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Concise International Chemical Assessment Document 14

TRIBUTYLTIN OXIDE

First draft prepared by Dr Robert Benson, United States Environmental Protection Agency, Denver, Colorado, USA

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

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

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organisation (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

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

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

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

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

Procedures

The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers’ comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers’ comments.

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

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their
CICAD PREPARATION FLOW CHART

1 Taking into account the comments from reviewers.
2 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.
3 Includes any revisions requested by the Final Review Board.
experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

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

This CICAD on tributyltin oxide (TBTO) was prepared by the United States Environmental Protection Agency (US EPA) and is based on an International Programme on Chemical Safety Environmental Health Criteria document on tributyltin compounds (IPCS, 1990) and on the US EPA’s Toxicological review on tributyltin oxide (US EPA, 1997). Data identified as of 1989 and 1996, respectively, were considered in these reviews. Additional information identified as of June 1998 has been included in this document. Information on the nature of the review processes and the availability of the source documents is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Tokyo, Japan, on 30 June – 2 July 1998. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card (ICSC 1282) for TBTO, produced by the International Programme on Chemical Safety (IPCS, 1996), has also been reproduced in this document.

In this document, the term TBTO is used when that specific chemical is intended. In the environment, however, tributyltin compounds are expected to exist mainly as tributyltin hydroxide, tributyltin chloride, and tributyltin carbonate. In those cases or when the identity of the specific chemical is not clear, the general term tributyltin is used.

TBTO is an effective biocidal preservative for wood, cotton textiles, paper, and paints and stains for residential homes. It is added as an antifouling agent in numerous formulations of marine paints. Tributyltin is present in most of these antifouling formulations as an organometallic copolymer. Tributyltin is slowly released from the painted surface as the polymer is hydrolysed in seawater, providing protection against encrustations for as long as 4–5 years.

As a result of its low water solubility and lipophilic character, tributyltin adsorbs readily onto particles. Its half-life in the water column ranges from a few days to weeks. Tributyltin may persist in sediments for several years. It bioaccumulates in organisms, with the highest concentrations found in liver and kidney. Uptake from food is more important than uptake directly from water.

No information is available on the toxicity of TBTO in humans following long-term exposure. Some data and case reports indicate that TBTO is a severe dermal and respiratory irritant. The data, however, are not adequate to characterize the exposure–response relationships. Some studies have quantified human exposure to tributyltin from the diet in Japan.

TBTO is moderately to highly acutely toxic to laboratory mammals in short-term studies. In numerous well-conducted studies, both short term and long term, the critical effect of TBTO is immunotoxicity (depression of immune functions dependent on the thymus). The no-observed-adverse-effect level (NOAEL) for immunosuppression in rats following long-term exposure is 0.025 mg/kg body weight per day. Benchmark dose analysis shows that the exposure corresponding to the lower confidence limit (95%) on dose for a 10% decrease in immunoglobulin (Ig) E titre in rats is 0.034 mg/kg body weight per day. In a carcinogenicity study in rats, there was an increased incidence of some tumours in some endocrine tissues. These tumours occur spontaneously with variable incidence in the strain of rat used in the study and are of unknown significance for a human health risk assessment. TBTO is not carcinogenic in mice. The weight of evidence shows that TBTO is not genotoxic. There is no indication that reproductive or developmental effects occur at an exposure below that identified as the NOAEL for immunotoxicity. Effects on reproduction and development occur only at exposures near those causing maternal toxicity. Data show that TBTO is a severe respiratory tract and skin irritant. Based on the NOAEL for immunotoxicity and an uncertainty factor of 100, a guidance value for oral exposure is 0.0003 mg/kg body weight per day. No adequate data are available to derive a guidance value for inhalation exposure.

TBTO is extremely hazardous to some aquatic organisms. It is an endocrine disruptor in some organisms. The concentration of tributyltin in some coastal waters is above a concentration causing severe adverse effects. Adverse effects have been sufficiently severe to lead to reproductive failure and population decline in some areas. The general hazard to the terrestrial environment is likely to be low.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Tributyltin oxide (CAS No. 56-35-9; C9H26Sn; bis-[tri-n-buty1tin]-oxide; tri-n-buty1tin oxide; TBTO; hexabutyl distannoxane) has the structural formula (CH3CH2CH2CH3)2Sn-O-Sn(CH3CH2CH2CH3)2. It is flammable but does not form explosive mixtures with air. TBTO is a mild oxidizing agent. In the presence of oxygen, light, or heat, slow breakdown occurs. The solubility of TBTO in water ranges from $<1$ to $>100$ mg/litre, depending on temperature and pH. 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 and is 3.54.
Tributyltin oxide

3. ANALYTICAL METHODS

Several methods are used for measuring tributyltin derivatives in water, sediment, and biota (IPCS, 1990). Atomic absorption spectrometry is the most common method used for all media. Flame atomic absorption spectrometry has a detection limit of 0.1 mg/litre in water. Flameless atomic absorption spectrometry, using atomization in an electric furnace with graphite, is more sensitive and allows detection limits of between 0.1 and 1.0 \( \mu \)g/litre. Recent modifications using a gas chromatograph equipped with a flame photometric detector allow a detection limit of 1 ng/litre (Tolosa et al., 1996). Tributyltin can be separated from the sample matrix by capillary supercritical fluid chromatography and determined by inductively coupled plasma mass spectrometry. A detection limit of 12.5 pg was obtained (Vela & Caruso, 1993). There are several different methods of extracting tributyltin from sediment and biota and forming volatile derivatives. The detection limits are 0.5 and 5.0 \( \mu \)g/kg for sediment and biota, respectively (Vela & Caruso, 1993).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

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, and leather processing and textile mills. Tributyltin in antifouling paints was first marketed in a form that allowed free release of the compound. More recently, controlled-release paints, in which the tributyltin is incorporated in a copolymer matrix, have become available. Rubber matrices have also been developed to give long-term slow release and lasting effectiveness for antifouling paints and molluscicides. Government restrictions have decreased the global use of tributyltin compounds in antifouling paints on small boats.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

As a result of its low water solubility and lipophilic character, tributyltin adsorbs readily onto particles (IPCS, 1990). Between 10% and 95% of TBTO introduced into water is estimated to undergo adsorption onto particulate matter. Progressive disappearance of adsorbed TBTO is due to degradation, not desorption. The degree of adsorption depends on the salinity of the water, the nature and size of particles in suspension, the amount of suspended matter, temperature, and the presence of dissolved organic matter.

The degradation of TBTO involves the splitting of the carbon–tin bond (IPCS, 1990). This can result from various processes — both physicochemical (hydrolysis and photodegradation) and biological (degradation by microorganisms and metabolism by higher organisms) — occurring simultaneously in the environment. Although the hydrolysis of organotin compounds occurs under conditions of extreme pH, it is barely evident under normal environmental conditions. Photodegradation occurs during laboratory exposures of solutions to ultraviolet light at 300 nm (and to a lesser extent at 350 nm). Under natural conditions, photolysis is limited by the wavelength range of sunlight and by the limited penetration of ultraviolet light into water. The presence of photosensitizing substances can accelerate photodegradation. Biodegradation depends on environmental conditions such as temperature, oxygenation, pH, the level of mineral elements, the presence of easily biodegradable organic substances for co-metabolism, and the nature of the microflora and its capacity for adaptation. It also depends on whether the TBTO concentration is lower or higher than the lethal or inhibitory threshold for the microorganisms. As with abiotic degradation, biotic breakdown of tributyltin is a progressive oxidative debutylation founded on the splitting of the carbon–tin bond. Dibutyltin derivatives, which are more readily degraded than tributyltin, are formed. Monobutyltins are mineralized slowly. Although anaerobic degradation occurs, there is a lack of agreement as to its importance; some consider it to be slow, whereas others believe that it is more rapid than aerobic degradation. Species of bacteria, algae, and wood-degrading fungi have been identified that can degrade TBTO. Estimates of the half-life of tributyltin in the environment vary widely. The half-life in the water column ranges from a few days to weeks. Tributyltin can persist in sediments for several years.

Bioconcentration factors (BCFs) of up to 7000 have been reported in laboratory investigations with molluscs and fish, and higher values have been reported in field studies (IPCS, 1990). Bioaccumulation in bivalves...
is especially high because of the low capacity for metabolism. In molluscs, uptake from food is more important than uptake directly from water. Higher BCFs in microorganisms (between 100 and 30 000) may reflect adsorption rather than uptake into cells (IPCS, 1990). A recent publication reported a range of BCFs in the Pacific oyster (Crassostrea gigas) of 2400–7800 (Li et al., 1997). Another recent publication reported a range of biomagnification factors in marine mammals of 0.6–6.0 (Madhusree et al., 1997).

Although it has been suggested that tributyltin accumulates in organisms because of its solubility in fat (IPCS, 1990), recent work suggests that this might not be the case. Although tributyltin residues in blubber of marine mammals have been reported (Iwata et al., 1994, 1995, 1997), levels were considerably higher in other tissues, notably liver (Iwata et al., 1994, 1995, 1997; Kannan et al., 1996, 1997, 1998; Kim et al., 1996a,b; Madhusree et al., 1997; Tanabe, 1998; Tanabe et al., 1998). Comparison of patterns of tributyltin residues with those of fat-soluble organochlorines in marine mammals showed marked differences. Unlike the organochlorines, tributyltin residues were the same in both sexes and remained constant after animals reached maturity. It has been suggested that transfer through milk to offspring, a marked trend with the organochlorines, does not occur with tributyltin. Cetaceans showed greater bioaccumulation than pinnipeds (Kim et al., 1996c). There has also been a report of accumulation in liver and kidney of seabirds (Guruge et al., 1997). Stüb et al. (1996) recently determined organotin compounds in the food web of a shallow freshwater lake; in birds in the food web, the highest concentrations of organotin compounds were also in liver and kidney, not in subcutaneous fat. The various authors cited suggest protein binding in liver to be the major mechanism of bioaccumulation.

There are a number of reports on the occurrence of tributyltin residues in marine organisms. Levels of total butyltin residues (the sum of detected tributyltin, dibutyltin, and monobutyltin) of 5–230 ng/g in muscle of fish (Kannan et al., 1995, 1996, 1997), 300 ng/g in liver and kidney of marine birds (Guruge et al., 1997), and 13–395 ng/g in muscle of marine mammals have been reported (Iwata et al., 1994, 1995, 1997; Kannan et al., 1997). In marine mammals, much higher total butyltin residues were reported for blubber (48–744 ng/g), kidney (25–3210 ng/g), and liver (40–11 340 ng/g) (Iwata et al., 1994, 1995, 1997; Kannan et al., 1996, 1997, 1998; Kim et al., 1996a,b,c; Madhusree et al., 1997; Tanabe, 1998; Tanabe et al., 1998). Geographical comparisons showed greater accumulation of residues close to coasts compared with the open sea and in the vicinity of developed compared with developing countries.

### 6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

#### 6.1 Environmental levels

Tributyltin compounds have been found in water, sediment, and biota in areas close to pleasure boating activity, especially in or near marinas, boat yards, and dry docks; in fish nets and cages treated with antifouling paints; and in areas near cooling systems (IPCS, 1990). The degree of tidal flushing and the turbidity of the water influence tributyltin concentrations. As reported in IPCS (1990), tributyltin levels have been found to reach 1.58 g/litre in seawater and estuaries; 7.1 g/litre in fresh water; 26.3 mg/kg in coastal sediments; 3.7 mg/kg in freshwater sediments; 6.39 mg/kg in bivalves; 1.92 mg/kg in gastropods; and 11 mg/kg in fish. However, these maximum concentrations of tributyltin should not be taken as representative, because a number of factors, such as paint particles in water and sediment samples, may give rise to anomalously high values. It has been found that measured tributyltin concentrations in the surface microlayer of both fresh water and seawater are up to two orders of magnitude above those measured just below the surface. However, it should be noted that recorded levels of tributyltin in surface microlayers may be highly affected by the method of sampling.

More recent data (collected up to the mid-1990s) have documented a decline in tributyltin levels in the environment, presumably due to the restrictions placed on the use of antifouling paints on vessels (CEFIC, 1994; Ruiz et al., 1996; Stronkhorst, 1996; Tolosa et al., 1996; NIVA, 1997; dela Cruz & Molander, 1998). Recent data have also documented a seasonal variation in the concentration of tributyltin in a freshwater marina; the concentration was highest in late spring and showed a progressive decline until winter (Fent & Hunn, 1991).

This same study also documented that the tributyltin concentration in sediment decreased progressively with depth. In areas where the tributyltin concentrations in water and sediment have been monitored in the same location, the concentration of tributyltin in the water has declined more rapidly than the concentration of tributyltin in sediment (Stronkhorst, 1996). The range of concentrations reported in coastal waters and estuaries is 1–10 ng/litre; the range reported for water in marinas and major ports is 20–460 ng/litre. Most of the sediment samples analysed contained less than 100 ng/kg, although some samples exceeded 1000 ng/kg. The highest value reported for a sediment sample obtained from a port in Sweden was 10 940 ng/kg. The range of concentrations reported in biota is 0.01–3 mg/kg (dela Cruz & Molander, 1998).
6.2 Human exposure

Information on tributyltin concentrations in various media that are relevant to estimation of human exposure is extremely limited, being restricted to data from Japan.\(^1\) It is unknown if this information is representative of other areas, and additional investigation is desirable.

Tsuda et al. (1995) investigated the daily intakes of tributyltin compounds from meals in Shiga Prefecture, Japan. Daily intakes of TBTO determined by the duplicate-portion method were 4.7 ± 7.0 \(\mu\)g/day in 1991 \((n = 39)\) and 2.2 ± 2.2 \(\mu\)g/day in 1992 \((n = 40)\). Using the market basket method, the daily intake was estimated at 6–9 \(\mu\)g/day in 1991 and 6–7 \(\mu\)g/day in 1992. The TBTO was found mostly in seafood.

Market basket studies in 10 local regions in Japan have shown that the national average daily intake of tributyltin (expressed as tributyltin chloride) was 3.7, 9.9, 5.4, 3.6, 2.9, 1.6, 1.5, and 2.3 \(\mu\)g/day in 1990, 1991, 1992, 1993, 1994, 1995, 1996, and 1997, respectively.\(^1\) Variation among the local regions reflects differences in food intake patterns as well as differences in tributyltin levels in local fisheries.

Recent preliminary data (Takahashi et al., 1998) suggest the potential for non-food sources of exposure — for example, consumer products such as rubber gloves and baking sheets.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Little definitive information is available on the pharmacokinetics of TBTO (see IPCS, 1990, and references therein). TBTO is absorbed from the gut (20–50%, depending on the vehicle) and via the skin of mammals (approximately 10%). Other data suggest absorption in the 1–5% range via the skin.\(^2\) TBTO can be transferred across the blood–brain barrier and from the placenta to the fetus. Following 14 days of oral administration, steady-state levels in tissue are reached after 3–4 weeks. Absorbed material is rapidly and widely distributed among tissues (principally the liver and kidney). Metabolism in mammals is rapid; metabolites are detectable in the blood within 3 h of TBTO administration. The principal metabolite appears to be the hydroxybutyl compound, which is unstable and rapidly splits to form the dibutyl derivative and butanol. In in vitro studies, it has been shown that TBTO is a substrate for mixed-function oxidases, but these enzymes are inhibited by very high concentrations of TBTO. The rate of TBTO loss differs with different tissues. TBTO and its metabolites are eliminated principally via the bile. The calculated half-time for elimination of TBTO residues in mice is 29 days (Brown et al., 1977).

Tributyltin metabolism also occurs in lower organisms, but it is slower, particularly in molluscs, than in mammals. The capacity for bioaccumulation is, therefore, much greater in lower organisms than in mammals.

There are some recent preliminary data (Takahashi et al., 1998) on the occurrence of total butyltin residues in human liver. The average concentration in four samples was 84 ng/g wet weight (range 59–96 ng/g). The concentration of tributyltin was less than the detection limit of 2 ng/g. The concentration of dibutyltin was 79% of the total.

8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

Extensive data are available on the toxicity of TBTO. Detailed descriptions of studies critical to the evaluation of TBTO follow; all other studies are described in US EPA (1997) or IPCS (1990). Collectively, these data establish that immunotoxicity is the critical effect of TBTO. A detailed evaluation of these effects is found in section 8.7. All studies involving repeated oral exposure are listed in Table 1.

8.1 Single exposure

TBTO is moderately to highly acutely toxic to laboratory mammals. Acute oral LD\(_{50}\) values range from 127 to 234 mg/kg body weight for the rat and average 85 mg/kg body weight for the mouse (IPCS, 1990). TBTO exhibits greater lethal potential when administered parenterally (20 and 16 mg/kg body weight in the rat and mouse, respectively) as opposed to orally, probably as a result of only partial absorption from the gut. Single-exposure studies using 100 mg TBTO/kg body weight by oral gavage (Funahashi et al., 1980) demonstrated a transient increase in adrenal weight shortly after exposure (returning to normal within 2 days) and a transient effect on thyroid follicles (distension with flat

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\(^1\) Dr J. Sekizawa’s (National Institute of Health Sciences, Tokyo, Japan) review of unpublished data.

\(^2\) Letter and attachments from J.A. Jonker, Elf Atochem, to D.J. Stenhouse, Health and Safety Executive, United Kingdom, dated 3 February 1997.
<table>
<thead>
<tr>
<th>Toxicity/species</th>
<th>Study length</th>
<th>End-point</th>
<th>LOAEL (mg/kg body weight per day)</th>
<th>NOAEL (mg/kg body weight per day)</th>
<th>Reference</th>
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<td></td>
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<tr>
<td>Monkey</td>
<td>22 weeks</td>
<td>Decreased leukocyte counts</td>
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<td>Karrer et al., 1992</td>
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<tr>
<td>Rat</td>
<td>24 months</td>
<td>Decreased survival, changes in kidney and organ weights, increased serum IgA and IgM</td>
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<td>0.19</td>
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<td>Mouse</td>
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<td>0.7 (frank effect level)</td>
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<tr>
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<td></td>
<td>gestation days 6–20</td>
<td>Increased ossification variations</td>
<td>5</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>gestation days 6–15</td>
<td>Decreased maternal weight</td>
<td>10</td>
<td>5</td>
<td>Crofton et al., 1989</td>
</tr>
<tr>
<td>Mouse</td>
<td>gestation days 6–15</td>
<td>Decreased maternal weight; increased skeletal abnormalities</td>
<td>23.4</td>
<td>11.7</td>
<td>Davis et al., 1987</td>
</tr>
<tr>
<td>Mouse</td>
<td>gestation days 6–15</td>
<td>Decreased maternal weight; increased resorptions; decreased fetal weight</td>
<td>40</td>
<td>20</td>
<td>Baroncelli et al., 1990</td>
</tr>
<tr>
<td>Mouse</td>
<td>gestation days 6–15</td>
<td>Haematology</td>
<td>–</td>
<td>20</td>
<td>Karrer et al., 1995</td>
</tr>
<tr>
<td><strong>Immunological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>28 days</td>
<td>Thymus-dependent immunity</td>
<td>5</td>
<td>0.5</td>
<td>Verdier et al., 1991</td>
</tr>
<tr>
<td>Rat</td>
<td>4 weeks</td>
<td>Lymph node haemorrhage</td>
<td>0.5</td>
<td>–</td>
<td>Krajnc et al., 1984; Vos et al., 1984</td>
</tr>
<tr>
<td>Rat</td>
<td>1 week; 4 weeks</td>
<td>Lymph node haemorrhage</td>
<td>0.4</td>
<td>–</td>
<td>Bressa et al., 1991</td>
</tr>
<tr>
<td>Rat</td>
<td>6 weeks</td>
<td>Virus titres</td>
<td>2</td>
<td>–</td>
<td>Garssen et al., 1995</td>
</tr>
<tr>
<td>Rat</td>
<td>6 weeks</td>
<td>Reduced thymus weight</td>
<td>8</td>
<td>2</td>
<td>VanLoveren et al., 1990</td>
</tr>
<tr>
<td>Rat</td>
<td>6 weeks</td>
<td>Reduced thymus-dependent immunity and non-specific resistance</td>
<td>2</td>
<td>–</td>
<td>Vos et al., 1984</td>
</tr>
<tr>
<td>Rat</td>
<td>6 weeks</td>
<td>Decreased IL2R alpha mRNA; reduced CD25 expression</td>
<td>0.5</td>
<td>–</td>
<td>VandeBriel et al., 1998</td>
</tr>
<tr>
<td>Rat</td>
<td>13–26 weeks</td>
<td>Reduced thymus weight</td>
<td>3</td>
<td>–</td>
<td>Funahashi et al., 1980</td>
</tr>
<tr>
<td>Rat</td>
<td>18 weeks</td>
<td>Reduced thymus weight</td>
<td>16</td>
<td>–</td>
<td>Carthew et al., 1992</td>
</tr>
<tr>
<td>Rat, aged</td>
<td>5 months</td>
<td>Thymus-dependent immunity</td>
<td>2.5</td>
<td>0.25</td>
<td>Vos et al., 1990</td>
</tr>
<tr>
<td>Rat, weanling</td>
<td>4.5 or 18 months</td>
<td>Thymus-dependent immunity</td>
<td>0.25</td>
<td>0.025</td>
<td>Vos et al., 1990</td>
</tr>
<tr>
<td>Mouse</td>
<td>gestation days 4–17 or 11–17</td>
<td>Humoral and cell-mediated immunity</td>
<td>0.1</td>
<td>–</td>
<td>Buckiova et al., 1992</td>
</tr>
<tr>
<td>Rat</td>
<td>10 doses to pre-weanlings</td>
<td>Depressed mitogen response</td>
<td>5</td>
<td>2.5</td>
<td>Smialowicz et al., 1989</td>
</tr>
</tbody>
</table>
epithelial cells). In addition, there were reversible effects on the pituitary and on levels of adrenocorticotropic hormones, thyroid-stimulating hormone, thyroxine, and serum cortisol. The acute dermal LD₅₀ in rabbits is about 9000 mg/kg body weight.

Truhaut et al. (1979) exposed mice to an aerosol of TBTO in olive oil for either a single 1-h period or seven 1-h periods on successive days, using TBTO concentrations in air ranging between 50 and 400 mg/m³. Exploratory behaviour was scored over 5-min periods 2 h after the single exposure was complete or 24 h after the last of the seven exposure periods. The lower two exposures caused a significant increase in exploratory behaviour (17% and 5% for 42 and 84 mg/kg body weight, respectively), whereas the higher exposures reduced exploratory behaviour (! 18% and ! 38% for 170 and 340 mg/kg body weight, respectively).

Schweinfurth & Gunzel (1987) summarized the results of several inhalation studies in laboratory animals. After a single 4-h exposure of rats to aerosols of TBTO, signs of irritation (nasal discharge, lung oedema, and congestion of the pulmonary circulation) and enteritis were observed. The LC₅₀ was 77 mg/m³ (total particles) or 65 mg/m³ (particles with a diameter <10 µm). In guinea-pigs exposed to aerosols of TBTO in olive oil at 200 mg/m³ and above, death occurred within 1 h of exposure. Ten male and 10 female rats were exposed to almost saturated vapours of TBTO (concentration not specified) without a single death occurring during exposure for 7 h or the following 14-day observation period. Only minor clinical signs (slight nasal discharge directly after exposure) were noted. For this study, the authors reported no information on particle size or the end-points evaluated.

8.2 Irritation and sensitization

TBTO is a potent skin irritant and an extreme eye irritant (IPCS, 1990). It is not a skin sensitizer (IPCS, 1990). Poitou et al. (1978) investigated the skin-sensitizing potential of TBTO in guinea-pigs using the Magnussen-Kligman method. The concentrations used for sensitization were 1% (intradermal phase) and 5% (topical phase). Using challenge concentrations of 0.25% and 0.1%, no sensitizing action was demonstrated in the 20 test animals. It is not clear from IPCS (1990) whether these challenge concentrations represented the maximum non-irritant concentrations or what positive control substances were used to verify the sensitivity of the assay. A recent study (Stringer et al., 1991) demonstrated contact sensitivity in the mouse.

8.3 Short-term exposure

Short-term studies focusing on effects on the immune system following oral exposure are listed in Table 1.

In the only study involving repeated inhalation exposure that reported effects in the respiratory tract, rats (10 males and 10 females per dose) were exposed in “nose-only” chambers for 4 h to TBTO doses of 0, 0.03 (vapour), 0.16 (vapour), or 2.8 (aerosol) mg/m³, 5 days/week, for a total of 21–24 treatments (Schweinfurth & Gunzel, 1987). At the highest dose, severe toxic effects were produced. Mortality was 5/10 in males and 6/10 in females. In addition, inflammatory reactions (not further specified) in the total respiratory tract and histological changes (not further specified) in the lymphatic organs were observed. No local or systemic changes were observed at the lower doses. The authors did not, however, report what end-points were evaluated.

8.4 Long-term exposure

8.4.1 Subchronic exposure

A large number of well-conducted subchronic studies have been conducted in rats focusing on toxicity to the immune system. These studies and their NOAELs and lowest-observed-adverse-effect levels (LOAELs) are listed in Table 1 and summarized in section 8.7.

Effects of TBTO (purity 96%) on haematology and serum chemistry were assessed in groups of three and four adult male cynomolgus monkeys that ingested doses of 0 or 0.160 mg/kg body weight per day, respectively, 6 days/week for 22 weeks (0 and 0.14 mg/kg body weight per day, actual intake) (Karrer et al., 1992). The TBTO was dissolved in vegetable oil and added to Tween 80-augmented pear juice, which the monkeys drank. Study end-points consisted of clinical observations, body weight, and standard haematology and clinical chemistry indices, including serum immunoglobulin (IgM and IgG) levels. A progressive decrease in total leukocyte counts occurred during the first 10 weeks of exposure (significantly [P < 0.05] lower than controls at weeks 8 and 10; 67% of control value at week 10). Leukocytes subsequently increased and were similar to controls between weeks 10 and 16, but decreased again between weeks 16 and 20 (61.5% of control value at week 20; P < 0.05). No significant alterations in differential leukocyte count, serum immunoglobulins, or other study parameters were observed. Based on decreased total leukocyte levels, 0.14 mg/kg body weight per day (the only dose tested) is a LOAEL in monkeys.
8.4.2 Chronic exposure and carcinogenicity

Well-conducted studies are available in rats and mice. A study in dogs (Schuh, 1992) is fatally flawed and is not reported. Long-term studies assessing effects on the immune system are reported in section 8.7 and listed in Table 1.

In a chronic toxicity/carcinogenicity study, groups of 60 male and 60 female Wistar rats were exposed to dietary TBTO (0.5, 5, and 50 mg/kg diet) for 2 years (Wester et al., 1987, 1988, 1990). Based on estimates of average body weight and food consumption from reported data, ingested dosages were approximately 0.019, 0.19, or 2.1 mg/kg body weight per day in males and 0.025, 0.25, or 2.5 mg/kg body weight per day in females. End-points that were evaluated included clinical abnormalities, survival, body weight, food and water consumption, and the incidence of neoplastic lesions. Haematology, urinalysis, clinical chemistry (including immunoglobulins IgG, IgM, and IgA), and endocrinology (total thyroxine and free thyroxine, thyrotropin, luteinizing hormone, follicle-stimulating hormone, insulin) were evaluated in 10 rats per sex per dose after approximately 3, 12, and 24 months (endocrinology not assessed at 3 months). Organ weights and histology were evaluated in 10 rats per sex per dose after 12 and 24 months, and histology was also evaluated in all moribund rats as well as rats surviving until 24 months.

No treatment-related adverse changes were found in males or females at the lowest dose. Serum immunoglobulin levels were significantly (P < 0.05, Student’s t-test) increased in the high-dose group. Concentrations of IgA were increased in both sexes after 12 and 24 months; at 24 months, levels of IgA were 508% of the control value in males (P < 0.001) and 294% of the control value in females (P < 0.01). Concentrations of IgG were significantly (P < 0.01) reduced in females after 3 months (42% of the standard serum value compared with 69–71% in controls and other treated groups) and 12 months (80% compared with 124–127%), but not after 24 months or in males. Concentrations of IgM were increased in both sexes after 3, 12, and 24 months; at 24 months, the IgM level was 258% of the standard serum value in males (P < 0.01) and 240% of the standard value in females (P < 0.01).

Other effects occurred predominantly in high-dose rats, including decreased survival, decreased body weight, and changes in organ weights. At termination, survival in females in the high-dose group was 54% versus 74% in controls; survival in males in the high-dose group was 40% versus 60% in controls. Terminal body weights at this dose were approximately 13% (male) and 9% (female) lower than controls. Absolute liver, kidney, adrenal gland (male only), and heart (male only) weights were increased and thyroid weight (female only) was decreased in high-dose rats at study termination; relative organ weights were not reported. The liver weight was increased 36% and 29% in males and females, respectively; the kidney weight was increased 29% and 33% in males and females, respectively; the adrenal weight in males and females was increased 630% and 44%, respectively; the heart weight in males was increased 13%; and the thyroid weight in females was decreased 26%.

Treatment-related non-neoplastic histological changes occurred in the liver, spleen, and thyroid of high-dose males and females. Histological effects after 12 months included slight bile duct changes (characterized by hyperplasia, cellular hypertrophy, and minimal infiltration of mononuclear cells or by cholangiofibrosis), decreased haemosiderin content in spleen (qualitative analysis only), and decreased thyroid follicular epithelial cell height. Examination after 24 months showed that only the histological changes in the thyroid persisted. There were no accompanying significant changes in concentrations of serum thyroid hormones. The incidence and severity of age-related degenerative changes in the kidney (nephrosis and vacuolation and pigmentation of the proximal tubular epithelium, suggestive of iron and/or lipofuscin) were increased in high-dose males and females after 24 months.

Neoplastic lesions were examined in the control and high-dose groups; if differences were observed, the intermediate-dose groups were also examined for those tumour types. Increased incidences of benign pituitary tumours, pheochromocytomas in the adrenal medulla, and parathyroid adenomas were noted. These data are shown in Table 2.

There are increases in the incidence of some benign spontaneous tumours at the high dose in some endocrine tissues. According to the authors, these tumours normally occur in this strain of rats with high and variable background incidence (Kroes et al., 1981; Wester et al., 1985). In the two data sets available for these tumour types in the strain of Wistar rats used by Wester et al. (1990), the reported background occurrence of pituitary tumours (adenomas plus carcinomas) in females was 52% and 55% and in males was 34% and 87%; the reported background incidence of pheochromocytomas (benign plus malignant) in females was 8% and 16% and in males was 22% and 58%. The authors reported no data on the background occurrence of parathyroid tumours.

There was no significant endocrine imbalance documented in the study. No significant change was observed in the serum levels of thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, insulin, total thyroxine, or free thyroxine. There was, however, a decrease in the free thyroxine:
lesions, particularly glomerular/interstitial amyloidosis of the kidney, were found. Incidences of renal amyloidosis were increased in females in all dose groups (50, 67.7, and 78.4%, respectively, compared with 34.8% in controls) but not in males. The progression of this lesion appeared to be more rapid in both sexes at the two highest doses, indicating a compound-related effect. There were no statistically significant increases in the incidence of any tumours or groups of tumours in males or females. TBTO was not carcinogenic in this study in mice. This study identified an effect level for mortality at 0.7 mg/kg body weight per day (the lowest dose tested) (Daly, 1992).

### 8.5 Genotoxicity and related end-points

The genetic effects of TBTO were evaluated in multiple in vivo and in vitro short-term tests (Davis et al., 1987). TBTO was not mutagenic in the rec assay in Bacillus subtilis, did not induce reverse mutations in Salmonella typhimurium strains TA1530, TA1535, TA1538, TA97, TA98, or TA100 in the presence or absence of a rat liver activation system (Davis et al., 1987). TBTO was mutagenic in S. typhimurium strain TA100 in a fluctuation test, but only in the presence of rat liver S9 (Aroclor-induced) and at cytotoxic concentrations. TBTO did not induce gene mutations in Schizosaccharomyces pombe, mitotic gene conversions in Saccharomyces cerevisiae, or sister chromatid exchange in Chinese hamster ovary cells in the presence or absence of rat or mouse liver S9. Structural chromosomal aberrations, endoreduplicated and polyploid cells, were observed in Chinese hamster ovary cells. The aberrations were observed only at 8 h after treatment (not at 15 or 24 h) and only at the highest concentration tested in the presence of S9. Cytotoxicity was also observed at this concentration. TBTO did not induce gene mutations in V79 Chinese hamster cells or in mouse lymphoma cells. It did not induce recessive lethal mutations in adult male Drosophila melanogaster by either feeding or injection. Doses of 0.37 or 0.74 mmol/litre did not increase the number of X-linked recessive

### Table 2: Neoplastic lesions in rats.a

<table>
<thead>
<tr>
<th>Concentration of TBTO (mg/kg diet)</th>
<th>Incidence of pituitary tumoursb</th>
<th>Incidence of adrenal pheochromocytomasb</th>
<th>Incidence of parathyroid adenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>0</td>
<td>22/50</td>
<td>34/50</td>
<td>3/50</td>
</tr>
<tr>
<td>0.5</td>
<td>32/50*</td>
<td>39/50*</td>
<td>3/50</td>
</tr>
<tr>
<td>5</td>
<td>22/50</td>
<td>29/50</td>
<td>3/50</td>
</tr>
<tr>
<td>50</td>
<td>35/50**</td>
<td>43/50***</td>
<td>34/50***</td>
</tr>
</tbody>
</table>

a From Wester et al. (1990).
b Statistical analysis was carried out according to Peto et al. (1980), one tailed. Values marked with asterisks differ significantly from the corresponding control values (* P < 0.05; ** P < 0.01; *** P < 0.001).
c The value differs significantly (chi-square test) from the corresponding control (P < 0.01).

total thyroxine ratio for both sexes at 12 and 24 months in the high-dose group and after 12 months in the mid-dose group. Although the pituitary tumours stained for the presence of prolactin, there was no correlation between the serum level of prolactin or the occurrence of hyperplastic or neoplastic mammary tissue and the presence of pituitary tumour.

Based on the constellation of changes (increased mortality, increased serum immunoglobulins, changes in organ weight, and histopathological changes) observed at the highest dose, the LOAEL is 2.1 mg/kg body weight per day and the NOAEL is 0.19 mg/kg body weight per day (Wester et al., 1987, 1988, 1990).

TBTO (purity 97.1%) was fed to groups of 50 male and 50 female CD-1 mice in dietary concentrations of 0, 5, 25, or 50 mg/kg for 18 months in a study primarily designed to assess carcinogenicity (Daly, 1992). Based on food consumption and body weight data, mean compound intake was reported to be 0, 0.7, 3.7, or 7.7 mg/kg body weight per day in males and 0, 0.9, 4.8, or 9.2 mg/kg body weight per day in females.

Statistically significant decreases in survival occurred in treated mice of both sexes. In males, survival after 18 months was 67, 52, 42, and 42% in the control, low-, mid-, and high-dose groups, respectively (P < 0.05, all doses). Survival in females at 18 months was 59, 48, 40, and 27% in the control, low-, mid-, and high-dose groups, respectively (P < 0.05 except for low-dose group). No information on cause of death was available. Other treatment-related effects included significantly decreased food consumption and increased absolute and relative liver weights in females at the high dose. Incidences of gross liver enlargement and discoloration were slightly increased in both sexes in all dose groups. The gross liver changes are not considered biologically significant because of the slight changes and absence of hepatic histopathological alterations. Increased incidences of common spontaneous non-neoplastic lesions, particularly glomerular/interstitial amyloidosis of
mutations. An increased number of micronuclei was observed in polychromatic erythrocytes of male BALB/c mice 48 h after a single oral dose of TBTO (60 mg/kg body weight). A reanalysis of the slides from the high-dose group, however, failed to confirm the increase in micronuclei (ICPS, 1990). A lower dose (30 mg/kg body weight) was ineffective. Neither dose induced micronuclei 30 h after treatment.

One report demonstrated that TBTO and triphenyltin chloride are co-clastogens in a whole mammalian system (Yamada & Sasaki, 1993). The frequency of micronuclei induced by mitomycin C in mouse peripheral reticulocytes was enhanced approximately 50% when 50 mg TBTO/kg body weight and 100 mg triphenyltin chloride/kg body weight were given orally to mice. No effect was observed when the chemicals were administered separately.

In aggregate, despite the limited positive findings at cytotoxic concentrations, the weight of evidence shows that TBTO is not genotoxic. This conclusion remains consistent with the previous evaluation by IPCS (1990).

8.6 Reproductive and developmental toxicity

Several well-conducted studies are available that investigated the effects of TBTO on the reproductive system and fetal development in rats and mice. The results of these studies are listed in Table 1. These studies show no evidence that TBTO is a significant reproductive or developmental toxicant in rodents. The developmental effects noted in the various studies occur at or near the exposure that also causes maternal toxicity (depressed body weight or impaired weight gain during pregnancy). The LOAELs for maternal toxicity in rats and mice are approximately 10 mg/kg body weight per day, with NOAELs of approximately 5 mg/kg body weight per day.

8.7 Immunological and neurological effects

8.7.1 Immunotoxicity

A large number of well-conducted studies have shown that TBTO causes depression of immune functions dependent on the thymus. Results from a number of short-term studies are listed in Table 1. Subchronic and chronic studies (Vos et al., 1990) are summarized in detail below and are listed in Table 1. The chronic study conducted by Vos et al. (1990) shows effects on thymus-dependent immune responses at a dose lower than that at which any other toxic effects have been observed. The Vos et al. (1990) study also establishes that weanling animals are more sensitive than adults to the effects of TBTO. For example, following subchronic exposure, the LOAEL in weanling rats was 0.25 mg/kg body weight per day, whereas the LOAEL in aged rats was 2.5 mg/kg body weight per day. The NOAELs were 0.025 and 0.25 mg/kg body weight per day, respectively. Data from Buckiova et al. (1992) and Smialowicz et al. (1989) also show that exposure of mice in utero and exposure of rat pups prior to weaning cause effects at exposures lower than those required for the same effects in adult animals.

In a subchronic immunotoxicity study (Vos et al., 1990; a companion to the chronic study summarized below), aged (1-year-old) male Wistar rats were exposed for 5 months to the same diets used in the principal study. Based on the authors’ statement from the chronic study (see below), estimated compound intake was 0, 0.025, 0.25, or 2.5 mg/kg body weight per day. End-points were the same as some of those evaluated in the chronic study.

Compound-related effects occurred only in the high-dose group and consisted of significantly decreased thymus weight (39% lower than controls, P < 0.01), impaired resistance to *Trichinella spiralis* (indicated by increased recovery of adult worms from the small intestine [780% higher than controls; P < 0.01] and number of larvae in muscle [80% higher; P < 0.001]), and impaired resistance to *Listeria monocytogenes* (indicated by approximately 300% increased splenic bacterial count; P < 0.05).

Subchronic and chronic immunotoxicity studies were conducted in which weanling SPF-derived Riv:TOX Wistar rats were fed TBTO (purity 95.3%) at concentrations of 0, 0.5, 5, or 50 mg/kg. Male rats (females not tested) were evaluated following exposure to TBTO for up to 18 months (Krajnc et al., 1987; Vos et al., 1990). The authors reported the 5 mg/kg dietary concentration to be equivalent to a dose of 0.25 mg/kg body weight per day, indicating that estimated test doses were 0.025, 0.25, and 2.5 mg/kg body weight per day. Body weight, absolute thymus weight, and absolute spleen weight were measured in groups of 18, 12, and 12 rats, respectively, following exposure for 4.5 months.

Immunological function studies for specific and non-specific resistance were performed in 9–12 rats per group after 4–6 or 15–17 months of exposure. Antigen-specific functional assays evaluated IgM and IgG responses to sheep red blood cells (immunized after 16 months); IgM and IgG responses to ovalbumin and delayed-type hypersensitivity (24-, 48-, and 72-h) responses to ovalbumin and *Mycobacterium tuberculosis* (immunized after 6 or 15 months of exposure); and resistance to oral infection by *T. spiralis* larvae (infected after 5.5 or 16.5 months).
Non-specific resistance was assessed by splenic clearance of intravenously injected L. monocytogenes bacteria (after 5 or 17 months of exposure) and natural cell-mediated cytotoxicity of spleen cells (after 4.5 or 16 months of exposure) and peritoneal cells (after 4.5 months of exposure only) using a 4-h 51Cr-release assay with YAC-lymphoma target cells. Non-specific end-points included the numbers of viable nucleated thymus and spleen cells and responses of thymus and spleen cells to T-cell and/or B-cell mitogens (phytohaem-agglutinin, concanavalin A, pokeweed mitogen, and/or Escherichia coli lipopolysaccharide) after exposure for 4.5 months (thymus and spleen) or 16 months (spleen only); and numbers of viable nucleated mesenteric lymph node cells with cell surface marker analysis (after 6 and 18 months of exposure; low-dose group not tested in this assay).

No significant effects were observed in the IgM or IgG responses to sheep red blood cells, the IgM or IgG responses to T. spiralis, the IgM or IgG responses to ovalbumin, or the delayed-type hypersensitivity responses to ovalbumin and M. tuberculosis.

Thymus weight was significantly reduced in the high-dose group (17% lower than controls, $P < 0.05$), although the response of thymocytes to T-cell mitogens was unaltered. No significant alterations in spleen weight, response of spleen cells to T- and B-cell mitogens, or body weight were found at any dose. Statistically significant changes occurred in the percentage of mesenteric lymph node T-lymphocytes in the high-dose group (20% lower than controls after 18 months of exposure) and B-lymphocytes in the mid-dose (60% higher than controls after 18 months) and high-dose (48% higher than controls after 18 months) groups; however, the absolute number of T-lymphocytes and B-lymphocytes per lymph node was not significantly altered. The low-dose group was not tested with these assays. The B-cell increase was an increase in the percentage of B-cells, but the interpretation of these data is equivocal, because they are counter-intuitive when viewed in context with the other effects, especially the IgE titres.

In vivo clearance of injected L. monocytogenes was impaired in rats exposed to the high dose for 17 months, as shown by the approximately sevenfold increase in number of viable bacteria per spleen, indicating that macrophage function was reduced. Resistance to infection by T. spiralis was suppressed in rats exposed to the mid or high dose, as shown by significantly reduced serum IgE titres (50 and 47% lower than controls after 16.5 months of exposure), increased numbers of larvae in muscle 42 days after infection (56% and 306% higher than controls after 16.5 months), and moderately reduced inflammatory reaction around cysts in parasitized musculature (qualitative assessment only).

There was no significant reduction in the activity of natural killer cells isolated from the peritoneal cavity following exposure of weanling or aged (1-year-old) rats to TBTO for 4.5 months. Also, there was no significant reduction in the activity of natural killer cells isolated from the spleen following exposure of weanling rats for 4.5 months. In contrast, the activity of natural killer cells isolated from the spleen was suppressed when weanling rats were exposed to all doses of TBTO for 16 months (31, 25, and 36% lower than controls, respectively, at an effector to target cell ratio of 100, and 32, 18, and 30% lower, respectively, at an effector to target cell ratio of 50). Based on these data, the effect did not progress significantly with dose. Because the authors considered these data equivocal in this experiment and because there was no clear treatment-related effect, the suppression of natural killer cell activity in this study is not considered biologically significant.

Essentially identical results on the immune system were observed when weanling rats were exposed for 4.5 or 16.5 months. Based on the depression of IgE titres and an increase in T. spiralis larvae in muscle, the LOAEL for immunotoxicity is 0.25 mg/kg body weight per day. The NOAEL is 0.025 mg/kg body weight per day (Krajnc et al., 1987; Vos et al., 1990).

Some recent studies suggest that the mechanism of the immunotoxic effects is related to induction of apoptosis (programmed cell death) within the thymus. Raffray & Cohen (1991) demonstrated that thymocytes in culture showed cellular changes consistent with apoptosis at concentrations of TBTO that did not affect cell viability. Raffray et al. (1993) showed that these effects occur independently of a requirement for protein synthesis and do not require fully conserved energetics (i.e., the effects occur despite depression of ATP levels to less than 20% of control values). Raffray & Cohen (1993) demonstrated a correlation between reduction of thymus weight in animals given a single oral dose of TBTO and evidence of apoptosis (increased DNA fragmentation) in thymic cell isolates (principally thymocytes) isolated from the animals during the period of thymic involution. These workers also showed that dibutyltin, the major metabolite of tributyltin, is less effective in inducing apoptosis in vitro, suggesting that the in vivo toxicity is directly attributable to tributyltin.

A study comparing immunotoxic effects in pre-weanlings and adult rats shows that some responses of the developing immune system are more sensitive to TBTO (Smialowicz et al., 1989). Adult (9 weeks old) male Fischer rats or pre-weanlings (3–24 days old) rats were dosed by oral gavage 3 times per week for a total of 10 doses. The adults were dosed with 5, 10, or 20 mg/kg body weight per dose; the pre-weanlings were dosed with 2.5, 5, or 10 mg/kg body weight per dose. Reductions in mitogen responses were observed in
adults at 10 and 20 mg/kg body weight and in pre-weanlings at 5 and 10 mg/kg body weight. The mixed lymphocyte reaction was suppressed in adults at 20 mg/kg body weight and in pre-weanlings at 10 mg/kg body weight. Finally, natural killer cell activity was suppressed only in pre-weanlings at 10 mg/kg body weight. In this study, the lowest LOAEL is 5 mg/kg body weight per day, and the lowest NOAEL is 2.5 mg/kg body weight per day.

Pregnant ICR mice were treated with TBTO in Tween 80:ethanol:saline (1:2:97) by gavage at 0.1 mg/kg body weight per day on gestation days 4–17 or 11–17 (Buckiova et al., 1992). Humoral and cell-mediated immune responses in offspring were assessed 4 and 8 weeks after birth. At 0.1 mg/kg body weight per day, the only dose tested, effects in the offspring included suppressed primary antibody responses to sheep red blood cells, ovalbumin, and lipopolysaccharide and increased number of leukocytes. Suppressed delayed-type hypersensitivity to sheep red blood cells and unspecified alterations in polyclonal proliferative responses of thymocytes and splenocytes were also observed. The significance of the LOAEL (0.1 mg/kg body weight per day), however, is unclear, because a full publication of the results is not available.

### 8.7.2 Neurotoxicity

Triethyltin and trimethyltin compounds have been shown to cause severe neurotoxicity (for a summary, see Boyer, 1989). Triethyltin causes interstitial oedema throughout the white matter in the spinal cord and various regions of the brain; less marked damage occurs in the peripheral nervous system. Trimethyltin also causes severe and permanent damage to the central nervous system. In this case, however, the effect is neuronal necrosis, rather than oedema. TBTO, in contrast, causes no severe neurological signs or morphological or histopathological changes in brain tissue. In a 4-week study, rats fed a dietary concentration of 320 mg/kg (equivalent to 30 mg/kg body weight per day) exhibited ptosis or enophthalmia and slight ataxia (Krajc et al., 1984). One chronic study in dogs (Schuh, 1992) also gave a slight suggestion of neurotoxicity (atactic gait and apathy). As noted above, however, this study is significantly flawed.

Crofton et al. (1989) measured brain weight and motor activity in developmental studies. There was some suggestion of neurotoxicity (based on decreased brain weight in pups) at exposures in excess of 10 mg/kg body weight per day, but no reported effects at 5 mg/kg body weight per day.

Organotin compounds, including tributyltin, have recently been shown to induce apoptosis in immortalized neuronal cell lines (Thompson et al., 1996) and in pheochromocytoma PC12 cells (Viviani et al., 1995). Although TBTO induces apoptosis in neural cells in vitro, it does not cause neurotoxicity in whole animals.

Although the potential for neurotoxicity has not been completely investigated with focused studies, there is no suggestion that neurotoxicity is likely a critical or co-critical effect.

### 9. EFFECTS ON HUMANS

No information was located regarding the toxicity of TBTO in humans following long-term exposure. Human data summarized by Boyer (1989) suggest that TBTO is a potent non-allergenic dermal irritant. There are several case reports claiming irritation of the respiratory tract following acute inhalation exposure of people to TBTO (Anon., 1991; Hay & Singer, 1991; Shelton et al., 1992; Wax & Dockstader, 1995). None of these reports, however, contains sufficient information to characterize the exposure–response relationship for the reported effects.

No epidemiological studies on TBTO were located in the literature.

### 10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

Triethyltin in the environment is very toxic to most taxa (see data cited in IPCS, 1990). Bivalves and gastropods are especially sensitive, and larval stages are more vulnerable than adults. The lowest reported effect concentrations for tributyltin are 2.4–4.8 ng/litre for induction of shell deformities in Pacific oyster and imposex development in dogwhelk (*Nucella lapillus*). Other low toxicity values reported are no-observed-effect concentrations (NOECs) of 80 ng/litre for *Daphnia magna*, 40 ng/litre for reduced viability of mussel (*Mytilus edulis*) larvae, and 10 ng/litre for reduced growth of hard-shell clams (*Mercenaria mercenaria*) and reduced egg production in a marine copepod (*Acartia tonsa*)

In the field, mainly the effects on oysters and prosobranchs have been studied. Most studies on imposex have examined populations of *N. lapillus*. It has been suggested that other prosobranchs are even more

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1 Imposex is the development of male characteristics by female gastropods.
Tributyltin oxide

sensitive, and other species have been suggested as indicator species (Matthiessen & Gibbs, 1998).

Matthiessen & Gibbs (1998) reviewed the evidence that TBTO-induced imposex and intersex in molluscs are the result of endocrine disruption. The effect is most likely the result of elevated testosterone titres that masculinize tributyltin-exposed females. The precise mechanism has not been fully described, but the weight of evidence suggests that TBTO acts as a competitive inhibitor of cytochrome P-450-mediated aromatase, leading to increased testosterone levels. Additional support for this mechanism has been presented by Bettin et al. (1996). Testosterone addition (500 ng/litre) induces faster and more intensive imposex development in N. lapillus than that induced by tributyltin. Simultaneous exposure to tributyltin and to the antiandrogen cyproterone acetate suppresses imposex development completely in N. lapillus and reduces it in Hinia reticulata. Furthermore, tributyltin-induced imposex development can be suppressed by adding estrogens. Inhibition of the cytochrome P-450-dependent aromatase using SH 489 (1-methyl-1,4-androstadiene-3,17-dione) and flavone induces development of imposex. Some recent data suggest that TBTO may also inhibit the formation of sulfur conjugates of testosterone and its active metabolites, thus interfering with its excretion.

There is a vast literature on the environmental effects of tributyltin. Most of the information below was condensed from IPCS (1990). Additional data published since this evaluation have also been included.

10.1 Aquatic environment

As tributyltin is used commercially to control bacteria and fungi, the substance is toxic to these taxa. The reported minimum inhibitory concentrations (MICs) range from 20 to 300 000 : g/litre. The MIC for sludge from municipal sewage treatment plants was reported as 25 : g/litre (IPCS, 1990). A recent study conducted in yeast suggests that the target for TBTO action is the mitochondrial ATPase (Veiga et al., 1997). TBTO reduced the respiratory capacity when vanillic or benzoic acid was the energy source. The ATP level of the cell was severely affected at a concentration of 1.19 mg/litre. The mitochondrial ATPase was strongly inhibited at a concentration of 0.3 mg/litre, whereas the activity of the plasma membrane ATPase was not affected by a concentration up to 17.9 mg/litre.

In the laboratory, effective concentrations for freshwater algae ranged from 5 : g/litre (4-h IC50 for growth, Ankistrodesmus falcatus) to 64 : g/litre (96-h EC50, Scenedesmus pannonicus). A 4-h IC50 for primary production of 3 : g/litre was reported for a natural community from Lake Ontario (IPCS, 1990). For marine and estuarine algae, most reported IC50 or EC50/LC50 values range from 0.1 to 15 : g/litre (IPCS, 1990). For motile spores of the green macroalga Enteromorpha intestinalis, a 5-day EC50 of 0.001 : g/litre for spor development and inhibition of settling was indicated (IPCS, 1990). Effects on community metabolism and nutrient dynamics in bladderwrack (Fucus vesiculosus) have been shown at 0.6 : g tributyltin/litre and above (Lindblad et al., 1989). Studies on pure cultures of marine algae show that these organisms do not adapt to tributyltin; the same EC50 values were obtained for cultures exposed for 12 weeks as for naive cells (IPCS, 1990).

For Lemma and Elodea species, reduction in growth was observed from 0.06 : g/litre following 10 days of exposure to TBTO. For the angiosperm Zostera marina, a NOEC of 0.1 mg/kg sediment was reported. The lethal concentration for the salt-marsh species Aster tripolium was 10 : g/kg mud (dry weight) (IPCS, 1990).

For Daphnia magna, the 48-h LC50 was 2.3 : g/litre; the NOEC has been estimated to be 0.5 : g/litre based on reversal of normal response to light (IPCS, 1990). The reported long-term toxicity value (21-day NOEC) for Daphnia magna is 0.19 : g/litre; the 96-h LC50 for Tubifex tubifex is 0.1 : g/litre (Fargasova, 1997).

For target snail adults, the 24-h LC50 was 30–400 : g/litre. The sensitivity of snails decreases with age, but eggs are more resistant than both young and adults. The lowest-observed-effect concentration (LOEC) for Biomphalaria and Bulinus is 0.001 : g/litre; the long-term NOEL for Lymnaea stagnalis is 0.32 : g/litre (IPCS, 1990).

Several field studies on the effects of tributyltin used as a molluscicide for schistosomiasis control in tropical areas have been reported (IPCS, 1990). For schistosome larvae in the aquatic stages, the LC50 was calculated to be 16.8 : g/litre for a 1-h exposure. The dose causing 99–100% suppression of cercarial infectivity of mice was between 2 and 6 : g/litre (IPCS, 1990).

Among marine aquatic invertebrates, larval stages are considerably more sensitive than adults. For example, the 48-h LC50 for the Pacific oyster is 1.6 : g/litre for larvae and 1800 : g/litre for adults; for the mussel M. edulis, the same values are 23 and 300 : g/litre, respectively. The larvae of brown shrimp (Crangon crangon) are also more sensitive than adults, the 96-h LC50 being 1.5 and 41 : g/litre, respectively (IPCS, 1990).

For subadults of the copepod Eurytemora affinis, the 72-h LC50 was reported as 0.6 : g/litre. For the mysid shrimp (Acanthomysis sculpta), the 96-h LC50 was reported as 0.41 : g/litre. For larvae of the lugworm
Ocenebra erinacea a number of other species in the field. These include
than 1 ng tributyltin/litre. Imposex has been observed in
virtually all females were sterilized at 3–5 ng tin/litre.
and above (IPCS, 1990). Some of the females retained
TBTO showed imposex development at 1–2 ng tin/litre
fertilization to metamorphosis (approximately 14 days),
shell clam (Mercenaria mercenaria) larvae has
been reported as approximately 0.1 : g/litre (IPCS, 1990).
A 22-day LC100 for adult polychaetes Nereis diversicolor was 4 : g/litre (IPCS, 1990). In another polychaete, Sabellastarte sanctijosephi, mortality occurred at 0.04–1.0 : g/litre (Langston, 1995).
It has been suggested that TBTO inhibits calcification of Pacific oysters below 20 ng tin/litre (Alzieu, 1991; Langston, 1995). These effects have also been observed in the field. In the early 1980s, a good correlation was found between field observations of occurrence of shell thickening and proximity of ports with large numbers of boats (IPCS, 1990).
Reduced growth of Pacific oyster spat has been shown at all concentrations above 20 ng TBT/litre (IPCS, 1990). Recently metamorphosed European oysters (Ostrea edulis) showed a severe reduction in growth rate over 10 days in 0.06 : g/litre. In spats of C. gigas, M. edulis, and carpet shell (Venerupis ducussata), growth was reduced at 0.24 : g/litre over 45 days. For adult mussels (M. edulis), shell length was reduced at 0.31 : g/litre following 66 days of exposure, and juvenile growth was reduced at 0.07 : g/litre. In a study of hard-shell clam (Mercenaria mercenaria) exposed from fertilization to metamorphosis (approximately 14 days), growth was reduced at 10 ng/litre and above.
In the laboratory, all female dogwhelks exposed to TBTO showed imposex development at 1–2 ng tin/litre and above (IPCS, 1990). Some of the females retained their breeding capacity at the lowest concentration, but virtually all females were sterilized at 3.5 ng tin/litre. From field observations, the NOEL has been set at less than 1 ng tributyltin/litre. Imposed has been observed in a number of other species in the field. These include Ocenebra erinacea, Ocenebrina aciculata, Hexaplex trunculus, Baccinum undatum, Littorina littorea, and Nassarius reticulatus (Oehlmann et al., 1996; Matthiasen & Gibbs, 1998).
In oysters (O. edulis), severe effects on reproduction occurred at 0.24 and 2.6 : g/litre; no larvae were released, gonads were undifferentiated, and no females developed (IPCS, 1990). At 0.01 : g/litre, egg production in exposed A. tonsa was significantly reduced (IPCS, 1990).
No effect on survival of grass shrimp (Palaemonetes pugio) was found after 96 h of exposure at 1 or 10 mg tributyltin/kg sediment, but exposure via water alone resulted in a 96-h LC50 of 20 : g/litre (IPCS, 1990). In sediments containing tributyltin, an LC50 of 1–10 mg/kg sediment was determined for Amphioxus (IPCS, 1990). No effects on survival of the mole crab (Emerita talpoida) were observed following 7 days of exposure at 10 : g/litre seawater and 4.5 mg/kg sand (IPCS, 1990). No mortality was observed in mysid shrimp (Acanthomysis sculpta), worms (Neanthes arenaceodentata), or clams (Macoma nasuta) exposed to concentrations in sediment of 155–610 : g/kg and concentrations in overlaying water of 0.2 : g/litre over 10–20 days (IPCS, 1990).
The reported short-term LC50 values for TBTO in freshwater fish obtained under static conditions range from 13 to 240 : g/litre (IPCS, 1990). The NOEL for the guppy (Poecilia reticulata) was estimated to be 0.01 : g/litre based on thymus atrophy, liver vacuolation, and hyperplasia of the haematopoietic tissue (Wester & Canton, 1987).
The toxicity of TBTO to marine fish is highly variable: 96-h LC50 values range between 1.5 and 36 : g/litre, with larval stages being more sensitive than adults (IPCS, 1990). Data have been reported for bleak (Alburnus alburnus), sole (Solea solea), armed bullhead (Ago- nus cataphractus), girella (Girella punctata), salt water goby (Chasmichthys dolichogratus), and chinook salmon (Oncorhynchus tshawytscha). There are indications that marine fish avoid TBTO concentrations of 1 : g/litre or more (IPCS, 1990). A recent study in flounder (Pla- tichthys flesus) showed that TBTO at 17.3 : g/litre caused mortality after 7–12 days, decreased the condition factor, resulted in gill lesions, and induced significant reduction of non-specific resistance. However, no marked effects on the relative thymus volume or on the specific immune system were noted (Grinwis et al., 1997).
Japanese medaka (Oryzias latipes) fed daily for 3 weeks with food containing tributyltin, polychlorinated biphenyls, or a combination of the two at 1 mg/kg body weight showed slight synergistic effects on reproduction, resulting in reduced spawning frequency, number of eggs, and proportion of fertile eggs (Oshima et al., 1998).
No effect on survival was found when eggs and larvae of frog (Rana temporaria) were exposed to TBT concentrations of 3 : g/litre or less; at 30 : g/litre,
however, significant mortality was observed (IPCS, 1990).

10.2 Terrestrial environment

Although the exposure of terrestrial organisms to tributyltin results primarily from its use as a wood preservative, tributyltin compounds are toxic to insects exposed topically or via feeding on treated wood (IPCS, 1990). The LD_{50} values for tributyltin compounds applied topically to the thorax of newly emerged insects range from 0.48% to 0.72% (dilutions with acetone) for the house fly (Musca domestica), from 0.29% to 0.69% for the mosquito (Anopheles stephensi), and from 0.52% to 0.87% for the cotton stainer (Dysdercus cingulatus). TBTO is toxic to honey bees (Apis mellifera) housed in hives made from TBTO-treated wood (1.9 kg/m^3). TBTO is toxic to bats (Pipistrellus pipistrellus) housed in roosting cages treated with TBTO, but this result was not statistically significant, owing to high mortality in controls. The acute toxicity of TBTO to wild mice (deer mice [Peromyscus maniculatus] and house mice [Mus musculus]) is moderate. The estimated dietary LC_{50} value, based on consumption of treated seeds used in repellency tests, is 200 mg/kg diet per day.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

A large number of studies have been conducted showing that TBTO causes depression of immune functions dependent on the thymus. These effects occur at doses lower than those that cause other toxicity (see Table 1). Accordingly, the critical effect for TBTO is immunotoxicity.

Based on the study of Vos et al. (1990), the critical effect is immunosuppression (reduced IgE titres and increase in T. spiralis larvae in muscle). The LOAEL is 0.25 mg/kg body weight per day, and the NOAEL is 0.025 mg/kg body weight per day. These values were based on the authors’ report that 5 mg/kg in the diet is equivalent to 0.25 mg/kg body weight per day. This study tested male animals only. Other studies show no evidence of gender differences in the toxic responses to TBTO. There is some evidence that a child might be more sensitive to the toxic effects of TBTO. For example, Smialowicz et al. (1989) showed that pre-weanling rats were more sensitive than adult rats. In addition, the principal study (Vos et al., 1990) showed that immunotoxic effects were observed when weanling rats were dosed for 4.5 or 16.5 months, whereas a companion study (Vos et al., 1990) showed that these effects were absent or occurred at a higher dose when adult (1-year-old) rats were dosed for 5 months.

Adequate data are not available to determine a no-effect or effect level following long-term inhalation exposure. The inhalation studies that are available document irritation to the respiratory system. There are no pharmacokinetic studies available with which to conduct a route-to-route extrapolation for extra-respiratory effects. TBTO might cause immunosuppression following chronic exposure by inhalation.

Cancer bioassays following oral exposure have been conducted in rats and mice. The bioassay in rats shows increases in benign pituitary tumours, in pheochromocytomas, and in parathyroid tumours at the highest dose tested. The significance of these tumours, which normally occur in this strain of rat with variable incidence, is unclear. The bioassay in mice showed no increase in tumours at any site. The weight of evidence shows that TBTO is not genotoxic.

11.1.2 Criteria for setting guidance values for TBTO

The no-effect level for immunosuppression (decrease in serum IgE titre) following long-term oral exposure in rats is 0.025 mg/kg body weight per day. Benchmark dose analysis shows that the exposure corresponding to the lower confidence limit (95%) on dose for a 10% decrease in serum IgE titre is 0.034 mg/kg body weight per day (US EPA, 1997). Application of uncertainty factors of 10 each for extrapolation from a laboratory animal species to humans and to protect sensitive humans gives a guidance value for oral exposure of 0.0003 mg/kg body weight per day (rounded from 0.00025 for the no-effect level or 0.00034 for the benchmark dose). No appropriate data are available to develop a guidance value for inhalation exposure or to estimate cancer risk.

11.1.3 Sample risk characterization

No human data are available to characterize the toxicity of TBTO, but a wealth of data from oral exposure in laboratory animals is available. The principal study and a variety of supporting studies convincingly demonstrate that the critical effect for TBTO is immunotoxicity. Some evidence indicates that young animals are more sensitive than adults to the immunotoxic effects. TBTO is not a reproductive or developmental toxicant. Insufficient data are available to determine the critical effect for TBTO following exposure by inhalation. Several case reports document severe irritation of the human respiratory system following acute inhalation exposure. The potential human hazard for carcinogenic-
Dietary exposure to tributyltin has been assessed in Japan. Consumption of aquatic organisms is the major route of human exposure. Data from market basket surveys from 1990 to 1997 estimated the average daily intake of tributyltin (expressed as tributyltin chloride) at 3.9 \( \mu \text{g/day} \). Using these data, correcting the exposure estimate to TBTO by multiplying by the ratio of the molecular weights (596/325), and assuming a body weight of 50 kg, the estimated daily exposure to TBTO in Japan is 0.00014 mg/kg body weight per day. This value is 47% of the guidance value.

Because of the limited and possibly unrepresentative information on human exposure available to the author and reviewers of the CICAD and the recent preliminary report (Takahashi et al., 1998) of a relatively high burden of tributyltin residues in liver resulting, perhaps, from non-food sources, additional investigation is warranted.

### 11.2 Evaluation of environmental effects

Because of their physical/chemical properties, tributyltin compounds concentrate in the surface microlayer and in sediments. Abiotic degradation does not appear to be a major mechanism of removal under environmental conditions. Although TBTO is biodegradable in the water column, this process is not rapid enough to prevent the occurrence of elevated tributyltin levels in some areas. The half-life in the water column ranges from a few days to weeks. Tributyltin may persist in sediment for several years. Bioaccumulation occurs in most aquatic organisms.

Tributyltin compounds are extremely hazardous to some aquatic organisms because of their toxicity at very low concentrations in water. Such concentrations seem to be prevalent in many coastal areas. Adverse effects on non-target invertebrates, particularly molluscs, have been reported in field studies, and these have been sufficiently severe to lead to reproductive failure and population decline. Adverse effects on the commercial production of shellfish have been successfully reversed by restrictions on the use of antifouling paints in some areas, and these restrictions are also leading to the reversal of imposex effects in gastropod populations. However, the concentrations of tributyltin measured in some coastal waters are still above those that induce severe effects in some gastropods. The effects on farmed fish indicate that tributyltin-containing paints should not be used on restraining nets.

The general hazard to the terrestrial environment is likely to be low. Tributyltin-treated wood could pose a hazard to terrestrial organisms living in close contact with it.

The enhancement of tributyltin concentrations in the surface microlayer may present a hazard to littoral organisms, neustonic species (including benthic invertebrate and fish larvae), and surface-feeding seabirds and wildfowl. Accumulation and low biodegradation of tributyltin in sediment may pose a hazard to aquatic organisms when these polluted sediments are disturbed by natural processes or dredging activities.

The general decline in tributyltin concentrations in the environment has been attributed to the restrictions placed on the use of antifouling paints on vessels. However, it should be noted that in some locations the concentration of tributyltin in the water is above that necessary to elicit severe adverse effects in some sensitive species.

### 12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

Tributyltin compounds were reviewed by the World Health Organization in 1989 (IPCS, 1990).

Information on international hazard classification and labelling is included in the International Chemical Safety Card reproduced in this document.

### 13. HUMAN HEALTH PROTECTION AND EMERGENCY ACTION

Human health hazards, together with preventative and protective measures and first aid recommendations, are presented in the International Chemical Safety Card (ICSC 1282) reproduced in this document.

#### 13.1 Human health hazards

Effects on the immune system may be observed following acute or repeated exposure to tributyltin.

#### 13.2 Advice to physicians

In case of poisoning, treatment is supportive. Following inhalation of aerosol, symptoms may not be
noticeable until a few hours have passed. Therefore, rest and medical observation are essential.

13.3 Health surveillance advice

Periodic medical examination of the immune system should be included in a health surveillance programme.

13.4 Spillage

TBTO is severely irritating to the skin and eyes. In case of spillage, therefore, emergency crew must wear proper equipment, including eye protection in combination with breathing protection. The compound should not be allowed to enter drains or watercourses.

14. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

Many countries have restricted the use of TBTO. Information on national regulations, guidelines, and standards may be obtained from UNEP Chemicals (IRPTC), Geneva.

The reader should be aware that regulatory decisions about chemicals taken in a certain country can be fully understood only in the framework of the legislation of that country. The regulations and guidelines of all countries are subject to change and should always be verified with appropriate regulatory authorities before application.
# TRIBUTYL Tin OXIDE

**CAS No:** 56-35-9  
**RTECS No:** JN8750000  
**UN No:** 3020  
**EC No:** 050-008-00-3

| Molecular mass: 596.07 |

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## Types of Hazard/Exposure

### Acute Hazards/Symptoms

#### Fire
- Combustible.
- Prevention: NO open flames.
- First Aid/Fire Fighting: In case of fire in the surroundings: all extinguishing agents allowed.

#### Explosion

### Exposure

#### Inhalation
- Prevention: Ventilation, local exhaust, or breathing protection.
- First Aid/Fire Fighting: Fresh air, rest. Half-upright position. Refer for medical attention.

#### Skin
- MAY BE ABSORBED! Redness. After delay skin burns.
- Prevention: Protective gloves. Protective clothing.
- First Aid/Fire Fighting: Rinse and then wash skin with water and soap. Refer for medical attention.

#### Eyes
- Redness. Pain.
- Prevention: Safety spectacles, face shield, or eye protection in combination with breathing protection.
- First Aid/Fire Fighting: First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.

#### Ingestion
- Prevention: Do not eat, drink, or smoke during work. Wash hands before eating.
- First Aid/Fire Fighting: Induce vomiting (ONLY IN CONSCIOUS PERSONS!). Give plenty of water to drink. Refer for medical attention.

## Spillage Disposal

Do NOT wash away into sewer. Carefully collect remainder, then remove to safe place. Do NOT let this chemical enter the environment. Chemical protection suit including self-contained breathing apparatus.

## Packaging & Labelling

<table>
<thead>
<tr>
<th>T Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>R: 21-25-36-38-48/23/25</td>
</tr>
<tr>
<td>S: (1/2)35-36/37/39-45</td>
</tr>
<tr>
<td>Note: A</td>
</tr>
<tr>
<td>UN Hazard Class: 6.1</td>
</tr>
<tr>
<td>UN Pack Group: II</td>
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</tbody>
</table>

## Emergency Response

Transport Emergency Card: TEC (R)-61G43b

## Storage

Provision to contain effluent from fire extinguishing.
## IMPORTANT DATA

<table>
<thead>
<tr>
<th>Physical State; Appearance</th>
<th>Routes of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIQUID</td>
<td>The substance can be absorbed into the body by inhalation of its aerosol, through the skin and by ingestion.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemical dangers</th>
<th>Inhalation risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>The substance decomposes on burning producing toxic fumes.</td>
<td>Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quickly.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occupational exposure limits</th>
<th>Effects of short-term exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLV (as tin): 0.1 mg/m³ A4, STEL 0.2 mg/m³ A4 (skin) (ACGIH 1997).</td>
<td>The substance irritates severely the eyes, the skin. Inhalation of the aerosol may cause lung oedema (see Notes). The substance may cause effects on the thymus, resulting in depression of the immune function.</td>
</tr>
</tbody>
</table>

## PHYSICAL PROPERTIES

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Boiling point</td>
<td>173°C</td>
</tr>
<tr>
<td>Melting point</td>
<td>-45°C</td>
</tr>
<tr>
<td>Relative density (water = 1)</td>
<td>1.17 at 20°C</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>poor</td>
</tr>
<tr>
<td>Vapour pressure, Pa at 20°C</td>
<td>0.001</td>
</tr>
<tr>
<td>Flash point</td>
<td>190°C c.c.</td>
</tr>
<tr>
<td>Octanol/water partition coefficient as log Pow</td>
<td>3.19</td>
</tr>
</tbody>
</table>

## ENVIRONMENTAL DATA

The substance is very toxic to aquatic organisms. In the food chain important to humans, bioaccumulation takes place, specifically in fish and molluscs. Avoid release to the environment in circumstances different to normal use.

## NOTES

The symptoms of lung oedema often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation is therefore essential. Immediate administration of an appropriate spray, by a doctor or a person authorized by him/her, should be considered.

## ADDITIONAL INFORMATION

<table>
<thead>
<tr>
<th>LEGAL NOTICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible for the use which might be made of this information</td>
</tr>
</tbody>
</table>

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REFERENCES


Wester PM, Canton JH (1987) Histopathological study of Poecilia reticulata (guppy) after long-term exposure to bis(tri-n-butyltin)oxide (TBTO) and di-n-butyltindichloride (DBTC). *Aquatic toxicology*, 10:143–163.


APPENDIX 1 — SOURCE DOCUMENTS

IPCS (1990): *Tributyltin compounds* (Environmental Health Criteria 116)

A WHO Task Group meeting on Environmental Health Criteria for Tributyltin Compounds was held at the Institute of Terrestrial Ecology, Monks Wood, United Kingdom, from 11 to 15 September 1989. The Task Group reviewed and revised the draft criteria document and made an evaluation of the risks for human health and the environment from exposure to tributyltin compounds.

Copies of this document may be obtained from:

International Programme on Chemical Safety
World Health Organization
Geneva, Switzerland

US EPA (1997): *Toxicological review on tributyltin oxide*

This document received internal peer review by EPA scientists, an external peer review by three well-qualified nongovernment scientists, and consensus review by EPA Program Offices and the 10 Regional Offices. Summaries of significant comments from external peer reviewers are included in an appendix to the document.

Copies of this document may be obtained from:

EPA Risk Assessment Hotline
513-569-7254 (phone)
513-569-7159 (fax)
rih.iris@epamail.epa.gov (Internet address)
www.epa.gov/iris (Website)

APPENDIX 2 — CICAD PEER REVIEW

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

Department of Health, London, United Kingdom
Health and Safety Executive, Bootle, United Kingdom
Health Canada, Ottawa, Canada
International Agency for Research on Cancer, Lyon, France
International Council on Metals and the Environment, Ottawa, Canada
József Fodor National Center of Public Health, Budapest, Hungary
Karolinska Institute, Stockholm, Sweden
National Chemicals Inspectorate (KEMI), Solna, Sweden
National Institute for Working Life, Solna, Sweden
National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands
United States Department of Health and Human Services (National Institute of Environmental Health Sciences, Research Triangle Park, USA)
United States Environmental Protection Agency (Office of Research and Development, National Center for Environmental Assessment, Washington, DC, USA)
World Health Organization, International Programme on Chemical Safety, Geneva, Switzerland
APPENDIX 3 — CICAD FINAL REVIEW BOARD

Tokyo, Japan, 30 June – 2 July 1998

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Dr C. DeRosa, Agency for Toxic Substances and Disease Registry, Center for Disease Control and Prevention, Atlanta, GA, USA

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Ms D. Willcocks, Chemical Assessment Division, Worksafe Australia, Camperdown, Australia (Rapporteur)

Professor P. Yao, Chinese Academy of Preventive Medicine, Institute of Occupational Medicine, Beijing, People’s Republic of China

Observers

Professor F.M.C. Carpanini, Secretary-General, ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals), Brussels, Belgium

Dr M. Ema, Division of Biological Evaluation, National Institute of Health Sciences, Osakai, Japan

Mr R. Green, International Federation of Chemical, Energy, Mine and General Workers’ Unions, Brussels, Belgium

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Mr T. Jacob, Dupont, Washington, DC, USA

Dr H. Koeter, Organisation for Economic Co-operation and Development, Paris, France

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Ms J. Matsui, Chemical Safety Policy Office, Ministry of International Trade and Industry, Tokyo, Japan

Mr R. Montaigne, European Chemical Industry Council (CEFIC), Brussels, Belgium

Dr A. Nishikawa, Division of Pathology, National Institute of Health Sciences, Tokyo, Japan

Dr H. Nishimura, Environmental Health Science Laboratory, National Institute of Health Sciences, Osaka, Japan

Ms C. Ohtake, Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Dr T. Suzuki, Division of Food, National Institute of Health Sciences, Tokyo, Japan

Dr K. Takeda, Mitsubishi Kagaku Institute of Toxicological and Environmental Sciences, Yokohama, Japan

Dr K. Tasaka, Department of Chemistry, International Christian University, Tokyo, Japan

Dr H. Yamada, Environment Conservation Division, National Research Institute of Fisheries Science, Kanagawa, Japan

Dr M. Yamamoto, Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Dr M. Yasuno, School of Environmental Science, The University of Shiga Prefecture, Hikone, Japan

Dr K. Ziegler-Skylakakis, GSF-Forschungszentrum für Umwelt und Gesundheit GmbH, Institut für Toxikologie, Oberschleissheim, Germany

Secretariat

Ms L. Regis, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Mr A. Strawson, Health and Safety Executive, London, United Kingdom

Dr P. Toft, Associate Director, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

1 Invited but unable to attend.
Résumé d'orientation


Dans le présent document, on utilise le terme d’oxyde de tributylétain chaque fois qu’il est question de ce composé en particulier. Toutefois dans l’environnement, les dérivés du tributylétain existent selon toute probabilité principalement sous la forme d’hydroxyde, de chlorure et de carbonate de tributylétain. Dans ce cas et lorsque l’identité du composé est douteuse, on utilise le terme général de tributylétain.

L’oxyde de tributylétain protège efficacement le bois, les cotonnades, le papier et les peintures murales contre l’attaque de la vermine. Il entre dans la composition de nombreuses peintures marines auxquelles on l’ajoute comme agent antialuminium. Il est présent dans ces produits sous la forme de copolymère organométallique. Lorsque le copolymère est hydrolysé par l’eau de mer, le tributylétain est lentement libéré de la surface peinte qu’il protège des incrustations pendant des durées pouvant aller jusqu’à 4 ou 5 ans.

Du fait de sa faible solubilité dans l’eau et de son caractère lipophile, le tributylétain s’adsorbe facilement sur les particules. Sa demi-vie dans la colonne d’eau va de quelques jours à plusieurs semaines. Il peut subsister dans les sédiments pendant plusieurs années. Il s’accumule dans l’organisme des animaux, ses organes d’élection étant le rein et le foie. L’absorption s’effectue davantage à partir des denrées alimentaires que directement à partir de l’eau.


Les études à court terme montrent que l’oxyde de tributylétain est modérément à fortement toxique pour les mammifères de laboratoire. Des études nombreuses et bien conduites, tant à court qu’à long terme, montrent que l’effet essentiel de l’oxyde de tributylétain réside dans son immunotoxicité (dépression des fonctions immunitaires thymo-dépendantes). La dose sans effet nocif observables (NOAEL) chez le rat est de 0,025 mg/kg de poids corporel par jour, le critère retenu étant une immunodépression après exposition de longue durée. L’expérience montre que l’oxyde de tributylétain n’est pas cancérigène pour la souris. L’expérience montre qu’il n’est pas non plus génotoxic. Rien n’indique qu’il exerce des effets nocifs sur la fonction de reproduction et le développement à des doses inférieures à la dose sans effet immunotoxic observable. De tels effets ne se produisent que lorsque la dose est voisine de celle qui est toxique pour la souris. Comme on l’a indiqué plus haut, les données révèlent un effet irritant prononcé sur la peau et les voies respiratoires. En s’appuyant sur la valeur de la dose sans effet immunotoxic observable et en appliquant un coefficient de sécurité de 100, on peut donner une valeur-guide de 0,0003 mg/kg p. c. par jour pour l’exposition par la voie buccale. On ne dispose pas de données suffisantes pour établir une valeur-guide dans le cas d’une exposition par inhalation.
L’oxyde de tributylétain est extrêmement dangereux pour certains organismes aquatiques. Dans certains cas, il bloque les fonctions endocrines. Dans les eaux littorales de quelques régions, il est présent à une concentration supérieure à celle qui produit de graves effets nocifs. Dans certaines régions, les effets constatés ont été suffisamment graves pour faire chuter la fécondité et réduire l’effectif de la population touchée. Le risque global pour l’environnement terrestre est vraisemblablement faible.
**RESUMEN DE ORIENTACIÓN**

Este CICAD sobre el óxido de tributilestaño (TBTO), preparado por la Agencia para la Protección del Medio Ambiente de los Estados Unidos (EPA), se basa en un documento sobre los Criterios de Salud Ambiental del Programa Internacional de Seguridad de las Sustancias Químicas relativo a los compuestos de tributilestaño (IPCS, 1990) y en el Examen toxicológico sobre el óxido de tributilestaño de la EPA de los Estados Unidos (US EPA, 1997). En estos exámenes se analizaron los datos identificados hasta 1989 y 1996, respectivamente. En el presente documento aparece también la información adicional obtenida hasta 1998. La información relativa a las características de los procesos de examen y la disponibilidad de los documentos originales figura en el apéndice 1. La información acerca del examen colegiado de este CICAD se presenta en el apéndice 2. Su aprobación tuvo lugar como evaluación internacional en una reunión de la Junta de Evaluación Final, celebrada en Tokio, Japón, del 30 de junio al 2 de julio de 1998. La lista de participantes en esta reunión de la Junta de Evaluación Final aparece en el apéndice 3. La Ficha internacional de seguridad química (ICSC 1282), preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1996), también se reproduce en el presente documento.

En este documento, el término de óxido de tributilestaño se aplica específicamente a este producto químico. Sin embargo, en el medio ambiente es más probable que los compuestos de tributilestaño se encuentren como hidróxido, cloruro o carbonato. En esos casos o cuando la identidad del producto químico específico no está clara, se utiliza el término general de tributilestaño.

El óxido de tributilestaño es un conservante biocida eficaz de la madera, los textiles de algodón, el papel y las pinturas y colorantes domésticos. Se añade como agente antincrustante en numerosas formulaciones de pinturas marinas. El tributilestaño está presente en la mayoría de esas formulaciones antincrustantes como copolímero organometálico. Se libera lentamente de la superficie pintada a medida que el polímero se hidroliza en el agua de mar, proporcionando una protección prolongada contra las incrustaciones de hasta cuatro o cinco años.

Debido a su baja solubilidad en agua y a su carácter lipófilo, el tributilestaño se adsorbe fácilmente en las partículas. Su semivida en la columna de agua oscila entre unos días y varias semanas. Puede persistir en los sedimentos durante varios años. Se bioacumula en los organismos, alcanzando las concentraciones más altas en el hígado y el riñón. La absorción a partir de los alimentos es más importante que la procedente directamente del agua.

No se dispone de información sobre la toxicidad del óxido de tributilestaño en el ser humano tras una exposición prolongada. Algunos datos e informes de casos ponen de manifiesto que produce irritación cutánea y respiratoria grave. Sin embargo, los datos no son suficientes para caracterizar la relación exposición-respuesta. En algunos estudios realizados en el Japón se ha cuantificado la exposición humana al tributilestaño procedente de los alimentos.

En estudios de corta duración con mamíferos de laboratorio, la toxicidad aguda del óxido de tributilestaño es entre moderada y alta. En numerosos estudios bien realizados, tanto de corta duración como prolongados, su efecto más importante es la inmunotoxicidad (depresión de las funciones inmunitarias dependientes del timo). La concentración sin efectos adversos observados (NOAEL) para la inmunosupresión en ratas tras una exposición prolongada es de 0,025 mg/kg de peso corporal al día. El análisis de las dosis de referencia pone de manifiesto que la exposición correspondiente al límite de confianza más bajo (95%) de la dosis que produce una disminución del 10% en la concentración de la inmunoglobulina (Ig) E en ratas es de 0,034 mg/kg de peso corporal al día. En un estudio de carcinogenicidad en ratas, se observó un aumento en la incidencia de algunos tumores en determinados tejidos endocrinos. Estos tumores se producen espontáneamente, con una incidencia variable en la estirpe de ratas utilizada en el estudio, y se desconoce su importancia en la evaluación del riesgo para la salud humana. El óxido de tributilestaño no es carcinógeno para los ratones. Las pruebas ponen de manifiesto que no es genotóxico. No hay indicios de que se produzcan efectos reproductivos o en el desarrollo con una exposición inferior a la establecida como NOAEL para la inmunotoxicidad. Estos efectos aparecen solamente con exposiciones próximas a las que causan toxicidad materna. Los datos demuestran que el óxido de tributilestaño produce una irritación cutánea y respiratoria grave. Teniendo en cuenta la NOAEL para la inmunotoxicidad y un factor de incertidumbre de 100, el valor guía para la exposición oral es de 0,0003 mg/kg de peso corporal al día. No se dispone de datos adecuados para extrapolar un valor guía aplicable a la exposición por inhalación.

El óxido de tributilestaño es enormemente peligroso para algunos organismos acuáticos. Es un perturbador endocrino en algunos organismos. La concentración de tributilestaño en determinadas aguas costeras es superior a la que produce efectos adversos graves. Estos efectos han sido suficientemente importantes para producir fracaso reproductivo y disminución de la población en algunas zonas. El peligro general para el medio ambiente terrestre es probablemente bajo.