June 2023

The SCOEL recommendation document covers the following substances:

Substance name	EC number	CAS RN
Bis(tributyltin) oxide (Tributyltin oxide)	200-268-0	56-35-9
Tributylstannyl benzoate (Tributyltin benzoate)	224-399-8	4342-36-3
Tributyltin chloride	215-958-7	1461-22-9
Tributyltin fluoride	217-847-9	1983-10-4
(Z,Z)-tributyl(octadeca-9,12-dienoyloxy)stannane (Tributyltin linoleate)	246-024-7	241424-25-2
Tributyl(methacryloyloxy)stannane (Tributyltin methacrylate)	218-452-4	2155-70-6
Stannane, tributyl-, mono(naphthenoyloxy) derivs. (Tributyltin naphthenate)	287-083-9	85409-17-2

This text is not part of the official SCOEL Recommendation and is provided to give additional helpful information to the reader as regards chemicals addressed by the SCOEL Recommendation. The list is non-exhaustive and is presented for information purposes only.

Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for tributyltin chloride

SCOEL/SUM/138

March 2011

European Commission

Table of Contents

Recommendation from the Scientific Committee on Occupational Exposure Limits for tributyltin compounds

8 hour TWA	: 0.02 mg/m^3 (based on TBTO data), which corresponds to 0,008 mg Sn/m^3
STEL (15 min)	: -
Additional classification	: -
BLV	: -

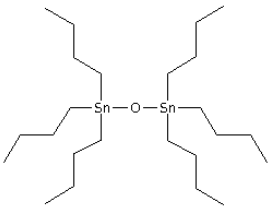
Substance identification

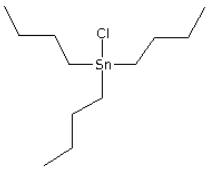
Tributyltin (TBT) compounds are organic derivatives of tin (SnIV) that are characterised by the presence of covalent bonds between three carbon atoms and a tin atom. They have the general formula (n-$C_4H_9)_3$ Sn-X, where X is an anion or covalently linked group. The most widely used of these compounds is tributyl tin oxide. Other industrially important tributyl tin compounds are tributyltin fluoride, tributyltin methacrylate (monomer or copolymer), tributyltin benzoate, tributyltin linoleate and tributyltin napthenate.

Name	EINECS no	CAS No	Molecular formula	Molecular mass
Tributyltin oxide	200-268-0	56-35-9	$C_{24}H_{54}OSn_2$	596
Tributyltin benzoate	224-399-8	4342-36-3	$C_{19}H_{32}O_2Sn$	411
Tributyltin chloride	215-958-7	1461-22-9	$C_{12}H_{27}ClSn$	325
Tributyltin fluoride	217-847-9	1983-10-4	$C_{12}H_{27}FSn$	309
Tributyltin linoleate	*	241424-25-2	$C_{30}H_{58}O_2Sn$	568.7
Tributyltin methacrylate	218-454-4	2155-70-6	$C_{16}H_{32}O_2Sn$	374.7
Tributyltin naphthenate	287-083-9	85409-17-2		about 500

*not in EINECS database

The molecular structures of TBT oxide (TBTO) and TBT chloride (TBTCl) are shown below.





This document is based on the IPCS Concise International Chemical Assessment Document (CICAD, IPCS 1999) for TBT oxide and the IPCS Monograph (1990) for TBT compounds, the references based therein and a limited number of more recent studies identified using the online database PubMed. Most of the studies are of TBT oxide or TBT chloride. There is very little readily available toxicological information for other TBT compounds.

Tributyl tin compounds are classified as T: R25, 48/23/25, Xi: R36/38 N: R50, 53. They are labelled as T, N R21, 25, 36/38, 48/23/25, 50/53 S(1/2), 35, 36/37/39, 45, 60, 61.

Physico-chemical properties

The chemistry of TBT compounds is dominated by reactions involving the bond between the TBT group and the anion or group comprising the remainder of the molecule. The nature of the anion or group bounded to the TBT group(s) influences the physico-chemical properties of TBT compounds, notably the relative solubility in water and non-polar solvents and the vapour pressure. TBTO is soluble in lipids and very soluble in a number of organic solvents (e.g., ethanol, ether, halogenated hydrocarbons). Its octanol/water partition coefficient (log K_{ow}) lies between 3.19 and 3.84 for distilled water. The vapour pressure of TBT compounds is very low. Therefore, TBT compounds exist as particles and aerosols

Tributyltin compound	Melting point (^{0}C)	Relative density (20^{0}C)	Vapour pressure at 20^{o}C (Pa)
oxide	<-45	1.17-1.18	$1x10^{-3}$
benzoate	20	about 1.2	$2x10^{-4}$
chloride	-16	about 1.2	$2x10^{-3}$
fluoride	240	1.25	-
linoleate	<0	1.05	$9x10^{-2}$
methacrylate	16	1.14	$3x10^{-2}$
naphthenate	<0	about 1.1	$9x10^{-5}$

1. Occurrence/Use

Tributyltin compounds have been registered as molluscicides, as antifoulants on boats, ships, quays, buoys, crab pots, fish nets, and cages, as wood preservatives, as slimicides on masonry, as disinfectants, and as biocides for cooling systems, power station cooling towers, pulp and paper mills, breweries, leather processing, and textile mills

Methods of exposure monitoring and analysis

NIOSH (1994) have published a method for the measurement of organotin compounds in air (NIOSH Analytical Method 5504, issue 2; www.cdc.gov/niosh) that was validated with TBTCl was validated over the range of 0.042 – 0.191 mg $Sn.m^{-3}$. The method involves collection onto a glass fibre filter coupled to an absorbent tube (XAD-2), separation by HPLC and analysis by Atomic Absorption (AA) graphite furnace. The method is suitable for the measurement of 5-50 mg Sn per sample (0.015-1 mgm^{-3} Sn for 300 L of air) and the limit of detection is reported as 1 mg Sn per sample.

OSHA (www.osha.gov) have published partially validated methods for TBT benzoate (ID222SG) and TBT fluoride (IDID223SG) that involve collection onto PVC filters, extraction with 1-propanol and analysis by AA graphite furnace. The limit of quantification is reported as 25 mgm^{-3} for both compounds. These methods were partially validated over the range of 0.05 – 0.2 mg $Sn.m^{-3}$ for both compounds. These methods need to be improved before they can be used for the control of exposure at the recommended OEL.

2. Health significance

2.1. Absorption, Distribution, Metabolism and Excretion

There is no information about the uptake and distribution of inhaled tributyltin compounds in humans.

Animal data suggest that approximately 20 to 50% of ingested TBTO is absorbed compared with between 1 and 10% following dermal application (IPCS, 1990). IPCS imply that the uptake of TBT from other TBT compounds would be expected to be similar.

Absorbed TBTO is rapidly and widely distributed among tissues with the highest concentrations being found in the liver and kidneys (IPCS, 1999). TBTO can be transferred across the blood-brain barrier and from the placenta to the foetus (IPCS, 1999). TBT compounds are rapidly metabolised and metabolites have been detected in blood within 3 hours of parenteral administration in animals. The major metabolites appear to be dibutyl and monbutyl tin compounds (IPCS, 1999).

2.2. Acute toxicity

2.2.1. Human data

Several case reports have described irritation of the respiratory tract following acute inhalation exposure of people to TBTO (see section 5.3). Symptoms including a burning sensation in the nose and forehead, headache, nose bleeding, cough, loss of appetite, nausea, and vomiting were reported in association with a persistent odour from paint

treated with TBTO used for mildew control (IPCS, 1999). There are no data linking levels of exposure to effects.

2.2.2. Animal data

TBT compounds are moderately to highly acutely toxic to laboratory mammals.

Some limited inhalation data are available for TBTO. Schweinfurth & Gunzel (1987) summarized the results of several inhalation studies in laboratory animals. After a single 4-hour exposure, rats displayed signs of irritation (nasal discharge, lung oedema, and congestion of the pulmonary circulation) and enteritis. The LC_{50} was 77 mg/m^3 (total particles) or 65 mg/m^3 (particles with a diameter less than 10 µm). In guinea-pigs exposed to aerosols of TBTO in olive oil at 200 mg/m^3 and above, death occurred within 1 hour of exposure. No deaths were observed and only minor clinical signs (slight nasal discharge) were noted following exposure of 10 male and 10 female rats to almost saturated vapours of TBTO (concentration not specified). Exposure of mice to either a single 1-hour period or seven 1-hour periods on successive days, to TBTO concentrations in air ranging between 50 and 400 mg/m^3 was associated with a change in animal exploratory behaviour (Truhaut *et al*, 1979).

Acute oral LD_{50} values summarised by IPCS (1990) for various TBT compounds including TBTO and TBTCl range from 127 to 234 mg per kg body weight in rats and 46 to 180 mg per kg in mice. Takagi et al., (1992) found similar LD_{50} values.. Reported effects include lesions of the bile duct, severe liver and kidney damage and brain haemorrhage. The acute dermal LD_{50} in rabbits is about 9,000 mg per kg body weight. The LD_{50} values for TBTO following parenteral administration are much lower than for oral administration being only 20 and 16 mg per kg body weight in the rat and mouse, respectively. This probably reflects poor absorption of TBTO from the gut giving rise to much lower systemic availability than following parenteral administration (IPCS, 1990).

There are some marked interspecies differences in susceptibility to effects on the liver. Ueno *et al* (2003) reported that 58.5 mg/kg TBTCl induced liver toxicity in mice as demonstrated by both clinical chemistry and histopathology at 24-hour after oral administration. In rats, the liver injury was detected at 24-hour by clinical chemistry but not by histopathology. No clear liver injury was detected in guinea pigs. The main metabolites at 24-hour were different in each species, indicating that the liver metabolism of TBTCl might vary per animal.

2.3. Irritation

IPCS (1999) cite several case reports claiming irritation of the respiratory tract following acute inhalation exposure of people to TBTO. TBTO is a skin and eye irritant and severe dermatitis can result from direct skin contact with TBTO. The irritant effects on skin may take about an hour to become noticeable (IPCS, 1999). Grace *et al* (1991) reported a case of irritant contact dermatitis due to TBTO on work clothes.

2.4. Sensitization

There is no evidence linking TBT to sensitisation.

2.5. Repeated dose toxicity

2.5.1. Human data

No information is available about the effects of TBT compounds in humans.

2.5.5. Animal data

A number of studies have been performed with TBT compounds in animals. Most of these studies have exposed animals by the oral route and only one inhalation study is available. Relatively few studies have investigated a wide range of toxicological endpoints and most of the available studies specifically focus on the immunological, neurological, endocrine or liver effects of TBT compounds.

Inhalation exposure

When groups of 10 male and 10 female Wistar rats were exposed for 4 h/day, 5d/wk to TBTO concentrations of 0, 0.03 (vapour), 0.16 (vapour), or 2.8 (aerosol) mg/m^3, for a total of 21 to 24 treatments, half the animals died at the highest dose. Unspecified inflammatory reactions in the respiratory tract and thymolysis and lymphocyte depletion of the thymus-dependent areas of the spleen and lymph nodes were reported in the 11 animals (5 males and 6 females) from the highest concentration group that died during the study. No such lesions were observed in the survivors, although in 3 survivors from the highest concentration group an increase in the number of macrophages containing nuclear debris were seen. No significant changes were seen in the weights of the thymus, spleen, or iliac lymph nodes in animals surviving the study. (Schweinfurth & Gunzel, 1983 and 1987). No local or systemic changes were observed at the lower concentrations.

Oral exposure

General toxicity

Following repeated oral administration, TBT compounds have been associated with reduced body weights, reduced survival and with adverse effects on the liver, kidneys, brain and immune system (Table 1). Increased mortality in mice has been reported at 0.7 mg per kg body weight per day for TBTO, and 2.1 mg per kg per day in rats. Effects on white blood cells have been reported in monkeys at 0.14 mg/kg/day.
For general toxic effects a NOAEL of 5 mg TBTO/kg feed is reported (Wester *et al.,* 1990), which is equivalent to 0.19 mg TBTO/kg bw/day for males and 0.25 mg TBTO/kg bw/day for females.

Immune function

A number of studies have found that TBT compounds affect the thymus, spleen, humoral and cell-mediated immunity and resistance to infection. (Tables 2 and 3). The unborn or newborn may be more susceptible to these effects than adults. Tryphonas *et al.*, (2004) found that *in utero* and post-natal treatment of F1 rats with 0.025 mg TBTCl/kg bw/day for up to 90 days affected humoral and cell mediated immunity as well as the number and function of cells which are involved in the host's immunosurveillance mechanisms against tumours and viral infection. However, due to inconsistency of the effects observed, this study is considered inadequate for setting an OEL.

A NOAEL of 0.025 mg/kg/day for immunotoxic effects in weanling or adult rats exposed to TBTO was reported by Kranjnc *et al*., 1987 and Vos *et al*., 1990. A large number of studies have investigated the mechanisms by which TBT compounds cause immunotoxic effects but these are not directly informative with regard to exposure-response relationships. For example, the mechanisms of the inhibitory effect of TBT on the cytotoxic activity of natural killer cells have been extensively studied (e.g. Aluoch and Whalen, 2005; Bariagaber and Whalen, 2003; Thomas *et al*, 2004). It has been suggested that the immunotoxicity associated with TBTO is related to induction of apoptosis (i.e. programmed cell death) within the thymus. Raffray and Cohen (1993) demonstrated that cellular changes consistent with apoptosis occurred *in vitro* at concentrations of TBTO that did not affect cell viability.

In the study by Vos *et a*l. 1990 with long-term oral application of TBTO, immunologic effects were more pronounced in "young" rats (starting exposure after weaning) than in "aged" rats (starting exposure at 1 year of age). In "young" and "aged" rats relevant effects on the immune system and histopathological effects (thymus) were observed with 50 mg TBTO/kg diet. In "young" rats, some immunotoxic effects were observed with 5 mg/kg diet. However, due to the high variability of these parameters and inconsistencies in the findings, the relevance of these findings may be low.

Neurotoxicity

Several studies have specifically examined the potential for TBT compounds to cause neurotoxic effects because both triethyltin and trimethyltin compounds have been shown to cause severe neurotoxicity (Boyer, 1989). The lowest dose of TBTO shown to affect brain chemistry is 2.5 mg/kg/day with a NOEL of 1.5 mg/kg/day (Yellapragada *et al.,* 1991). Overt evidence of neurotoxicity has only been observed at much higher levels of exposure (Table 4).

A number of studies have investigated the mechanisms underlying TBT neurotoxicity but are not directly informative concerning exposure-response relationships (e.g. Thompson *et al*, 1996; Viviani *et al*, 1995; Yallaprada *et al*, 1990; Ueha *et al*, 1996; Cameron *et al*, 1991; Mizuhashi *et al,* 2000; Konno *et al*, 2001).

Effects on hormone activity

A number of mechanistic studies have investigated the effects of TBT compounds on hormone activity. High doses of TBTO (100 mg per kg body weight) have been shown to interfere with thyroid and pituitary activity in male rats (Funahashi *et al,* 1980). The results of several studies suggest that TBT may interfere with aromatase, an enzyme involved in the production of oestrogen (Cooke, 2002; Heidrich *et al*, 2001; Saitoh *et al*, 2001; Omura *et al*, 2001; Nakanishi *et al*, 2002). Inhibition of testosterone production has also been demonstrated (e.g. Nakajima *et al*, 2003, Ohno *et al,* 2005). TBTCl has been reported to have no oestrogenic activity in standard assays (Nielsen and Rasmussen, 2004). None of these studies provide exposure-response information relevant to setting an exposure standard.

Other effects

There is limited evidence that TBT could interact with enzymes that might lead to adverse cardiovascular effects (e.g. Berg *et al*, 2003; Kodavanti *et al*, 1991).

2.6. Mutagenicity

The genetic effects of TBTO have been evaluated in multiple *in vivo* and *in vitro* short-term tests and although some positive results have been reported at cytotoxic concentrations, the majority of test results have been negative and the IPCS (1999) did not consider TBTO to be a genotoxin.
TBTCl was tested positive in a modified Ames test (Hamasaki *et al.,* 1993) and a REC-assay (Hamasaki *et al.,* 1992), both without metabolic activation, but negative in the SOS chromotest (Hamasaki *et al.,* 1992).

2.7. Carcinogenicity

2.7.1. Human data

No human data are available.

2.7.2. Animal data

In a chronic toxicity/carcinogenicity study, groups of 60 male and 60 female Wistar rats were exposed to dietary TBTO for 2 years (Wester *et al*, 1987; 1988; 1990). Ingested dosages were approximately 0.019, 0.19, or 2.1 mg per kg body weight per day in males and 0.025, 0.25, or 2.5 mg per kg body weight per day in females. No treatment-related adverse changes were found in males or females at the lowest dose. The study found statistically significant increased incidences of benign pituitary tumours (43/50 and 35/50 in the top-dose males and females, respectively vs 34/50 and 22/50 in male and female controls), phaeochromocytomas in the adrenal medulla 33/50 and 34/50 in top-dose males and females, respectively vs 16/50 and 3/50 in male and female controls), and parathyroid adenomas (6/43 in top dose males vs 0/39 in male controls). Because of the high spontaneous incidence of these tumours in the strain of rats used, the variable incidences in the treated groups, and the absence of a clear dose-response relationship, the increased incidences of these tumours is not considered to be related to the exposure to TBTO.

Daly (1992) found no evidence that TBTO was carcinogenic in mice exposed for 18 months to up to 9.2 mg/kg/day.

Overall the data do not suggest that TBTO is likely to be carcinogenic.

2.8. Reproductive and developmental toxicity

2.8.1. Human data

There are no human data or inhalation data related to developmental toxicity

2.8.2. Animal data

A large number of studies have investigated the effects of oral administration of TBTCl and TBTO in rats and mice. TBT compounds cross the placenta but the transfer of organotin compounds to pups during lactation appears to be minimal. Cooke *et al*

(2004) reported that stomach levels of TBT were below the levels of detection in suckling pups at maternal doses of up to 2.5 mg/kg/day.

Fertility

Exposure to TBT adversely affects both male and female fertility (Tables 5 and 6). Adverse effects on male sperm production have been reported in rats following treatment with TBTCl at 10 mg/kg/day during puberty with no effects at 5 mg/kg/day. Significantly increased implantation failure and post implantation loss has been found at maternal doses of TBTCl of 16.3 mg/kg/day or more. In two generation studies, adverse effects on male reproductive organs were reported at a dose equivalent to about 6.25 mg/kg/day and evidence of possible masculisation of female offspring at only 0.25 mg/kg/day (Table 5).

Developmental toxicity

There is no evidence that TBT compounds are teratogenic and developmental effects are largely associated with maternal toxicity (IPCS, 1999). For TBTO the LOEL is about 10 mg/kg/day in rats and mice and the NOAEL 1 (mouse) – 5 (rat) mg/kg/day (Crofton *et al*., 1989; Davis *et al.,* 1987)
However, in the publication by Cooke *et al.* 2004 (given TBTCl at doses of 0.025, 0.25, and 2.5 mg/kg bw/day), effects on pup growth and liver weight have been found at 0.025 mg/kg/day. body weight. This study present some limitations: data are only shown in a figure and individual numbers of the different dose groups and information on statistical significance are not given. There seems to be a trend towards reduced body weight gain at the end of the exposure period of the pups (postnatal days 60 or 80).

For the evaluation of effects of pregnant women at the workplace, prenatal exposure and therefore birth weights of the pups and effects during early lactation are relevant. There seems to be no effect at the end of lactation.

The effects on pups after weaning are an aspect of general toxicity. Since in the study by Vos *et al.* (1990), exposure of pups starting from weaning did not lead to body weight changes up to higher doses (0,25 mg TBTO/kg bw/day) the relevance of the body weight changes observed by Cooke *et al.* (2004) at a dose of 0.025 mg TBTCl/kg bw/day may be questioned.

Liver weights (absolute wet weights and liver to brain weight ratio) were significantly reduced in females on day 60 post weaning at 0.025 and 2.5 mg/kg bw/day and in males on day 90 post weaning at 2.5 mg/kg bw/day. Since no histopathological effects were observed in the liver, the toxicological relevance of reduced liver weights is low.

Therefore, the effects on pup growth and liver weights after postnatal exposure have not been used to derive an OEL.

Administration of TBTCl or TBT Acetate (TBTA) during the later stages of gestation is associated with cleft palate and other skeletal deformations with a lowest effect level of 16 mg/kg/day with TBTA (Noda *et al*, 1991).

Recommendation

There are very few human data available about the effects of short- and long-term exposure to TBT compounds.
TBT compounds are known to cause irritation of the respiratory tract, eyes and skin, but exposure data are not available.
In animal studies TBT compounds have been shown to cause respiratory irritation, effects on immune function, liver, kidneys and the central nervous system. There appears to be relatively little difference in the toxicity of different TBT compounds.

Increased mortality was reported in mice exposed to 0.7 mg per kg body weight per day for 18 months.
There is no convincing evidence suggesting that TBT compounds are likely to be carcinogenic.

Unspecified inflammatory reactions in the respiratory tract and immunotoxic effects in the lymphatic organs were observed in rats that died when exposed to an aerosol of 2.8 mg/m^3 TBTO for 4h/d, 5d/wk for about 4 wks. No such lesions were observed in survivors or in rats exposed to 0.03 or 0.16 mg TBTO/m^3 (Schweinfurth and Günzel 1983 and 1987).
Adverse effects on male fertility have been reported at a TBTO dose of about 6.25 mg/kg bw/day in two generation studies and evidence of possible masculinisation of female offspring at 0.25 mg/kg bw/day. Young animals appeared to be more susceptible than aged animals for which the NOAEL for immunologic effects after long-term exposure was 5 mg TBTO/kg diet, equivalent to 0.25 mg TBTO/kg bw/day, whereas in young animals the NOAEL was 0.5 mg TBTO/kg diet, equivalent to 0.025 mg TBTO/kg bw/day (Vos et al., 1990). However, due to the variability in the parameters observed and the inconsistencies in the findings, the relevance of the findings in young rats may be low.

Using the NOAEL of 0.16 mg/m^3 (0.03 mg Sn/m^3) in the 4 wks inhalation study (Schweinfurth and Günzel, 1987) as point of departure and taking into account the NOAEL of 0,25 mg TBTO/kg bw/day (0.35 mg TBTO/m$^{3)}$ from the long-term dietary study with aged rats (Vos et al.,1990), the limited data available and the short duration of the inhalation study an Uncertainty Factor of 10 is applied leading to an OEL of 0.02 mg TBTO/m^3 (0.008 mg Sn/m^3) is proposed

The acute and short-term exposure data show that a short-term exposure limit is not indicated. Furthermore, the limited data available suggest that the dermal route is of minor importance, a skin notation is, therefore, not needed.

Some measurements difficulties may be foreseen at the proposed limit since the methods of exposure monitoring and analysis available heve been validated at a range which is higher than the proposed OEL.

Table 1: Summary of repeated dose experiments with TBT compounds

TBT Compound	Species	Exposure regime	Outcome	Study
TBTO (purity 95.9 or 97.4%)	Groups of 4 male and 4 female dogs	0, 0.2, 1 or 5 mg/kg/day for 12 months	High dose group showed apathy, ataxia, emaciation and dehydration, changes in clinical chemistry and urine indices, liver damage, atrophy of bone marrow, spleen, testis and epididymis; changes in liver enzymes and atrophy of lymph nodes (mid and high dose); reduced serum immunoglobulin concentrations in low and high dose groups; Study considered significantly flawed by IPCS (1990). NOAEL:: 1 mg/kg/day	Schuh (1992)
TBTO (purity 96%)	Groups of 3 and 4 adult male monkeys	0 or 0.14 mg/kg/day, 6 days/week for 22 weeks	decreased total leukocyte levels at 0.14 mg/kg/day (LOAEL). No other changes in haematological or serum parameters. Other parameters not investigated	Karrer *et al*., (1992)
TBTO	Groups of 60 male and 60 female Wistar rats	Ingested dosages approximately 0.019, 0.19, or 2.1 mg/kg/day in males and 0.025, 0.25, or 2.5 mg/kg/day in females	No treatment-related adverse effects have been observed at the low and mid-dose. The high dose group showed increased serum immunoglobulin levels, decreased survival, decreased body weight, and changes in organ weights. Absolute liver, kidney, adrenal gland (male only), and heart (male only) weights were increased and thyroid weight (female only) decreased in high-dose group. After 12 months, high dose animals showed slight bile duct changes, decreased haemosiderin content in spleen and decreased thyroid follicular epithelial cell height. Only the histological changes in the thyroid persisted at 24 months but there were no significant changes in concentrations of serum thyroid hormones. The incidence and severity of age-related degenerative changes in the kidney were increased in high-dose animals after 24 mo	(Wester *et al*., 1987, 1988, 1990)
TBTO (purity 97.1%)	Groups of 50 male and 50 female mice	mean intake of 0, 0.7, 3.7, or 7.7 mg/kg/day in males and 0, 0.9, 4.8, or 9.2 mg/kg/day in females for 18	Significant reduction in survival in treated mice compared with controls but no information on cause of death given. Significant reduction in food consumption and increase in liver weights in high-dose females and an increased incidence of common spontaneous non-neoplastic lesions, particularly glomerular/interstitial amyloidosis of the kidney. Renal amyloidosis were increased in females in all dose groups and the progression of this lesion appeared to be more rapid in both sexes at	Daly (1992)

		months	the two highest doses.	
TBTA	Rats	16, 8, or 4 mg /kg subchronic	Histopathologic lesions were found in lungs, liver, intestine and kidney and there was a reduction in mean lymphocyte count for rats receiving 10 or 20 mg TBTA/kg, and a reduction in monocyte count in the 20 mg TPTA/kg group.	Attahiru *et al* (1991)
pure and commercial TBTO and TBTCl	Rats	5 ppm and 25 ppm in the diet for 1 month For a rat consuming 5% of its body weight as food per day, the received doses were 0.25 and 1.25 mg/kg/day	Mean body weight gain and the food consumption was significantly less in rats treated with 25 ppm pure TBTO or pure TBTCl as compared to control rats or rats receiving commercial TBTO. Rats treated for 7 days with TBTO showed atrophy of the thymus with severe lymphocytic depletion in the cortex. After 28 days of exposure, most of the lesions reversed and the thymus became markedly smaller than in control rats. Seven days of exposure to TBTO increased liver weight but this change was reversed during a further 3-week exposure. Changes in the rats treated with the commercial TBTO were very similar. Rats treated with TBTCl showed lower tin levels and less immunotoxicity as compared to those treated with TBTO.	Bressa *et al* (1991)

Table 2: Investigations of immunotoxicity of TBTO following oral administration reviewed by IPCS (1999)

Species	Exposure regime	LOAEL mg/kg/day	NOAEL mg/kg/day	Outcome	Study
Rat	28 days	5	0.5	Thymus-depended immunity	Verdier *et al* (1991)
Rat	4 weeks	0.5	-	Lymph node haemorrhage	Krajne *et al* (1984), Vos *et al* (1984)
Rat	1 week; 4 weeks	0.4	-	Virus titres	Bressa *et al* (1991)
Rat	6 weeks	8	-	Reduced thymus weight	Garssen *et al* (1995)
Rat	6 weeks	2	2	Reduced thymus-dependent immunity and non-specific resistance	Van Louveren *et al* (1990)
Rat	6 weeks	0.5	-	Decreased IL+2R alpha mRNA; reduced CD25 expression	Vos *et al* (1984)
Rat	13-26 weeks	3	-	Reduced thymus weight	Vanderbeil *et al* (1998)
Rat	18 weeks	16	-	Reduced thymus weight	Funahashi *et al* (1990)
Rat	5 months	2.5	-	Thymus-dependent immunity	Carthew *et al* (1992)
Rat, aged Rat weanling	4.5 or 18 months	0.25	0.25 0.025	Thymus-dependent immunity	Vos *et al* (1990)
Mouse	Gestation days 4-17 or 11-17	0.1	-	Humoral and cell-mediated immunity	Buckiova *et al* (1992)
Rat	10 doses to pre-weanlings	5	2	Depressed mitogen response	Smialowicz *et al* (1989)

Table 3: Other investigations of the immunotoxicity of TBT compounds

TBT Compound	Species	Exposure regime	Outcome	Study
TBTO	Rats	Ten daily doses	Thymic involution in adults exposed to 2.5 mg/kg, suppressed mitogen response at 5 mg/kg, enhanced PFC response at 2.5 mg/kg. Thymic involution at 5 mg/kg 3 times/week in adults or pre-weanlings. Reductions in mitogen responses in adults dosed intermittently at 10 and 20 mg/kg and in pre-weanlings at 5 and 10 mg/kg. Natural Killer cell activity suppressed in pups dosed intermittently at 10 mg/kg. Within 3 weeks following the last exposure TBTO all parameters returned to normal in adults but not in pre-weanlings.	Smialowicz *et al* (1990)
TBTO (purity 95.3%)	Weanling rats	0.025, 0.25, and 2.5 mg/kg/day for up to 18 months.	Thymus weight significantly reduced in the high-dose group; no significant effects were observed in the IgM or IgG responses to sheep red blood cells, *T. spiralis* or ovalbumin, or the delayed-type hypersensitivity responses to ovalbumin and *M. tuberculosis*. No significant alterations in spleen weight, response of spleen cells to T- and B-cell mitogens, or body weight. Statistically significant changes in the percentages but not numbers of mesenteric lymph node T-lymphocytes in the high-dose group and B-lymphocytes in the mid-dose and high-dose groups. Impaired clearance of injected *L. monocytogenes* in rats exposed to the high dose for 17 months and resistance to infection by *T. spiralis* was suppressed in rats exposed to the mid or high dose. LOAEL identified as 0.25 mg/kg/day and the NOEL as 0.025 mg/kg/day.	Krajnc *et al* (1987) and Vos *et al*. (1990)
TBTCl	Rats	0.025, 0.25 and 2.5 mg/kg/day from day 8 of gestation, through lactation and post-weaning until pups reached the age of 30 days (male and female), 60 days (female) and 90 days (male).	At 30 days, the mean percent and absolute natural killer (NK) cell numbers were increased in male and females at 2.5 mg/kg/day. At 60 days, female rats had increased mean serum IgM levels at the low and high doses, increased mean percentage CD4(+)8(+) (immature) T lymphocytes at the middle and high doses, a non-linear exposure-response increase in NK cell activity, and increased mean numbers of *L. monocytogenes* colony-forming bacteria on Days 2 and 3 post-infection. The 90-day male rats had decreased mean serum IgA levels at the middle dose group; increased IgM levels at the high dose group, increased IgG levels at the middle and high doses and	Tryphonas *et al* (2004)

			decreased IgG2(a) in the high dose compared to the control; a dose-related increase in the mean percentage NK cell numbers and increased mean NK cell activity The delayed-type hypersensitivity response to oxazolone was increased in the low and middle doses and decreased in the high dose. Thymus atrophy was observed at the high dose across all ages.	
	Mice	single dose of TBTO or TBTCl at 0.3, 3.0, 30 mM/kg (178.8, 1780, 17800 mg/kg TBTO or 97.5, 975 or 9750 mg/kg TBTCl)	Recovered peritoneal macrophages showed significant elevations in nitric oxide and TNF-alpha production TBTO/kg-treated groups but not in TBTCl groups. Background TNF-alpha production (without stimulation) was also elevated in TBTO-treated animals but suppressed in TBTCl-treated animals. Oxidative burst activity was elevated at 0.3 mM TBTO/kg. TGF-beta1 production was not altered by either treatment.	Kergosien and Rice (1998)

Table 4: Investigations of the neurotoxicity of TBT compounds

TBT Compound	Species	Exposure regime	Outcome	Study
TBTCl	Rats	single oral acute at doses of 0, 6.3, 12.5, 25.0 or 50.0 mg/kg	Body weight gain in the 50.0-mg/kg group was significantly lowered; TBTCl caused a dose-related decrease in motor activity during darkness. The 24-h total daily and 12-h nocturnal activity was decreased at doses of 12.5 mg/kg and above. The acquisition of shock avoidance responses was inhibited in all TBTCl-treated groups in a dose-dependent manner. In a similar experiment where TBTCl was delivered intraperitoneally at 0, 1.6 or 3.3 mg/kg,body weight gain in the 3.3 mg/kg group was significantly lowered. The 24-hr total daily and 12-hr nocturnal activity in the TBTCl-treated groups were decreased in a dose-dependent manner These decreases in gradually returned to the control levels.	Ema *et al* (1991a)
TBTO	Rats	4 weeks - 30 mg/kg/ day	Tosis or enophthalmia and slight ataxia	(Krajnc *et al*., 1984).
TBTO (purity 95.9 or 97.4%)	Dogs	12 months – 0, 0.2, 1, 5 mg/kg/day	Atactic gait and apathy in highest dose group; IPCS (1999) identified serious deficiencies in the undertaking and reporting of this study	Schuh (1992)
TBTO	Rat	LOEL 10 mg/kg/day NOEL 5 mg/kg/day	Decreased brain weight in pups in developmental study	Crofton *et al*. (1989)
TBTCl	Mice	0, 1, 5, 25, or 125 ppm feed for one month	Significant reduction in body weight at 125 ppm from day 5 to day 16 during the treatment period. Effects on neurotransmitters -DA metabolism in the midbrain - HVA/DA ratio in the midbrain of the 125 ppm-treated group was significantly elevated; assuming consumption of 13% of body weight/day, 125 ppm = 16.25 mg/kg/day	Tsunoda *et al* (2004)
TBTO	Rats	37.5 or 75 mg/kg for 3 consecutive days	Nervous signs appeared in treated animals and 12 and 30% of animals died respectively. Levels of brain dopamine, norepinephrine and serotonin decreased in a dose-dependent manner and the activities of brain total ATPase, Mg (2+)-ATPase and Na (+)/K (+)- ATPase were suppressed. Histopathological changes in brain included hyperaemia, focal haemorrhages in vacuolated myelinated fibres, chromatolysis/ complete necrosis of neurons amd degenerative changes/ complete	Elsabbagh *et al* (2002)

			absence of purkinje cells in the cerebellum	
	Rats	2.5 mg/kg/day for 6 days	Significant loss of body weight and inhibition of Ca(2+)-ATPase activity was found in brain synaptic membranes No effects were found in rats exposed to 1.5 mg/kg/day.	Yallapragada *et al* (1991)

Table 5: Investigations of reproductive and developmental toxicity of TBTCl in rats following oral administration

Exposure regime	Outcome	Study
Male rats dosed during puberty at 5, 10 or 20 mg/kg/day for 10 days	Reduced testicular sperm counts at 20 mg/kg and reduced epididymal sperm counts at 10 and 20 mg/kg. Some motion parameters of sperms in the vas deferens also changed at 20 mg/kg.	Yu *et al* (2003)
Dams dosed with 0, 0.025, 0.25 or 2.5 mg /kg body weight from day 8 of gestation until weaning Post weaning, pups were gavaged daily with the same dose of TBTC till 30 days after birth	No effects on dams' body weights, food consumption, litter size, sex ratio or survival of pups to weaning, All doses affected pup growth, enhanced food conversion to body mass in females but a decreased conversion in males. Reduced liver, spleen and thymus weights. In male pups dosed at 2.5 mg/kg/day, reduced serum thyroxine levels observed. Elevated enzyme levels indicated hepatotoxicity, but no histopathology observed; Significant decreases liver weights in female pups exposed to 0.025 mg/kg/day	Cooke *et al* (2004)
Dams dosed with 0.25, 2.5, 10, or 20 mg/kg from days 0-19 or 8-19 of gestation.	Significant reduction in maternal weight gain, increase in post-implantation loss, decrease in litter size and foetal weight at 20 mg/kg. No external malformations or change in sex ratios. Significant increase in normalized anogenital distances in male foetuses at 0.25 mg/kg/day or more for exposure from days 0-19. Delayed skeletal ossification at 10 or 20 mg/kg/day. Effects on maternal thyroid hormones at 2.5 mg/kg/day or greater.	Adeeko *et al* (2003)
2-generation study using dietary concentrations of 5, 25, and 125 ppm TBTCl in males - For a rat consuming 5% of its body weight as food per day, the received doses would have been equivalent to 0.25, 1.25 and 6.25 mg/kg/day	The weights of the testis and epididymis were decreased and homogenization-resistant spermatid and sperm count were reduced in the 125 ppm TBTCl group. Some minimal histopathologic changes were also observed in the testis of this group. The serum 17beta-estradiol concentration was also reduced in the 125 ppm group in the F1 generation and in the 25 ppm and 125 ppm TBTCl groups, respectively, in the F2 generation. However, the serum concentrations of luteinizing hormone (LH) and testosterone were not decreased in these groups.	Omura *et al* (2001)
2-generation study using dietary concentrations of 5, 25, and 125 ppm TBTCl in females - For a rat consuming 5% of its body weight as food per day, the received	Reduced number, body weight and the percentage of live pups, reduced growth of female pups in the 125 ppm group coupled with a delay in vaginal opening and impaired oestrous cyclicity. A dose related increase anogenital distance at all exposure levels suggesting TBTCl may exert a masculinising effect on female neonates.	Ogata *et al* (2001)

doses would have been equivalent to 0.25, 1.25 and 6.25 mg/kg/day		
Pseudopregnant rats exposed to 4.1, 8.1, 16.3 and 32.5 mg/kg on pseudopregnant days 0 to 3 or 8.1, 16.3, 32.5 and 65.1 mg/kg on days 4 to 7	Significant reduction in uterine weight and serum progesterone levels at 16.3 mg/kg and above. Significant reduction in serum progesterone levels at doses of 8.1 mg/kg and above on days 0 to 3. No effects on ovarian weight and number of corpora lutea.	Harazono and Ema (2000)
8.1, 16.3, or 32.5 mg/kg on days 0-3 of pregnancy, or at 8.1, 16.3, 32.5, or 65.1 mg/kg on days 4-7 of pregnancy	Significant increase in the rate of implantation failure at 16.3 mg/kg or more on days 0-3, significant increase in the incidence of post-implantation loss at 16.3 mg/kg or more following dosing on days 4-7. No increased incidence of foetal malformations in any group.	Harazono *et al* (1998)

Table continued overleaf

Exposure regime	Outcome	Study
Single dose of TBTCl at 100 mg/kg on either day 7, day 8, or day 9 and at 200 mg/kg on either day 7, day 8, day 9, day 10, day 11, day 12, day 13, day 14, or day 15 of pregnancy.	Reduced maternal body weight gain immediately following administration. Significant increase in post-implantation loss after administration of TBTCl on day 7, day 8, and day 9 at 100 and 200 mg/kg and on day 10 and day 11 at 200 mg/kg. Significant increase in external malformations at 100 and 200 mg/kg on day 8 or at 200 mg/kg on day 11, day 12, day 13, and day 14, with the greatest effect following administration on day 13. Cleft palate was observed exclusively after administration during late organogenesis.	Ema *et al* (1997)
0, 8.1, 12.2 or 16.3 mg/kg on day 0 through day 7 of pregnancy	Significant increase in pregnancy failure at 12.2 and 16.3 mg/kg. In females with successful pregnancy, the numbers of corpora lutea, implantations and post-implantation loss per litter were comparable across all groups. No increase in the incidence of malformed foetuses was found in any TBTCl-treated groups.	Harazono *et al* (1996)
165 or 330 mumol kg-1330, 660, 1320, 2640 or 5280 mumol kg-1 on days 13-15 of pregnancy (53.6 or107.25, mg/kg)	significant decrease in the maternal weight gain at both doses; significant decrease in the foetal weight was found at 107.25 mg/kg. A significantly and markedly increased incidence of foetuses with cleft palate was noted in both groups	Ema *et al* (1996)
40 or 80 mg kg-1 by gastric intubation on days 7 and 8 of pregnancy	significantly decrease in maternal weight gain and increased postimplantation embryo loss, no significant increase in incidence of malformed foetuses	Ema *et al* (1995)
of 25, 50 or 100 mg/kg on days 7-9, days 10-12 or days 13-15 of pregnancy.	A significant increase in the incidence of post-implantation loss was found in the groups treated on days 7-9 at 25 and 50 mg/kg and on days 10-12 at 100 mg/kg. Significant increase incidence of malformed foetuses in groups treated on days 10-12 at 100 mg/kg and on days 13-15 at 25, 50 and 100 mg/kg. Predominant malformation was cleft palate.	Ema *et al* (1995)
0, 5, 9, 15, 25 mg /kg /day from day 7 to 15 of pregnancy	Maternal toxicity (decreased body weight gain and food consumption) at 25, 15 and 9 mg/kg/day with clinical signs of toxicity (sedation, diarrhoea and salivation) at 25 mg/kg. At 25 mg/kg, 70 % of the dams and all foetuses died. Statistically significant reductions in the female foetal body weight at 9 and 5 mg/kg/day. No external, skeletal and internal malformations or delay in ossification observed. Two foetuses with dilatation of the renal pelvis were found in 9 and 5 mg/kg/day dose group. Statistically significant increases of placental weight in all TBTC1-treated groups.	Itami *et al* (1990)
1 and 5 mg/kg during gestation	Behavioural effects in offspring	Gardlund *et al* (1991)

Table 6: Investigations of reproductive and developmental toxicity of TBTO following oral administration (from IPCS, 1999)

Species	Exposure regime	LOAEL mg/kg/day	NOAEL mg/kg/day	outcome	Study
Rat	Gestation days 6-19	9 5	5 -	Decreased maternal weight Increased ossification variations	Schroeder (1981)
Rat	Gestation days 6-20	10 10	5 5	Decreased maternal weight Decreased pup weight and survival	Crofton *et al* (1989)
Mouse	Gestation days 6-15	11.7 23.4	5 1	Decreased maternal weight Decreased foetal weight, increased skeletal abnormalities	Davis *et al* (1987)
Mouse	Gestation days 6-15	40 40	2 2	Decreased maternal weight Increased resorptions; decreased foetal weight	Baroncelli *et al* (1990)
Mouse	Gestation days 6-15	-	2	Haematology	Karrer *et al* (1995)

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