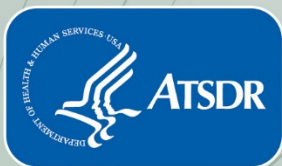




Toxicological Profile for S,S,S-Tributyl Phosphorotrithioate (Tribufos)

March 2020



U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Patrick N. Breyse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to “...effectuate and implement the health related authorities” of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to “...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances” under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

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CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Rae T. Benedict, Ph.D. (Lead)
G. Daniel Todd, Ph.D.
Malcolm Williams, D.V.M., Ph.D.

David W. Wohlers, Ph.D.
Mario Citra, Ph.D.

ATSDR, Division of Toxicology and Human Health
Sciences, Atlanta, GA

SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:

Includes ATSDR; National Center for Environmental Health (NCEH); National Institute of Occupational Health and Safety (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

Additional reviews for science and/or policy:

ATSDR, Division of Community Health Investigations; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice; EPA/Office of Pesticide Programs.

PEER REVIEWERS

1. Edna F. Pereira, Ph.D., Associate Professor, University of Maryland School of Medicine, Baltimore, Maryland;
2. Michael Eddleston, M.D., Ph.D., Department of Pharmacology, Toxicology, and Therapeutics, University/BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom; and
3. Richard A Fenske, Ph.D., M.P.H., Associate Chair, Environmental and Occupational Health Sciences, Professor, Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington.

These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

The common name, tribufos, is used throughout this Toxicological Profile for S,S,S-Tributyl phosphorotrithioate (systematic name). Tribufos (Chemical Abstracts Service [CAS] Registry Number 78-48-8) is a colorless to pale yellow liquid with a skunk-like odor (Tomlin 2003). Tribufos is used only as a defoliant (a chemical that removes leaves) for cotton plants (CalEPA 2004; Tomlin 2003). Tribufos is not for residential use or other non-occupational uses. The U.S. Geological Survey (USGS) Pesticide National Synthesis Project estimated that approximately 2 million pounds of tribufos were applied to cotton crops in 2013 (USGS 2016) and about 2.8 million pounds were applied in 2016 (USGS 2019). Approximately 9–16 million acres of cotton are planted annually in the United States, and tribufos is one of several defoliants that may be applied to these crops (USDA 2016a). It is applied as a liquid product by aerial or groundboom spraying (EPA 2006b).

In the atmosphere, tribufos is degraded by reacting with photochemically generated hydroxyl radicals; its estimated atmospheric half-life is approximately 2 hours (EPA 2012h; Meylan and Howard 1993). Tribufos exhibits low vapor pressure and a low Henry's Law constant; therefore, tribufos is not likely to volatilize readily from water. Although a low vapor pressure suggests that tribufos is not likely to volatilize from soil surfaces, a field dissipation study indicated that volatilization from soils under hot and humid conditions may be an important environmental fate process (Potter et al. 2002). Tribufos is expected to have little or no mobility in soil based upon experimentally determined soil adsorption coefficients. There is uncertainty regarding the overall persistence of tribufos in soil; half-lives of 5–745 days in soil have been reported (Bayer 2008; CalEPA 2004; EPA 2006b). For further details, see Section 5.4.

Exposure to tribufos within the general population is extremely low. The primary exposure pathway is ingestion of cotton products like cottonseed oil or cottonseed meal that may contain tribufos residues. The U.S. Environmental Protection Agency (EPA) estimated acute and chronic dietary intakes (99.9th percentiles) of 0.050 and 0.003 µg/kg/day for the U.S. population (EPA 2006b). Inhalation exposure to tribufos is expected to be negligible for the general population with the exception of those persons who reside near treated cotton fields. Since tribufos is rarely detected in groundwater or drinking water, this is not considered an important exposure pathway for the general population. Tribufos was 1 of 30 chemicals monitored during the Fourth Unregulated Contaminant Monitoring Rule (UCMR) program,

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which is intended to collect nationally representative data for contaminants possibly present in drinking water, but that do not have regulatory standards. At a detection limit of 0.07 µg/L, tribufos was detected in only 2 out of 11,829 drinking water samples tested. Workers who apply tribufos to cotton fields or maintain and harvest cotton plants will receive higher levels of inhalation and dermal exposure than the general population. EPA (2006b) estimated the absorbed daily dose of workers during and following application to range from about 1 to 25 µg/kg/day depending upon job function.

1.2 SUMMARY OF HEALTH EFFECTS

Tribufos is an organophosphorus compound considered to be of moderate toxicity compared to other organophosphates. A principal effect of organophosphate toxicity is inhibition of acetylcholinesterase (AChE), which is a neurotransmitter. This inhibition may result in accumulation of AChE at receptors leading to a variety of neurological effects (see Section 2.15 for more detailed information on neurological effects). Tribufos has been shown to cause AChE inhibition in the brain of experimental animals. AChE is also expressed in red blood cells (RBCs). Tribufos has been shown to cause inhibition of brain AChE and RBC AChE in experimental animals. Substances that cause RBC AChE inhibition are considered to cause inhibition of AChE in the nervous system as well. ATSDR considers $\geq 20\%$ inhibition of neural or RBC AChE activity to represent an adverse effect. The degree of RBC AChE inhibition does not always correlate with the severity of acute signs of organophosphorus toxicity, especially with respect to chronic exposure scenarios.

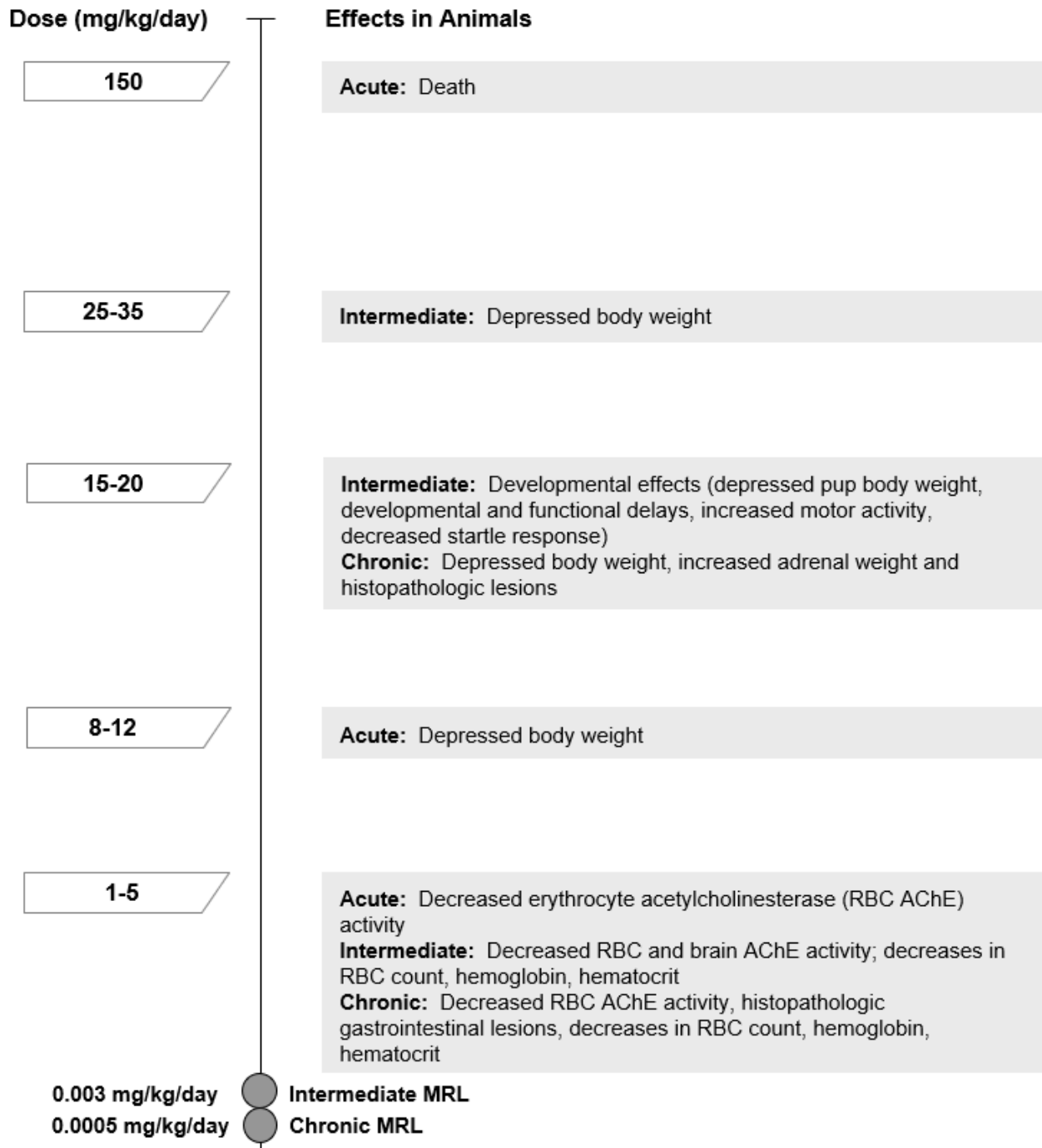
Limited human data are available regarding the toxicity of tribufos. Information on the toxicity of tribufos derives primarily from oral studies conducted in experimental animals. As illustrated in Figure 1-1, the most sensitive effects in animals following oral exposure to tribufos appear to be AChE inhibition, decreases in selected hematology parameters, and gastrointestinal lesions. Limited animal data suggest that AChE inhibition is the most sensitive effect of inhalation exposure.

Neurological Effects. Intermittent inhalation exposure of rats to tribufos aerosol at 59.5 mg/m³ for 13 weeks resulted in clinical signs of neurological effects (e.g., altered gait, decreased movement, constricted pupils, piloerection, aggressive behavior, sensitivity to touch, convulsions, salivation), decreased RBC and brain AChE activity, and depressed amplitude of a- and b-waves in electroretinographic tests (EPA 1992b). Single gavage dosing of experimental animals at 20–80 mg/kg or repeated oral dosing at 1–15 mg/kg/day resulted in decreased RBC and/or brain AChE activity (Astroff and Young 1998; CalEPA 2004; EPA 1990a, 1990b, 1990c, 1991b, 1992c, 1992d, 2012a, 2012b, 2012c, 2012d,

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2012e, 2012f). Collectively, results from acute-duration oral studies in rats indicate that neonates are more sensitive than adults to tribufos neurotoxicity as assessed by clinical signs such as incoordination, unsteadiness, and tremors (EPA 2012a, 2012b, 2012d, 2012e).

Figure 1-1. Health Effects Found in Animals Following Oral Exposure to Tribufos



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Hematological Effects. Dietary intake of tribufos by rats at estimated doses as low as 1.8–2.3 mg/kg/day, resulted in statistically significant decreases in RBC counts, hemoglobin, and hematocrit at 6 and 12 months (CalEPA 2004; EPA 1992d). Effects indicative of tribufos treatment-related anemia were observed in mice at estimated oral doses in the range of 48.02–63.04 mg/kg/day; the effects included decreases in mean RBC count, hemoglobin, and hematocrit (EPA 1990a).

Gastrointestinal Effects. Significantly increased incidences of vacuolar degeneration in the small intestine were noted in mice receiving tribufos from the diet at estimated doses of 8.28–11.14 mg/kg/day for up to 90 weeks (EPA 1990a). Histopathologic lesions at higher doses (48.02–63.04 mg/kg/day) included rectal lesions and edema in the caecum as well. The California Environmental Protection Agency (CalEPA) summarized results from an unpublished study in which rats receiving tribufos from the diet at estimated doses \geq 1.8–2.3 mg/kg/day for up to 2 years exhibited significantly increased incidences of vacuolar degeneration and hyperplasia in the small intestines (CalEPA 2004).

Cancer Effects. Tribufos was not carcinogenic to rats receiving tribufos from the diet for 2 years or beagle dogs exposed via the diet for 364 days. However, in a study of CD-1 mice receiving tribufos from the diet for up to 90 weeks, significantly increased incidences of small intestine adenocarcinoma and liver hemangiosarcoma were observed in males; females exhibited significantly increased incidence of alveolar/bronchiolar adenoma and nonsignificantly increased incidence of small intestine adenocarcinoma. It should be noted that small intestine adenocarcinoma is a rare tumor type in CD-1 mice. A Health Effects Division Carcinogenicity Peer Review Committee for EPA's Office of Pesticide Programs evaluated the weight-of-evidence regarding the carcinogenic potential of tribufos and concluded that tribufos should be considered unlikely to be carcinogenic at low doses, but likely to be carcinogenic at high doses. The EPA committee stated that human exposure to tribufos would not likely approach the dose level associated with tumors in the tribufos-treated mice. A Health Effects Division Carcinogenicity Peer Review Committee for EPA concluded that, according to EPA's 1996 proposed Guidelines for Carcinogen Risk Assessment, tribufos should be classified as *likely to be carcinogenic to humans*, based on findings of increased liver tumors in male mice, increased lung tumors in female mice, and increased small intestine tumors (rare tumors) in both sexes of mice from the 90-week study.

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of an intermediate-duration inhalation MRL for tribufos. As discussed in Appendix A, the inhalation database was not considered adequate for

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derivation of acute- or chronic-duration inhalation MRLs. As presented in Figure 1-2, the available inhalation data for tribufos suggest that the nervous system is a sensitive target of toxicity following inhalation exposure.

Figure 1-2. Summary of Sensitive Targets of Tribufos – Inhalation

The nervous system is the most sensitive target of tribufos inhalation exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.



The oral database was considered adequate for derivation of intermediate- and chronic-duration oral MRLs for tribufos. The oral database was not considered adequate for derivation of an acute-duration oral MRL. As presented in Figure 1-3, the nervous and hematological systems and gastrointestinal tract are the most sensitive targets of toxicity following oral exposure. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

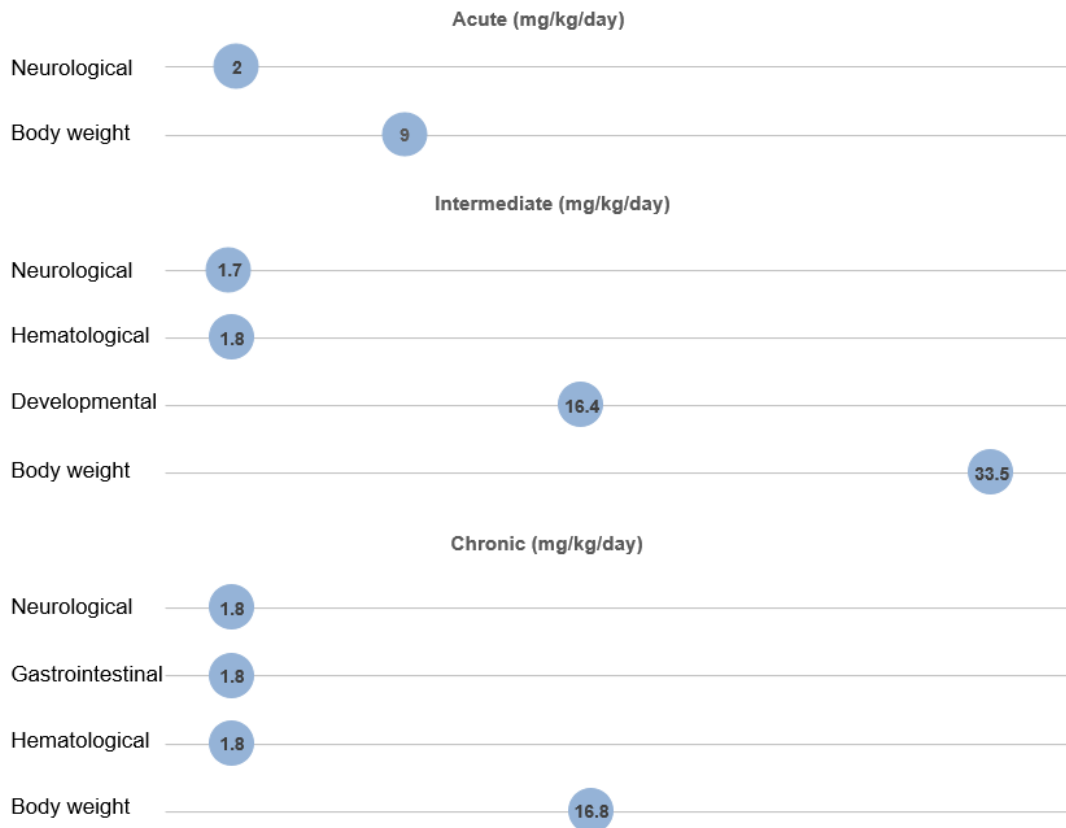
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Figure 1-3. Summary of Sensitive Targets of Tribufos – Oral

The nervous and hematological systems and gastrointestinal tract are the most sensitive targets of tribufos oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.

No data were available for humans.



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Table 1-1. Minimal Risk Levels (MRLs) for Tribufos^a

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (mg/m ³)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.04	Decreased RBC AChE activity	1.22 (NOAEL _{HEC})	30	EPA 1992b
Chronic					
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.003	Decreased RBC AChE activity	0.28 (NOAEL)	100	Astroff et al. 1998
Chronic	0.0005	Pathologic lesions in small intestines	0.05 (BMDL ₁₀)	100	CalEPA 2004

^aSee Appendix A for additional information.

AChE = acetylcholinesterase; BMDL₁₀ = 95% lower confidence limit on the BMD (subscript denotes benchmark response: i.e., ₁₀ = dose associated with 10% extra risk); HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level; RBC = red blood cell

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of tribufos. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤ 14 days), intermediate (15–364 days), and chronic (≥ 365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to tribufos, but may not be inclusive of the entire body of literature.

Animal inhalation studies are presented in Table 2-1 and Figure 2-2. Animal oral studies are presented in Table 2-2 and Figure 2-3. Animal dermal studies are presented in Table 2-3.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the

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Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of tribufos are indicated in Table 2-2 and Figure 2-3.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

As an organophosphorus compound, tribufos inhibits the action of acetylcholinesterase (AChE), resulting in muscarinic cholinergic effects (e.g., glandular secretions [salivation, lacrimation, rhinitis], miosis, bronchoconstriction, vasodilation, hypotension, diarrhea, nausea, vomiting, urinary incontinence, and bradycardia) and nicotinic cholinergic effects (e.g., tachycardia, mydriasis, fasciculations, cramping, twitching, muscle weakness, and muscle paralysis). Central nervous system toxicity includes respiratory depression, anxiety, insomnia, headache, apathy, drowsiness, dizziness, loss of concentration, confusion, tremors, convulsions, and coma. These effects usually occur within a few minutes to 24 hours after dosing.

In addition to its presence and function in central and peripheral nervous tissue, AChE is also expressed in RBCs (Silman and Sussman 2005). According to Chou and Williams-Johnson (1998), a 20–59% inhibition of neural or RBC AChE (i.e., 20–59% decrease in AChE activity) may be considered a less serious effect in the absence of more serious indicators of neurotoxicity. A $\geq 60\%$ inhibition of neural or RBC AChE is considered a serious effect in the presence or absence of additional signs of neurotoxicity. However, the degree of RBC AChE inhibition does not always correlate with the severity of acute signs of organophosphorus toxicity, especially with respect to chronic exposure scenarios.

The health effects of tribufos have been evaluated mainly in unpublished animal studies. As illustrated in Figure 2-1, the oral exposure route was employed in the majority of animal studies. The most examined endpoints in animal studies were body weight (68% of the animal studies) and neurotoxicity (72% of the animal studies).

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Animal studies suggest that the nervous system is the most sensitive target of tribufos toxicity. Other relatively sensitive targets following oral exposure include the blood and gastrointestinal tract.

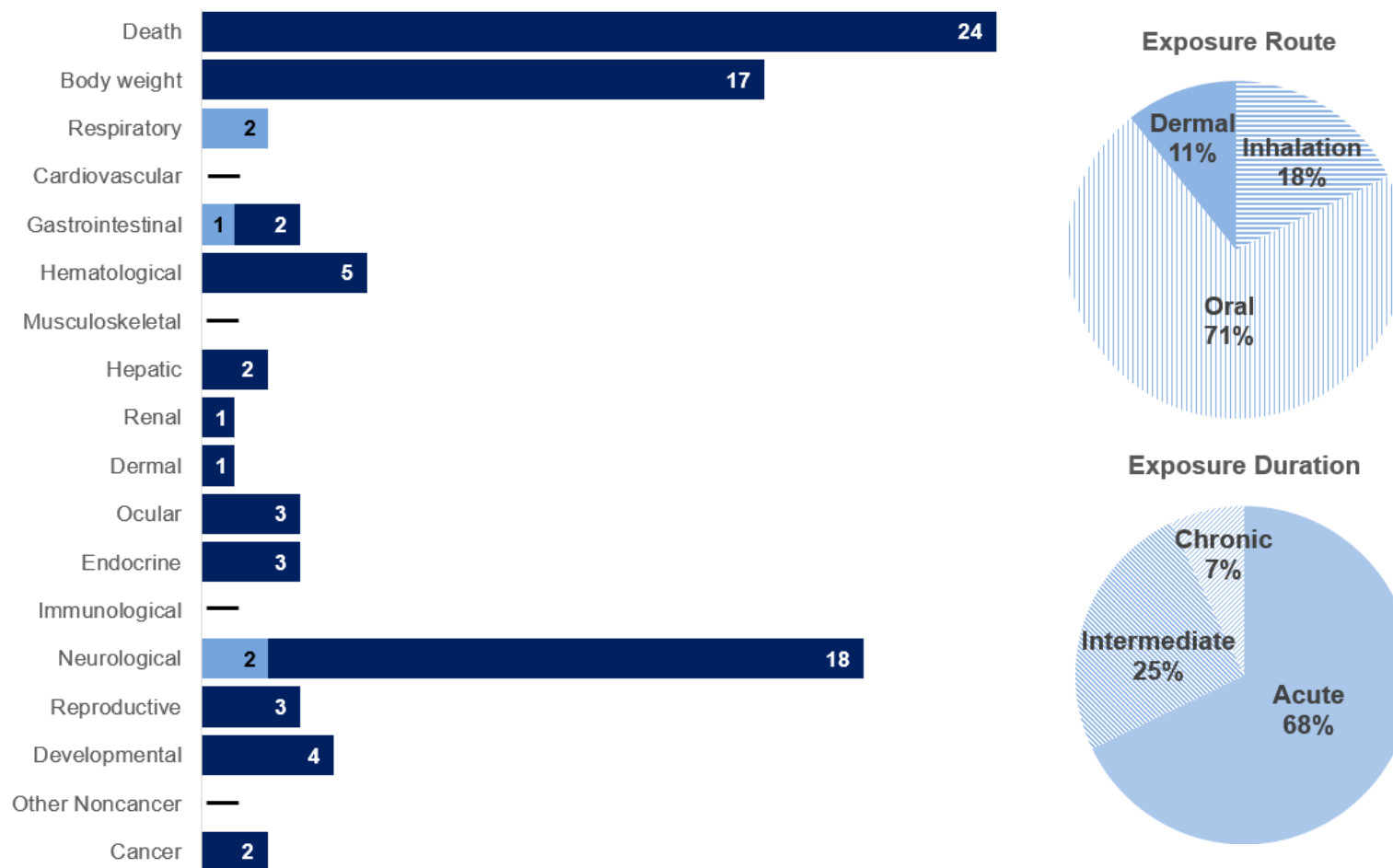
- **Neurological effects.** Inhalation exposure of experimental animals to tribufos aerosol has been associated with clinical signs of neurological effects (e.g., altered gait, decreased movement, constricted pupils, piloerection, aggressive behavior, sensitivity to touch, convulsions, salivation), decreased RBC and brain AChE activity, and depressed amplitude of a- and b-waves in electroretinographic tests. Decreased RBC and/or brain AChE activity has been associated with oral exposure as well.
- **Hematological effects.** Decreases in RBC counts, hemoglobin, and hematocrit have been observed following oral exposure of experimental animals to tribufos.
- **Gastrointestinal effects.** Histopathologic gastrointestinal tract lesions have been associated with oral exposure of experimental animals to tribufos.

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Figure 2-1. Overview of the Number of Studies Examining Tribufos Health Effects

Most studies examined the potential body weight and neurological effects of tribufos

Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 28 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

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Table 2-1. Levels of Significant Exposure to Tribufos – Inhalation

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/m ³)	Parameters monitored	Endpoint	NOAEL (mg/m ³)	Less serious LOAEL (mg/m ³)	Serious LOAEL (mg/m ³)	Effects
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 6 M, 6 F	One 4-hour exposure (nose-only)	M: 0, 2,920, 5,690, 6,030 F: 0, 1,590, 2,920, 3,190	BW, CS, GN, LE	Death			4,650 M 2,460 F	4-hour LC ₅₀
EPA 1991a, 1992a									
INTERMEDIATE EXPOSURE									
2	Rat (Wistar) 10 M, 10 F	13 weeks 5 days/week 6 hours/day (head-only)	0, 0.93, 2.43, 12.2, 59.5	BH, BW, CS, EA, GN, HE, HP, LE, OP, OW, UR	Bd wt Hemato Hepatic Renal Ocular Endocr Neuro	59.5 59.5 59.5 59.5 59.5 12.2 M 59.5 F 2.43 ^b	59.5 M		Increased adrenal weight and cortical fat deposition Up to 65% decreased RBC AChE activity
EPA 1992b									

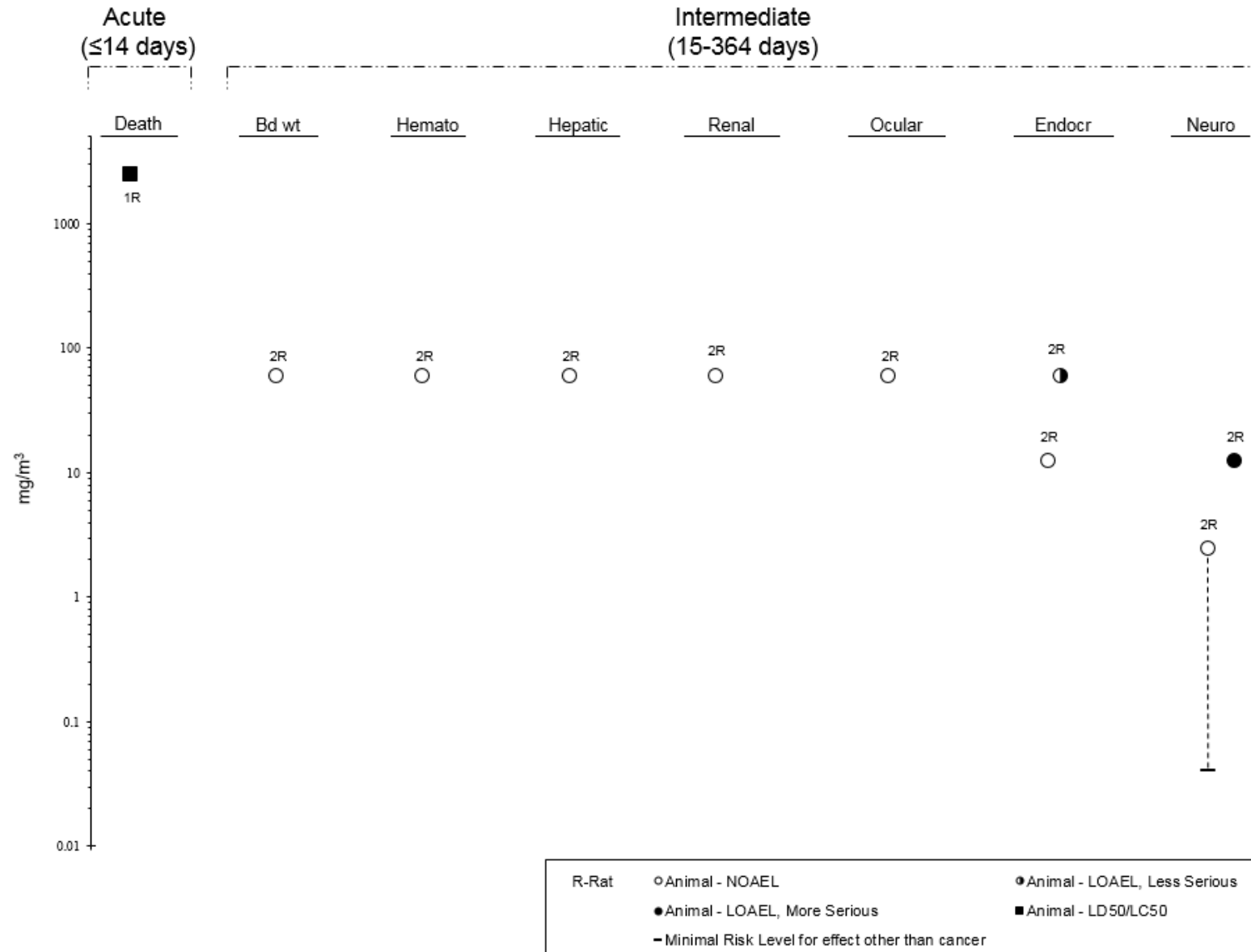
^aThe number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

^bUsed to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.04 mg/m³; based on a NOAEL of 2.43 mg/m³, adjustment for intermittent exposure, conversion to a human equivalent concentration, and a total uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

AChE = acetyl cholinesterase; Bd wt or BW = body weight; BH = behavioral; CS = clinical signs; EA = enzyme activity; Endocr = endocrine; F = female(s); GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; LC₅₀ = lethal concentration, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; OP = ophthalmology; OW = organ weight; RBC = red blood cell; UR = urinalysis

2. HEALTH EFFECTS

Figure 2-2. Levels of Significant Exposure to Tribufos – Inhalation



2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Tribufos – Oral

[illegible]

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Tribufos – Oral

[illegible]

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Tribufos – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
9	Rat (Sprague-Dawley; 11-day-old pups) 8 M, 8 F	11 days 1 time/day (GO)	0, 0.1, 1, 5	BW, CS, EA, GN, LE, OW	Neuro	1		5	66–69% decreased RBC AChE activity
EPA 2012e									
10	Rat (Sprague-Dawley; young adults) 8 F	11 days 1 time/day (GO)	0, 0.1, 1, 5	BW, CS, EA, GN, LE, OW	Neuro	1		5	64% decreased RBC AChE activity at 24 hours postdosing
EPA 2012e									
11	Rat (Sprague-Dawley) 10 F	GDs 6–19 1 time/day (GO)	0, 0.3-0.8, 7, 28	BW, CS, DX, EA, FI, GN, LE	Bd wt	7		28	27% depressed mean maternal body weight gain
					Neuro	0.3		7	75% decreased maternal RBC AChE activity
					Develop	7	28		6% lower mean fetal body weight in male fetuses; concomitant 27% depressed mean body weight gain in dams
EPA 2012f									
12	Rat (Sherman); unspecified numbers/sex/group	Once (GO)	NS	LE	Death			233 M 150 F	LD ₅₀
Gaines 1969									

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Tribufos – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
13	Rabbit (American Dutch) 17 F	GDs 7–19 1 time/day (G)	0, 1, 3, 9	BW, CS, DX, EA, FI, FX, GN, LE, MX, OW, TG	Bd wt	3	9		No maternal body weight gain versus 5% body weight gain among controls
					Neuro			1	70% decreased maternal RBC AChE activity on GD 20
					Repro	9			
					Develop	9			

EPA 1990c**INTERMEDIATE EXPOSURE**

14	Rat (Sprague-Dawley) 30 M, 30 F per generation	2 generations (F) 10 weeks pre-mating, mating up to 28 days, 3 weeks of gestation, 3 weeks of lactation	M: 0, 0.28, 2.0–2.9, 17.6–20.63 F: 0, 0.27–0.81, 2.03–6.77, 18.07–49.61	BW, CS, DX, EA, FI, FX, GN, HP, LE, MX, TG	Bd wt	17.6 M 18.07 F			No effect at highest dietary level; calculated dose ranges for F0 and F1 parental rats; include separately-calculated doses to females for pre-mating, gestation, and lactation phases
					Neuro	0.28 ^b M 0.31 F	2 M 2.25 F		RBC AChE activity decreased by 35 and 37% in F0 males and females, respectively, in pre-mating phase
					Repro	17.6 M 18.07 F			Lowest dose in a particular range considered a NOAEL

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Tribufos – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Develop	2.0 M 2.03 F		17.6 M 18.07 F	Decreases in number of live pups born, litter size, pup viability, lactational pup body weights, number of live pups on LD 21; NOAEL, serious LOAEL values represented by lowest dose in range for F0 and F1 parental exposure
Astroff et al. 1998; EPA 1992c									
15	Rat (Fischer 344) 50 M, 50 F	Up to 2 years (F)	M: 0, 0.2, 1.8, 16.8 F: 0, 0.2, 2.3, 21.1	BC, BW, CS, EA, FI, GN, HE, HP, LE, OP, OW	Hemato	0.2 M 0.2 F	1.8 M 2.3 F		Decreases in RBC count, hemoglobin, and hematocrit in mid- and high-dose groups at 3- and 6-month evaluations
CalEPA 2004; EPA 1992d									
16	Rat (Wistar) 30 F	42 days GD 0–LD 21 (F)	Gestation: 0, 0.4, 3.4–3.5, 16.4–18.2 Lactation: 0, 0.6–1.0, 6.1–9.9, 33.5–55.4	BW, CS, DX, EA, FI, OF, OW	Bd wt	6.1	33.5		8–12% lower mean maternal body weight during lactation
					Neuro	0.4		3.4	76% decreased RBC AChE activity (lowest dose in range for gestation listed as serious LOAEL)
					Repro	16.4			Lowest dose in range for gestation considered a NOAEL

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Tribufos – Oral

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2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Tribufos – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
18	Mouse (CD-1) 15 M, 15 F	8 weeks (F)	M: 0, 3.4, 9.4, 40, 140 F: 0, 5.6, 14.3, 54, 132	BW, CS, EA, FI, LE	Bd wt	140 M 132 F			
					Neuro	3.4 M 5.6 F	9.4 M 14.3 F		37 and 44% decreased RBC AChE activity (males and females, respectively)
CalEPA 2004									
19	Dog (beagle) 4 M, 4 F	364 days (F)	M: 0, 0.1, 0.4, 1.7 F: 0, 0.1, 0.4, 2.0	BC, BW, CS, EA, FI, HE, OP, UR	Bd wt	1.7 M 2.0 F			
					Ocular	1.7 M 2.0 F			
					Neuro	0.4 M 0.4 F	1.7 M 2.0 F		At treatment day 91, RBC AChE activity decreased by 24 and 29% in males and females, respectively
CalEPA 2004; EPA 1991b									
CHRONIC EXPOSURE									
20	Rat (Fischer 344) 50 M, 50 F	2 years (F)	M: 0, 0.2, 1.8, 16.8 F: 0, 0.2, 2.3, 21.1	BC, BW, CS, EA, FI, GN, HE, HP, LE, OP, OW	Bd wt	1.8 M 2.3 F	16.8 M 21.1 F		15% depressed mean body weight gain
					Gastro	0.2 M ^c 0.2 F	1.8 M 2.3 F		Vacuolar degeneration and hyperplasia in small intestines
					Hemato	0.2 M 0.2 F	1.8 M 2.3 F		Decreases in RBC count, hemoglobin, and hematocrit at 12 months (some values returned to normal by 18 and 24 months)

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Tribufos – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
CalEPA 2004; EPA 1992d									
21	Mouse (CD-1) 50 M, 50 F	90 weeks (F)	M: 0, 1.5, 8.4, 48.1 F: 0, 2.0, 11.3, 63.1	BW, CS, EA, FI, GN, HE, HP, LE, OW	Endocr	1.8 M 2.3 F	16.8 M 21.1 F		Enlarged adrenals, increased adrenal weight, vacuolar degeneration
					Neuro	0.2 M 0.2 F	1.8 M 2.3 F		27–28% decreased RBC AChE activity
					Death			48.1 M 63.1 F	M: 28% decreased survival F: 24% decreased survival
					Bd wt	48.1 M 63.1 F			
					Gastro	1.5 M 2.0 F	8.4 M 11.3 F		Vacuolar degeneration in small intestine
					Hemato	1.5 M 11.3 F	8.4 M 63.1 F		Splenic extramedullary hematopoiesis
					Hepatic	48.1 M 11.3 F	63.1 F		Hepatocellular hypertrophy
					Endocr	8.4 M 11.3 F	48.1 M 63.1 F		Degeneration and pigmentation in adrenals
					Neuro	1.5 M 2.0 F	8.4 M 11.3 F		42 and 37% decreased RBC AChE activity in males and females, respectively

2. HEALTH EFFECTS

Table 2-2. Levels of Significant Exposure to Tribufos – Oral

Figure key ^a	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Cancer			48.1 M 63.1 F	CEL M: small intestine adenocarcinoma, hemangiosarcoma. CEL F: alveolar/bronchiolar adenoma

CalEPA 2004; EPA 1990a

^aThe number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

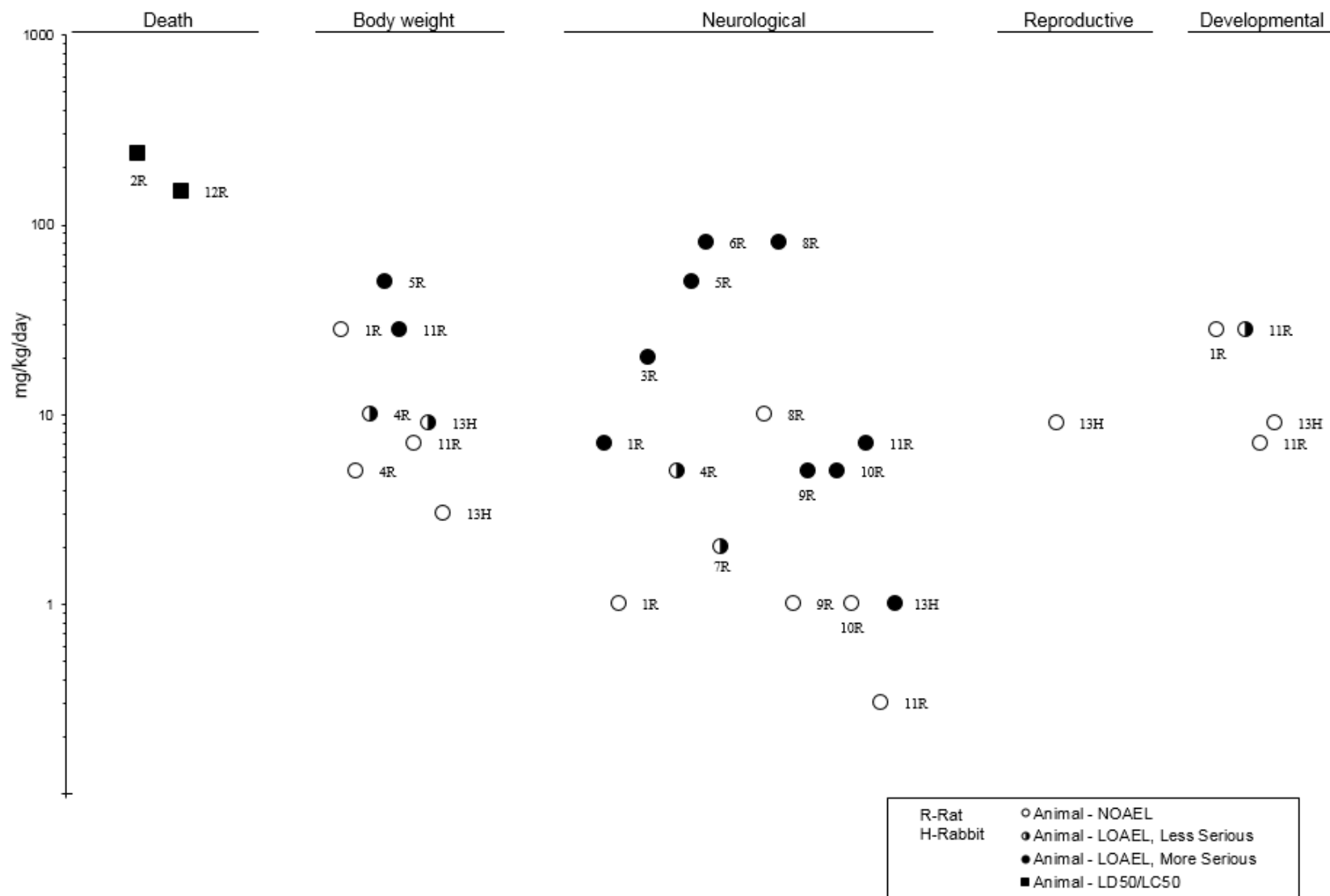
^bUsed to derive an intermediate-duration oral MRL of 0.003 mg/kg/day based on tribufos-induced decreased RBC AChE activity. The NOAEL of 0.28 mg/kg/day was divided a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). Refer to Appendix A for more detailed information regarding derivation of the intermediate-duration oral MRL for tribufos.

^cStudy result used to derive a chronic-duration oral MRL of 0.0005 mg/kg/day based on tribufos-induced vacuolar degeneration in the small intestine. Benchmark dose analysis of incidence data for vacuolar degeneration resulted in a point of departure (BMDL₁₀) of 0.05 mg/kg/day; a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied. Refer to Appendix A for more detailed information regarding derivation of the chronic-duration oral MRL for tribufos.

AChE = acetylcholinesterase; BC = serum (blood) chemistry; Bd wt or BW = body weight; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EA = enzyme activity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; FX = fetal toxicity; (G) = gavage; (GO) = gavage in oil; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD = lactation day(s); LD₅₀ = dose estimated to cause death in 50% of treated animals; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; MX = maternal toxicity; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OP = ophthalmology; OW = organ weight; PFC = plaque-forming cell; PND = postnatal day(s); Repro = reproductive; RBC = red blood cell; TG = teratogenicity; UR = urinalysis; WI = water intake

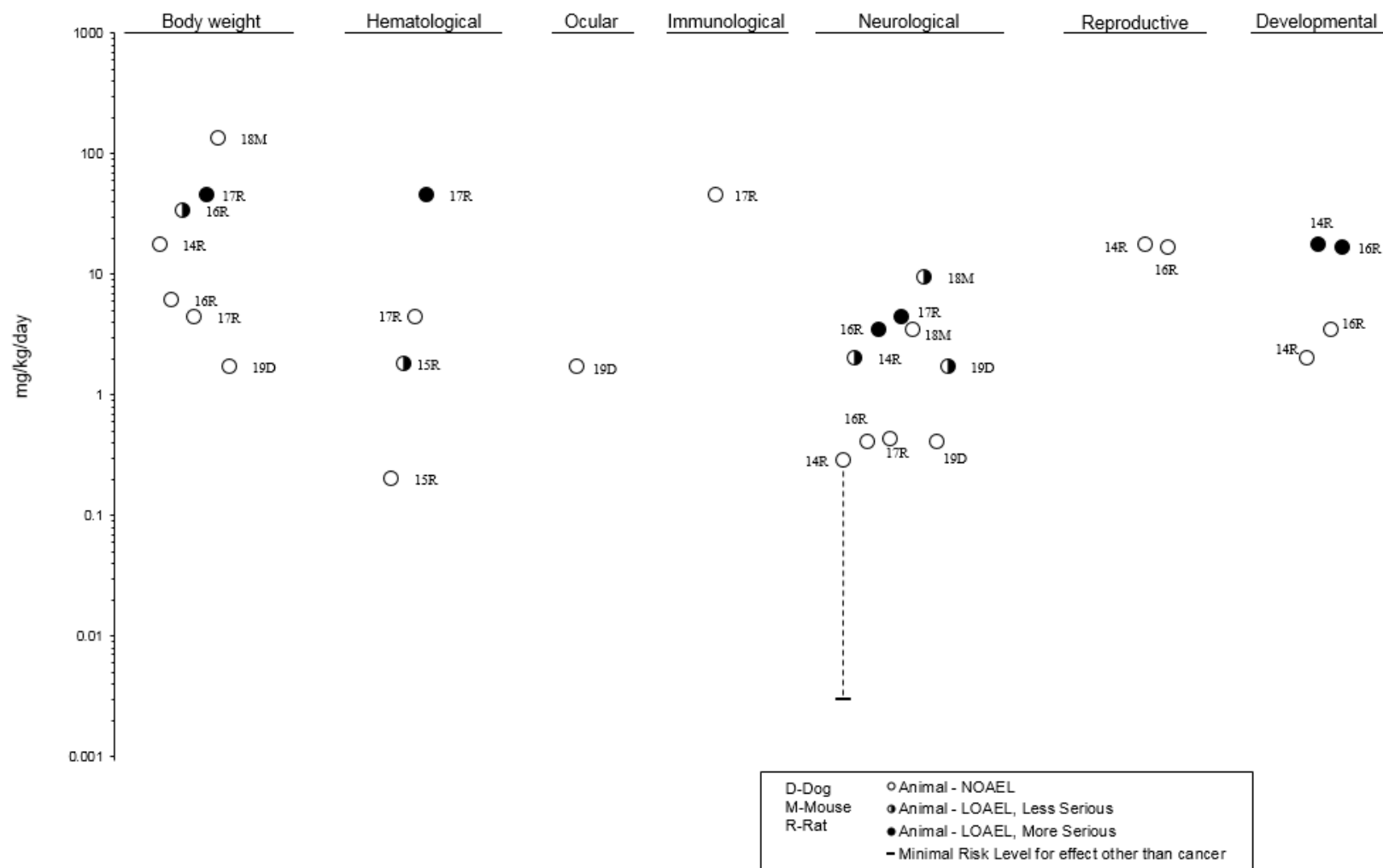
2. HEALTH EFFECTS

Figure 2-3. Levels of Significant Exposure to Tribufos – Oral
Acute (≤ 14 days)



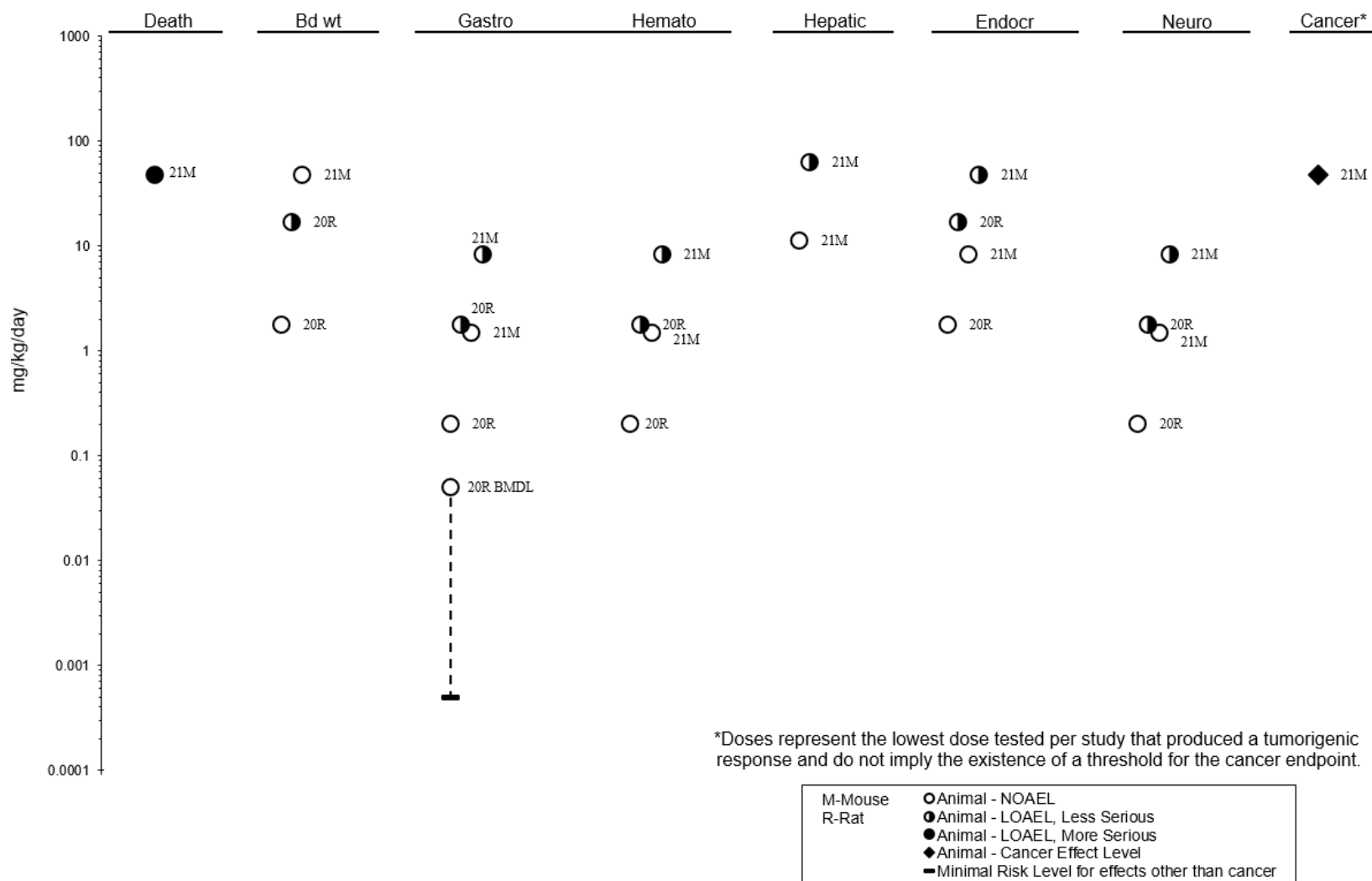
2. HEALTH EFFECTS

Figure 2-3. Levels of Significant Exposure to Tribufos – Oral
Intermediate (15-364 days)



2. HEALTH EFFECTS

Figure 2-3. Levels of Significant Exposure to Tribufos – Oral
Chronic (≥ 365 days)



2. HEALTH EFFECTS

Table 2-3. Levels of Significant Exposure to Tribufos – Dermal

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE								
Rat (Sherman) NS	Once for unspecified duration	NS	LE	Death			360 M 168 F	LD ₅₀
Gaines 1969								
Rabbit (NS) 5/sex	One 24-hour exposure	500, 1,000, 2,000	BW, CS, GN, LE	Death			1,093	LD ₅₀ for combined sexes
EPA 1993b								
INTERMEDIATE EXPOSURE								
Rabbit (New Zealand) 5 M, 5 F	21 days 5 days/week 6 hours/day	0, 2, 11, 29	BC, BW, CS, EA, FI, GN, HE, LE, OP, OW	Death Bd wt Hemato Dermal Ocular Neuro	 29 29 2 29 2 M	 11 2 F	29 11	1/5 males and 4/5 females died or were sacrificed <i>in extremis</i> Mild to moderate application site irritation 20% decreased RBC AChE activity 11 mg/kg/day: 70% decreased RBC AChE activity, muscle fasciculations
EPA 1993d								

AChE = acetyl cholinesterase; BC = biochemistry; Bd wt or BW = body weight; CS = clinical signs; EA = enzyme activity; F = female(s); FI = food intake; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; LD₅₀ = lethal concentration, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OP = ophthalmology; OW = organ weight; RBC = red blood cell

2. HEALTH EFFECTS

2.2 DEATH

No information was located regarding death in humans exposed to tribufos.

Limited information is publicly available regarding lethality in rats exposed to tribufos by inhalation. Calculated 4-hour LC₅₀ values (exposure concentration associated with 50% mortality) were 4,650 and 2,460 mg/m³ for male and female rats, respectively (EPA 1991a, 1992a).

Single-dose gavage treatment of rats with tribufos resulted in oral LD₅₀ values in the range of 150–435 mg/kg/day (EPA 1993a; Gaines 1969); females were more sensitive than males. Decreased survival was observed among male and female mice administered tribufos in the diet for up to 90 weeks at concentrations resulting in estimated tribufos doses of 48.1 and 63.1 mg/kg/day, respectively (EPA 1990a).

An acute LD₅₀ value of 1,093 mg/kg was reported for male and female rabbits (combined sexes) administered tribufos by single 24-hour occluded dermal application and observed for up to 14 days postadministration (EPA 1993b). Gaines (1969) reported respective acute dermal LD₅₀ values of 360 and 168 mg/kg for male and female Sherman rats administered tribufos dermally at unspecified dose levels for an unspecified exposure duration and observed for up to 14 days postdosing. The lowest lethal doses to the males and females were 200 and 100 mg/kg, respectively. In a study of young adult New Zealand white rabbits receiving repeated 6-hour occluded dermal application of tribufos, 1/5 males and 4/5 females dosed at 29 mg/kg/day died or were sacrificed *in extremis* between days 12 and 19 (EPA 1993d). Most of the rabbits dosed at 29 mg/kg/day exhibited clinical signs of muscular fasciculations, tremors, and decreased movement.

2.3 BODY WEIGHT

No information was located regarding body weight in humans exposed to tribufos.

Available information regarding body weight effects in experimental animals following inhalation exposure is limited to results from a single study in which intermittent, head-only exposure of Wistar rats to tribufos aerosol at up to 59.5 mg/m³ resulted in no apparent body weight effects (EPA 1992b).

2. HEALTH EFFECTS

Effects on body weight in experimental animals have been reported following acute-, intermediate-, and chronic-duration oral exposure to tribufos. Depressed body weight (12–27% less than controls) was noted among rats repeatedly exposed by gavage or receiving tribufos from the diet at doses in the range of 10–33.5 mg/kg/day (CalEPA 2004; EPA 1992d, 2005a, 2012a, 1012f). Pregnant rabbits dosed at 9 mg/kg/day during gestation days (GDs) 7–19 exhibited no body weight gain (EPA 1990c). Dietary treatment of female Han Wistar rats for 4 weeks at an estimated dose of 44.62 mg/kg/day resulted in 41% depressed mean body weight gain (EPA 2013).

Body weight was not affected by repeated dermal exposure of New Zealand rabbits to tribufos at 29 mg/kg/day (EPA 1993d).

2.4 RESPIRATORY

Limited information was located regarding the potential for tribufos-induced respiratory effects in humans. One study compared self-reported symptoms among 232 residents of three towns in cotton-growing areas during the 1987 cotton defoliation season (exposed group) with self-reported symptoms among 175 residents of non-cotton-growing agricultural communities (unexposed group) (Scarborough et al. 1989). Tribufos was one of the defoliant used at the time of the study. The exposed group was subdivided into a group with high likelihood of exposure (n=142) and a group with low likelihood of exposure (n=92) based on respondents' reports of whether or not nearby fields had been sprayed. The presence of tribufos in air was confirmed using monitoring data for tribufos collected near the centers of the three towns by the California Air Resources Board during the study period. Using the unexposed group as reference, a relative risk (RR) of 1.7 (95% CI 1.1, 2.5) was reported for cough among the group with low probability of exposure; a RR of 1.6 (95% CI 1.1, 2.3) for throat irritation was reported for the group with high probability of exposure. Limitations of the study include small numbers of subjects, self-reporting of symptoms, lack of quantitative tribufos exposure data, and lack of consideration of other airborne substances, including other defoliant and desiccant products used to defoliate cotton.

A subsequent study evaluated possible associations between cotton defoliation and respiratory cause mortality in communities surrounding cotton fields during and immediately following cotton defoliation (Ames and Gregson 1995). The study included cotton defoliation periods during the years 1970–1990. Mortality data for “all respiratory causes” of death and “all natural causes” were collected from the California Department of Health Services; the mortality data were divided into two groups: respiratory mortality in the San Joaquin Valley cotton-growing areas and respiratory mortality in the rest of the state.

2. HEALTH EFFECTS

The proportions of respiratory-caused mortality (number of deaths due to respiratory causes during the cotton defoliation period of each year divided by the respiratory deaths during the rest of that year in cotton-growing areas divided by a similar proportion of respiratory cause mortality in non-cotton-growing areas) ranged from 0.798 to 1.153 and exhibited a statistically significant ($p < 0.05$) pattern of increases for 15 of the 21 years. However, the pattern of increases was not explained by amounts of defoliant (tribufos and folex) used. Limitations of this study include lack of quantitative tribufos exposure data and lack of accounting for other possible airborne contaminants, including unrelated particulates that may have been at increased levels during harvest seasons.

Nose-only exposure of Sprague-Dawley rats to tribufos aerosol for 4 hours resulted in respiratory effects that included clinical signs and gross pathology (dyspnea, nasal discharge, discolored lungs and nasal bones); however, publicly-available summaries of the unpublished study did not specify exposure concentration(s) causing these effects (EPA 1991a, 1992a). Unspecified changes in respiration were reported among Wistar rats repeatedly exposed (head-only) to tribufos aerosol at 59.5 mg/m³ for 13 weeks (EPA 1992b). Minor changes in histology of nasal and paranasal cavities and lungs were attributed to vehicle (polyethylene glycol 400) rather than tribufos.

No information was located regarding respiratory effects in experimental animals following oral or dermal exposure to tribufos.

2.5 CARDIOVASCULAR

No information was located regarding cardiovascular effects in humans or experimental animals following inhalation, oral, or dermal exposure to tribufos.

2.6 GASTROINTESTINAL

Human data are limited to results from the study described in Section 2.4 (Respiratory Effects). The study results include RRs of 1.9 (95% CI 1.1, 3.2) for nausea and 2.0 (95% CI 1.1, 3.6) for diarrhea within a group (n=142) with high probability for exposure to tribufos during the 1987 cotton defoliation season (Scarborough et al. 1989). As noted earlier, limitations of the study include small numbers of subjects, self-reporting of symptoms, lack of quantitative tribufos exposure data, and lack of consideration of other airborne substances, including other defoliant and desiccant products used to defoliate cotton.

2. HEALTH EFFECTS

In a study of male and female CD-1 mice receiving tribufos from the diet for up to 90 weeks, significantly increased incidences of vacuolar degeneration in the small intestine were noted in males at 8.28 mg/kg/day (8/50 versus 0/50 controls) and females at 11.14 mg/kg/day (11/50 versus 0/50 controls) (EPA 1990a). Histopathologic lesions at a higher dose level (48.02 and 63.04 mg/kg/day for males and females, respectively) included vacuolar degeneration, dilation/distension, and mucosal hyperplasia of the small intestine; rectal lesions (inflammation, ulceration, and necrosis in males; ulceration in females); and edema in the caecum (females). CalEPA (2004) summarized results from an unpublished study in which Fischer 344 rats were administered tribufos in the diet at 0, 4, 40, or 320 ppm for up to 2 years; estimated tribufos doses were 0, 0.2, 1.8, and 16.8 mg/kg/day, respectively, for the males and 0.2, 2.3, and 21.1 mg/kg/day, respectively, for the females. Incidences of vacuolar degeneration of the small intestines for the 0, 4, 40, and 320 ppm groups were 0/20, 0/10, 7/10, and 18/20, respectively, for the males and 0/20, 0/10, 8/10 and 16/20, respectively, for the females at 12-month interim sacrifice and 0/50, 1/50, 24/50, and 37/50, respectively, for the males and 0/50, 0/50, 19/50, and 35/50, respectively, for the females at 24-month terminal sacrifice. In addition, CalEPA (2004) reported incidences of hyperplasia in the small intestines (0/50, 3/50, 23/50, and 34/50, respectively, for the males and 1/50, 0/50, 11/50, and 30/50, respectively, for the females) at 24-month terminal sacrifice.

No information was located regarding gastrointestinal effects in experimental animals following inhalation or dermal exposure to tribufos.

2.7 HEMATOLOGICAL

No information was located regarding hematological effects in humans exposed to tribufos.

There was no evidence of hematological effects in Wistar rats following intermittent head-only exposure to tribufos aerosol at up to 59.5 mg/m³ for 13 weeks (EPA 1992b). Dietary exposure of Fischer 344 rats to tribufos at estimated doses ≥ 1.8 resulted in statistically significant decreases in RBC counts, hemoglobin, and hematocrit, but some of these values had returned to normal by 18 and 24 months (CalEPA 2004; EPA 1992d). At terminal sacrifice, significant increases in RBC count and hematocrit were noted in high-dose (16.8 mg/kg/day) males and significant increases in hemoglobin and hematocrit were observed in high-dose (21.1 mg/kg/day) females, indicating the possible involvement of some compensatory mechanism. In a 90-week dietary study of mice, significant decreases in RBC count, hemoglobin, and hematocrit (indicative of treatment-related anemia) were observed at estimated tribufos doses of 48.02 and 63.04 mg/kg/day for males and females, respectively (EPA 1990a). Available

2. HEALTH EFFECTS

secondary source summaries (CalEPA 2004; EPA 1990a, 1992d) of these unpublished studies did not include quantitative data regarding the magnitude of hematological changes; therefore, it is impossible to judge the seriousness of the changes.

In a 21-day repeated-dose dermal study, young adult New Zealand rabbits repeatedly exposed by occluded application at up to 29 mg/kg/day exhibited no signs of tribufos-induced effects on RBCs, white blood cells (WBCs), platelets, hemoglobin, or hematocrit (EPA 1993d).

2.8 MUSCULOSKELETAL

No information was located regarding musculoskeletal effects in humans or experimental animals following exposure to tribufos.

2.9 HEPATIC

No information was located regarding hepatic effects in humans exposed to tribufos.

There was no evidence of hepatotoxicity (serum liver enzymes, histopathology results) following intermittent head-only exposure of Wistar rats to tribufos aerosol at up to 59.5 mg/m³ for 13 weeks (EPA 1992b). Significantly increased incidence of hepatocellular hypertrophy (6/50, severity 1.8 out of 5.0; versus 0/50 controls) was reported for female CD-1 mice receiving tribufos from the diet for up to 90 weeks at an estimated dose of 63.04 mg/kg/day (EPA 1990a). The toxicological significance of this finding is questionable in the absence of other indicators of tribufos-induced hepatotoxicity. No information was located regarding hepatic effects in experimental animals following dermal exposure to tribufos.

2.10 RENAL

No information was located regarding renal effects in humans exposed to tribufos.

Available information in experimental animals is limited to results from a single study. There was no evidence of renal toxicity (based on results of urinalysis and histopathological evaluations) following intermittent head-only exposure of Wistar rats to tribufos aerosol at up to 59.5 mg/m³ for 13 weeks (EPA 1992b).

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2.11 DERMAL

No information was located regarding dermal effects in humans exposed to tribufos.

Available information in experimental animals is restricted to a report of mild to moderate contact-site dermal irritation in both sexes of young adult New Zealand rabbits receiving repeated occluded dermal applications of tribufos for up to 3 weeks at dose levels ≥ 11 mg/kg/day (EPA 1993d).

2.12 OCULAR

No information was located regarding ocular effects in humans exposed to tribufos.

Exophthalmos (abnormal protrusion of the eyeballs) was observed in Wistar rats intermittently exposed to tribufos aerosol at up to 59.5 mg/m^3 for 13 weeks (EPA 1992b). There was no other evidence of ocular effects, as judged by ophthalmologic examinations. This effect was considered a result of direct ocular contact with airborne tribufos aerosol.

No signs of treatment-related ocular effects were observed during ophthalmological examinations of beagle dogs receiving tribufos from the diet for 364 days at estimated doses of 1.7–2.0 mg/kg/day (EPA 1991b). In a 2-year study of Fischer 344 rats, treatment-related ocular effects (cataracts, corneal opacity, corneal neovascularization, iritis, and/or uveitis) were observed in males and females receiving tribufos from the diet at estimated doses of 16.8–21.1 mg/kg/day (CalEPA 2004; EPA 1992d). According to the available secondary sources of information for the unpublished study, the study pathologist considered these effects to have been secondary to retinal atrophy (a neurological effect).

No signs of treatment-related adverse ocular effects were observed during ophthalmologic examinations performed on young adult New Zealand rabbits following repeated occluded dermal applications of tribufos for up to 3 weeks at dose levels as high as 29 mg/kg/day (EPA 1993d). There was no indication of treatment-related ocular irritation among male rabbits during 3–6 days of observation following instillation of 0.1 mL of tribufos into the conjunctival sac of one eye (EPA 1993c).

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2.13 ENDOCRINE

No information was located regarding endocrine effects in humans exposed to tribufos.

Increased adrenal weight and increased incidence of cortical fat deposit in adrenals were observed in male (but not female) Wistar rats following intermittent head-only exposure to tribufos aerosol at 59.5 mg/m³ for 13 weeks (EPA 1992b). Significantly increased incidences of degeneration/pigmentation in the adrenal glands (males: 39/50 versus 17/50 controls; females: 38/49 versus 18/50 controls) were reported in a study of CD-1 mice receiving tribufos from the diet for up to 90 weeks at estimated doses of 48.02 mg/kg/day (males) and 63.04 mg/kg/day (females) (EPA 1990a). CalEPA (2004) summarized results from an unpublished study in which Fischer 344 rats were administered tribufos in the diet at up to 320 ppm for up to 2 years; significantly increased incidences of vacuolar degeneration in adrenal glands were reported in the high-dose groups at 12-month interim sacrifice (estimated doses of 16.8 and 21.1 mg/kg/day to the males and females, respectively). No information was located regarding endocrine effects in experimental animals following dermal exposure to tribufos.

2.14 IMMUNOLOGICAL

No information was located regarding immunological effects in humans exposed to tribufos.

Available information in experimental animals is restricted to results from a single study in which female Han Wistar rats received tribufos from the diet for 4 weeks at estimated doses up to 44.62 mg/kg/day and intravenous injection of sheep red blood cells (SRBC) 4 days prior to terminal sacrifice to evaluate production of anti-SRBC IgM (plaque-forming cell [PFC] assay) (EPA 2013). There was no significant tribufos-induced effect on numbers of PFCs/spleen or the PFC response to SRBCs.

2.15 NEUROLOGICAL

Human data are limited. Evaluation of the results from the study described in Section 2.4 (Respiratory Effects) yielded a RR of 1.7 (95% CI 1.3, 2.4) for fatigue for a group (n=142) with high probability for exposure to tribufos during the 1987 cotton defoliation season (Scarborough et al. 1989). As noted earlier, limitations of the study include small numbers of subjects, self-reporting of symptoms, lack of quantitative tribufos exposure data, and lack of consideration of other airborne substances, including other defoliant and desiccant products used to defoliate cotton.

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Lotti et al. (1983) reported a 50% decrease in the enzyme, neuropathy target esterase (NTE), in lymphocytes from seven workers repeatedly exposed (during 9–34 days) to tribufos and folex during mixing and/or aerial and ground application of the compounds during one season of cotton defoliation. NTE is the target enzyme in organophosphate-induced delayed neuropathy (OPIDN). Exposure was assessed by sampling air in the breathing zone; collection of material deposited on cloth patches attached to thighs, chest, upper arms, and neck; and collection of material rinsed from hands. The results implicated dermal deposition as the major route of exposure. There were no signs of exposure-related effects on peripheral nerve function or neuromuscular transmission, and no exposure-related effects on RBC AChE activity. Furthermore, there were no signs of OPIDN among the workers evaluated 3 weeks following cessation of tribufos and folex use.

Clinical signs of tribufos-induced neurotoxicity (e.g., abnormal posture, ataxia, hypoactivity, muscle tremors, excitability) were reported in Sprague-Dawley rats exposed nose-only to tribufos aerosol (mass median aerodynamic diameter [MMAD] 1.4–1.55 μm ; 69–78% of particles $<2\text{ }\mu\text{m}$ in diameter) for 4 hours; however, the available summary of the unpublished study did not specify tribufos concentrations (range 1,590–6,030 mg/m^3) or frequency of observed signs of neurotoxicity (EPA 1991a). Intermittent, head-only exposure of Wistar rats to tribufos aerosol at 59.5 mg/m^3 for 13 weeks resulted in clinical signs of neurological effects (e.g., altered gait, decreased movement, constricted pupils, piloerection, aggressive behavior, sensitivity to touch, convulsions, salivation), decreased brain AChE activity (40% less than that of controls), $>60\%$ decreased RBC AChE activity, and depressed amplitude of a- and b-waves in electroretinographic tests (considered a neurological effect rather than an ocular effect) (EPA 1992b). There were no indications of adverse electroretinographic effects or clinical signs of neurotoxicity at lower exposure levels (0.93, 2.43, or 12.2 mg/m^3); however, the 12.2 mg/m^3 exposure level also resulted in $>60\%$ decreased RBC AChE activity, which ATSDR considers a serious adverse effect (Chou and Williams-Johnson 1998). In a 2-year study of Fischer 344 rats receiving tribufos from the diet at estimated doses of 16.8–21.1 $\text{mg}/\text{kg}/\text{day}$, treatment-related ocular effects (cataracts, corneal opacity and neovascularization, iritis, uveitis) were considered secondary to retinal atrophy (a neurological effect) (CalEPA 2004; EPA 1992d).

CalEPA (2004) summarized results from three unpublished studies designed to investigate the potential for inhaled tribufos to cause OPIDN and cholinergic signs in hens subjected to scenarios ranging from a single 4-hour exposure to intermittent exposures for 3 weeks. Following a single 4-hour exposure, the lowest-observed-effect level (LOEL) for cholinergic signs was on the order of 2-fold lower than the

2. HEALTH EFFECTS

LOEL for OPIDN (391 and 878 mg/m³, respectively). However, following five consecutive 6-hour exposures, the LOEL for OPIDN was nearly 2-fold lower than the LOEL for cholinergic signs (145 and 246 mg/m³, respectively). Although studies of hens are useful for hazard identification, applicability of the dose-response in hens to humans is uncertain. Therefore, hen study results are not included in Table 2-1 or Figure 2-2.

Table 2-4 summarizes results from studies that evaluated the effects of oral exposure to tribufos on indicators of neurological effects (e.g., RBC and brain AChE activity; clinical signs of neurotoxicity) in experimental animals. Single gavage dosing of rats at 20–80 mg/kg typically resulted in >60% decreased RBC and/or brain AChE activity (EPA 2012a, 2012b, 2012c, 2012d). Available study reports and Data Evaluation Reports (DERs) for acute-duration repeated-dose oral exposure of rats to tribufos identified NOAELs of 0.3–1.0 mg/kg/day and serious LOAELs of 1–15 mg/kg/day for >60% decreased RBC and/or brain AChE activity (Astroff and Young 1998; EPA 1990b, 2012a, 2012e, 2012f). The lowest LOAEL for clinical signs of neurotoxicity was 5 mg/kg/day for decreased movement, unsteadiness, and prostration among 11-day-old Sprague-Dawley rat pups gavaged once per day for 11 days (EPA 2012e). In intermediate-duration oral studies, the lowest less serious LOAELs were 1.7 mg/kg/day for 24% decreased RBC activity in beagle dogs and 2.25 mg/kg/day for 29% decreased brain AChE activity in Sprague-Dawley rats; serious LOAELs for >60% decreased RBC and/or brain AChE activity were as low as 3.4 mg/kg/day for 76% decreased RBC activity in Wistar rats (EPA 2005a) and 16.4 mg/kg/day for 74% decreased brain AChE activity in Wistar rats (EPA 2005a). The 16.4 mg/kg/day dose level in Wistar rats also resulted in slight tremors.

In chronic oral studies, rats appeared to be more sensitive to tribufos neurotoxicity. Male Fischer 344 rats exhibited 27% decreased RBC AChE activity at a dose level of 1.8 mg/kg/day and 60% brain AChE activity and atrophy of ocular nerves at 16.8 mg/kg/day (CalEPA 2004; EPA 1992d). Male CD-1 mice exhibited 42% decreased RBC AChE activity at 8.4 mg/kg/day and 37% decreased brain AChE activity at 48.1 mg/kg/day and atrophy of ocular nerves at 16.8 mg/kg/day in the absence of clinical signs of neurotoxicity (CalEPA 2004; EPA 1990a).

Abou-Donia et al. (1979) administered tribufos orally (in gelatin capsule) to groups of hens (5/group) once per day for up to 3 months at doses ranging from 0.1 to 80 mg tribufos/kg/day. The study included a group of vehicle controls. No treatment-related effects were observed in hens treated with 0.1 mg tribufos/kg/day. Dose-related increased incidence and severity and decreased onset of clinical signs of OPIDN (ataxia) were noted in all hens given 0.5–80 mg tribufos/kg/day, beginning as early as treatment

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Table 2-4. NOAELs and LOAELs for Neurological Effects (RBC and/or Brain AChE Inhibition, Clinical Signs, Pathological Lesions) in Mammalian Species Orally Exposed to Tribufos

Tribufos doses (in mg/kg or mg/kg/day) associated with NOAELs and LOAELs for RBC and brain AChE inhibition, clinical signs, and pathological lesions								
Study design (doses in mg/kg or mg/kg/day)	RBC AChE (percent inhibition)			Brain AChE (percent inhibition)			Clinical signs and/or pathological lesions	Reference
	NOAEL ^a	LOAEL ^b	Serious LOAEL ^c	NOAEL ^a	LOAEL ^b	Serious LOAEL ^c		
Acute-duration exposure								
Young adult female Sprague-Dawley rats GO 1 time (0, 80)	ND	ND	80 (>80%)	ND	80 (15-20%)	ND	80; no clinical signs	EPA 2012c
Young adult female Sprague-Dawley rats GO 1 time (0, 2, 10, 80)	10	ND	80 (74%)	80	ND	ND	80; no clinical signs	EPA 2012d
11-day-old Sprague-Dawley rat pups GO 1x (0, 50)	M: ND F: ND	M: ND F: ND	M: 50 (88%) F: 50 (87%)	ND	ND	M: 50 (74%) F: 50 (76%)	50; decreased movement	EPA 2012b
11-day-old Sprague-Dawley rat pups GO 1x (0, 20, 40, 50)	M: ND F: ND	M: 20 (59%) F: ND	M: 40 (76%) F: 20 (71%)	M: 20 F: ND	M: 40 (52%) F: 20 (34%)	M: ND F: 50 (60%)	40; decreased movement	EPA 2012a
11-day-old Sprague-Dawley rat pups GO 1 time (0, 2, 10, 50)	M: 2 F: ND	M: 10 (47%) F: 2 (27%)	M: 50 (86%) F: 50 (89%)	M: 10 F: 10	ND ND	M: 50 (76%) F: 50 (75%)	10; decreased movement: 50; decreased movement, incoordination, unsteadiness	EPA 2012d
Young adult female Sprague-Dawley rats GO 1 time/day, 11 days (0, 0.1, 1, 5)	1	ND	5 (64%)	5	ND	ND	5; no clinical signs, with exception of salivation in one mid-dose rat and one high-dose rat	EPA 2012e
11-day-old Sprague-Dawley rat pups GO 1 time/day, 11 days (0, 0.1, 1, 5)	M: 1 F: 1	M: ND F: ND	M: 5 (66%) F: 5 (69%)	M: 1 F: 1	M: 5 (20%) F: 5 (21%)	ND	5; decreased movement, unsteadiness, prostration	EPA 2012e
11-day-old Sprague-Dawley rat pups GO 1 time/day, 11 days (0, 5, 10, 15, 20)	M: ND F: ND	M: 5 (49%) F: 5 (36%)	M: 15 (83%) M: 15 (66%)	M: ND F: 5	M: 5 (23%) F: 10 (32%)	M: ND F: ND	10–15; decreased movement, unsteadiness, hind limb splay: 20; severe clinical signs	EPA 2012a
Pregnant Sprague-Dawley rats G 1 time/day, GDs 6–15 (0, 1, 7, 28)	1	ND	7 (71%)	7	28 (58%)	ND	28; no signs, with exception of salivation in two high-dose dams	Astroff and Young 1998; EPA 1990b
Pregnant Sprague-Dawley rats GO 1 time/day, GDs 6–19 (0, 0.3–0.8, 7, 28)	0.3 ^d	ND	7 (75%)	0.3 ^d	7 (22%)	28 (81%)	28; no clinical signs	EPA 2012f

2. HEALTH EFFECTS

Table 2-4. NOAELs and LOAELs for Neurological Effects (RBC and/or Brain AChE Inhibition, Clinical Signs, Pathological Lesions) in Mammalian Species Orally Exposed to Tribufos

Tribufos doses (in mg/kg or mg/kg/day) associated with NOAELs and LOAELs for RBC and brain AChE inhibition, clinical signs, and pathological lesions								
Study design (doses in mg/kg or mg/kg/day)	RBC AChE (percent inhibition)			Brain AChE (percent inhibition)			Clinical signs and/or pathological lesions	Reference
	NOAEL ^a	LOAEL ^b	Serious LOAEL ^c	NOAEL ^a	LOAEL ^b	Serious LOAEL ^c		
Pregnant American Dutch rabbits G 1 time/day, GDs 7–19 (0, 1, 3, 9)	ND	ND	1 (70%)	9	ND	ND	9; no clinical signs	EPA 1990c
Intermediate-duration exposure								
Female Han Wistar rats, diet for 4 weeks (0, 0.43, 4.32, 44.62)	0.43	ND	4.32 (66%)	4.32	ND	44.62 (78%)	44.62; no clinical signs	EPA 2013
Wistar rat dams, diet GD 1–LD 21 GDs (0, 0.4, 3.4–3.5, 16.4–18.2) LDs (0, 0.6–1.0, 6.1–9.9, 33.5–55.4)	0.4 ^e	NA	3.4 (76%) ^e	0.4 ^e	3.4 (22%) ^e	16.4 (74%) ^e	16.4 ^e ; slight tremors in five dams on day of parturition	EPA 2005a
Sprague-Dawley rats, diet for 2 generations								Astroff et al. 1998; EPA 1992c
F0 M (0, 0.28, 2.00, 17.6)	0.28	2.00 (35%)	ND	2.00	17.6 (36%)	ND	7.6; no clinical signs	
F0 F (0, 0.31, 2.25, 20.04)	0.31	2.25 (37%)	ND	0.31	2.25 (29%)	20.04 (81%)	20.04; no clinical signs	
F1 M (0, 0.28, 2.09, 20.63) ^f	0.28	2.09 (26%)	ND	2.09	20.63 (33%)	ND	20.63; no clinical signs	
F1 F (0, 0.31, 2.40, 22.93)	0.31	2.40 (28%)	ND	0.31	2.40 (29%)	22.93 (81%)	22.93; no clinical signs	
CD-1 mice, diet for 8 weeks								CalEPA 2004
M: (0, 3.4, 9.4, 40, 140)	3.4	9.4 (37%)	40 (64%)	40	140 (26%)		140; no clinical signs	
F: (0, 5.6, 14.3, 54, 132)	5.6	14.3 (44%)	54 (64%)	54	132 (29%)		132; no clinical signs	
Beagle dogs, diet for up to 364 days								CalEPA 2004; EPA 1991b
M (0, 0.1, 0.4, 1.7)	0.4	1.7 ^g (24%)	ND	NA ^h	NA ^h	NA ^h	1.7; no clinical signs	
F (0, 0.1, 0.4, 2.0)	0.4	2.0 ^g (29%)	ND	NA ^h	NA ^h	NA ^h	2.0; no clinical signs	

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Table 2-4. NOAELs and LOAELs for Neurological Effects (RBC and/or Brain AChE Inhibition, Clinical Signs, Pathological Lesions) in Mammalian Species Orally Exposed to Tribufos

Tribufos doses (in mg/kg or mg/kg/day) associated with NOAELs and LOAELs for RBC and brain AChE inhibition, clinical signs, and pathological lesions								
Study design (doses in mg/kg or mg/kg/day)	RBC AChE (percent inhibition)			Brain AChE (percent inhibition)			Clinical signs and/or pathological lesions	Reference
	NOAEL ^a	LOAEL ^b	Serious LOAEL ^c	NOAEL ^a	LOAEL ^b	Serious LOAEL ^c		
Chronic-duration exposure								
CD-1 mice, diet for 90 weeks								CalEPA
M (0, 1.5, 8.4, 48.1)	1.5	8.4 (42%)	ND	8.4	48.1 (38%)	ND	48.1; no clinical signs	2004; EPA
F (0, 2.0, 11.3, 63.1)	2.0	11.3 (37%)	ND	11.3	63.1 (27%)	ND	63.1; no clinical signs	1990a
Fischer 344 rats, diet for 2 years								CalEPA
M (0, 0.2, 1.8, 16.8)	0.2	1.8 (27%)	ND	1.8	ND	16.8 (60%)	16.8; atrophy ocular nerves	2004; EPA
F (0, 0.2, 2.3, 21.1)	0.2	2.3 (28%)	ND	2.3	ND	21.1 (68%)	21.1; atrophy ocular nerves	1992d

^a<20% decrease in RBC and/or brain AChE represents a NOAEL.

^b20–59% decrease in RBC and/or brain AChE activity represents a less serious adverse effect.

^c≥60% decrease in RBC and/or brain AChE activity represents a serious adverse effect.

^dLow test substance concentrations measured in the 1 mg/kg/day dose group resulted in estimated time-weighted average dosing in the range of 0.3–0.8 mg/kg/day; using a conservative approach, the lowest dose in the range is considered the NOAEL.

^eThe available study summary included only ranges of doses during gestation and lactation periods; using a conservative approach, the NOAELs and LOAELs are considered the low end of a given range for gestational exposure.

^fF1 parental rats had been exposed *in utero* and lactationally as well.

^gAt treatment day 91.

^hBrain AChE activity was only assessed at day 371 (i.e., 7 days following cessation of tribufos treatment).

AChE = acetylcholinesterase; d = day(s); F = female(s); F0 = first generation parental; F1 = second generation parental; G = gavage; GD = gestation day; GO = gavage in oil; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; M = male(s); NA = not applicable; ND = not determined; NOAEL = no-observed-adverse-effect level; RBC = red blood cell

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day 8 in the 80 mg/kg/day dose group. Signs of OPIDN persisted until death or terminal sacrifice during a 30-day observation period following cessation of tribufos dosing. Doses of 40 and 80 mg/kg/day also resulted in typical signs of cholinergic effects; hens in the 40 and 80 mg/kg/day dose groups were subsequently administered atropine sulfate in an attempt to counteract the cholinergic effects. However, after several days, the hens exhibited unsteadiness, followed by general weakness, malaise, loss of balance, tremors, paralysis, and death. Hens administered tribufos at 20 mg/kg/day developed similar (but milder) signs with recovery after 8–11 days. This effect was termed a “late acute” effect because it was not relieved by atropine sulfate and was not considered to be associated with AChE activity.

Francis et al. (1985) reported clinical signs of OPIDN as early as 11–28 days following the initiation of dosing in hens repeatedly administered tribufos orally (gelatin capsule, corn oil vehicle) at 21–30 mg/kg/day.

2.16 REPRODUCTIVE

No information was located regarding reproductive effects in humans exposed to tribufos.

No apparent reproductive effects were observed in studies that employed gavage dosing of tribufos to pregnant animals, including Sprague-Dawley rat dams treated during GDs 6–15 (Astroff and Young 1998; EPA 1990b) or GDs 6–19 (EPA 2012f) at doses as high as 28 mg/kg/day, or maternal American Dutch rabbits treated during GDs 7–19 at up to 9 mg/kg/day (EPA 1990c). No apparent reproductive effects were observed in a study of Wistar rat dams receiving tribufos from the diet throughout gestation and lactation at estimated doses up to 16.4–18.2 mg/kg/day (EPA 2005a). No reproductive effects were observed in a 2-generation study of Sprague-Dawley rats receiving tribufos from the diet for approximately 8–9 weeks prior to mating, and throughout mating, gestation, and lactation at estimated doses as high as 17.6–22.93 mg/kg/day during the premating phase (Astroff et al. 1998; EPA 1992c).

2.17 DEVELOPMENTAL

No information was located regarding developmental effects in humans exposed to tribufos.

There were no signs of treatment-related fetal effects in a study of Sprague-Dawley rat dams gavaged with tribufos during GDs 6–15 at doses as high as 28 mg/kg/day (Astroff and Young 1998; EPA 1990b) or a study of maternal American Dutch rabbits gavaged during GDs 7–19 at doses as high as 9 mg/kg/day

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(EPA 1990c). In another study of Sprague-Dawley rat dams gavaged during GDs 6–19, there were no signs of treatment-related fetal effects, with the exception of significantly lower mean male fetal body weight (6% lower than that of controls) at 28 mg/kg/day (EPA 2012f).

Several indicators of treatment-related developmental effects were noted in a study of male and female Sprague-Dawley rats administered tribufos in the diet during 8–9 weeks pre mating and throughout mating, gestation, and lactation for 2 generations (Astroff et al. 1998; EPA 1992c). At estimated pre mating doses in the range of 17.6–22.93 mg/kg/day (high-dose groups), mean body weights of F1 and F2 pups during lactation ranged from 14 to 30% lower than controls; however, decreased food consumption and depressed mean maternal body weight among the high-dose F0 and F1 dams during lactation may have been at least partially responsible for the effects on pup body weights. Other significant indicators of tribufos-induced developmental effects in the high-dose groups from one or both generations included decreased numbers of live pups/number of pregnant females, decreased numbers of pups born/number of implantation sites, decreased pup viability, decreased numbers of live pups on lactation day 21, and decreased mean litter size. However, these effects occurred at maternally-toxic doses.

In another study, groups of Wistar rat dams received tribufos from the diet at estimated doses up to 16.4–18.2 mg/kg/day during gestation and 33.5–55.4 mg/kg/day during lactation (EPA 2005a). Maternal effects were noted in the high-dose maternal rats and included tremors and decreased body weight during lactation. Indicators of treatment-related developmental effects were noted in the high-dose group and included 16–23% depressed pup mean body weight during lactation, delayed preputial separation, delayed development of righting reflex, decreased motor activity at postnatal day (PND) 13 and increased motor activity at PND 17, and decreased auditory startle amplitude at PND 22. There were no apparent treatment-related effects on pup motor activity or auditory startle response at PNDs 38 or 60.

2.18 OTHER NONCANCER

Hypothermia was reported among Wistar rats intermittently exposed (head-only) to tribufos aerosol (MMAD 1.2–1.3 μm) for 13 weeks at an analytically-determined concentration of 59.5 mg/m³ (EPA 1992b). A clinical sign of treatment-related hypothermia (i.e., cold to the touch) was reported as early as 4 hours postdosing in young Sprague-Dawley rat pups (11 days of age) administered tribufos by gavage for 11 days at doses ≥ 10 mg/kg/day (EPA 2012a); similar treatment by single gavage dose at 50 mg/kg resulted in the same effect (EPA 2012b).

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Ray and coworkers (Little and Ray 1979; Ray 1980; Ray and Cunningham 1985) reported hypothermic responses in rats, mice, and guinea pigs (but not rabbits) administered tribufos via single intraperitoneal injection at doses in the range of 10–200 mg/kg; a dose-response relationship was noted and the effect lasted from several hours to several days at environmental temperatures below thermoneutrality (30–31°C). Based on findings of little effect on basal metabolism at thermoneutrality, lack of apparent effect on heat conservation mechanisms (peripheral vasoconstriction and piloerection), and normal adrenal catecholamine secretion in response to handling or acute cold exposure in tribufos-treated animals but marked reduction in the tribufos-induced hypothermic response upon injection of noradrenaline (but not atropine), the investigators suggested a selective action of tribufos (or a metabolite) on a central thermogenic control process.

2.19 CANCER

No information was located regarding tribufos-induced cancer in humans.

There were no indications of treatment-related increased incidences of malignant or benign tumors among male and female Fischer 344 rats receiving tribufos from the diet for 2 years at estimated doses as high as 16.8–21.1 mg/kg/day (CalEPA 2004; EPA 1992d) or male and female beagle dogs receiving tribufos from the diet for 364 days at estimated doses as high as 1.7–2.0 mg/kg/day (EPA 1991b). However, in a study of male and female CD-1 mice receiving tribufos from the diet for up to 90 weeks, significantly increased incidences of adenocarcinoma in the small intestine (9/50 versus 0/50 controls) and hemangiosarcoma in the liver (7/50 versus 1/50 controls) were observed in males at an estimated dose level of 48.02 mg/kg/day (EPA 1990a). High-dose (63.04 mg/kg/day) female mice exhibited significantly increased incidence of alveolar/bronchiolar adenoma (15/50 versus 5/50 controls) and nonsignificantly increased incidence of adenocarcinoma of the small intestine (4/50 versus 0/50 controls). It should be noted that adenocarcinoma of the small intestine is a rare tumor type in CD-1 mice.

A Health Effects Division Carcinogenicity Peer Review Committee for EPA's Office of Pesticide Programs evaluated the weight-of-evidence regarding the carcinogenic potential of tribufos (EPA 1997). The committee noted increased liver tumors in male mice, increased lung tumors in female mice, and increased small intestine tumors (rare tumors) in both sexes of mice at high oral doses (48.02 mg/kg/day in males and 63.04 mg/kg/day in females) (EPA 1990a). The committee also noted that the tribufos-related increases in mouse tumors occurred only at doses eliciting severe noncancer toxicity as well and

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recommended a nonlinear (margin of exposure) approach for extrapolating to lower dose levels. The committee (EPA 1997) identified a lack of tribufos-induced tumors in a rat study (EPA 1992d), a lack of human data, no apparent concern for mutagenicity, no identified structural analogs of concern, and no mechanistic or mode-of-action data in its assessment. The committee concluded that tribufos should be considered unlikely to be carcinogenic at low doses, but likely to be carcinogenic at high doses. The EPA committee stated that human exposure to tribufos would not likely approach the dose level associated with tumors in the tribufos-treated mice.

The International Agency for Research on Cancer (IARC 2019) does not include a classification for tribufos. The National Toxicology Program 14th Report on Carcinogens (NTP 2016) does not include tribufos.

2.20 GENOTOXICITY

Limited publicly-available information was located. Tribufos did not induce sister chromatid exchanges in Chinese hamster V79 cells exposed for 32 hours or two cell cycles at doses in the range of 2.5–20 µg/mL either with (Chen et al. 1982b) or without (Chen et al. 1982a) exogenous metabolic activation (rat liver S9 mix). Results from several unpublished studies were evaluated in EPA’s Human Health Risk Assessment for tribufos (EPA 2000a) and CalEPA’s Risk Characterization Document for tribufos (CalEPA 2004); a summary of the results follows; exposure duration information was not presented in available secondary sources. Tribufos was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 at concentrations the range of 667–10,000 µg/plate either with or without exogenous metabolic activation. Tribufos did not induce chromosomal aberrations in Chinese hamster ovary cells at concentrations of 0.04, 0.007, 0.013, 0.025, or 0.05 µL/mL without exogenous metabolic activation (cytotoxicity noted at 0.025 and 0.05 µL/mL) or 0.007, 0.013, 0.025, 0.05, or 0.01 µL/mL with exogenous metabolic activation (cytotoxicity noted at 0.05 and 0.1 µL/mL). Tribufos did not induce sister chromatid exchanges in another study of Chinese hamster V79 cells exposed at up to 18.9 µg/mL in the absence of exogenous metabolic activation. Tribufos did not induce unscheduled deoxyribonucleic acid (DNA) synthesis in rat primary hepatocytes at concentrations in the range of 0.0001–0.03 µg/mL (cytotoxicity noted at concentrations >0.006 µg/mL).

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2.21 MECHANISMS OF ACTION

No tribufos-specific information was located regarding mechanisms of toxicity. Tribufos (and other organophosphorus compounds) induce toxicity resulting predominantly from the inhibition of AChE in the central and peripheral nervous system. AChE is responsible for terminating the action of the neurotransmitter, acetylcholine, in cholinergic synapses. The action of acetylcholine does not persist long as it is hydrolyzed by AChE and rapidly removed. As an anticholinesterase organophosphate, tribufos inhibits AChE by reacting with the active site to form a stable phosphorylated complex incapable of destroying acetylcholine at the synaptic gutter between the pre- and postsynaptic nerve endings or neuromuscular junctions of skeletal muscles resulting in accumulation of acetylcholine at these sites. This leads to continuous or excessive stimulation of cholinergic fibers in the postganglionic parasympathetic nerve endings, neuromuscular junctions of the skeletal muscles, and cells of the central nervous system that results in hyperpolarization and receptor desensitization. These cholinergic actions involving end organs (heart, blood vessels, secretory glands) innervated by fibers in the postganglionic parasympathetic nerves result in muscarinic effects, which are manifested as miosis, excessive glandular secretions (salivation, lacrimation, rhinitis), nausea, urinary incontinence, vomiting, abdominal pain, diarrhea, bronchoconstriction or bronchospasm, increased bronchosecretion, vasodilation, bradycardia, and hypotension. Nicotinic effects are due to accumulation of acetylcholine at the skeletal muscle junctions and sympathetic preganglionic nerve endings. Nicotinic effects are manifested as muscular fasciculations, weakness, mydriasis, tachycardia, and hypertension. The central nervous system effects are due to accumulation of acetylcholine at various cortical, subcortical, and spinal levels (primarily in the cerebral cortex, hippocampus, and extrapyramidal motor system). The central nervous system effects are manifested as respiratory depression, anxiety, insomnia, headache, restlessness, tension, mental confusion, loss of concentration, apathy, drowsiness, ataxia, tremor, convulsion, and coma.

As noted previously, organophosphorus compounds such as tribufos inhibit RBC and brain AChE. However, the degree of RBC AChE inhibition does not always correlate with the severity of acute signs of organophosphorus toxicity, especially when individuals are chronically exposed to organophosphorus compounds. For example, RBC AChE activity was reduced by as much as 40–80% from baseline in farm workers who were chronically exposed to organophosphorus pesticides, but otherwise presented no overt clinical sign or symptom of organophosphorus intoxication (Ames et al. 1989; Farahat et al. 2011; Singleton et al. 2015). On the other hand, prenatal exposure to levels of organophosphorus pesticides not anticipated to induce substantial AChE inhibition was associated with abnormal neonatal reflexes, pervasive development disorder, cognitive deficits, and tremors in children ranging from 2 to 7 years of

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age (Bouchard et al. 2011; Gunier et al. 2016; Marks et al. 2010; Rauh et al. 2012, 2015; Rosas and Eskenazi 2008; Stein et al. 2016). A meta-analysis of results from 14 studies published between 1960 and 2012 found a significant association between long-term exposure to low levels of organophosphorus pesticides and impairment of a number of neurological functions, including working memory, attention, psychomotor speed, executive function, and visuospatial ability (Ross et al. 2013).

Relatively high-dose inhalation, oral, or dermal exposure of hens to tribufos resulted in OPIDN (Abou-Donia et al. 1979; Francis et al. 1985). Husain (2014) reviewed possible mechanisms of OPIDN and concluded that the initial mechanism involves phosphorylation and subsequent aging of the enzyme, NTE; a second mechanism appears to involve disruption of calcium homeostasis. It was suggested that OPIDN results from loss of NTE's phospholipid activity, which causes malfunction of endoplasmic reticulum and perturbation of axonal transport and glial-axonal interactions. Although tribufos-induced OPIDN has been demonstrated in hens, no cases of OPIDN have been reported in humans exposed to tribufos.

Numerous studies have also provided evidence of non-enzymatic functions mediated by AChE that include axonal outgrowth (Bigbee et al. 2000), synaptogenesis (Sternfeld et al. 1998), cell adhesion (Bigbee and Sharma. 2004), and neuronal migration (Dori et al. 2005). These non-enzymatic actions of AChE appear to be especially critical for synaptic development (Silman and Sussman 2005).

AChE-unrelated mechanisms, which are likely to differ from one organophosphorus compound to another, have been proposed to explain the effects of long-term exposure to low levels. Organophosphorus compounds can directly interact with nicotinic and muscarinic receptors (Albuquerque et al. 1985; Bomser and Casida 2001; Jett et al. 1991) and structural proteins such as tubulin, kinesin, and dynein (Androutsopoulos et al. 2013; Terry 2012). These and other non-AChE mechanisms, including exacerbated oxidative stress (Garry 2004; Ray 1998), imbalanced intracellular Ca²⁺ homeostasis, increased signaling mediated by inflammatory mediators such as interleukins and cytokines, changes in cellular signaling mediated by neurotrophin receptors and protein kinases, and mitochondrial disruption, have been proposed to contribute to the toxicity of organophosphorus compounds (Androutsopoulos et al. 2013; Banks and Lein 2012; Terry 2012). However, no information was located to suggest that such non-AChE mechanisms are involved in tribufos toxicity.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Tribufos is readily absorbed following oral or dermal exposure. Inhaled tribufos is absorbed through the lung, although quantitative data are not available.
- Absorbed tribufos is widely distributed.
- Tribufos undergoes oxidation, hydrolysis, and conjugation reactions in mammals. A reactive sulfoxide intermediate is involved when enzymes and a reducing agent are present.
- Tribufos and its metabolites are rapidly excreted, predominantly in urine.

No information was located regarding the toxicokinetics of tribufos in humans. CalEPA (2004) reviewed both publicly-available and unpublished animal studies that assessed the toxicokinetics of tribufos. The following information was summarized using results from publicly-available studies (Hur et al. 1992; Sahali et al. 1994; Wing et al. 1984), EPA DERs (EPA 2000b), and the CalEPA (2004) review.

3.1.1 Absorption

No studies were located regarding the extent of absorption following inhalation of tribufos. However, findings of decreased RBC and brain AChE activity and clinical signs of neurotoxicity in rats following nose-only or head-only exposure to tribufos aerosol is confirmation that inhaled tribufos is absorbed from the lung (EPA 1991a, 1992a, 1992b). Absorption is rapid and extensive following oral exposure to tribufos. Among rats administered ^{14}C -tribufos by gavage once at 5 or 100 mg/kg or for 14 days at 5 mg/kg/day, approximately 55–80% of the administered radioactivity was recovered in the urine within 24 hours postdosing, indicating that extensive absorption from the gastrointestinal tract had occurred (CalEPA 2004).

The extent of absorption following dermal exposure to tribufos is species- and dose-dependent. Following dermal application of ^{14}C -tribufos to rats for 10 hours at doses of 1.93, 12.4, or 100 $\mu\text{g}/\text{cm}^2$, radioactivity excreted in the 7-day urine accounted for approximately 26% (high-dose) and 36% (low-dose) of the administered dose; the feces accounted for 3.2–3.6% of the administered dose (CalEPA 2004). Mean dermal absorption rates of 47.5, 47.9, and 33.9% were calculated for low-, mid-, and high-dose groups, respectively. Following a single 8-hour dermal application of ^{14}C -tribufos to male rhesus monkeys at 3.5 $\mu\text{g}/\text{cm}^2$, the mean absorbed dose was reported to be 6.96% of the administered dose; a total of 6.24% of the administered radioactivity was recovered in the urine (mostly within 72 hours postadministration); and 0.72% was recovered in the feces (CalEPA 2004; EPA 2000b).

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3.1.2 Distribution

No information was located regarding distribution following inhalation exposure of humans or animals to tribufos. However, findings of decreased RBC and brain AChE activity and clinical signs of neurotoxicity in rats following nose-only or head-only exposure to tribufos aerosol (EPA 1991a, 1992a, 1992b) is confirmation of absorption and distribution.

Oral administration of tribufos has been demonstrated to result in rapid distribution and elimination in rats. Following gavage administration of ^{14}C -tribufos to rats for 3 days at 5 or 100 mg/kg/day, <3% of the administered radioactivity was detected in the tissue and carcass at 72 hours postadministration; the liver contained the highest amount, followed by fat, lung, kidney, blood, gastrointestinal tract, spleen, bone, heart, gonads, muscle, and brain (CalEPA 2004). Following 3 consecutive daily administrations of encapsulated ^{14}C -tribufos to a lactating goat at 0.82 mg/kg/day (approximately 25 times the maximum tribufos residue level anticipated in animal feed), radioactivity was detected in liver (3.45 ppm), kidney (0.35 ppm), fat (0.19 ppm), muscle, (0.06 ppm), and milk (0.12 ppm), indicating relatively widespread distribution (Sahali et al. 1994).

No information was located regarding distribution following dermal exposure of humans to tribufos. However, detection of radioactivity in the urine and feces of rats and monkeys following dermal application of ^{14}C -tribufos is confirmation of absorption and distribution (CalEPA 2004; EPA 2000b).

3.1.3 Metabolism

Metabolism of tribufos in animal systems has been studied both *in vivo* (Abou-Donia 1979; CalEPA 2004; Fujioka and Casida 2007; Hur et al. 1992; Sahali et al. 1994) and *in vitro* (Fujioka and Casida 2007; Hur et al. 1992; Levi and Hodgson 1985; Wing et al. 1983, 1984). Chemical structures for tribufos and selected metabolites (identified or proposed) are depicted in Figure 3-1. Numbers for each chemical are identified by bracketed numbers in the figure and following text; proposed metabolites are presented in brackets. Tribufos [1] can undergo hydrolysis at one of its SulfurPhosphorus (SP) bonds to form S,S-dibutyl phosphorodithioate [2] and n-butyl mercaptan [3]. This step may involve initial oxidation to an active sulfoxide intermediate. S,S-Dibutyl phosphorodithioate [2] can undergo hydrolysis at one of its SP bonds to form S-butyl phosphorothioate [4] and n-butyl mercaptan [3]. S-Butyl phosphorothioate [4]

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

can be further hydrolyzed to form phosphate [5] and n-butyl mercaptan [3]. S,S-Dibutyl phosphorodithioate [2] and its glutathione conjugate have been detected in liver extracts from mice following intraperitoneal injection of tribufos (Fujioka and Casida 2007). S,S-Dibutyl phosphorodithioate [2] was a major metabolite in urine from rats following intraperitoneal injection of tribufos; S,S-dibutyl phosphorodithioate [2] was also a product of *in vitro* incubation of tribufos with mouse liver microsomes (Hur et al. 1992). S,S-Dibutyl phosphorodithioate [2] and S-butyl phosphorothioate [3] were detected as minor urinary metabolites following oral administration of tribufos to a lactating goat (Sahali et al. 1994). Although n-butyl mercaptan [3] has not been detected *in vivo* as a tribufos metabolite in mammals, its glutathione conjugate was identified in liver extracts from tribufos-treated mice (Fujioka and Casida 2007) and in the urine from a tribufos-treated goat (Sahali et al. 1994). n-Butyl mercaptan [3] was also detected in the excreta of hens administered an oral dose of tribufos (Abou-Donia 1979). Phosphate [5] was found as the major phosphorus compound in the urine of tribufos-treated rats (Hur et al. 1992).

Figure 3-1. Chemical Structures for Tribufos and Selected Metabolites

$\begin{array}{c} \text{SCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\ \\ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{S}-\text{P}=\text{O} \\ \\ \text{SCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \end{array}$ <p>S,S,S-Tributyl phosphorotrithioate (Tribufos) [1]</p>	$\begin{array}{c} \text{SCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\ \\ \text{HO}-\text{P}=\text{O} \\ \\ \text{SCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \end{array}$ <p>S,S-Dibutyl phosphorodithioate [2]</p>	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{SH}$ <p>n-Butyl mercaptan [3]</p>
$\begin{array}{c} \text{SCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\ \\ \text{HO}-\text{P}=\text{O} \\ \\ \text{OH} \end{array}$ <p>S-Butyl phosphorothioate [4]</p>	$\begin{array}{c} \text{O}^- \\ \\ \text{O}^--\text{P}=\text{O} \\ \\ \text{O}^- \end{array}$ <p>Phosphate [5]</p>	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ <p>Butyric acid [6]</p>
$\begin{array}{c} \text{SCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\ \\ \text{HS}-\text{P}=\text{O} \\ \\ \text{SCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \end{array}$ <p>S,S-Dibutyl phosphorotrithioate [7]</p>	$\begin{array}{c} \text{SCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\ \\ \text{CH}_3\text{CH}_2\text{CH}_2\text{CHS}-\text{P}=\text{O} \\ \quad \\ \text{OH} \quad \text{SCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \end{array}$ <p>S,S-Dibutyl, S-1-hydroxybutyl phosphorotrithioate [8]</p>	$\begin{array}{c} \text{O} \\ \\ \text{CH}_3\text{CHCH}_2\text{CH}_2-\text{S}-\text{CH}_3 \\ \\ \text{OH} \\ \\ \text{O} \end{array}$ <p>3-Hydroxybutyl methyl sulfone [9]</p>

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n-Butyl mercaptan [3] can be converted to butyric acid [6], which undergoes fatty acid catabolism to form other fatty acids, lipids, and amino acids. n-Butyl mercaptan [3] can also react with other endogenous substances such as proteins, cysteine, and other endogenous thiols. Tribufos is extensively metabolized, as demonstrated by the detection of 17 unidentified metabolites in the urine of tribufos-treated rats (CalEPA 2004) and numerous mainly unidentified metabolites in the liver, urine, tissue, and milk from a tribufos-treated goat (Sahali et al. 1994).

Other tribufos metabolites have been identified. S,S-Dibutyl phosphorotrithioate [7] was detected as a minor metabolite in liver extracts from tribufos-treated mice (Fujioka and Casida 2007), a major metabolite in urine from tribufos-treated rats (Hur et al. 1992), and a major metabolite of tribufos oxidative metabolism in a mouse liver microsome-NADPH system *in vitro* (Hur et al. 1992). It was suggested that S,S-dibutyl phosphorotrithioate [7] may form via mixed function oxidase-mediated oxidation of tribufos to a reactive intermediate such as S,S-dibutyl, S-1 hydroxybutyl phosphorotrithioate [8] and its subsequent conversion (Hur et al. 1992). Sahali et al. (1994) also identified 3-hydroxybutylmethyl sulfone [9] as a major metabolite in tissue, milk, and urine; its glucuronide conjugate in urine; and its sulfate conjugate in urine and kidney from a tribufos-treated lactating goat.

Findings that tribufos-induced AChE inhibition *in vitro* could be dramatically increased in the presence of microsomal oxidase activation systems and NADPH (Levi and Hodgson 1985; Wing et al. 1984) suggest that an initial step in tribufos metabolism *in vivo* may be its oxidation to a more reactive sulfoxide. Hur et al. (1992) and Fujioka and Casida (2007) proposed such a step based on results obtained from rats; Sahali et al. (1994) proposed a similar step based on results from a lactating goat.

Merphos (tributyl phosphorotrithioite) is a plant defoliant that is readily transformed in the environment to tribufos (tributyl phosphorotrithioate). Therefore, workers who use merphos would likely be exposed to tribufos as well.

3.1.4 Excretion

No information was located regarding the extent of elimination and excretion following inhalation exposure to tribufos. Following single oral dosing of rats with ¹⁴C-tribufos at 5 mg/kg, as much as 95–98% of the radioactivity was recovered in the urine and feces during 72 hours postdosing (CalEPA 2004). Recoveries in the urine were 55% for males and 66% for females; recoveries in the feces were 42% for males and 30% for females. Relatively similar results were obtained following single gavage dosing at

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

100 mg/kg. Repeated gavage dosing at 5 mg/kg/day for 14 consecutive days resulted in a higher percentage of radioactivity in the urine (73% for males and 80% for females) and a lower percentage of radioactivity in the feces (24% for males and 15% for females). Only 1% of the administered radioactivity was recovered in expired air.

As stated previously in Section 3.1.1, during 7 days following a 10-hour dermal application of ^{14}C -tribufos to rats, the urine and feces accounted for 26–36 and 3.2–3.6%, respectively, of the administered radioactivity (CalEPA 2004). Following 8-hour dermal application of ^{14}C -tribufos to rhesus monkeys, the urine and feces accounted for 6.24 and 0.72%, respectively, of the administered radioactivity, mostly recovered within 72 hours postadministration (CalEPA 2004; EPA 2000b).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

No PBPK models are available for tribufos.

3.1.6 Animal-to-Human Extrapolations

The general pharmacokinetic behavior of tribufos is expected to be similar in humans and laboratory animals. Following oral exposure, tribufos is rapidly absorbed, widely distributed, and metabolized to at least one reactive intermediate and other metabolites, which are primarily quickly eliminated in the urine (see Section 3.1.4). Although animals and humans share these similarities, potential differences in pharmacokinetic behavior and biotransformation in blood and target tissues, particularly at toxic levels, have not been extensively studied. Mice and rats are generally more resistant than humans to toxicity of organophosphorus compounds such as tribufos, in part because mice and rats have relatively higher levels

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of circulating carboxylesterases (enzymes that metabolize organophosphorus compounds) (Pereira et al. 2014). Therefore, extrapolation from animals to humans includes an appreciable degree of uncertainty.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to tribufos are discussed in Section 5.7, Populations with Potentially High Exposures.

Although data exist regarding age-related susceptibility to selected organophosphorus compounds, no information was located regarding potential age-related differences in susceptibility to tribufos toxicity in humans. Results from acute-duration oral studies in rats indicate that neonates may be more sensitive than adults to tribufos neurotoxicity, as assessed by clinical signs. Single gavage dosing of 11-day-old Sprague-Dawley rat pups resulted in decreased movement at 10 mg/kg and additional clinical signs (unsteadiness, incoordination, and/or body tremors) at 40–50 mg/kg (EPA 2012a, 2012b, 2012d). Repeated dosing at 5 mg/kg resulted in decreased movement, unsteadiness, and prostration, as well as 20–21% decreased brain AChE activity (EPA 2012e). Repeated dosing at ≥ 10 mg/kg/day resulted in decreased movement, unsteadiness, and hind limb splay (EPA 2012a). No cageside signs of neurotoxicity were seen in young adult female Sprague-Dawley rats administered tribufos by gavage once at up to 80 mg/kg (EPA 2012c, 2012d) or for 11 days at up to 5 mg/kg/day (EPA 2012e). There was no effect on brain AChE activity among the young adult female rats dosed for 11 days at 5 mg/kg/day (EPA 2012e).

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Studies on experimental animals showed that starvation depressed liver microsomal enzyme (P-450) activity due to actual loss of the enzyme protein (Boyd and Carsky 1969). Thus, dietary deficiency could potentially alter tribufos toxicity by diminishing its metabolism in the liver. Hereditary factors may also contribute to population sensitivity to tribufos. A small percentage of the population is affected by plasma cholinesterase (ChE) deficiency, an inherited condition in which plasma ChE (also known as butyrylcholinesterase [BuChE] or pseudocholinesterase) activity is lower than normal. Plasma ChE is a nonspecific cholinesterase enzyme that hydrolyzes many different choline-based esters. ChE deficiency results in delayed metabolism of selected xenobiotics (e.g., succinylcholine, mivacurium, procaine, heroin, cocaine). Since plasma ChE is strongly inhibited by tribufos (Astroff et al. 1998; EPA 1990b, 1992c), it is expected that individuals with ChE deficiency will be unusually sensitive to these xenobiotics. Congenital low plasma ChE activity may also increase subpopulation sensitivity to tribufos exposure. In ChE-deficient individuals, less tribufos would be bound in the blood and more unbound tribufos would be circulated to targets of tribufos toxicity. Ueyama et al. (2007) demonstrated significantly increased plasma ChE and RBC and brain AChE inhibition in streptozotocin-induced diabetic rats compared to normal rats, an indication that diabetics may be more susceptible to organophosphate-induced neurotoxicity.

Gender-specific differences in sensitivity to treatment-related cognitive deficits have been observed in rats, mice, and guinea pigs exposed to the organophosphorus pesticide, chlorpyrifos (Aldridge et al. 2005; Johnson et al. 2009; Levin et al. 2001; Mamczarz et al. 2016). Although similar gender-specific differences have not been reported for tribufos, it is one of a number of organophosphorus pesticides that share similarities in toxicity profiles.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to tribufos are discussed in Section 3.3.1. The National Report on Human Exposure to

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Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see <http://www.cdc.gov/exposurereport/>). If available, biomonitoring data for tribufos from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by tribufos are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

There are no known biomarkers of exposure specific to tribufos. Results from a rat study indicate that orally-administered tribufos is rapidly distributed, highly metabolized, and rapidly eliminated mainly as numerous mostly unidentified metabolites in the urine, and to a lesser extent, in the feces (CalEPA 2004). Some 18 radioactive tribufos metabolites were detected in urine of rats treated with radiolabeled tribufos; however, only butyl-gamma-glutamylcysteinylglycine disulfide was identifiable (CalEPA 2004). It is not likely that tribufos metabolites would serve as reliable indicators of exposure to tribufos.

3.3.2 Biomarkers of Effect

Exposure to very high levels of tribufos could result in excessive sweating, constricted pupils, unconsciousness, and difficulty with breathing. However, these effects are common to many organophosphorus compounds and carbamate pesticides and are not specific to tribufos. Decreased

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

activities of the enzymes BuChE, AChE, and/or NTE in blood serve as biomarkers of effect from exposure to substances (including tribufos) that inhibit these enzymes. However, decreased activity of these enzymes is not a biomarker specific to tribufos. Due to high interindividual variability in “normal” BuChE activity in the blood, repeat measurements of BuChE activity may be necessary to determine whether activity increases over time postexposure.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Tribufos is one of many organophosphorus compounds that inhibit AChE. Significant occupational exposure to tribufos could occur in workers who are exposed to other similarly-acting compounds. Neurotoxic effects in such individuals would be the result of a variety of factors, including cumulative dose, relative potency of each individual compound, and potential synergistic and/or antagonistic interactions.

Although no studies were located that specifically assessed dermal absorption of tribufos in the presence of other chemicals, it is reasonable to assume that some substances (e.g., solvents, etc.) might influence the rate and extent of absorption of AChE-inhibiting organophosphorus compounds (such as tribufos) upon dermal contact.

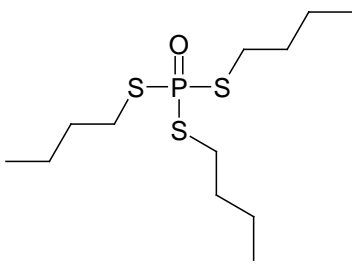
A variety of chemicals may interfere with the toxicity of tribufos indirectly by influencing its metabolism through their actions on drug metabolizing enzymes involved in hydrolysis, reduction, oxidation, and/or conjugation of xenobiotics (Parkinson and Ogilvie 2008). The duration and intensity of action of tribufos are largely determined by the speed at which it is metabolized in the body by oxidative and hydrolytic liver enzymes. Numerous drugs, insecticides, carcinogens, and other chemicals are known to induce the activity of liver microsomal drug-metabolizing enzymes. Thus, exposure to enzyme inducers concurrent with or after exposure to tribufos may result in accelerated bioactivation to a potentially more potent anticholinesterase metabolite. The extent of toxicity mediated by this phenomenon would depend on the rate at which tribufos and/or a potentially more potent metabolite would be hydrolyzed to less toxic metabolites, a process that is also accelerated by enzyme induction. Similarly, concurrent exposure to tribufos and mixed-function oxidase (MFO) enzyme-inhibiting substances may increase the toxicity of tribufos by decreasing the rate of hydrolytic dealkylation and hydrolysis. The balance between activation and detoxification determines the biological significance of these chemical interactions with tribufos.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Table 4-1 lists common synonyms, trade names, and other pertinent identification information for tribufos.

Table 4-1. Chemical Identity of Tribufos

Characteristic	Information	Reference
Chemical name	S,S,S-Tributyl phosphorotrithioate	EPA 2006b
Synonym(s) and registered trade name(s)	Butifos; butiphos; butyl phosphorotrithioate; merphos oxide; tribufos; tribuphos; DEF; DEF 6; Folex	CalEPA 2004; EPA 2006b
Chemical formula	$C_{12}H_{27}OPS_3$	EPA 2006b
Chemical structure		EPA 2006b
CAS Registry Number	78-48-8	EPA 2006b

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Tribufos is a colorless to pale yellow liquid with a strong mercaptan-like odor that arises from butyl disulfide and butyl mercaptan that are formulation impurities and degradation products of tribufos (NRA 1998). Table 4-2 lists important physical and chemical properties of tribufos.

Table 4-2. Physical and Chemical Properties of Tribufos

Property	Information	Reference
Molecular weight	314.54	Tomlin 2003
Color	Colorless to pale yellow	Tomlin 2003
Physical state	Liquid	Tomlin 2003
Melting point	-<25°C	Tomlin 2003

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Tribufos

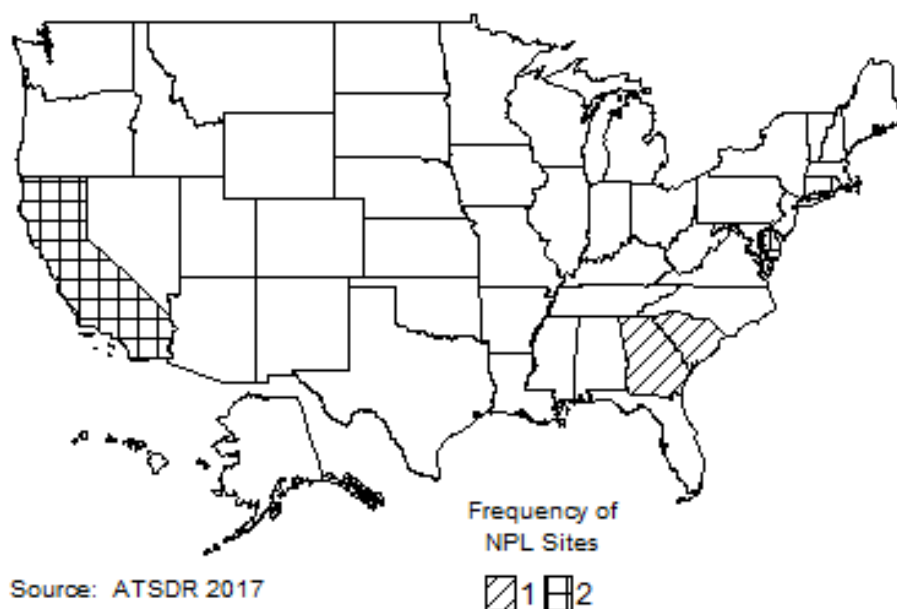
Boiling point	210°C at 750 mm Hg	Tomlin 2003
Density at 20°C	1.057 at 20°C	Tomlin 2003
Odor	Mercaptan-like odor	Tomlin 2003
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20°C	2.3 mg/L at 20°C	Tomlin 2003
Organic solvents	Soluble in aliphatic, aromatic, and chlorinated hydrocarbons and alcohols; completely miscible in dichloromethane, n-hexane, 2-propanol, and toluene	Tomlin 2003
Partition coefficients:		
Log K _{ow}	5.7	Tomlin 2003
Log K _{oc}	3.7–4.10	EPA 1987
Vapor pressure at 25°C	5.3x10 ⁻⁶ mm Hg	Tomlin 2003
Henry's law constant at 25°C	2.94x10 ⁻⁷ atm-m ³ /mole	Fendinger and Glotfelty 1990
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	
Conversion factors	1 µg/m ³ = 0.078 ppbv 1 ppbv = 12.82 µg/m ³	Calculated using the ideal gas law and assuming temperature of 25°C and 1 atm
Explosive limits	No data	

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Tribufos has been identified in at least 4 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which tribufos has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, all are located within the continental United States.

Figure 5-1. Number of NPL Sites with Tribufos Contamination



- Humans may be exposed to tribufos in food and drinking water; however, monitoring data suggest low occurrence in both of these media as tribufos is solely used as a defoliant for cotton. Non-dietary routes, such as dermal and inhalation exposure, may occur due to spray drift for populations living in cotton-growing areas.
- Workers who mix and apply tribufos to cotton plants may have dermal and inhalation exposure to this substance.
- The Henry's law constant and vapor pressure of tribufos suggest a low potential for volatilization; however, field studies have indicated that volatilization from environmental media is not negligible under hot, moist conditions that are typical during tribufos usage.
- Tribufos is unlikely to leach in soils and contaminate underlying groundwater, although it may reach surface water from runoff and erosion of treated cotton fields or from spray drift when applied aerially near a water body.
- Tribufos is stable to hydrolysis under neutral and acidic conditions; however, it is likely to hydrolyze slowly under alkaline conditions. Microbial degradation (biodegradation) is likely to be the most important transformation route of tribufos in soil, water, and sediment.

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5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL**5.2.1 Production**

As stated previously, tribufos belongs to the organophosphate family of chemicals. Tribufos is produced commercially by reacting tributanethiol with phosphorous trichloride in the presence of a base (Elvers et al. 1992).

Table 5-1 summarizes information on facilities that produced, processed, or used tribufos in 2017 (TRI17 2019). Toxics Release Inventory (TRI) data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use S,S,S-Tributyl Phosphorotrithioate

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AL	1	100,000	999,999	1, 3, 4, 7
LA	1	10,000	99,999	10

^aPost office state abbreviations used.

^bAmounts on site reported by facilities in each state.

^cActivities/Uses:

- | | | |
|----------------------|-----------------------------|--------------------------|
| 1. Produce | 6. Reactant | 11. Manufacture Aid |
| 2. Import | 7. Formulation Component | 12. Ancillary |
| 3. Used Processing | 8. Article Component | 13. Manufacture Impurity |
| 4. Sale/Distribution | 9. Repackaging | 14. Process Impurity |
| 5. Byproduct | 10. Chemical Processing Aid | |

Source: TRI17 2019 (Data are from 2017)

According to the EPA Chemical Data Reporting (CDR) database, in 2012, there were two manufacturers of tribufos: the Amvac Chemical Company, that manufactured 2,089,000 pounds, and the Bayer Corporation, which declared its production volume as confidential business information for 2012 (EPA 2016). Updated data from the CDR indicated that the national aggregate production volume was <25,000 pounds in 2015 (EPA 2019a). Data obtained from the National Pesticide Information Retrieval System (NPIRS) show that there are four companies that formulate tribufos into end-use products. These companies and their products are listed in Table 5-2.

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Table 5-2. U.S. Companies Manufacturing Tribufos Products

Company	Registered product	Active ingredients
Amvac Chemical Corporation	Folex 6 EC	70.5% tribufos
	DEF Technical Defoliant	97.9% tribufos
	DEF 6 Emulsifiable Defoliant	70.5% tribufos
Loveland Products Inc.	DFT 6 EC Cotton Defoliant	70.5% tribufos
RedEagle International LLC	Tribufos Technical	99.5% tribufos
	Tribufos 6	70.5% tribufos
Axion AG Products LLC	AX Tribufos 6	70.5% tribufos

Source: NPIRS 2019

5.2.2 Import/Export

Data from the CDR indicated that neither Amvac nor Bayer import tribufos into the United States from other countries; however, they do not report whether or not tribufos was exported to other nations.

5.2.3 Use

Tribufos is a plant growth regulator that is used exclusively as a defoliant for cotton plants in preparation for machine harvesting (EPA 2006b; Tomlin 2003). Tribufos is absorbed by the leaves and stimulates an abscission layer between the plant stem and the leaf petioles, resulting in the dropping of the entire green leaf. Tribufos is also used to reduce or prevent losses from boll rot organisms by separating the organism's habitat from the cotton crop. An estimated 4.5 million pounds of tribufos was used in 1999; tribufos was applied as a defoliant to approximately 35% of the 14 million acres of cotton fields in the United States (EPA 2006b). The USGS Pesticide National Synthesis Project estimated that approximately 2.8 million pounds of tribufos were applied to cotton crops in 2016 (USGS 2019). Tribufos is usually applied as a tank-mix for use as an emulsifiable concentrate with other defoliants via aerial spraying or groundboom spraying at an application rate of 0.50–0.75 pounds active ingredient per acre (lbs ai/A). The maximum application rate is 1.125 lbs ai/A in all states with a restricted entry interval of 7 days, but may be applied at an application rate of 1.875 lbs ai/A if used alone in California and Arizona (EPA 2000a, 2006b). The state of California restricts application of tribufos within a half-mile of residential areas.

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5.2.4 Disposal

The best way to dispose of tribufos is to mix the appropriate amount and apply the full amount to the cotton crops. Immediately after application, workers should remove all unused product and follow labelled instructions for disposal (CPCR 1992). Containers containing tribufos may be triple rinsed for recycling or reconditioning, if applicable. Otherwise, the container must be punctured and disposed into a sanitary landfill or by any other means approved by state and local authorities (CPCR 1992).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥ 10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes $\geq 25,000$ pounds of any TRI chemical or otherwise uses $>10,000$ pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

Estimated releases of 10 pounds (~ 0.004 metric tons) of tribufos to the atmosphere from one domestic manufacturing and processing facility in 2017, accounted for 100% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2019). These releases are summarized in Table 5-3.

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Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use S,S,S-Tributyl Phosphorotrithioate^a

Reported amounts released in pounds per year ^b									
State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		
							On-site ^j	Off-site ^k	On- and off-site
AL	1	10	0	0	0	0	10	0	10
LA	No data								
Total	1	10	0	0	0	0	10	0	10

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI17 2019 (Data are from 2017)

5.3.2 Water

There were no estimated releases of tribufos to surface water from the one domestic manufacturing and processing facility in the 2017 TRI (TRI17 2019). This estimate included releases to waste water treatment and publicly owned treatment works (POTWs) (TRI17 2019).

Runoff, erosion of contaminated soil, and spray drift from aerial application are the main environmental fate processes that result in tribufos contamination of surface waters. Potter et al. (2003) studied the runoff potential of three defoliant, including tribufos, applied to strip and conventionally tilled cotton in a 1.9 hectare (4.7 acre) field located in south central Georgia. The runoff of tribufos applied at a rate of 0.31 kg/hectare (approximately 15–25% of the label use rate) was approximately 12.8% of the applied amount in the strip tilled plot and 14.5% of the amount applied in the conventional tillage plot following a 45-minute simulated rainfall event that occurred shortly after application.

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5.3.3 Soil

There were no estimated releases of tribufos to soil or through underground injection from the one domestic manufacturing and processing facility in 2017 (TRI17 2019).

5.4 ENVIRONMENTAL FATE**5.4.1 Transport and Partitioning**

Air. Based on its vapor pressure (5.3×10^{-6} mm Hg at 25°C), tribufos released to the atmosphere via aerial or boom spraying would be expected to exist in both the vapor and particulate phases (Eisenreich et al. 1981). Vapor-phase tribufos will react with photochemically generated hydroxyl radicals, while particulate-phase tribufos will be removed from the atmosphere by wet and dry deposition.

Water. Soil column leaching experiments using four different types of soils indicated that tribufos applied to the top of the columns remained within 4 cm of the surface and <1% was observed in the leachate water. Field dissipation studies in which tribufos was applied to mature cotton plants on 0.2 hectare research plots also indicated a low potential for leaching (Potter et al. 2002). Over the course of the 3-year monitoring period, tribufos was not detected in shallow groundwater wells installed in the plots or in drainage water at the outer surface of the plots that collected shallow subsurface water flow. These data suggest that tribufos is unlikely to leach in soils and contaminate underlying groundwater. The low potential for leaching is supported by monitoring studies that show that tribufos is rarely detected in groundwater. Tribufos may reach surface water from runoff and erosion flux of treated field soils or from spray drift when applied aerially or from a groundboom near a water body.

The measured Henry's Law constant of tribufos is 2.94×10^{-7} atm-m³/mole (see Table 4-2), which suggests that volatilization from water and soil surfaces will occur slowly. Its large soil adsorption coefficient also suggests that adsorption to soil and sediment may attenuate the rate of volatilization. Tribufos applied at 1 µg to 100 mL of seawater and aerated at 50 mL/minute was volatilized 12% after a 7-day incubation period; however, no volatilization was observed following the addition of 10 g of sediment to seawater/tribufos mixtures (EPA 1981). A study that compared the dissipation rates of tribufos applied to soils under laboratory and field conditions concluded that volatilization may not be negligible, particularly under hot and moist meteorological conditions (Potter et al. 2002). Calculated dissipation half-times (DT₅₀) for tribufos were approximately 25 times greater in controlled laboratory studies (14.2–18.8 days)

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in which volatilization was minimal as compared to the field study for this soil (<1–1.6 days) in which volatilization could occur. Assuming that the degradation rates under both field and laboratory conditions were similar, the authors suggested that volatilization may be an important environmental fate process for tribufos applied to cotton crops. Even at the highest levels recorded in drift studies (high of 1,189 ng/m³ or 0.001189 mg/m³), data indicate that the exposure is nearly 40 times lower than the intermediate-duration inhalation MRL of 0.04 mg/m³, so health effects are unlikely from an exposure scenario that involves only tribufos that volatilizes from treated cotton fields. Furthermore, tribufos has a short atmospheric half-life, and monitoring studies indicate that atmospheric levels decrease quickly due to the short half-life.

Sediment and Soil. Tribufos adsorbs strongly to soils and is expected to be practically immobile. The K_{oc} values of tribufos applied to a sandy soil (88% sand, 7% silt, 5% clay, 1% organic matter, pH 4.2), sandy loam (56% sand, 30% silt, 14% clay, 1.1% organic matter, pH 6.6), silt loam (17% sand, 66% silt, 17% clay, 2.9% organic matter, pH 5.9), and clay loam (21% sand, 50% silt, 29% clay, 2.2% organic matter, pH 6.4) were 12,684, 10,465, 4,870, and 9,115, respectively (EPA 1987).

Other Media. Tribufos does not significantly bioaccumulate in edible tissues of aquatic organisms. Bluegill sunfish exposed to tribufos at a mean concentration of 6.2 µg/L for 35 days had a bioconcentration factor (BCF) of 300 for edible tissue and a whole-body BCF of 730; a BCF of 1,300 was reported for nonedible (viscera) residues (EPA 2008). Following a 14-day depuration period, 71–88% of the tribufos residues were reported to be eliminated from the fish. Pinfish exposed to tribufos had a measured BCF value of 350 following a 96-hour static test; however, the time period may not have been long enough to reach steady state (EPA 1981). According to CalEPA (2000), multiple 5 mg/kg gavage doses of tribufos to rats resulted in no evidence of bioaccumulation; CalEPA (2000) cited an unpublished study as the source of information.

5.4.2 Transformation and Degradation

Air. Vapor-phase tribufos in the ambient atmosphere will be degraded by reaction with photochemically generated hydroxyl radicals. A second-order hydroxyl radical rate constant of 7.9×10^{-11} cm³/molecule-second was estimated using a structure estimation method (EPA 2012h; Meylan and Howard 1993). This corresponds to an atmospheric half-life of approximately 1.6 hours assuming an atmospheric hydroxyl radical concentration of 1.5×10^6 hydroxyl radicals per cm³ of air and a 12-hour sunlight day (EPA 2012h). Tribufos may be susceptible to direct photolysis by sunlight, since it absorbs photons in the

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environmental ultraviolet (UV) spectrum (wavelengths >290 nm); however, it was shown to undergo direct photolysis slowly in laboratory photoreactor experiments (Woodrow et al. 1983).

Water. Tribufos is reported to be stable to hydrolysis under neutral and acidic conditions (EPA 2006b, 2008). Under alkaline conditions (pH 9), the half-life of tribufos was reported to be 124 days, with desbutylthio tribufos reported to be the major breakdown product (CalEPA 2004). There was no evidence of degradation when tribufos was exposed to sunlight for 30 days in a pH 5 aqueous solution (EPA 2008). Using a structure estimation method based upon molecular fragment descriptors, a hydrolysis half-life of 1.5 years was estimated at pH 7 and a half-life of 111 days was estimated at pH 9 (EPA 2012h).

The degradation of several pesticides from raw water obtained from the Little Miami River (a small river receiving industrial and farm runoff) was studied over an 8-week incubation period in sealed glass jars under sunlight and artificial light settings (Eichelberger and Lichtenberg 1971). A 10- μ g/L sample of merphos was introduced into the river water where it was subsequently converted to tribufos within 1 hour. After 1 week, only 50% of the initially present tribufos was recovered. Recovery of tribufos after 2, 4, and 8 weeks was only 30, 10, and 5%, respectively. The dissipation of tribufos in a seawater (100 mL) and sediment (10 g) mixture was studied under sterile and nonsterile conditions (EPA 1981). In the nonsterilized system, only 20% of the initially applied tribufos was present after a 5-day incubation period and it all had partitioned to the sediment column. In contrast, 77% of the initially applied tribufos was present in the sterilized system after 7 days.

The anaerobic aquatic metabolism half-lives for tribufos applied at a rate of 1.1 mg/kg to a flooded silty clay pond sediment (0.8% sand, 41.5% silt, 57.7% clay, 3.1% organic matter, pH 7.3) were 180 and 120 days in two separate experiments (EPA 2008). The only reported metabolite was 1-butane sulfonic acid.

Sediment and Soil. EPA (2006b) reported an aerobic soil metabolism half-life of 745 days (EPA 2006b) and the California Department of Pesticide Regulation reported an aerobic soil metabolism half-life for tribufos of 198 days (CalEPA 2004). The aerobic soil degradation study used by EPA (2006b) was a sandy loam (58% sand, 27% silt, 15% clay, 3.8% organic matter, pH 6.8) and 14 C labeled tribufos was applied at a nominal rate of 7 ppm and incubated in the dark at 25°C for 360 days (EPA 1991c). Tribufos was 97.7–100.2% of the applied radioactivity immediately after application and declined to 62.3–66.8% after 360 days. Methyl-des butylthio tribufos was identified as the only extractable metabolite, reaching 0.8–1.2% of the applied radioactivity after 181 days. Volatile organics represented

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2.9–3.9% of the radioactivity at the end of the experiment and $^{14}\text{CO}_2$ was 2.9–7.0% of the applied radioactivity at the end of the incubation period. Unextractable compounds represented 15.4–18% of the radioactivity at 360 days and the material balance range was 91–108.9%. The calculated half-life was reported to be of limited value since it involves extrapolation well beyond the time limits of the incubation period. The same soil was employed to test the persistence of tribufos under anaerobic conditions. ^{14}C -labeled tribufos was applied at a nominal rate of 7 ppm and incubated in the sandy loam for 60 days under nitrogen-rich anaerobic conditions (EPA 1990d). At the end of the study, 73.0–84.4% of the radioactivity was recovered as tribufos. An anaerobic soil metabolism half-life of 389 days was calculated; however, it was of limited value since it exceeds the incubation period and no positive controls were used.

Other laboratory degradation and field dissipation studies suggest that tribufos is not as persistent as the previous studies would suggest. Potter et al. (2002) examined the dissipation of tribufos under controlled laboratory and field conditions using four soils used to grow cotton that were acclimated to tribufos. Using a soil spiking application rate of 1 ppm, the DT_{50} values under controlled laboratory conditions ranged from approximately 1 to 19 days using a nonlinear fitting procedure. Half-lives of about 5–16 days were calculated using data from the first 28 days of the incubation period and a linear fitting procedure.

The length of incubation effects half-life calculations. Longer half-lives (70–109 days) were calculated when data for the entire incubation period (666 days) were used; however, isolating soils for this length of time is expected to have a negative impact on microbial communities responsible for degradation of the substance. Moreover, the degradation of many pesticides in soil is biphasic, with an initial rapid degradation period over the course of the first few weeks and a gradual decline in the rate of degradation over longer incubation times. This aging process is often observed for pesticides such as DDT that adsorb strongly to soils and eventually become sequestered in the soil, which decreases its bioavailability to microorganisms (Alexander 1995; ATSDR 2002). The concentration versus time profile resembles a “hockey-stick” type outline with relatively rapid degradation observed initially followed by a flattening of the curve over long periods of time (Alexander 1995).

Potter et al. (2002) concluded that an appropriate value for the DT_{50} or the half-life of tribufos in acclimated soils maintained at its field capacity and a temperature of 29°C should be on the order of 5–20 days. A field dissipation study conducted on a 0.2-hectare plot located in Tifton, Georgia had a calculated DT_{50} value that was about 25 times lower (0.6 days) than the laboratory values for this soil

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(14.2–18.8 days). It should be noted that this field had also been amended with an application of poultry litter 1 year prior to the experiments conducted. Although some of the dissipation was attributed to runoff from rain events during the monitoring period, the authors also assumed that some loss was due to volatilization from the soil plot and that this fate process should be included in model simulation exercises when evaluating the environmental fate of tribufos (Potter et al. 2002). The shorter persistence times in this study as compared to the study submitted for the registration of tribufos may be due to the lower application rates used and the properties of the soils. Each of the soils used in the findings by Potter et al. (2002) had been exposed to tribufos during its application to cotton crops in prior years, whereas the soil used in the registration study does not appear to have been acclimated to tribufos.

The shorter dissipation times in soils acclimated to tribufos appear to be supported by data submitted by the Bayer Crop Science Corporation to the EPA High Production Volume Challenge Program. In the Robust Summary submitted by Bayer, the rates of aerobic biodegradation of ^{14}C -labeled tribufos in five cotton-growing soils obtained from Georgia, Mississippi, California, Texas, and Arkansas were reported. Tribufos applied at the maximum application rate of 1.9 pounds per acre (approximately 1 ppm for a 6-inch depth with soil density 1.5 g/cm^3) had half-lives of 9.8, 30.3, 99, 143.6, and 173.3 days in the soils from California, Texas, Georgia, Arkansas, and Mississippi, respectively (Bayer 2008). Degradation was measured by CO_2 evolution and appeared to be correlated with the pH of the soil. Soils with $\text{pH} > 6.3$ had greater CO_2 evolution as compared to soils with lower pH. The amount of $^{14}\text{CO}_2$ evolution at the end of the experiments ranged from 37.6% in the Mississippi soil to 72.3% in the Texas soil.

The large differences in the apparent degradation times of tribufos in these studies may be due to the higher application rate used in the registration study, which may have resulted in toxicity to the microorganisms or a prolonged adaptation period. The nominal application rate was 7 times greater in the registration study than the other studies. Moreover, the soils used in the field studies by Potter et al. (2002) and Bayer (2008) were reported to have been previously exposed to tribufos in preceding planting seasons, suggesting acclimated microorganisms. It is unclear whether the sandy loam used in the registration process had been previously exposed to tribufos. The 745-day half-life appears to be an outlier considering the data reflected in the laboratory and field studies by Potter et al. (2002).

Tribufos was stable in a soil photolysis experiment in which it was incubated at a fortification level of 9.2 ppm in a sandy loam soil (48.02% sand, 49.65% silt, 2.33% clay, 1.45% organic matter, pH 6.6) and irradiated for 30 days with natural sunlight in Kentucky from February 4, 1988 through March 5, 1988 (EPA 1988).

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5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to tribufos depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of tribufos in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on tribufos levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-4 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-5.

Table 5-4. Lowest Limit of Detection Based on Standards^a

Media	Detection limit	Reference
Air	0.10 ng/m ³	Majewski et al. 1998
Drinking water	0.0033 µg/L	EPA 2012g
Surface water and groundwater	0.00946 µg/L	CDFA 2013
Soil	0.01 mg/kg	EPA 2014
Sediment	0.01 mg/kg	EPA 2014
Whole blood	27 ppt	Kuklenyik 2009

^aDetection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-5. Summary of Environmental Levels of Tribufos

Media	Low	High	For more information
Outdoor air (ppbv)	0.0021	0.47	Section 5.5.1
Indoor air (ppbv)	No data	No data	
Surface water (ppb)	Not detected	0.01	Section 5.5.2
Ground water (ppb)	Not detected	Not detected	Section 5.5.2
Drinking water (ppb)	Not detected	0.07	Section 5.5.2
Food (ppb)	Not detected	2,000	Section 5.5.4
Soil	No data	No data	

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Detections of tribufos in air, water, and soil at NPL sites are summarized in Table 5-6.

Table 5-6. Tribufos Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median ^a	Geometric mean ^a	Geometric standard deviation ^a	Number of quantitative measurements	NPL sites
Water (ppb)			No data		
Soil (ppb)	412,000	222,000	5.68	2	2
Air (ppbv)			No data		

^aConcentrations found in ATSDR site documents from 1981 to 2015 for 1,854 NPL sites (ATSDR 2017). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Since tribufos is used exclusively as a cotton defoliant and has a short atmospheric half-life, it is usually only detected in ambient air in cotton-growing regions where it has been applied. Fifty meters from a cotton field that was treated with the defoliant, tribufos was detected at levels of 1,189 ng/m³ (Hermann and Seiber 1981). These levels dropped to 450 and 24 ng/m³ at 24 and 72 hours post treatment, respectively. Tribufos was also detected in air samples at a maximum concentration of 6,080 ng/m³ collected at a second cotton field being treated with the defoliant merphos. Tribufos was detected at levels ranging from 2.7 (detection limit) to 87.4 ng/m³ at 10 residential locations in Kern County, California near a cotton field being treated with defoliants (Kilgore et al. 1984). Two weeks postapplication, tribufos was detected at its detection limit in only 1 out of 40 air samples obtained in these 10 locations. Tribufos was detected in 10% of the air samples collected from a research vessel traveling the Mississippi River from New Orleans, Louisiana to St. Paul, Minnesota at a maximum concentration of 0.04 ng/m³ (Majewski et al. 1998).

Tribufos was detected in 6 out of 36 samples of air obtained from urban communities in California at a mean concentration of 1.3 ng/m³ and in 121 out of 125 samples of air from rural communities in high-use agricultural areas at a mean concentration of 64 ng/m³ (Lee et al. 2002). Tribufos was not detected in air samples that were collected in Parlier, California during a 12-month monitoring study of 40 pesticides conducted by the California Department of Pesticide Regulation to determine residential exposure to pesticides for persons living in agricultural communities in the San Joaquin Valley near Fresno, California (CalEPA 2009; Wofford et al. 2014). Tribufos was detected in the ambient air of four

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sampling locations in Monterey, California at a mean concentration of 68 ng/m³ (maximum=340 ng/m³) from September to November 1987 (Baker et al. 1996).

5.5.2 Water

Due to its tendency to adsorb strongly to soil surfaces, tribufos is not expected to leach to lower soil horizons and contaminate underlying groundwater in the cotton fields where it was applied. Tribufos was not detected in 569 wells that were sampled in North America (California and Texas) from 1984 to 1988 based upon data from the USGS Pesticides in Groundwater Database (Barbash and Resek 1996; EPA 1992e, 2006b). Tribufos was not detected in 465 wells sampled in 16 counties (Colusa, Fresno, Kern, Kings, Los Angeles, Madera, Merced, Orange, Riverside, San Bernardino, San Diego, San Mateo, Santa Cruz, Stanislaus, Tulare, and Ventura) located in California (CalEPA 2004). Tribufos was identified, not quantified, in one groundwater sample obtained during a monitoring study in 28 counties in California (Cohen 1986).

Winchell and Snyder (2014) compared the levels of various pesticides in drinking water monitoring studies to levels predicted using EPA Tier 1 and Tier 2 modelling approaches. The highest estimated drinking water concentration for tribufos using the Tier 2 linked programs, Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS), was 14 µg/L, which was about 3 orders of magnitude larger than the maximum measured value observed from drinking water monitoring studies (0.016 µg/L) from 12 unspecified sites monitored for 1–2 years with 11–37 samples obtained per year. This result was consistent with data from the other pesticides discussed in the study whereby predicted values greatly exceeded observed concentrations from monitoring studies. Tribufos was detected in 12 out of 12 raw drinking water and 11 out of 12 filtered drinking water samples at a median level of 0.02 µg/L, collected in Cairo, Egypt near a location where it was being used as a cotton defoliant (Potter et al. 2007). Tribufos was monitored for during the Fourth UCMR, which monitors the frequency and level of occurrence of 30 unregulated contaminants in the nation's public water systems between 2018 and 2020. Data from the July 2019 summary indicated that tribufos was detected in 2 out of 11,829 samples above the minimum reporting level of 0.07 µg/L (EPA 2019b). It was only detected above the minimum reporting level in 2 out of the 2,342 public water systems that reported results.

Tribufos was detected in 2 out of 810 surface water samples collected from 1991 to 2003 in the state of California at the detection limit 0.01 µg/L (CalEPA 2004). Tribufos was not detected in water samples

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analyzed from 2000 to 2005 in the Clackamas River basin in Oregon (USGS 2008). Tribufos was not detected in seven discrete water samples collected from the Potomac River basin (Kolpin et al. 2013).

Tribufos was detected in fogwater samples at concentrations of 250 ng/L (0.250 ppb) in Parlier, California and 800 ng/L (0.800 ppb) in Corcoran, California (Glottfelty et al. 1987).

5.5.3 Sediment and Soil

Any tribufos that is applied aerially or by boom spraying that is not intercepted by the cotton plants may reach the underlying soil surface. In a study of six plots of soil used to grow cotton, tribufos was applied at a rate of 0.3 kg/hectare (Potter et al. 2002). Using the measured application rate and the concentration of tribufos in the upper 2 cm of the soil, it was estimated that between 5.3 and 49% of the applied tribufos reached the soil surface. The highest value was obtained for a plot where the cotton plants were already partially defoliated and the authors suggested that the tribufos fraction that typically reaches the soil surface ranges from about 8 to 24% of the initially applied amount (Potter et al. 2002).

Sediment samples obtained from the Lake Olathe watershed and Cedar Lake located in northeast Kansas had no positive detections for tribufos (n=5 for both lakes) at a detection limit of 0.20 µg/kg (USGS 2002).

5.5.4 Other Media

Since tribufos is applied exclusively to cotton crops, it is rarely detected in food items, although exposure to tribufos can occur from residues present in cottonseed oil or meal or as a result of consumption of livestock that may have been fed cotton gin-byproducts, cottonseed hulls, or cottonseed meal. A field test in which tribufos was applied at the maximum application rate resulted in average tribufos residues in cottonseed, cottonseed meal, hulls, crude cottonseed oil, and refined cottonseed oil of 7.266, 0.065, 1.043, 0.581, and 0.213 ppm, respectively (EPA 2000a)

Data from the United States Department of Agriculture (USDA) 2014 Pesticide Data Program report showed that tribufos was not detected in 2,341 samples of fruits or vegetables (USDA 2016b). There were no detections in apples (n=177); blueberries, fresh (n=354); blueberries, frozen (n=5); celery (n=348); grape juice (n=531); strawberries (n=176); summer squash (n=270) sweet corn, fresh (n=78); sweet corn, frozen (n=12); or watermelon (n=390).

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The Food and Drug Administration (FDA) conducts a Total Diet Study in which food items are analyzed 4 times annually, once in each of the major geographical regions of the country (west, north central, south, and northeast). Each round of sampling is referred to as an individual market basket survey and for each market basket survey, samples of selected food and beverages are obtained from cities within the region. Tribufos was detected at a concentration of 0.0060 ppm in 1 out of 44 samples of potato chips analyzed during the FDA Total Diet Market Basket Surveys conducted in 1991–2003 and 2003–2004 (FDA 2006). It was also detected at trace levels (0.0003 ppm) in one of four samples of catfish, pan cooked with an unspecified oil. It was not detected in any of the other food items in this survey. Older Total Diet Studies also suggest that tribufos is rarely detected in food items. It was identified once in an unspecified number of potato samples analyzed during the 1980–1982 Market Basket Survey (Gartrell et al. 1986). It was not detected in any of the other 12 food items in this survey. Tribufos was detected in 2 out of 6,391 samples of U.S. domestic agricultural commodities at concentrations of 0.50 and >2.0 ppm in FDA studies conducted from 1981 to 1986; it was not detected in 1,239 imported agricultural commodities (Hundley et al. 1988). According to data from the FDA Pesticide Program Monitoring Database, tribufos was not detected in any domestic or imported foods (n=6,704) analyzed in 2013 (FDA 2013).

Tribufos was detected on cotton bolls and other parts of the plant after application. Levels of tribufos on cotton bolls were 3.91 and 2.36 µg/g (ppm) following application by ground and aerial spraying, respectively (CalEPA 2000). These levels decreased to around 0.1 µg/g (ppm) 2 weeks postapplication. In 2001, the FDA collected a total of 478 domestic and 67 imported animal feed samples and analyzed these items for pesticide residues (FDA 2001). Tribufos was detected in six feed samples at a concentration range of 0.030–0.150 ppm and a median value of 0.074 ppm.

5.6 GENERAL POPULATION EXPOSURE

Tribufos is used to defoliate cotton plants; it is not for residential use or other non-occupational uses. A 2000 human health risk assessment for tribufos published by the EPA Health Effects Division (HED) concluded that the primary route of exposure to tribufos for the general public is through the ingestion of food (EPA 2000a). Inhalation exposure to tribufos is expected to be negligible for the general population, with the exception of those persons who reside near cotton fields that are treated with tribufos. Since tribufos is rarely detected in groundwater or drinking water, this is not considered an important exposure pathway for the general population.

5. POTENTIAL FOR HUMAN EXPOSURE

Tribufos residues that may be present in cottonseed oil or cottonseed meal could be directly ingested, or exposure could result from ingestion of meat or milk products from livestock that are fed cottonseed products. One sample of catfish that was pan-cooked with an unspecified oil tested positive for tribufos and 1 out of 44 samples of potato chips had quantifiable levels of tribufos (6 samples had trace levels) in the FDA Total Diet Market Basket Surveys conducted in 1991–2003 and 2003–2004 (FDA 2006). No other samples tested positive for tribufos. EPA (2006b) estimated acute and chronic dietary intakes (99.9th percentiles) of 0.050 and 0.003 µg/kg/day for the U.S. population calculated using the Dietary Exposure Evaluation Model (DEEM). The DEEM uses food consumption data from the USDA Continuing Survey of Food Intakes (CSFII) and anticipated tribufos residues on food items to estimate exposure.

Gunderson (1988, 1995a, 1995b) employed data from the 1982–1984, 1984–1986, and 1986–1991 Total Diet Market Basket Surveys to estimate the mean dietary intakes of selected pesticides, including tribufos, in the U.S. general population. The mean daily intakes for tribufos in µg/kg/day for different age and gender groups are provided in Table 5-7. Tribufos levels in the food commodities used to derive these intakes were all well below the current EPA tolerances, which are 0.01–0.15 ppm for milk and animal meats and 40 ppm in cotton gin byproducts (EPA 2015).

Table 5-7. Mean Daily Intakes of Tribufos (µg/kg/day) for the U.S. Population

	1982–1984 Market Basket Surveys ^a	1984–1986 Market Basket Surveys ^b	1986–1991 Market Basket Surveys ^c
6–11 Months old	<0.0001	<0.0001	<0.0001
2 Years old	0.0004	0.0002	0.0001
14–16 Years old, female	0.0002	0.0001	<0.0001
14–16 Years old, male	0.0002	0.0001	<0.0001
25–30 Years old, female	0.0001	0.0001	<0.0001
25–30 Years old, male	0.0001	0.0001	<0.0001
60–65 Years old, female	<0.0001	<0.0001	<0.0001
60–65 Years old, male	<0.0001	<0.0001	<0.0001

^aGunderson 1988.

^bGunderson 1995a.

^cGunderson 1995b.

Workers who apply tribufos to cotton plants are expected to receive greater exposure through dermal and inhalation routes than the general population. Total daily, seasonal, and lifetime exposure estimates by

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the dermal and inhalation routes for agricultural workers have been summarized in the risk characterization for tribufos document compiled by the California Department of Pesticide Regulation and are reproduced in Table 5-8 (CalEPA 2004). Exposure to tribufos tends to be seasonal since cotton defoliation is generally performed on mature bolls approximately 10–14 days prior to the anticipated harvest (Barber et al. 2013). Although harvest timing of cotton in the United States differs by region, it is typically performed in fall (September–November) (USDA 2010). However, the harvest may also extend into December or early January in some states. Mixers/loaders stock the aircraft with tribufos, while flaggers stand at the end of the fields to provide the pilot with a flight path. Field workers who enter treated fields may be dermally exposed to treated surfaces in the area where they are working. For tribufos, a restricted entry interval (REI) of 7 days has been established for postapplication activities including raking, picking, tramping, and module builder operations (EPA 2000a).

Table 5-8. Estimated Occupational Exposure Scenarios for Tribufos

Job category	Absorbed daily dose (ADD) ^a	Seasonal average daily dose (SADD) ^b	Lifetime average daily dose (LADD) ^c
	µg/kg/day		
Handlers			
Mixer/loader (aerial)	4.6	2.1	0.15
Pilot	5.1	2.4	0.17
Flagger	4.4	2.1	0.14
Mixer/loader (ground)	8.5	4.0	0.28
Applicator (ground)	0.7	0.3	0.02
Field workers			
Irrigators/weeders (4 days)	25.5	11.9	0.84
Irrigators/weeders (7 days)	11.3	5.3	0.37
Picker operator	5.0	2.3	0.17
Module build operator	1.9	0.9	0.06
Raker	3.4	1.6	0.11
Tramper	8.3	3.9	0.27

^aAbsorbed daily dosage assumes 7.1% dermal absorption, 50% respiratory uptake of tribufos as a vapor with occupational exposure, inhalation rate of 14 L/minute, body weight of 75.9 kg, and 8-hour workday; the value represents the geometric mean for handlers and the arithmetic mean for harvesters based on the distribution of the data.

^bSeasonal average daily dosage assumes that workers are exposed 21 days in a 45-day season.

^cLifetime average daily dosage assumes an exposure over 40 years of a 70-year lifespan.

Source: CalEPA 2004

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5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Agricultural workers who use tribufos as a defoliant in cotton fields will have higher exposure to this substance than the general population. This includes personnel who mix or load tribufos for aerial or ground-based spraying, pilots, flaggers, or workers who tend to the cotton plants post application.

Comparison of the data presented in Tables 5-7 and 5-8 indicates that dermal and inhalation exposure to workers treating cotton fields with tribufos will be several orders of magnitude greater than the average daily dietary intakes of the general population. Also, field workers who tend to cotton plants are potentially exposed to high levels of tribufos from postapplication residues.

Children of agricultural employees who work with tribufos are potentially exposed to residues from their parent's work clothing. Researchers have studied organophosphate residues in vehicles and homes of agricultural workers in the state of Washington and determined that the transport of pesticides from the workplace to the residence on a worker's clothing or person could lead to exposure to family members (Curl et al. 2002; Loewenherz et al. 1997; Lu et al. 2000). Take-home exposures to family members can be reduced by changing out of work clothes and shoes before entering the home and laundering work clothes separately from other family clothing.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of tribufos is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of tribufos.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to tribufos that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of tribufos. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

6.2 IDENTIFICATION OF DATA NEEDS

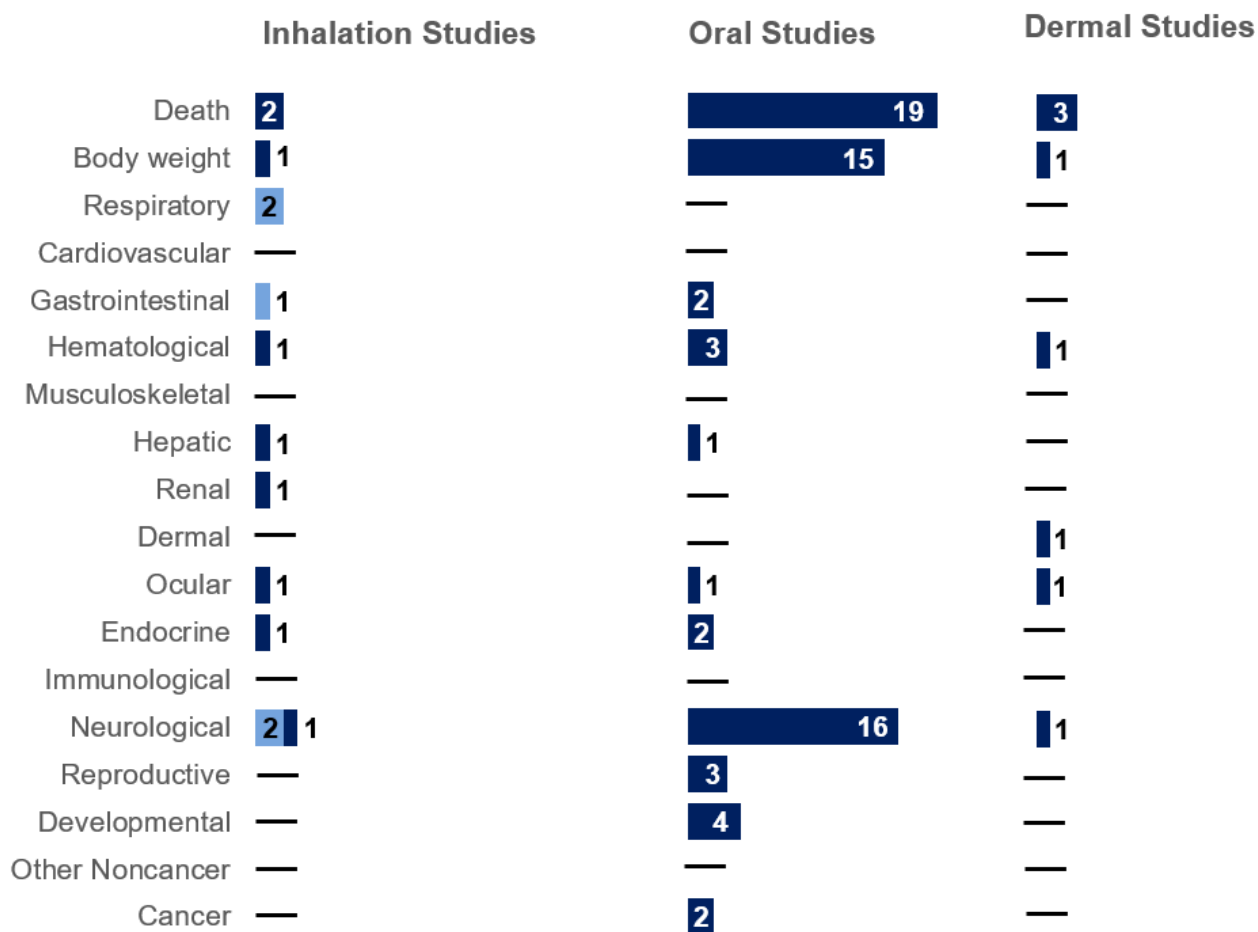
Missing information in Figure 6-1 should not be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

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Figure 6-1. Summary of Existing Health Effects Studies on Tribufos By Route and Endpoint*

Potential neurological and body weight effects were the most studied endpoints

The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints

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Acute-Duration MRLs. No adequate data were located regarding the effects of acute-duration exposure to tribufos in humans. Acute-duration animal studies that employed inhalation or dermal exposure routes were designed to evaluate lethality (EPA 1991a, 1992a, 1993b; Gaines 1969). A well-designed acute-duration inhalation study in an animal species is needed in order to derive an acute-duration inhalation MRL for tribufos.

Acute-duration oral animal studies evaluated body weight, clinical signs, AChE activity, and/or developmental endpoints (Astroff and Young 1998; EPA 1990b, 1990c, 2012a, 2012b, 2012c, 2012d, 2012e, 2012f). The lowest LOAEL for tribufos-mediated body weight effects was 9 mg/kg/day in a rabbit study (EPA 1990c). NOAELs for developmental endpoints in rat and rabbit studies ranged from 7 to 28 mg/kg/day (Astroff and Young 1998; EPA 1990b, 1990c, 2012f). Collectively, the acute-duration oral studies identified decreased RBC AChE activity as the most sensitive tribufos-mediated effect from acute-duration oral exposure. A rabbit study (EPA 1990c) identified the lowest LOAEL (1 mg/kg/day) for tribufos-induced RBC AChE inhibition. The effect occurred at the lowest dose tested and represented a serious effect (>60% RBC AChE inhibition). Results from available rat studies identified LOAELs at doses ≥ 5 times higher than the serious LOAEL from the rabbit study. A well-designed acute-duration oral toxicity study in rabbits treated at lower dose levels than the serious LOAEL of 1 mg/kg/day is needed to identify the threshold of tribufos-induced toxicologically-significant RBC AChE inhibition.

Intermediate-Duration MRLs. No adequate data were located regarding the effects of intermediate-duration exposure to tribufos in humans. Systemic and neurological endpoints were evaluated in one intermediate-duration inhalation study of rats (EPA 1992b) and one intermediate-duration dermal study of rabbits (EPA 1993d). One intermediate-duration oral study of rats evaluated the potential for tribufos to induce an immune response (EPA 2013). Several intermediate-duration oral studies in laboratory animals evaluated systemic and neurological endpoints (Astroff et al. 1998; CalEPA 2004; EPA 1991b, 1992c, 1992d, 2005a, 2013). Available data were considered adequate for derivation of intermediate-duration inhalation and oral MRLs for tribufos.

Chronic-Duration MRLs. No data were located regarding the effects of chronic-duration exposure to tribufos in humans. No data were located regarding the effects of chronic-duration inhalation or dermal exposure in laboratory animals. Systemic and neurological endpoints have been adequately assessed in chronic-duration oral studies of laboratory animals (CalEPA 2004; EPA 1990a, 1991b, 1992d). The chronic-duration oral animal data were considered adequate for derivation of a chronic-duration oral

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MRL for tribufos. A well-designed chronic-duration inhalation study in animals is needed in order to derive a chronic-duration inhalation MRL for tribufos.

Health Effects. Adverse effects have been observed in experimental animals following inhalation or oral exposure to tribufos. However, the general population is not likely to be exposed to environmental levels of tribufos high enough to cause similar effects.

Respiratory Effects. Cough and throat irritation were reported in residents living in cotton growing areas in which tribufos was used (Scarborough et al. 1989). Another epidemiological study found an increase in deaths from respiratory causes (Ames and Gregson 1995). As discussed in Section 2.4, interpretation of the results of these study is limited by study deficiencies. Limited data are available regarding respiratory effects in experimental animals exposed to tribufos aerosols. Clinical signs and gross pathology (dyspnea, nasal discharge, discolored lungs and nasal bones) were reported among rats exposed nose-only to tribufos for 4 hours.

Neurological Effects. Repeated inhalation exposures of experimental animals to tribufos have resulted in clinical signs of neurological effects such as altered gait, decreased movement, constricted pupils, piloerection, aggressive behavior, sensitivity to touch, convulsions, salivation, decreased RBC and brain AChE activity, and depressed amplitude of a- and b-waves in electro-retinographic tests.

Hematological Effects. Effects such as decreases in RBC counts, hemoglobin content, and hematocrit have been reported in experimental animals repeatedly exposed to tribufos by inhalation or oral routes.

Gastrointestinal Effects. An epidemiological study found an increased risk of nausea and diarrhea among residents with a high probability of tribufos exposure (Scarborough et al. 1989); as noted in Section 2.6, there are a number of deficiencies that limit the interpretation of the study results. Degenerative effects in the gastrointestinal tract have been reported among experimental animals receiving tribufos from the diet for intermediate- and chronic-duration exposure periods.

Epidemiology and Human Dosimetry Studies. Available human data are limited. One study reported increased risk of self-reported symptoms (cough, throat irritation) among 232 residents of three

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towns in cotton-growing areas where tribufos was used during the 1987 cotton defoliation season (Scarborough et al. 1989). Another study provided evidence for increased mortality from respiratory causes among residents in San Joaquin Valley cotton-growing areas during the cotton defoliation period (Ames and Gregson 1995). No quantitative exposure-response data are available for tribufos. Human populations with potential for exposure to tribufos should continue to be monitored for potential exposure-related health effects.

Quantitative data for humans exposed by inhalation, oral, and/or dermal routes would be useful to directly evaluate the hazards of human exposure to tribufos, especially among tribufos production workers, applicators of tribufos to cotton crops, workers involved in harvest of cotton, and populations living near areas where tribufos is applied. Of particular interest would be studies of individuals exposed to tribufos alone, but not other organophosphorus compounds known to act as AChE inhibitors.

Biomarkers of Exposure and Effect.

Exposure. Tribufos in blood or urine serves as the only reliable biomarker of exposure. Tribufos is rapidly metabolized to numerous metabolites that have been detected in urine of rats treated with radiolabeled tribufos; however, only butyl-gamma-glutamylcysteinylglycine disulfide was identifiable (CalEPA 2004). It is not likely that tribufos metabolites would serve as reliable indicators of exposure to tribufos. Additional studies could be designed to identify tribufos metabolites in blood, urine, and/or feces that could serve as biomarkers of exposure to tribufos. However, available data indicate that many of the tribufos metabolites likely include endogenous products such as fatty acids and amino acids that would not serve as biomarkers of exposure to tribufos *per se*.

Effect. The most prominent effect of tribufos toxicity is its effect on AChE activity and resulting clinical signs of neurotoxicity at relatively high doses. However, these effects are not specific to tribufos.

Absorption, Distribution, Metabolism, and Excretion. Available animal data demonstrate that tribufos can be absorbed via the lung, gastrointestinal tract, and skin (CalEPA 2004; EPA 1991a, 1992a, 1992b, 2000b). Tribufos is rapidly distributed in the blood; the liver typically contains the highest concentration of absorbed tribufos. Metabolism of tribufos in animal systems has been studied both *in vivo* (Abou-Donia 1979; CalEPA 2004; Fujioka and Casida 2007; Hur et al. 1992; Sahali et al. 1994) and *in vitro* (Fujioka and Casida 2007; Hur et al. 1992; Levi and Hodgson 1985; Wing et al. 1983, 1984). Evidence that tribufos is extensively metabolized includes the detection of 17 unidentified metabolites in

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the urine of tribufos-treated rats (CalEPA 2004), 22 mainly unidentified metabolites in the liver from a tribufos-treated goat, and differing metabolic profiles (mainly unidentified tribufos metabolites) in urine, tissue, and milk from the goat (Sahali et al. 1994). Most of the radioactivity from orally-administered ^{14}C -tribufos to rats was recovered in the urine (and feces to a lesser extent) within 72 hours postdosing (CalEPA 2004). As stated previously, numerous unidentified metabolites were found in the urine and feces. Additional animal studies could be designed to identify specific tribufos metabolites.

Comparative Toxicokinetics. No human data were located regarding the toxicokinetics of tribufos in humans, thus precluding comparisons between humans and laboratory animals.

Children's Susceptibility. No information was located regarding age-related differences in susceptibility to tribufos toxicity in humans. Results from acute-duration oral studies in rats suggest that neonates may be somewhat more sensitive than young adults to tribufos neurotoxicity as assessed by clinical signs (EPA 2012a, 2012b, 2012c, 2012d, 2012e). If human populations with potential for significant exposure to tribufos can be identified, such populations should be evaluated for potential age-related differences in susceptibility to tribufos toxicity.

Physical and Chemical Properties. Data for the physical and chemical properties of tribufos have been summarized in Chapter 4. Measured values are available for the most important properties (EPA 2000a, 2006b; HSDB 2010; Tomlin 2003) and no data needs are identified at this time.

Production, Import/Export, Use, Release, and Disposal. Available data indicate that tribufos is produced, processed, or used at only two U.S. facilities. Only seven U.S. registered products contain tribufos. It is not imported to the United States and there are no data regarding its export. The sole registered use for tribufos is as a cotton plant defoliant. The two U.S. facilities dispose of tribufos via the air. Tribufos commercial information is updated yearly in the TRI, which provides lists of facilities and emissions. No data needs are identified at this time.

Environmental Fate. Based upon the Henry's Law constant and vapor pressure of tribufos, volatilization is not expected to be an important environmental fate process; however, field studies conducted by Potter et al. (2002) indicated that volatilization may be a significant process under field conditions, particularly under warm and humid conditions that exist in cotton-growing regions. Additional volatilization studies are needed to determine the relative importance of this transport process. In addition, a great deal of uncertainty exists in the aerobic biodegradation half-life of tribufos. EPA

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(2006b) assigned a half-life of >700 days, while other studies have suggested significantly shorter persistence in soils (Bayer 2008; Potter et al. 2002). Additional research regarding the volatilization potential and the degradation half-life are important because these values are used in modeling studies that estimate tribufos levels in ecological and human health risk assessments.

Bioavailability from Environmental Media. Tribufos does not significantly bioaccumulate in aquatic organisms (EPA 1981, 2008). Moreover, since it only has limited applications to cotton crops, it is not expected to be a major contaminant in natural waters. No data needs are identified regarding its bioavailability from water. Because tribufos must penetrate the leaf surface to act as a defoliant, it is known to be taken up from the surface of plants; however, its bioavailability in soils by the root system is not well understood. Substances such as tribufos that adsorb strongly to soils often have low bioavailability to plants; therefore, uptake of tribufos by the root system of cotton plants is not expected to be an important fate process.

Food Chain Bioaccumulation. There is no evidence that tribufos bioaccumulates in either terrestrial or aquatic food chains (CalEPA 2000; EPA 1981, 2006b, 2008). No data needs are identified at this time.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of tribufos in contaminated media at hazardous waste sites are needed. These data could then be used in combination with the known body burden of tribufos to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Limited data exist regarding human exposure levels of tribufos to the general population and to applicators who apply it. A data need for biological monitoring of occupationally exposed individuals has been identified. Since tribufos is only applied to cotton, monitoring data of groundwater surrounding cotton-growing regions for the presence of tribufos would be useful to assess potential exposure to populations that reside in these locations.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children are exposed to very low levels of tribufos through dietary routes. Estimates on the average daily intake are available (Gunderson 1988, 1995a, 1995b). Tribufos is very rarely detected in food sources and the estimated intakes are low; however, tribufos levels have not been assessed in milk of lactating mothers or in maternal/fetal cord blood obtained from individuals living

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near, or working in, sites where tribufos is sprayed. This information is needed for adequate assessment of the potential for exposure of developing fetuses/infants to tribufos.

6.3 ONGOING STUDIES

No active projects were identified in the National Institutes of Health (NIH) Research Portfolio Online Reporting Tools, Expenditures and Results (RePORTER) regarding ongoing research related to tribufos (RePORTER 2019).

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding tribufos in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for tribufos.

Table 7-1. Regulations and Guidelines Applicable to Tribufos

Agency	Description	Information	Reference
Air			
EPA	RfC	No data	EPA 2000a, 2006
WHO	Air quality guidelines	No data	WHO 2010
Water & Food			
EPA	Drinking water standards and health advisories	No data	EPA 2018a
	National primary drinking water regulations	No data	EPA 2009
	Acute RfD	0.01 mg/kg/day ^a	EPA 2000a
	Chronic RfD	0.001 mg/kg/day ^b	
	Tolerances for pesticide chemical residues in or on food commodities		EPA 2019c
	Milk	0.01 ppm	
	Meat/meat byproducts (cattle, goat, hog, horse, sheep)	0.02 ppm	
	Fat (cattle, goat, hog, horse, sheep)	0.15 ppm	
	Undelinted cottonseed	4 ppm	
	Cotton gin byproducts	40 ppm	
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	Substances Added to Food	No data ^c	FDA 2019
Cancer			
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	Unlikely human carcinogen at low doses; likely human carcinogen at high doses	EPA 1997
IARC	Carcinogenicity classification	No data	IARC 2019

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Table 7-1. Regulations and Guidelines Applicable to Tribufos

Agency	Description	Information	Reference
Occupational			
ACGIH	TLV (TWA)	No data	ACGIH 2018
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	No data	OSHA 2018a
	PEL (8-hour TWA) for shipyards and construction	No data	OSHA 2018b
	PEL (8-hour TWA) for construction	No data	OSHA 2018c
NIOSH	REL (up to 10-hour TWA)	No data	NIOSH 2018
Emergency Criteria			
EPA	AEGLs-air	No data	EPA 2018b
DOE	PACs-air	No data	DOE 2018

^aThe acute RfD of 0.01 mg/kg/day was derived from a NOAEL of 1 mg/kg/day based on decreases in plasma, and a LOAEL of 7 mg/kg/day for RBC ChE activity in a prenatal developmental toxicity study in rats.

^bThe chronic RfD of 0.001 mg/kg/day was derived from a NOAEL of 0.1 mg/kg/day based on plasma ChE inhibition in a chronic toxicity study in dogs.

^cThe Substances Added to Food inventory replaces the EAFUS list.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; ChE = cholinesterase; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FAO = Food and Agricultural Organization of the United Nations; FDA = Food and Drug Administration; FQPA = Food Quality Protection Act; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; LOAEL = Lowest observed adverse effect level; NIOSH = National Institute for Occupational Safety and Health; NOAEL = No observed adverse effect level; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PAD = population adjusted dose; PEL = permissible exposure limit; RBC = red blood cell; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit value; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥ 365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

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Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 74-48-8
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: Available acute-duration inhalation data were not considered adequate for derivation of an acute-duration inhalation MRL for tribufos.

Rationale for Not Deriving an MRL: No exposure-response human data are available. Available acute-duration inhalation information for tribufos in experimental animals is restricted to a single acute lethality study that reported 4-hour LC₅₀ values of 4,650 and 2,460 mg/m³ for male and female Sprague-Dawley rats, respectively. This study is inadequate for deriving an acute-duration inhalation MRL for tribufos.

Agency Contacts (Chemical Managers): Rae T. Benedict, Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 74-48-8
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.04 mg/m³
Critical Effect: Decreased red blood cell acetylcholinesterase (RBC AChE) activity
Reference: EPA 1992b
Point of Departure: NOAEL of 2.43 mg/m³ (NOAEL_{HEC} of 1.22 mg/m³)
Uncertainty Factor: 30
LSE Graph Key: 2
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.04 mg/m³ has been derived for tribufos based on decreased RBC AChE activity among female Wistar rats exposed to tribufos aerosol for 6 hours/day, 5 days/week for 13 weeks (EPA 1992b). The MRL is based on a NOAEL_{HEC} of 1.22 mg/m³ and a total uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: No exposure-response human data are available. Available animal data are restricted to a single well-designed of rats intermittently exposed to tribufos aerosol for 13 weeks (EPA 1992b). In the study, decreased RBC AChE activity was the most sensitive effect of tribufos toxicity.

Selection of the Principal Study: The 13-week inhalation study of Wistar rats (EPA 1992b) is the only available intermediate-duration inhalation study. The study monitored multiple parameters and endpoints and thus was considered adequate in design to serve as basis for deriving an intermediate-duration inhalation MRL for tribufos.

Summary of the Principal Study:

EPA. 1992b. Data evaluation report. Study of the subchronic inhalation toxicity to rats in accordance with OECD guideline No. 413; J. Pauluhn; Bayer AG, FRG; Report No: 102697; June 2, 1992; MRID 423998-01.

Groups of Wistar rats (10/sex/group) were exposed (head-only) to tribufos aerosol (MMAD 1.2–1.3 µm) for 6 hours/day, 5 days/week for 13 weeks at nominal concentrations of 0, 1, 2, 12, or 60 mg/m³ (analytically-determined concentrations of 0, 0.93, 2.43, 12.2, and 59.5 mg/m³, respectively). Body weights were monitored, and appearance and behavior were evaluated before and after exposure (not during exposure) and on days without exposure. Rectal temperatures were determined for five rats/sex/group monthly immediately following exposure. Blood samples were obtained monthly for hematology and clinical chemistry evaluations. Urine was collected individually during the 12th exposure week for urinalysis. Eye examinations were performed on all rats prior to the first exposure and near the end of the study. Electroretinographic tests were performed on five rats/sex from controls and 59.5 mg/m³ groups during week 10 and on five rats/sex from controls and each exposure group prior to terminal sacrifice. At necropsy, selected organs and tissues (adrenals, brain, heart, kidneys, liver, lungs, spleen, thymus, thyroid, ovaries, and testes) were removed and weighed. Histopathological examinations were performed on samples from all major organs and tissues.

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The most sensitive effect of repeated inhalation exposure to tribufos was that of decreased RBC AChE activity at various time points during the 13-week study. There were no tribufos exposure-related deaths or signs of morbidity. Three rats were sacrificed or died as a result of nontreatment-related causes. Clinical signs were noted in all rats of the 59.5 mg/m³ exposure group and included altered gait, decreased movement, changes in respiration, narrowed eyelids, constricted pupils, piloerection and unpreened coat, aggressive behavior, sensitivity to touch, convulsions with spastic head movements, salivation, exophthalmos (abnormal protrusion of eyeballs), and hypothermia. No clinical signs were observed at lower tribufos exposure levels. There were no exposure-related adverse effects on body weight, hematology, urinalysis, or clinical chemistry assessments, with the exception of RBC and brain AChE activity in males (Table A-1) and females (Table A-2). In male rats, significantly lower RBC AChE activity was observed in the 1 mg/m³ exposure group (27% less than controls) at week 0 (but not at other time points) and in the 2.43 mg/m³ exposure group (26 and 21% less than controls at exposure weeks 0 and 8, respectively, but not at other time points); these results are considered spurious and not related to tribufos exposure. Significantly decreased RBC AChE activity was noted for all time points (weeks 0, 4, 8, 12, and 13) among 12.2 mg/m³ male and female rats (25–65% less than controls) and 59.5 mg/m³ (49–91% less than controls). At sacrifice, brain AChE activity among male and female rats was significantly decreased only at the 59.5 mg/m³ exposure level (40% less than controls). Treatment-related 20–59% RBC AChE inhibition is considered to represent a less serious adverse effect and ≥60% inhibition is considered to represent a serious adverse effect in the absence of more clear indicators of neurotoxicity (Chou and Williams-Johnson 1998). Ophthalmological examinations revealed no signs of tribufos exposure-related effects. However, at the 59.5 mg/m³ exposure level, male and female rats exhibited significantly depressed amplitude of a- and b-waves in electroretinographic testing, which was considered a tribufos-induced adverse effect. Male rats of the 59.5 mg/m³ exposure level exhibited significantly increased mean absolute and relative adrenal weight and significantly increased cortical fat deposition in the adrenals (magnitudes not included in the available DER). Minor changes in histology of the nasal and paranasal cavities and lungs were noted across all groups and were considered related to inhalation of vehicle rather than tribufos.

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Table A-1. Effect of Tribufos Aerosol on RBC and Brain AChE Activity in Male Wistar Rats Exposed for 6 Hours/Day, 5 Days/Week for 13 Weeks

Exposure parameters			
Testing week	Exposure level (mg/m ³)	Mean RBC AChE activity in kU/L (change from controls)	Mean brain AChE activity in U/g (change from controls)
0	0	1.44	NA
	0.93	1.05 (-27%) ^a	NA
	2.43	1.06 (-26%) ^b	NA
	12.2	0.92 (-36%) ^c	NA
	59.5	0.63 (-56%) ^c	NA
4	0	0.74	NA
	0.93	0.63 (-15%)	NA
	2.43	0.64 (-14%)	NA
	12.2	0.37 (-50%) ^c	NA
	59.5	0.09 (-88%) ^c	NA
8	0	0.78	NA
	0.93	0.69 (-12%)	NA
	2.43	0.62 (-21%) ^b	NA
	12.2	0.35 (-55%) ^c	NA
	59.5	0.08 (-90%) ^c	NA
12	0	1.18	NA
	0.93	1.15 (-3%)	NA
	2.43	1.11 (-6%)	NA
	12.2	0.45 (-62%) ^c	NA
	59.5	0.13 (-89%) ^c	NA
13	0	0.80	12.01
	0.93	0.76 (-5%)	11.78 (-2%)
	2.43	0.64 (-20%)	12.23 (+2%)
	12.2	0.28 (-65%) ^c	11.78 (-2%)
	59.5	0.15 (-81%) ^c	7.15 (-40%) ^c

^aNot statistically significantly different from control.

^bStatistically significantly different from control ($p \leq 0.05$), but considered spurious due to lack of significant change at other time points.

^cStatistically significantly different from control ($p \leq 0.01$).

AChE = acetylcholinesterase; kU = kiloU, where U = a measure of enzymatic activity (1 U = amount of an enzyme that catalyzes the conversion of 1 μ mol of substrate per minute); NA = not applicable; RBC = red blood cell

Source: EPA 1992b

Table A-2. Effect of Tribufos Aerosol on RBC and Brain AChE Activity in Female Wistar Rats Exposed for 6 Hours/Day, 5 Days/Week for 13 Weeks

Exposure parameters			
Testing week	Exposure level (mg/m ³)	Mean RBC AChE activity in kU/L (change from controls)	Mean brain AChE activity in U/g (change from controls)
0	0	1.32	NA
	0.93	1.20 (-9%)	NA
	2.43	1.35 (+2%)	NA
	12.2	0.99 (-25%) ^a	NA
	59.5	0.67 (-49%) ^b	NA
4	0	0.90	NA
	0.93	0.91 (+1%)	NA
	2.43	0.96 (+5%)	NA
	12.2	0.36 (-60%) ^b	NA
	59.5	0.17 (-81%) ^b	NA
8	0	0.62	NA
	0.93	0.65 (+5%)	NA
	2.43	0.69 (+11%)	NA
	12.2	0.32 (-48%) ^b	NA
	59.5	0.07 (-89%) ^b	NA
12	0	1.09	NA
	0.93	1.10 (+1%)	NA
	2.43	1.14 (+5%)	NA
	12.2	0.41 (-62%) ^a	NA
	59.5	0.10 (-91%) ^b	NA
13	0	0.92	11.69
	0.93	0.93 (+1%)	11.87 (+2%)
	2.43	0.81 (-12%)	11.64 (-0%)
	12.2	0.33 (-64%) ^b	11.45 (-2%)
	59.5	0.12 (-87%) ^b	6.99 (-40%) ^b

^aStatistically significantly different from control (p≤0.05).

^bStatistically significantly different from control (p≤0.01).

AChE = acetylcholinesterase; kU = kiloU, where U = a measure of enzymatic activity (1 U = amount of an enzyme that catalyzes the conversion of 1 μmol of substrate per minute); NA = not applicable; RBC = red blood cell

Source: EPA 1992b

Selection of the Point of Departure for the MRL: The most sensitive effect of repeated inhalation exposure to tribufos was that of decreased RBC AChE activity at various time points during the 13-week study. Benchmark dose (BMD) analysis of the critical effect dataset (RBC AChE activity) was performed on the datasets for RBC AChE activity in the male and female rats at the 13-week timepoint. Although the publicly-available DER (EPA 1992b) of the unpublished study included only mean values for RBC AChE activity without a measure of variance, standard deviation values were reported in the unpublished study (MRID42399801). All available continuous variable models in EPA's Benchmark Dose Software

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(BMDS, Version 3.1.1) were fit to the data for RBC AChE activity in the male and female rats separately using a benchmark response (BMR) of 20% change from controls.

None of the models provided adequate fit to the modeled variance ($p < 0.05$) for males or females using either constant or nonconstant variance. Therefore, a BMD approach to deriving an intermediate-duration inhalation MRL was not used. However, an intermediate-duration inhalation MRL for tribufos can be derived using a NOAEL/LOAEL approach. The principal study identified a NOAEL of 2.43 mg/m^3 and a serious LOAEL of 12.2 mg/m^3 for $>60\%$ decreased RBC AChE activity in male and female Wistar rats. The NOAEL (2.43 mg/m^3) serves as the point of departure (POD) for deriving an intermediate-duration inhalation MRL for tribufos.

Adjustment for Intermittent Exposure: The NOAEL of 2.43 mg/m^3 was adjusted from intermittent to continuous exposure as follows:

$$\text{NOAEL}_{\text{ADJ}} = 2.43 \text{ mg/m}^3 \times 6 \text{ hours/24 hours} \times 5 \text{ days/7 days} = 0.43 \text{ mg/m}^3$$

Human Equivalent Concentration: A regional deposited dose ratio (RDDR_{ER}) of 2.839 for extrapulmonary effects (RBC AChE inhibition) in female Wistar rats (slightly lower than the RDDR_{ER} of 2.926 for the males and therefore considered slightly more protective) was used to extrapolate from rats to humans. The RDDR_{ER} was calculated using EPA's software (Version 2.3) (EPA 1994) for calculating RDDR_{ER}s and the parameters listed in Table A-3.

Table A-3. Parameters^a Used to Calculate the Regional Deposited Dose Ratio (RDDR_{ER}) for Tribufos-induced Extrapulmonary Effects Using EPA's Software (Version 2.3) and RDDR_{ER} Values for Male and Female Wistar Rats

Biological parameters ^b	Wistar rat		Human
	Male	Female	
Surface area			
Extrathoracic	15 cm ²	15 cm ²	200 cm ²
Tracheobronchial	22.5 cm ²	22.5 cm ²	3,200 cm ²
Pulmonary	0.34 m ²	0.34 m ²	54 m ²
Minute ventilation	122.1 mL	160.1	147.24 mL
Body weight	217 g	156 g	70 kg
RDDR _{ER}	2.926	2.839	—

^aMass median aerodynamic diameter (MMAD) = $1.2 \text{ }\mu\text{m}$; geometric standard deviation = $1.4 \text{ }\mu\text{m}$ (EPA 1992b).

^bParameters are default values for rats and humans from the U.S. Environmental Protection Agency (EPA) software, except for default subchronic body weights for male and female Wistar rats (EPA 1988) because quantitative body weight data were not included in the available DER (EPA 1992b).

Source: EPA 1992b

The human equivalent concentration was calculated using Equation 4-5 (EPA 1994) as follows:

$$\text{NOAEL}_{\text{HEC}} = \text{NOAEL}_{\text{ADJ}} \times \text{RDDR}_{\text{ER}} = 0.43 \text{ mg/m}^3 \times 2.839 = 1.22 \text{ mg/m}^3$$

Uncertainty Factor: The NOAEL_{HEC} of 1.22 mg/m^3 was divided by a total uncertainty factor of 30:

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- 3 for extrapolation from animals to humans using dosimetric adjustment
- 10 for human variability

MRL = NOAEL_{HEC} ÷ uncertainty factors

$$1.22 \text{ mg/m}^3 \div (3 \times 10) = 0.04 \text{ mg/m}^3$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Available animal studies that evaluated the effects of intermediate-duration oral exposure to tribufos identified decreased RBC AChE activity as the most sensitive effect of tribufos toxicity (Astroff et al. 1998; CalEPA 2004; EPA 1991b, 1992c, 2005a, 2013).

Agency Contacts (Chemical Managers): Rae T. Benedict, Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 74-48-8
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: No human or animal data were located regarding health effects from chronic-duration inhalation exposure to tribufos.

Rationale for Not Deriving an MRL: No chronic-duration inhalation data are available.

Agency Contacts (Chemical Managers): Rae T. Benedict, Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 74-48-8
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: Available acute-duration oral data were not considered adequate for derivation of an acute-duration inhalation MRL for tribufos.

Rationale for Not Deriving an MRL: No human data are available. Acute-duration oral animal studies evaluated body weight, clinical signs, AChE activity, reproductive, and/or developmental endpoints (Astroff and Young 1998; EPA 1990b, 1990c, 2012a, 2012b, 2012c, 2012d, 2012e, 2012f). The lowest LOAEL for tribufos-mediated body weight effects was 9 mg/kg/day in a rabbit study (EPA 1990c). NOAELs for developmental endpoints in rat and rabbit studies ranged from 7 to 28 mg/kg/day (Astroff and Young 1998; EPA 1990b, 1990c, 2012f). Collectively, the acute-duration oral studies identified decreased RBC AChE activity as the most sensitive tribufos-mediated effect from acute-duration oral exposure. Table A-4 summarizes NOAELs and LOAELs for tribufos-mediated effects on RBC AChE activity following intermediate-duration oral exposure. The rabbit study (EPA 1990c) identified the lowest LOAEL (1 mg/kg/day) for tribufos-induced RBC AChE inhibition. The effect occurred at the lowest dose tested and represented a serious effect (>60% RBC AChE inhibition). ATSDR does not derive an MRL based on a serious LOAEL in the absence of an identified NOAEL. Results from available rat studies were not considered appropriate PODs for deriving an acute-duration oral MRL for tribufos because they identified LOAELs at doses ≥ 5 times higher than the serious LOAEL from the rabbit study in the absence of NOAELs. Therefore, ATSDR elected not to derive an acute-duration oral MRL for tribufos.

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Table A-4. NOAELs and LOAELs for RBC AChE Inhibition Following Acute-Duration Oral Exposure to Tribufos

Study design (doses in mg/kg/day)	Dose (RBC AChE % inhibition)			Reference
	NOAEL ^a	LOAEL ^b	Serious LOAEL ^c	
Young adult female Sprague-Dawley rats GO, 1 time (0, 80)	ND	ND	80 (up to 90%)	EPA 2012c
Young adult female Sprague-Dawley rats GO, 1 time (0, 2, 10, 80)	10	ND	80 (74%)	EPA 2012d
11-Day-old Sprague-Dawley rat pups GO, 1 time (0, 50)	M: ND F: ND	M: ND F: ND	M: 50 (90%) F: 50 (92%)	EPA 2012b
11-Day-old Sprague-Dawley rat pups GO, 1 time (0, 20, 40, 50)	M: ND F: ND	M: 20 (59%) F: ND	M: 40 (76%) F: 20 (71%)	EPA 2012a
11-Day-old Sprague-Dawley rat pups GO, 1 time (0, 2, 10, 50)	M: 2 F: ND	M: 10 (47%) F: 2 (27%)	M: 50 (86%) F: 50 (89%)	EPA 2012d
Young adult female Sprague-Dawley rats GO, 1 time/day, 11 days (0, 0.1, 1, 5)	1	ND	5 (64%)	EPA 2012e
11-Day-old Sprague-Dawley rat pups GO, 1 time/day, 11 days (0, 0.1, 1, 5)	M: 1 F: 1	M: ND F: ND	M: 5 (66%) F: 5 (69%)	EPA 2012e
11-Day-old Sprague-Dawley rat pups GO, 1 time/day, 11 days (0, 5, 10, 15, 20)	M: ND F: ND	M: 5 (49%) F: 5 (36%)	M: 15 (83%) M: 15 (66%)	EPA 2012a
Pregnant Sprague-Dawley rats, G, 1 time/day, GDs 6–15 (0, 1, 7, 28)	1	ND	7 (71%)	Astroff and Young 1998; EPA 1990b
Pregnant Sprague-Dawley rats GO, 1 time/day GDs 6–19 (0, 0.3–0.8, 7, 28)	0.3 ^d	ND	7 (75%)	EPA 2012f
Pregnant American Dutch rabbits G, 1 time/day, GDs 7–19 (0, 1, 3, 9)	ND	ND	1 (70%)	EPA 1990c

^a<20% decrease in RBC and/or brain AChE represents a NOAEL.

^b20–59% decrease in RBC and/or brain AChE activity represents a less serious adverse effect.

^c≥60% decrease in RBC and/or brain AChE activity represents a serious adverse effect.

^dLow test substance concentrations measured in the 1 mg/kg/day dose group resulted in estimated time-weighted average dosing in the range of 0.3–0.8 mg/kg/day; using a conservative approach, the lowest dose in the range is considered the NOAEL.

AChE = acetylcholinesterase; F = females; G = gavage; GD = gestation day; GO = gavage in oil; LOAEL = lowest-observed-adverse-effect level; M = males; ND = not determined; NOAEL = no-observed-adverse-effect level; RBC = red blood cell

Agency Contacts (Chemical Managers): Rae T. Benedict, Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 74-48-8
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.003 mg/kg/day
Critical Effect: Decreased red blood cell acetylcholinesterase (RBC AChE) activity
Reference: Astroff et al. 1998; EPA 1992c
Point of Departure: NOAEL of 0.28 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 14
Species: Rat

MRL Summary: An intermediate-duration oral MRL of 0.003 mg/kg/day has been derived for tribufos based on decreased RBC AChE activity in Sprague-Dawley rats administered tribufos in the diet in a 2-generation toxicity study (Astroff et al. 1998; EPA 1992c). The MRL is based on a NOAEL of 0.28 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Potential candidate critical effects for deriving an intermediate-duration oral MRL for tribufos are summarized in Table A-5. Quantitative data were not available for the reported hematological effects in the rat study summarized by CalEPA (2004) and EPA (1992d). Therefore, the neurological effect (tribufos-mediated decreased RBC AChE activity) was selected as the critical effect for deriving an intermediate-duration oral MRL for tribufos.

Table A-5. Summary of Potential Candidate Critical Effects for Deriving an Intermediate-Duration Oral MRL for Tribufos from Dietary Studies

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hematological effects					
Fischer 344 rat	3- and 6-month evaluations in 2-year study	0.2 M 0.2 F	1.8 M 2.3 F	Decreases in RBC count, hemoglobin, hematocrit (quantitative data not available)	CalEPA 2004; EPA 1992d
Neurological effects					
Sprague-Dawley rat	2 generations (premating–lactation)	F0 M: 0.28 F0 F: 0.31	F0 M: 2.00 F0 F: 2.25	35 and 37% decreased RBC AChE activity in F0 males and females, respectively, during premating	Astroff et al. 1998; EPA 1992c

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Table A-5. Summary of Potential Candidate Critical Effects for Deriving an Intermediate-Duration Oral MRL for Tribufos from Dietary Studies

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Han Wistar rat	4 weeks	0.43	4.32	66% decreased RBC AChE activity (serious LOAEL)	EPA 2013
Wistar rat	42 days (GD 0–LD 21)	0.4	3.4	76% decreased RBC AChE activity (serious LOAEL)	EPA 2005a
CD-1 mouse	8 weeks	3.4 M 5.6 F	9.4 M 14.3 F	37 and 44% decreased RBC AChE activity in males and females, respectively	CalEPA 2004
Beagle dog	364 days	0.4 M 0.4 F	1.7 M 2.0 F	24 and 29% decreased RBC AChE activity in males and females, respectively	EPA 1991b

AChE = acetyl cholinesterase; F = female(s); GD = gestation day; LD = lactation day; LOAEL = lowest observed adverse effect level; M = male(s); NOAEL = no-observed-adverse-effect level; RBC = red blood cells

Selection of the Principal Study: The 364-day dietary study in dogs (CalEPA 2004; EPA 1991b) and the 2-generation dietary study in rats (Astroff et al. 1998; EPA 1992c) identified similar LOAEL values (1.7 mg/kg/day for male dogs versus 2.0 and 2.09 mg/kg/day for the F0 and F1 male rats, respectively). The NOAEL for the F0 and F1 male rats (0.28 mg/kg/day) was slightly lower than the NOAELs for the F0 and F1 female rats (0.31 mg/kg/day) and the male dogs (0.4 mg/kg/day). Furthermore, the rat study employed more animals per dose group than the dog study (10 rats/sex/dose versus 4 dogs/sex/dose). Therefore, the 2-generation rat study was selected as the principal study for deriving an intermediate-duration oral MRL for tribufos.

Summary of the Principal Study:

Astroff AB, Freshwater KJ, Eigenberg DA. 1998. Comparative organophosphate-induced effects observed in adult and neonatal Sprague-Dawley rats during the conduct of multigeneration toxicity studies. *Reprod Toxicol* 12(6):619-645.

EPA. 1992c. A two-generation dietary reproduction study in rats using tribufos (DEF). D.A. Eigenberg, Mobay, Corporate Toxicology Department, study number 88-971-AK; Sept 10, 1991. MRID 420401-01. Memorandum. Tribufos (DEF) reproduction studies. U.S. Environmental Protection Agency.

Groups of Sprague-Dawley rats (30/sex/group) were administered tribufos in the diet for 10 weeks prior to mating and up to 21 or 28 days of mating, and throughout 3 weeks of gestation (F0 males and females) and 3 weeks of lactation (F0 females) at concentrations of 0, 4, 32, or 260 ppm. Groups of F1 offspring (30/sex/group) were continued on the same treatment schedule as their parents to produce F2 weanlings. Parental rats were monitored for clinical signs, body weight, and food consumption. Estrous cyclicity was evaluated in selected female parental rats. At sacrifice (F0 and F1 parental males following delivery of F1 and F2 litters, respectively; F0 and F1 parental females at F1 and F2 pup weaning, respectively), parental rats were subjected to comprehensive gross pathological examination; histopathological examinations were performed on reproductive organs and tissues, pituitary, and gross lesions. Plasma ChE and RBC AChE activities were determined from 10 parental rats/sex from each generation at 56 days (F0) and 62 days (F1) of premating tribufos treatment and again at terminal sacrifice, at which time brain tissue was removed and processed for brain AChE activity determination. F1 pups surviving to lactation

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day 21 and all F2 pups were monitored periodically for body weight during the lactation period. F1 litters were culled to four pups/litter on lactation day 4. Plasma ChE activity and RBC and brain AChE activities were determined for one F1 and one F2 pup of each sex from each of 10 litters at lactation days 4 and 21. Selected reproductive endpoints, fertility, and fetal and pup viability were evaluated.

The study authors calculated tribufos doses (reported in Astroff et al. 1998) based on dietary concentrations, food intake, and body weight data. At dietary concentrations of 4, 32, and 260 ppm, author-calculated tribufos doses to F0 parental rats were 0.28, 2.0, and 17.6 mg/kg/day, respectively, for the males and 0.31, 2.25, and 20.04 mg/kg/day, respectively, for the females during pre-mating treatment. Calculated doses to dams were 0.27, 2.03, and 18.07 mg/kg/day, respectively, during gestation and 0.81, 6.13, and 42.23 mg/kg/day, respectively, during lactation. Author-calculated tribufos doses to F1 parental rats were 0.28, 2.09, and 20.63 mg/kg/day, respectively, for the males, and 0.31, 2.40, and 22.93 mg/kg/day, respectively, for the females during pre-mating treatment. Calculated doses to the F1 dams were 0.28, 2.08, and 19.03 mg/kg/day, respectively, during gestation and 0.84, 6.77, and 49.61 mg/kg/day, respectively, during lactation.

There were no remarkable clinical signs or gross or histopathologic findings among adults or pups of either generation. Body weight was not affected in male or female F0 parental rats during the premating phase. Gestational body weight of high-dose F0 dams was 7% lower than that of controls on GD 20; maternal body weight was decreased by 8–12% throughout the lactation period and was accompanied by decreased maternal food consumption (approximately 20% less than that of controls). Significantly lower mean body weights were observed in high-dose F1 parental rats during the 10-week pre-mating phase (quantitative data for F1 males were not presented in the available DER). The high-dose F1 dams exhibited approximately 25% lower mean body weight than controls at the beginning of the pre-mating phase, which decreased in magnitude to approximately 8% less than controls at the end of the pre-mating period. During gestation, the high-dose mean maternal body weight was significantly lower (approximately 6% less than that of controls) only at the end of gestation. During lactation, the high-dose F1 dam mean body weight was significantly less (approximately 10%) than that of controls at all time periods and was accompanied by significantly decreased maternal food consumption during lactation weeks 2 and 3 (magnitude not specified; however, appears to have been approximately 10%). High-dose F1 pup mean body weight ranged from 11% lower than that of controls on lactation day 0 to 21–30% lower on lactation days 4–21, which may reflect decreased gestational body weight and decreased food consumption of the high-dose parental dams during lactation. High-dose F1 pup mean body weight gain during lactation was 32% less than that of controls. High-dose F2 pup mean body weight was significantly less (approximately 14–22%) than that of controls during lactation days 7–21, which may reflect, in part, decreased gestational body weight, decreased food consumption of the high-dose parental F1 dams during lactation, and/or decreased quality of rat milk produced during lactation. High-dose F2 pup mean body weight gain during lactation was approximately 25% less than that of controls.

The high-dose F0 dams exhibited significantly lower indices for gestation, birth, viability, and lactation. Mean litter size was significantly lower than that of controls. The high-dose F1 dams exhibited significantly lower indices for birth, viability, and lactation. The significant effects on reproduction, fertility, and pup viability and body weight occurred at a dose level resulting in significantly lower mean body weight and food consumption among the F0 dams during gestation and lactation and the F1 dams from pre-mating through lactation.

Decreased plasma ChE activity was observed in low-dose F0 females, mid-dose F0 males and females and F1 parental females, and high-dose F0 and F1 parental males and females. Among pups, effects on plasma ChE were limited to mid- and high-dose F1 male and female pups, mid- and high-dose F2 male pups, and high-dose F2 female pups.

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Mid- and high-dose F0 and F1 parental rats exhibited significantly decreased RBC AChE activity (26–53% less than that of controls). At terminal sacrifice, significantly decreased brain AChE activity (29–35% less than that of controls) was noted in mid-dose F0 and F1 parental rats. At the high-dose level, brain AChE activity was decreased by 33–35% in F0 and F1 parental males and by 80% in F0 and F1 parental females. Toxicologically significant decreases in pup AChE activity were restricted to high-dose groups at sacrifice on lactation day 21 and included 24% decreased RBC AChE activity in F2 males and 23 and 38% decreased RBC AChE activity in high-dose F1 and F2 females, respectively.

Selection of the Point of Departure for the MRL: The dataset for the F0 male rats was considered preferable to the dataset for the F1 male rats because it represented the greatest magnitude of RBC AChE inhibition at the lowest LOAEL (35% inhibition at 2.0 mg/kg/day for F0 males versus 26% inhibition at 2.09 mg/kg/day for the F1 males). A BMD modeling approach was considered to identify a potential POD for deriving an intermediate-duration oral MRL for tribufos based on the results from the F0 male rats of the 2-generation study. For BMD analysis, mean RBC AChE activity data (Table A-6) were fit to continuous models in EPA's BMDS (version 3.1.1) using a BMR of 20% decrease from control. The following procedure for fitting continuous data was used. Adequate model fit was judged by three criteria: χ^2 goodness-of-fit p-value ($p \geq 0.1$), visual inspection of the dose-response curve, and scaled residual (> -2 and $< +2$) at the data point (except the control) closest to the predefined BMR. Among models providing adequate fit to the data, the lowest BMDL was selected as the POD when the difference between the BMDLs estimated from these models was > 3 -fold; otherwise, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was chosen.

Table A-6. Day 56 RBC AChE Activity in F0 Male Sprague-Dawley Rats Administered Tribufos in the Diet from 10 Weeks Prior to Mating to Delivery of F1 Pups

Concentration in food (ppm)	0	4	32	260
Dose (mg/kg/day)	0	0.28	2	17.6
Number of rats	10	10	10	10
Mean RBC AChE activity (IU/mL)	2.85	2.83	1.96 ^a	1.35 ^a
Standard deviation	0.16	0.17	0.09	0.04

^aSignificantly different from control ($p < 0.05$).

AChE = acetylcholinesterase; RBC = red blood cell

Source: Astroff et al. 1998; EPA 1992c

BMD analysis of the datasets for the F0 male rats from the 2-generation dietary study (Astroff et al. 1998; EPA 1992c) resulted in inadequate fit using either constant variance or nonconstant variance. Therefore, a NOAEL/LOAEL approach was applied to derive an intermediate-duration oral MRL for tribufos. The NOAEL of 0.28 mg/kg/day for the F0 male rats was selected as the POD.

Adjustment for Intermittent Exposure: Not applicable

Uncertainty Factor: The NOAEL of 0.28 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

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$$\begin{aligned} \text{MRL} &= \text{NOAEL} \div \text{uncertainty factors} \\ 0.28 \text{ mg/kg/day} &\div (10 \times 10) = 0.003 \text{ mg/kg/day} \end{aligned}$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The selection of the NOAEL of 0.28 mg/kg/day for F0 male rats of the principal study (Astroff et al. 1998; EPA 1992c) as basis for an intermediate-duration oral MRL for tribufos is supported by results from several studies (Table A-5).

Agency Contacts (Chemical Managers): Rae T. Benedict, Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 74-48-8
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 0.0005 mg/kg/day
Critical Effect: Vacuolar degeneration in small intestines
Reference: CalEPA 2004; EPA 1992d
Point of Departure: BMDL₁₀ of 0.05 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 20
Species: Rat

MRL Summary: A chronic-duration oral MRL of 0.0005 mg/kg/day has been derived for tribufos based on vacuolar degeneration in the small intestines of Fischer 344 rats administered tribufos in the diet for 2 years (CalEPA 2004; EPA 1992d). The MRL is based on a BMDL₁₀ of 0.05 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Chronic-duration oral studies of mice and rats identified tribufos-mediated effects on red blood cell acetylcholinesterase (RBC AChE) activity and nonneoplastic lesions in the small intestine as the most sensitive effects. Table A-7 summarizes NOAELs and LOAELs for these tribufos-mediated effects. Based on NOAELs and LOAELs, rats appear to be more sensitive than mice to tribufos toxicity following oral exposure. Therefore, the rat data were considered the more appropriate species for consideration of MRL derivation. In the rat study, the lowest LOAEL is 1.8 mg/kg/day for tribufos-induced RBC AChE inhibition and for histopathologic lesions in the small intestines. Therefore, tribufos-mediated histopathologic intestinal lesions and RBC AChE inhibition in the rats were initially selected to represent critical effects for deriving a chronic-duration oral MRL for tribufos. Although selected hematological values in the 1.8 mg/kg/day dose group of rats were significantly different from those of controls at interim evaluation, at least some values had returned to normal at 2 years. Therefore, hematological changes were not considered as a basis for MRL derivation.

Table A-7. NOAELs and LOAELs for RBC AChE Activity and Incidences of Nonneoplastic Lesions in the Small Intestine of Rats and Mice Following Chronic-Duration Oral Exposure to Tribufos

Effect Species (duration)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Decreased RBC AChE activity			
Mouse (90 weeks)			CalEPA 2004; EPA 1990a
Males	1.5	8.4	
Females	2.0	11.3	
Rat (2 years)			CalEPA 2004; EPA 1992d
Males	0.2	1.8	
Females	0.2	2.3	

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Table A-7. NOAELs and LOAELs for RBC AChE Activity and Incidences of Nonneoplastic Lesions in the Small Intestine of Rats and Mice Following Chronic-Duration Oral Exposure to Tribufos

Effect Species (duration)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Vacuolar degeneration in small intestine			
Mouse (90 weeks)			CalEPA 2004; EPA 1990a
Males	1.5	8.4	
Females	2.0	11.3	
Rat (1-year interim sacrifice)			CalEPA 2004; EPA 1992d
Males	0.2	1.8	
Females	0.2	2.3	
Rat (2-year terminal sacrifice)			CalEPA 2004; EPA 1992d
Males	0.2	1.8	
Females	0.2	2.3	
Hyperplasia in small intestine			
Rat (2-year terminal sacrifice)			CalEPA 2004; EPA 1992d
Males	0.2	1.8	
Females	0.2	2.3	

AChE = acetylcholinesterase; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; RBC = red blood cell

Selection of the Principal Study: Available animal studies include a 90-week dietary study of CD-1 mice (CalEPA 2004; EPA 1990a) and a 2-year dietary study of Fischer 344 rats (CalEPA 2004; EPA 1992d). The mouse study (CalEPA 2004; EPA 1990a) identified NOAELs of 1.5 and 2.0 mg/kg/day for males and females, respectively, and LOAELs of 8.4 and 11.3 mg/kg/day for males and females, respectively, based on decreased RBC AChE activity (>20% less than respective controls) and significantly increased incidences of vacuolar degeneration in the small intestine (males and females) and extramedullary hematopoiesis in the spleen (males). The NOAELs and LOAELs from the mouse study (CalEPA 2004; EPA 1990a) are higher than those identified in the rat study (CalEPA 2004; EPA 1992d) that identified a NOAEL of 0.2 mg/kg/day (males and females) and LOAELs of 1.8 and 2.3 mg/kg/day (males and females, respectively) for >20% RBC AChE inhibition and increased incidences of histopathologic lesions (vacuolar degeneration and hyperplasia) in the small intestine. Therefore, the rat study (CalEPA 2004; EPA 1992d) was selected as the principal study for deriving a chronic-duration oral MRL for tribufos.

Summary of the Principal Study:

CalEPA. 2004. S,S,S-Tributyl phosphorotrithioate (tribufos) risk characterization document (Revision No. 1). California Environmental Protection Agency, Department of Pesticide Regulation. www.cdpr.ca.gov/docs/risk/rcd/def_r1.pdf.

EPA. 1992d. Memorandum: Tribufos (DEF), rat combined chronic/oncogenicity study. Technical grade tribufos (DEF): A chronic feeding study in the Fischer 344 rat, W.R. Christenson, Miles Inc. Study No. 88-271-AA, Report # 102675, May 1, 1992. MRID 423351-01. U.S. Environmental Protection Agency.

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Groups of Fischer 344 rats (50/sex/dose) were administered tribufos in the diet for 2 years at nominal concentrations of 0, 4, 40, or 320 ppm (recovery from food was 96.5%) (CalEPA 2004; EPA 1992d). CalEPA (2004) reported mean tribufos doses as 0, 0.2, 1.8, and 16.8 mg/kg/day, respectively, for the males and 0, 0.2, 2.3, and 21.1 mg/kg/day, respectively, for the females. Other groups of rats (10 or 20/sex/group) were included for interim sacrifice at 12 months. Still other rats (20/sex/group) were included for 12- and 24-month histopathologic evaluation of brain, spinal cord, sciatic nerves and their branches, and eyes and optic nerves. Rats were monitored for survival, clinical signs, body weight, and food intake. Ophthalmologic examinations were performed at the start of dosing and just prior to terminal sacrifice. Electroretinographic examinations were performed on selected 2-year animals and all surviving 2-year neurotoxicity animals just prior to terminal sacrifice. Blood was collected from 20 rats/sex/group at 3, 6, 12, 18, and 24 months on study for hematological and clinical chemistry evaluation (including plasma ChE and RBC AChE activity); where possible, the same rats were used at each time interval. Determination of brain AChE activity was made at terminal sacrifice. Urine was collected for urinalysis (collection time schedule not specified in available study summaries). Gross pathological examinations were performed on all rats at termination. Organs and tissues weighed were adrenals, brain, heart, kidneys, liver, lungs, spleen, testes, ovaries, and thymus. Tissues were collected and processed for histopathological examination.

The high-dose rats exhibited increased incidences of pale eyes, ocular opacity, rough coats, rash, raised zones on the skin, urine stains, clear discharge, soft feces, and diarrhea (CalEPA 2004). A slight (but not statistically significant) decrease in survival was observed in both sexes of high-dose rats. Both sexes of high-dose rats exhibited slightly increased mean food consumption, but approximately 15% depressed mean body weight gain.

There were no signs of treatment-related ocular effects at 12-month interim evaluation. At 24-month examination, the high-dose rats exhibited significantly increased incidences of cataracts, corneal opacity, corneal neovascularization, and iritis and/or uveitis. High-dose females also exhibited significantly increased incidence of lens opacity. High-dose male and female rats exhibited high rates of bilateral unrecordable (flat) responses in the electroretinographic tests; significantly increased incidences of bilateral retinal atrophy were noted in high-dose rats at 1-year sacrifice and 2-year sacrifice. Significantly increased incidences of optic nerve atrophy were noted in high-dose rats at 2-year sacrifice. Histopathologic examination of the eye at 2 years confirmed uveitis, cataract, and neovascularization in the high-dose males and females.

Mid- and high-dose rats exhibited significant decreases in RBC counts, hemoglobin, and hematocrit at 6 and 12 months, but some of these values had returned to normal by 18 and 24 months. At terminal sacrifice, significant increases in RBC count and hematocrit were noted in high-dose males and significant increases in hemoglobin and hematocrit were observed in high-dose females, indicating the possible involvement of some compensatory mechanism. The low-dose treatment level was considered a NOAEL for hematological effects and the mid-dose level a LOAEL.

At 6-month evaluation, mid- and high-dose groups exhibited decreases in plasma glucose, cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total protein, albumin, and globulin; and increases in blood urea nitrogen (BUN), triglycerides, and creatine kinase. By 24-month evaluation, some of these values had returned to control levels (AST, ALT, creatine kinase, and triglycerides) in mid- and high-dose groups. Other values (total protein, albumin, globulin, and BUN) returned to control levels only in the mid-dose rats. The toxicological significance of the changes in clinical chemistry is questionable in the absence of histopathological changes in liver, kidney, or heart. Urinalysis revealed no apparent treatment-related effects.

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At study termination, mean plasma ChE activity was significantly decreased at all dose levels (16 and 6% lower in low-dose males and females, respectively; 56 and 60% lower in mid-dose males and females, respectively; 80 and 83% lower in high-dose males and females, respectively). Mean RBC AChE activity was significantly decreased in mid- and high-dose groups (27 and 28% lower in mid-dose males and females, respectively; 48 and 47% lower in high-dose males and females, respectively). Brain AChE activity was significantly decreased only at the high-dose level (60 and 68% lower in males and females, respectively).

Gross pathologic examinations revealed abnormal consistency and discoloration in the small intestine of both sexes at mid- and high-dose levels, enlarged adrenals in high-dose males and females, and ocular opacity in high-dose males. Mid- and high-dose groups of male and female rats exhibited increased incidences of histopathologic lesions in the small intestines (vacuolar degeneration and hyperplasia) at 1-year interim sacrifice and 2-year terminal sacrifice (Table A-7). The lesions in the small intestine accompanied gross findings of abnormal consistency and discoloration. Significantly increased incidences of vacuolar degeneration were noted in adrenal glands from high-dose rats (35/49 males versus 6/50 controls; 41/50 females versus 10/50 controls). This lesion was accompanied by gross pathology (enlarged adrenals) and significantly increased adrenal weight. There was no evidence of dose-related increased incidences of histopathologic lesions in the brain, spinal cord, or sciatic nerve and no indications of treatment-related increased incidences of benign or malignant tumors at any site. The study identified a NOAEL of 0.2 mg/kg/day (males and females) and LOAELs of 1.8 mg/kg/day (males) and 2.3 mg/kg/day (females) for 27–28% decreased RBC AChE activity and increased incidences of nonneoplastic lesions in the small intestine. Changes in selected hematology parameters, observed in mid- and high-dose rats at 3-, 6-, and 12-month interim evaluations, had at least partially returned to normal by terminal sacrifice.

Selection of the Point of Departure for the MRL: As shown in Table A-7, RBC AChE inhibition and histopathologic lesions (vacuolar degeneration and hyperplasia) in the small intestines in the 2-year rat study represent the lowest LOAEL (1.8 mg/kg/day) for adverse effects among available study results. BMD analysis is preferable to a NOAEL/LOAEL approach for identifying an appropriate point of departure for MRL derivation. The datasets for vacuolar degeneration and for hyperplasia in the small intestines of the rats are amenable to BMD analysis. BMD analysis of the dataset for RBC AChE inhibition is precluded by lack of mean RBC AChE activity and variance data in publicly-available summaries (CalEPA 2004; EPA 1992d) of the unpublished study.

Incidence data for vacuolar degeneration at 1- and 2-year sacrifice and for hyperplasia at 2-year sacrifice (Table A-8) were fit to all dichotomous models in EPA's BMDS (version 3.1.1) using a BMR of 10% change from control incidence. Adequate model fit was judged by three criteria: chi-square goodness-of-fit p-value ($p \geq 0.1$), visual inspection of the dose-response curve, and scaled residual (> -2 and $< +2$) at the data point (except the control) closest to the predefined BMR. Among models providing adequate fit to the data, the lowest BMDL₁₀ was selected as the POD when the difference between the BMDLs estimated from these models was > 3 fold; otherwise, the BMDL₁₀ from the model with the lowest Akaike's Information Criterion (AIC) was chosen.

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Table A-8. Incidence Data for Selected Nonneoplastic Lesions in the Small Intestine of Male and Female Fischer 344 Rats Administered Tribufos in the Diet for 1 Year (Interim Sacrifice) or 2 Years (Terminal Sacrifice)

		Interim sacrifice (1 year)	Terminal sacrifice (2 years)	
Exposure level (ppm)	Estimated dose (mg/kg/day)	Vacuolar degeneration	Hyperplasia	Vacuolar degeneration
Males				
0	0	0/20 (0%)	0/50 (0%)	0/50 (0%)
4	0.2	0/10 (2%)	3/50 (6%)	1/50 (2%)
40	1.8	7/10 ^a (70%)	23/50 ^a (46%)	24/50 ^a (48%)
320	16.8	18/20 ^a (90%)	34/50 ^a (68%)	37/50 ^a (74%)
Females				
0	0	0/20 (0%)	1/50 (2%)	0/50 (0%)
4	0.2	0/10 (0%)	0/50 (0%)	0/50 (0%)
40	2.3	8/10 ^a (80%)	11/50 ^b (22%)	19/50 ^a (38%)
320	21.1	16/20 ^a (80%)	30/50 ^a (60%)	35/50 ^a (70%)

^aSignificantly different from control according to Fisher's exact test ($p < 0.001$).

^bSignificantly different from control according to Fisher's exact test ($p < 0.01$).

Source: CalEPA 2004

The Loglogistic, Logprobit, and dichotomous Hill models provided adequate fit to the data for vacuolar degeneration in the male rats at 1-year interim sacrifice (Table A-9); the Logprobit model was selected as the best-fitting model (lowest BMDL₁₀). BMD analysis of small intestine vacuolar degeneration in the male rats at 2-year terminal sacrifice resulted in inadequate fit to the data. The Logprobit model provided adequate fit to the data for hyperplasia in the male rats at 2-year terminal sacrifice (Table A-10).

The dichotomous Hill model provided adequate fit to the data for vacuolar degeneration in the female rats at 1-year interim sacrifice (Table A-11). The Loglogistic and Logprobit models provided adequate fit to the data for vacuolar degeneration (Table A-12) in the small intestine of the female rats at 2-year terminal sacrifice; the Logprobit model was selected as the best-fitting model (lowest AIC). The Loglogistic and Logprobit models provided adequate fit to the data for hyperplasia (Table A-13) in the small intestine of the female rats at 2-year terminal sacrifice; the Loglogistic model was selected as the best-fitting model (lowest AIC).

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Table A-9. Results from BMD Analysis of Incidences of Male Fischer 344 Rats with Vacuolar Degeneration in the Small Intestine at 1-Year Interim Sacrifice During Dietary Exposure to Tribufos

Model	DF	χ^2	χ^2 Goodness-of-fit p-value ^a	Scaled residuals ^b			AIC	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Gamma ^c	2	10.39	0.006	-0.63	2.77	2.77	38.42		
Logistic	2	19.73	0.00	3.80	-0.43	3.80	49.88		
Loglogistic ^d	2	2.54	0.28	-0.95	1.03	1.03	32.52	0.24	0.08
Logprobit^e	2	2.67	0.26	-0.90	1.20	1.20	32.62	0.25	0.05
Multistage (1-degree) ^f	2	10.39	0.006	-0.63	2.77	2.77	38.42		
Multistage (2-degree) ^f	3	10.39	0.02	-0.63	2.77	2.77	36.42		
Multistage (3-degree) ^f	3	10.39	0.02	-0.63	2.77	2.77	36.42		
Probit	2	20.03	0.00	3.88	-0.37	3.88	49.7		
Weibull ^c	2	10.39	0.006	-0.63	2.77	2.77	38.42		
Dichotomous Hill	2	<0.001	1.00	-0.002	<0.001	-0.002	29.22	1.15	0.16

^aValues <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

^eSelected model. The Loglogistic, Logprobit, and dichotomous Hill models provided adequate fit to the data. BMDLs for models providing adequate fit differed by >3-fold; therefore, the model with the lowest BMDL₁₀ was selected (Logprobit).

^fBetas restricted to ≥ 0 .

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); BMDL₁₀ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., ₁₀ = dose associated with 10% extra risk); DF = degree of freedom

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Table A-10. Results from BMD Analysis of Incidences of Male Fischer 344 Rats with Hyperplasia in the Small Intestine Following Dietary Exposure to Tribufos for 2 Years

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Gamma ^c	2	28.59	0.00	-0.38	4.66	4.66	185.23		
Logistic	2	36.33	0.00	4.90	-0.43	4.90	197.95		
Loglogistic ^d	3	10.67	0.01	0.27	1.98	-2.58			
Logprobit^e	2	3.41	0.18	-0.001	1.41	1.41	161.85	0.20	0.07
Multistage (1-degree) ^f	2	28.59	0.00	-0.38	4.66	4.66	185.23		
Multistage (2-degree) ^f	2	28.59	0.00	-0.38	4.66	4.66	185.23		
Multistage (3-degree) ^f	2	28.59	0.00	-0.38	4.66	4.66	185.23		
Probit	2	20.03	0.00	3.88	-0.37	3.88	49.7		
Weibull ^c	2	28.59	0.00	-0.38	4.66	4.66	185.23		
Dichotomous Hill	0	3.93	NA	-0.001	-1.12	1.44	166.44		

^aValues <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

^eSelected model. The Logprobit model was the only one to provide adequate fit to the data.

^fBetas restricted to ≥ 0 .

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); BMDL₁₀ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., ₁₀ = dose associated with 10% extra risk); DF = degree of freedom; NA = not applicable (degrees of freedom = 0, saturated model, goodness of fit p-value could not be calculated)

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Table A-11. Results from BMD Analysis of Incidences of Female Fischer 344 Rats with Vacuolar Degeneration in the Small Intestine at 1-Year Interim Sacrifice During Dietary Exposure to Tribufos

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Gamma ^c	3	21.32	0.00	-0.49	4.20	4.20	49.23		
Logistic	2	25.36	0.00	4.36	-0.36	4.36	60.34		
Loglogistic ^d	3	6.84	0.08	1.85	-1.59	1.85	39.39		
Logprobit	2	5.54	0.06	-1.15	1.86	1.86	40.90		
Multistage (1-degree) ^e	3	21.32	0.00	-0.49	4.20	4.20	49.23		
Multistage (2-degree) ^e	3	21.32	0.00	-0.49	4.20	4.20	49.23		
Multistage (3-degree) ^e	3	21.32	0.00	-0.49	4.20	4.20	49.23		
Probit	2	20.03	0.00	3.88	-0.37	3.88	49.7		
Weibull ^c	3	21.32	0.00	-0.49	4.20	4.20	49.23		
Dichotomous Hill^f	2	0.002	1.00	-0.025	0.03	0.03	34.03	0.71	0.18

^aValues <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

^eBetas restricted to ≥ 0 .

^fSelected model. The dichotomous Hill model was the only model to provide adequate fit to the data.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); BMDL₁₀ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., ₁₀ = dose associated with 10% extra risk); DF = degree of freedom

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Table A-12. Results from BMD Analysis of Incidences of Female Fischer 344 Rats with Vacuolar Degeneration in the Small Intestine Following Dietary Exposure to Tribufos for 2 Years

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Gamma ^c	3	21.42	0.00	-0.89	4.11	4.11	147.70		
Logistic	2	35.44	0.00	4.83	-0.40	4.83	171.52		
Loglogistic ^d	3	6.13	0.11	-1.28	1.70	1.70	136.91	0.68	0.47
Logprobit^e	2	3.99	0.14	-1.24	1.38	1.38	136.86	0.60	0.29
Multistage (1-degree) ^f	2	21.42	0.00	-0.89	4.11	4.11	147.70		
Multistage (2-degree) ^f	3	21.42	0.00	-0.89	4.11	4.11	147.70		
Multistage (3-degree) ^f	3	21.42	0.00	-0.89	4.11	4.11	147.70		
Probit	2	35.08	0.00	4.86	-0.44	4.86	170.57		
Weibull ^c	2	21.42	0.00	-0.89	4.11	4.11	149.70		
Dichotomous Hill	0	<0.01	NA	-0.02	<0.01	-0.02	135.49		

^aValues <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

^eSelected model. The loglogistic and logprobit models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close; therefore, the model with the lowest AIC was selected (logprobit).

^fBetas restricted to ≥ 0 .

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); BMDL₁₀ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., ₁₀ = dose associated with 10% extra risk); DF = degree of freedom; NA = not applicable (degrees of freedom = 0, saturated model, goodness of fit p-value could not be calculated)

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Table A-13. Results from BMD Analysis of Incidences of Female Fischer 344 Rats with Hyperplasia in the Small Intestine Following Dietary Exposure to Tribufos for 2 Years

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Gamma ^c	2	6.54	0.04	-1.14	2.14	2.14	140.82		
Logistic	2	15.49	<0.01	3.16	-0.19	3.16	150.78		
Loglogistic^{d,e}	2	3.01	0.22	-1.18	1.02	-1.18	138.03	1.37	0.93
Logprobit	1	2.02	0.16	-1.05	0.66	-1.05	138.81	1.23	0.60
Multistage (1-degree) ^f	2	6.54	0.04	-1.14	2.14	2.14	140.82		
Multistage (2-degree) ^f	2	6.54	0.04	-1.14	2.14	2.14	140.82		
Multistage (3-degree) ^f	2	6.54	0.04	-1.14	2.14	2.14	140.82		
Probit	2	14.97	<0.01	3.14	-0.24	3.14	150.09		
Weibull ^c	2	6.54	0.04	-1.14	2.14	2.14	140.82		
Dichotomous Hill	0	1.01	NA	-0.71	-0.00	0.71	139.19		

^aValues <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

^eSelected model. The Loglogistic and Logprobit models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close; therefore, the model with the lowest AIC was selected (Loglogistic).

^fBetas restricted to ≥ 0 .

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); BMDL₁₀ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., ₁₀ = dose associated with 10% extra risk); DF = degree of freedom; NA = not applicable (degrees of freedom = 0, saturated model, goodness of fit p-value could not be calculated)

The most conservative POD for deriving a chronic-duration oral MRL for tribufos is the BMDL₁₀ of 0.05 mg/kg/day for vacuolar degeneration in the small intestine of the male rats at 1-year interim sacrifice generated from the logprobit model (Table A-14). Visual inspection of the dose-response curve for the logprobit model indicated adequate fit to the mean data (Figure A-1).

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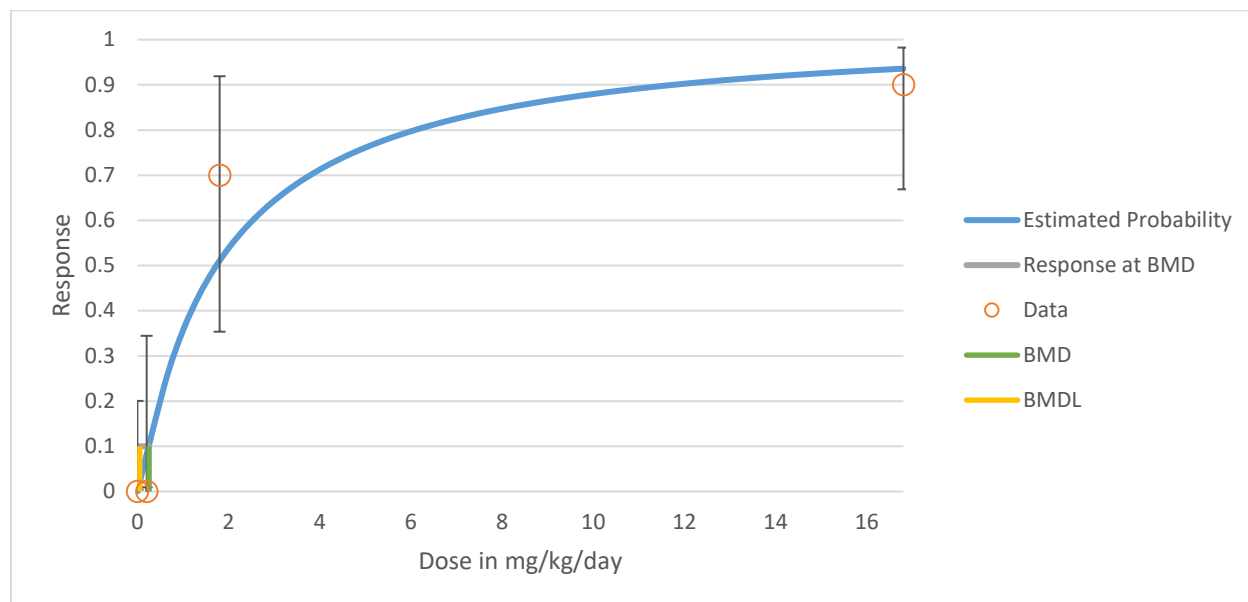
Table A-14. Potential PODs for Deriving a Chronic-Duration Oral MRL for Tribufos Based on BMD Analysis of Nonneoplastic Lesions in the Small Intestine of Rats Administered Tribufos in the Diet for up to 2 Years

Effect Species (duration)	BMDL ₁₀ (mg/kg/day)	Reference
Vacuolar degeneration in small intestine		
Rat (1-year interim sacrifice)		CalEPA 2004; EPA 1992d
Males	0.05 ^a	
Females	0.18	
Rat (2-year terminal sacrifice)		CalEPA 2004; EPA 1992d
Males	Inadequate fit	
Females	0.29	
Hyperplasia in small intestine		
Rat (2-year terminal sacrifice)		CalEPA 2004; EPA 1992d
Males	0.07	
Females	0.93	

^aSelected as the POD for deriving a chronic-duration oral MRL for tribufos.

BMD = benchmark dose; BMDL₁₀ = 95% lower confidence limit on the BMD using 10% change from control incidence as the benchmark response (BMR); MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; POD = point of departure

Figure A-1. Dose-Response Curve for Logprobit Model Data for Vacuolar Degeneration in the Small Intestine from Male Fischer 344 Rats Administered Tribufos in the Diet for 1 Year During a 2-Year Oral Study



Adjustment for Intermittent Exposure: Not applicable

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Uncertainty Factor: The BMDL₁₀ of 0.05 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = BMDL₁₀ ÷ uncertainty factors

0.05 mg/kg/day ÷ (10 x 10) = 0.0005 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Histopathologic lesions in the small intestines were observed in CD-1 mice receiving tribufos from the diet for 90 weeks at estimated doses of 8.4 and 11.13 mg/kg/day for males and females, respectively (EPA 1990a).

Agency Contacts (Chemical Managers): Rae T. Benedict, Ph.D.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR TRIBUFOS

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to tribufos.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for tribufos. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of tribufos have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of tribufos are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for tribufos released for public comment in 2018. The following main databases were searched in March 2019:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for tribufos. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures

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and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to tribufos were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database	search date	Query string
PubMed		
03/2019		(78-48-8[rn] OR "butyl phosphorotrithioate"[nm] OR "B 1,776"[tw] OR "B 1776"[tw] OR "Butifos"[tw] OR "Butiphos"[tw] OR "Butyl phosphorotrithioate"[tw] OR "butyphos"[tw] OR "DEF 6"[tw] OR "DEF Defoliant"[tw] OR "De-Green"[tw] OR "E-Z-Off D"[tw] OR "Fosfall"[tw] OR "Fos-Fall A"[tw] OR "Fossfall"[tw] OR "Ortho phosphate defoliant"[tw] OR "Phosphorotrithioic acid, S, S, S-tributyl ester"[tw] OR "S, S, S-Tributyl phosphorotrithioate"[tw] OR "S, S, S-Tributyl trithiophosphate"[tw] OR "S, S, S-Tributylphosphorotrithioate"[tw] OR "S, S, S-Tributyltrithiophosphate"[tw] OR "TBPT"[tw] OR "TBTP"[tw] OR "Tribufos"[tw] OR "Tribuphos"[tw] OR "Tributyl phosphorotrithioate"[tw] OR "tributyl S, S, S-phosphorotrithioate"[tw] OR "Tributyl trithiophosphate"[tw] OR "Tributylphosphorotrithioate"[tw] OR "Tributyltrithiophosphate"[tw] OR ("DEF"[tw] AND (defoliant OR defoliants OR "Defoliants, Chemical"[mh] OR "Defoliants, Chemical"[pa])) OR ("Phosphorotrithioic"[tw] AND ("tributyl"[tw] OR "butyl"[tw])) AND (2014/12/01 : 3000[dp] OR 2015/12/01 : 3000[mhda] OR 2015/12/01 : 3000[crdat] OR 2015/12/01 : 3000[edat]) OR ("DEF, total"[tw] OR "Merphos oxide"[tw] OR "S,S,S-Tributyl phosphorotrithioic acid"[tw] OR "Tributyl phosphorotrithioic acid"[tw])
Toxline		
03/2019	Year of Publication 2014 through 2019	(78-48-8[rn] OR "B 1,776" OR "B 1776" OR "Butifos" OR "Butiphos" OR "Butyl phosphorotrithioate" OR "butyphos" OR "DEF 6" OR "DEF Defoliant" OR "De-Green" OR "E-Z-Off D" OR "Fosfall" OR "Fos-Fall A" OR "Fossfall" OR "Ortho phosphate defoliant" OR "Phosphorotrithioic acid, S,S,S-tributyl ester" OR "S,S,S-Tributyl phosphorotrithioate" OR "S,S,S-Tributyl trithiophosphate" OR "S,S,S-Tributylphosphorotrithioate" OR "S,S,S-Tributyltrithiophosphate" OR "TBPT" OR "TBTP" OR "Tribufos" OR "Tribuphos" OR "Tributyl phosphorotrithioate" OR "tributyl S,S,S-phosphorotrithioate" OR "Tributyl trithiophosphate" OR "Tributylphosphorotrithioate" OR "Tributyltrithiophosphate") AND (ANEUPPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
		("DEF, total" OR "Merphos oxide" OR "S,S,S-Tributyl phosphorotrithioic acid" OR "Tributyl phosphorotrithioic acid") AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter		
03/2019	L1	931 SEA FILE=TOXCENTER 78-48-8
	L2	849 SEA FILE=TOXCENTER L1 NOT PATENT/DT
	L3	847 SEA FILE=TOXCENTER L2 NOT TSCATS/FS
	L4	30 SEA FILE=TOXCENTER L3 AND ED>=20151201

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Table B-2. Database Query Strings

Database search date	Query string
L7	47 SEA FILE=TOXCENTER L3 AND PY>2014
L8	47 SEA FILE=TOXCENTER L4 OR L7
L9	47 DUP REM L8 (0 DUPLICATES REMOVED) ANSWERS '1-47' FROM FILE TOXCENTER
L *** DEL	47 S L4 OR L7
L *** DEL	47 S L4 OR L7
L10	47 SEA FILE=TOXCENTER L9
L11	41 SEA FILE=TOXCENTER L10 NOT MEDLINE/FS D SCAN L11

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via Chemview	
03/2019	Compound searched: 78-48-8
NTP	
03/2019	"Tributylphosphorotrithioate" 78-48-8 "Butifos" "Butiphos" "Butyl phosphorotrithioate" "butyphos" "DEF 6" "DEF Defoliant" "TBPT" "TBTP" "Tribufos" "Tribuphos" "Tributyl phosphorotrithioate" "tributyl S, S, S-phosphorotrithioate" "Tributyltrithiophosphate"
Regulations.gov	
03/2019	78-48-8
NPIRS	
03/2019	78-48-8
NIH RePORTER	
08/2019	Text Search: "Butifos" OR "Butiphos" OR "Butyl phosphorotrithioate" OR "butyphos" OR "Fosfall" OR "Fos-Fall A" OR "Fosfall" OR "Ortho phosphate defoliant" OR "Phosphorotrithioic acid, S, S, S-tributyl ester" OR "S, S, S-Tributyl phosphorotrithioate" OR "S, S, S-Tributyl trithiophosphate" OR "S, S, S-Tributylphosphorotrithioate" OR "S, S, S-Tributyltrithiophosphate" OR "Tribufos" OR "Tribuphos" OR "Tributyl phosphorotrithioate" OR "tributyl S, S, S-phosphorotrithioate" OR "Tributyl trithiophosphate" OR "Tributylphosphorotrithioate" OR "Tributyltrithiophosphate" OR "TBPT" OR "TBTP" OR "DEF 6" OR "DEF Defoliant" OR "De-Green" OR "E-Z-Off D" OR "Phosphorotrithioic" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2019 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 67
- Number of records identified from other strategies: 38
- Total number of records to undergo literature screening: 105

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B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on tribufos:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

- Number of titles and abstracts screened: 105
- Number of studies considered relevant and moved to the next step: 38

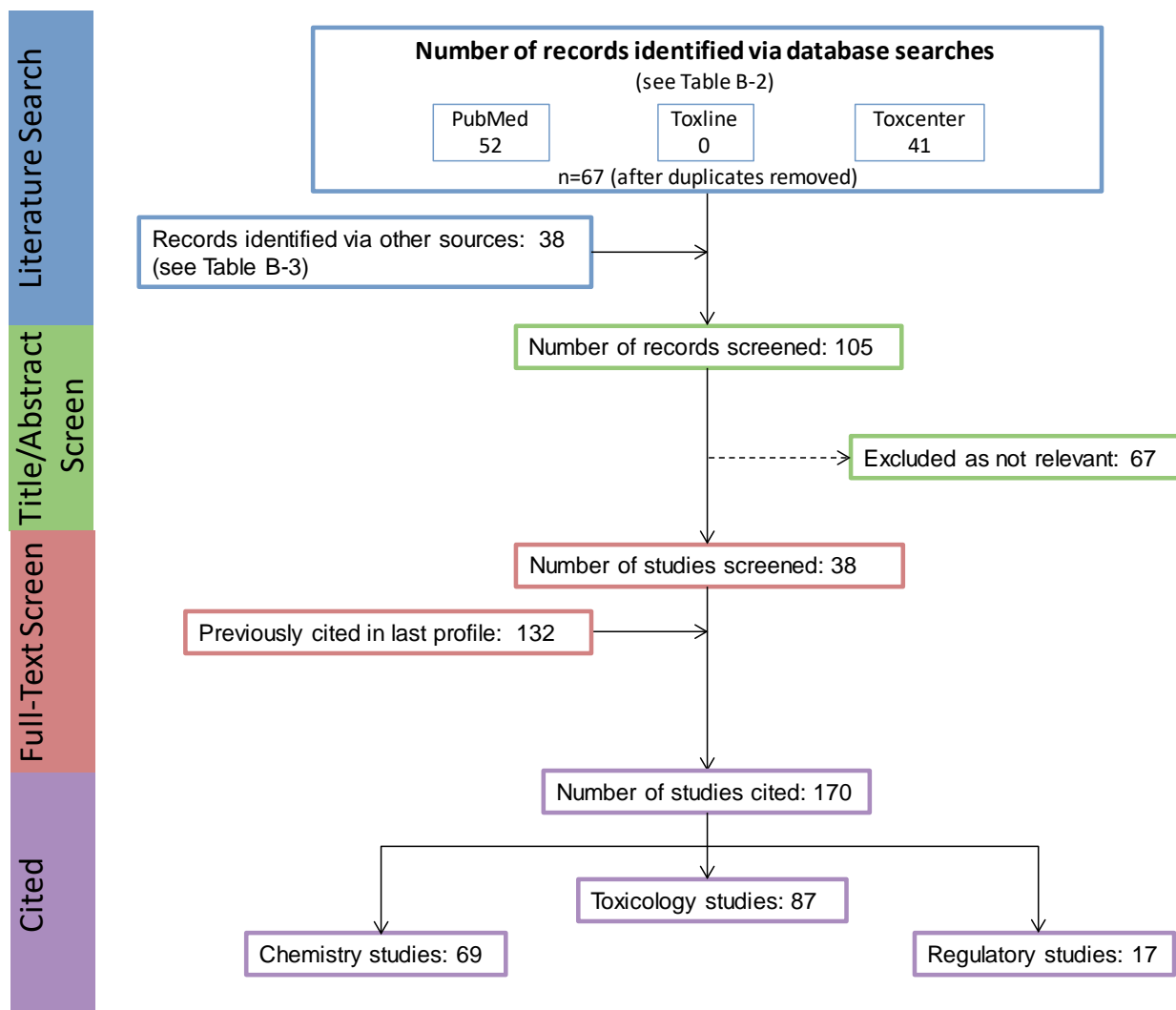
Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 38
- Number of studies cited in the pre-public draft of the toxicological profile: 132
- Total number of studies cited in the profile: 170

A summary of the results of the literature search and screening is presented in Figure B-1.

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Figure B-1. March 2019 Literature Search Results and Screen for Tribufos



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

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substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

- (1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.
- (2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).
- (4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to "Chemical X" via feed for 2 years. For a

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more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

- (6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).
- (7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.
- (8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.
- (9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.
- (10) Reference. The complete reference citation is provided in Chapter 8 of the profile.
- (11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

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- (14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.
- (15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).
- (17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.
- (18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

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Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral								
	4	5	6	7	8	9		
	Species	Exposure	Doses	Parameters	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL
Figure key ^a	(strain) No./group	parameters	(mg/kg/day)	monitored		(mg/kg/day)	(mg/kg/day)	(mg/kg/day)
Effect								
2	CHRONIC EXPOSURE							
51	Rat (Wistar)	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt Hemato Hepatic	25.5 138.0	138.0	
3	40 M, 40 F						6.1 ^c	Decreased body weight gain in males (23–25%) and females (31–39%) Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
10	Aida et al. 1992							
52	Rat (F344)	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic Renal Endocr	36.3 20.6 36.3	36.3	Increased incidence of renal tubular cell hyperplasia
	George et al. 2002							
59	Rat (Wistar)	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F	Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
	58M, 58F							
	Tumasonis et al. 1985							

^aThe number corresponds to entries in Figure 2-x.

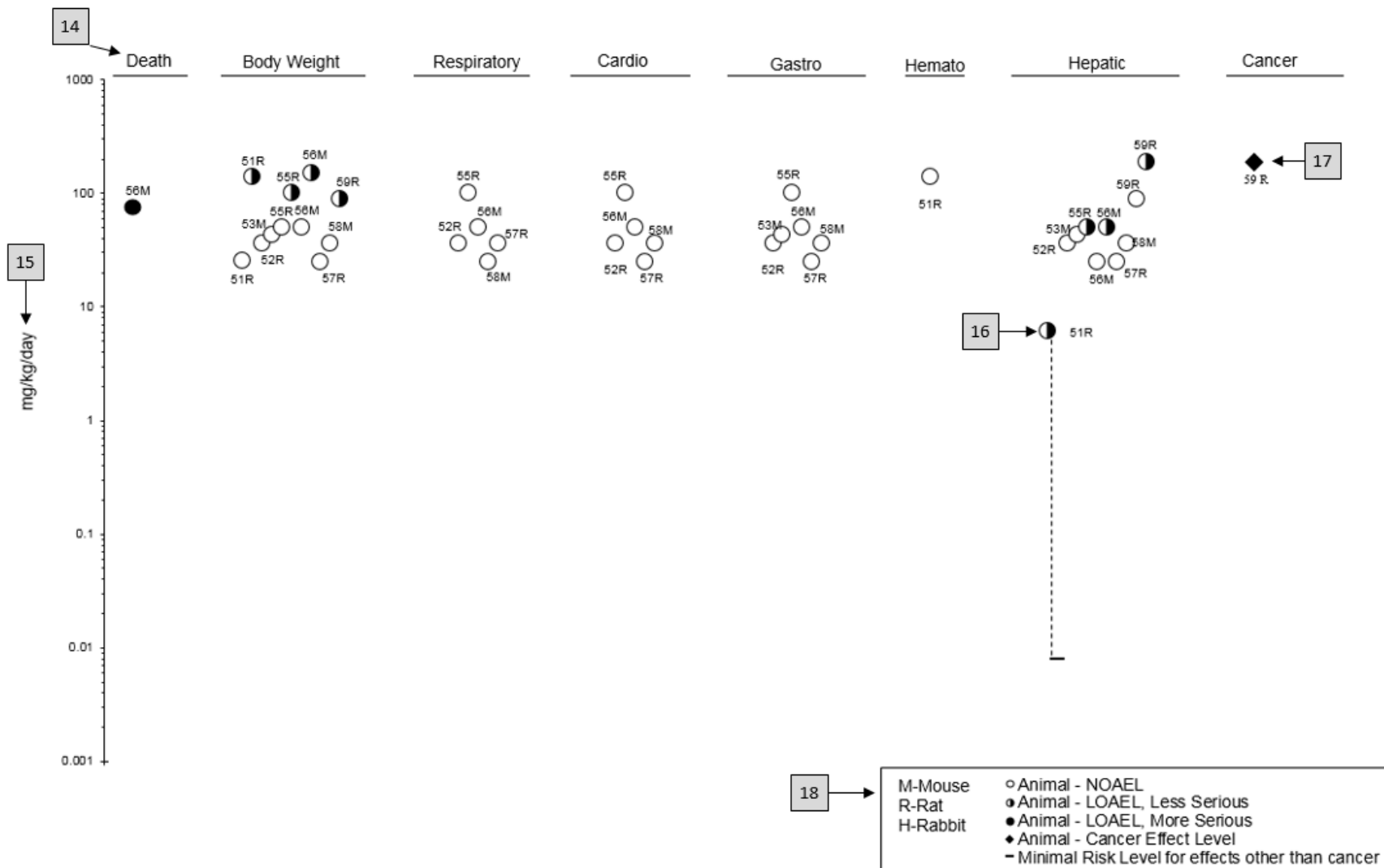
^bUsed to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the BMDL₀₅ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

^cUsed to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the BMDL₁₀ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

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Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral

13 → Chronic (≥ 365 days)



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2	Children and Other Populations that are Unusually Susceptible
Section 3.3	Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)

Internet: <http://www.atsdr.cdc.gov>

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see <https://www.atsdr.cdc.gov/csem/csem.html>).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see <https://www.atsdr.cdc.gov/MHMI/index.asp>). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see <https://www.atsdr.cdc.gov/toxfaqs/Index.asp>).

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Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: <https://www.cdc.gov/nceh/>.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: <https://www.cdc.gov/niosh/>.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: <https://www.niehs.nih.gov/>.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: <http://www.aoec.org/>.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: <http://www.acoem.org/>.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: <http://www.acmt.net>.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at <http://pehsu.net/findhelp.html>.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: <http://www.aapcc.org/>.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤ 14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research but are not actual research studies.

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Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥ 365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

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Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration_(LO) (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀)—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose_(LO) (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀)—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

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Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

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Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m³ or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥ 1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

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Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD _x	dose that produces a X% change in response rate of an adverse effect
BMDL _x	95% lower confidence limit on the BMD _x
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

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FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ -glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kgg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC ₅₀	lethal concentration, 50% kill
LC _{Lo}	lethal concentration, low
LD ₅₀	lethal dose, 50% kill
LD _{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT ₅₀	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

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NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTE	neurotoxic target esterase
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

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USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result