans, 10 ♂, 20 ♀	3-generation study 0, 20, 125, 375 mg/kg diet (about 0, 1.5, 9.4, 28.1 mg/kg body weight and day) di- <i>n</i> -octyltin maleate	0, about 0.39, 2.43, 7.25	cannibalism of offspring increased, number of runts increased, body weight decreased, postnatal mortality increased about 5.2 mg/kg body weight: F ₁ : number of cold pups and runts increased about 7.25 mg/kg body weight: F ₀ : degeneration of testes; F ₁ : litter size decreased, survival rate of foetuses decreased	ATOCHEM 1968
Rat, Long-Evans, 10 ♂, 20 ♀	3-generation study 0.20, 125, 375 mg/kg diet (about 0, 1.5, 9.4, 28.1 mg/kg body weight and day) DOT (IOMA) ₂	0, about 0.24, 1.48, 4.44	about 4.44 mg/kg body weight: F ₀ : degeneration of testes; F ₁ : litter size decreased, survival rate of foetuses decreased	ATOCHEM 1968
Rat, Wistar, 52 ♂/♀	OECD 422 ♂: 33 days, ♀: 2 weeks before mating up to day 5 of lactation, 0, 500, 1500, 7500 mg/kg diet (♂: about 31, 92, 460 mg/kg body weight and day, ♀: about 34, 110, 525 mg/kg body weight and day) TOT (90.8%)	♂: 0, about 6.5, 19.1, 95.7, ♀: 0, about 7.1, 22.9, 109.2	about 95.7/109.2 mg/kg body weight: F ₀ : +F ₁ : NOAEL (toxicity, developmental toxicity)	Organotin Environmental Programme 2004

PND: postnatal day

for effects on fertility and developmental toxicity (see Section 5.5.2) was about 2.3 mg tin/kg body weight and day (OECD 2006; Parametrix Inc. 2006 c).

In another 2-generation study, tin was administered with the diet to Sprague Dawley rats in the form of a mixture of 78.8% DOT(IOMA)₂ and 16.9% MOT(IOMA)₃ at dose levels of 0, approx. 0.22, 0.67 or 2.23 mg tin/kg body weight and day. The male F₀ animals received the mixture from ten weeks before mating up to the end of the three-week mating period. The female F₀ animals were treated from ten weeks before mating, during pregnancy, and up to the end of lactation. The animals of the F₁ generation were mated 14 weeks after weaning. Here, exposure was continued up to the end of mating (male animals) or up to the end of lactation (female animals). The relative thymus weight of the F₀ animals was reduced at 2.23 mg tin/kg body weight and day. An increased mortality of the offspring was observed at 2.23 mg tin/kg body weight and day (see Section 5.5.2). The NOAEL for the systemic and developmental toxicity of tin was 0.22 mg tin/kg body weight and day (Schering AG 1996; see Table 3). The NOAEL for fertility was 0.67 mg tin/kg body weight and day.

In another 90-day toxicity study, in which Wistar rats were given tin in the form of DOTC (92%) at dose levels of 0, approx. 0.18, 1.8 or 5.2 mg/kg body weight and day (see Section 5.2.2), satellite groups comprising ten female and male animals per dose group were mated, and the pups investigated on postnatal day 4. Increased thymus atrophy was found in the parent animals of all dose groups. Therefore, a NOAEL for maternal toxicity was not obtained. No effects on the number of implantations were found up to doses of about 5.2 mg tin/kg body weight and day, though the gestation index was reduced at about 1.8 mg tin/kg body weight and day and above (Organotin Environmental Programme 2005). The NOAEL for the effects of tin on fertility and developmental toxicity (see Section 5.5.2) was here about 0.18 mg tin/kg body weight and day.

In two three-generation studies male and female Long-Evans rats were given di-*n*-octyltin maleate or DOT(IOMA)₂ at dose levels of 0, 20, 125 or 375 mg/kg diet. This corresponds to daily tin doses of 0, approx. 0.39, 2.43, 7.25 mg/kg body weight (di-*n*-octyltin maleate) or 0, approx. 0.24, 1.48, 4.44 mg/kg body weight (DOT(IOMA)₂). After an exposure lasting about 80 days, the female F₀ animals were mated with two male animals each for a period of two weeks. After weaning, the offspring were removed and rejected, and the parent animals mated again after ten days. From this second litter, randomly selected animals (excluding the runts) were again mated. This procedure was continued through all three generations. Fertility was reduced in the animals of each of the three highest dose groups; in addition, litter sizes were smaller, and the survival rate in the F₁ offspring was lower. As no changes were found in the reproductive organs of the female animals but degeneration of the testes was found in the male animals, the reduced fertility is attributed to the effects occurring in the male animals (ATOChem 1968). In this study, the investigations are only described in summary form.

No substance-related effects in parent animals and offspring occurred up to the highest dose in a feeding study with TOT carried out in Wistar rats according to

OECD test guideline 422 at dose levels of 0, approx. 7.1, 22.9 or 109 mg tin/kg body weight and day (female animals) (purity: 90.8%), (Organotin Environmental Programme 2004).

Summary

In rats, impaired fertility in the form of a reduced gestation index is only found at toxic doses. As, in three-generation studies, histological changes in the testes of the offspring were observed only at relatively high doses of di-*n*-octyltin compounds (≥ 4.4 mg tin/kg body weight and day; ATOCHEM 1968), the reduced gestation index at lower doses (tin ≥ 1.8 mg/kg body weight and day; Organotin Environmental Programme 2005) is presumably due to the foetotoxic effects (postimplantation losses and stillbirths).

5.5.2 Developmental toxicity

Prenatal toxicity

The available studies on prenatal toxicity are listed in Table 4 and Table 5. In these studies, an adequate assessment of maternal toxicity is not possible due to the absence of details on thymus weight and/or other immunological parameters.

In two studies, a mixture of DOT(IOMA)₂ (80%) and MOT(IOMA)₃ (20%) was administered to NMRI mice at daily dose levels of 0, about 3.1, 4.7 or 7.1 mg tin/kg body weight or about 10.5 or 15.5 mg tin/kg body weight from days 6 to 17 of gestation. One dam in the highest dose group died. The body weight gain was slightly but not significantly reduced in the dams of the two highest dose groups, and the relative liver weight was significantly reduced in the highest dose group. The relative and absolute thymus weight was reduced at 7.1 mg tin/kg body weight and day and above. Foetotoxic effects such as increased resorption rates, reduced foetus weight as well as cleft palates were found at doses of 10.5 or 15.5 mg tin/kg body weight and day. In addition, bent limbs and increased malformations, mainly exencephaly, were found at 15.5 mg tin/kg body weight and day. The number of variations such as supernumerary cervical and lumbar ribs and delayed ossification was increased in the low dose groups (3.1 to 7.1 mg tin/kg body weight and day). The NOAEL for maternal toxicity was 4.7 mg tin/kg body weight and day. The authors did not derive a NOAEL for developmental toxicity (Faqi et al. 2001). The findings of the low dose groups from 3.1 to 7.1 mg tin/kg body weight and day consisted of variations or delayed development, with partly high spontaneous incidences. They showed no clear dose dependency (see Table 4). The incidences of supernumerary lumbar ribs in the three lower doses, i.e. 68.5%, 67.8% and 76.0% were significantly higher than in the control group (47.1%). However, incidences of 78% and 55% were obtained in the second study using higher doses, which showed no significant increase compared with the control group (52%) and also no dose-dependency. The significantly increased incidences of unossified digits and supernumerary cervical ribs, which were only observed in the low dose group, also showed no dose-depen-

Table 4 Skeletal anomalies in mice foetuses after exposure to DOT(IOMA)₂ (80%) and MOT(IOMA)₃ (20%) from gestation days 6 to 17 (Faqi et al. 2001)

Effects	Dose (mg tin/kg body weight and day)			
	0	about 3.1	about 4.7	about 7.1
Foetuses (n)	280	312	323	364
Resorptions	21 (7.5%)	20 (6.4%)	19 (5.9%)	35 (9.6%)
Digit unossified	3 (1.1%)	8 (2.3%)*	6 (1.9%)	16 (4.4%)*
Hindpaw incompletely ossified	–	3 (1.0%)	7 (2.2%)	34 (9.3%)*
Os frontale misshapened	45 (16.0%)	42 (13.4%)	56 (17.4%)	92 (25.2%)*
Parietale incompletely ossified	52 (18.5%)	39 (12.5%)	55 (17.0%)	89 (24.4%)*
Supernumerary ribs (cervical)	24 (8.6%)	51 (16.3%)*	27 (8.4%)	53 (14.5%)*
Supernumerary ribs (lumbar)	132 (47.1%)	214 (68.5%)*	219 (67.8%)*	277 (76.0%)*
	Dose (mg tin/kg body weight and day)			
	0	about 10.5	about 15.5	
Foetuses (n)	191	206	183	
Resorptions	16 (8%)	30 (13%)	36 (16%)	
Digit unossified	no data	no data	no data	
Supernumerary ribs (cervical)	23 (12%)	19 (8.7%)	15 (8.2%)	
Supernumerary ribs (lumbar)	100 (52%)	171 (78%)	101 (55%)	
Cleft palate	3 (1.6%)	12 (5.5%)*	17 (9.3%)*	
Exencephaly	–	–	13 (7.1%)	

*significant (no other details)

dency. These showed no increase in the second study either (see Table 4) and are thus not considered relevant for evaluation. The dose level of 7.1 mg tin/kg body weight and day is derived by the Commission as being the relevant LOAEL for the developmental toxicity of tin. At this dose the incidences of misshapen *os frontale* and of incomplete ossification of hindpaws and *os parietale* were significantly increased. Therefore, the NOAEL for developmental and maternal toxicity of tin is 4.7 mg tin/kg body weight and day.

An 80:20 mixture of DOT(IOMA)₂ and MOT(IOMA)₃ in doses of 0, about 0.15, 0.77 or 3.9 mg tin/kg body weight and day was administered orally to rats from gestation days 6 to 15. In the dams of the highest dose group, body weight gain was reduced and the number of dead foetuses increased in one dam. Skeletal and visceral investigations of the foetuses revealed no substance-related changes. The NOAEL for maternal toxicity (i.e. reduced body weight gain) and developmental toxicity is about 0.77 mg tin/kg body weight and day (Schering AG 1991).

Table 5 Studies on the prenatal developmental toxicity of n-octyltin compounds

Species, strain, No. of animals per group	Exposure	Exposure [mg tin/kg body weight/day]	Findings referred to tin	References
Mouse, NMRI, 22–30	GD 6–17	0, about 3.1, 4.7, 7.1, 10.5, 15.5	about 3.1 mg/kg body weight: F ₁ : supernumerary cervical and lumbar ribs, delayed ossification (relevance questionable)	Faqi et al. 2001
	0, 20, 30, 45, 67, 100 mg/kg body weight and day, gavage DOT(IOMA) ₂ (80%) + MOT (IOMA) ₃ (20%) study GD 18		about 4.7 mg/kg body weight: F ₀ : NOAEL (maternal toxicity, developmental toxicity), F ₁ : supernumerary lumbar ribs (relevance questionable) about 7.1 mg/kg body weight: F ₀ : absolute and relative thymus weight decreased, F ₁ : supernumerary cervical and lumbar ribs, delayed ossification at about 10.5 mg/kg body weight and above: F ₀ : no effect, F ₁ : resorptions increased, postimplantation loss increased, foetus weight decreased, cleft palates increased at about 15.5 mg/kg body weight: F ₀ : relative thymus weight decreased, relative liver weight decreased, resorptions increased, F ₁ : foetuses weight decreased, cleft palates increased, hind- and forelimbs bentincreased, exencephaly increased	
Rat, no other details	GD 6–15	0, about 6.58, 19.75, 39.51	about 6.58 mg/kg body weight: NOAEL (maternal toxicity, developmental toxicity) at about 19.75 mg/kg body weight and above: F ₀ : food intake decreased, F ₁ : foetuses weight decreased, delayed ossification, incomplete ossification of 5th sternbrae	Ciba-Geigy AG 1983 d
	0, 20, 60, 120 mg/kg body weight and day, gavage MOT(¹⁴ C-IOMA) ₃ (67%) + DOT(¹⁴ C-IOMA) ₂ (33%) no data on study		about 39.51 mg/kg body weight: F ₀ : body weight gain decreased	

Table 5 (Continued)

Species, strain, No. of animals per group	Exposure	Exposure [mg tin/kg body weight/day]	Findings referred to tin	References
Rat, Han-Wistar, 25	GD 6–15 0, 1, 5, 25 mg/kg body weight and day; gavage DOT(IOMA)₂ (80%) + MOT (IOMA)₃ (20%) study GD 21	0, about 0.15, 0.77, 3.9	about 0.77 mg/kg body weight: F ₀ , F ₁ : NOAEL (maternal toxicity and developmental toxicity) about 3.9 mg/kg body weight: F ₀ : corrected body weight decreased, body weight gain decreased, F ₁ : dead foetuses increased (7 dead foetuses, all from one dam)	Schering AG 1991
Rabbit, New Zealand, 23–24 per group	GD 6–18 0, 1, 10, 100 mg/kg body weight and day, gavage DOT(IOMA)₂ (80%) + MOT (IOMA)₃ (20%) study GD 28	0, about 0.16, 1.55, 15.5	about 0.16 mg/kg body weight: NOAEL (developmental toxicity) at about 1.55 mg/kg body weight and above: NOAEL (maternal toxicity), F ₁ : non-ossified sections in skull increased (not significant) about 15.5 mg/kg body weight: F ₀ : haemorrhagic discharge (3/24), abortions increased, F ₁ : postimplantation loss (early resorptions) increased, visceral anomalies (greatly distended renal pelvis and small vessels branching off the aortic arch) increased, non-ossified sections in skull, sternum and tarsal bones, foetus weight decreased, living foetuses decreased	Schering AG 1992

GD: gestation day

An 80:20 mixture of DOT(IOMA)₂ and MOT(IOMA)₃ in doses of 0, approx. 0.16, 1.55 or 15.5 mg tin/kg body weight and day was also administered to New Zealand rabbits from gestation days 6 to 18. An increase in early resorptions and visceral anomalies (such as greatly distended renal pelvis, undersized blood vessels and small vessels branching off the aortal arch), ossification disorders, reduced foetus weights and a lower number of living foetuses were found at 15.5 mg tin/kg body weight and day. Even at about 1.55 mg/kg body weight and day, ossification disorders occurred but were not significant. Incompletely ossified skull bones occurred in 57.1% of the high-dose foetuses, in 23.7% of the mid-dose foetuses, but only in 12.1 and 9.3% of the low-dose and control foetuses, respectively. Therefore, the authors regarded the findings in the mid dose group and above – in spite of absent statistical significance – as being a treatment-related effect. The NOAEL for developmental toxicity in this study is about 0.16 mg tin/kg body weight and day, the NOAEL for maternal toxicity (haemorrhagic discharge, abortions) about 1.55 mg tin/kg body weight and day (Schering AG 1992). As no immunological parameters such as thymus weight were investigated, a conclusive statement about maternal NOAEL or LOAEL is not possible. A dose of 0.54 mg tin/kg body weight and day is obtained from a benchmark calculation (BMDS software of EPA Version 1.4.1) for an increase in the incidence of delayed ossification by 5% above the control value (see Figure 1).

In a study only available in the form of an abstract, pregnant rats (no other details) received by gavage a 67:33 mixture MOT(IOMA)₃:DOT(IOMA)₂ corresponding to doses of 0, approx. 6.6, 19.8 or 39.5 mg tin/kg body weight and day from days 6 to 15 of gestation. The NOAEL for maternal and developmental toxicity was 6.6 mg tin/kg body weight and day. At 19.8 mg tin/kg body weight and day and above, the food intake of the dams was significantly reduced, and also the body weight at the highest dose. At 19.8 mg tin/kg body weight and day and above, growth retardation and delayed ossification of the hindlimbs and the sternebrae were observed in the foetuses. These signs were evaluated as secondary effects of maternal toxicity (no other details; Ciba-Geigy AG 1983 d). There are no details as to the doses at which immunotoxic effects occurred.

Postnatal toxicity

In a two-generation study (see Section 5.5.1) Sprague Dawley rats were given about 3.17 mg/kg body weight and day 99.3% pure MOT(IOMA)₃ with the diet. This was the NOAEL for fertility and toxicity in parent animals and offspring (Schering AG 1996).

In the satellite groups of a 90-day rat study already described (see Section 5.5.1) above (according to OECD test guideline 421) with oral administration of MOTC (85.50%) and DOTC (11.07%) at dose levels of 0, about 0.2, 2.3 or 10.9 mg tin/kg body weight and day (OECD 2006; Parametrix Inc. 2006 c), in which ten male and female animals per group and dose were mated and the offspring investigated on postnatal day 4, maternal effects (thymus atrophy) occurred at about 2.3 mg tin/kg

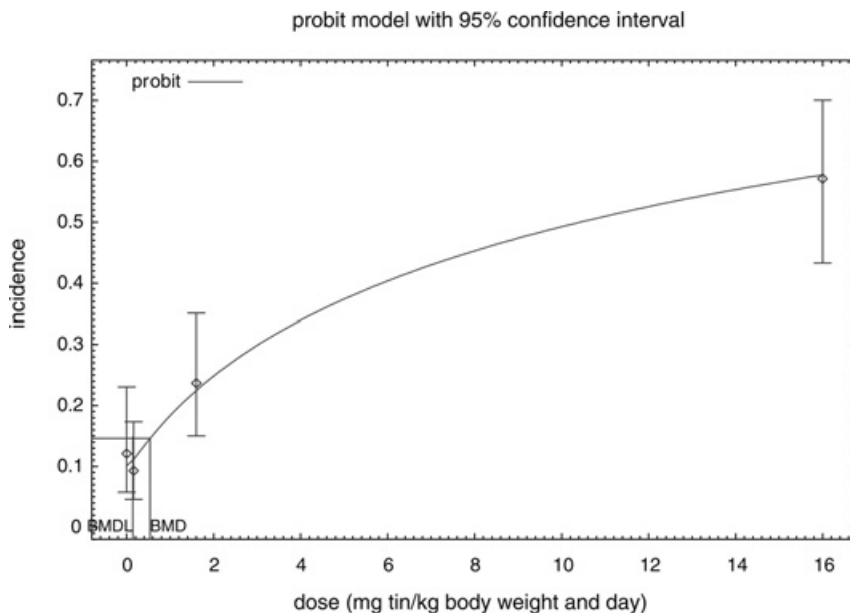


Figure 1 Benchmark calculation for a 5% increase in the incidence of delayed ossification in rabbits (study by Schering AG 1992)

body weight and day. Developmental toxicity such as postimplantation loss, reduced litter size and increased mortality were found in the offspring at about 10.9 mg tin/kg body weight and day. The NOAEL for maternal toxicity was about 0.2 mg tin/kg body weight and day. The NOAEL for postnatal developmental toxicity was about 2.3 mg tin/kg body weight and day (see Section 5.5.1, Table 3).

In a two-generation study (see Section 5.5.1) Sprague Dawley rats were given a mixture of 78.8% DOT(IOMA)₂ and 16.9% MOT(IOMA)₃ with the diet in doses of 0, approx. 0.22, 0.67 or 2.23 mg tin/kg body weight and day. At 0.67 mg tin/kg body weight and day and above, the number of stillbirths was slightly but not significantly increased in the F₁ offspring. The authors regarded this effect as possibly substance-related, though this seems to be less plausible due to the findings in the high dose group (increased number of stillbirths in the F₂ but not in the F₁ generation). At this dose, however, the relative thymus weight was reduced in the F₁ offspring on postnatal day 22 (significant in female animals, not significant in male animals). At the end of exposure this was also significantly reduced in the adult male F₁ offspring. At the high dose of 2.23 mg tin/kg body weight and day, weight at birth and postnatal body weight gain were reduced in the F₁ offspring. Mortality was increased only between postnatal days 4 and 21. In contrast, already perinatal (stillbirth) as well as postnatal mortality was increased in the F₂ offspring (Schering AG 1996; see Table 3). The NOAEL in this study was 0.22 mg tin/kg body weight

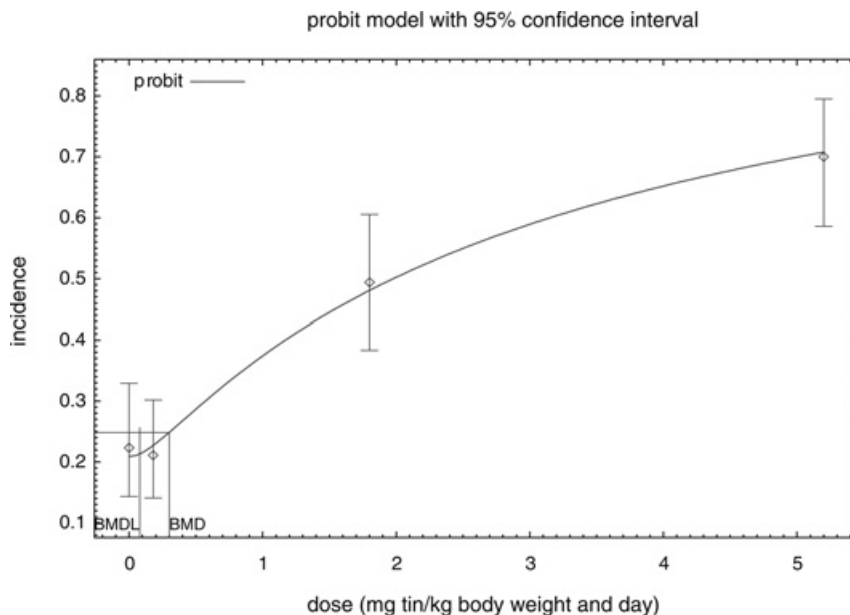


Figure 2 Benchmark calculation of postimplantation loss in rats after DOTC administration (5% increase; study by the Organotin Environmental Programme 2005)

and day for parent animals and offspring. As no difference can be made in this study whether the reduced thymus weights were produced by postnatal exposure or whether changes in the thymus can also be produced by prenatal exposure, these findings are considered to be relevant for evaluation.

In a further 90-day toxicity study with satellite groups (according to OECD test guideline 421) (see Section 5.5.1), female Wistar rats received DOTC (92%) in doses of 0, approx. 0.18, 1.8 or 5.2 mg tin/kg body weight and day. Ten female and male animals per dose group were mated and the offspring investigated on postnatal day 4. Increased thymus atrophy was found in the dams of all dose groups. A NOAEL for maternal toxicity was thus not obtained. At about 1.8 mg tin/kg body weight and day and above, increased postimplantation loss, stillbirths and increased mortality of the offspring occurred (see Section 5.5.1, Table 3; Organotin Environmental Programme 2005). The dose of about 0.18 mg tin/kg body weight and day is regarded as NOAEL for developmental toxicity. A dose of 0.3 mg tin/kg body weight and day is obtained from a benchmark calculation (see Figure 2) for an increase in the incidence of postimplantation losses by 5% above the control value. For the 5% total increase in mortality (number of living offspring on postnatal day 4 in relation to the number of animals living and born dead) the dose is 0.26 mg tin/kg body weight and day (see Figure 3). It is to be noted that the data are from a screening study with a correspondingly lower number of animals (7–8 dams per

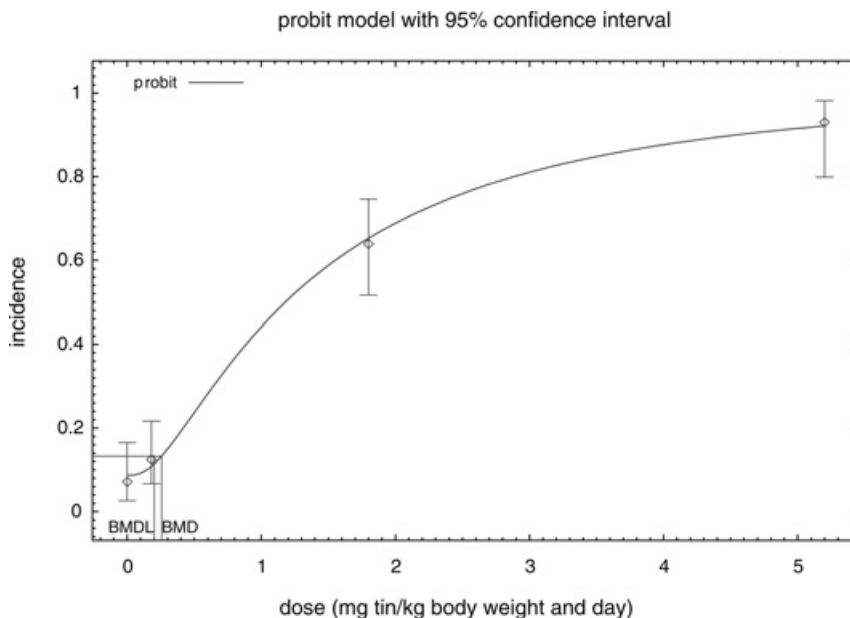


Figure 3 Benchmark calculation on total mortality in offspring (5% increase; study by the Organotin Environmental Programme 2005)

dose group). An increase in incidence by 5% is thus a conservative estimate. In calculating with a 10% increase in mortality compared with the control group, adapted to the lower statistical power of a study using a lower number of animals, the calculated benchmark dose is 0.38 mg tin/kg body weight and day.

In a screening test carried out according to OECD test guideline 422 using TOT (see Section 5.5.1), no impaired fertility, reproductive behaviour or developmental toxicity occurred up to a maternally toxic dose of about 95.68 mg tin/kg body weight and day (in male animals) or about 109.2 mg tin/kg body weight and day (in female animals) (Organotin Environmental Programme 2004).

Summary

Out of the investigated *n*-octyltin compounds, the di-*n*-octyltin compounds were found to be the most powerful immunotoxic and developmental toxic agents.

Ossification disorders and variations, but no malformations, were observed as main effects in mice, rats and rabbits in the studies on prenatal toxicity. These effects do not seem to appear until maternal immunotoxicity is reached. However, maternal immunotoxicity was mostly not measured in the studies on prenatal toxicity. Therefore, no conclusive statement on maternal toxicity is possible from such studies. In those one- and two-generation studies in which immunotoxic effects

were measured, the prenatal and postnatal mortality in the offspring occurred only at maternally (immuno)toxic doses, which were, however, not lethal for the dams.

The lowest NOAEL in a prenatal developmental toxicity study in rabbits, in which a 80:20 mixture of DOT(IOMA)₂ and MOT(IOMA)₃ was administered, was obtained at 0.16 mg tin/kg body weight and day. At 1.55 mg tin/kg body weight and day, an increase in non-ossified sections in the skull was found, though not statistically significant (Schering AG 1992). The lowest NOAEL for developmental toxicity in rats in a screening test in accordance with OECD test guideline 421 after administration of DOTC (92%) was determined as 0.18 mg tin/kg body weight and day, an immunotoxic dose. At 1.8 mg tin/kg body weight and day and above, prenatal, perinatal and and postnatal mortality was increased (Organotin Environmental Programme 2005). In a two-generation study in rats with an 80:20 mixture of DOT (IOMA)₂ and MOT(IOMA)₃, the thymus weight was reduced at 0.67 mg tin/kg body weight and day and above in the offspring by the end of the lactation period (Schering AG 1996).

5.6 Genotoxicity

5.6.1 In vitro

The available in vitro studies on the genotoxicity of *n*-octyltin compounds are listed in Table 6.

Each by itself or as a mixture, MOTC and DOTC were found not to be mutagenic in studies with *Salmonella typhimurium* in the presence and absence of a metabolic activation system. DOT(IOMA)₂ and TOT were also negative in the same test system. DOTC showed no mutagenicity in *Saccharomyces cerevisiae*, CHO cells, calf thymus DNA, primary rat hepatocytes and human fibroblasts. DOTC showed a slightly positive result in mouse lymphoma cells without metabolic activation. In this study, the highest, only slightly cytotoxic, concentration produced a 5-fold increase in mutation frequency, the positive control with ethylmethane sulfonate a 71-fold increase. This study is not included in the evaluation due to lacking information on the respective mutation frequencies and standard deviations.

The great majority of in vitro studies with *n*-octyltin compounds was negative.

5.6.2 In vivo

The results of available studies are shown in Table 7.

In a micronucleus test with mice, MOTC was negative at doses up to 2000 mg/kg body weight (about 702 mg tin/kg body weight). DOTC and TOT were also negative up to the same dose in a micronucleus test carried out according to OECD

Table 6 Studies on the genotoxicity of *n*-octyltin compounds in vitro

Endpoint	Test system	Substance	Concentration range	Effective concentration*	Cytotoxicity*	Result		References
						-m.a.	+ m.a.	
Gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	MOTC	up to 10.0 µl/plate (about 4.9 mg tin/plate)	no data	no data	-	-	OECD 2006
Gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	MOTC	up to 10.0 µl/plate (about 4.9 mg tin/plate)	no data	no data	-	-	OECD 2006
Gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	MOTC	up to 10.0 µl/plate (about 4.9 mg tin/plate)	no data	no data	-	-	OECD 2006
Gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538, Escherichia coli Wpvr	67% mono- <i>n</i> -octyltin tetradecyl thioglycolate + 33% di- <i>n</i> -octyltin tetradecyl thioglycolate	up to 5000 µg/plate (about 603 mg tin/plate)	-	-	-	-	Ciba-Geigy AG 1981
Gene mutation	CHO-V79 cells	MOTC	up to 100 µg/ml (about 49 µg tin/ml)	no data	no data	-	-	OECD 2006
Gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	DOTC	up to 10 µl/plate (about 31 µg tin/plate)	-	10 µl/plate except TA98	-	-	Schering AG 1978 a
Gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	DOTC	up to 5000 µg/plate (about 1425 µg tin/plate)	-	at 5000 µg/plate only in TA1535 + TA1537	-	-	Schering AG 1978 b

Table 6 (Continued)

Endpoint	Test system	Substance	Concentration range	Effective concentration*	Cytotoxicity*	Result -m.a. + m.a.	References
Gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538, Escherichia coli W/puvrA	67% mono- <i>n</i> -octyltin tetradecyl thioglycolate + 33% di- <i>n</i> -octyltin tetradecyl thioglycolate	up to 5000 µg/plate,** (about 603 µg tin/plate)	-	-	-	Ciba-Geigy AG 1981
Gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537	DOTC	up to 5120µg/0.1 ml** (about 1469 µg tin/0.1 ml)	no data	at 5120 (except TA100)	-	Ciba-Geigy AG 1983 a
Gene mutation	Saccharomyces cerevisiae D4	DOTC	up to 10 µl/plate (about 3.1 µg tin/plate)	-	10 µl/plate	-	Schering AG 1978 a
Gene mutation	Saccharomyces cerevisiae D4	DOTC	up to 5000 µg/plate (about 1425 µg tin/plate)	-	-	-	Schering AG 1978 b
Chromo-some loss	Saccharomyces cerevisiae D61.M	DOTC	up to 10 000 µg/ml (about 2850 µg tin/ml)	10 000	10 000	2 of 3: - + 1 of 3:	Ciba Geigy 1986 b
Test for covalent DNA binding	V79 cells	DOTC	up to 10 µg/ml (about 2.8 µg tin/ml)	no data	no data	-	Ciba-Geigy AG 1989 a
Test for covalent DNA binding	calf thymus DNA	DOTC	50 µl (about 15.7 µg tin)	no data	no data	-	Ciba-Geigy AG 1988

Table 6 (Continued)

Endpoint	Test system	Substance	Concentration range	Effective concentration*	Cytotoxicity*	Result -m.a. + m.a.	References
DNA repair synthesis	primary hepatocytes	DOTC, purity 99.9%	up to 56.14 µg/ml (about 16 µg tin/ml), real, analytically determined concentration, as precipitation of substance in solution	-	-	-	Ciba-Geigy AG 1984 c
DNA repair synthesis	human fibroblasts	DOTC	up to 140.34 µg/ml ** (about 40 µg tin/ml)	-	-	-	Ciba-Geigy AG 1983 c
Gene mutation TK ^{+/-}	L5178Y mouse lymphoma cells	DOTC	up to 3.2 µg/ml (about 0.9 µg tin/ml) up to 2.5 µg/ml (about 0.7 µg tin/ml)	from 0.5	from 2	+ -	Ciba-Geigy AG 1984 a
Gene mutation HPRT (OECD 476)	V79 cells	DOTC, purity 96.3%	up to 90 µg/ml (about 25.6 µg tin/ml), 4 h	-	90	-	Schering AG 1989 a
Gene mutation	V79 cells, clone 65/3	DOTC	up to 60 µg/ml (about 17.1 µg tin/ml)	no data	from 31 (3 h) at and above 0.98 (21 h)	-	Ciba-Geigy AG 1989 b

Table 6 (Continued)

Endpoint	Test system	Substance	Concentration range	Effective concentration*	Cytotoxicity*	Result		References
						-m.a.	+ m.a.	
Gene mutation	<i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	80% DOT (IOMA) ₂ + 20% MOT (IOMA) ₃	0.001 up to 5 µl/plate (about 0.8 µg tin/plate)	no data	no data			Schering AG 1977
Gene mutation	<i>Saccharomyces cerevisiae</i> D4	80% DOT(IOMA) ₂ + 20% MOT (IOMA) ₃	0.001 up to 5 µl/plate (about 0.8 µg tin/plate)	no data	no data			Schering AG 1977
Gene mutation	<i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537	TOT	62 up to 5000 µg/plate (about 13 up to 1040 µg tin/plate), purity 91%	no data	no data			Organotin Environmental Programme 2002
Gene mutation	<i>Escherichia coli</i> WP2uvrA	TOT	62 up to 5000 µg/plate (about 13 up to 1040 µg tin/plate), purity 91%					Organotin Environmental Programme 2002

*: unless indicated otherwise, the data reported in this table refer to µg/ml;

**: substance started precipitating in the medium at the highest concentration;

-m.a.: without metabolic activation;

+m.a.: with metabolic activation

Table 7 Studies on the genotoxicity of *n*-octyltin compounds in vivo

Test system	Species	Substance	Dose and test conditions	Result	References
Micronucleus test	Mouse, NMRI, 15 ♂/♀ per group	MOTC	500, 1000, 2000 mg/kg body weight (about 175.5, 351, 702 mg tin/kg body weight), single, gavage, per group 5 animals investigated after 24, 48 and 72 h	–	Schering AG 1989 b
Host-mediated assay	Mouse, DBA/2f/ BOM, 4 ♂, mouse lymphoma cells L5178Y	DOTC, purity 99.9%	5000 mg/kg body weight (about 1425 mg tin/kg body weight), single, gavage	–	Ciba-Geigy AG 1984 b
SCE in bone marrow	Chinese hamster, 4 ♂/♀ per group	DOTC	up to 5000 mg/kg body weight (about 1425 mg tin/kg body weight), single, oral, analysis 24 hours after administration	–	Ciba-Geigy AG 1983 b
Micronucleus test (OECD test guideline 474)	Rat, Wistar, 5 ♂ per group	DOTC	500, 1000, 2000 mg/kg body weight (about 142.5, 285, 570 mg tin/kg body weight), per group 5 animals investigated after 24 h, only in 2000 mg/kg body weight also after 48 hours 5 animals examined, cytotoxicity at 2000 mg/kg body weight, positive control mitomycin C	–	Organotin Environmental Programme 2003 a
Micronucleus test (analogous to OECD test guideline 474)	Mouse, CFLP, 5 ♂/♀ per group	80% DOT(IOMA) ₂ + 20% MOT(IOMA) ₃ in water with 1 % methyl cellulose	2250, 4500, 9000 mg/kg body weight (about 348, 696, 1391.4 mg tin/kg body weight; total dose, administered in 2 portions at 24 hours intervals), gavage, animals investigated after 30 h	–	Schering AG 1980 b

Table 7 (Continued)

Test system	Species	Substance	Dose and test conditions	Result	References
Micronucleus test (analogous to OECD test guideline 474)	Mouse, CD1, 20 ♂/♀ per group	80% DOT(IOMA) ₂ + 20% MOT(IOMA) ₃ in water with 1 % methyl cellulose	4500 mg/kg body weight (about 695.7 mg tin/kg body weight; total dose, administered in 2 portions at 24 hours intervals). gavage, 12, 24, 36, 48 hours after 2nd dose examination of 5 ♂/♀ per group, from 36 h on: dyspnoea and tremor	–	Schering AG 1980 b
Micronucleus test (OECD test guideline 474)	Mouse, Swiss, 5 or 10 ♂/dose	TOT (89% purity)	0, 500, 1000, 2000 mg/kg body weight (about 104, 208, 416 mg tin/kg body weight); gavage, single, animals investigated after 24 and 48 hours	–	Organotin Environmental Programme 2003 c

test guideline 474 in rats (DOTC, about 570 mg tin/kg body weight) or mice (TOT, about 416 mg tin/kg body weight). DOTC also showed negative results up to 5000 mg/kg body weight (about 1425 mg tin/kg body weight) in SCE (sister chromatid exchange) studies in the bone marrow of Chinese hamsters, and in the host-mediated assay in mice with mouse lymphoma cells up to 5000 mg/kg body weight (about 1425 mg tin/kg body weight). A mixture of DOT(IOMA)₂ and MOT(IOMA)₃ (80:20) was negative in the mouse micronucleus test after oral administration of up to 9000 mg/kg body weight (about 1391.4 mg tin/kg body weight).

This means that all in vivo studies with *n*-octyltin compounds were negative.

5.7 Carcinogenicity

In a 24-month carcinogenicity feeding study, described in detail in the documentation entitled “Di-*n*-octyltin compounds, mono-*n*-octyltin compounds” (documentation “Di-*n*-octyltin compounds, Mono-*n*-octyltin compounds” 1996, translation of the 1992 German), male and female rats (F3 hybrid of the RII 1/Tif × RH 2/Tif, Ciba-Geigy breed) were given a mixture of MOTC (66.3%) and DOTC (32.5%) as well as tin tetrachloride (1.2%) in daily doses of about 0, 0.08, 0.22, 0.72 or 1.79 mg tin/kg body weight in male, and about 0, 0.08, 0.24, 0.75 or 1.95 mg tin/kg body weight in female animals (see Table 8). In the highest dose group of the female animals, the incidence of lymphomas of the thymus (11/55 vs 2/57 in the controls) and the incidence of primary tumours of the thymus (total number of lymphomas and benign thymomas) (13/55 vs 2/57 in the control animals) were significantly increased. In both cases, the trend test showed a clear dose-effect relationship. In addition, the incidence of generalized malignant lymphomas (no other details) was slightly but, according to the authors, significantly increased in male animals at 0.72 and 1.79 mg tin/kg body weight and day and in female animals at 1.95 mg tin/kg body weight and day (4/60 each vs 1/60 and 0/60 in male and female controls, respectively; no data as to which test was used; Ciba-Geigy AG 1986 a).

As the occurrence of generalized malignant lymphomas (no other details) in male and female rats was just above the border of statistical significance (see Table 8), and there is a high variation in the frequency of these tumours in the strain used (no other details) (see Table 9 in documentation “Di-*n*-octyltin compounds, Mono-*n*-octyltin compounds” 1996, translation of the 1992 German), these findings are considered to be random results (see documentation 1992). As, also with the *n*-butyltin compounds, effects occurred in organs of the immune system after repeated oral administration (with tri-*n*-butyltin oxide: thymus regression and lymphocyte depletion in spleen and lymph nodes; with *n*-butyltin compounds: findings in organs of the lymphatic system; see documentation “*n*-Butyltin Compounds”, 2008), the findings in the thymus do seem relevant and are thus included in the evaluation.

An increased tumour incidence caused by MOTC and DOTC, especially in the thymus, the main target organ of toxicity, was found in the rat. In the documenta-

Table 8 Study of the carcinogenicity of a mixture of MOTC and DOTC in rats

Author:	Ciba-Geigy AG (1986 a)				
Substance:	MOTC (66.3%), DOTC (32.5%), tin tetrachloride (1.2%)				
Species:	Rat, F3 hybrid of RII 1/Tif x RII 2/Tif (Ciba-Geigy breed), 60 ♂, ♀ per group				
Administration:	with the diet				
Concentration:	0.5, 15.50, 150 mg/kg diet (♂ about 0, 0.08, 0.22, 0.72 or 1.79 mg tin/kg body weight and day; ♀ about 0, 0.08, 0.24, 0.75 or 1.95 mg tin/kg body weight and day)				
Duration:	24 months				
Toxicity:	at about 0.72 mg tin/kg body weight and day and above: leukocytes increased (♀), relative thymus weight increased (♂); at about 1.79/1.95 mg tin/kg body weight and day: relative heart weight increased (♀), relative thymus weight increased (♀)				
Tumours:	Dose of MOTC + DOTC [mg tin/kg body weight and day]				
Male rats	0	0.08	0.22	0.72	1.79
Generalized malignant lymphoma (no other details)	1/60(1.7%)	1/60(1.7%)	2/60 (3.3%)	4/60 (6.6%)*	4/60 (6.6%)* T: p < 0.05
Primary tumour of the thymus	3/58 (5%)	3/55 (5%)	1/57(1.7%)	5/57 (8.8%)	3/59 (5.1%)
Lymphoma of the thymus	2/58 (3.4%)	2/55 (3.6%)	1/57 (1.7%)	4/57 (7%)	3/59 (5.1%)
Female rats	0	0.08	0.24	0.75	1.95
Generalized malignant lymphoma (no other details)	0/60 (0%)	0/60 (0%)	0/60 (0%)	1/60 (1.7%)	4/60 (6.6%)* T: p < 0.01
Primary tumour of the thymus	2/57 (3.5%)	3/57 (5.2%)	1/55 (1.8%)	3/56 (5.3%)	13/55 (23.6%)* T: p < 0.01
Lymphoma of the thymus	2/57 (3.5%)	2/57 (3.5%)	1/55(1.8%)	3/56 (5.3%)	11/55 (20%)* T: p < 0.01

* according to authors' calculation, significantly different to control group

T: trend test according to calculations by the Commission

tion of 1992 (documentation "Di-n-octyltin compounds, Mono-n-octyltin compounds" 1996, translation of the 1992 German), it was shown that a thymus atrophy in offspring occurred at a dose similar to that with a tumour-inducing effect after dietary administration of DOTC from 10 days to 6 weeks. This shows a lympho-toxic effect in rats at about 1.79 mg tin/kg body weight and day and above, the

Table 9 Historical data on the incidence of generalized malignant lymphomas in untreated control rats (observed tumours per total number of animals investigated microscopically) (no study period given; Ciba-Geigy AG 1986 a; documentation "Di-n-octyltin compounds, Mono-n-octyltin compounds" 1996, translation of the 1992 German)

Study No.	Male animals	%	Female animals	%
1	4/69	5.8	2/70	2.86
2	3/80	3.75	0/80	0
3	0/80	0	1/80	1.25
4	0/80	0	2/80	2.5
5	1/80	1.25	1/80	1.25
6	2/80	2.5	1/80	1.25
7	2/80	2.5	3/80	3.75
8	2/80	2.5	0/80	0

highest dose used in the carcinogenicity study. In the documentation of 1992 (documentation "Di-n-octyltin compounds, Mono-n-octyltin compounds" 1996, translation of the 1992 German), the fact was furthermore considered that, in the rat thymus, a compensatory proliferation of specific cell populations could have been induced as response to the toxic effects after long-term exposure. Hyperplasia as a result of continuous tissue damage and tissue repair is a known process in carcinogenesis. In addition, an association between the thymus tumours observed and immunosuppressive effects of DOTC is possible. On the basis of this observation it was discussed in 1992 that an increased tumour incidence is only to be expected after exposure to DOTC, which produces tissue damage. With an initial age of four weeks, the rats used were younger than usual at the start of the study (according to the OECD test guideline, six-week-old animals are used), and thus more sensitive. Although a spontaneous thymus regression starts at sexual maturity in rats, the species retains lifelong thymoproliferative ability. In contrast, a transformation of thymus parenchyma into fatty tissue occurs in humans at and beyond puberty, which is for the most part completed at an age of about 40 years. Here, only a residual lymphoproliferative activity remains. An overactive regeneration process of the thymus as result of exposure to DOTC, such as is plausible for the rat on life-long exposure after discontinuation of DOTC, is thus considered to be probable in humans (see documentation "Di-n-octyltin compounds, Mono-n-octyltin compounds" 1996, translation of the 1992 German). But as the ability to form T- and B-lymphocytes is retained in humans for life also without an active thymus, a disturbance of this function could then occur in another organ, and is thus relevant for humans. In animal studies, *n*-octyltin compounds not only produced thymomas but also generalized lymphomas. In humans, a carcinogenic effect of *n*-octyltin compounds on the lymphatic system also beyond the age of forty is therefore not to be excluded.

In agreement with the present state of knowledge, a different emphasis has been placed on the findings already available in 1992:

- It can no longer be assumed that the transformation of thymus parenchyma into fatty tissue is complete in all exposed workers and thus less sensitive to disturbances by *n*-octyltin compounds. In addition, the lymphatic system is not made up of the thymus only. As the ability to form T- and B-lymphocytes is retained in humans for life also without an active thymus, a disturbance of this function could then be produced in another organ, and is thus relevant for humans.
- As, also with the *n*-butyltin compounds, effects occurred in organs of the immune system after repeated oral administration (with tri-*n*-butyltin oxide: thymus regression and lymphocyte depletion in spleen and lymph nodes; with other *n*-butyltin compounds: findings in organs of the lymphatic system; see documentation “*n*-Butyltin Compounds”, 2008), the effects of MOTC and DOTC on the thymus are considered relevant for evaluation.
- More recent studies indicate that *n*-octyltin compounds might be able to disturb tissue-specific repair mechanisms (see Section 2). These effects are not age-dependent or species-specific, and thus relevant for evaluation in humans.

Comparison of the incidence of generalized malignant lymphomas in the carcinogenicity study described (see Table 8) with that of historical control animals (see Table 9) shows that a mixture of MOTC and DOTC must be considered carcinogenic in male and female rats after oral administration.

In a two-year feeding study, which does not meet present-day requirements, carried out in 1966 with beagle dogs (investigation of four male animals after three and six months, and three male and female animals per group after two years), and in Long-Evans rats (investigation of 20 male and female animals after three or six months, and 25 male and female animals per group after two years) following dietary administration of DOT(IOMA)₂ or di-*n*-octyltin maleate up to 4.4 or 5.8 mg tin/kg body weight and day, no substance-related tumours or pathological findings were observed (M&T Chemicals Inc. 1966).

6 Manifesto (MAK value, classification)

In a carcinogenicity study with dietary administration of 66.3% mono-*n*-octyltin trichloride and 32.5% di-*n*-octyltin dichloride, the incidence of lymphomas of the thymus and the sum of lymphomas and benign thymomas was significantly increased in the highest dose group of female rats (1.95 mg tin/kg body weight and day).

In addition, the occurrence of generalized malignant lymphomas in the male rats of both highest dose groups and in the female animals of the highest dose group was slightly increased; according to the authors this increase was statistically significant (Ciba-Geigy AG 1986 a). Effects on organs of the immune system were also observed

with *n*-butyltin compounds (tri-*n*-butyltin oxide producing thymus regression and lymphocyte depletion in spleen and lymph nodes and findings in the organs of the lymphatic system with other *n*-butyltin compounds; see documentation “*n*-Butyltin Compounds”, 2008). Although no tumours were induced in these cases, it is the Commission’s opinion that relevance for humans cannot be excluded (see also Section 2, Mechanism of Action). The available studies on genotoxicity are negative. As the alkyltin cation is made responsible for the toxic effects (Schüürmann and Markert 1998) and similar effects also occur with the other *n*-octyltin compounds, all *n*-octyltin compounds are classified in Carcinogenicity Category 4.

n-Octyltin compounds are nevertheless not classified in any of the categories for germ cell mutagens, as no genotoxic effects are found with these substances.

The systemic NOAEL for di-*n*-octyltin-bis(2-ethylhexyl mercaptoacetate) in a 90-day study is 0.08 mg tin/kg body weight and day for reduced relative thymus weight as endpoint. Taking this NOAEL as basis, this would yield a concentration of 0.056 mg tin/m³ (oral absorption 10%, 100% estimated inhalation absorption, 70 kg body weight, 10 m³ air per working day).

Di-*n*-octyltin compounds have a slight to moderate irritant effect. However, a NOAEC for its local irritant effect after repeated inhalation is lacking. Therefore, the MAK value for the more irritating *n*-butyltin compounds of 0.004 ml tin/m³ (ppm) or 0.02 mg tin/m³ is provisionally adopted to cover both the systemic and local effects. Also in analogy to the *n*-butyltin compounds, *n*-octyltin compounds are classified into peak limitation category I, with an excursion factor of 1. In the light of future inhalation studies with *n*-octyltin compounds it might become necessary to increase the MAK value and the excursion factor of the peak limitation.

In mice, rats and rabbits, *n*-octyltin compounds cause ossification disorders and variations, but especially prenatal and postnatal mortality at maternal (immuno) toxic, but non-lethal doses. The lowest NOAEL of 0.16 mg tin/kg body weight and day was obtained in a prenatal developmental toxicity study with rabbits. At 1.55 mg tin/kg body weight and day, a non-significant increase in non-ossified sections in the skull was found. The lowest NOAEL for the developmental toxicity in rats was determined to be 0.18 mg tin/kg body weight and day, an immunotoxic dose. At 0.67 mg tin/kg body weight and day and above, the thymus weight was reduced in the offspring at the end of the lactation period. Prenatal, perinatal and postnatal mortality was increased at 1.8 mg tin/kg body weight and day and above. The lowest NOAEL of 0.16 mg tin/kg body weight and day obtained in a study with rabbits corresponds to a concentration in the air of about 0.11 mg tin/m³ assuming 10% oral absorption and the LOAEL of 0.67 and 1.8 mg tin/kg body weight and day to a concentration of 0.47 or 1.26 mg/m³. As the difference between the MAK value and the NOAEL for developmental toxicity as well as the LOAEL for effects on the thymus and prenatal and postnatal mortality is not sufficiently large, the *n*-octyltin compounds are assigned to pregnancy risk group B.

No quantitative data on absorption through the skin in humans are available. The amount of dermal absorption can be calculated neither from in vitro data nor using models. The octyl tin compounds are designated with an “H” in analogy to

the *n*-butyltin compounds, in which the absorbed quantity of tin via a 2000 cm² sized skin surface after exposure to tri-*n*-butyltin oxide for one hour is higher than that after inhalation when the MAK value are observed (see documentation “*n*-Butyltin Compounds”, 2008).

There are no data on sensitization in humans. The animal studies available are not sufficient to confirm contact or respiratory sensitization. Therefore, no designation with “Sa” or “Sh” is made. However, for *n*-octyltin compounds whose organic ligands have already been designated with “Sa” or “Sh” this designation will be retained.

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