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

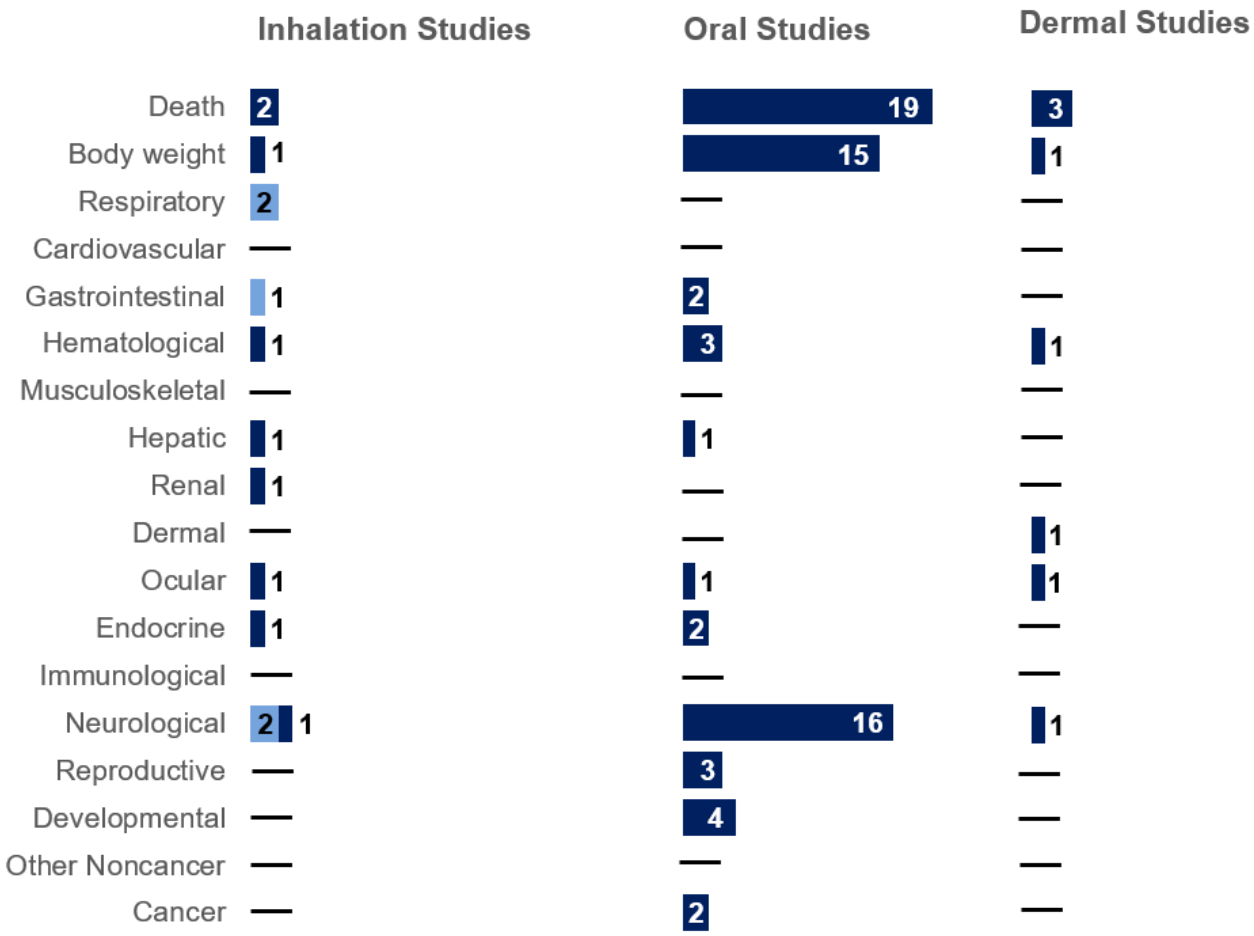
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to tribufos that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of tribufos. The number of human and 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.

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

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

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

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

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

(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

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).