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 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 (99.9^{th} 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,

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

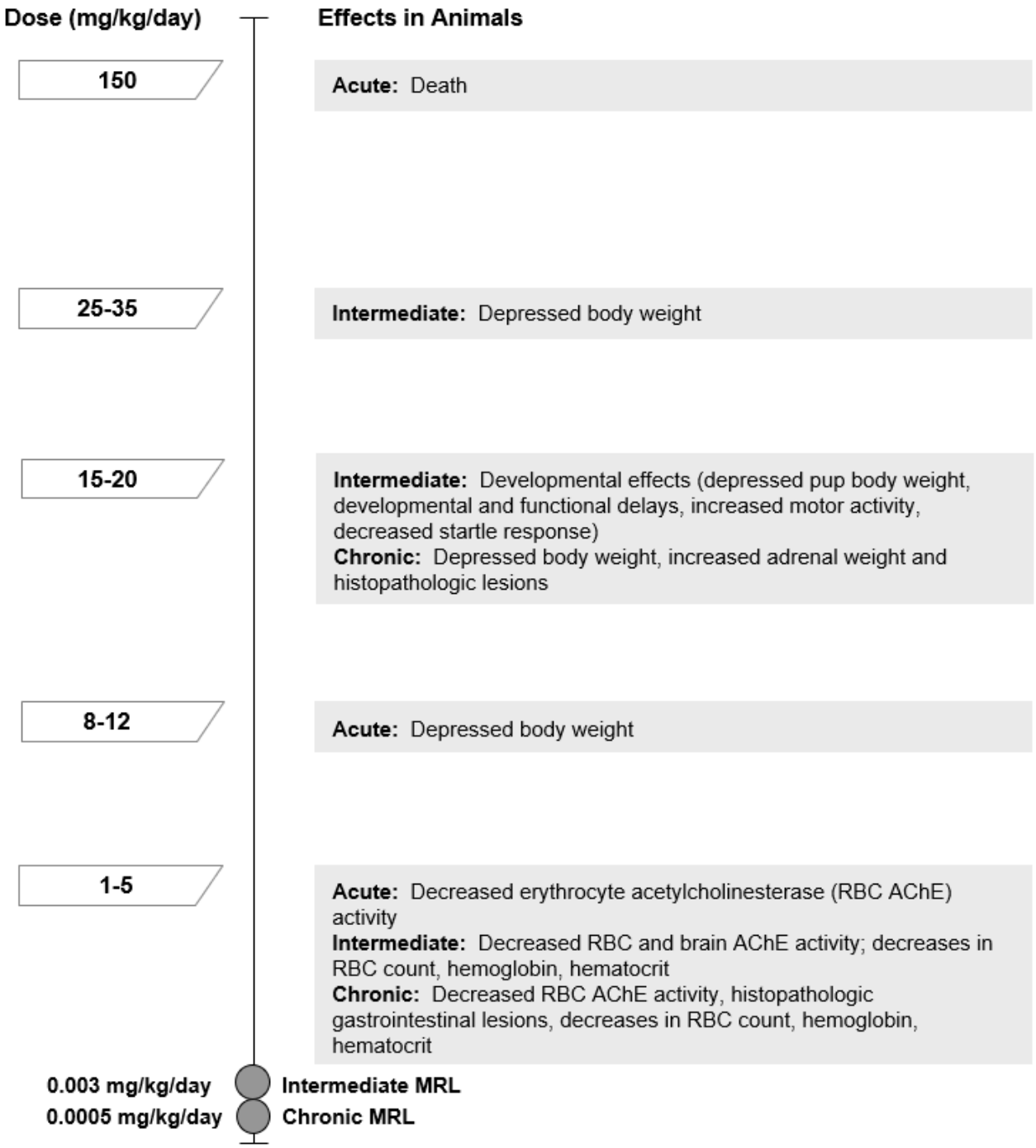
Tribufos is an organophosphorus compound considered to be of moderate toxicity compared to other organophosphates. A principal effect of organophosphate toxicity is inhibition of acetylcholinesterase (AChE), which is a neurotransmitter. This inhibition may result in accumulation of AChE at receptors 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 ≥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/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 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,

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



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 ≥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

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.

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.

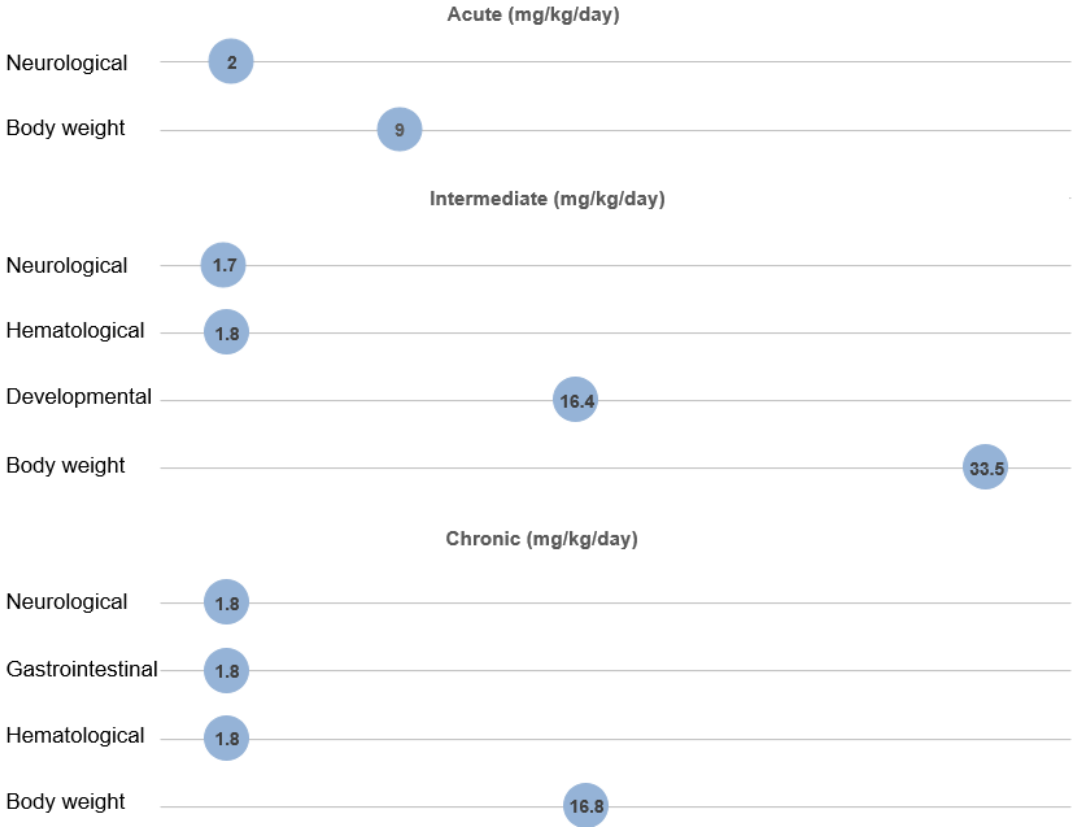


Table 1-1. Minimal Risk Levels (MRLs) for Tribufos[a]

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

[a]See Appendix A for additional information.

AChE = acetylcholinesterase; $BMDL_{10}$ = 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