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

Draft for Public Comment

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Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch
1600 Clifton Road NE
Mailstop F-57
Atlanta, Georgia 30329-4027

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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 public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. 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 and EPA.

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 and the associated acute, subacute, and chronic health effects;

(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, subacute, 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. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov.
Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch

Regular Mailing Address:
1600 Clifton Road, N.E.
Mail Stop F-57
Atlanta, Georgia 30329-4027

Physical Mailing Address:
4770 Buford Highway
Building 102, 1st floor, MS F-57
Chamblee, Georgia 30341

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 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 National Priorities List, 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.

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 is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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

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: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (e.g.,death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Chapter 1	**How Can (Chemical X) Affect Children?**
Chapter 1	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

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).

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/.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for tribufos. The panel consisted of the following members:

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 tribufos' physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT FOR S,S,S-TRIBUTYL PHOSPHOROTRITHIOATE (TRIBUFOS)

This Public Health Statement summarizes the Agency for Toxic Substances and Disease Registry's (ATSDR) findings on tribufos, including chemical characteristics, exposure risks, possible health effects from exposure, and ways to limit exposure.

The U.S. Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are sites targeted for long-term federal clean-up activities. The EPA has found tribufos in at least 4 of the 1,832 current or former NPL sites. The total number of NPL sites evaluated for tribufos is not known. But the possibility remains that as more sites are evaluated, the sites where tribufos is found may increase. This information is important because these future sites may be sources of exposure, and exposure to tribufos may be harmful.

If you are exposed to tribufos, many factors determine whether you'll be harmed. These include how much you are exposed to (dose), how long you are exposed (duration), how often you are exposed (frequency), and how you are exposed (route of exposure). You must also consider the other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

WHAT IS TRIBUFOS?

Tribufos is a colorless to pale yellow liquid with a skunk-like odor; it is used only as a defoliant (a chemical that removes leaves) for cotton plants. Removing the leaves keeps certain pests that may be found on the leaves from damaging the cotton before it is picked.

WHAT HAPPENS TO TRIBUFOS WHEN IT ENTERS THE ENVIRONMENT?

When tribufos is sprayed onto cotton crops in cotton-growing states such as California, Texas, Mississippi, Louisiana, and Georgia, some of it may be found in the air at or near treated fields and in nearby water or soil. Tribufos does not travel long distances in air. Half of the tribufos that enters the air will break down within 2 hours. Therefore, people who live in states where cotton is not grown are not expected to be exposed to it from the air. Tribufos is not expected to move from soil to groundwater. We do not know how long tribufos will remain in soil, but we do know that it is slow to break down. Tribufos does not readily move from soil or water to air. Tribufos does not become more concentrated in aquatic organisms than the concentration in the water where they live.

HOW MIGHT I BE EXPOSED TO TRIBUFOS?

Most people will not be exposed to tribufos unless they live near an area where tribufos is used to defoliate cotton plants. Tribufos is not for residential use or other non-occupational uses. Some cotton-containing products such as cottonseed oil and cottonseed meal may contain very low amounts of tribufos, and you could possibly be exposed to it if you use these products for cooking. You may also be exposed to tribufos if you consume meat or milk from livestock fed tribufos-containing cottonseed products.

HOW CAN TRIBUFOS ENTER AND LEAVE MY BODY?

If you were to breathe air containing tribufos, it could enter your blood through your lungs. Tribufos could rapidly enter your blood if you were to eat food or drink water containing tribufos. However, it is not likely that you would come into contact with food or water containing tribufos. Tribufos can be absorbed through the skin. Once in the body, tribufos is rapidly broken down and eliminated from the body within 1-3 days, mainly in the urine. Tribufos has not been shown to accumulate in any particular body organ or tissue.

For more information on how tribufos enters and leaves the body, see Section 3.4.

HOW CAN TRIBUFOS AFFECT MY HEALTH?

Most people are not likely to be exposed to levels of tribufos high enough to cause signs and symptoms of acute toxicity. In the unlikely event that you were to be exposed to very high levels of tribufos, you might experience include excessive sweating, very small pupils, diarrhea, drowsiness, unconsciousness, and difficulty with breathing. You might also experience tearing of the eyes, runny nose, diarrhea, nausea, vomiting, loss of bladder control, and loss of muscle control. These effects would likely occur within a few minutes to 24 hours after high-level exposure, depending upon the extent and route of exposure. It is not known whether long-term exposure to low levels of tribufos might cause harmful effects in humans, including cancer. EPA evaluated results from carcinogenicity studies of rats and mice. There was no evidence of tribufos-related cancer in the rats. Tumors of the small intestine, liver, and lungs were reported in mice that were fed tribufos in the diet for nearly 2 years at levels many times higher than levels allowed in human food sources. Based on the results from the mouse study, a special EPA 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 concluded that human exposure to tribufos would not approach the dose level associated with tumors in the tribufos-treated mice.

Further information on the health effects of tribufos in humans and animals can be found in Chapters 2 and 3.

HOW CAN TRIBUFOS AFFECT CHILDREN?

This section discusses potential health effects of tribufos exposure in humans from when they're first conceived to 18 years of age.

We do not know whether children would be more sensitive than adults to tribufos toxicity. We do not know whether exposure to tribufos might cause birth defects or other developmental effects in people. Levels of exposure to tribufos high enough to affect the health of pregnant rats caused decreased numbers of rats born and decreased survival. These exposure levels were many times higher than levels allowed in human food sources.

HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO TRIBUFOS?

If your doctor finds that you have been exposed to significant amounts of tribufos, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate. You may also contact the state or local health department with health concerns.

People who live near agricultural areas where tribufos is used should stay away from the treated area. Air currents and water runoff can spread tribufos. If you are aware that tribufos is being sprayed, you may want to go indoors during spraying and stay there for a few hours after spraying is complete. Agricultural workers who come into contact with tribufos should consider changing work clothes before entering the home and washing work clothes separately from other family clothing.

ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO TRIBUFOS?

There are no reliable medical tests to determine whether you have been exposed to tribufos. If exposure to tribufos is suspected, your doctor may request testing to determine the activity of the enzymes butyrylcholinesterase (BuChE) and/or acetylcholinesterase (AChE) in your blood. Your doctor may also

need to check your red blood cell and hemoglobin levels because low levels of these blood elements could cause lower-than-normal activity of AChE in your blood.

WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but are not enforceable by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed as "not-to-exceed" levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (e.g., an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

The EPA has set acceptable limits for tribufos residues (tribufos and/or its breakdown products that stick to food or crops eaten by humans or animals). In or on food commodities (animal fat, meat, meat byproducts), 0.02–0.15 parts per million (ppm) is considered acceptable. Residues in undelinted cotton seeds can be up to 4 ppm. Byproducts from cotton gins (machines that process cotton) may have up to 40 ppm.

For more information on regulations and advisories, see Chapter 8.

WHERE CAN I GET MORE INFORMATION?

If you have any questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below. You may also contact your doctor if experiencing adverse health effects or for medical concerns or questions. ATSDR can also provide publicly available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or

- Write to:
  Agency for Toxic Substances and Disease Registry
  Division of Toxicology and Human Health Sciences
  1600 Clifton Road NE
  Mailstop F-57
  Atlanta, GA 30329-4027

Toxicological profiles and other information are available on ATSDR's web site: http://www.atsdr.cdc.gov.

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2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO S,S,S-TRIBUTYL PHOSPHOROTRITHIOATE (TRIBUFOS) IN THE UNITED STATES

Tribufos is a colorless to pale yellow liquid that is used exclusively as a plant growth regulator in the defoliation of cotton plants. 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. Typically, anywhere from 9 to 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. It is applied as a liquid product by aerial or ground boom spraying.

In the atmosphere, tribufos is degraded by reacting with photochemically generated hydroxyl radicals. Its estimated atmospheric half-life is approximately 2 hours. Given its low vapor pressure and Henry's Law constant, volatilization from water and soil surfaces is expected to occur slowly; however, a field dissipation study indicated that volatilization from soils under hot and humid conditions may be an important environmental fate process. 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. The EPA Registration Eligibility Decision (RED) document reported an aerobic soil metabolism half-life of 745 days and the California Department of Pesticide Regulation reported an aerobic soil metabolism half-life for tribufos of 198 days. Laboratory and field tests using soils acclimated to tribufos reported much shorter persistence times. Laboratory studies had fitted half-lives of about 5–109 days, depending upon the length of the incubation period. Field studies reported half-lives of 9.8–173.3 days in soils from different states. For further details, see Section 6.3.2.

Exposure to tribufos to the general population is extremely low. The primary exposure pathway is ingestion of cotton products like cottonseed oil or cottonseed meal that may contain residues of this substance. 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. 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. 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 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.

2.2 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 results in the accumulation of acetylcholine at acetylcholine receptors leading to cholinergic responses in the peripheral (muscarinic and nicotinic) and central nervous system and neuromuscular junctions. AChE inhibition may lead to muscarinic cholinergic features such as excessive glandular secretions (salivation, lacrimation, rhinitis), miosis, bronchoconstriction, vasodilation, hypotension, diarrhea, nausea, vomiting, urinary incontinence, and bradycardia. Nicotinic cholinergic features include 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, depending upon the extent of exposure.

In this Toxicological Profile, "less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose toxicological significance to the organism is not entirely clear. 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). In addition to its presence and function in central and peripheral nervous tissue, AChE is also expressed in red blood cells (RBCs). 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 ≥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.

Numerous animal studies identify levels of exposure to tribufos resulting in RBC and/or brain AChE inhibition that could be classified as less serious or serious effects; most studies also identified a no-observed-adverse-effect level (NOAEL). The tribufos-mediated effect on AChE activity was independent of exposure route. For example, inhibition of RBC and brain AChE was reported in Sprague-Dawley rats that were exposed nose-only to tribufos aerosol and rats that ingested tribufos. It also appears that inhibition of AChE activity is independent of exposure duration because RBC and/or brain AChE inhibition was reported in inhalation studies of single 4-hour exposures and 13 weeks of repeated

exposure, as well as in oral studies that included single administration and repeated dosing for durations ranging from 10 days to 2 years.

Results from acute-duration oral studies in rats indicate that neonates may be more sensitive than adults to tribufos neurotoxicity. For example, a single gavage dose of 2 mg/kg to 11-day-old rat pups resulted in decreased movement and decreased RBC AChE activity, whereas there was no evidence of neurotoxicity in young adult female rats dosed at up to 10 mg/kg. In another study, clinical signs and decreased brain AChE activity were observed in 21-day-old rat pups that had been gavaged with tribufos at 5 mg/kg/day for 11 days, whereas similarly-treated young adult female rats exhibited no clinical signs or evidence of decreased brain AChE activity. However, the magnitude of decreased RBC AChE activity in the 21-day-old rats was similar to that observed in the young adult female rats. Slight tremors were observed in rat dams administered tribufos orally during gestation. Retinal atrophy and optic nerve atrophy were noted in rats administered tribufos in the diet for 2 years. Clinical signs (e.g., tremors, muscle fasciculations, decreased movement) were observed in rabbits administered tribufos by single or repeated dermal application.

Signs of tribufos-induced neurotoxicity (e.g., cholinergic effects, late acute effects, organophosphate-induced delayed neuropathy [OPIDN]) were observed in hens repeatedly exposed to tribufos by inhalation, oral, and/or dermal routes. Increasing exposure level was associated with increasing severity and earlier onset of effects. Phosphorylation and subsequent aging of an enzyme called neuropathy target esterase (NTE) is considered a mechanism in the development of OPIDN. Although studies of hens are useful for hazard identification, applicability of the dose-response in hens to humans is uncertain. One human study found a 50% decrease in NTE in lymphocytes from seven workers repeatedly exposed (during 9–34 days) to tribufos (S,S,S-tributyl phosphorotrithioate [merphos oxide]) and folex (S,S,S-tributyl phosphorotrithioite [merphos], which is rapidly transformed in the environment to merphos oxide) during mixing and/or aerial and ground application of the compounds during one season of cotton defoliation. However, these workers exhibited no clinical signs of neurotoxicity. Furthermore, there were no signs of OPIDN among the workers evaluated 3 weeks following cessation of tribufos and folex use. Tribufos has not been demonstrated to elicit OPIDN in mammals.

Clinical signs of treatment-related hypothermia have been reported in studies of rodents following inhalation or oral exposure to tribufos at relatively high exposure levels. Depressed body weight gain was observed in rodents receiving tribufos orally for acute, intermediate, and chronic exposure durations. There is some indication of tribufos-related hematological effects in rats and mice following intermediate-

and chronic-duration oral exposure. In a study of mice receiving tribufos from the diet for up to 90 weeks, estimated doses ≥8 mg/kg/day resulted in histopathological lesions in the small intestine; high-dose (48–63 mg/kg/day) mice also exhibited pathological lesions of the adrenal glands. Similar effects were observed in rats receiving tribufos from the diet for up to 2 years at estimated doses in the range of 1.8–21.1 mg/kg/day. Tribufos does not appear to be a reproductive toxicant. Available animal data indicate some potential for tribufos-induced developmental effects other than neurodevelopmental effects; however, these effects typically occurred at maternally-toxic doses. Predominantly negative results have been reported in testing of tribufos for genotoxicity.

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 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.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been established for tribufos. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. 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 within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional

uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

An acute-duration inhalation MRL was not derived for tribufos due to the lack of adequate human or animal data. One study reported significant relative risks for cough, fatigue, eye and throat irritation, nausea, and diarrhea among residents from towns in cotton-growing areas (Scarborough et al. 1989). Another study found no significant association between respiratory-caused mortality and pounds of the defoliants tribufos and folex used in communities surrounding cotton fields during and immediately following cotton defoliation (Ames and Gregson 1995). Lotti et al. (1983) reported a 50% decrease in NTE in lymphocytes from seven workers repeatedly exposed to tribufos and folex via aerial and ground application of the compounds during one season of cotton defoliation. However, the workers exhibited no signs or symptoms of exposure-related neurotoxicity. Furthermore, there were no signs of OPIDN among the workers evaluated 3 weeks following cessation of tribufos and folex use. Each of these studies had major limitations, including multiple chemical exposures. No other human data were located for tribufos.

Available acute-duration inhalation information for tribufos in animals is restricted to a single acute lethality study that reported 4-hour LC_{50} values of 4,650 and 2,460 mg/m^3 for male and female Sprague-Dawley rats, respectively. Lethality is not a basis for MRL derivation.

- A provisional MRL of 0.04 mg/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to tribufos based on decreased RBC AChE activity in rats.

No adequate human data were located. An animal study assessed the toxic effects of intermittent exposure to aerosols of tribufos for 13 weeks (EPA 1992b) and serves as the basis for deriving a provisional intermediate-duration inhalation MRL for tribufos. Groups of Wistar rats (10/sex/group) were exposed (head-only) to tribufos aerosol (mass median aerodynamic diameter [MMAD] 1.2–1.3 µm) for 6 hours/day, 5 days/week for 13 weeks at analytical concentrations of 0, 0.93, 2.43, 12.2, or 59.5 mg/m^3. Clinical signs were noted in all rats of the 59.5 mg/m^3 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. Significantly decreased RBC AChE activity was noted for all time points (weeks 0, 4, 8, 12, and 13) among 12.2 mg/m^3 male and female rats (25–65% less than controls) and 59.5 mg/m^3 (49–91% less than controls). At sacrifice, brain AChE activity among male and female rats was significantly decreased only at the 59.5 mg/m^3 exposure level (40% less than controls). Additional exposure-related effects observed at the highest exposure level included depressed amplitude of a- and b-waves in electroretinographic testing (males and females) and significant increases in mean absolute and relative adrenal weight and cortical fat deposition (males).

The most sensitive effect of repeated inhalation exposure to tribufos in the rats was decreased RBC AChE activity at various time points during the 13-week study. Available published data (EPA 1992b) did not include measures of variance to mean RBC AChE activity, thus precluding a benchmark approach to derivation of an MRL. The provisional intermediate-duration inhalation MRL for tribufos was derived using a NOAEL/LOAEL (lowest-observed-adverse-effect level) 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) served as the point of departure (POD) for deriving a provisional intermediate-duration inhalation MRL for tribufos.

The NOAEL of 2.43 mg/m^3 was adjusted from intermittent to continuous exposure (0.43 mg/m^3), converted to a human equivalent concentration (1.22 mg/m^3), and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability). Refer to Appendix A for more detailed information regarding derivation of the provisional intermediate-duration inhalation MRL for tribufos.

A chronic-duration inhalation MRL was not derived for tribufos due to the lack of human or animal data.

Oral MRLs

An acute-duration oral MRL was not derived for tribufos. No human data were located. Acute-duration oral animal studies evaluated body weight, clinical signs, AChE activity, and/or developmental end points (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 end points 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. Serious LOAELs in the range of 5–7 mg/kg/day were identified in rat studies (Astroff and Young 1998; EPA 1990b, 2012e, 2012f). A serious LOAEL of 1 mg/kg/day (the lowest dose tested) was identified in the study that employed daily gavage of pregnant rabbits during gestation days (GDs) 7–19 (EPA 1990c). The rabbit study identified the lowest LOAEL (1 mg/kg/day) for tribufos-induced RBC AChE inhibition. However, because the effect occurred at the lowest dose tested and represented a serious effect (>60% RBC AChE inhibition), the result was not considered an appropriate basis for deriving an acute-duration oral MRL for tribufos. A benchmark dose (BMD) approach was considered based on the RBC AChE activity data from the rabbit study and a 20% decrease in RBC AChE activity from controls as the benchmark response (BMR). However, the dataset was not considered amenable to BMD analysis because the lowest dose tested (1 mg/kg/day) represented a nearly 70% decrease in RBC AChE activity compared to controls. BMD modeling results for this dataset would be associated with a high degree of uncertainty regarding the dose predicted to result in a 20% decrease in RBC AChE activity. Results from available rat studies identified serious LOAELs at doses 5–7 times higher than the serious LOAEL from the rabbit study; therefore, results from the rat studies were not further considered for acute-duration oral MRL derivation. For these reasons, ATSDR elected not to derive an acute-duration oral MRL for tribufos and noted that the general population is not likely to experience toxicologically-significant acute-duration oral exposure to tribufos.

- A provisional MRL of 0.003 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to tribufos based on tribufos-induced effects on RBC AChE activity in rats.

No human data were located. The results from available animal studies identify decreased RBC AChE activity as the most sensitive effect from intermediate-duration oral exposure to tribufos. A 2-generation rat study (Astroff et al. 1998; EPA 1992c) and a 364-day dog study (CalEPA 2004; EPA 1991b) identified the lowest NOAELs (0.28–0.4 mg/kg/day) and lowest less serious LOAELs (1.7–2.4 mg/kg/day) for decreased RBC AChE activity and were therefore considered as potential candidates for deriving a provisional intermediate-duration oral MRL for tribufos. 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 a provisional intermediate-duration oral MRL for tribufos. 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). 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 to mean data ($p<0.1$). Therefore, a NOAEL/LOAEL approach was applied to derive a provisional intermediate-duration oral MRL for tribufos. The NOAEL of 0.28 mg/kg/day for the F0 male rats of the 2-generation study was selected as the POD for deriving a provisional intermediate-duration oral MRL for tribufos. The NOAEL of 0.28 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in a provisional intermediate-duration oral MRL of 0.003 mg/kg/day. Refer to Appendix A for more detailed information regarding derivation of the provisional intermediate-duration oral MRL for tribufos.

- A provisional MRL of 0.0008 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to tribufos based on incidence of vacuolar degeneration in the small intestine of rats.

No human data were located. Available animal studies include a 90-week dietary study in CD-1 mice (CalEPA 2004; EPA 1990a) and a 2-year dietary study in 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). Available data for RBC AChE activity from the mouse study (CalEPA 2004; EPA 1990a) were inadequate to perform BMD analysis due to the lack of data regarding variance (standard deviation or standard error) associated with the mean. Furthermore, the NOAELs and LOAELs from the mouse study (CalEPA 2004; EPA 1990a) are higher than the NOAEL (0.2 mg/kg/day for males and females) and LOAELs (1.8 and 2.3 mg/kg/day for males and females, respectively) for >20% RBC AChE inhibition and increased incidences of histopathologic lesions in the small intestine of the rats (CalEPA 2004; EPA 1992d). Available data for tribufos-related effects on RBC AChE activity in the rat study were inadequate to perform BMD analysis due to the lack of data regarding mean RBC AChE activity and variance (standard deviation or standard error). The lowest LOAEL for chronic-duration oral exposure was 1.8 mg/kg/day for 27% decreased RBC AChE activity in male rats; the corresponding NOAEL was 0.2 mg/kg/day (CalEPA 2004; EPA 1992d). Incidence data for tribufos-induced vacuolar degeneration in the small intestine at 1-year interim sacrifice and 2-year terminal sacrifice and the incidence data for hyperplasia in the small intestine at 2-year terminal sacrifice were

amenable to BMD analysis. A POD of 0.08 mg/kg/day for vacuolar degeneration in the small intestine of the male rats at 1-year interim sacrifice represents the most conservative POD among the best-fitting models for 1-year interim and 2-year terminal sacrifice datasets for males and females. The POD of 0.08 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in a provisional chronic-duration oral MRL of 0.0008 mg/kg/day for tribufos. Refer to Appendix A for more detailed information regarding derivation of the provisional chronic-duration oral MRL for tribufos.

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3. HEALTH EFFECTS

3.1 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.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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 first by route of exposure (inhalation, oral, and dermal) and then by health effect (e.g., death, systemic, immunological, neurological, reproductive, developmental, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure 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 end point 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 Agency has established guidelines and policies that are used to classify these end points. 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.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of tribufos are indicated in Table 3-2 and Figure 3-2.

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

The common name, tribufos, is used throughout this Toxicological Profile for S,S,S-tributyl phosphorotrithioate. Tribufos is an organophosphorus pesticide; a principal effect of tribufos is inhibition of AChE, the enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine, independent of the route of exposure or exposure duration (Astroff and Young 1998; Astroff et al. 1998; EPA 1990a, 1990c, 1991b, 1992b, 1992d, 1993d, 2005a, 2012a, 2012b, 2012c, 2012d, 2012e, 2012f, 2013a). Inhibition of AChE results in the accumulation of acetylcholine and leads to overactivation of cholinergic (muscarinic and nicotinic) receptors in the peripheral and central nervous systems. In humans and laboratory animals, overactivation of muscarinic receptors causes excessive glandular secretions (salivation, lacrimation, rhinitis), miosis, bronchoconstriction, vasodilation, hypotension, diarrhea, nausea, vomiting, urinary incontinence, and bradycardia. Tachycardia, muscle fasciculations, cramping, twitching, muscle weakness, and muscle paralysis are associated with nicotinic receptor overstimulation. Central nervous system toxicity of organophosphorus pesticides such as tribufos 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, depending upon the extent of exposure.

AChE is found in central and peripheral nervous tissue and in RBCs. Inhibition of RBC AChE by organophosphorus compounds such as tribufos is used as a biomarker of effect for hazard identification.

According to Chou and Williams-Johnson (1998), a 20–59% inhibition of neural or RBC AChE (measured as decrease in AChE activity) may be considered a less serious effect even in the absence of more serious indicators of neurotoxicity; a ≥60% inhibition of neural or RBC AChE is considered a serious effect even in the absence of more serious indicators of neurotoxicity. The designations of less serious and serious effects on AChE activity are applicable to acute responses to acute-, intermediate-, and/or chronic-duration exposures to organophosphorus compounds such as tribufos. In this Toxicological Profile, "less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose toxicological significance to the organism is not entirely clear. A ≥60% inhibition of neural or RBC AChE is considered a serious effect (Chou and Williams-Johnson 1998). Multiple animal studies identify levels of exposure to tribufos resulting in RBC and/or brain AChE inhibition that could be classified as less serious and/or serious effects; most studies also identified a NOAEL (i.e., <20% neural and/or RBC AChE inhibition). The animal studies typically identified RBC AChE inhibition at exposure levels below those resulting in other signs of tribufos-induced adverse effects; this indicates that RBC AChE inhibition may represent the most sensitive effect of tribufos toxicity. Most of these studies are unpublished and were submitted to EPA's Office of Prevention, Pesticides, and Toxic Substances. Only selected results from some of the unpublished studies are publicly-available as cleared reviews in the form of Data Evaluation Reports (DERs).

3.2.1 Inhalation Exposure

3.2.1.1 Death

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

Limited information is publicly available regarding lethality in laboratory animals exposed to tribufos by inhalation. A 4-hour nose-only exposure of male Sprague-Dawley rats to tribufos aerosol (MMAD 1.4–1.55 μm; 69–78% of particles <2 μm in diameter) at analytically-determined concentrations of 2,920, 5,690, or 6,030 mg/m^3 resulted in mortality of 1/6, 4/6, and 5/6 rats, respectively; similar exposure of female rats at concentrations of 1,590, 2,920, or 3,190 mg/m^3 resulted in mortality of 1/6, 3/6, and 6/6 females, respectively (EPA 1991a, 1992a). Calculated 4-hour LC_{50} values (exposure concentration associated with 50% mortality) were 4,650 and 2,460 mg/m^3 for males and females, respectively. No tribufos exposure-related deaths occurred among 2–3-month-old male and female Wistar rats exposed (head-only) to tribufos aerosol (MMAD 1.2–1.3 μm) at analytically-determined mean concentrations of 0.93–59.5 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (EPA 1992b).

3.2.1.2 Systemic Effects

No information was located regarding cardiovascular, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, or body weight effects in humans exposed to tribufos by inhalation. No information was located regarding cardiovascular, musculoskeletal, or dermal effects in laboratory animals exposed to tribufos by inhalation.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Limited information was located regarding 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 defoliants 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. 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

Table 3-1. Levels of Significant Exposure to Tribufos – Inhalation

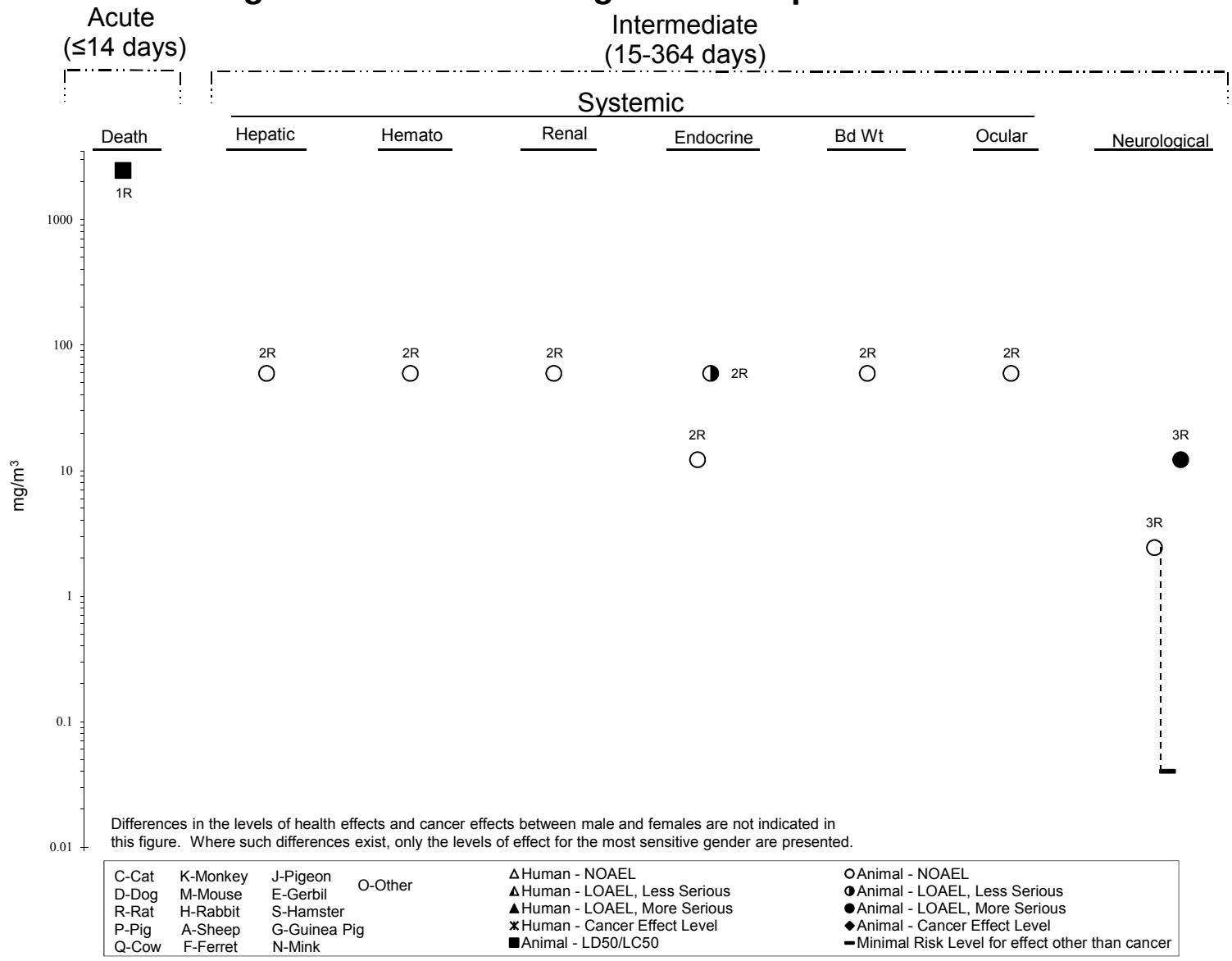
Figure key[a]	Species (strain) No./group	Exposure parameters/ Concentrations (mg/m^3)	Parameters monitored	System	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Results	Reference (compound)
ACUTE EXPOSURE									
Death									
1	Rat (Sprague-Dawley) 6/sex	One 4-hr exposure (nose-only) M: 0, 2920, 5690, 6030 F: 0, 1590, 2920, 3190	BW CS GN LE				4650 M 2460 F (4-hr LC_{50})	M: 1/6, 4/6, 5/6 deaths in low-, mid-, and high-exposure groups. F: 1/6, 3/6, 6/6 deaths in low-, mid-, and high-exposure groups.	EPA 1991a, 1992a Tribufos
INTERMEDIATE EXPOSURE									
Systemic									
2	Rat (Wistar) 10/sex	13 wk 5 d/wk 6 hr/d (head-only) 0, 0.93, 2.43, 12.2, 59.5	BH BW CS EA GN HE HP LE OP OW UR	Hemato Hepatic Renal Endocr Ocular BW	59.5 59.5 59.5 12.2 M 59.5 F 59.5 59.5	59.5 M		Endocrine effects: increased adrenal weight and cortical fat deposition in males.	EPA 1992b Tribufos
Neurological									
3	Rat (Wistar) 10/sex	13 wk 5 d/wk 6 hr/d (head-only) 0, 0.93, 2.43, 12.2, 59.5	BH BW CS EA GN HE HP LE OP OW UR		2.43[b]		12.2	At 12.2 mg/m^3, up to 65% decreased RBC AChE activity. At 59.5 mg/m^3, up to 91% decreased RBC AChE activity and 40% decreased brain AChE activity.	EPA 1992b Tribufos

[a]The number corresponds to entries in Figure 3-1.

[b]Used to derive an intermediate-duration inhalation MRL of 0.04 mg/m^3 based on tribufos-induced decreased RBC AChE activity. The rat NOAEL of 2.43 mg/m^3 was adjusted from intermittent to continuous exposure and converted to a human equivalent concentration; a total uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability) was applied. Refer to Section 2.3 and Appendix A for more detailed information regarding derivation of the intermediate-duration inhalation MRL for tribufos.

AChE = acetylcholinesterase; BH = behavioral; BW = body weight; CS = clinical signs; d = day(s); EA = enzyme activity; Endocr = endocrine; F = female(s); GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; OP = ophthalmology; OW = organ weight; RBC = red blood cell; UR = urinalysis; wk = week(s)

Figure 3-1. Levels of Significant Exposure to Tribufos - Inhalation



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 defoliants (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 exposed (head-only) to tribufos aerosol at 59.5 mg/m^3 for 6 hours/day, 5 days/week 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.

Gastrointestinal Effects. Human data are limited to results from the study described in Section 3.2.1.2 (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.

Hematological Effects. Available information is limited to results from a single study in which there was no evidence of hematological effects following head-only exposure of Wistar rats to tribufos aerosol at up to 59.5 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (EPA 1992b). Tribufos-induced effects on RBC AChE activity are discussed in Section 3.2.1.4 (Neurological Effects).

Hepatic Effects. Available information is limited to results from a single study in which there was no evidence of hepatotoxicity (serum liver enzymes, histopathology results) following head-only exposure of Wistar rats to tribufos aerosol at up to 59.5 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (EPA 1992b).

Renal Effects. Available information is limited to results from a single study in which there was no evidence of renal toxicity (based on results of urinalysis and histopathological evaluations) following head-only exposure of Wistar rats to tribufos aerosol at up to 59.5 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (EPA 1992b).

Endocrine Effects. Available information is limited to results from a single study in which head-only exposure of Wistar rats to tribufos aerosol at 59.5 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks resulted in increased adrenal weight and increased incidence of cortical fat deposit in adrenals of males (but not females) (EPA 1992b). The study identified NOAELs of 12.2 mg/m^3 for males and 59.5 mg/m^3 for females.

Ocular Effects. Human data are limited to the study described in Section 3.2.1.2 (Respiratory Effects) in which self-reported symptoms in a group of residents in cotton-growing areas with high probability of exposure to tribufos during the 1987 cotton defoliation season (n=142) yielded a RR of 1.8 (95% CI 1.3, 2.5) for eye irritation (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.

Limited information was located regarding ocular effects in laboratory animals exposed to airborne tribufos. Exophthalmos (abnormal protrusion of the eyeballs) was observed in Wistar rats exposed to tribufos aerosol at up to 59.5 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks; there was no other evidence of ocular effects, as judged by ophthalmologic examinations (EPA 1992b). See Section 3.2.3.1 (Ocular Effects) for information regarding ocular effects in animals considered to be a result of direct ocular contact with airborne tribufos aerosol.

Body Weight Effects. Available information is limited to results from a single study in which head-only exposure of Wistar rats to tribufos aerosol at up to 59.5 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks resulted in no apparent body weight effects (EPA 1992b).

Other Systemic Effects. Hypothermia was reported among Wistar rats exposed (head-only) to tribufos aerosol (MMAD 1.2–1.3 µm) 6 hours/day, 5 days/week for 13 weeks at an analytically-determined concentration of 59.5 mg/m^3 (EPA 1992b). See Sections 3.2.2.2 (Other Systemic Effects) and

3.2.4 (Other Routes of Exposure) for additional information regarding tribufos-induced hypothermic responses.

3.2.1.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological or lymphoreticular effects in humans or animals following inhalation exposure to tribufos.

3.2.1.4 Neurological Effects

Human data are limited. Evaluation of the results from the study described in Section 3.2.1.2 (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.

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 (MMAD 1.4–1.55 μm; 69–78% of particles <2 μm in diameter) for 4 hours; however, the available summary of the unpublished did not specify tribufos concentrations (range 1,590–6,030 mg/m^3) or frequency of observed signs of neurotoxicity (EPA 1991a). Head-only exposure of Wistar rats to tribufos aerosol at 59.5 mg/m^3 for 6 hours/day, 5 days/week 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 is considered a serious adverse effect according to ATSDR guidance. Most interim and terminal evaluations of AChE activity at exposure levels ≤2.43 mg/m^3 revealed either no significant exposure-related effect or decreases of <20% in AChE activity, which is not considered an adverse effect according to ATSDR guidance (i.e., the study identified a NOAEL of 2.43 mg/m^3 for neurological effects).

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 daily 6-hour exposures, 5 days/week 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 LOEL for OPIDN (391 and 878 mg/m^3, 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/m^3, 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 3-1 or Figure 3-1.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

No information was located regarding the following effects in humans or animals exposed to tribufos by inhalation:

3.2.1.5 Reproductive Effects
3.2.1.6 Developmental Effects
3.2.1.7 Cancer

3.2.2 Oral Exposure

3.2.2.1 Death

No information was located regarding death in humans following oral exposure to tribufos.

Acute LD_{50} values of 435 and 234 mg/kg were reported for male and female rats, respectively, administered a single gavage dose of tribufos and observed for up to 14 days postadministration (EPA 1993a). Mortality rates among males dosed at 294, 429, or 552 mg/kg were 0/5, 3/5, and 4/5, respectively; mortality rates among females dosed at 192, 235, or 294 mg/kg were 0/5, 4/5, and 4/5, respectively. Rats found dead exhibited fluid and discoloration in stomach and duodenum and pale liver. Gaines (1969) reported respective acute oral LD_{50} values of 233 and 150 mg/kg for male and female Sherman rats administered tribufos by gavage at unspecified dose levels and observed for up to 14 days postdosing. The lowest lethal doses to the males and females were 175 and 100 mg/kg, respectively. All 11-day-old male and female Sprague-Dawley rat pups administered tribufos by gavage at 20 mg/kg were

sacrificed within 6–8 hours postdosing due to the severity of clinical signs; there were no deaths among other 11-day-old pups dosed at 5–15 mg/kg/day for up to 11 days (EPA 2012a). In a 90-week study of male and female CD-1 mice administered tribufos in the diet, significantly decreased survival was noted for males and females at calculated tribufos doses of 48.02 and 63.04 mg/kg/day, respectively (EPA 1990a). No treatment-related deaths were observed among 2 generations of Sprague-Dawley rats receiving tribufos from the diet at estimated doses as high as 17.6–22.93 mg/kg/day during premating and mating; dams received estimated doses as high as 18.07–19.03 mg/kg/day during gestation and 42.23–49.61 mg/kg/day during lactation (Astroff et al. 1998; EPA 1992c).

3.2.2.2 Systemic Effects

No human data are available for systemic effects associated with oral exposure to tribufos. No data were located regarding respiratory, cardiovascular, musculoskeletal, renal, or dermal effects in animals exposed to tribufos by the oral route.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Gastrointestinal 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,

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

Figure key[a]	Species (strain) No./group	Exposure parameters/ Doses (mg/kg)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference (compound)
ACUTE EXPOSURE									
Death									
1	Rat (NS) 5/sex	Once (GO) M: 294, 429, 552 F: 192, 235, 294	BW CS GN LE				435 M 234 F (LD_{50})	M: 0/5, 3/5, 4/5 deaths in low-, mid-, and high-dose groups. F: 0/5, 4/5, 4/5 deaths in low-, mid-, and high-exposure groups.	EPA 1993a Tribufos
2	Rat (Sherman); unspecified numbers/sex/ group	Once (GO) Unspecified doses	LE				233 M 150 F (LD_{50})	Lowest lethal doses to males and females were 175 and 100 mg/kg, respectively	Gaines 1969 Tribufos
Systemic									
3	Rat (Sprague-Dawley; 11-day-old pups) 2-4/sex at scheduled sacrifice 4, 6, 8, 24, or 48 hr postdosing	Once (GO) 0, 50	BW CS EA GN LE OW	BW			50	All vehicle control pups exhibited body weight gain at 24 and 48 hours postdosing; tribufos-treated pups exhibited actual body weight loss at 24 and 48 hours postdosing.	EPA 2012b
4	Rat (Sprague-Dawley; 11-day-old pups) 3-4/sex	Up to 11 d (GO) 1 x/d 0, 5, 10, 15, 20	BW CS EA	BW	5	10		At 10 and 15 mg/kg/d, mean terminal body weights were up to 17% lower than sex-matched controls. The 20 mg/kg/d dose group was terminated after the first dose due to severity of clinical signs.	EPA 2012a Tribufos
5	Rat (Sprague-Dawley) 10 dams	GD 6-19 (GO) 1 x/d 0, 0.3-0.8, 7, 28	BW CS DX EA FI GN LE	BW	7		28	Depressed mean maternal BW gain at 28 mg/kg/d (27% less than controls).	EPA 2012f Tribufos
6	Rat (Sprague-Dawley) 33 dams	GD 6-15 (G) 1 x/d 0, 1, 7, 28	BW CS DX EA FI FX GN LE MX OW TG	BW	28				Astroff and Young 1998; EPA 1990b Tribufos
7	Rabbit (American Dutch) 17 does	GD 7-19 (G) 1 x/d 0, 1, 3, 9	BW CS DX EA FI FX GN LE MX OW TG	BW	3	9		No maternal body weight gain compared to approximately 5% mean body weight gain for vehicle controls.	EPA 1990c Tribufos

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

Figure key[a]	Species (strain) No./group	Exposure parameters/ Doses (mg/kg)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference (compound)
Neurological									
8	Rat (Sprague-Dawley; 11-day-old pups) 2-4/sex at scheduled sacrifice 4, 6, 8, 24, or 48 hr postdosing	Once (GO) 0, 50	BW CS EA GN LE OW				50	79-92% decreased AChE activity during 48 hours postdosing (greatest decrease at 24 hours); up to 76% decreased brain AChE activity (greatest decrease at 6-8 hours).	EPA 2012b Tribufos
9	Rat (Sprague-Dawley; 11-day-old pups) 3-4/sex	Once (GO) 0, 20, 40, 50	BW CS EA GN LE OW			20 M	40 M 20 F	At 20 mg/kg/d, 59 and 71% decreased RBC AChE activity among males and females, respectively; 34% decreased brain AChE activity among females. At 40 mg/kg/d, up to 79% decreased RBC AChE activity and up to 52% decreased brain AChE activity. At 50 mg/kg/d, up to 83% decreased RBC AChE activity and up to 60% decreased brain AChE activity.	EPA 2012a Tribufos
10	Rat (Sprague-Dawley; 11-day-old pups) 8/sex	Once (GO) 0, 2, 10, 50	BW CS EA GN LE OW		2 M	10 M 2 F	50	At 2 mg/kg/d, 27% decreased RBC AChE activity among females. At 10 mg/kg/d, 47 and 33% decreased RBC AChE activity among males and females, respectively. At 50 mg/kg/d, 86-89% decreased RBC AChE activity and 75-76% decreased brain AChE activity.	EPA 2012d Tribufos
11	Rat (Sprague-Dawley; young adults) 24 F	Once (GO) 0, 80	BW CS EA GN LE OW				80	RBC AChE activity ranged from 9% less than controls at 2 hours postdosing to >80% less than controls at 24-48 hours postdosing	EPA 2012c Tribufos
12	Rat (Sprague-Dawley; young adults) 8 F	Once (GO) 0, 2, 10, 80	BW CS EA GN LE OW		10		80	74% decreased RBC AChE activity.	EPA 2012d Tribufos

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

Figure key[a]	Species (strain) No./group	Exposure parameters/ Doses (mg/kg)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference (compound)
13	Rat (Sprague-Dawley; 11-day-old pups) 3-4/sex	Up to 11 d (GO) 1 x/d 0, 5, 10, 15, 20	BW CS EA			5	15	At 5 mg/kg/d, 36-49% decreased RBC AChE activity; males exhibited 23% decreased brain AChE activity. At 10 mg/kg/d, 25-51% decreased RBC AChE activity; 32-37% decreased brain AChE activity. At 15 mg/kg/d, 66-83% decreased RBC AChE activity; 46-47% decreased brain AChE activity.	EPA 2012a Tribufos
14	Rat (Sprague-Dawley; 11-day-old pups) 8/sex	11 d (GO) 1 x/d 0, 0.1, 1, 5	BW CS EA GN LE OW		1		5	66-69% decreased RBC AChE activity and 20-21% decreased brain AChE activity.	EPA 2012e Tribufos
15	Rat (Sprague-Dawley; young adults) 8 F	11 d (GO) 1 x/d 0, 0.1, 1, 5	BW CS EA GN LE OW		1		5	At 5 mg/kg/d, 64% decreased RBC AChE activity.	EPA 2012e Tribufos
16	Rat (Sprague-Dawley) 33 dams	GD 6-15 (G) 1 x/d 0, 1, 7, 28	BW CS DX EA FI FX GN LE MX OW TG		1		7	At 7 mg/kg/d, 71.2% decreased RBC AChE activity among 5 dams sacrificed on GD 16. At 28 mg/kg/d, 87.3% decreased RBC AChE activity and 57.6% decreased brain AChE activity among 5 dams sacrificed on GD 16. Fetal brain AChE activity was similar among controls and all tribufos-treated groups.	Astroff and Young 1998; EPA 1990b Tribufos
17	Rat (Sprague-Dawley) 10 dams	GD 6-19 (GO) 1 x/d 0, 0.3-0.8, 7, 28	BW CS DX EA FI GN LE		0.3		7	At 7 mg/kg/d, 75% decreased maternal RBC AChE activity and 22% decreased maternal brain AChE activity. At 28 mg/kg/d, 89% decreased maternal RBC AChE activity and 81% decreased maternal brain AChE activity. Fetal RBC and brain AChE activity levels were similar among controls and all tribufos-treated groups.	EPA 2012f Tribufos

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

Figure key[a]	Species (strain) No./group	Exposure parameters/ Doses (mg/kg)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference (compound)
18	Rabbit (American Dutch) 17 does	GD 7-19 (G) 1 x/d 0, 1, 3, 9	BW CS DX EA FI FX GN LE MX OW TG				1	At 1 mg/kg/d, 70% decreased maternal RBC AChE activity on GD 20. At 3 mg/kg/d, 85% decreased maternal RBC AChE activity on GD 20. At 9 mg/kg/d, 93% decreased maternal RBC AChE activity on GD 20.	EPA 1990c Tribufos
Reproductive									
19	Rabbit (American Dutch) 17 does	GD 7-19 (G) 1 x/d 0, 1, 3, 9	BW CS DX EA FI FX GN LE MX OW TG		9				EPA 1990c Tribufos
Developmental									
20	Rat (Sprague-Dawley) 33 dams	GD 6-15 (G) 1 x/d 0, 1, 7, 28	BW CS DX EA FI FX GN LE MX OW TG		28				Astroff and Young 1998; EPA 1990b Tribufos
21	Rat (Sprague-Dawley) 10 dams	GD 6-19 (GO) 1 x/d 0, 0.3-0.8, 7, 28	BW CS DX EA FI GN LE		7	28		6% lower mean fetal body weight in male fetuses; concomitant 27% depressed mean body weight gain in dams.	EPA 2012f Tribufos
22	Rabbit (American Dutch) 17 does	GD 7-19 (G) 1 x/d 0, 1, 3, 9	BW CS DX EA FI FX GN LE MX OW TG		9				EPA 1990c Tribufos
INTERMEDIATE EXPOSURE									
Systemic									
23	Rat (Han Wistar) 10 F	4 wk (diet) 0, 0.43, 4.32, 44.62	BW CS EA FI GN LE OF OW WI	Hemato BW	4.32 4.32		44.62 44.62	23% increased mean relative spleen weight, 80% depressed mean body weight gain during first 11 days, 16% less food intake during first week, 29% less water intake during 4 weeks.	EPA 2013a Tribufos

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

Figure key[a]	Species (strain) No./group	Exposure parameters/ Doses (mg/kg)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference (compound)
24	Rat (Wistar) 30 F	42 d (diet) GD 0-LD 21 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	BW	6.1	33.5		8-12% lower mean maternal body weight during lactation only; no effects on food or water intake.	EPA 2005a Tribufos
25	Rat (Sprague-Dawley) 30/sex/gen	2 gen (diet) 10 wk premating, mating up to 28 d, 3 wk of gestation, 3 wk 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	BW	17.6 M 18.07 F			No body weight effect at highest dietary level. Calculated doses are listed as ranges for the F0 and F1 parental rats and include separately-calculated doses to females for premating, gestation, and lactation phases.	Astroff et al. 1998; EPA 1992c Tribufos
26	Rat (Fischer-344) 50/sex	Up to 2 yr (diet) 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 interim evaluations.	CalEPA 2004; EPA 1992d Tribufos
27	Mouse (CD-1) 15/sex	8 wk (diet) M: 0, 3.4, 9.4, 40, 140 F: 0, 5.6, 14.3, 54, 132	BW CS EA FI LE	BW	140 M 132 F				CalEPA 2004 Tribufos
28	Dog (beagle) 4/sex	364 d (diet) M: 0, 0.1, 0.4, 1.7 F: 0, 0.1, 0.4, 2.0	BC BW CS EA FI HE OP UR	Ocular BW	1.7 M 2.0 F 1.7 M 2.0 F				EPA 1991b Tribufos
Immunological/Lymphoreticular									
29	Rat (Han Wistar) 10 F	4 wk (diet) 0, 0.43, 4.32, 44.62	BW CS EA FI GN LE OF OW WI		44.62			In a PFC assay, no effects on numbers of PFCs/spleen or PFC response to sheep RBCs.	EPA 2013a Tribufos

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

Figure key[a]	Species (strain) No./group	Exposure parameters/ Doses (mg/kg)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference (compound)
Neurological									
30	Rat (Han Wistar) 10 F	4 wk (diet) 0, 0.43, 4.32, 44.62	BW CS EA FI GN LE OF OW WI		0.43		4.32	At 4.32 mg/kg/d, 66% decreased RBC AChE activity. At 44.62 mg/kg/d, 90% decreased RBC AChE activity and 78% decreased brain AChE activity.	EPA 2013a Tribufos
31	Rat (Wistar) 30 F	42 d (diet) GD 0-LD 21 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		0.4		3.4	At 3.4 mg/kg/d, 76% decreased RBC AChE activity and 22% decreased brain AChE activity (the lowest dose in the range for the gestation period is listed as the NOAEL and serious LOAEL to be conservative). The high-dose group exhibited 87% decreased RBC AChE activity and 22% decreased brain AChE activity.	EPA 2005a Tribufos
32	Rat (Sprague-Dawley) 30/sex/gen	2 gen (diet) 10 wk premating, mating up to 28 d, 3 wk of gestation, 3 wk 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		0.28[b] M 0.31 F	2 M 2.25 F		RBC AChE activity decreased by 35 and 46% in mid-dose F0 males and females, respectively, in pre-mating phase. Brain AChE activity decreased >29% in mid- and high-dose F0 and F1 parental rats (>80% in high-dose females). RBC AChE activity decreased by 23-38% in high-dose F1 and F2 pups at lactation day 21.	Astroff et al. 1998; EPA 1992c Tribufos
33	Mouse (CD-1) 15/sex	8 wk (diet) M: 0, 3.4, 9.4, 40, 140 F: 0, 5.6, 14.3, 54, 132	BW CS EA FI LE		3.4 M 5.6 F	9.4 M 14.3 F	40 M 54 F	37 and 44% decreased RBC AChE activity at 3.4 and 5.6 mg/kg/day (males and females, respectively) 64% decreased RBC AChE activity at 40 mg/kg/day (males) and 54 mg/kg/day (females).	CalEPA 2004
34	Dog (beagle) 4/sex	364 d (diet) M: 0, 0.1, 0.4, 1.7 F: 0, 0.1, 0.4, 2.0	BC BW CS EA FI HE OP UR		0.4 M 0.4 F	1.7 M 2.0 F		At treatment day 91, RBC AChE activity decreased by 24% in high-dose males and up to 29% in high-dose females. No apparent effects on brain AChE activity.	EPA 1991b Tribufos

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

Figure key[a]	Species (strain) No./group	Exposure parameters/ Doses (mg/kg)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference (compound)
Reproductive									
35	Rat (Wistar) 30 F	42 d (diet) GD 0-LD 21 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		16.4				EPA 2005a Tribufos
36	Rat (Sprague-Dawley) 30/sex/gen	2 gen (diet) 10 wk premating, mating up to 28 d, 3 wk of gestation, 3 wk 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		17.6 M 18.07 F			Lowest dose in a particular range is considered the NOAEL.	Astroff et al. 1998; EPA 1992c Tribufos
Developmental									
37	Rat (Wistar) 30 F	42 d (diet) GD 0-LD 21 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		3.4	16.4		16-23% Depressed lactational pup body weight, delays in preputial separation and development of righting reflex, decreased locomotor and motor activity at PND 13, increased motor activity at PND 17, decreased auditory startle amplitude at PND 22.	EPA 2005a Tribufos
38	Rat (Sprague-Dawley) 30/sex/gen	2 gen (diet) 10 wk premating, mating up to 28 d, 3 wk of gestation, 3 wk 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		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 lactation day 21. The NOAEL and serious LOAEL values are represented by the lowest dose in a range for F0 and F1 parental exposure.	Astroff et al. 1998; EPA 1992c Tribufos

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

Figure key[a]	Species (strain) No./group	Exposure parameters/ Doses (mg/kg)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference (compound)
CHRONIC EXPOSURE									
Death									
39	Mouse (CD-1) 50/sex	90 wk (diet) 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				48.1 M 63.1 F	Survival: 20/50 high-dose males versus 34/50 controls; 19/50 high-dose females versus 31/50 controls.	EPA 1990a Tribufos
Systemic									
40	Rat (Fischer-344) 50/sex	2 yr (diet) 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	Gastro Hemato Endocr BW	0.2 M[c] 0.2 F 0.2 M 0.2 F 1.8 M 2.3 F 1.8 M 2.3 F	1.8 M 2.3 F 1.8 M 2.3 F 16.8 M 21.1 F 16.8 M 21.1 F		Gastrointestinal effects: Vacuolar degeneration in small intestines. Hematological effects: decreases in RBC count, hemoglobin, and hematocrit in mid- and high-dose groups at 12-month interim evaluation (some values returned to normal by 18 and 24 months). Endocrine effects: enlarged adrenals, increased adrenal weight, and vacuolar degeneration. Body weight effects: 15% depressed mean body weight gain.	CalEPA 2004; EPA 1992d Tribufos
41	Mouse (CD-1) 50/sex	90 wk (diet) 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	Gastro Hemato Hepatic Endocr BW	1.5 M 2.0 F 1.5 M 11.3 F 48.1 M 11.3 F 8.4 M 11.3 F 48.1 M 63.1 F	8.4 M 11.3 F 8.4 M 63.1 F 63.1 F 48.1 M 63.1 F		Gastrointestinal effects: Dose-related increased incidences of histopathologic lesions in small intestine of mid- and high-dose mice. Hematological effects: Extramedullary hematopoiesis in spleen of mid- and high-dose males; hematological changes indicative of anemia in high-dose males and females. Endocrine effects: Degeneration and pigmentation in adrenals of high-dose males and females.	EPA 1990a Tribufos

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Figure key[a]	Species (strain) No./group	Exposure parameters/ Doses (mg/kg)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference (compound)
Neurological									
42	Rat (Fischer-344) 50/sex	2 yr (diet) 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		0.2 M 0.2 F	1.8 M 2.3 F	16.8 M 21.1 F	Mid-dose males and females: 27-28% decreased RBC AChE activity. High-dose males and females: 47-48% decreased RBC AChE activity, 60-68% decreased brain AChE activity, optic nerve atrophy, bilateral retinal atrophy, unrecordable electroretinographic responses.	CalEPA 2004; EPA 1992d Tribufos
43	Mouse (CD-1) 50/sex	90 wk (diet) 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		1.5 M 2.0 F	8.4 M 11.3 F		34-55% decreased RBC AChE activity in mid- and high-dose mice; 27-37% decreased brain AChE activity in high-dose mice.	EPA 1990a Tribufos
Cancer									
44	Mouse (CD-1) 50/sex	90 wk (diet) 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				CEL: 48.1 M CEL: 63.1 F	M: Small intestine adenocarcinoma, hemangiosarcoma. F: Alveolar/bronchiolar adenoma	EPA 1990a Tribufos

[a]The number corresponds to entries in Figure 3-2.

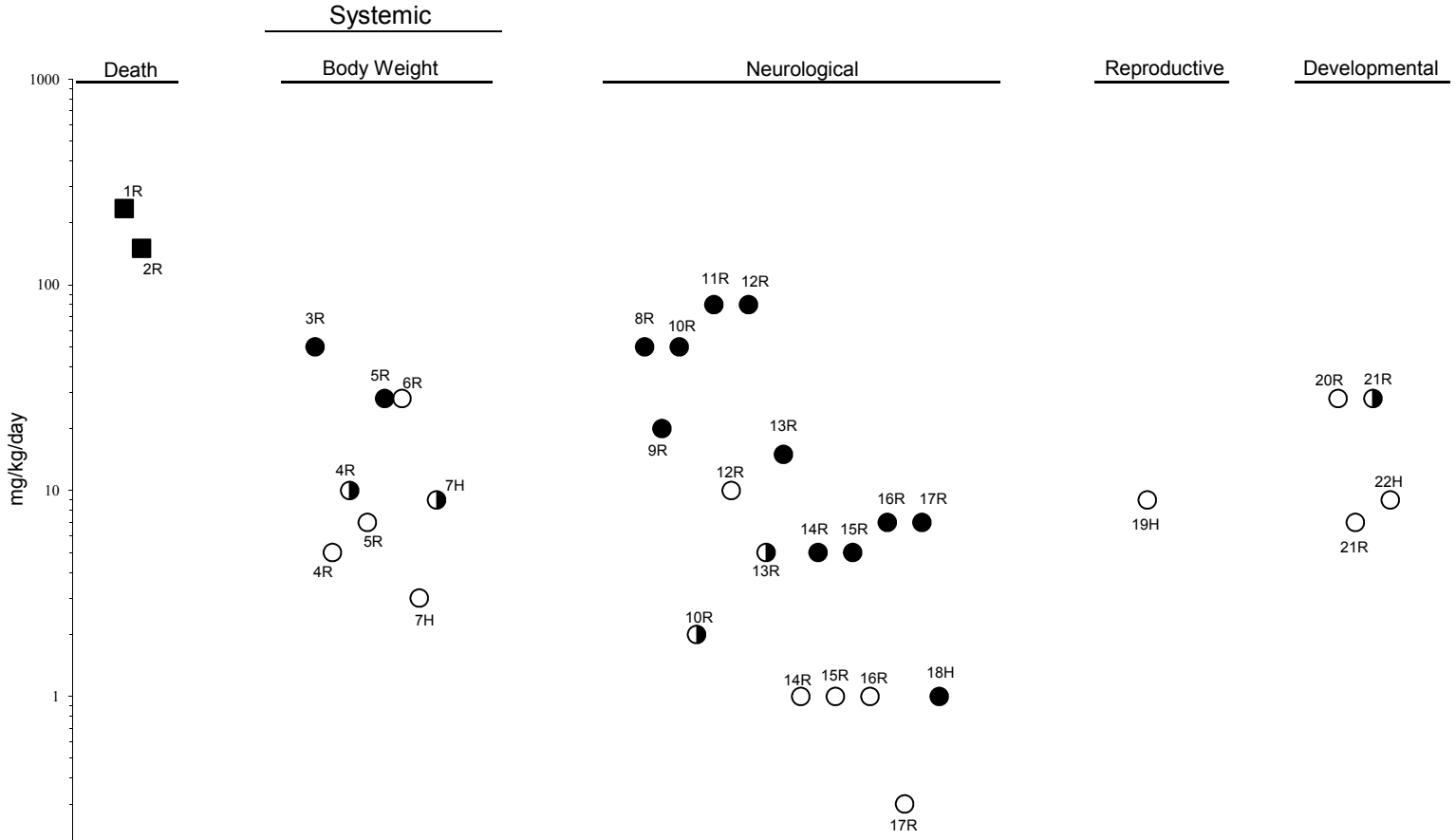
[b]Used to derive an intermediate-duration oral MRL of 0.003 mg/kg/day based on tribufos-induced decreased RBC AChE activity. The NOAEL of 0.28 mg/kg/day was divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). Refer to Section 2.3 and Appendix A for more detailed information regarding derivation of the intermediate-duration oral MRL for tribufos.

[c]Study result used to derive a chronic-duration oral MRL of 0.0008 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 ($BMDL_{10}$) of 0.08 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 Section 2.3 and Appendix A for more detailed information regarding derivation of the chronic-duration oral MRL for tribufos.

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

Figure 3-2. Levels of Significant Exposure to Tribufos - Oral

Acute (≤14 days)



Differences in the levels of health effects and cancer effects between male and females are not indicated in this figure. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

C-Cat	K-Monkey	J-Pigeon	O-Other
D-Dog	M-Mouse	E-Gerbil	
R-Rat	H-Rabbit	S-Hamster	
P-Pig	A-Sheep	G-Guinea Pig	
Q-Cow	F-Ferret	N-Mink	

△Human - NOAEL	○Animal - NOAEL
◭Human - LOAEL, Less Serious	◑Animal - LOAEL, Less Serious
▲Human - LOAEL, More Serious	●Animal - LOAEL, More Serious
✖Human - Cancer Effect Level	◆Animal - Cancer Effect Level
■Animal - LD50/LC50	━Minimal Risk Level for effects other than cancer

Figure 3-2. Levels of Significant Exposure to Tribufos - Oral *(Continued)*

Intermediate (15-364 days)

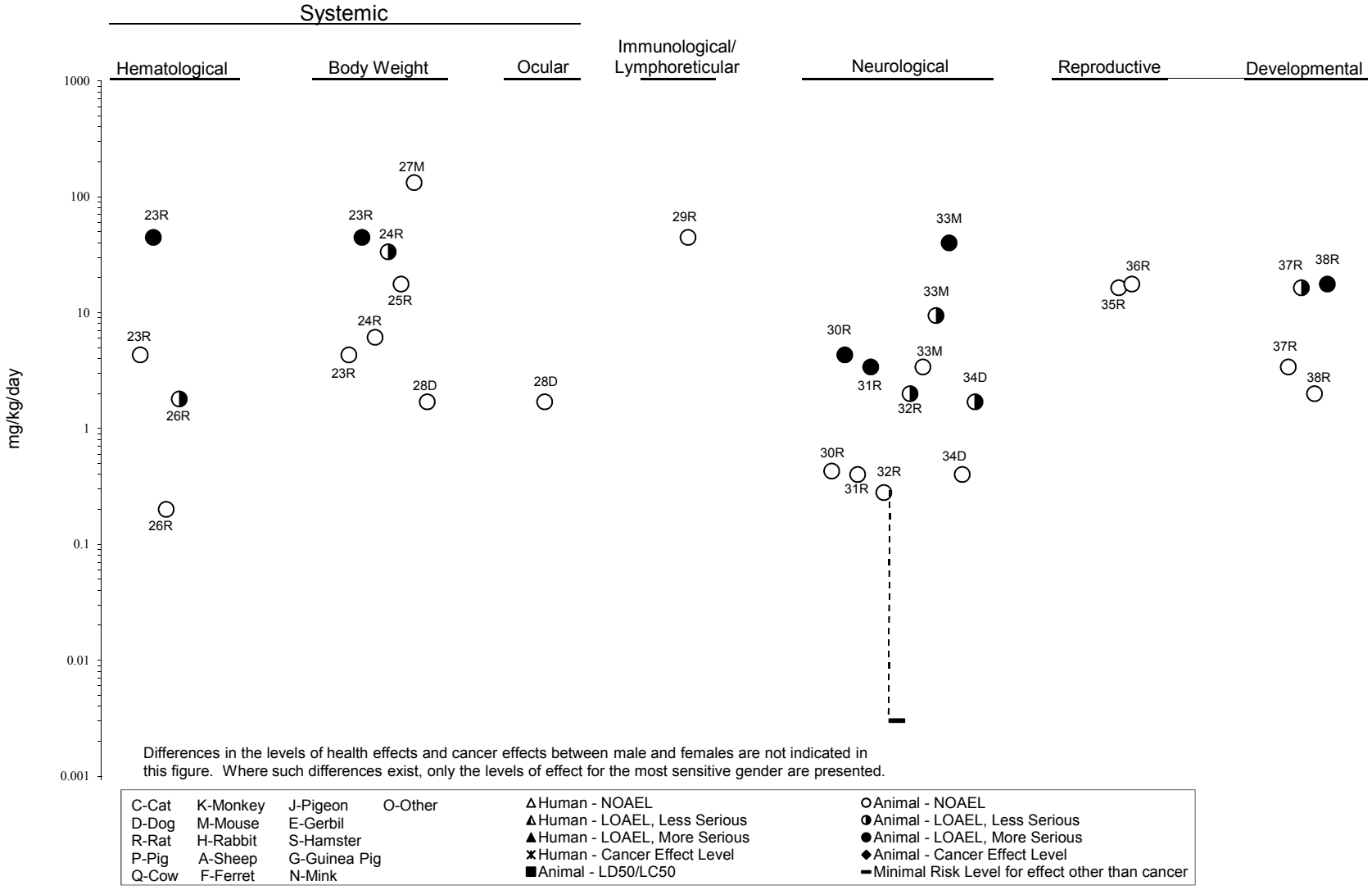
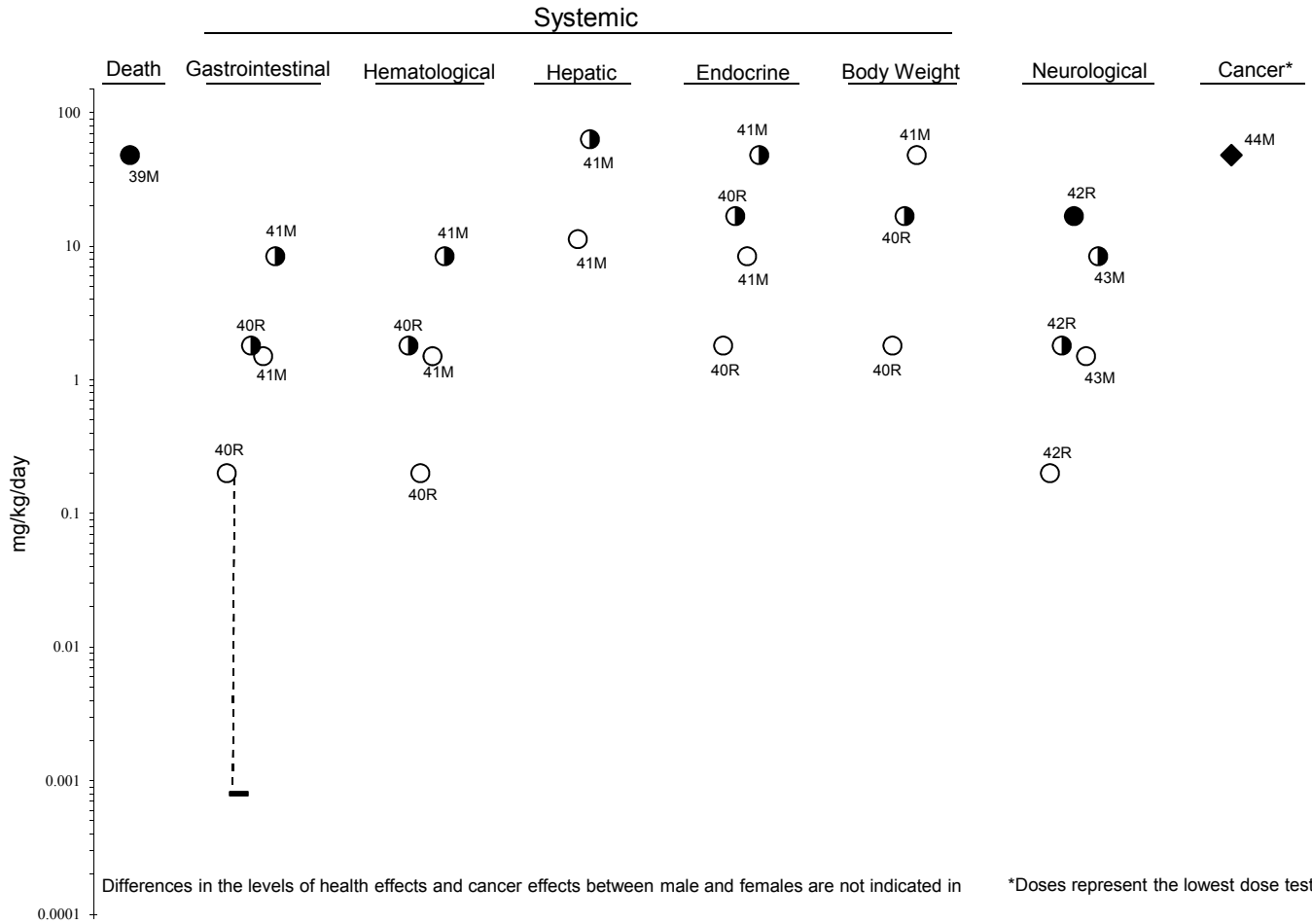


Figure 3-2. Levels of Significant Exposure to Tribufos - Oral *(Continued)*

Chronic (≥365 days)



Differences in the levels of health effects and cancer effects between male and females are not indicated in

*Doses represent the lowest dose tested per study that produced a tumorigenic

C-Cat	K-Monkey	J-Pigeon	O-Other
D-Dog	M-Mouse	E-Gerbil	
R-Rat	H-Rabbit	S-Hamster	
P-Pig	A-Sheep	G-Guinea Pig	
Q-Cow	F-Ferret	N-Mink	

△Human - NOAEL	○Animal - NOAEL
◭Human - LOAEL, Less Serious	◑Animal - LOAEL, Less Serious
▲Human - LOAEL, More Serious	●Animal - LOAEL, More Serious
✕Human - Cancer Effect Level	◆Animal - Cancer Effect Level
■Animal - LD50/LC50	━Minimal Risk Level for effects other than cancer

respectively, for the males and 1/50, 0/50, 11/50, and 30/50, respectively, for the females) at 24-month terminal sacrifice.

Hematological Effects. Available information is limited to dietary exposure to tribufos in a 2-year study of Fischer 344 rats (CalEPA 2004; EPA 1992d) and a 90-week study in CD-1 mice (EPA 1990a). In the rat study, dietary concentrations of 40 and 320 ppm (estimated tribufos doses of 1.8 and 16.8 mg/kg/day, respectively, for males and 2.3 and 21.1 mg/kg/day, respectively, for females) resulted in statistically 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 (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 the mouse study, effects indicative of tribufos treatment-related anemia were observed at the highest concentration (estimated tribufos doses of 48.02 and 63.04 mg/kg/day for males and females, respectively) and included decreases in selected values (e.g., mean RBC count, hemoglobin, hematocrit) (EPA 1990a). Changes in some hematology values were observed at lower doses, but were generally <10% different from control values and did not exhibit clear dose-response relationships. Available secondary source summaries (CalEPA 2004; EPA 1990a, 1992d) of the unpublished studies did not include quantitative data regarding the magnitude of hematological changes; therefore, it is impossible to judge the seriousness of the changes.

Hepatic Effects. Available information is limited to a report of significantly increased incidence of hepatocellular hypertrophy (6/50, severity 1.8 out of 5.0; versus 0/50 controls) among female CD-1 mice receiving tribufos from the diet for up to 90 weeks at a concentration resulting in 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.

Endocrine Effects. Significantly increased incidences of degeneration/pigmentation in the adrenal glands were reported in a study of male and female CD-1 mice (males: 39/50 males versus 17/50 controls; females: 38/49 versus 18/50 controls) receiving tribufos from the diet for up to 90 weeks at a concentration resulting in 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).

Ocular Effects. Available information is limited. No signs of treatment-related ocular effects were observed during ophthalmological examinations of beagle dogs administered tribufos in the diet for 364 days at concentrations resulting in tribufos doses up to 1.7–2.0 mg/kg/day (EPA 1991b). In a 2-year rat study, treatment-related ocular effects (cataracts, corneal opacity, corneal neovascularization, iritis and/or uveitis) were observed in male and female Fischer 344 rats administered tribufos in the diet at a concentration resulting in estimated tribufos 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).

Body Weight Effects. Effects on body weight have been reported following acute-, intermediate-, and chronic-duration oral exposure to tribufos. Significantly depressed mean body weight (27% less than controls) was noted among pregnant Sprague-Dawley rats dosed at 28 mg/kg/day during GDs 6–19 (EPA 2012f). Pregnant American Dutch rabbits dosed at 9 mg/kg/day during GDs 7–19 exhibited no body weight gain (EPA 1990c). Eleven-day-old male and female Sprague-Dawley rat pups dosed at 10 mg/kg/day for 11 days exhibited 14–15% lower mean terminal body weight than controls (EPA 2012a). Dietary exposure of Wistar rat dams throughout gestation and lactation to an estimated tribufos dose of 33.5 mg/kg/day (EPA 2005a) resulted in 8–12% lower mean maternal body weight during the lactation period. Dietary treatment of female Wistar rats for 4 weeks at an estimated dose of 44.62 mg/kg/day resulted in 41% depressed mean body weight gain (EPA 2013a). Approximately 15% depressed mean body weight gain was observed in male and female Fischer 344 rats administered tribufos in the diet for 2 years at estimated doses of 16.8 and 21.1 mg/kg/day, respectively (CalEPA 2004; EPA 1992d).

Other Systemic Effects. 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 (cold to the touch) as early as 4 hours postdosing (EPA 2012b). See Sections 3.2.1.2 (Other Systemic Effects) and 3.2.4 (Other Routes of Exposure) for additional information regarding tribufos-induced hypothermic responses.

3.2.2.3 Immunological and Lymphoreticular Effects

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

The NOAEL value for immunological and lymphoreticular effects in rats is recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

Table 3-3 summarizes results from rat, mouse, rabbit, and dog 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). 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), considered a serious adverse effect (Chou and Williams-Johnson 1998). Available study reports and 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 AChE activity (Astroff and Young 1998; EPA 1990b, 1990c, 2012a, 2012e, 2012f).

A NOAEL of 0.43 mg/kg/day and a serious LOAEL of 4.32 mg/kg/day for >60% decreased RBC AChE activity were identified in a study of female Han Wistar rats administered tribufos in the diet for 4 weeks (EPA 2013a). The highest estimated dose level (44.62 mg/kg/day) resulted in >60% decreased brain AChE activity as well.

In a study of Wistar rats administered tribufos in the diet throughout gestation and lactation, estimated tribufos doses in the range of 3.4–9.9 mg/kg/day elicited >60% decreased RBC AChE activity and 22% decreased brain AChE activity; the high-dose group (estimated dose range of 16.4–55.4 mg/kg/day) exhibited >60% decreased RBC and brain AChE activities (EPA 2005a). The maternal NOAEL was 0.4–1.0 mg/kg/day. There was no significant effect on pup RBC or brain AChE activity at any maternal dose level.

Table 3-3. 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, pathological lesions							
	RBC AChE (% inhibition)			Brain AChE (% inhibition)				
Study design (doses in mg/kg or mg/kg/day)	NOAEL[a]	LOAEL[b]	Serious LOAEL[c]	NOAEL[a]	LOAEL[b]	Serious LOAEL[c]	Clinical signs and/or pathological lesions	Reference
Acute-duration exposure								
Young adult female Sprague-Dawley rats GO 1x (0, 80)	ND	ND	80 (90%)	ND	80 (20%)	ND	80; no clinical signs	EPA 2012c
Young adult female Sprague-Dawley rats GO 1x (0, 2, 10, 80)	10	ND	80 (74%)	80	ND	ND	80; no clinical signs	EPA 2012d
11-d-old Sprague-Dawley rat pups GO 1x (0, 50)	M: ND F: ND	M: ND F: ND	M: 50 (90%) F: 50 (92%)	ND	ND	M: 50 (74%) F: 50 (76%)	50; decreased movement	EPA 2012b
11-d-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-d-old Sprague-Dawley rat pups GO 1x (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 1x/d, 11 d (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-d-old Sprague-Dawley rat pups GO 1x/d, 11 d (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-d-old Sprague-Dawley rat pups GO 1x/d, 11 d (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

Table 3-3. 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, pathological lesions							
Study design (doses in mg/kg or mg/kg/day)	RBC AChE (% inhibition)			Brain AChE (% inhibition)			Clinical signs and/or pathological lesions	Reference
Pregnant Sprague-Dawley rats G 1x/d, GD 6-15 (0, 1, 7, 28)	1	ND	7 (69%)	7	28 (59%)	ND	28; no signs, with exception of salivation in 2 high-dose dams	Astroff and Young 1998; EPA 1990b
Pregnant Sprague-Dawley rats GO 1x/d, GD 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
Pregnant American Dutch rabbits G 1x/d, GD 7-19 (0, 1, 3, 9)	ND	ND	1 (69.8%)	9	ND	ND	9; no clinical signs	EPA 1990c
Intermediate-duration exposure								
Female Han Wistar rats, diet for 4 wk (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 gen								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 (80%)	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)[f]	0.31	2.40 (28%)	ND	0.31	2.40 (29%)	22.93 (80%)	22.93; no clinical signs	
CD-1 mice, diet for 8 wk								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 d								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	

Table 3-3. 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, pathological lesions							
Study design (doses in mg/kg or mg/kg/day)	RBC AChE (% inhibition)			Brain AChE (% inhibition)			Clinical signs and/or pathological lesions	Reference
Chronic-duration exposure								
CD-1 mice, diet for 90 wk								CalEPA 2004;
M (0, 1.5, 8.4, 48.1)	1.5	8.4 (42%)	ND	8.4	48.1 (37%)	ND	48.1; no clinical signs	EPA 1990a
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	
Fischer 344 rats, diet for 2 yr								CalEPA 2004;
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	EPA 1992d
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	

[a]<20% decrease in RBC and/or brain AChE represents a NOAEL.
[b]20–59% 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.
[d]Low 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.
[e]The 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.
[f]F1 parental rats had been exposed in utero and lactationally as well.
[g]24 and 29% decreased RBC AChE activity in males and females, respectively, at treatment day 91.
[h]Brain AChE activity was only assessed at day 371 (i.e., 7 days following cessation of tribufos treatment).

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

In a 2-generation study of male and female Sprague-Dawley rats administered tribufos in the diet for up to 10 weeks prior to mating and throughout mating and gestation (males and females) and lactation (females), a >25% reduction in RBC AChE activity in F0 and F1 parental rats was associated with estimated tribufos doses in the range of 2.0–2.4 mg/kg/day during the premating period; at terminal sacrifice, these F0 and F1 parental rats exhibited >28% decreased brain AChE activity (Astroff et al. 1998; EPA 1992c). At terminal sacrifice, F0 and F1 parental males receiving tribufos doses in the range of 17.6–20.63 mg/kg/day exhibited 33–35% decreased brain AChE activity, whereas 80% decreased brain AChE activity was noted in high-dose (20.04–22.93 mg/kg/day) F0 and F1 parental females. The high-dose group of pups sacrificed on lactation day 21 exhibited 24–38% decreased RBC AChE activity, but no apparent treatment-related effect on brain AChE activity.

A study of beagle dogs administered tribufos in the diet for 364 days identified a NOAEL of 0.4 mg/kg/day and LOAELs of 1.7 and 2.0 mg/kg/day (the highest dose level tested) for a maximum of 24 and 29% decreased RBC AChE activity in males and females, respectively, at treatment day 91 (EPA 1991b). At terminal sacrifice (day 371), RBC AChE activity was decreased by <20%. There were no apparent effects on brain AChE activity in males or females.

Mice appear to be somewhat less sensitive than rats and dogs to tribufos-related effects on AChE activity following intermediate-duration oral exposure. Male and female CD-1 mice were administered tribufos in the diet for 8 weeks (CalEPA 2004). Evaluation of RBC AChE activity in the male and female mice revealed NOAELs of 3.4 and 5.6 mg/kg/day, respectively, LOAELs of 9.4 and 14.3 mg/kg/day, respectively, and serious LOAELs of 40 and 54 mg/kg/day, respectively. Evaluation of brain AChE activity revealed NOAELs of 40 and 54 mg/kg/day, respectively, and LOAELs of 140 and 132 mg/kg/day, respectively.

Two studies evaluated tribufos-induced effects on RBC and/or brain AChE activity in laboratory animals associated with chronic-duration oral exposure (CalEPA 2004; EPA 1990a, 1992d). A 90-week dietary study of male and female CD-1 mice identified NOAELs of 1.64 and 2.08 mg/kg/day, respectively, and LOAELs of 8.28 and 11.14 mg/kg/day, respectively, for 37–42% decreased RBC AChE activity (EPA 1990a). At the highest dose level (estimated dose levels of 48.02 and 63.04 mg/kg/day for males and females, respectively), brain AChE activity was decreased by 27–37%. A study of male and female Fischer 344 rats administered tribufos in the diet for 2 years identified a NOAEL of 0.2 mg/kg/day and estimated LOAELs of 1.8 and 2.3 mg/kg/day, respectively, for 27–28% decreased RBC AChE activity (CalEPA 2004; EPA1992d). The highest estimated dose level (16.8 and 21.1 mg/kg/day for males and

females, respectively), elicited 47–48% decreased RBC AChE activity and 60–68% decreased brain AChE activity.

The potential for tribufos to induce clinical signs of toxicity has been assessed in multiple animal studies that employed the oral exposure route. Collectively, the results from acute-duration oral studies in rats indicate that neonates are more sensitive than adults to tribufos neurotoxicity as assessed by clinical signs (Table 3-3). Eleven-day-old Sprague-Dawley rat pups were gavaged with tribufos once or repeatedly (daily for 11 days) and observed for clinical signs of toxicity. Single gavage dosing resulted in the appearance of 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 the appearance of decreased movement, unsteadiness, and prostration (EPA 2012e). Repeated dosing at ≥10 mg/kg/day resulted in the appearance of decreased movement, unsteadiness, and hind limb splay (EPA 2012a). No cageside clinical 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). No clinical signs of neurotoxicity were observed in repeated-dose gestational gavage studies of Sprague-Dawley rat dams administered tribufos at doses as high as 28 mg/kg/day (Astroff and Young 1998; EPA 1990b, 2012f) or American Dutch rabbits treated at up to 9 mg/kg/day (EPA 1990c).

Studies of intermediate- or chronic-duration oral exposure to tribufos did not include dose levels high enough to elicit overt signs of acute toxicity. There were no clinical signs of toxicity in 2 generations of male and female Sprague-Dawley rats administered tribufos in the diet for up to 10 weeks prior to mating and throughout mating and gestation (males and females) and lactation (females) at estimated tribufos doses as high as 17.6–22.93 mg/kg/day during the premating period, and no clinical signs of neurotoxicity in their pups (Astroff et al. 1998; EPA 1992c). In a study of female Wistar rats administered tribufos in the diet during gestation and lactation (ca. 42 days), the only reported clinical sign was that of slight tremors in 5/20 high-dose dams (estimated gestational dose of 16.4–18.2 mg/kg/day) on the day of parturition (EPA 2005a). No clinical signs of neurotoxicity were observed in dietary studies of adult female Han Wistar rats treated for 4 weeks at estimated tribufos doses up to 44.62 mg/kg/day (EPA 2013a), male and female CD-1 mice treated for 8 weeks at doses as high as 132–140 mg/kg/day (CalEPA 2004), 9-month-old beagle dogs treated for up to 364 days at doses as high as 1.7–2.0 mg/kg/day (EPA 1991b), male or female Fischer 344 rats treated for up to 2 years at estimated doses as high as 16.8–21.1 mg/kg/day (CalEPA 2004; EPA 1992d), or male or female CD-1 mice treated for up to 90 weeks at estimated doses as high as 48.02–63.04 mg/kg/day (EPA 1990a). However, retinal atrophy and optic

nerve atrophy (neurological effects) were observed in rats administered tribufos in the diet for 2 years at estimated doses in the range of 16–21 mg/kg/day (CalEPA 2004; EPA 1992d).

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 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.

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 3-2 or Figure 3-2.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

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 American Dutch rabbit does 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 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).

The highest NOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

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 American Dutch rabbit does gavaged during GDs 7–19 at doses as high as 9 mg/kg/day (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 premating and throughout mating, gestation, and lactation for 2 generations (Astroff et al. 1998; EPA 1992c). At estimated premating 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 decreases 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.

Groups of Wistar rat dams were administered tribufos in 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). 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.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

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 1997a). 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 recommended a nonlinear (margin of exposure) approach for extrapolating to lower dose levels. The committee (EPA 1997a) 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 2016) does not include a classification for tribufos. The National Toxicology Program 13th Report on Carcinogens (NTP 2014) does not include tribufos.

3.2.3 Dermal Exposure

3.2.3.1 Death

No information was located regarding death in humans following dermal exposure to tribufos.

An acute LD_{50} value of 1,093 mg/kg was reported for male and female rabbits (5/sex/dose) administered tribufos by single 24-hour occluded dermal application at 500, 1,000, or 2,000 mg/kg and observed for up to 14 days postadministration (EPA 1993b). There were no deaths at 500 mg/kg; the 1,000 mg/kg dose level resulted in 2 deaths per sex, and all 10 rabbits treated at 2,000 m/kg died. Clinical signs included tremors, muscle fasciculations, decreased motor activity, ataxia, and diarrhea. Gaines (1969) reported respective acute dermal LD_{50} 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 (5/sex/dose) receiving 6-hour occluded dermal application of tribufos (2, 11, or 29 mg/kg/day) 5 days/week for up to 3 weeks, 1/5 male and 4/5 female rabbits dosed at 29 mg/kg/day died or were sacrificed in extremis between days 12 and 19 (EPA 1993d). Most high-dose rabbits exhibited clinical signs of muscular fasciculations, tremors, and decreased movement.

3.2.3.2 Systemic Effects

No data were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, or endocrine effects associated with dermal exposure of humans or animals to tribufos.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-4.

Hematological Effects. Available information is restricted to results from a 21-day repeated-dose study in which young adult New Zealand white rabbits (5/sex/group) receiving 6-hour occluded dermal

Table 3-4. Levels of Significant Exposure to Tribufos – Dermal

Species (strain) No./group	Exposure parameters/ Doses (mg/kg)	Parameters monitored	System	NOAEL (mg/kg/d)	Less serious LOAEL (mg/kg/d)	Serious LOAEL (mg/kg/d)	Results	Reference (compound)
ACUTE EXPOSURE								
Death								
Rat (Sherman) unspecified numbers/sex/group	Once at unspecified doses for unspecified time period	LE				360 M 168 F (LD_{50})	Lowest lethal doses to males and females were 200 and 100 mg/kg, respectively	Gaines 1969 Tribufos
Rabbit (NS) 5/sex	One 24-hr exposure 500, 1000, 2000	BW CS GN LE				1093 (LD_{50} for combined sexes)	0/5, 2/5, 5/5 deaths in low-, mid-, and high-dose groups of each sex.	EPA 1993b Tribufos
INTERMEDIATE EXPOSURE								
Death								
Rabbit (New Zealand) 5/sex	21 d 5 d/wk 6 hr/d 0, 2, 11, 29 (analytically-determined)	BC BW CS EA FI GN HE LE OP OW				29	1/5 males and 4/5 females died or were sacrificed in extremis.	EPA 1993d Tribufos
Systemic								
Rabbit (New Zealand) 5/sex	21 d 5 d/wk 6 hr/d 0, 2, 11, 29 (analytically-determined)	BC BW CS EA FI GN HE LE OP OW	Hemato Dermal Ocular BW	29 2 29 29	11		Mild to moderate application site dermal irritation in both sexes at 11 and 29 mg/kg/d.	EPA 1993d Tribufos
Neurological								
Rabbit (New Zealand) 5/sex	21 d 5 d/wk 6 hr/d 0, 2, 11, 29 (analytically-determined)	BC BW CS EA FI GN HE LE OP OW		2 M	2 F	11	70% decreased RBC AChE activity and muscle fasciculations in both sexes at 11 mg/kg/d.	EPA 1993d Tribufos

AChE = acetylcholinesterase; BC = serum (blood) chemistry; BW = body weight; CS = clinical signs; d = day(s); EA = enzyme activity; F = female(s); FI = food intake; GN = gross necropsy; HE = hematology; Hemato = hematological; hr = hour(s); LE = lethality; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; NS = not specified; OP = ophthalmology; OW = organ weight; RBC = red blood cell; wk = week(s)

applications of tribufos (0, 2, 11, or 29 mg/kg/day) 5 days/week for up to 3 weeks (EPA 1993d). There were no signs of tribufos-induced effects on RBCs, white blood cells (WBCs), platelets, hemoglobin, or hematocrit at any dose level.

Dermal Effects. Available information is restricted to a report of mild to moderate contact-site dermal irritation in both sexes of young adult New Zealand white rabbits (5/sex/group) receiving 6-hour occluded dermal applications of tribufos, 5 days/week for up to 3 weeks at dose levels of 11 and 29 mg/kg/day (but not 2 mg/kg/day) (EPA 1993d).

Ocular Effects. No signs of treatment-related adverse ocular effects were observed during ophthalmologic examinations performed on young adult New Zealand white rabbits (5/sex/group) following repeated 6-hour occluded dermal applications of tribufos, 5 days/week 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 six male rabbits following instillation of 0.1 mL of tribufos into the conjunctival sac of one eye and observation for 3 days postapplication (6 days for two rabbits) (EPA 1993c).

3.2.3.3 Immunological and Lymphoreticular Effects

No adequate data were located regarding immunological and/or lymphoreticular effects in humans or animals associated with dermal exposure to tribufos.

3.2.3.4 Neurological Effects

Available human data are limited to a single study. Lotti et al. (1983) reported a 50% decrease in 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. 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.

In a study of rabbits receiving single 24-hour occluded dermal application of tribufos at 500, 1,000, or 2,000 mg/kg, clinical signs included tremors, muscle fasciculations, decreased motor activity, ataxia, and

diarrhea in some animals; however, the publicly-available DER of the study did not specify the dose(s) associated with these clinical signs (EPA 1993b).

Abou-Donia et al. (1979) demonstrated clinical signs of OPIDN in hens administered repeated doses of tribufos (applied to the comb) at 20 or 40 mg/kg/day for 3 months; dose-related clinical signs appeared as early as 18 days following the initiation of treatment. Francis et al. (1985) reported clinical signs of OPIDN among hens administered tribufos dermally at doses as low as 6–8 mg/kg/day for 101 days; signs of OPIDN became apparent at 98–109 days following the initiation of treatment.

Although studies of hens are useful for hazard identification, applicability of the dose-response in hens to humans is uncertain.

No human or animal data were located regarding the following effects associated with dermal exposure to tribufos:

3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects
3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

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.

3.3 GENOTOXICITY

Limited publicly-available information was located. Tribufos did not induce sister chromatid exchanges in Chinese hamster V79 cells exposed for 32 hours or 2 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) and 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 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).

3.4 TOXICOKINETICS

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 2000c), and the CalEPA (2004) review.

3.4.1 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 μg/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 single 8-hour dermal application of ^{14}C-tribufos to male rhesus monkeys at 3.5 μg/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); 0.72% was recovered in the feces (CalEPA 2004; EPA 2000c).

3.4.2 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.

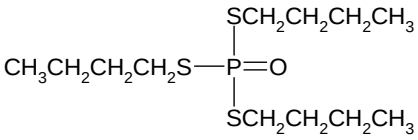
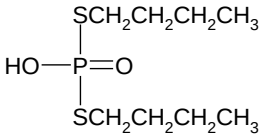
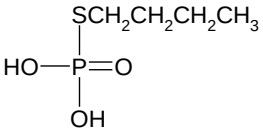
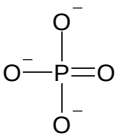
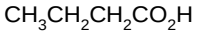
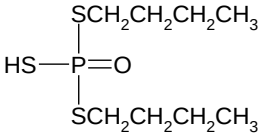
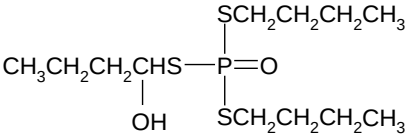
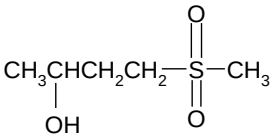
Oral administration of tribufos has been demonstrated to result in rapid distribution and elimination in rats. Following gavage administration of ^{14}C-tribufos to rats for 3 days at 5 or 100 mg/kg/day, <3% of the administered radioactivity was detected in the tissue and carcass at 72 hours postadministration; the liver contained the highest amount, followed by fat, lung, kidney, blood, gastrointestinal tract, spleen, bone, heart, gonads, muscle, and brain (CalEPA 2004). The results indicate that oral administration of tribufos to rats resulted in rapid distribution and elimination. 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 2000c).

3.4.3 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 3-3. Numbers for each chemical are

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

 S,S,S-Tributyl phosphorotrithioate (Tribufos) [1]	 S,S-Dibutyl phosphorodithioate [2]	 n-Butyl mercaptan [3]
 S-Butyl phosphorothioate [4]	 Phosphate [5]	 Butyric acid [6]
 S,S-Dibutyl phosphorotrithioate [7]	 S,S-Dibutyl, S-1-hydroxybutyl phosphorotrithioate [8]	 3-Hydroxybutyl methyl sulfone [9]

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] 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).

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. Sahali et al. (1994) detected radioactivity in fatty acids from milk and fat of a lactating goat dosed orally with ^{14}C-tribufos. 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).

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-hydroxybutyl-

methyl 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.

3.4.4 Elimination and Excretion

No information was located regarding the extent of elimination and excretion following inhalation exposure to tribufos. Following single oral dosing of rats with ^{14}C-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). Recovery in the urine was 55% for males and 66% for females; recovery in the feces 42% for males and 30% for females. Relatively similar results were obtained following single gavage dosing at 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 3.4.1, 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 2000c).

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

Physiologically based pharmacokinetic (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 end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. However, if the uptake and disposition of the chemical substance(s) are adequately described, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994).

PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

If PBPK models for tribufos exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

No PBPK models are available for tribufos.

3.5 MECHANISMS OF ACTION

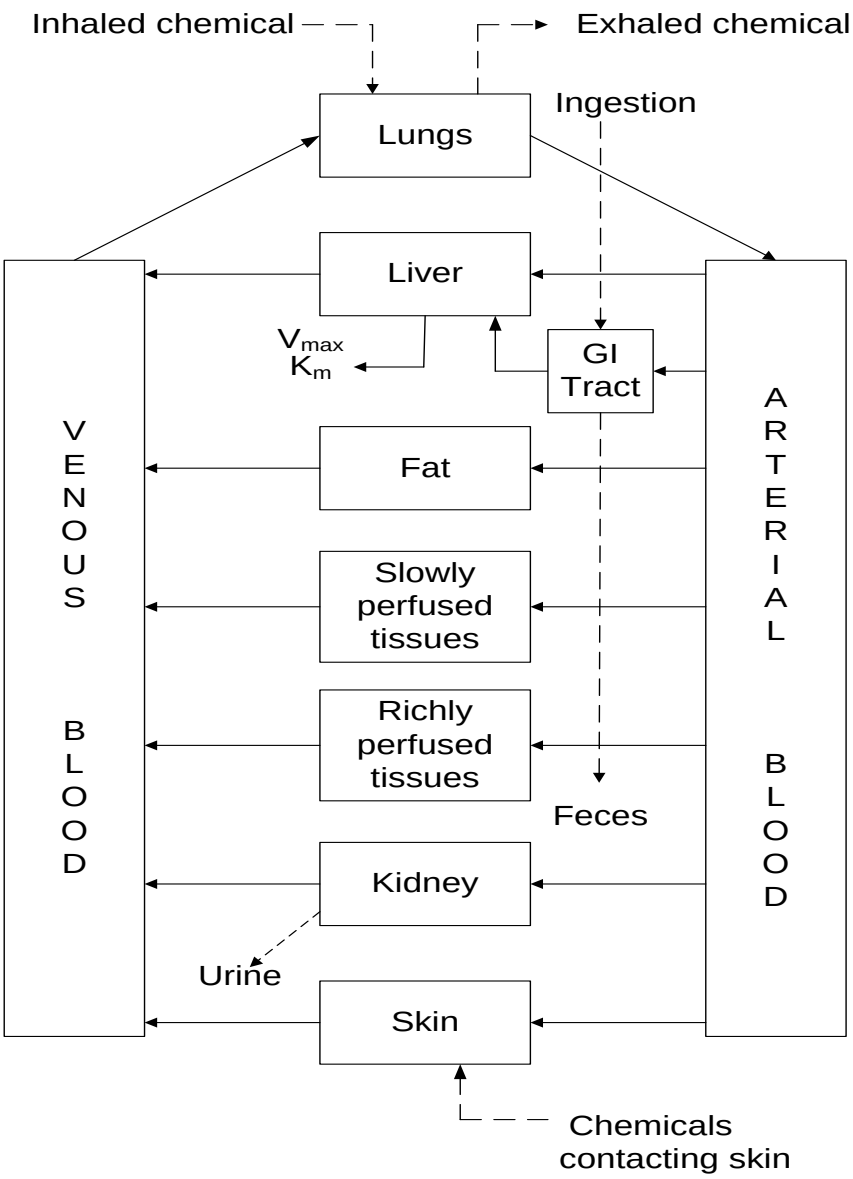
3.5.1 Pharmacokinetic Mechanisms

No studies were located in which mechanisms of absorption were assessed for tribufos. It is expected that absorption is accomplished via passive diffusion. It is generally understood that tribufos does not appreciably accumulate in any specific body tissues and that absorbed tribufos is rapidly metabolized and eliminated. No information was located regarding mechanisms of elimination and excretion of parent compound or metabolites of tribufos.

3.5.2 Mechanisms of Toxicity

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

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: Krishnan and Andersen 1994

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 farmworkers 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 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 recent 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 organophosphorus compound-induced delayed neuropathy (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.

3.5.3 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 reactive intermediates and other metabolites, which are primarily quickly eliminated in the urine (see Section 3.4). 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 of circulating carboxylesterases (enzymes that metabolize organophosphorus compounds (Pereira et al. 2014). Therefore, extrapolation from animals to humans includes an appreciable degree of uncertainty.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*,

initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997b). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans or animals after exposure to tribufos.

No *in vitro* studies were located regarding endocrine disruption of tribufos.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when most biological systems will have fully developed. 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. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to adverse health effects from exposure to hazardous chemicals, but whether there is a difference depends on the chemical(s) (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to exposure-related health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life that are most sensitive to disruption from exposure to hazardous substances. Damage from exposure in one stage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). Past literature has often described the fetus/infant as having an immature (developing) blood-brain barrier that is leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the brain, there are differences between fetuses/infants and adults that are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective

vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; whether these mechanisms provide protection for the developing brain or render it more vulnerable to toxic injury is an important toxicological question. Chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns given their low glomerular filtration rate and not having developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

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)

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers 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. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to tribufos are discussed in Section 3.8.1.

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 effects caused by tribufos are discussed in Section 3.8.2.

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 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Tribufos

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.

3.8.2 Biomarkers Used to Characterize Effects Caused by Tribufos

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 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.

3.9 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.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to tribufos than will most persons exposed to the same level of tribufos 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 result in reduced detoxification or excretion of tribufos, or compromised function of organs affected by tribufos. Populations who are at greater risk due to their unusually high exposure to tribufos are discussed in Section 6.7, Populations with Potentially High Exposures.

The magnitude of tribufos toxicity, like the toxicity of any xenobiotic, is affected by the rate of its metabolic biotransformation to both more and less toxic substances (Parkinson and Ogilvie 2008). The newborns of several animal species, including humans, have a reduced ability to metabolize xenobiotics. However, the effect of decreased metabolism on tribufos-induced neurotoxicity has not been demonstrated.

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 protein 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, 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 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.

Results for the organophosphorus pesticide, chlorpyrifos, indicate that neonatal exposure of rats and mice, and prenatal exposure of guinea pigs suggest that cognitive deficits are more pronounced among males than females (Aldridge et al. 2005; Johnson et al. 2009; Levin et al. 2001; Mamczarz et al. 2016).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to tribufos. Because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to tribufos. When specific exposures have occurred, poison control centers, board certified medical toxicologists, board-certified occupational medicine physicians and/or other medical specialists with expertise and experience treating patients highly exposed to tribufos can be consulted for medical advice. The following texts provide specific information about treatment following exposures to tribufos:

Aaron CK. 2007. Organophosphates and carbamates. In: Shannon MW, Borron SW, Burns MJ, eds. Haddad and Winchester's clinical management of poisoning and drug overdose. 4th ed. Philadelphia, PA: WB Saunders Company, 1171-1184.

Eddleston M. 2015. Insecticides: Organic phosphorus compounds and carbamates. In: Hoffman RS, Howland MA, Lewin NE, et al., eds. Goldfrank's Toxicologic Emergencies. 10th ed. New York, NY. McGraw-Hill, 1409-1424.

EPA. 2013b. Organophosphate insecticides. In: Recognition and management of pesticide poisonings. 6th ed., U.S. Environmental Protection Agency, EPA735K13001, 43-55. https://www.epa.gov/sites/production/files/2015-01/ documents/rmpp_6thed_final_lowresopt.pdf. December 1, 2016.

Tribufos is one of a group of organophosphorus compounds that act as AChE inhibitors. Cases of suspected organophosphate poisoning should initially be resuscitated (if necessary) and stabilized. Available texts regarding methods to reduce toxic effects describe methods common to treatment of poisoning by such organophosphorus compounds in general. The following information was extracted in part from the documents listed above.

Additional relevant information can be found in the front section of this profile under QUICK REFERENCE FOR HEALTH CARE PROVIDERS.

3.11.1 Reducing Peak Absorption Following Exposure

Following dermal contamination with organophosphorus compounds, most texts recommend washing the skin with copious amounts of soap and water. Contaminated clothing, including leather garments, should be destroyed. After oral ingestion, activated charcoal is recommended for many organophosphorus compounds, although it may only be modestly effective (Eddleston et al. 2008). Cathartics may be unnecessary as intestinal motility is increased. In patients who have ingested a life-threatening dose, gastric lavage may be performed with care as long as the airway can be adequately protected. Treatment of inhaled organophosphates is mostly supportive as respiratory distress is a common effect of poisoning.

3.11.2 Reducing Body Burden

Absorbed tribufos is rapidly distributed, extensively metabolized, and rapidly eliminated from the body. Consequently, efforts at reducing body burdens of poisoned persons may not be critical to the outcome. Dialysis and hemoperfusion are not indicated in poisonings with most organophosphorus compounds because the compounds are fat soluble and are found in relatively low concentrations in the many tissues to which they are distributed.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Respiratory failure and hypoxemia are the primary cause of death in AChE-poisoning patients; initial treatment includes ensuring an adequate airway and stabilization of cardiorespiratory function. If patients develop convulsions, anticonvulsants (generally midazolam or diazepam) may be used. Symptomatic patients require rapid intravenous administration of atropine, titrated against heart rate, blood pressure, and pulmonary function (aiming for blood pressure >80 mmHg systolic, heart rate >80 beats per minute, and lungs clear of crepitations and wheeze). Atropine is a competitive muscarinic antagonist that reverses the effect of excess acetylcholine in both central and peripheral tissues. Once a patient is stabilized ('atropinized'), an infusion should be set up, initially aiming to administer 20–30% of the total dose to atropinize the patient, thereafter titrated to effect.

Patients need to be cared for in a high dependency unit, and observed for recurrence of cholinergic features until they are completely well. Recurrence requires further bolus dosing; appearance of anticholinergic toxicity requires a reduction in the atropine infusion rate. Central nervous system toxicity should occur only transiently in atropine-treated patients who receive carefully titrated atropine doses.

Intubation and mechanical ventilation may be required; in such cases, succinylcholine should not be used because it is broken down by BuChE; prolonged effects and paralysis will occur if BuChE is inhibited by tribufos.

Pralidoxime chloride (2-PAM) is a quaternary amine oxime that reverses the phosphorylation of non-aged AChE and thereby restores activity. Oximes function by nucleophilic attack on the phosphorylated enzyme; the oxime-phosphonate is then split off, leaving the regenerated enzyme. Unfortunately, the effectiveness of oximes is uncertain; however, oximes (when available) should be administered as soon as possible after exposure.

3.12 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 the National Toxicology Program (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.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They 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.

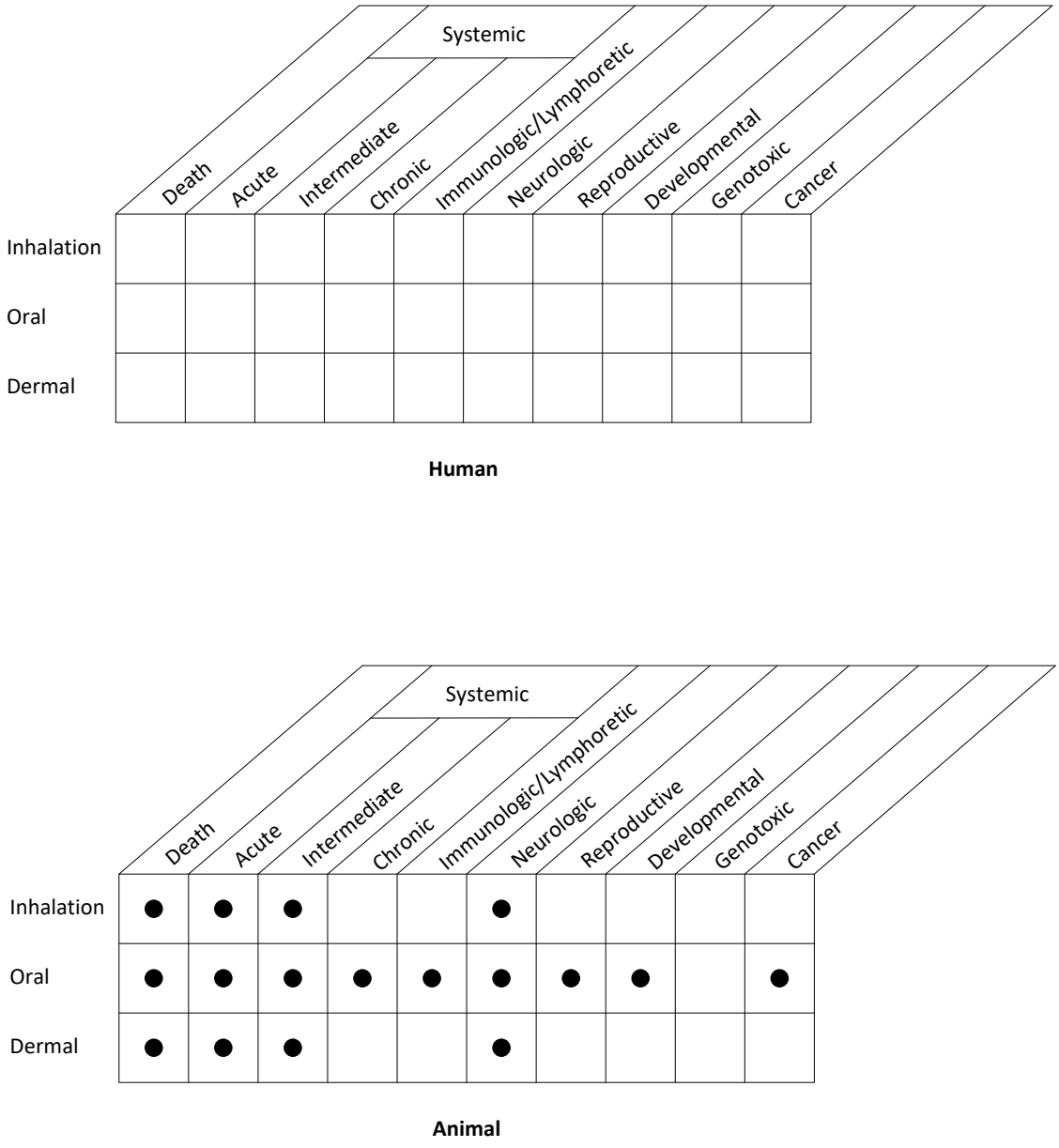
3.12.1 Existing Information on Health Effects of Tribufos

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to tribufos are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of tribufos. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure 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* (Agency for Toxic Substances and Disease Registry 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.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. 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). Several animal studies evaluated the effects of acute-duration oral exposure to tribufos; two studies were designed to evaluate lethality (EPA 1993a; Gaines 1969) and several studies included evaluations of systemic and neurological end points (Astroff and Young 1998; EPA 1990b, 1990c, 2012a, 2012b, 2012c, 2012d, 2012e, 2012f). Available animal studies provide adequate insight into the AChE-inhibiting action of tribufos in acute oral exposures. 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,

Figure 3-5. Existing Information on Health Effects of Tribufos



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.

Intermediate-Duration Exposure. No adequate data were located regarding the effects of intermediate-duration exposure to tribufos in humans. Systemic and neurological end points 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 2013a). Several intermediate-duration oral studies in laboratory animals evaluated systemic and neurological end points (Astroff et al. 1998; CalEPA 2004; EPA 1991b, 1992c, 1992d, 2005a, 2013a). The potential for tribufos to cause systemic effects (other than neurotoxicity) has been adequately assessed for inhalation, oral, and dermal exposure routes. As previously stated, quantitative data for exposed human populations would be useful in evaluation of the hazards of human exposure to tribufos.

Chronic-Duration Exposure and Cancer. 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 end points have been adequately assessed in chronic-duration oral studies of laboratory animals (CalEPA 2004; EPA 1990a, 1991b, 1992d). Additional chronic-duration animal studies do not appear necessary. The potential for tribufos to induce cancer was evaluated in rats (CalEPA 2004; EPA 1992d) and mice (EPA 1990a). Tribufos was not carcinogenic in the rat study at oral doses as high as 17–21 mg/kg/day, but was associated with increased incidence of tumors in the small intestine and liver of male mice and lung tumors in female mice at oral doses in the range of 48–63 mg/kg/day (EPA 1990a). The potential carcinogenicity of tribufos in rats should be further evaluated at high doses in the range of those employed in the mouse study. If human populations with potential for long-term exposure to tribufos can be identified, such populations could be followed to assess the potential for tribufos-induced noncancer and/or cancer effects.

Genotoxicity. A limited number of studies was located regarding the potential genotoxicity of tribufos. Tribufos did not induce sister chromatid exchanges in Chinese hamster V79 cells (CalEPA 2004; Chen et al. 1982a, 1982b; EPA 2000a) or chromosomal aberrations in Chinese hamster ovary cells (CalEPA 2004; EPA 2000a). Tribufos was not mutagenic in several strains of *S. typhimurium* and did not

induce unscheduled DNA synthesis in rat primary hepatocytes (CalEPA 2004; EPA 2000a). Tribufos does not appear to be a genotoxic agent; additional studies do not appear necessary at this time.

Reproductive Toxicity. The potential for tribufos-induced reproductive toxicity has not been evaluated in human populations. No evidence of reproductive toxicity was found in a study of female Wistar rats administered tribufos in the diet throughout gestation and lactation at estimated doses up to 16.4–55.4 mg/kg/day (EPA 2005a) or in Sprague-Dawley rats administered tribufos in the diet for 2 generations (including 10 weeks of premating treatment) at doses as high as 18 mg/kg/day (Astroff et al. 1998; EPA 1992c). Additional animal studies do not appear necessary. If human populations with potential for significant exposure to tribufos can be identified, such populations could be followed to assess the potential for tribufos induced-reproductive toxicity.

Developmental Toxicity. The potential for tribufos-induced developmental toxicity has not been evaluated in human populations. Depressed lactational pup body weight, delays in preputial separation and development of the righting reflex, alterations in motor and locomotor activity, and decreased auditory startle amplitude were noted in a study of female Wistar rats administered tribufos in the diet throughout gestation and lactation at estimated doses in the range of 16.4–55.4 mg/kg/day (EPA 2005a). Decreases in numbers of live pups at birth, litter size, and pup survival and viability were observed in a study of Sprague-Dawley rats administered tribufos in the diet for 2 generations (including 10 weeks of premating treatment) at a dose level of approximately 18 mg/kg/day (Astroff et al. 1998; EPA 1992c). NOAELs in these studies were in the range of 2–3.4 mg/kg/day. Additional developmental toxicity studies in animals should be designed to evaluate possible tribufos-related effects on behavior and cognitive function and brain morphometry. If human populations with potential for significant exposure to tribufos can be identified, such populations could be followed to assess the potential for tribufos-induced developmental toxicity.

Immunotoxicity. No information was located regarding the potential for tribufos-induced immunological effects in humans. One oral study in rats found no evidence of a tribufos-induced immune response in a plaque-forming cell assay (EPA 2013a). An additional animal study could be designed to further assess the potential immunotoxicity of tribufos. If human populations with potential for significant exposure to tribufos can be identified, such populations could be followed to assess the potential for tribufos-induced immunotoxicity.

Neurotoxicity. Available human data are limited to a single study. Lotti et al. (1983) reported a 50% decrease in NTE in lymphocytes from seven workers repeatedly exposed to tribufos and folex via aerial and ground application of the compounds during one season of cotton defoliation. There were no clinical signs of exposure-related neurotoxicity or 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. Animal data are available for inhalation, oral, and dermal exposure routes (Astroff and Young 1998; Astroff et al. 1998; CalEPA 2004; EPA 1990b, 1990c, 1992b, 1991b, 1992c, 1992d, 1993d, 2005a, 2012a, 2012b, 2012c, 2012d, 2012e, 2012f, 2013a). If human populations with potential for significant exposure to tribufos can be identified, such populations should be followed to assess the potential for tribufos-induced neurotoxicity. Such studies should include the evaluation of potential mechanisms of organophosphorus pesticide-induced neurotoxicity. See Section 3.5.2 (Mechanisms of Toxicity) for more detailed information regarding potential mechanisms of toxicity relevant to tribufos exposure.

Epidemiological and Human Dosimetry Studies. As stated previously, no adequate data were located regarding tribufos toxicity in exposed human populations. If human populations with potential for significant exposure to tribufos can be identified, such populations should be evaluated.

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 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, 2000c). 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.

Methods for Reducing Toxic Effects. Methods exist for reducing the toxic effects of organophosphorus compounds (including tribufos) that act as AChE inhibitors. Methods mainly involve interfering with the inhibitory effect of tribufos on AChE and supportive therapy. Additional treatments could be developed to more effectively counteract AChE inhibition and consequent clinical signs of neurotoxicity. It is not likely that methods for reducing peak absorption could be developed because tribufos is rapidly absorbed and highly metabolized; numerous unidentified tribufos metabolites have been detected in urine and feces shortly following exposure of laboratory animals to tribufos.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

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.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

No ongoing studies examining the toxicity or toxicokinetics of tribufos were identified in the National Institute of Health (NIH) RePORTER (2016) database.

4. CHEMICAL AND PHYSICAL INFORMATION

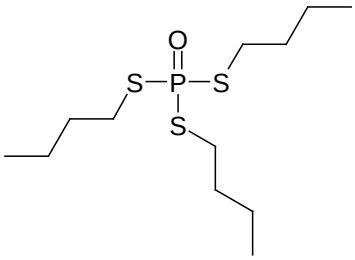
4.1 CHEMICAL IDENTITY

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

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 4-1. Chemical Identity of Tribufos

Characteristic	Information[a]	Reference
Chemical name	S,S,S-Tributyl phosphorotrithioate	EPA 2006b
Synonym(s)	Butifos; butiphos; butyl phophorotrithioate; merphos oxide; tribufos; tribuphos	CalEPA 2004; EPA 2006b
Registered trade name(s)	DEF; DEF 6, Folex	EPA 2006b
Chemical formula	$C_{12}H_{27}OPS_3$	EPA 2006b
Chemical structure[e]		EPA 2006b
Identification numbers:		
CAS registry	78-48-8	EPA 2006b
NIOSH RTECS	No data	
EPA hazardous waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMDG shipping	No data	
HSDB	668	HSDB 2010
NCI	No data	
EPA/OPP Pesticide Code	074801	EPA 2006b

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; OPP = Office of Pesticide Programs; RTECS = Registry of Toxic Effects of Chemical Substances

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
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	5.3×10^{-6} mm Hg	Tomlin 2003
Henry's law constant at 25°C	2.94×10^{-7} atm-m^3/mole	Fendinger and Glotfelty 1990
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits in air	No data	
Conversion factors	No data	
Explosive limits	No data	

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Table 5-1 summarizes information on facilities that produced, processed, or used tribufos in 2014 (TRI14 2015). 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.

Tribufos is produced commercially by reacting butyl mercaptan with phosphorous oxychloride in the presence of a base (HSDB 2010). According to the EPA Chemical Data Reporting (CDR) database, in 2012, there were two manufacturers of tribufos: the Amvac Chemical Company, that manufactures 2,089,000 pounds annually, and the Bayer Corporation, who declared its production volume as confidential business information for 2012 (EPA 2016a). Data obtained from the National Pesticide Information Retrieval System show that there are four companies that formulate tribufos into end-use products. These companies and their products are listed in Table 5-2.

5.2 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.

5.3 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). The process of defoliation separates the habitat of boll rot organisms (which cause injury to the boll, lint, and seed of cotton plants) from the cotton crop. It was estimated that about 4.5 million pounds of tribufos was used in 1999 and that approximately 35% of the 14 million acres used to grow cotton in the United States use it as a defoliant (EPA 2006b). The USGS Pesticide National Synthesis Project estimated that approximately 2 million pounds of tribufos were applied to cotton crops in 2013 (USGS 2016). 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.

Table 5-1. Facilities that Produce, Process, or Use Tribufos

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	10,000	99,999	1, 4
LA	1	10,000	99,999	10

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI14 2015 (Data are from 2014)

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 2016

5.4 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).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

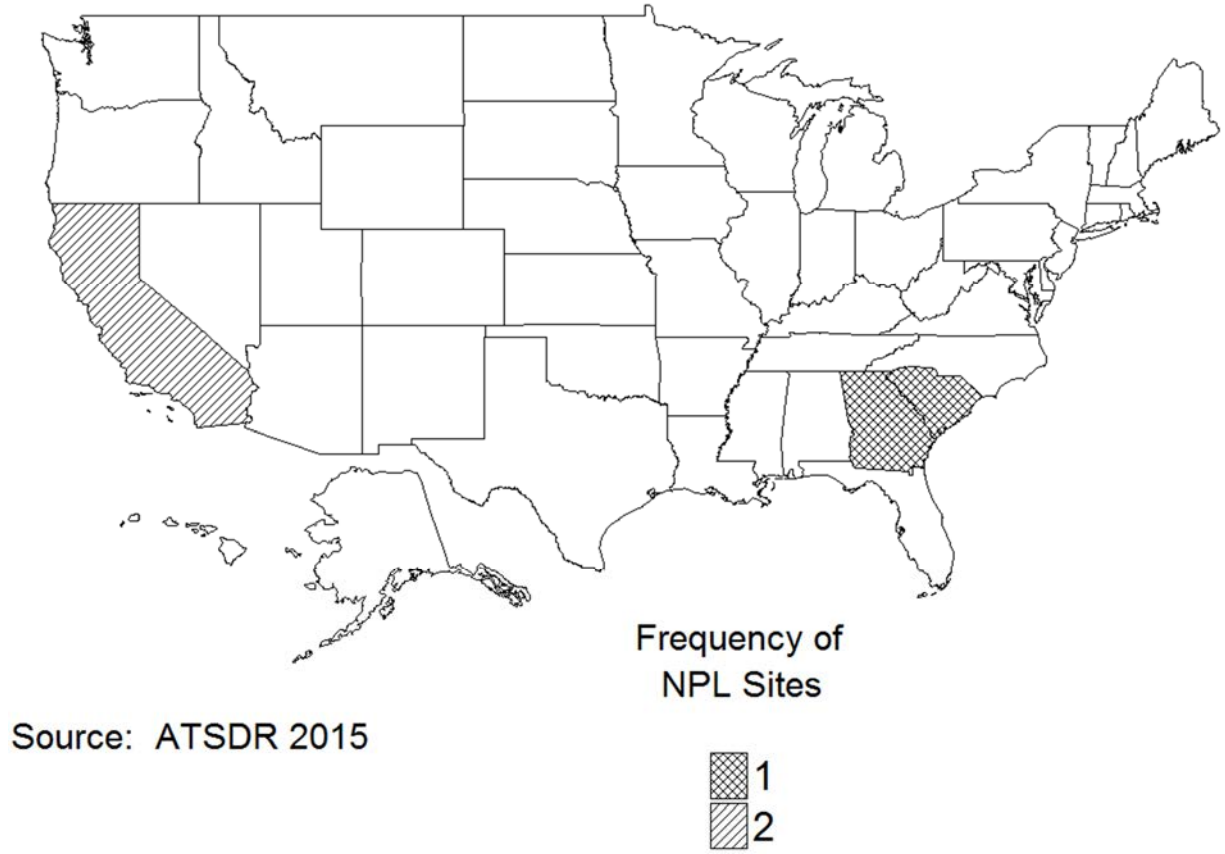
Tribufos has been identified in at least 4 of the 1,832 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2015). However, the number of sites in which tribufos has been evaluated is not known. The frequency of these sites can be seen in Figure 6-1.

Tribufos is a plant growth regulator that is used exclusively as a cotton defoliant (Tomlin 2003). It is released directly to the environment from aerial spraying or groundboom spraying of cotton plants. It is also an oxidation product of the defoliant merphos; however, merphos is no longer registered for use in the United States. The USGS Pesticide National Synthesis Project estimated that approximately 2 million pounds of tribufos were applied to cotton crops in 2013 (USGS 2016). When tribufos was applied to a cotton field, the average tribufos residues in cottonseed, cottonseed meal, hulls, crude cottonseed oil, and refined cottonseed oil were 7.266, 0.065, 1.043, 0.581, and 0.213 ppm, respectively (EPA 2000a).

Vapor-phase tribufos degrades fairly rapidly in the atmosphere with a half-life of approximately 2 hours. Particulate-phase tribufos is removed from the atmosphere by wet and dry deposition. Tribufos adsorbs strongly to soil surfaces and has low potential to leach into groundwater. The vapor pressure and Henrys Law constant for tribufos suggests that volatilization from soil and water surfaces occurs slowly (EPA 2006b, 2008); however, a field dissipation study that attempted to account for the mass balance of tribufos applied to cotton plants suggested that volatilization from soils under hot and humid conditions may be an important environmental fate process (Potter et al. 2002).

The overall persistence of tribufos in soils has a high degree of variability. The EPA Interim Reregistration Eligibility Decision for Tribufos (EPA 2006b) reported an aerobic soil biodegradation half-life of 745 days in a sandy loam (EPA 2006b); however, other laboratory and field dissipation studies have reported much shorter degradation times. In a submission to the EPA High Production Volume Challenge Program by the Bayer Crop Science Corporation, the half-lives of tribufos in five cotton growing soils obtained from California, Texas, Georgia, Arkansas, and Mississippi were 9.8, 30.3, 99, 143.6, and 173.3 days, respectively (Bayer Crop Science 2008). Potter et al. (2002) suggested that an appropriate value for the half-life of tribufos in soils is 5–20 days based upon field and laboratory studies using four cotton growing soils that were acclimated to tribufos.

Figure 6-1. Frequency of NPL Sites with Tribufos



Since tribufos is only used as a defoliant of cotton plants, exposure to the general population is low. The primary route of exposure for the general population is expected to occur through ingestion of food products that are prepared using cottonseed oil or cottonseed meal that could contain tribufos residues (EPA 2000a, 2006b). Since tribufos is rarely detected in groundwater or drinking water, exposure to tribufos from ingestion of water is expected to be negligible. Persons residing near cotton fields where tribufos has been applied may be subject to inhalation exposure routes. Since tribufos is only used in cotton growing regions of the United States and does not possess long-range atmospheric transport (transport in the air for several hundred to several thousand kilometers) potential, inhalation exposure for the rest of the U.S. population will be negligible. Estimated acute and chronic dietary intakes (99.9^{th} percentiles) of 0.050 and 0.003 µg/kg/day of tribufos were calculated for the U.S. population (EPA 2006b). Occupational exposure is significantly higher for workers who apply tribufos as a cotton defoliant and for field workers who harvest or tend to the treated cotton fields. The calculated absorbed daily dose of tribufos for agricultural workers was estimated to range from about 0.7 to 25.5 µg/kg/day, depending upon job function (CalEPA 2004).

6.2 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 2005b). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more 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 ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005b).

6.2.1 Air

Estimated releases of 10 pounds of tribufos to the atmosphere from 2 domestic manufacturing and processing facilities in 2014, accounted for about 100% of the estimated total environmental releases from facilities required to report to the TRI (TRI14 2015). These releases are summarized in Table 6-1.

6.2.2 Water

There were no reported releases of tribufos to surface water from two domestic manufacturing and processing facilities in 2014 (TRI14 2015).

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 defoliants, including tribufos, applied to strip and conventionally tilled cotton fields located in south central Georgia. The runoff of tribufos applied at a rate of 0.31 kg/hectare 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.

6.2.3 Soil

There were no reported releases of tribufos to soils from two domestic manufacturing and processing facilities in 2014 (TRI14 2015).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Based on its vapor pressure (see Table 4-2), 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.

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,

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Tribufos[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	1	10	0	0	0	No data	10	No data	10
LA	1	0	0	0	0	No data	0	No data	0
Total	2	10	0	0	0	0	10	0	10

[a]The 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.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI14 2015 (Data are from 2014)

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).

Additional 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 (see Section 6.4.2). 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 $2.94x10^{-7}$ atm-m^3/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 (DT_{50}) for tribufos were approximately 25 times greater in controlled laboratory studies (14.2–18.8 days) 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/m^3 or 0.001189 mg/m^3), data indicate that the exposure is nearly 40 times lower than the provisional intermediate-duration inhalation MRL of 0.04 mg/m^3, 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 discussed in Section 6.4.1 indicate that atmospheric levels decrease quickly due to the short half-life.

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 bioconcentration factors (BCF) of 1,300 for nonedible (viscera) residues and 300 for edible tissue, and the whole-body BCF was 730 (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.

6.3.2 Transformation and Degradation

6.3.2.1 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} cm^3/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 cm^3 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 environmental ultraviolet (UV) spectrum (wavelengths >290 nm); however, it was shown to undergo direct photolysis slowly in laboratory photoreactor experiments (Woodrow et al. 1983).

6.3.2.2 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).

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-µg/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. At weeks 2, 4, and 8, 70, 90, and >95%, of the tribufos was dissipated, 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, respectively, in two experiments, and the only metabolite was reported as 1-butane sulfonic acid (EPA 2008).

6.3.2.3 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 2.9–3.9% of the radioactivity at the end of the experiment and $^{14}CO_2$ 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 1990e). 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} times 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. 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 (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 some loss was due to volatilization from the soil plot and 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 appears to be supported by data submitted by the Bayer Crop Science Corporation to the EPA High Production 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 Crop Science 2008). Degradation was measured by CO_2 evolution and appeared to be correlated with the pH of the soil. Soils

with pH >6.3 had greater CO_2 evolution as compared to soils with lower pH. The amount of $^{14}CO_2$ evolution at the end of the experiments ranged from 37.6% (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 Crop Science (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).

6.4 LEVELS MONITORED OR ESTIMATED 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. The analytical methods available for monitoring tribufos in a variety of environmental media are detailed in Chapter 7.

6.4.1 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/m^3 (Hermann and Seiber 1981). These levels dropped to 450 and 24 ng/m^3 at 24 and 72 hours post treatment, respectively. Tribufos was also detected in air samples at a maximum concentration of 6,080 ng/m^3 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/m^3 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/m^3 (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/m^3 and in 121 out of 125 samples of air from rural communities in high-use agricultural areas at a mean concentration of 64 ng/m^3 (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 sampling locations in Monterey, California at a mean concentration of 68 ng/m^3 (maximum=340 ng/m^3) from September to November 1987 (Baker et al. 1996).

6.4.2 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 has been 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 PRZM/EXAMS was 14 µg/L, which was about three 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 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 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 a concentration of 250 ng/L (0.250 ppb) in Parlier, California and 800 ng/L (0.800 ppb) in Corcoran, California (Glotfelty et al. 1987).

6.4.3 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).

6.4.4 Other Environmental 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 Pesticide Data Program (USDA PDP) 2014 report, showed that tribufos was not detected in 2,341 samples of fruits or vegetables (USDA 2016a). This included 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); and watermelon (n=390). 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 from 1991 to 2003 and from 2003 to 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 2013b).

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.

6.5 GENERAL POPULATION AND OCCUPATIONAL 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. 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 from 1991 to 2003 and from 2003 to 2004 (FDA 2006). No other samples tested positive for tribufos. EPA (2006b) estimated acute and chronic dietary intakes (99.9^{th} percentiles) of 0.050 and 0.003 µg/kg/day for the U.S. population calculated using the Dietary Exposure Evaluation Model (DEEM), which 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 6-2. 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 2015a).

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 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 6-3 (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). Harvest timing of cotton in the United States differs by region, but is typically performed in fall (September–November); however, the harvest may also extend into December

Table 6-2. 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

[a]Gunderson 1988.
[b]Gunderson 1995a.
[c]Gunderson 1995b.

Table 6-3. Estimated Occupational Exposure Scenarios for Tribufos

Job category	ADD	SADD	LADD
		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

ADD = absorbed daily dosage assuming 7.1% dermal absorption, 50% respiratory uptake of tribufos as a vapor with occupational exposure, an inhalation rate of 14 L/minute, a 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; LADD = lifetime average daily dosage assuming an exposure over 40 years of a 70-year lifespan; SADD = seasonal average daily dosage assuming workers are exposed 21 days in a 45-day season

Source: CalEPA 2004.

or early January in some states (USDA 2010). 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).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume than adults. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and may spend more time outdoors. Children also are closer to the ground and have not yet developed the adult capacity to judge and take actions to avoid hazards (NRC 1993).

Similar to adults, most children in the general population will have low exposures to tribufos through the ingestion of food. The EPA used the DEEM model to calculate the acute and chronic dietary exposures for the U.S. population from cottonseed oil and cottonseed meal as well as residues in meat and milk that may be contaminated with tribufos through feeding livestock cottonseed meal. For non-nursing infants <1 years of age, the acute and chronic dietary exposures (99.9th percentiles) were estimated as 0.060 and 0.001 µg/kg/day, respectively (EPA 2006b). For all children aged 1–6 years, the acute and chronic dietary exposures (99.9th percentiles) were estimated as 0.085 and 0.006 µg/kg/day, respectively. Gunderson (1988, 1995a, 1995b) used data from FDA Market Basket Surveys and estimated dietary intake of tribufos by children in the range of <0.0001–0.0004 µg/kg/day.

No studies were identified that assessed tribufos levels in mothers' milk or cord blood.

6.7 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 6-2 and 6-3 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 that 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 before entering the home, and laundering work clothes separately from other family clothing.

6.8 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 health effects (and techniques for developing methods to determine such health effects) of tribufos.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health 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.

6.8.1 Identification of Data Needs

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. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2014, became available in October of 2015. This database is updated yearly and should provide a list of industrial production facilities and emissions.

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 as 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 Crop Science 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 so that the information obtained on levels of tribufos in the environment can 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 and 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.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. The information amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance; however, no exposure registries for tribufos were located. Tribufos is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. Tribufos will be considered in the future when chemical selection is made for sub-registries to be established.

6.8.2 Ongoing Studies

No ongoing research identified in the NIH RePORTER (2016) database was located.

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring tribufos, its metabolites, and other biomarkers of exposure and effect to tribufos. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Although analytical methods are available to detect and quantify tribufos in blood serum; biological monitoring is typically performed by analysis of urine samples since organophosphates are only present in the bloodstream for a short time.

Kilgore et al. (1984) described a method for the quantification of tribufos in urine samples of exposed individuals using gas chromatography (GC) equipped with a flame photometric detector (FPD). Ten to 25 mL urine samples were diluted with aqueous sodium sulfate and extracted 4 times with methylene chloride. The combined extracts were analyzed using GC/FPD. Percent recovery averaged 87.1±3.5 using a fortification range of 8–80 ppb. The detection limit was 10 ppb.

Barr et al. (2002) discussed a method for the analysis of 29 pesticides including several organophosphates in human serum using high resolution gas chromatography/mass spectrometry (HRGC/MS). Serum preparation involved denaturation with ammonium sulfate followed by centrifugation and solid-phase extraction (SPE) using methylene chloride as an eluent. Although the method did not test for tribufos, the detection limit for other organophosphates was in the low pg/g (ppt) range. The automated detection and analysis of 39 parent organophosphate pesticides, including tribufos, in blood serum was comprehensively discussed by Kuklenyik (2009). Accelerated solvent extraction (ASE) using ethyl acetate at 1,500 PSI and temperature gradients of 20–100°C was shown to yield greater recoveries when compared to other methods such as SPE, lyophilization, or traditional liquid-liquid extraction using a

solid carrier. ASE recoveries for tribufos ranged from 64.4 to 93.0%, while liquid-liquid extractions and lyophilization with various solvents yielded recoveries <40%. An additional cleanup step was accomplished by transferring the ASE extract to a silica or aluminum oxide sorbent filled cartridge and washing it with a polar solvent to remove residual lipids. GC coupled tandem MS or high-performance liquid chromatography (HPLC) coupled tandem MS using atmospheric pressure chemical ionization (APCI) positive ion mode produced detection limits in the ppt range for the organophosphates.

Table 7-1 summarizes several analytical methods for measuring parent tribufos in biological tissues or personal air.

7.2 ENVIRONMENTAL SAMPLES

Table 7-2 lists the methods used for determining tribufos in environmental samples. Air samples are usually collected using a high volume sampler for ambient air or low volume personnel air samplers for personnel air samples. Tribufos is concentrated using a resin filter and the trapped tribufos is then extracted using an appropriate organic solvent such as acetone or methylene chloride and analyzed using GC/FPD. This detector is highly sensitive for the detection of sulfur- and phosphorous-containing species. Detection is accomplished through the formation of excited sulfur and hydrogen phosphorous oxide species and the measurement of the chemiluminescent emissions from these species. The GC is equipped with filters that operate in the phosphorous-specific mode (526 nm) or sulfur-specific mode (394 nm). The methods are sensitive, with detection limits in the ng/m^3 range (Hermann and Seiber 1981; Kilgore et al. 1984).

EPA Method 8141 discusses the analysis of merphos by GC/FPD in water and soil matrices (EPA 2000c). This method is applicable to tribufos since merphos is readily oxidized to tribufos under environmental conditions. Water samples are typically extracted at neutral pH using methylene chloride and a separatory funnel method or continuous liquid-liquid extracting method. Soil or other solid samples are extracted by Soxhlet extraction using 1:1 mixtures of hexane:acetone or methylene chloride:acetone. Reported detection limits are 0.20 µg/L (ppb) in water and 10 µg/kg (ppb) in soil matrices.

A data evaluation report (DER) reviewed by EPA and used for registration purposes discussed an analytical method for the analysis of tribufos in soil. A 100 g soil sample was extracted with a hexane:acetone (95:5) mixture followed by filtration and drying with anhydrous sodium sulfate (EPA

Table 7-1. Analytical Methods for Determining Tribufos in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Personal air	Air samples collected with low volume personnel air samplers consisting of nuclepore filter, glass fiber filter containing XAD-4 resin; Soxhlet extraction using acetone	GC/FPD	2.7 ng/m^3	94.9±6.8	Kilgore et al. 1984
Urine	Samples collected and stored at -20°C diluted with 2% Na_2SO_4 and extracted with methylene chloride	GC/FPD	10 ppb (10 µg/L)	87.1±3.5	Kilgore et al. 1984
Blood serum	ASE extraction at 1,500 PSI and 20–100 C followed by additional cleanup with polar solvents	HPLC/MS/MS	27 ppt (0.027 µg/L)	64.4–93	Kuklenyik 2009
Kidney	Homogenize with anhydrous sodium sulfate and a mixture of 2% ethanol in ethyl acetate; centrifugation followed by GPC cleanup	GC/MS	0.01 ppb (0.01 ng/g)	82–85	Russo et al. 2002
Liver	Homogenize with anhydrous sodium sulfate and a mixture of 2% ethanol in ethyl acetate; centrifugation followed by GPC cleanup	GC/MS	0.01 ppb (0.01 ng/g)	92–95	Russo et al. 2002

ASE = accelerated solvent extraction; FPD = flame photometric detector; GC = gas chromatography; GPC = gel permeation chromatography; HPLC = high performance liquid chromatography; HRGC = high-resolution gas chromatography; MS = mass spectrometry

Table 7-2. Analytical Methods for Determining Tribufos in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	High volume samplers collected air onto XAD-4 resin; extraction with ethyl ether and cleanup with Florisil	GC/FPD	0.1 ng/m^3	83–86	Hermann and Seiber 1981
Air	Air pulled through primary and secondary PUF samplers; Soxhlet extraction using 250 mL hexane:acetone (1:1) solution	GC/MS	0.10 ng/m^3 (reporting level based on 100 m^3 volume)	Not reported	Majewski et al. 1998
Air	High volume air samplers collected air onto XAD-4 resin, Soxhlet extraction using acetone	GC/FPD	2.7 ng/m^3	98.7±6.6	Kilgore et al. 1984
Water	Extraction with methylene chloride followed by drying with sodium sulfate and dilution with acetone	GC/MSD	0.00946 ppb (µg/L)	88 (mean)	CDFA 2013
Water	Extraction at a neutral pH with methylene chloride using a separatory funnel (EPA Method 3510), a continuous liquid-liquid extractor (EPA Method 3520), SPE (EPA Method 3535), or other appropriate technique	GC/FPD	0.20 ppb (µg/L)	79–81 (separatory funnel extraction) 79–80 (liquid extraction)	EPA 2000b[b]
Water	Collection and storage followed by SPE	HPLC/MS	0.01 ppb (µg/L)	78–85	Potter et al. 2007
Soil	Soil samples are extracted with hexane-acetone (1:1) or methylene chloride-acetone (1:1) using one of the Soxhlet extraction methods (EPA Method 3540 or 3541), pressurized fluid extraction (EPA Method 3545), microwave extraction (EPA Method 3546), ultrasonic extraction (EPA Method 3550), or other appropriate technique	GC/FPD	10 ppb (µg/kg)	53–62%	EPA 2000b[a]
Soil and sediment	Triple extraction using hexane:acetone (95:5) mixture followed by filtration and drying with anhydrous sodium sulfate; cleanup with florisil	GC/FPD	3 ppb	79–85%	EPA 1998

Table 7-2. Analytical Methods for Determining Tribufos in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fruits and vegetables	Homogenization and extraction using acetone or methylene chloride followed by SPE cleanup	GC/FPD	0.4 ppb (estimated limit of quantification)	100–123%	Podhorniak et al. 2001
Pork, mutton, beef, rabbit, chicken tissue	Extraction with 35 mL of cyclohexane+ethyl acetate (1+1) followed by blender homogenization and GPC cleanup	LC/MS/MS	50 µg/kg (ppb)	79–88%	Pang et al. 2006

[a]Method for merphos (CASRN 150-50-5); however, merphos readily oxidizes to tribufos.

EPA = Environmental Protection Agency; FPD = flame photometric detector; GPC = gel permeation chromatography; LC = liquid chromatography; MS = mass spectrometry; MSD = mass selective detector; PUF = polyurethane foam; SPE = solid-phase extraction

1998). Final cleanup was performed using activated magnesium silicate columns washed with extraction solvent. Analysis was performed using GC/FPD. The mean recoveries of tribufos were 79 and 85% at 10 and 100 ppb spiking levels, respectively. The detection limit was reported as 3 ppb. A second soil and sediment extraction and quantification process was deemed unsatisfactory by the EPA and is further explained in EPA (2014a).

7.3 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 health effects (and techniques for developing methods to determine such health effects) of tribufos.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health 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.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Tribufos in the blood or urine would serve as a biomarker of exposure. Tribufos was rapidly and extensively metabolized to form numerous (mostly unidentified) urinary metabolites in rats (CalEPA 2004). It is not likely that any of the tribufos metabolites would serve as reliable and unique indicators of exposure to tribufos.

Effect. Decreased 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. Tribufos neurotoxicity is related to its

inhibitory effect on AChE; however, this is not unique to tribufos, but common to exposures involving other organophosphate pesticides and when using antimalarial or antidepressant medicines.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Adequate methods are available to detect tribufos in environmental media primarily using GC/FPD, which is highly sensitive for the detection of sulfur and phosphorous containing species. No data needs are identified.

7.3.2 Ongoing Studies

No ongoing research identified in the NIH RePORTER (2016) database was located.

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8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance-specific estimates that are intended to serve as screening levels. They are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived a provisional intermediate-duration inhalation MRL of 0.04 mg/m^3 for tribufos based on a NOAEL of 2.43 mg/m^3 for neurological effects in rats (EPA 1992b). The provisional MRL was derived by converting the duration-adjusted NOAEL to a human equivalent concentration and application of a total uncertainty factor of 30 (3 for animal to human extrapolation using dosimetric conversion and 10 for human variability). See Appendix A for detailed information regarding MRL derivation.

ATSDR has derived a provisional intermediate-duration oral MRL of 0.003 mg/kg/day for tribufos based on a NOAEL of 0.28 mg/kg/day and a LOAEL of 2.0 mg/kg/day for 35% decreased RBC AChE activity in F0 parental male rats administered tribufos in the diet for 56 days of premating treatment (Astroff et al. 1998; EPA 1992c). The NOAEL of 0.28 mg/kg/day was divided by a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability). See Appendix A for detailed information regarding MRL derivation.

ATSDR has derived a provisional chronic-duration oral MRL of 0.0008 mg/kg/day for tribufos based on BMD analysis of incidences of vacuolar degeneration in the small intestine of Fischer 344 rats administered tribufos in the diet for up to 2 years (CalEPA 2004). The resulting $BMDL_{10}$ of 0.08 mg/kg/day was divided by a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability). See Appendix A for detailed information regarding MRL derivation.

EPA's Office of Pesticide Programs (EPA 2000a) derived an acute dietary reference dose (RfD) of 0.01 mg/kg/day for tribufos based on a NOAEL of 1 mg/kg/day and a LOAEL of 7 mg/kg/day for decreases in plasma and RBC ChE activity in pregnant rats gavaged on GDs 6–16 (EPA 1990b). The NOAEL of 1 mg/kg/day was divided by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for intraspecies variation).

EPA (2000a) derived a chronic dietary RfD of 0.001 mg/kg/day for tribufos based on a NOAEL of 0.1 mg/kg/day and a LOAEL of 0.4 mg/kg/day for plasma ChE inhibition in dogs administered tribufos in the diet for 1 year (EPA 1991b).

The international and national regulations, advisories, and guidelines regarding tribufos in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Tribufos

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2016
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines	No data	WHO 2011
NATIONAL			
Regulations and guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	No data	ACGIH 2015
AIHA	ERPGs	No data	AIHA 2015
TERA	WEELs	No data	TERA 2014
DOE	PACs	No data	DOE 2016
EPA	AEGLs	No data	AEGLs 2016
	Hazardous air pollutant	No data	EPA 2014b 42 USC 7412
NIOSH	REL (up to 10-hour TWA)	No data	NIOSH 2015
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2015b 29 CFR 1910.1000, Table Z-1
	PEL (8-hour TWA) for shipyards	No data	OSHA 2015c 29 CFR 1915.1000 Table Z
	PEL (8-hour TWA) for construction	No data	OSHA 2015a 29 CFR 1926.55 Appendix A
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	No data	EPA 2015b 40 CFR 116.4
	Drinking water standards and health advisories	No data	EPA 2012g
	National primary drinking water standards	No data	EPA 2009
	National recommended water quality criteria	No data	EPA 2016b, 2016c
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No data	EPA 2015c 40 CFR 117.3

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Tribufos

Agency	Description	Information	Reference
NATIONAL (*cont.)*			
c. Food			
EPA	Tolerances for pesticide chemical residues in or on food commodities		EPA 2015a 40 CFR 180.272
	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	4.0 ppm	
	Cotton gin byproducts	40 ppm	
FDA	EAFUS	No data	FDA 2013a
d. Other			
ACGIH	Carcinogenicity classification	No data	ACGIH 2015
EPA	Carcinogenicity classification	Unlikely carcinogenic at low doses, likely carcinogenic at high doses[a]	EPA 1997a
	Acute RfD	$1x10^{-2}$ mg/kg/day	
	Chronic RfD	$1x10^{-3}$ mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity	No data	EPA 2015d 40 CFR 302.4
	Effective date of toxic chemical release reporting	1/1/95	EPA 2015e 40 CFR 372.65
	TSCA chemical lists and reporting periods	No data	EPA 2015f 40 CFR 712.30
DHHS	Carcinogenicity classification	No data	NTP 2014

[a]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 1997a). 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.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; BEI = biological exposure index; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DHHS = Department of Health and Human Services; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health concentrations; MCL = maximum contaminant level; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfD = oral reference dose; STEL = short-term exposure limit; TERA = Toxicology Excellence for Risk Assessment; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; WHO = World Health Organization

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10. GLOSSARY

Absorption—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 or less, 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 (Kd)—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)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

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—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of 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—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

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

Ceiling Value—A concentration that must not be exceeded.

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

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. At least one exposed group is compared to one unexposed group.

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 one 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—The amount of a substance to which a person is exposed over some time period. Dose is a measurement of exposure.

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

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 insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance 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.

Epidemiology—Refers to 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.

Exposure—Contact with a substance by swallowing, breathing, or touching the skin.

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.

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.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

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$_{(50)}$ (LC_{50})—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$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—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.

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.

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

Mortality—Death; 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. A mutation is a change 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. Effects may be produced at this dose, but 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 OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

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 end points. 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.

Physiologically Based Pharmacokinetic (PBPK) Model—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: 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 the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

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 reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater 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.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio 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.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

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

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or 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.

10. GLOSSARY

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (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 and are not based on a consideration of cancer effects. 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 no-observed-adverse-effect level/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 and longer) 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.

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 levels. 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 F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 78-48-8
Date: April 2018
Profile Status: Final Draft for Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 3
Species: Rat

Provisional Minimal Risk Level: 0.04 [ ] mg/kg/day [x] mg/m^3

Reference: 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

Experimental design: 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/m^3 (analytical concentrations of 0, 0.93, 2.43, 12.2, and 59.5 mg/m^3, 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/m^3 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.

Effect noted in study and corresponding doses: 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 results of nontreatment-related causes. Clinical signs were noted in all rats of the 59.5 mg/m^3 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/m^3 exposure group (27% less than controls) at week 0 (but not at other time points) and in the 2.43 mg/m^3 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/m^3 male and female rats (25–65% less than controls) and 59.5 mg/m^3 (49–91% less than controls). At sacrifice, brain AChE activity among male and female rats was significantly decreased only at the 59.5 mg/m^3 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).

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]

[a]Not statistically significantly different from control.
[b]Statistically significantly different from control ($p \leq 0.05$), but considered spurious due to lack of significant change at other time points.
[c]Statistically 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 µmol 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]

[a]Statistically significantly different from control ($p \leq 0.05$).
[b]Statistically 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 µmol of substrate per minute); NA = not applicable; RBC = red blood cell

Source: EPA 1992b

Ophthalmological examinations revealed no signs of tribufos exposure-related effects. However, at the 59.5 mg/m^3 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/m^3 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.

Dose and end point used for provisional MRL derivation: A NOAEL of 2.43 mg/m^3; the next higher exposure level (12.2 mg/m^3) represents a serious LOAEL (i.e., >60% decreased RBC AChE activity in male and female rats).

[x] NOAEL [ ] LOAEL

Uncertainty Factors used in provisional MRL derivation:

[ ] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans using dosimetric conversion
[x] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The NOAEL of 2.43 mg/m^3 was adjusted from intermittent to continuous exposure as follows:

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

A regional deposited dose ratio ($RDDR_{ER}$) of 2.839 for extrarespiratory effects (RBC AChE inhibition) in female Wistar rats was used to extrapolate from rats to humans. The $RDDR_{ER}$ was calculated using EPA's software (Version 2.3) (EPA 1994) for calculating RDDRs 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 Extrarespiratory Effects Using EPA's Software (Version 2.3) and $RDDR_{ER}$ Values for Male and Female Wistar Rats

	Wistar rat		
Biological parameters[b]	Male	Female	Human
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	–

[a]Mass median aerodynamic diameter (MMAD) =1.2 µm; geometric standard deviation =1.4 µm (EPA 1992b).
[b]Parameters 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:

$$\mathbf{NOAEL_{HEC} = NOAEL_{ADJ} \times RDDR_{ER} = 0.43\ mg/m^3 \times 2.839 = 1.22\ mg/m^3}$$

The $NOAEL_{HEC}$ of 1.22 mg/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability) resulting in a provisional intermediate-duration inhalation MRL of 0.04 mg/m^3.

Was a conversion used from intermittent to continuous exposure? Yes.

Other additional studies or pertinent information that lend support to this provisional MRL: The principal study (EPA 1992b) was the only available intermediate-duration inhalation study.

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 78-48-8
Date: April 2018
Profile Status: Final Draft for Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 32
Species: Rat

Provisional Minimal Risk Level: 0.003 [x] mg/kg/day [ ] ppm

Reference: 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.

Experimental design: 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 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 end points, fertility, and fetal and pup viability were evaluated.

Effect noted in study and corresponding doses: 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, but 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.

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.

The study identified NOAELs of 0.28 mg/kg/day for F0 and F1 males and 0.31 mg/kg/day for F0 and F1 females, LOAELs of 2.0 and 2.25 mg/kg/day for F0 males and females, respectively, based on 35–37% decreased RBC AChE activity during premating treatment, and LOAELs of 2.09 and 2.40 mg/kg/day for F1 parental males and females, respectively, based on 26–28% decreased RBC AChE activity during premating treatment. The NOAEL of 0.28 mg/kg/day for F0 males was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in a provisional intermediate-duration oral MRL of 0.003 mg/kg/day for tribufos.

Dose and end point used for provisional MRL derivation: NOAEL of 0.28 mg/kg/day associated with a LOAEL of 2.0 mg/kg/day for decreased RBC AChE activity in F0 male rats at day 56 premating in the 2-generation dietary study.

[x] NOAEL [ ] LOAEL [ ] Benchmark

Uncertainty Factors used in provisional MRL derivation:

[ ] 10 for use of a LOAEL
[x] 10 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this provisional MRL: The selection of the NOAEL of 0.28 mg/kg/day for F0 male rats of the principal study (CalEPA 2004; EPA 1992c) is supported by results from several studies (see Table A-4).

Table A-4. NOAELs and LOAELs for RBC AChE Inhibition Associated with Intermediate-Duration Oral Exposure to Tribufos

	Dose in mg/kg/day			
Study type/ treatment period	NOAEL	LOAEL (% inhibition)	Serious LOAEL (% inhibition)	Reference
Female rat 4 weeks	0.43	ND	4.32 (66%)	EPA 2013a
Mouse 8 weeks	M: 3.4 F: 5.6	M: 9.4 (37%) F: 14.3 (44%)	M: 40 (64%) F: 54 (64%)	CalEPA 2004
Female rat 21 days gestation 21 days lactation	0.4–1.0	ND	3.4–9.9 (76%)	EPA 2005a
Rat (2-generation; premating period) F0: 56 days F1: 62 days	F0 M: 0.28 F0 F: 0.31 F1 M: 0.28[a] F1 F: 0.31[a]	F0 M: 2.00 (35%) F0 F: 2.25 (37%) F1 M: 2.09 (26%) F1 F: 2.40 (28%)	ND ND ND ND	Astroff et al. 1998; EPA 1992c
Dog up to 364 days	0.4	M: 1.7 (24%)[b]	ND	CalEPA 2004; EPA 1991b

[a]F1 parental rats had been exposed to tribufos via their mothers during 6 weeks of gestational and lactational exposure as well.
[b]At treatment day 91.

AChE = acetylcholinesterase; F = females; F0 = first generation parental; F1 = second generation parental; LOAEL = lowest-observed-adverse-effect level; M = males; ND = not determined; NOAEL = no-observed-adverse-effect level; RBC = red blood cell

Among the rat studies, NOAELs ranged from 0.28 to 1 mg/kg/day, less serious LOAELs ranged from 2.0 to 2.4 mg/kg/day, and serious LOAELs ranged from 3.4 to 9.9 mg/kg/day. A dog study that employed dietary exposure for 364 days identified a NOAEL of 0.4 mg/kg/day and a LOAEL of 1.7 mg/kg/day for 24% decreased RBC AChE activity on treatment day 91 (CalEPA 2004; EPA 1991b). Results from the mouse study identified NOAELs (3.4 and 5.6 mg/kg/day for males and females, respectively) and less serious LOAELs (9.4 and 14.3 mg/kg/day for males and females, respectively) that approach an order of magnitude higher than those identified in the rat studies. Therefore, the results from the mouse study were not further considered as a potential POD for deriving a provisional intermediate-duration oral MRL for tribufos. The 4-week dietary study in female rats (EPA 2013a) identified a NOAEL of 0.43 mg/kg/day; the next higher dose (4.32 mg/kg/day) represented a serious LOAEL (66% RBC AChE inhibition); the dataset was not considered amenable to BMD analysis due to a high degree of uncertainty regarding a predicted dose associated with a 20% decrease in RBC AChE activity. A NOAEL/LOAEL approach was not employed because the NOAEL and LOAEL were higher than NOAELs and LOAELs identified in the 2-generation dietary rat study (Astroff et al. 1998; EPA 1992c). Results from the study of female rats administered tribufos in the diet during gestation and lactation (EPA 2005a) were not considered for provisional MRL derivation due to the lack of ability to associate RBC AChE activity with discrete oral doses of tribufos because the doses to the dams during lactation were significantly greater than those during gestation and RBC AChE activity was measured only following lactation. The 2-generation rat study (Astroff et al. 1998; EPA 1992c) and the 364-day dog study (CalEPA 2004; EPA 1991b) identified the lowest less serious LOAELs (1.7–2.4 mg/kg/day) for decreased RBC AChE activity and were therefore considered as potential candidates for deriving a provisional intermediate-duration oral MRL for tribufos.

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 a provisional intermediate-duration oral MRL for tribufos. 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). BMD analysis of the datasets for the F0 male and female rats and the F1 female rats from the 2-generation dietary study (Astroff et al. 1998; EPA 1992c) resulted in inadequate fit to mean data ($p<0.1$). Therefore, a NOAEL/LOAEL approach was applied to derive a provisional intermediate-duration oral MRL for tribufos.

Agency Contact (Chemical Manager): Rae Benedict, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 78-48-8
Date: April 2018
Profile Status: Final Draft for Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 40
Species: Rat

Provisional Minimal Risk Level: 0.0008 [x] mg/kg/day [ ] ppm

References: 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.

Experimental design: 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 (analytical 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. A comprehensive set of tissues was collected and processed for histopathological examination.

Effect noted in study and corresponding doses: 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.

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 vacuolar degeneration in the small intestine at 1-year evaluation (7/10 and 18/20, respectively, for males versus 0/10 low-dose males and 0/20 controls; and 8/10 and 16/20, respectively, for females versus 0/10 low-dose females and 0/20 controls). At terminal sacrifice, mid-and high-dose males and females exhibited significantly increased incidences of vacuolar degeneration and hyperplasia in the small intestine. Incidences of vacuolar degeneration in control, low-, mid-, and high-dose groups were 0/50, 1/50, 24/50, and 37/50, respectively, for males and 0/50, 0/50, 19/50, and 35/50, respectively, for females. Incidences of hyperplasia were 0/50, 3/50, 23/50, and 34/50, respectively, for males, and 1/50, 0/50, 11/50, and 30/50, respectively, for females. 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.

Table A-5 summarizes the incidence data for vacuolar degeneration and hyperplasia in the small intestine of male and female Fischer rats administered tribufos in the diet for 1 year (interim sacrifice) and 2 years (terminal sacrifice). Incidence data for vacuolar degeneration at 1- and 2-year sacrifice and for hyperplasia at 2-year sacrifice were fit to all available dichotomous models in EPA's BMDS (version 2.6.0) using a BMR of 10% increased incidence from control incidence. 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 all models providing adequate fit to the data, the lowest $BMDL_{10}$ was selected as the POD when the difference between the BMDLs estimated from these models was >3 fold; otherwise, the $BMDL_{10}$ from the model with the lowest Akaike's Information Criterion (AIC) was chosen.

Table A-5. 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%)

[a]Significantly different from control according to Fisher's exact test ($p<0.001$).
[b]Significantly different from control according to Fisher's exact test ($p<0.01$).

Source: CalEPA 2004

Table A-6 presents potential PODs for deriving a provisional chronic-duration oral MRL for tribufos based on incidences of vacuolar degeneration or hyperplasia in the small intestine of the rats. None of the dichotomous models provided adequate fit to hyperplasia in male or female rats at terminal sacrifice, to vacuolar degeneration in female rats at 1-year interim sacrifice, or to vacuolar degeneration in male rats at 2-year terminal sacrifice. Among those models providing adequate fit to the data, the loglogistic model provided the lowest $BMDL_{10}$ of 0.08 mg/kg/day based on vacuolar degeneration in the male rats at 1-year interim sacrifice. The $BMDL_{10}$ of 0.08 mg/kg/day served as the POD for deriving a provisional chronic-duration oral MRL because it represents the lowest POD (and therefore the most health protective) among potential BMD-based and NOAEL/LOAEL-based PODs. The $BMDL_{10}$ of 0.08 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in a provisional chronic-duration oral MRL of 0.0008 mg/kg/day for tribufos. Figure A-1 presents the loglogistic model dose-response curve for vacuolar degeneration in the small intestine of the male rats sacrificed at 1 year of dietary exposure to tribufos.

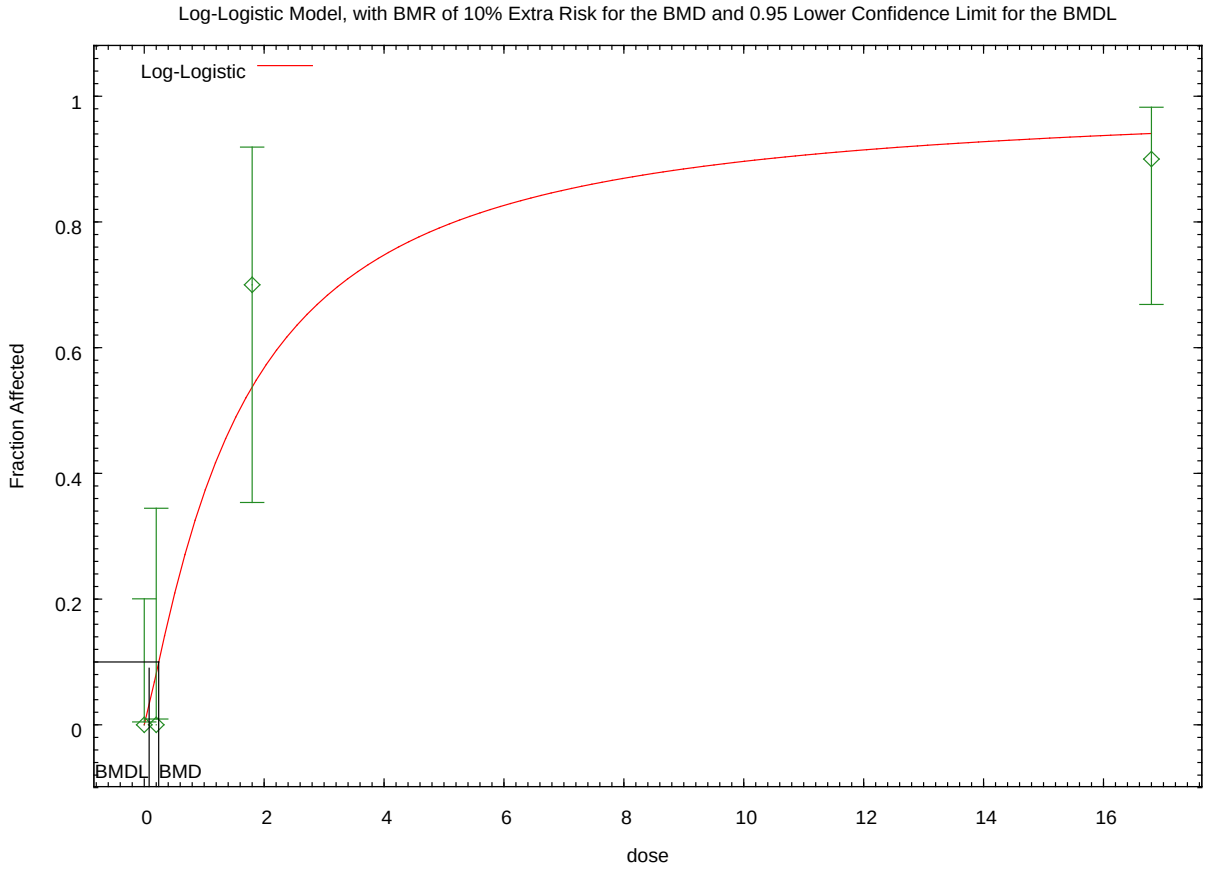
Table A-6. Potential PODs for Deriving a Provisional Chronic-Duration Oral MRL for Tribufos Based on Incidences of Nonneoplastic Lesions in the Small Intestine of Male and Female Fischer 344 Rats Administered Tribufos in the Diet for up to 2 Years[a]

	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)[b]
1-Year interim sacrifice				
Male				
Vacuolar degeneration	**0.2**	**1.8**	**ND**	**0.08[c]**
Female				
Vacuolar degeneration	0.2	2.3	ND	ND[d]
2-Year terminal sacrifice				
Male				
Vacuolar degeneration	0.2	1.8	ND	ND[d]
hyperplasia	0.2	1.8	ND	ND[d]
Female				
Vacuolar degeneration	0.2	1.8	ND	0.29
hyperplasia	0.2	1.8	ND	0.93

[a]Lesion incidence data were reported in CalEPA (2004) and confirmed by SRC, Inc. upon inspection of the unpublished study source (not publicly available).
[b]$BMDL_{10}$ values are from best-fitting models.
[c]Selected as the most conservative POD for deriving a provisional chronic-duration oral MRL for tribufos.
[d]None of the models in the BMD software provided adequate fit to the data.

BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscript denotes benchmark response: i.e., $_{10}$ = dose associated with 10% extra risk); LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure

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




```
================================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File: C:/Users/wohlers/Downloads/BMDS2601/Data/lnl_Dax_Setting.(d)
        Gnuplot Plotting File:
C:/Users/wohlers/Downloads/BMDS2601/Data/lnl_Dax_Setting.plt
                                              Sun Jul 03 15:09:27 2016
 ================================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

```
   User has chosen the log transformed model

                Default Initial Parameter Values
                   background =            0
                    intercept =    -0.708747
                        slope =      1.18142

          Asymptotic Correlation Matrix of Parameter Estimates

    ( *** The model parameter(s)  -background have been estimated at a boundary point,
or have been specified by the user, and do not appear in the correlation matrix )

              intercept        slope
intercept             1        -0.48
     slope        -0.48            1

                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
    Variable       Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
    background        0               NA
    intercept       -0.536561      0.54497          -1.60468           0.53156
       slope         1.16749       0.332121          0.516548          1.81844

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.

                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -12.6103         4
   Fitted model        -14.2609         2       3.30115      2          0.1919
  Reduced model        -40.7516         1       56.2826      3         <.0001

           AIC:         32.5218

                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      20.000        0.000
    0.2000     0.0820         0.820     0.000      10.000       -0.945
    1.8000     0.5373         5.373     7.000      10.000        1.032
   16.8000     0.9403        18.807    18.000      20.000       -0.761

 Chi^2 = 2.54      d.f. = 2        P-value = 0.2812

   Benchmark Dose Computation
Specified effect =           0.1
Risk Type        =      Extra risk
Confidence level =          0.95
             BMD =       0.241131
            BMDL =      0.0821289
```

Dose and end point used for provisional MRL derivation: $BMDL_{10}$ of 0.08 mg/kg/day for vacuolar degeneration in the small intestine

[ ] NOAEL [ ] LOAEL [x] Benchmark

Uncertainty Factors used in provisional MRL derivation:

[ ] 10 for use of a LOAEL
[x] 10 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this provisional MRL: 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). Table A-7 summarizes NOAELs and LOAELs for tribufos-mediated effects on RBC AChE activity and nonneoplastic lesions in the small intestine following chronic-duration oral exposure. 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 in the small intestine. Therefore, the rat study (CalEPA 2004; EPA 1992d) was selected as the principal study for deriving a provisional chronic-duration oral MRL for tribufos.

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

Study type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
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	
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

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

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points 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?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived 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. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" 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 end point 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 end point 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 (UF) 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 substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

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, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures 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 Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(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 Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is 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) Health Effect. The major categories of health effects included in LSE tables and figures include death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. 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 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "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.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive a provisional intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(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 end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A 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.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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 acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects 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/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which a provisional intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the provisional MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

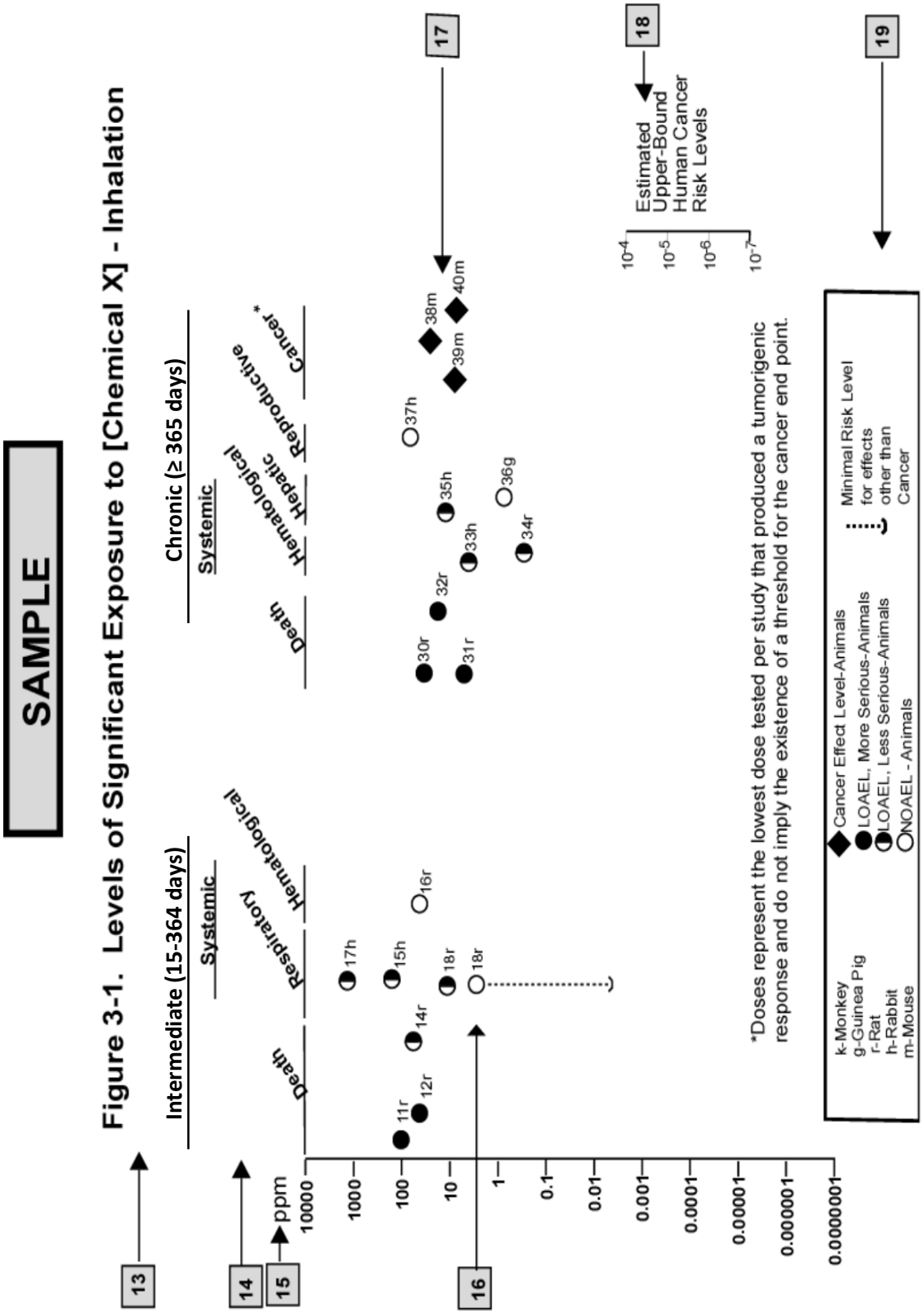
(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive a provisional intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).


SAMPLE
Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation
Intermediate (15-364 days)
Chronic (≥ 365 days)
Systemic
Death
Respiratory
Hematological
Hepatic
Reproductive
Cancer *
ppm
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0.0000001
11r
12r
14r
15h
16r
17h
18r
18r
30r
31r
32r
33h
34r
35h
36g
37h
38m
39m
40m
Estimated Upper-Bound Human Cancer Risk Levels
10^{-4}
10^{-5}
10^{-6}
10^{-7}
*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.
k-Monkey
g-Guinea Pig
r-Rat
h-Rabbit
m-Mouse
Cancer Effect Level-Animals
LOAEL, More Serious-Animals
LOAEL, Less Serious-Animals
NOAEL - Animals
Minimal Risk Level for effects other than Cancer
13
14
15
16
17
18
19

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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
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
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	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	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
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
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TOC	total organic carbon
TPQ	threshold planning quantity
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
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