UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: March 20, 2008

MEMORANDUM

SUBJECT: *Tributyltin Compounds* – Revised Toxicology Chapter in Support of Issuance of the Reregistration Eligibility Decision (RED) for Tributyltin Oxide, Tributyltin Maleate and Tributyltin Benzoate. PC Code(s): 083001, 083118, 083106. CAS Registry Number(s): 56-35-9, 4027-18-3, 4342-36-3. DP#: D

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Attached is the toxicology chapter in support of issuance of the reregistration eligibility decision (RED) for the Tributyltin Compounds: Tributyltin Oxide, Tributyltin Maleate and Tributyltin Benzoate.

REVISED TOXICOLOGY CHAPTER

FOR

TRIBUTYLTIN-CONTAINING CHEMICALS

Tributyltin Oxide (PC Code 083001)
Tributyltin Maleate (PC Code 083118)
Tributyltin Benzoate (PC Code 083106)

Reregistration Case Number: 2620

March 30, 2008

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1.0 INTRODUCTION

Use Patterns

Tributyltin containing compounds are used primarily as bacteriocides, microbiocides, fungicides, algaecides, slimicides, virucides, miticides and insecticides. For issuance of the reregistration eligibility decision, the three chemicals included under the general tributyltin classification are: tributyltin oxide (PC Code 083001), tributyltin benzoate (PC Code 083106), and tributyltin maleate (PC Code 083118). Examples of some of the primary uses sites in which TBTO containing products are found include: agricultural premises and equipment; oilfield/petrochemical injection water systems; industrial recirculating water cooling systems; animal kennels, medical premises; material preservation (textiles, metalworking fluids, plastics, construction materials, etc); and non-pressure treated wood preservation.

Hazard Characterization

Tin compounds, organic and inorganic, have been studied in a variety of animals but primarily in rodents following the oral route of ingestion. There are limited data on the effects of tins in humans and that primarily comes from reports of industrial and individual accidental exposures. The ATSDR report (2003) on tins also states that of the various effects described after tin exposure in animal studies, hematological signs of anemia and gastrointestinal distension appear to be best identified as tin-related. Gastrointestinal effects described in humans following ingestion of tin compounds were nausea, vomiting and diarrhea. In experimental animals, as reported by CDC (1991), dietary exposure to tributyltin oxide has resulted in weight loss, immunosuppression and microcytic anemia. CDC's epidemiological notes (1991) reports that tributyltin oxide dermal exposure in humans produces irritant effects, including erythemia, follicular inflammation and pruritus and has been identified as a potent non-allergenic dermal irritant. Industrial and residential exposure to vapors and fumes of organotin compounds cause eye and throat irritation.

There is some evidence that many of the tributyltin compounds cause similar toxic effects. In 1990, the World Health Organization (WHO, Environmental Health Criteria 119) reported that tributyltin compounds are skin, eye and respiratory irritants. Neither tributyltin oxide or tributyltin maleate cause allergy in dermal guinea-pig sensitization studies. Generally, liver, hematological and immune system effects have been observed in short- and long-term animal toxicity tests.

Published literature for tributyltin oxide identifies immunotoxicity as the chemical's primary toxicological action in laboratory mammals: tributyltin oxide, and related compounds, dibutyltin and dioctyltin, are reported immunotoxic and thymolytic agents. Later reviews by EPA/IRIS (1997) and the WHO (1999) identify a large body of information demonstrating the critical effect for tributyltin oxide as depression of thymus-dependent immunological responses. Immunological effects are in evidence in short- and long-term studies in rats and mice where exposure to tributyltin oxide has been linked to decreased immunoglobulin levels, decreased thymus weight, various inflammation responses.

Reproductive and developmental toxicity due to tributyltin oxide and/or tributyltin benzoate occurred at or near the exposure that also caused maternal toxicity and was generally characterized by decreased body weight or body weight gains. However, studies do exist that

show pre-weanling rat pups to be more sensitive to the immunologic effects of tributyltin oxide than adult rats in their thymus-dependent immunity.

Some organotin compounds are known to have neurotoxicity effects. Triethytin and trimethyltin cause neuronal edema and necrosis of the central nervous system. A few studies that were investigating other effects also showed some minor toxicities of tributyltin on the nervous system (reduced brain weight, decreased motor activity, lympho- and hepatobiliary toxicity). However, oral exposure to tributyltin oxide in these studies did not cause severe neurological signs or result in morphological or histopathological changes in brain tissue. Based on the evidence from available studies conducted with tributyltin oxide, there is no suggestion that neurotoxicity is a likely critical or co-critical effect.

It is unclear if tributyltin oxide is a carcinogen in rats, however, it is not a carcinogen in mice and does not appear to be genotoxic. EPA has assigned tributyltin oxide to category D (U.S., 1987) or to the "cannot be determined" category for carcinogenicity (U.S. EPA, 1996) based on high spontaneous incidences of tumors in Wistar rats, incidence variability in the treated groups and absence of a dose-effect relationship. Therefore the significance of the increases in benign pituitary tumors, pheichromocytomas and parathyroid tumors at the highest tested doses in rats remains unclear.

2.0 BRIDGING OF TRIBUTYLTIN OXIDE, MALEATE AND BENZOATE TOXICITY DATABASES

In 2005, the OPP's Health Effects Division evaluated the existing tributyltin toxicity database to support a risk management decision for a proposed new non-food use registration of tributyltin maleate (TBTM) as a miticide for the treatment of finished carpet, rug backings and fibers. The existing toxicity database for tributyltin maleate consists of an acute oral toxicity study and a dermal sensitization study conducted with the technical grade active ingredient. This limited database was considered inadequate to support the new registration and an evaluation of the toxicity database for the related chemical, tributyltin oxide, was conducted for the purposes of data bridging. It was determined that tributyltin oxide and tributyltin maleate may be considered toxicologically equivalent, with the provision that specific studies be submitted to the Agency for bridging of the databases. These data included: an immunotoxicity study in mice or rats, a 90-day neurotoxicity study in rats, a developmental toxicity study in rats and a dermal absorption study in rats. As for bridging of the tributyltin oxide and tributyltin benzoate toxicity databases, the registrant proposed using data from the TBT Consortium on bis(tributyltin)oxide (TBTO) to support TBTB use based on the higher tin content of TBTO and the consequent greater toxicity, thus making TBTO a Worst Case chemical (SRRD/GCSB Transmittal Sheet for TBT-containing chemicals data requirements/data gaps, dated 3/21/90). This request would apply to Subdivision Testing Guidelines 81-1, 81-2, 82-2, 83-3a, 84-2a, 84-2b and 84-4. In this case, the Agency determined that the registrant can use tributyltin oxide data to support registration of tributyltin benzoate-containing products if they supply bridging studies: a dermal absorption study and a 90-day oral study (with immunological and neurological toxicity data) for each of the technical grade active ingredients. To date, none of the study data gaps identified for tributyltin maleate or tributyltin benzoate have been submitted to the Agency.

The Antimicrobials Division's Toxicity Endpoint Selection Committee (ADTC) met on January 17, 2008 to evaluate the available toxicology data for the tributyltin-containing compounds; tributyltin oxide, tributyltin maleate and tributyltin benzoate. At this time, the issue of bridging the available toxicity data for these three organotins was re-evaluated. The Committee

determined that the oxide, maleate and benzoate forms of tributyltin are considered toxicologically equivalent based on similar structure and physical chemical properties (e.g., dissociation constants). However, to fully assess whether exposure to these compounds will result in similar toxicities, Tier 1 toxicity testing is required for each chemical. These tests include acute toxicity (oral, dermal, inhalation, eye and dermal irritation and skin sensitization), subchronic (oral) toxicity, prenatal developmental toxicity and the full battery of mutagenicity tests. The outstanding data requirements for tributyltin oxide, tributyltin maleate and tributyltin benzoate are identified in tables 1 and 2.

Table 1. Toxicological Data Requirements for Non-food Uses of Tributyltin Compounds

Test	Technical Grade Active Ingredient		
	MRID	**Required**	**Satisfied**
Tributyltin Oxide			
870.1100 Acute Oral Toxicity	00085004, 92172013, 00085003, 92172004	Yes	Yes
870.1200 Acute Dermal Toxicity	---	Yes	No
870.1300 Acute Inhalation	---	Yes	No
870.2400 Acute Eye Irritation	---	Yes	No
870.2500 Acute Dermal Irritation	---	Yes	No
870.2600 Skin Sensitization	00104789, 92172014	Yes	Yes
870.3100 90-Day (oral) Subchronic - Rodent	41127001	No	No
870.3150 90-Day (oral) Subchronic - Non-rodent	41131001	No	No
870.3200 21-Day (dermal) Subchronic - Rodent	---	No	---
870.3250 90-Day (dermal) Subchronic - Rodent	---	Yes	No
870.3465 90-Day (inhalation) Subchronic - Rodent	---	No	---
870.3700 Prenatal Developmental - Rodent	00137158, 92172016	Yes	Yes
870.3700 Prenatal Developmental - Non-rodent	40141901, 92172006	Yes	Yes
870.3800 Reproduction & Fertility Effects - Rodent	41693801	Yes	Yes
870.4100 Chronic - Rodent	40623201	Yes	Yes*
870.4100 Chronic - Non-rodent	42549801	Yes	No
870.4300 Combined Chronic-Toxicity/Carcinogenicity - Rat	40623201	Yes	Yes
870.4200 Carcinogenicity - Mouse	42265001	Yes	Yes
870.5100 Bacterial Reverse Mutation Test	42170001	Yes	Yes
870.5375 In Vitro Chromosome Aberration Test – Human Lymphocytes	40253005	Yes	Yes
870.5450 to 870.5915 Mutagenicity Tests (1 Study)	---	Yes	No
870.6200 90-day neurotoxicity - Hen	---	No	---
870.6200 90-day neurotoxicity - Mammal	---	No	---
870.7485 Metabolism	01246480, 40253002	Yes	Yes
870.7600 Dermal penetration	40050003	Yes	Yes**
Tributyltin Maleate			

Table 1. Toxicological Data Requirements for Non-food Uses of Tributyltin Compounds			
Test	**Technical Grade Active Ingredient**		
	MRID	**Required**	**Satisfied**
870.1100 Acute Oral Toxicity	43851201	Yes	Yes
870.1200 Acute Dermal Toxicity	---	Yes	No
870.1300 Acute Inhalation	---	Yes	No
870.2400 Acute Eye Irritation	---	Yes	No
870.2500 Acute Dermal Irritation	---	Yes	No
870.2600 Skin Sensitization	44142303	Yes	Yes
870.3250 90-Day (dermal) Subchronic -Rodent	---	Yes	No
870.3700 Prenatal Developmental - Rodent	---	Yes	No
870.5100 to 870.5915 Mutagenicity Testing (3 studies)	---	Yes	No
Tributyltin Benzoate			
870.1100 Acute Oral Toxicity	42415801	Yes	Yes
870.1200 Acute Dermal Toxicity	42415802	Yes	Yes
870.1300 Acute Inhalation	---	Yes	No
870.2400 Acute Eye Irritation	---	Yes	No
870.2500 Acute Dermal Irritation	42415803	Yes	Yes
870.2600 Skin Sensitization	---	Yes	No
870.3200 21-Day (dermal) Subchronic - Rodent	43177201	Yes	No
870.3250 90-Day (dermal) Subchronic - Rodent	---	Yes	No
870.3700 Prenatal Developmental - Rodent	42903101	Yes	Yes
870.5300 *In vitro* Mammalian Cell Gene Mutation Test	42412501	Yes	Yes
870.5395 Mammalian Erythrocyte Micronucleus Test	42412502, 42966201	Yes	Yes
870.5550 Unscheduled DNA Syntheses	42412503, 42412504, 42966203, 42966201	Yes	No

*Chronic toxicity study data requirement in rodents is satisfied by the combined chronic toxicity/carcinogenicity study conducted in rodents.

**Study does not satisfy a guideline requirement, however, it provided useful information that is adequate for risk assessment purposes.

Table 2. Generic Data Gaps for Tributyltin Compounds	
Guideline Number	**Study Type**
Tributyltin Oxide	
870.1200	Acute Dermal Toxicity
870.1300	Acute Inhalation Toxicity
870.2400	Acute Eye Irritation
870.2500	Acute Dermal Irritation
870.3250	90-Day (dermal) Subchronic - Rodents
870.5450 to 870.5915	Mutagenicity Test (1 Study)
Tributyltin Maleate	

870.1200	Acute Dermal Toxicity
870.1300	Acute Inhalation Toxicity
870.2400	Acute Eye Irritation
870.2500	Acute Dermal Irritation
870.3250	90-Day (dermal) Subchronic -Rodents
870.3700	Prenatal Developmental - Rats
870.5100 to 870.5915	Mutagenicity Tests (3 studies)
Tributyltin Benzoate	
870.1300	Acute Inhalation Toxicity
870.2400	Acute Eye Irritation
870.2600	Skin Sensitization
870.3250	90-Day (dermal) Subchronic - Rats
870.5450 to 870.5915	Mutagenicity Test (1 study)

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of database for Acute Toxicity: The acute toxicity database for the tributyltin compounds is considered incomplete; the battery of acute toxicity studies required for labeling purposes has not been submitted by the registrants for each of the tributyltin compounds (tributyltin oxide, tributyltin maleate and tributyltin benzoate) grouped in this hazard assessment. The available data does show that exposure to tributyltin oxide and tributyltin maleate can result in severe oral and dermal toxicities (Toxicity Category II). However, tributyltin oxide and tributyltin maleate are not dermal sensitizers. Dermal and oral exposures to tributyltin benzoate can potentially cause moderate (Toxicity category III) to severe (Toxicity category II) toxicities, respectively.

Table 3. Acute Toxicity Profile for Technical (95.0- 97.5 % a.i.) Tributyltin Compounds

Guideline Number	Study Type	MRID Number	Results	Toxicity Category
Tributyltin Oxide				
870.1100 (§ 81-1)	Acute Oral – Rat	00085004, 92172013	LD_{50} =180 mg/kg (males) LD_{50} =150 mg/kg (females) LD_{50} =170 mg/kg (combined)	II
870.1100 (§ 81-1)	Acute Oral – Rat	00085003, 92172004	LD_{50} =193 mg/kg (males) LD_{50} =123 mg/kg (females) LD_{50} =160 mg/kg (combined)	II
870.2600 (§ 81-6)	Skin Sensitization – Guinea pigs	00104789, 92172014	Non sensitizer	Not applicable
Tributyltin Maleate				
870.1100	Acute Oral – Rat	43851201	LD_{50} = 224.7 mg/kg	II

(§ 81-1)				
870.2600 (§ 81-6)	Skin Sensitization – Guinea pigs	44142303	Non sensitizer. Not sensitizing; minimal irritation in response to induction, but no increase in response to challenge dose	Not applicable
Tributyltin Benzoate				
870.1100 (§ 81-1)	Acute Oral – rat Purity	42415801	LD_{50} =115 mg/kg (males) LD_{50} =115 mg/kg (females) LD_{50} =115 mg/kg (combined)	II
870.1200 (§ 81-2)	Acute Dermal – rat Purity	42415802	LD_{50} > 2000 mg/kg (combined)	III
870.2500 (§ 81-5)	Primary Dermal Irritation – rabbit Purity	42415803	Severe Irritation	I

4.2 Subchronic Toxicity

Adequacy of database for Subchronic Toxicity: Limited data exists for determining the subchronic toxicity of tributyltin oxide, tributyltin maleate and tributyltin benzoate. The database for subchronic toxicity of these organotins is considered incomplete: the available studies are either non-guideline range-finding studies or they are not adequate for regulatory purposes.

870.3100 Subchronic (90-Day Oral Range-Finding) - Mice

In a 90-day oral toxicity study (MRID 41127001), bis (tri-n-butyltin) oxide (TBTO; 97.1% a.i., Lot # KYRDO-064M) was administered to 10 CD-1® mice/sex/dose in the diet at dose levels of 0, 4, 20, 80, or 200 ppm (equivalent to 0.7, 3.8, 15.1, or 36.9 mg/kg/day in males; 1.0, 4.9, 17.9, or 46.9 mg/kg /day in females) for 13 weeks.

One 200 ppm male mouse was found dead on Day 64 and one 200 ppm female mouse was sacrificed in a moribund condition on Day 27. Both animals exhibited severe hepatocellular necrosis with abscess formation. Severe lung edema was also observed in the male. Treatment-related decreases in mean body weight were observed in the 200 ppm mice during the first half of the study. This was reversed in the second half of the study with mean body weights increased in 80 ppm mice from Week 5 through study termination. There were no consistent treatment-related trends in body weight changes or body weight gain. Only females treated with ≥80 ppm TBTO had reduced mean food consumption. The predominant clinical sign of toxicity was redness, swelling, and scabs on the ears. These effects were observed in ≥80 ppm males and ≥20 ppm females. Ear inflammation was likely a dermal response to exposure to the test article in the food while eating.

Hematological measurements showed decreased mean hemoglobin concentration, percent hematocrit, and erythrocyte counts ≥80 ppm males and/or females. Mean platelet count was elevated in 200 ppm males and ≥80 ppm females. Mean total leukocyte count was increased in

≥80 ppm males. Clinical chemistry results showed increased mean alkaline phosphatase levels in 200 ppm males and females. Increased total protein and blood urea nitrogen were observed in females treated with ≥ 80 ppm TBTO. Increased organ weights (adrenal, liver, spleen) were observed in both sexes following treatment with ≥ 80 ppm TBTO. Reduced testes weights were also noted in ≥ 80 ppm males.

Gross changes included nodules/masses and discoloration of the liver, thickening of the gallbladder and/or bile duct, enlargement of the spleen, and ear lesions (swelling, redness and/or scabs). Clinical signs, gross lesions and organ weight changes were supported by microscopic evaluations. The predominant microscopic findings were limited to the liver, bile duct, gallbladder and spleen of animals treated with ≥80 ppm TBTO in the diet for 90 days, although mild treatment-related effects were noted at lower doses.

This range-finding oral toxicity study is classified as **Unacceptable/Non-guideline** and does not satisfy the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in rodents. The major deficiency is the inconclusive stability of the diet formulations. Without conclusive stability confirmation of the diet formulations, the reported doses received by the mice in this feeding study are not reliable. Therefore, this study is not adequate for regulatory purposes.

870.3200 Subchronic (21-Day Dermal Range-finding) Toxicity – Dogs

In a non-guideline, range-finding oral toxicity study (MRID 41131001), 2 Beagle dogs/sex/dose were exposed daily via gavage (1 mL/kg) to Tributyltin oxide (>96.1% a.i., Batch No.: 2288) in arachis oil for up to 19 weeks. The animals (Groups 1-4) were dosed at 0, 0.1, 0.5, or 2.5 mg/kg during Weeks 1-5; 0, 0.2, 1.0, or 5.0 mg/kg during Weeks 6-10; and 0, 10, 1.0, or 5.0 mg/kg during Weeks 11-19.

Two male dogs from the 5 mg/kg/day group received misapplications into the lungs at the end of Week 8 and were sacrificed 5 days later. During Weeks 12 and 14, respectively, two male dogs from the 10 mg/kg/day group also received misapplications into the lungs and were sacrificed later that same day.

At 1.0 mg/kg/day, the following treatment-related effects were noted: (i) increased alkaline phosphatase (ALP, incr 61-130%, not statistically significant [NS], Weeks 13 and 18); (ii) decreased relative albumin (↓ 8%, $p<0.01$, Week 18); (iii) increased relative total α-globulins (↑ 15-16%, NS, Weeks 9, 13, and 18); (iv) increased relative total β-globulins (↑ 4-14%, NS, Weeks 9, 13, and 18); (v) decreased A/G ratio (decr 14-18%, $p<0.05$, Weeks 13 and 18); and (vi) marked increases in absolute (↑ 34%) and relative (to body, incr 26%) liver weights.

At 2.5 mg/kg/day, the following effects were noted: (i) increased ALP (↑ 64-102%, $p<0.05$ or NS, Weeks 1, 4, and 5); (ii) decreased relative albumin (↓ 6%, $p<0.05$, Week 4); (iii) decreased A/G ratio (decr 15%, $p<0.05$, Week 4); (iv) decreased hematocrit (↓ 9%, $p<0.05$, Week 4); and (v) decreased hemoglobin (↓ 13%, $p<0.01$, Week 4). No clear-cut evidence of the decreases in hematocrit and hemoglobin were observed during Weeks 9, 13, or 18; however, it was noted that evaluation was made difficult by the loss of animals (2 males each) in Groups 2 and 4.

At 5.0 mg/kg/day, sialorrhea was observed in one female on 6 days at the end of the study after treatment for approximately 13 weeks. Additionally, the following treatment-related effects in clinical chemistry and hematology parameters were noted: (i) decreased relative albumin (↓ 15-

16%, p<0.01, Weeks 9, 13, and 18); (ii) increased relative total α-globulins (↑ 32-50%, NS or p<0.01, Weeks 9, 13, and 18); (iii) increased relative total β-globulins (↑ 18-20%, NS or p<0.05, Weeks 9, 13, and 18); (iv) decreased A/G ratio (↓ 31-33%, p<0.01, Weeks 9, 13, and 18); (v) increased glutamic oxaloacetic transaminase (GOT, ↑ 70%, NS, Week 18); (vi) increased glutamic pyruvic transaminase (GPT, ↑ 53%, NS, Week 18); (vii) decreased glucose (↓ 16%, p<0.05, Weeks 13 and 19); (viii) increased leucocyte counts (↑ 56-104%, p<0.05, Weeks 9 and 18); (ix) increased neutrophil counts (↑ 55-184%, p<0.05, Weeks 9 and 18); and (x) marked increases in absolute (↑ 28%) and relative (↑ 51%) liver weights.

At 10 mg/kg/day, slight to moderate emaciation was observed in the two remaining females and ruffled fur was noted in one female starting at Week 18. It was stated that the two females in Group 2 showed marked body weight losses (p<0.05) of -1.0 to -2.3 kg. No tabular body weight data were provided; however, terminal body weight was decreased by 31% in this group compared to controls. During Weeks 11-19, decreases (p<0.05 or NS) were noted in mean body weight gain (-1.7 kg treated compared to 0.0 kg controls), food consumption (↓ 30%), and water consumption (↓ 26%). Additionally, the following hematology and clinical chemistry findings were noted at this dose: (i) slight increase in leucocyte count (↑ 45%, p<0.05, Week 13); (ii) increased fibrinogen (↑ 76-87%, p<0.05, Weeks 13 and 18); (iii) increased ALP (↑ 51-170%, NS, Weeks 13 and 18); (iv) decreased relative albumin (↓ 14-15%, p<0.01, Weeks 13 and 18); (v) increased relative total α-globulins (↑ 41-47%, p<0.01, Weeks 13 and 18); (vi) increased relative total β-globulins (↑ 12-16%, NS, Weeks 13 and 18); (vii) decreased A/G ratio (↓ 29-33%, p<0.01, Weeks 13 and 18); (viii) increased GPT (↑ 339%, NS, Week 18); (ix) decreased calcium (↓ 11%, p<0.05, Week 18); and (x) increased granulopoiesis index (↑ 92%, p<0.01, Week 19). The increased granulopoiesis index indicates a decrease in mature granulocytopoietic cells and is in accordance with the decrease in neutrophils noted in the peripheral blood of these animals.

At 10 mg/kg/day, marked increases in absolute (↑ 22%) and relative (↑ 74%) liver weights were noted. Absolute and relative thymus weights were decreased by 69-78% compared to controls, which corresponded with the gross finding (small thymus size) noted at this dose. The decreases noted in absolute (↓ 55% each) and relative (↓ 38-39%) iliac and mesenteric lymph node weights indicated an effect on the lymphatic tissue. It was stated that this is a known effect of TBTO from short-term feeding studies in rats (Schweinfurth and Günzel, 1987). The following treatment-related histopathological effects (# affected/2 treated vs. 0 controls) were noted in the two females that survived to scheduled sacrifice: (i) thymus, marked to complete thymocyte depletion (2); (ii) spleen, acute hyperemia (2) and reduction of lymphocytes involving the periarteriolic lymphocytic sheets (PALS), pyknotic lymphocytes, and the follicles (1-2); (iii) iliac lymph node, reduction of lymphocytes involving the follicle (2) and inconspicuous germinal centers (2); (iv) mesenteric lymph node, reduction of lymphocytes involving the follicle (2) and medulla (2), and inconspicuous germinal centers (1); (v) liver, Cytoplasmic vacuolization (2) and presence of giant mitochondria (2); and (vi) ovary, inhibition of follicle maturation (2).

Increases noted in absolute (↑ 28-53%) and relative (↑ 29-76%) spleen weight were within the historical control range; however, these findings were considered to be related to treatment as increased blood content (acute hyperemia) was observed histologically in all treated groups.

The following findings were considered to be of equivocal toxicity: (i) slight increases (p<0.05) in specific gravity (↑ 1-2%) at 5 and 10 mg/kg/day during week 18; (ii) increased sedimentation rate after 24 hours (↑ 227%) in the 10 mg/kg/day animals at Week 18 (value was not statistically significant, but the value of one animal was outside the historical range); and (iii) minimal to moderate increase of mucous in the gall bladder noted in 1 animal each at 1.0 mg/kg/day and

above (vs. 0 controls), which corresponded with the gross observation of granulated surface in two animals.

This oral range-finding study is classified as **Acceptable/Non-guideline.** Although this study does not satisfy the guideline requirement for a subchronic toxicity study [(OPPTS 870.3200] in non-rodents, it contains useful information that supports the critical effect of tributyltin oxide observed in published literature, specifically, immunotoxicity of the thymus.

4.3 Prenatal Developmental Toxicity

Adequacy of database for Prenatal Developmental Toxicity: The database for prenatal developmental toxicity consists of three acceptable studies; two conducted with tributyltin oxide (rat and rabbit) and one conducted with tributyltin benzoate (rabbits). This database is considered complete for tributyltin oxide and tributyltin benzoate, however, a prenatal toxicity study conducted in the rat with tributyltin maleate remains an outstanding data requirement.

870.3700 Prenatal Developmental (Gavage) Toxicity – Rat

In a developmental toxicity study (MRID 00137158), tributyltin oxide (TBTO, 96.9% a.i., Lot No.VNR00-605K) in Mazola® corn oil was administered via gastric intubation (gavage) to pregnant female CD® (Sprague-Dawley derived) rats at doses of 5, 9 and 18 mg/kg/day from gestation days 6 through 19, inclusive. Initially the dose levels were set at 6, 12 and 24 mg/kg/day for the low, mid and high dose groups, respectively; however, analysis of weekly samples of dosing solutions prepared by Bio/dynamics and used for the first three weeks of treatment yielded concentrations less than anticipated. Thereafter, dose levels were changed to 5, 9, and 18 mg/kg/day for the low mid and high dose groups, respectively to reflect the actual dose levels administered to the animals. Females were sacrificed on Day 20 of gestation and recovered fetuses were evaluated for external, soft tissue and skeletal malformations. The parameters that were evaluated included maternal mortality, pregnancy rates, in-life observations, body weight change data, uterine implantation data (i.e., number of implantations, resorptions, fetuses) and gross postmortem examination data. Fetuses were weighed, sexed and evaluated for anomalies. Ossification variation data were recorded during the fetal skeletal evaluations.

At the 9 mg/kg dose level, one female died and a second female was killed in moribund condition with the former being attributed to dosing-related injury. Mean weight change for the 9 mg/kg/day females, during the 6-19 day gestation period was lower compared to the control, but was not statistically significant. Staining of fur in the ano-genital area and the incidence of fetuses with at least one ossification variation were significantly increased in the mid-dose females. No treatment effect was evident in uterine implantation data, fetal sex distribution data or fetal weight data. There were no mortalities in the 18 mg/kg/day dose group. Weight gain during the gestation period was lower than controls and there was increased incidence of fur staining in the ano-genital area. There was an increase in the mean number of resorption sites, increase in the percentage of resorptions to implants, with a slightly reduced litter size in the high dose group. There was a decrease in mean fetal weight. No maternal toxicity was evident at the 5 mg/kg dose level. **The Maternal Toxicity NOAEL was 5 mg/kg/day. However, the definitive Maternal Toxicity LOAEL could not be identified due to the lack of toxicity in maternal animals.**

At the 9 mg/kg/day dose level, the types and incidences of ossification variations observed in this group were generally similar to the control group; however, the incidence of fetuses with rudimentary structures was notably increased. No developmental toxicity was noted in mid-dose fetuses. There was an increase in the mean number of resorption sites, increase in the percentage of resorptions to implants, with a slightly reduced litter size in the high dose group. There was a decrease in mean fetal weight. The incidence of high-dose fetuses with ossification was increased and fetuses exhibited an increase in the incidence of rudimentary structures (small discrete ossification(s) adjacent to the last thoracic or first lumbar vertebral transverse process (es)), asymmetrical sternebrae, 14th rib pair and cervical ossifications. The incidence of malformed fetuses was also increased (6.4%), the most prominent malformation being cleft palate that was observed in 17 fetuses. The incidence of fetuses with rudimentary structures was notably increased at all dose levels (litter incidence data were not provided). **The Developmental Toxicity NOAEL is less than 5 mg/kg/day (not established). The Developmental Toxicity LOAEL is equal to or less than 5 mg/kg/day based on increased incidences of ossification variations.**

This study is classified as **Unacceptable-Guideline/Upgradable.** It does not satisfy the guideline requirement for a prenatal developmental toxicity study (OPPTS 870.3700; OPP §83-3, OECD 414) in rats.

870.3700 Prenatal Developmental (Gavage) Toxicity – Rat

In a developmental study (MRID 42903101), groups of Crl: CD® (SD) BR VAF/Plus strain rats received the test substance tributyltin benzoate (Lot No: 1446-6, purity 97.1%) via intra-gastric intubation at doses of 0, 1.0, 4.5 and 20.0 mg/kg/day from 6 through 15 of pregnancy, inclusive. On Day 20, the females were killed and subjected to post mortem examination litter values were determined and fetuses examined for visceral and skeletal abnormalities.

One female in the 4.5 mg/kg/day group totally resorbed her litter at an early stage of pregnancy having shown signs of impaired respiration, hunched posture and piloerection. Fetal examination revealed an increased incidence of extracervical ribs and one fetus with a double outlet of the right ventricle (and an interventricular septal defect), a finding consistent with those observed at the higher dosage. Maternal toxicity was seen at the 20 mg/kg/day group, clinically manifested as initial body weight loss, reduced food and increased water consumption. At an early stage of pregnancy, four females were observed to have completely resorbed their litters. Among the females that retained live fetuses till day 20 of pregnancy, mean fetal weight and consequently litter weights were lower than those seen in the control group. Increased incidences of fetuses and litters with visceral and skeletal malformations were observed. These included cardiovascular and eye defects as well as disturbance of axial development of the skeletal system. The percentage of fetuses with unossified sternebrae and asymmetric/bipartite sternebrae was also found to have increased in the 20 mg/kg/day dose group. At 1.0 mg/kg/day, there were no adverse effects of treatment on the parent female. **The Maternal Toxicity NOAEL is 1.0 mg/kg/day and the Maternal Toxicity LOAEL is 4.5 mg/kg/day based on increased incidences of post-dose salivation, wet coat, and impaired respiration.**

There was an increase in the number of fetuses and litters with extra cervical ribs and one fetus with the unusual finding of a double outlet of the right ventricle (and an interventricular septal defect), findings consistent with those at 20 mg/kg/day (HDT). In the high dose group, mean fetal and litter weights were lower than those seen in the control group. Increased incidences of fetuses and litters with visceral and skeletal malformations were observed. These included

cardiovascular and eye defects as well as disturbance of axial development of the skeletal system. The percentage of fetuses with unossified sternebrae and asymmetric/bipartite sternebrae was also found to have increased in the 20 mg/kg/day dose group. At 1.0 mg/kg/day, there were no signs of developmental toxicity. **The Developmental Toxicity NOAEL is 1.0 mg/kg/day and the Developmental Toxicity LOAEL is 4.5 mg/kg/day**, **based on increased resorption, a dose related increased in incidence of double outlet of right ventricle (and an intraventricular septal defect) along with increased incidence of extracervical ribs at this dosage.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a developmental toxicity study (OPPTS 870.3700; OPP §83-3, OECD 414) in rats.

870.3700 Prenatal Developmental (Gavage) Toxicity – Rabbit

In a developmental toxicity study (MRID 40141901), TBTO (>95 % a.i., Lot No. KY-RDO-064-M) was administered to three groups of 20 inseminated New Zealand White female rabbits via oral gavage at doses of 0.2, 1.0 and 2.5 mg/kg/day from gestation days (gd) 6 through 18, inclusive. The control group was dosed with a comparable regimen of 0.5 mL/kg of Mazola® corn oil. Throughout gestation, all females were observed twice daily for appearance and behavior, and body weights were recorded at appropriate intervals. On gestation day 29, all surviving females were sacrificed for a scheduled Cesarean section. The uterus and ovaries were excised and the trimmed uterus and contents were weighed. All fetuses were weighed, sexed and examined for external, skeletal and visceral anomalies and developmental variations.

No compound related deaths were observed in any dose group. A marked increase in the incidence of abortion was observed in the 2.5 mg/kg/day group when compared with the control group and historical data. None of the clinical findings in the 0.2 and 1.0 mg/kg/day treatment groups were suggestive of treatment-related effects. A statistically significant ($p < 0.05$) mean body weight loss was observed in the 2.5 mg/kg/day group from gestation days 6-18. This represented the only treatment-related effect on maternal body weight gain in the study.

Intrauterine survival and growth of the fetuses were not affected by oral administration of TBTO in the 0.2 and 1.0 mg/kg/day groups. A slight but statistically insignificant decrease in mean fetal weights was noted at the 2.5 mg/kg/day dose level. When compared with the control group, there were no observable differences in the types and frequency of fetal malformations and developmental variations indicative of a response to treatment at all levels tested. Post mortem examination of the dams did not reveal any consistent changes which could be considered treatment-related. **The Maternal Toxicity NOAEL is 1.0 mg/kg/day and the Maternal Toxicity LOAEL is 2.5 mg/kg/day, based on increased incidence of abortion and decreased mean maternal body weight gain.**

A slight but statistically insignificant decrease in mean fetal weights was noted at the 2.5 mg/kg/day dose level. When compared with the control group, there were no observable differences in the types and frequency of developmental toxicity observations indicative of a response to treatment at all levels tested. **The Developmental Toxicity NOAEL is equal to or greater than 2.5 mg/kg/day and the Developmental Toxicity LOAEL is greater than 2.5 mg/kg/day (not established) due to the absence of any developmental toxicity at the highest dose tested.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a prenatal developmental toxicity study (OPPTS 870.3700; OPP §83-3, OECD 414) in rabbits.

4.4 Reproductive Toxicity

Adequacy of database for Reproductive Toxicity: The database for reproductive toxicity of Tributyltin oxide is considered complete and adequate for regulatory purposes.

870.3800 Reproduction and Fertility Effects- Rat

In a two-generation reproduction toxicity study (MRID 41693801), Tributyltin oxide (97.1%; Lot # KRYDO – 064M) was administered in the diet to 30 Sprague Dawley rats/sex/dose group at dietary levels of 0, 0.5, 5, or 50 ppm for two successive generations. The P generation animals were fed the test diets for approximately 10 weeks prior to mating to produce the F1 litters. All litters were weaned on PND 21, and one F1 weanling/sex/litter was randomly selected to be a parent of the next generation, following the same procedures described for the first generation, with the exception that the pre-mating period was 15 weeks for the F1 parents.

There were no treatment-related mortalities. A total of 8 parental rats died during the study, but the incidence was low (≤2 rats per sex/dose group/generation) and unrelated to dose. At 50 ppm, anogenital staining was observed in 9/30 P females at Week 16.
During **pre-mating**, there were no treatment-related effects on body weights, body weight gains, or food consumption in either sex in the P generation. However, in the F1 generation, body weights were decreased ($p \leq 0.05$) throughout pre-mating in the 50 ppm males (↓7-24%). Relative food consumption in these animals was increased ($p \leq 0.05$) at Weeks 20 (↑28%), 21 (↑15%), 22 (↑10%), and 28 (↑9%). Because absolute food consumption was not presented, it is difficult to interpret these data. These apparent increases in relative food consumption may reflect comparable absolute food consumption combined with decreased body weights. During the **mating and post-mating** periods in the males, findings similar to those observed during pre-mating were noted. Body weights, body weight gains, and food consumption in the 50 ppm P males were comparable to controls throughout Weeks 11-18. Weekly body weights remained decreased by 9-10% ($p \leq 0.01$) throughout Weeks 35-42 in the 50 ppm F1 males, with an initial increase of 8% ($p \leq 0.05$) in relative food consumption at Week 38. In the 50 ppm F1 females, body weights were decreased by 15% at Week 19 and by 8% at Week 21; otherwise, values were comparable to controls. During **gestation**, there were no effects of treatment on body weights, body weight gains, or food consumption in either generation. During **lactation**, there were no effects of treatment on body weights or body weight gains. Absolute and relative (to body weight) **thymus** weights were decreased (↓26-38%; $p \leq 0.01$) in the F1 males and females at 50 ppm. Terminal body weight was decreased by 9% ($p \leq 0.01$) in the F1 males at this dose. In the DER from the initial review of this study, the reviewers stated that the weight and histopathology of the thymus in the pups should have been evaluated since an effect on the thymus at an early age may impact negatively upon the adult human immune system. In a memo dated 07/13/92, the Toxicology Branch of the EPA recommended that special studies on the potential immune toxicity of the test material to neonates should be conducted. Numerous *in vitro* and *in vivo* studies summarized in a Toxicological Review have indicated that tributyltin oxide caused depression of immune functions dependent on the thymus. In light of this weight of evidence, the decreased thymus weights in the current study were considered treatment-related, and the lack of organ weight and histopathology data on the pups was not considered to be a deficiency. In the P females, absolute (NS) and relative ($p \leq 0.05$) weights of the **iliac node** were decreased at 5 and 50 ppm. Additionally at 50 ppm, discolored **mesenteric lymph node** was observed in the

F1 males (3/30 treated vs 1/30 controls) and females (5/30 treated vs 0/30 controls). The incidences of pigments/erythrocytes in the reticuloendothelial cells in the mesenteric lymph nodes were higher at this dose in the P males (79% treated vs 66% controls), P females (77% vs 31%), F1 males (80% vs 60%), and F1 females (80% vs 78%). Incidences of reticuloendothelial hyperplasia were increased in the P males (45% treated vs 38% controls), P females (60% vs 41%), F1 males (77% vs 56%), and F1 females (76% vs 61%). Additionally in the P generation, increased incidences of erythrocytes in the sinuses of the mesenteric lymph nodes were noted in the males (72% treated vs 38% controls) and females (50% vs 28%). In the **prostate**, increased incidence of interstitial lymphocytes were observed at 50 ppm in the P generation (11/30 treated vs 5/30 controls) and F1 generation (8/30 treated vs 2/30 controls). However, because there was no functional impairment on the reproductive performance in either generation and there were no other microscopic findings in the reproductive organs, this finding is considered toxicologically unimportant. **The LOAEL for parental toxicity is 50 ppm (equivalent to mg/kg/day 3.47/3.93 in males/females) based on: anogenital staining in the P dams; decreased body weights in the F1 males and females during pre-mating and continuing in the F1 males during the mating and post-mating periods; and decreased absolute and relative thymus weights in the F1 males. The parental NOAEL is 5 ppm (equivalent to 0.33/0.39 mg/kg/day in males/females).**

There were no adverse effects of treatment on gestation duration, the numbers of implantations or pups born, the sex ratio, or on the live birth, viability, lactation, or litter survival indices. There were no effects of treatment on the number of days until mating (pre-coital interval), or on the mating, pregnancy, or fertility indices in either generation.
The LOAEL for reproductive toxicity was not observed (greater than 50 ppm). The reproductive NOAEL is 50 ppm (equivalent to 3.47/3.93 mg/kg/day in males/females).

Pup body weights were decreased ($p \leq 0.05$) in the F1 litters on PND 14 and 21 (↓14-17%) and in the F2 litters on PND 7, 14, and 21 (↓14-20%). These decreases occurred in the latter part of the lactation period and increased in magnitude with time. There were no treatment-related macroscopic findings, and no organs or tissues from the pups were examined microscopically.
The LOAEL for offspring toxicity is 50 ppm (equivalent to 3.47/3.93 mg/kg/day in males/females) based on decreased pup body weights in both generations. The NOAEL is 5 ppm (equivalent to 0.33/0.39 mg/kg/day in males/females).

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a two-generation reproduction study [OPPTS 870.3800; OECD 416] in the rat.

4.5 Chronic Toxicity

870.4100 Chronic Toxicity

Adequacy of database for Chronic Toxicity: The database for chronic toxicity of tributyltin oxide is considered complete and adequate for regulatory purposes.

In a chronic oral toxicity study in dogs (MRID 42549801), bis (tri-*n*-butyltin) oxide (TBTO; 95.9-97.1% a.i.; Batch #s 0830 and 5425) in arachis (peanut) oil was administered by daily oral gavage (dose volume 1.0 mL/kg) to four beagle dogs/sex/dose group daily for at least 52 weeks at doses of 0, 0.2, 1.0, or 5.0 mg/kg/day.

Tin was found in the pooled urine samples of all dose groups, including controls, beginning on Week 1. Urinary tin levels continued to increase in the treated groups over the course of treatment; however, levels were not determined in the controls at Weeks 2, 5, 12, or 26. At Week 52, tin levels in the 1.0 and 5.0 mg/kg/day groups had increased approximately 10-fold over Week 1 levels, while levels in the 0.2 mg/kg/day group had increased approximately 4-fold. However, tin levels in the controls had increased approximately 2.5-fold during treatment. This finding strongly suggested that the controls had been exposed to the test compound repeatedly over the course of treatment. It is the opinion of the reviewers that establishment of a LOAEL and NOAEL are not possible due to this major deficiency.

No adverse, treatment-related effects were observed on nervous system functions, ophthalmoscopic examinations, cardiovascular function, or urinalysis parameters.

Multiple indications of **immunotoxicity** were observed at 1.0 mg/kg/day. Marked to severe involution of the thymus was noted in 2/4 males. Atrophy of the following organs or lymphatic tissues was observed: (i) the spleen in 1/4 males; (ii) the cortex/paracortex of the mesenteric lymph node in 1/4 males; (iii) the cortex/paracortex of the iliac lymph node in 3/4 males and 1/4 females; and (iv) the Peyer's patches of the ileum in 2/4 males and 3/4 females. In the females, decreased ($p \leq 0.05$) immunoglobulin G (↓24-32%; NS at 1.0 mg/kg/day at Weeks 26 and 52) and a (↓59-72%) were observed at Weeks 13, 26, and 52. Decreased ($p \leq 0.05$) immunoglobulin A (↓38-68%) was noted in the males at Weeks 13 (NS), 26 (NS at 1.0 mg/kg/day), and 52. Additionally at this dose, thymus diminished in size was observed in one male, ALP was increased ($p \leq 0.05$) by 147% in two males, and decreased spermiogenesis and tubular degeneration was noted in the testis of 1/4 males.

Systemic toxicity was observed at 5.0 mg/kg/day. Two males and three females were killed *in extremis* between Weeks 32 and 47, following episodes of reduced food intake and severe body weight loss. In general, a combination of clinical signs of toxicity was observed in each of these affected dogs, following a similar pattern with regard to onset and course. After an initial period of reduced food consumption and concomitant body weight loss, (clinical signs noted were emaciation and sometimes exsiccosis), the dogs appeared apathetic and their obviously unsteady gait was judged as atactic. This reaction to treatment was observed in all of the prematurely killed dogs, as well as in one male survivor. Additionally, one male was noted with clinical signs resembling an epileptiform attack during the last week prior to sacrifice. An increase in the incidence of vomiting and marked sialorrhea was also observed in these animals. Individual body weights were generally decreased in the males and females throughout the study. Overall (Weeks 1-53) body weight losses were observed in both sexes; however, it must be noted that only two males and one female survived to study termination. Examination of weekly food consumption data revealed dramatic decreases on several occasions in the males. Decreases in weekly food consumption were also observed in the females, but not to the same magnitude as the males. It was stated that water consumption generally paralleled food consumption. Blood sedimentation rate (24 h) was observed to be increased (not significant [NS]) due to extremely high values for two males and two females on several occasions. Nucleated bone marrow cells were decreased, although it was unclear which cell population contributed to this decrease. Fibrinogen levels were increased in the males at Weeks 13, 26, and 52, due to markedly increased levels in one male. Fibrinogen levels were also increased in a male whose values were not included in the group means. In the females, fibrinogen levels were increased during Weeks 13 and 26. Also, fibrinogen levels were increased in all moribund sacrificed dogs at the time of euthanasia. Alanine aminotransferase was increased in two males and four females; alkaline phosphatase was increased in three males and three females; and γ-glutamyl transferase was

increased in all males and females, all at multiple occasions. Absolute and relative (to body) liver weights were increased by 18-63% in the males and by 40-117% in the females. Gross pathological changes were confined in all but one case to animals killed *in extremis*. Multifocal areas of whitish discoloration was noted in the liver of 2/4 males (one at study termination) and 2/4 females, and all lobes of the liver enlarged was observed in 1/4 females, all compared to 0 controls. The following lesions in the liver were observed at 5.0 mg/kg/day vs. 0 controls: (i) fatty change, predominantly mid-zonal in 3/4 males and females; (ii) ballooning of the hepatocytes, mid-zonal and/or foci of single cells in 3/4 males and 4/4 females; (iii) focal hepatocellular necrosis in 1/4 males and females; (iv) pigment deposition (lipofuscin) in single degenerated cells in 3/4 males and 4/4 females; and (v) local sinusoidal fibrosis in 1/4 females. Decreased spermiogenesis and tubular degeneration of the testis, and atrophy of the epididymis were both observed in 2/4 males

Increased indications of **immunotoxicity** were also observed at 5.0 mg/kg/day. In the females, decreased ($p \leq 0.05$) immunoglobulin G (↓28-38%) and a (↓71-83%) were observed at Weeks 13, 26, and 52. Decreased ($p \leq 0.05$) immunoglobulin A (↓59-72%) was noted in the males at Weeks 13 (NS), 26, and 52. Absolute and relative spleen (↓ 14-76%) and thymus (↓ 47-64%) weights were decreased. Spleen diminished in size was noted in 2/4 males and 3/4 females, and thymus diminished in size was noted in 2/4 males and 3/4 females, both compared to 0 controls. The following lesions were observed in 0 controls except where noted. Marked to severe involution of the thymus was observed in 4/4 males and females. Atrophy of the spleen was observed in 2/4 males and 3/4 females. Atrophy of the lymphatic tissue of the spleen was noted in the males at a similar incidence to controls (both 1/4); however, the severity was increased in the treated dogs (average severity 3.0 vs. 1.0 in controls). Atrophy of the lymphatic tissue of the spleen was also noted in 4/4 females. Atrophy of the lymphatic tissue in the lymph nodes was observed in the mesenteric nodes in 4/4 males and females and in the iliac lymph nodes in 2/4 males and 3/4 females. Atrophy of the Peyer's patches in the ileum was noted in 4/4 males and females. Atrophy of the bone marrow was noted in 2/4 males and 3/4 females.

Multiple microscopic finding indicative of immunotoxicity (detailed above) were noted at 1.0 mg/kg/day, particularly in the males. At 5.0 mg/kg/day, increased severity of immunotoxicity and indications of systemic toxicity (including mortality, clinical signs of toxicity, overall body weight losses, decreased body weights and food and water consumption, increased blood sedimentation rate, decreased nucleated bone marrow cellularity, increased hepatic enzymes, increased liver weight, decreased spleen and thymus weights, and gross pathological findings in the liver, spleen, and thymus) were observed.

This study is classified as **Unacceptable/Guideline (Not upgradeable)** and does not satisfy the guideline requirements for a chronic oral toxicity study [OPPTS 870.4100] in dogs. The analyses of the dosing solutions were inadequate, and the presence of tin in the urine of the control dogs suggests exposure of the control group to the test compound.

4.6 Carcinogenicity

Adequacy of database for Carcinogenicity: The database for carcinogenecity of tributyltin oxide is considered complete and adequate for regulatory purposes. There are no carcinogenicity studies submitted for tributyltin maleate or tributyltin benzoate.

870.4200 Carcinogenicity

In a carcinogenicity study (MRID 42265001), bis(tri-n-butyltin) oxide (97.1% pure, lot KYRDO-064M) was administered to 50 CD-1 mice sex/dose in diet at dose levels of 0, 5, 25, or 50 ppm (equivalent to 0.7, 3.7, and 7.7 mg/kg/day for low-, mid-, and high-dose males, respectively, and 0.9, 4.8, and 9.2 mg/kg/day for low-, mid-, and high-dose females, respectively) for 18 months.

Toxicity was observed at the low dose, with signs including decreased survivorship in males and increased body weight gain in females. At 25 and 50 ppm, signs of toxicity included decreased survivorship, increased body weights and body weight gain, decreased food consumption (high-dose females only), increased absolute and relative liver weight (high-dose females only), and an increased incidence of severe renal amyloidosis. **The LOAEL is 0.7 mg/kg/day for males and 0.9 mg/kg/day for females based on increased mortality and increased body weight gain. The NOAEL is not established (less than 5 ppm; 0.7/0.9 mg/kg/day for males/females).**

Under the conditions of this study, there were no treatment-related increases in tumor incidence in treated animals when compared to controls. Dosing is considered adequate based on toxic effects (i.e., decreased survivorship, increased body weight and body weight gain, decreased food consumption, increased absolute and relative liver weight, and an increased incidence of severe renal amyloidosis) observed.

This carcinogenicity study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

870.4300 Combined Chronic Toxicity/Carcinogenicity

In a combined chronic toxicity/carcinogenicity study (MRID 40623201), 50 Wistar rats/sex/dose were exposed to bis (tributyltin) oxide (95.3% a.i.; Lot No.: CH 356) for up to 106 weeks in the diet at concentrations of 0, 0.5, 5, or 50 ppm (approximately equivalent to 0, 0.025, 0.25, and 2.5 mg/kg bw/day based on a conversion factor of 1 ppm = 0.05 mg/kg bw/day). Additionally, 10 rats/sex/dose were treated similarly for up to 52 weeks. Only 8-10 rats/sex/dose were examined for non-neoplastic lesions and usually only the control and 50 ppm groups were examined microscopically.

No adverse, treatment-related effect was observed on food consumption.

At 50 ppm, **systemic toxicity** was observed. Mortality was increased in both sexes and began to be apparent after Week 94. Survival was approximately 40% treated vs 70% controls in males and 52% treated vs 74% controls in females. Increased incidences of the following clinical signs were observed: emaciation, ataxia, and crusty nostrils in both sexes; and depression in males. Additionally, posterior paresis was increased in the males, although this effect was not clearly related to dose. Decreased body weights were observed in males during Weeks 67-95 and females during Weeks 83-95. Terminal (Week 106) body weights were decreased in both sexes. Body weight gains were decreased during the interval of Weeks 51-95 by 314% in males (a weight loss) and by 56% in females. Overall body weight gains (Weeks 0-106) were decreased by 16% in males and 12% in females. Increased water consumption was observed in males generally from Weeks 24-92.

At 50 ppm, toxicity was also noted in the kidney, thyroid, adrenal gland, and pituitary gland as discussed below.

The clearest effect of the compound in this study was **nephrotoxicity**. Decreased serum creatinine levels were observed in both sexes during Months 12 and 24, and increased blood urea level was noted in the females on Months 3 and 24. In the females, the following differences were observed during urinalysis: (i) increased urinary volume throughout the study; (ii) increased creatinine clearance at Month 3; and (iii) decreased osmolality throughout the study. At Week 52, increased incidences of hydronephrosis were observed in both sexes. At Week 106, increased absolute and relative to body kidney weights were observed in both sexes. At Week 106 in the kidney, increased incidences greenish pigments and granular surface in both sexes were observed. At Week 106, increased incidence and severity of slight to marked renal vacuolation/ pigmentation was noted in the males (not clearly dose-related) and females (dose-related).

At Months 12 and 24, decreases were noted in free thyroxin in males and free thyroxin/thyroxin in both sexes. Decreased absolute and relative **thyroid** gland weights were noted in males at Week 52, but were similar to controls at Week 106. Decreased absolute and relative thyroid weights were observed in females at Week 106. Decreased epithelial height in the thyroid was noted at Weeks 52 and 106 in both sexes, but was not clearly dose-related in males at Week 106.

At Week 52, increased absolute **adrenal gland** weights were observed in both sexes and increased relative to body adrenal weights were noted in females. However, these weights were similar to controls at Week 106. Enlarged adrenals were noted in both sexes at Week 106.

Luteinizing hormone was decreased in the females at Months 12 and 24. At Week 52, increased incidences of **pituitary gland** cysts were observed in females. At Week 106, increased absolute and relative to body pituitary weights were observed in both sexes. An increased incidence of gross pituitary hemorrhagic tumors was observed in males at Week 106.

Although depression of thymus-dependent immunological response is a known effect of the test compound, there was limited evidence of this effect in this study. At 50 ppm, decreased lymphocytes were noted in both sexes throughout the study, and statistically significant decreases were observed in females at Month 12 (↓ 20%) and in both sexes at Month 24 (↓ 27-28%). Serum IgG levels were decreased in the 50 ppm females throughout the study (↓ 25-38%). No effect was noted on the thymus. Without further corroborating evidence of an immunosuppressant effect, these findings were not considered adverse. Serum IgM levels were increased throughout treatment in both sexes.

Other organs may have been affected at 50 ppm, but the evidence was unclear. Increased incidences of atrophy/calcification of the testes, atrophy of accessory male glands, and hypertrophy/inflammation of the accessory male glands were observed. Histological data did not corroborate a treatment-related effect. A concurrently submitted reproductive toxicity study (MRID 41693801) did not corroborate organ toxicity at doses up to 50 ppm. Tumor-like lesions were noted in the uterus in 50 ppm females. However, histopathological analysis did not corroborate organ toxicity or a neoplastic effect.

At 5 ppm, some indicators of organ toxicity were noted that became more evident at 50 ppm; however, these effects were not considered adverse due to the type of abnormality, the lack of magnitude of difference from control, and the general lack of sufficient findings to be considered clearly adverse to the organ system/animal. The following findings were noted at 5 ppm: (i) increased water consumption in males generally from Weeks 1-88 (↑ 7-29%); (ii) increased urinary volume in the females at Month 24 (↑ 45%); (iii) increased incidences of greenish

pigments in kidneys (24% treated vs 10% controls) and granular surface on kidneys (48% treated vs 34% controls) in males; and (iv) decreased free thyroxin/thyroxin in females (↓ 12%).

The LOAEL is 50 ppm (approximately equivalent to 2.5 mg/kg bw/day), based on increased mortality, systemic toxicity (ataxia, emaciation and decreased body weight/body weight gain in males and females) and organ toxicity (kidney, thyroid, adrenal glands, and pituitary). The NOAEL is 5 ppm (approximately equivalent to 0.25 mg/kg bw/day).

At 50 ppm, increased ($p \leq 0.01$) incidences of the following tumors were observed (% in treated vs controls) at Week 106: (i) anterior pituitary tumor in males (86% vs 68%) and females (70% vs 44%); (ii) combined malignant and benign pheochromocytomas in males (66% vs 32%) and females (68% vs 6%); and (iii) parathyroid adenoma in males (12% vs 0%). The incidence of malignant pheochromocytomas was also increased in the males (12% vs 6%) and females (8% vs 0%). An increased (not statistically significant) incidence of granular tumors in the brain was observed in the 50 ppm males (6% vs 0%). Evidence from immunohistochemistry suggested that the pituitary tumors were prolactinomas; these tumors were often fatal. The incidences of other neoplasias in the treated groups were similar to controls. The conclusion documented by the EPA in support of summary information on the integrated risk information system was that: "Although the data on tumor occurrence in this study are questionable, the tumors in these endocrine organs are of unknown biological significance for a human health risk assessment. The results are also inconclusive because of the increased mortality at the high dose and because dose spacing reduces the statistical power."

At the doses tested, there was a treatment-related increase in tumor incidence in the pituitary, adrenal gland, and parathyroid when compared to concurrent controls. However, these results are considered inconclusive, and the tumors in these endocrine glands are of unknown biological significance for human health risk assessment. Dosing was considered adequate based on toxicity observed systemically and toxicity in the kidney, thyroid, adrenal glands, and pituitaries.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for an oral chronic/carcinogenicity study [OPPTS 870.4300, OECD 453] in rats.

4.7 Mutagenicity

Adequacy of database for Mutagenicity: The tributyltin-containing chemical database for mutagenicity is considered incomplete (Table 4). Acceptable data submitted to the Agency shows that tributyltin oxide did not induce positive responses in a reverse gene mutation *Salmonella typhimurium* assay in the presence or absence of S9 metabolic activation and was not mutagenic in an *in vitro* human lymphocyte chromosome aberration test. Similarly, tributyltin benzoate was non-mutagenic in an *in vitro* CHO/HGPRT gene mutation assay and an *in vivo* cytogenetics micronucleus assay in mice. An Unscheduled DNA Synthesis assay in cultured rat hepatocytes conducted with tributyltin benzoate was classified unacceptable and this study does not satisfy the guideline requirement for a mutagenicity study.

Table 4. Summary of Mutagenicity Studies for Technical (97.1 – 103.0%a.i.) Tributyltin Compounds

Guideline No./ Study Type	MRID Number/ Citation	Dosing and Animal Information	Results
870.5100 Bacterial Reverse Mutation Test	MRID 42170001 Lang, R. (1986) Evaluation in the Ames	*Salmonella typhimurium* TA 1535, TA 100, TA1537, TA 1538, and	**Negative** No evidence of mutagenic

Table 4. Summary of Mutagenicity Studies for Technical (97.1 – 103.0%a.i.) Tributyltin Compounds			
Guideline No./ Study Type	**MRID Number/ Citation**	**Dosing and Animal Information**	**Results**
	Salmonella/Microsome Mutagenicity Test: ZK 21.955: Lab project Number: TX6106. Unpublished study prepared by Schering Ag. 29 p. **Tributyltin Oxide**	TA 98 Purity: 97.1 ± 3.4 % and 103 ± 5.6% 0.0001, 0.00025, 0.0005, 0.001, 0.0025, 0.005, 0.01, 0.02 and 0.03 µl/plate (without metabolic activation) 0, 0.001, 0.0025, 0.005, 0.01, 0.02, 0.03, 0.04 and 0.05, 0.08 or 0.15 µl/plate (with metabolic activation)	activity in the presence or absence of metabolic activation (S9 from rat liver) in strains of *S. typhimurium.* **Acceptable/Guideline**
870.5375 *In vitro* Chromosome Aberration Test (Rat)	MRID 40253005 Brunneman, A. (1986) Evaluation of the Clastogenic Potential in the Human Lymphocyte Test: ZK 21.955: Lab. Proj. ID IC 4/86. Un-published study prepared by Schering AG. 23 p. **Tributyltin Oxide**	human lymphocyte Purity 97.1 ± 3.4% and 103.0 ± 5.6% 0.0025, 0.005, 0.01, 0.025, 0.05, 0.1, 0.25, 0.5 and 1.0 µg/ml (without activation) 0.01, 0.025, 0.05, 0.1, 0.25, 0.5, 1.0, 2.5 and 5.0 µg/ml with metabolic activation	**Negative** There was no evidence of chromosome aberration induced when compared with the negative control. However, at higher concentrations reduction in the mitotic index was observed. **Acceptable/Guideline**
870.5300 *In vitro* Mammalian Cell Gene Mutation Test	MRID 42412501 Bakke, J. (1991) Evaluation of Cotin 310 in the CHO/HGPRT Gene Mutation Assay: Final Report: Lab Project Number: LSC-2112-200: 2112-G200-91. Unpublished study prepared by SRI International. 22 p. **Tributyltin Benzoate**	Chinese Hamster ovary - K1 cells Purity: 97.1 ± 3.4 % and 103 ± 5.6 % 0.143, 0.179, 0.224, 0.28 and 0.35 µg/ml (without activation) 0.33, 0.41, 0.51, 0.64, 0.80 µg/ml with activation	**Negative** There was no evidence of a concentration-related, positive response that induced mutant colonies. **Acceptable/Guideline**
870.5395 Mammalian Erythrocyte Micronucleus Test	MRID 42412502 O'Loughlin, K. (1991) Bone Marrow Erythrocyte Micronucleus Assay of Cotin 310 in Swiss Webster Mice: Lab Project Number: 2112-C100-91. Unpublished study prepared by SRI International. 41 p. MRID 42966201 Mahoney, D. (1992) Analysis of Tributylin Benzoate:	Swiss Webster Mice (five males and five females) Purity 97.1 ± 3.4% and 103.0 ± 5.6% 0, 25, 50, 100, 200, or 400 mg/kg/day (Preliminary/Range finding assay) 0, 50, 100 or 200	**Negative** There was not a significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time. **Acceptable/Guideline**

Table 4. Summary of Mutagenicity Studies for Technical (97.1 – 103.0%a.i.) Tributyltin Compounds			
Guideline No./ Study Type	**MRID Number/ Citation**	**Dosing and Animal Information**	**Results**
	Product Chemistry: Chemical Purity: Lab Project Number: 239-39. Unpublished study prepared by Huls America Inc. 9 p. **Tributyltin Benzoate**	mg/kg/day (Micronucleus assay)	
870.5550 Unscheduled DNA synthesis (Rat)	MRID 42412503 Bakke, J. (1990) Evaluation of the Potential of Cotin 310 to Induce Unscheduled DNA Synthesis in the In vitro Hepatocyte DNA Repair Assay Using the Male F-344 Rat: Final Report: Lab Project Number: LSC-1482: 1482-VO1-90. Unpublished study prepared by SRI International. 21 p. MRID 42412504, 42966203 (Supplemental Amendment) Bakke, J. (1992) Evaluation of the Potential of Cotin 310 to Induce Unscheduled DNA Synthesis in the In vitro Hepatocyte DNA Repair Assay Using the Male F-344 Rat: Final Report, Amendment One: Lab Project Number: LSC 1482: 1482-VO1-90. Unpublished study prepared by SRI International. 7 p. MRID 42966201 Mahoney, D. (1992) Analysis of Tributylin Benzoate: Product Chemistry: Chemical Purity: Lab Project Number: 239-39. Unpublished study prepared by Huls America Inc. 9 p. **Tributyltin Benzoate**	Rat Hepatocyte cells Purity 97.1 ± 3.4% and 103.0 ± 5.6% First UDS assay: 1, 5, 10, 25, 50, 100, 250, 500, 750 and 1000 µg/ml (did not satisfy the minimum required concentrations for evaluating Unscheduled DNA synthesis) Second and third assay: 0.005, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5, 10 and 25 µg/ml were tested. Mechanical failure of the incubator prevented completion of these experiments. Fourth (Preliminary) and Fifth (Repeat) assay: 0.005, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5, 10 and 25 µg/ml were tested.	No conclusion can be drawn for the mutagenic potential of Cotin 310 (tributyltin benzoate) when tested iin an *in vitro* rat hepatocyte DNA repair assay. **Unacceptable/Guideline**

4.8 Neurotoxicity

There was no evidence of neurotoxicity in any of the mammalian toxicity studies submitted to the Agency for tributyltin oxide, tributyltin maleate or tributyltin benzoate. The World Health Organization (WHO) has also evaluated the potential neurotoxicity of various organotin compounds in published literature studies and their assessment cited below (excerpt from CICAD 14, Tributyltin Oxide, WHO, Geneva, 1999):

"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 Krajnc 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."

4.9 Metabolism and Pharmacokinetics

Adequacy of database for Metabolism and Pharmacokinetics: The existing toxicity database for tributyltin oxide contains two metabolism studies; one conducted in rats and the second conducted in mice. Most of the ^{113}Sn-labeled tributyltin oxide administered to rats was eliminated via the bile and feces, with a very small moiety of tributyltin oxide eliminated renally. Metabolites were not identified in this study, however, the literature on biotransformation of tributyltin oxide suggest that this compound may by dealkylated to the di- and mono-tin moieties in addition to degradation to inorganic tin. In mice, high levels of ^{14}C- tributyltin oxide were identified in the feces, suggesting this as the major route of excretion. Fat and Lung tissue exhibited high retention of tributyltin oxide. Although both studies do not satisfy the guideline requirement for a metabolism study [OPPTS 870.7485], they contain useful information that is adequate for regulatory purposes.

According to the World Heath Organization (*CICAD 14, Tributyltin Oxide, WHO, Geneva, 1999)*, "Little definitive information is available on the pharmacokinetics of tributyltin oxide (TBTO). 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. 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 hydroxylbutyl compound, which is unstable and rapidly splits to form the dibutyl derivative and butanol. In vitro studies, it has been shown that TBTO is a substrate for mixed function oxidases, but these enzymes are inhibited by 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 of elimination of TBTO residues in mice is 29 days."

870.7485 Metabolism and Pharmacokinetics - Rats

In a metabolism study (MRID 40253002), ^{113}Sn-labelled tributyltin oxide (>99%a.i., batch ES 1873-3) was administered to 3 or 6 female Wistar-Han (SPF) rats/dose methods. An intravenous (1 ethanol: 1 water) or gavage (peanut oil) single dose was administered at levels of 1 mg/kg or 25 mg/kg ^{113}Sn-tributyltin oxide, respectively. Blood was collected from 3 rats/dose method at 5, 15, 30, and 60 min and 2, 4, 6, 8, 12, 18, 24, 36, 48, and 72 hours after dosing. Plasma and whole blood were analyzed for radioactivity and metabolites. In an excretion study where 3-6 rats/dose method were kept in metabolism cages, excreta were collected at 24, 48, and 72 hours post dosing, and were analyzed for radioactivity and metabolites. The whole carcass and gastrointestinal tracts of 3 rats/dose method were analyzed separately 48 hours after dosing for radioactivity; the gastrointestinal tracts of 3 rats/dose method were analyzed for radioactivity 72 after dosing.

Plasma. In the intravenous dose group at five minutes post injection, 853±138 ng/mL of ^{113}Sn-TBTO equivalent was found in total plasma and 784±145 ng/mL of the parent compound equaling 92% was found. After 10 minutes, the first of three peaks in concentration were observed, with the other peaks at 4.9 hours and 19.7 hours. By 48 hours, the concentration was down to 4.3±0.8 ng/mL and below the limit of detection by 72 hours. In the gavage dose group, the time point of measurement of the peak plasma level was 24 hours, with the concentration of that peak being 0.54±0.07 µg/mL (0.066% of dose/plasma volume). The absorption of the test substance in plasma had a half-life of 9.5 hours. The maximum active ingredient concentration of total reactivity was measured 8 hours post administration, with a value of 156 ng/mL, and levels were below detection by 72 hours post application.

Blood. Overall, higher concentrations of ^{113}Sn-TBTO were found in the blood than the plasma. The concentrations in the blood were on average 2-3 times higher, with the largest difference around 24 hours post administration for the intravenous test group and 2 hours post administration for the gavage test group.

Urine and Feces. In the intravenous test group, the half-life of the test substance in urine was approximately 8 hours. Up to 24 hours post administration, 9% of the dose had been eliminated via the urine and 31% with feces. By the end of the study (72 hours post administration), 14% of the dose was found in the urine and 52% in feces. The ratio of elimination of urine and feces was about 1:4, with the balance of TBTO and equivalents eliminated by both routes reaching 66% of the dose by 72 hours, when the plasma values were below detection. In the gavage test group, up to 24 hours post administration, 4% of the dose had been eliminated via urine and 1% with feces. By 72 hours post administration, 11% of the dose was found in the urine and 62% of the dose in feces. The ratio of elimination of urine and feces was about 1:6, with the balance of the TBTO and equivalents eliminated by both routes reaching 72% of the dose. The elimination values did not fit a first order kinetics curve, so a half-life could not be determined.

Remaining Body. At 48 hours post administration, an average of 27% of the dose equivalents had been localized in the rat's bodies (excluding the GI tract) via intravenous administration and 14% of the dose equivalents via gavage administration. Similarly, 3% of the dose equivalents were found in the GI tract via intravenous administration and 57% via gavage administration. These numbers were decreased to 9% and 4%, for intravenous and gavage administration, respectively, by 72 hours post administration.

Metabolite(s). The concentration of the parent compound and metabolites in plasma and urine were determined. The HPLC analysis showed that 5 extractable metabolites were observed along with the parent; intravenous administration had 2 metabolites besides the parent compound

whereas gavage administration had 5 metabolites. Extraction efficiency in the plasma and urine (pH 8) was 90%.

This metabolism study is classified as **Acceptable/Non-guideline.** Although it and does not satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats, this study contains useful information that is adequate for regulatory purposes.

870.7485 Metabolism and Pharmacokinetics – Mice

In a metabolism study (MRID 01246480), [^{14}C] bis (tri-n-butyltin) oxide (TBTO) was administered to 5 female COBS albino mice/dose/time period in drinking water at nominal dose levels of 0, 0.51, 3.75, or 18.5 ppm. In one experiment, mice were administered ^{14}C-TBTO in drinking water for up to thirty days; five animals/dose were sacrificed after each time point: 5, 10, 15, 20, 25, or 30 days. In a second experiment, animals were administered ^{14}C-TBTO in drinking water for 31 days. At the end of the test period, 5 animals/dose were sacrificed, while the remaining mice were placed on non-^{14}C-TBTO water for an additional 15 days before sacrifice. Feces and urine were collected on a daily basis from the mice in Experiment 2, and organs were excised from all animals for analysis.

Concentrations of ^{14}C-TBTO were greatest in the kidneys, fat, liver, and spleen. Concentrations were found to be proportional to administered dose except in the kidney. Fifteen days following treatment, a marked decrease in ^{14}C-TBTO levels was observed in the liver and kidney, while the fat and lung tissue exhibited relatively high retention. Feces were found to possess high levels of ^{14}C-TBTO, suggesting this is the major route of excretion.

This metabolism study is classified as **Acceptable/Non-guideline.** Although this study does not satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rodents, when reviewed together with the metabolism study conducted in rats (MRID 40253002), it provides information that identifies the major route of excretion for tributyltin oxide as the feces.

5.0 Dermal Penetration

There is no acceptable guideline dermal absorption study available in the tributyltin toxicity database. The existing dermal absorption study conducted in baboons with tributyltin oxide was classified unacceptable due to less than 50% recovery of the administered dose. In addition, there are no adequate dermal toxicity studies. A submitted dermal range-finding study conducted in rats with tributyltin benzoate does not fulfill the guideline requirement; however, it does serve to establish a maximum tolerable dose (250 mg/kg/day) for a guideline dermal toxicity study. Typically, a default dermal adsorption factor of 100 % would be appropriate for risk assessment purposes in the absence of data; however, the Agency has estimated that 10-15% of the labeled compound reaches the systemic circulation. Therefore, a 15% dermal absorption for route-to-route extrapolation is appropriate for assessing the risk to humans from dermal exposure of tributyltin oxide.

6.0 Immunotoxicity

Non-Guideline 18-Month Immunotoxicity (oral) Study - Rat

Published Literature: Vos, J.G., A. DeKlerk, E.I. Krajnc, V. Van Loveren, and J. Rozing. 1990. Immunotoxicity of bis(tri-n-butyltin)oxide in the rat: Effects on thymus- dependent immunity and on nonspecific resistance following long-term exposure in young versus aged rats. Toxicol. Appl. Pharmacol. 105: 144-155 (*Excerpt from EPA/IRIS Summary of Tributyltin Oxide, 1997 follows):*

"Subchronic and chronic immunotoxicity studies were conducted in which weanling SPF-derived Riv:TOX Wistar rats were fed bis(tri-n-butyltin)oxide [tributyltin oxide (TBTO), purity 95.3%] in concentrations of 0, 0.5, 5.0 or 50 ppm. Male rats (females not tested) were evaluated following exposure to TBTO for up to 18 months (Vos et al., 1990; Krajnc et al., 1987). The authors reported the 5 ppm dietary concentration to be equivalent to a dose of 0.25 mg/kg-day, indicating that estimated test doses were 0.025, 0.25 and 2.5 mg/kg-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. Immunologic function studies for specific and nonspecific resistance were performed in 9-12 rats/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- hour) responses to ovalbumin and mycobacterium tuberculosis (immunized after 6 or 15 months exposure), and resistance to oral infection by Trichinella spiralis larvae (infected after 5.5 or 16.5 months). Nonspecific resistance was assessed by splenic clearance of i.v. injected Listeria monocytogenes bacteria (after 5 or 17 months exposure), and natural cell-mediated cytotoxicity of spleen cells (after 4.5 or 16 months exposure) and peritoneal cells (after 4.5 months exposure only) using a 4-hour 51Cr-release assay with YAC-lymphoma target cells. Nonspecific endpoints 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 (phytohemagglutinin, concanavalin A, pokeweed mitogen and/or E. 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 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 Trichinella spiralis, the IgM or IgG responses to ovalbumin or the delayed-type hypersensitivity responses to ovalbumin and mycobacterium 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 exposure) and B-lymphocytes in the mid-dose group (60% higher than controls after 18 months) and in the high-dose group (48% higher than controls after 18 months); however, the absolute number of T- lymphocytes and B-lymphocytes per lymph node were not altered significantly. The low-dose group was not tested with these assays. The B-cell increase was an increase in the percent 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 titers.

In vivo clearance of injected L. monocytogenes was impaired in rats exposed to the high dose for 17 months, as shown by the approximately seven- fold increased 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 titers (50 and 47% lower than controls after 16.5 months 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 peritoneum 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. The authors considered these data equivocal in this experiment. Because there was no clear treatment-related effect, EPA will not use the suppression of natural killer cell activity from this study to estimate the reference dose.

Essentially identical results on the immune system were observed following 4.5 or 16.5 months of exposure. **Based on the depression of IgE titers and the increase in T. spiralis larvae in muscle following 16.5 months of exposure, the LOAEL for immunotoxicity is 0.25 mg/kg-day (5 ppm diet). The NOAEL is 0.025 mg/kg-day (0.5 ppm diet).**" [Krajnc et al., 1987; Vos et al., 1990]

Additional Published Literature for Immunotoxicity (*Excerpt from CICAD 14, Tributyltin Oxide, WHO, Geneva, 1999):*

"A large number of well-conducted studies have shown that TBTO causes depression of immune functions dependent on the thymus." 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. This 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.

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 preweanlings 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-weanling (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 preweanlings 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."

7.0 Classification of Carcinogenic potential

There are no data in humans concerning development of cancer following exposure to tributyltin oxide (TBTO) and other organotin chemicals. Cancer bioassays following oral exposure have been conducted in rats and mice. In the carcinogenicity study conducted in rats, increases in the incidence of benign pituitary tumors, pheochromocytomas, and parathyroid tumors were observed at the highest dose levels tested. However, the significance of these tumors which normally occur in this strain of rat with variable incidence, is unclear. Furthermore, the carcinogenicity study in mice showed no increase in tumors at any site or dose tested. There are no structure-activity relationships suggesting that TBTO might be a carcinogen. Based on high spontaneous incidences of tumors in Wistar rats, incidence variability in the treated groups, absence of a dose-effect relationship and no evidence of genotoxicity in the battery of mutagenicity tests, EPA has assigned TBTO to category D (U.S., 1987) or to the "cannot be determined" category for carcinogenicity (U.S. EPA, 1996).

8.0 FQPA (Special Sensitivity) Considerations

Although the labeled uses for the tributyltin-containing chemicals have no direct or indirect food exposures and no established food tolerances, there remains the potential for special sensitivity to children from residential exposure to these chemicals. A Special Sensitivity factor can be applied to a selected dose if there is evidence of increased susceptibility to children from non-dietary exposures to pesticides.

The developmental and prenatal database for tributyltin oxide and tributyltin benzoate is considered complete and adequate for regulatory purpose, whereas a prenatal developmental toxicity study conducted in rats is required for tributyltin maleate to satisfy the bridging requirement. Results of the submitted studies show no evidence of pre- or postnatal special

sensitivity to the fetuses and offspring of rats or rabbits; one developmental toxicity study in the rat conducted with tributyltin oxide, one developmental toxicity study in the rat conducted with tributyltin benzoate, and one reproduction toxicity study in rats conducted with tributyltin oxide.

In contrast, there is some evidence in several published literature studies that a child might be more sensitive to the toxic effects of tributyltin oxide. According to the EPA/IRIS, Toxicological Review of Tributyltin Oxide (July, 1997), tributyltin oxide causes depression of immune functions dependent on the thymus, particularly in young animals. This is a critical effect that occurs at doses lower than those causing other toxicities. "For example, Smialowicz et al. (1989) showed that immunotoxic effects were observed when weanling rats were dosed for 4.5 or 16.5 months. A companion study (Vos, et al., 1990) showed that these effects were absent or occurred at a higher dose when adult rats (1 year old) were dosed for 5 months." Based on the numerous published literature studies on the immunotoxicity of tributyltin oxide, application of this factor would provide adequate protection to the most sensitive population, children. Therefore, a special children's sensitivity factor of 10x was applied to the tributyltin oxide dose/endpoint (BMD_{10} = 0.03 mg/kg/day) selected for all residential exposure scenarios.

9.0 Endocrine Disruptor Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that EPA include evaluations of potential effects in wildlife. For pesticides, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). When the appropriate screening and/or testing protocols being considered under the EDSP have been developed, tributyltin oxide, tributyltin maleate and tributyltin benzoate may be subject to additional screening and/or testing to better characterize effects related to endocrine disruption.

10.0 Toxicity Endpoint Selection

Table 5: Summary of Toxicology Endpoint Selection for Tributyltin Compounds			
Exposure Scenario	**Dose Used in Risk Assessment (mg/kg/day)**	**Special Sensitivity*, UF, Target MOE, for Risk Assessment**	**Study and Toxicological Effects**
Dietary Risk Assessments			
Acute Dietary (females 13-49 and general population)	No appropriate endpoints were identified in the oral toxicity studies that represent a single dose effect for the general population and females 13-49. In addition, the current use patterns for the tributyltin-containing chemicals do not indicate the potential for direct or indirect dietary exposures. Therefore, an acute dietary risk assessment is not required.		
Chronic Dietary (all populations)	**BMD_{10}** = 0.03 mg/kg/day based on immunosupression (established by EPA/IRIS and used to estimate the oral RfD).	**Special Sensitivity** = 10 **UF** = 100 (10x inter-species extrapolation, 10x intra-species variation) **Chronic RfD (cRfD) =** 0.00003 mg/kg/day Although the current use patterns for the tributyltin-containing chemicals do not indicate the potential for chronic dietary exposures, this endpoint is selected for future reference. A chronic dietary risk assessment is not required at this time.	**Open Literature Study** **Vos et al.**, (1990) Immunotoxicity of bis (tri-n-butyltin) oxide in the rat: Effects on thymus-dependent immunity and on nonspecific resistance following long-term exposure in young vs aged rats. Toxicol. Appl. Pharmacol. 105:144-155. **NOAEL** = 0.025 mg/kg/day **LOAEL** = 0.25 mg/kg/day based on immunotoxicity (depression of IgE titers and increase in T. spiralis larvae in muscle) following 4 months and 16.5 months of exposure to Tributyl Tin Oxide. (Review by EPA/IRIS, 1997).
Non-Dietary Risk Assessments			

Table 5: Summary of Toxicology Endpoint Selection for Tributyltin Compounds			
Exposure Scenario	**Dose Used in Risk Assessment (mg/kg/day)**	**Special Sensitivity*, UF, Target MOE, for Risk Assessment**	**Study and Toxicological Effects**
Incidental Oral Short-Term (1-30 days) and Intermediate-Term (1- 6 months)	**BMD_{10}** = 0.03 mg/kg/day based on immunosupression (established by EPA/IRIS and used to estimate the oral RfD).	**Special Sensitivity** = 10 **UF** = 100 (10x inter-species extrapolation, 10x intra-species variation) **Target MOE res.** = 1000	**Open Literature Study** **Vos et al.**, (1990) Immunotoxicity of bis (tri-n-butyltin) oxide in the rat: Effects on thymus-dependent immunity and on nonspecific resistance following long-term exposure in young vs aged rats. Toxicol. Appl. Pharmacol. 105:144-155. **NOAEL** = 0.025 mg/kg/day **LOAEL** = 0.25 mg/kg/day based on immunotoxicity (depression of IgE titers and increase in T. spiralis larvae in muscle) following 4 months and 16.5 months of exposure to Tributyl Tin Oxide. (Review by EPA/IRIS, 1997).
Dermal (all durations)	**BMD_{10}** = 0.03 mg/kg/day based on immunosupression (established by EPA/IRIS and used to estimate the oral RfD).	**Special Sensitivity** = 10 **UF** = 100 (10x inter-species extrapolation, 10x intra-species variation) **Target MOE occ.** = 100 **Target MOE res.** = 1000	**Open Literature Study** **Vos et al.**, (1990) Immunotoxicity of bis (tri-n-butyltin) oxide in the rat: Effects on thymus-dependent immunity and on nonspecific resistance following long-term exposure in young vs aged rats. Toxicol. Appl. Pharmacol. 105:144-155. **NOAEL** = 0.025 mg/kg/day **LOAEL** = 0.25 mg/kg/day based on immunotoxicity (depression of IgE titers and increase in T. spiralis larvae in muscle) following 4 months and 16.5 months of exposure to Tributyl Tin Oxide. (Review by EPA/IRIS, 1997).

Table 5: Summary of Toxicology Endpoint Selection for Tributyltin Compounds			
Exposure Scenario	**Dose Used in Risk Assessment (mg/kg/day)**	**Special Sensitivity*, UF, Target MOE, for Risk Assessment**	**Study and Toxicological Effects**
Inhalation (all durations)	**BMD_{10}** = 0.03 mg/kg/day based on immunosupression (established by EPA/IRIS and used to estimate the oral RfD).	**Special Sensitivity** = 10 **UF** = 100 (10x inter-species extrapolation, 10x intra-species variation) **Target MOE occ.** = 100 **Target MOE res.** = 1000	**Open Literature Study** **Vos et al.**, (1990) Immunotoxicity of bis (tri-n-butyltin) oxide in the rat: Effects on thymus-dependent immunity and on nonspecific resistance following long-term exposure in young vs aged rats. Toxicol. Appl. Pharmacol. 105:144-155. **NOAEL** = 0.025 mg/kg/day **LOAEL** = 0.25 mg/kg/day based on immunotoxicity (depression of IgE titers and increase in T. spiralis larvae in muscle) following 4 months and 16.5 months of exposure to Tributyl Tin Oxide. (Review by EPA/IRIS, 1997).
Dermal Absorption	Although there is no guideline dermal toxicity study (range-finding study only) and no acceptable dermal absorption study (75% recovery of ^{113}Sn-tributyltin oxide), a 15% dermal absorption factor for tributyltin oxide has been used (EPA/HED) for route-to-route extrapolation.		
Carcinogenicity	EPA has assigned tributyltin oxide to category D (U.S., 1987) or to the "cannot be determined" category for carcinogenicity (U.S. EPA, 1996) based on high spontaneous incidences of tumors in Wistar rats, incidence variability in the treated groups and absence of a dose-effect relationship.		

UF = uncertainty factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, RfD = reference dose, MOE = margin of exposure, NA = Not Applicable

*The Special Sensitivity factor is applied to a selected dose if there is evidence of increased susceptibility to children from non-dietary exposures to pesticides. Several published literature studies show that tributyltin oxide causes depression of immune functions dependent on the thymus, particularly in young animals. This is a critical effect that occurs at doses lower than those causing other toxicities. Therefore, application of this factor provides adequate protection to the most sensitive population, children.

11. Toxicity Profile Tables

Acute Toxicity Profile Table – (See Section 4, Acute Toxicity, Table 3)

Subchronic, Chronic and other Toxicity Profiles Table (Table 6)

Table 6. Toxicity Profile for Tributyltin Oxide, Tributyltin Maleate and Tributyltin Benzoate			
Guideline No./ Study Type	**MRID No./ Citation**	**Dosing and Animal Information**	**Results**
Range-finding Toxicity			
Non-guideline Range-finding Study in Mice	MRID 41127001 Daly, I. (1989) A three month oral range-finding toxicity study in mice with bis (tri-n-butyltin) oxide (TBTO). Bio/dynamics, Inc. (East Millstone, New Jersey). Unpublished.	CD-1® mice (male and female) Purity 97.1 % a.i. 0, 4, 20, 80, or 200 ppm (equivalent to 0.7, 3.8, 15.1, or 36.9 mg/kg bw/day in males; 1.0, 4.9, 17.9, or 46.9 mg/kg bw/day in females) for 13 weeks (diet).	**NOAEL = 4 ppm** (equivalent to 0.7 mg/kg bw/day in males; 1.0 mg/kg bw/day in females). **LOAEL = 20 ppm** (equivalent to 3.8 mg/kg bw/day in males; 4.9 mg/kg bw/day in females) based on mild hepatotoxicity and dermal irritation in the ear observed in male mice. The **Unacceptable/Non-guideline**
Non-guideline Range-finding Study in Dogs	MRID 41131001 Schweinfurth, H. (1987) Tributyltin oxide: Systemic toxicity study in Beagle dogs with daily oral (intragastric) administration over a total of 18-19 weeks. Schering AG, Berlin, Germany. Laboratory Project ID: TX 87.054, August 5, 1987. Unpublished.	Beagle dogs Purity >96.1% a.i. 0, 0.1, 0.5, or 2.5 mg/kg during Weeks 1-5; 0, 0.2, 1.0, or 5.0 mg/kg during Weeks 6-10; and 0, 10, 1.0, or 5.0 mg/kg during Weeks 11-19.	Exposure to Tributyltin oxide caused elevated alkaline phosphatase and slight changes in serum protein composition at 1.0 mg/kg/day after 13-14 weeks of exposure. While further biochemical changes and suspected effects on red and white blood cells were observed at 2.5 mg/kg/day after 5 weeks of exposure and at 5.0 mg/kg/day after 13-14 weeks of exposure, there was no evidence of organ toxicity. At 10 mg/kg/day, general toxic effects leading to weight loss and lymphotoxic effects, vacuolization of the liver cells and inhibition of follicle maturation in the ovaries (secondary effect) were observed. A dose of 10 mg/kg/day was considered to be too toxic of a dose for the 1-year oral dog study; therefore, dose levels of 0.2, 1.0, and 5.0 mg/kg/day were recommended for the 1-year study. **Unacceptable/Non-guideline**
21-Day Dermal Toxicity			
870.3200 21-Day Dermal Toxicity Study in Rats	MRID 43177201 Naas, Dennis J. (1990) Three week dermal range-finding study in rats with Tributyltin Benzoate. WIL Research Laboratories, Inc. (Ashland, Ohio). Laboratory study number WIL-159010, December 18, 1990. Unpublished.	Dorsal skin of Crl:CD®BR rats Purity not provided 0, 250, 500, 1000, or 2000 mg/kg/day for 6 hours/day	The maximum tolerable dose for a subsequent 90-day toxicity study was determined to be 250 mg/kg/day. **Unacceptable/Non-guideline**

Prenatal Developmental Toxicity			
870.3700 Prenatal Developmental Toxicity Study	MRID 00137158 Schroeder, R.; Hogan, G. (1981) A Teratology Study in Rats with Tributyltin Oxide: Project No. 80-2497A. Final rept. (Unpublished study received Jan 16, 1984 under 5204-1; prepared by Bio/dynamics, Inc., submitted by M & T Chemicals Inc., Rahway, NJ; CDL:252178-A). MRID 92172016 Schroeder, R. (1992) M&T Chemicals, Inc. Phase 3 Reformat of MRID 00137158. A Teratology Study in Rats with Tributyltin Oxide: Project No. 80-2497A. Prepared by Bio/dynamics, Inc. 83 p.	Female pregnant CD® (Sprague-Dawley derived) rats Purity not reported 0, 5, 9, 18 mg/kg/day (via gastric intubation (gavage)	**Maternal Toxicity** **NOAEL** = 5 mg/kg/day **LOAEL = could not be identified due to the lack of data.** **Developmental Toxicity** **NOAEL** is less than 5 mg/kg/day **LOAEL** is equal to or less than 5 mg/kg/day based on increased incidences of ossification variations. **Unacceptable/Upgradeable**
870.3700 Prenatal Developmental Toxicity Study	MRID 40141901 Nemec, M. (1987) (Tributyltin Oxide) - A Teratology Study in Rabbits with TBTO: Laboratory Project ID: WIL-B0002. Unpublished study prepared by Wil Research Laboratories, Inc. 210 p. MRID 92172006 Stevens, A. (1990) M&T Chemicals, Inc. Phase 3 Summary of MRID 40141901. A Teratology Study in Rabbits with TBTO: Project No. WIL-B0002. Prepared by Wil Research Laboratories, Inc. 7 p.	New Zealand White female rabbits Purity >95% 0, 0.2, 1.0, 2.5 mg/kg/day (oral gavage)	**Maternal Toxicity** **NOAEL** = 1.0 mg/kg/day **LOAEL** = 2.5 mg/kg/day, based on increased incidence of abortion and decreased mean maternal body weight gain. **Developmental Toxicity** **NOAEL** = is equal to or greater than 2.5 mg/kg/day **LOAEL**= is greater than 2.5 mg/kg/day (could not be established) **Acceptable/Guideline**
870.3700 Prenatal Developmental Toxicity Study	MRID 42903101 Bryson, A. (1993) Tributyltin Benzoate: A Study of the Effect on Pregnancy of the Rat: Lab Project Number: NDX/41: NDX 41/921129. Unpublished study prepared by Huntingdon Research Centre Ltd. 106 p.	Cr1: CD® (SD) BR VAF/Plus strain rats Purity 97.1% a.i. 0, 1.0, 4.5 and 20.0 mg/kg/day (intragastric intubation)	**Maternal Toxicity** **NOAEL** = 1.0 mg/kg/day **LOAEL** = 4.5 mg/kg/day based on increased incidences of post-dose salivation, wet coat, and impaired respiration. **Developmental Toxicity** **NOAEL** = 1.0 mg/kg/day **LOAEL** = 4.5 mg/kg/day, based on increased resorption, a dose related increased in incidence of double outlet of right ventricle (and an intraventricular septal defect) along

			with increased incidence of extracervical ribs at this dosage. **Acceptable/Guideline**
Reproduction and Fertility Rates			
870.3800 Reproduction and Fertility effects	MRID 41693801 Schroeder, R.E. (1990) A two generation reproductions study in rats with bis (tri-*n*-butyltin) oxide. Bio/dynamics, Inc., East Millstone, NJ. Laboratory Project No.: 88-3261, October 22, 1990. Unpublished	Sprague Dawley rats Purity 97.1% 0, 0.5, 5, or 50 ppm for two successive generations (diet)	**Parental Toxicity** **NOAEL** = 5 ppm (equivalent to 0.33/0.39 mg/kg/day in males/females). **LOAEL** = 50 ppm (equivalent to mg/kg/day 3.47/3.93 in males/females) based on anogenital staining in the P dams; decreased body weights in the F1 males and females during pre-mating and continuing in the F1 males during the mating and post mating periods; and decreased absolute and relative thymus weights in the F1 males. **Reproductive Toxicity** **NOAEL** = 50 ppm (equivalent to 3.47/3.93 mg/kg/day in males/females) **LOAEL** = greater than 50 ppm (not established) **Offspring Toxicity** **NOAEL** = 5 ppm (equivalent to 0.33/0.39 mg/kg/day in males/females). **LOAEL** = 50 ppm (equivalent to 3.47/3.93 mg/kg/day in males/females) based on decreased pup body weights in both generations **Acceptable/Guideline**
Chronic Toxicity			
870.4100 Chronic Toxicity	MRID 42549801 Schuh, W. (1992) Bis (tri-*n*-butyltin) oxide (TBTO; ZK 21.955): 12-month chronic oral toxicity study in beagle dogs. Schering AG, Berlin, Germany. Laboratory Project ID: Study Number TX 85.330, September 4, 1992. Unpublished.	Beagle dogs Purity 95.9-97.1% a.i. 0, 0.2, 1.0, or 5.0 mg/kg/day for 52 weeks (oral gavage)	Multiple microscopic finding indicative of immunotoxicity (detailed above) were noted at 1.0 mg/kg/day, particularly in the males. At 5.0 mg/kg/day, increased severity of immunotoxicity and indications of systemic toxicity (including mortality, clinical signs of toxicity, overall body weight losses, decreased body weights and food and water consumption, increased blood sedimentation rate, decreased nucleated bone marrow cellularity, increased hepatic enzymes, increased liver weight, decreased spleen and thymus weights, and gross pathological findings in the liver, spleen, and thymus) were observed. **Unacceptable/Guideline (not upgradeable)**
Carcinogenicity			
870.4200 Carcinogenicity	MRID 42265001 Daly, I. (1992) An	CD-1 mice	**LOAEL = 0.7 mg/kg/day (males)** **LOAEL = 0.9 mg/kg/day (females),**

	eighteen month oncogenicity feeding study in mice with bis (tri-n-butyltin) oxide (TBTO). Bio/dynamic, Inc. Project No. 87-3131, March 27, 1992. Unpublished	Purity 97.1% pure 0, 5, 25, or 50 ppm (equivalent to 0.7, 3.7, and 7.7 mg/kg/day for low-, mid-, and high-dose males, respectively, and 0.9, 4.8, and 9.2 mg/kg/day for low-, mid-, and high-dose females, respectively) for 18 months (diet)	based on decreased survivorship and increased body weight gain**.** **Acceptable/Guideline**
Combined Chronic Toxicity/Carcinogenicity			
870.4300 Combined chronic toxicity/Carcinogenicity	MRID 40623201 Wester, P.W.; Krajnc, E.I.; et al. (1988) Bis (tributyltin) oxide – Two year feeding study in rats with bis (tri-*n*-butyltin) oxide. RIVM, Bilthoven, The Netherlands. Laboratory Report No.: 658112 002, February 25, 1988. Unpublished.	Wistar rats Purity 95.3% a.i. 0, 0.5, 5, or 50 ppm (approximately equivalent to 0, 0.025, 0.25, and 2.5 mg/kg bw/day (diet)	**NOAEL** = 5 ppm (approximately equivalent to 0.25 mg/kg bw/day). **LOAEL** = 50 ppm (approximately equivalent to 2.5 mg/kg bw/day) based on increased mortality, systemic toxicity (ataxia, emaciation and decreased body weight/body weight gain in males and females) and organ toxicity (kidney, thyroid, adrenal glands, and pituitary. **Acceptable/Guideline**
Metabolism and Pharmacokinetics			
870.7485 Metabolism and Pharmacokinetics	MRID 01246480 Evans, W., D. Smith, and N. Cardarelli (date of study not provided) Accumulation and excretion of [1-^{14}C] bis (tri-n-butyltin) oxide in mice. Environmental Management Laboratory, The University of Akron (Akron, Ohio). Unpublished.	Female COBS albino mice Purity not reported 0, 0.51, 3.75, or 18.5 ppm	Concentrations of ^{14}C-TBTO were greatest in the kidneys, fat, liver, and spleen. Concentrations were found to be proportional to administered dose except in the kidney. Tissue accumulations were concentration dependent. The quantities absorbed were rapidly cleared when ingestion ceased. **Acceptable/Non-guideline**
870.7485 Metabolism and Pharmacokinetics	MRID 40253002 Humpel, M. (1986) Toxicokinetics of ^{113}Sn-labelled tributyltin oxide after intravenous (1 mg/kg) and intragastric (25 mg/kg) administration to rats: bioavailability, excretion, and biotransformation. Schering AG, Berlin, Germany. Laboratory report numbers IC-Kl 3, KI 84 061, and KI 84 062. January 23, 1986. Unpublished.	Female Wistar-Han (SPF) rats Purity (>99%a.i) 1 mg/kg or 25 mg/kg	Absorption was very delayed after gavage administration, with a half-life of 9.5 hours. The intravenously administered ^{113}Sn-labeled TBTO is rapidly distributed, with only 3% of the dose remaining in plasma volume after 5 minutes post administration. Based on the high volume of distribution and the binding to the cellular constituents of the blood, authors conclude that TBTO has a pronounced affinity for tissues. **Acceptable/Non-guideline**
Dermal Penetration			
870.7600 Dermal Penetration	MRID 40050003 Hümel, M. (1985) Series 85-2: Percutaneous absorption of tributyltin oxide (TBTO) through intact skin of baboon. Scherling AG, Berlin 65,	Male baboon Purity not reported Dose volume 0.5 mL/25 cm^2 skin	The total recovery of radioactively labeled ^{113}Sn-Tributyltin oxide was less than 50%, perhaps due to the incomplete removal of unabsorbed TBTO on the skin surface as a result of extensive spreading from the site of application. However, reviewer

	Germany. Laboratory Project ID IC-KI 2, June 12, 1985. Unpublished		generated data indicates that the total recovery was approximately 75%. **Unacceptable/Non-guideline**
Published Literature			
Non Guideline Literature Study	Vos et al., (1990) Immunotoxicity of bis(tri-n-butyltin)oxide in the rat: Effects on thymus-dependent immunity and on nonspecific resistance following long-term exposure in young vs aged rats. Toxicol. Appl. Pharmacol. 105:144-155.	Wistar Rats Purity: 95.3% active ingredient Exposure to TBTO for up to 18 months Dietary concentrations: 0.025, 0.25 and 2.5 mg/kg-day.	**NOAEL** = 0.025 mg/kg/day **LOAEL** = 0.25 mg/kg/day based on immunotoxicity (depression of IgE titers and increase in T. spiralis larvae in muscle) following 4 months and 16.5 months of exposure to Tributyl Tin Oxide. (Review by EPA/IRIS, 1997).

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