TOXICOLOGICAL PROFILE FOR PHOSPHATE ESTER FLAME RETARDANTS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Phosphate Ester Flame Retardants, Draft for Public Comment was released in September 2009. This edition supersedes any previously released draft or final profile.

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 (proposed)
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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 the toxic substances each profile describes. 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 profiles focus 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. A health effects summary describes the adequacy of information to determine a substance's health effects. ATSDR identifies data needs that are significant to protection of public health.

Each profile:

(A) Examines, summarizes, and interprets 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) Determines whether adequate information on the health effects of each substance is available or being developed to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identifies 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 federal, state, and local health professionals; interested private sector organizations and groups; and members of the public.

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

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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List 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.

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 will 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 (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:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 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) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

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. 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.

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.

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, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-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.

Referrals

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.

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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 (proposed) 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 phosphate ester flame retardants. The panel consisted of the following members:

1. Sam Kacew, Ph.D., Associate Director of Toxicology, University of Ottawa, McLaughlin Center for Population Health, Ottawa, ON, Canada

2. Richard K. Miller, Ph.D., Professor of Environmental Medicine, University of Rochester School of Medicine and Dentistry, Department of Obstetrics and Gynecology, Rochester, NY

3. Michael Pereira, Ph.D., Professor, Division of Hematology and Oncology, College of Medicine and Public Health, Ohio State University, Columbus, OH

These experts collectively have knowledge of phosphate ester flame retardants' 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

This public health statement tells you about phosphate ester flame retardants and the effects of exposure to them.

This profile discusses the following phosphate ester flame retardants: tris(2-chloroethyl) phosphate (TCEP), tributyl phosphate (TnBP), tris(2-butoxyethyl) phosphate (TBEP), tris(1,3-dichloro-2-propyl) phosphate (TDCP), triphenyl phosphate (TPP), tris(2-chloroisopropyl) phosphate (TCPP), triisobutyl phosphate (TiBP), and tricresyl phosphate (TCP).

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Phosphate ester flame retardants have been found in at least 8 of the 1,699 current or former NPL sites. Although the total number of NPL sites evaluated for these substances is not known, the possibility exists that the number of sites at which phosphate ester flame retardants are found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to these substances may be harmful.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to phosphate ester flame retardants, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with them. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT ARE PHOSPHATE ESTER FLAME RETARDANTS?

Description	Phosphate ester flame retardants are human-made chemicals added to consumer and industrial products for the purpose of reducing flammability. Phosphate ester flame retardants are composed of a group of chemicals with similar properties but slightly different structures. Phosphate esters are typically liquids at room temperature; however, some are solids.
Uses	Phosphate esters are flame retardants, plasticizers, hydraulic fluids, solvents, extraction agents, antifoam agents, and coatings for electronic devices.

For more information on the physical and chemical properties of phosphate esters and their production, disposal and use, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO PHOSPHATE ESTER FLAME RETARDANTS WHEN THEY ENTER THE ENVIRONMENT?

Sources	Phosphate ester flame retardants are released to the environment from industrial sources and disposal of consumer products containing flame retardants.
Breakdown	Phosphate ester flame retardants can change chemical composition in the environment.
• **Air**	There is no specific information available for the eight phosphate ester flame retardants discussed in this document; however, in general, these compounds are degraded by chemical reactions in the air. If they attach themselves to particles, they can settle out onto the ground. .
• **Water and soil**	Generally, most phosphate esters are poorly soluble in water and adsorb strongly to soils. These compounds are commonly detected in water due to their widespread use in commercial products. Phosphate esters are subject to biodegradation in aquatic and terrestrial environments.

1.3 HOW MIGHT I BE EXPOSED TO PHOSPHATE ESTER FLAME RETARDANTS?

Routes of exposure	Humans can be exposed by a combination of oral, inhalation, and dermal routes.
Food—primary source of exposure	Ingesting contaminated food: Most foods have been found to contain trace amounts of phosphate ester flame retardants due to their wide use in plastics and presence in the environment.
Air	Breathing contaminated outdoor air: Hydraulic fluid is the primary source of phosphate esters in outdoor air. Breathing contaminated indoor air: Indoor air can contain phosphate ester flame retardants from certain plastics, adhesives, foams, or electronics.
Water and soil	Drinking water contaminated with phosphate esters due to leaching from plastics or industrial waste water discharge. By skin contact with contaminated soil: Hydraulic fluid spills or industrial waste water used for agriculture can result in the presence of phosphate esters in soil.
Children	Young children may be at a higher risk of exposure since they are more likely to put phosphate ester flame retardant treated materials in their mouths.

1.4 HOW CAN PHOSPHATE ESTER FLAME RETARDANTS ENTER AND LEAVE MY BODY?

Enter the body	
• **Humans**	There is virtually no information about the entrance of these substances into the body. However, TDCP had been found in human tissues and body fluids, so we know that this substance can enter the body possibly by inhaling aerosols or dusts or ingesting contaminated food or water. Adverse health effects seen in humans after exposure to TCP indicate that this substance can enter the body and pass into the bloodstream.
• **Animals**	Oral – Studies found that TDCP, TCEP, TCP, and TnBP can easily pass from the stomach and intestines into the blood stream. Dermal – Less amounts entered the body through the skin of rats and only very small amounts through the skin of pigs.

Leave the body	
• Humans	There is no information on how these chemicals leave your body, but based on studies in animals, phosphate ester flame retardants may be broken down in the body and the breakdown product may be eliminated in the urine. However, there are no studies in humans to prove that this actually happens.
• Animals	Neither phosphate ester flame retardants nor their breakdown products seemed to accumulate in the body. Most breakdown products were eliminated in the urine in 2–3 days.

1.5 HOW CAN PHOSPHATE ESTER FLAME RETARDANTS AFFECT MY HEALTH?

This section looks at animal and human studies concerning potential health effects.

Workers	Long-term exposure of workers to TDCP, TCP, or TPP was not associated with adverse health effects. No information was available regarding exposure to other phosphate ester flame retardants.
General population	Almost no information is available regarding health effects in members of the general population exposed to the phosphate ester flame retardants discussed in this profile. However, accidental ingestion of a component of TCP, tri-*o*-cresyl phosphate, has caused adverse effects on the nervous system. There have been a few cases of allergic reactions to consumer products that contain TPP, but a study that examined several hundred people exposed to plastics and glues that contained TPP or TCP did not find any allergic reactions.

Laboratory animals	One way to learn about the effects of phosphate ester flame retardants is to see how they affect test animals. Almost all studies in animals have administered these substances orally and generally at levels much higher than what can be expected from environmental exposures. TCEP given to rats for 16 weeks or longer caused brain lesions. When given for 2 years, it also caused lesions in the kidneys. TCEP also decreased the fertility of mice that were exposed for 18 weeks before mating. TnBP induced lesions in the urinary bladder of rats when given for 10 weeks or longer. TBEP caused liver lesions in rats after the rats ate food that contained TBEP for 18 weeks. A study showed that rats that ate food containing TCP for 2 years developed lesions in the ovary and adrenal gland and male mice developed liver lesions. TCP also decreased fertility in rats and mice. Rats that ate food containing TDCP for 2 years developed lesions in the kidneys and liver. The few studies that examined the effects of TPP, TiBP, and TCPP in animals did not report significant adverse health effects.
Cancer	There is not enough information available to determine with certainty whether or not phosphate ester flame retardants produce cancer in humans. Studies of workers employed in the manufacture of TDCP and TCP did not find significant associations between exposure and cancer. No information was available regarding the carcinogenic potential of the other phosphate esters to humans. Rats that received oral doses of TCEP for 2 years developed kidney tumors. Feeding mice a diet that contained TCEP for 18 months induced tumors in the kidney, liver, and stomach, and also induced leukemia. Long-term administration of TnBP to rats and mice induced tumors in the urinary bladder and the liver, respectively. Feeding rats with a diet that contained TDCP for 2 years produced tumors in the liver, kidneys, testes, and adrenal gland. Neither the EPA nor the Department of Health and Human Services (DHHS) has classified the carcinogenic potential of the phosphate esters discussed in this profile. The International Agency for Research on Cancer (IARC) determined that TCEP is not classifiable as to its carcinogenicity to humans.

1.6 HOW CAN PHOSPHATE ESTER FLAME RETARDANTS AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Effects in humans	There are no studies that examined the health effects of the phosphate ester flame retardants discussed in this profile on pregnant women or on their embryo or fetus. There are no studies that examined the health effects in children of the phosphate ester flame retardants discussed in this document.
Laboratory animals	In general, exposure of rodents during gestation to TCEP, TnBP, TBEP, TDCP, TPP, or TCPP did not result in adverse effects to the fetuses or newborn animals. However, continuous exposure of two generations of mice to TCEP reduced the number of male pups born alive in the third generation. A similar study with TnBP in rats found that pups born to exposed rats had lower body weight during the first weeks of life than pups born to untreated rats. Studies in rats and mice also found that exposure to TCP before and during pregnancy can increase the number of pups born dead.
Exposure of the fetus	There is no information regarding transfer of phosphate ester flame retardants to the fetus across the placenta in pregnant women.
Human breast milk	No studies have been conducted to determine whether phosphate ester flame retardants can be detected in human breast milk from women exposed at work or from the general population.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO PHOSPHATE ESTER FLAME RETARDANTS?

Food	Avoid food that is generally high in phosphate ester content as indicated by the current market basket for the U.S. Total Diet study.
Air	Avoid installation or use of materials that are known to contain phosphate ester-based flame retardants in indoor environments to minimize exposure to them via air and particulate matter.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PHOSPHATE ESTER FLAME RETARDANTS?

Detecting exposure	Phosphate ester flame retardants can be measured in blood and urine, but this is not a routine test that can be performed in a doctor's office. You should, however, see a physician if you believe that you have been exposed to high levels of these substances. No studies have been conducted to measure these chemicals in blood samples from groups of people representative of the U.S. general population.
Measuring exposure	The presence of phosphate ester flame retardants in your blood may indicate that you have been exposed to these substances and some amount entered your bloodstream. The presence of phosphate ester flame retardants in your blood does not necessarily indicate that adverse health effects will occur. Additional studies are needed to help to determine the health effects associated with exposure to these substances.

1.9 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. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but cannot be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels. These are levels of a toxic substance in air, water, soil, or food that do not exceed a critical value. This critical value is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

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 provides it.

Some regulations and recommendations for phosphate ester flame retardants include the following:

Levels in workplace air set by OSHA	OSHA set a legal limit of 3 and 5 mg/m^3 for TPP and TnBP, respectively, in air averaged over an 8-hour work day.
Food	The EPA has permitted TnBP, TBEP, and TPP for use in nonfood pesticide products.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences (proposed)
1600 Clifton Road NE
Mailstop F-62
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PHOSPHATE ESTER FLAME RETARDANTS IN THE UNITED STATES

Phosphate esters are a class of anthropogenic organic compounds found in the environment due to their release from commercial and industrial products. They are pervasive throughout the world due to their extensive industrial and commercial use since the 1940s. Phosphate esters represent an important class of commercial additives used as flame retardants, plasticizers, hydraulic fluids, solvents, extraction agents, antifoam agents, adhesives, and coatings for electronic devices.

Human exposure to phosphate ester flame retardants can occur via ingestion of food and water, and through contact with water, air, or soil containing phosphate esters. The most likely route of exposure to the general population is through ingestion of food and water containing phosphate esters or inhalation of vapors or particulates released from flame retardant materials. The dermal route can account for exposure if contact with flame-retarded textiles occurs. Oral exposure could occur in young children from dissolution of phosphate ester treated materials since children are more likely to suck on these materials. The ranges of expected exposure through food are generally 0.5–20 ng/kg/day for adults and 0.1–40 ng/kg/day for children under 2 years of age. These estimated intakes are significantly lower than the doses administered to laboratory animals. Workers in industries that manufacture phosphate esters or products containing phosphate esters are subject to a greater exposure risk than the general population.

Concentrations of phosphate esters in ambient outdoor air are not well known, as few studies address this subject. The presence of phosphate esters in outdoor air likely originates from hydraulic fluid volatilization and diffusion of plasticizers. Concentrations were in the low $\mu g/m^3$ range when detected near airports and low ng/m^3 range outside of office buildings. Indoor air is well documented to contain a wide array of phosphate esters at concentrations in the $\mu g/m^3$ range. Concentrations measured indoors typically range from ng/m^3 to $\mu g/m^3$.

Surface water is the most likely place to find anthropogenic phosphate ester flame retardants. Concentrations of 0.5 µg/L are commonplace in rivers, lakes, and groundwater, but effluent and waste water have been documented to contain up to 15 µg/L of select phosphate esters, predominantly tributyl phosphate (TnBP) or triphenyl phosphate (TPP). Tris(2-chloroethyl) phosphate (TCEP) has also been found in water in above average concentrations. Groundwater is less likely to contain phosphate esters

due to their potential to adsorb to soils and sediments; however, TCEP has a particularly high mobility in soil and is more likely to be found in groundwater than the other phosphate esters discussed. For a more complete discussion of phosphate ester flame retardants found in the environment, see Chapter 6.

2.2 SUMMARY OF HEALTH EFFECTS

Limited information was located in the database available for review regarding adverse health effects in humans exposed to the phosphate ester flame retardants covered in this profile. Studies of subjects occupationally exposed to tris(1,3-dichloro-2-propyl) phosphate (TDCP) found no apparent medical conditions related to exposure. The time-weighted average exposure concentration was estimated to have been ≤0.4–0.5 μg/m^3. Examination of the mortality experience in 289 workers employed in the manufacture of TDCP also found no significant association between exposure and any specific cause of death. Examinations conducted over the years of small groups of operators in a TPP production plant did not reveal any usual frequency of symptoms, or physical or laboratory findings as compared to unexposed groups. The estimated weighted average concentration of TPP vapor mist and dust was 3.5 mg/m^3. A few individual cases of allergic dermal reactions to TPP have been reported. However, a much bigger study of 343 patients seen at a dermatology clinic reported that no individuals showed allergic reactions to TPP. Negative results also were reported in that study in 839 patients exposed to tricresyl phosphate (TCP). Examination of mortality rates among 737 workers at a plant that manufactured Kronitex® (mainly cresyl phosphate esters) showed no significant differences between the workers and unexposed comparison groups. Clinical neurological examination and measurements of nerve conduction velocity in workers from the same plant did not show clinically significant detrimental effects due to exposure to aryl phosphates. Air samples collected from air and personal areas were low, generally <5 ppb.

It should be noted that there are many reports of neurotoxic effects in humans attributed to exposure to food items contaminated with tri-*o*-cresyl phosphate (TOCP) ranging from single cases to episodes involving thousands of individuals. TOCP occurs as a contaminant in commercial TCP mixtures, usually in low concentrations (<0.1%). TOCP is a subject of this profile only to the extent that it contributes to the overall toxicity of currently used TCP mixtures.

No studies were located regarding immunological effects or on effects on human reproduction of the flame retardants covered in this profile. In addition, no studies were available in pregnant women or children.

2. RELEVANCE TO PUBLIC HEALTH

The great majority of the studies in animals have been conducted by the oral route of exposure. However, two 3-week studies in rabbits exposed to TPP and tris(2-butoxyethyl) phosphate (TBEP) by skin application evaluated hematology and clinical chemistry parameters and gross and microscopic morphology of tissues and found virtually no toxicity with daily dermal doses of up to 1,000 mg/kg/day of each substance. The only significant effect observed was slight edema, atonia, and desquamation at the application site of rabbits applied the lowest dose of 10 mg TBEP/kg/day. In rabbits treated with 1,000 mg TBEP/kg/day, microscopic examination of the treated sites showed squamous cell hyperplasia, hyperkeratosis, erosions-ulcers, acute-subacute inflammation, and congestion and hemorrhage, in various combinations.

The information available from oral studies does not support treating these chemicals as a class for purposes of risk assessment based on the different toxicities exhibited by each one of them. For TCEP, TnBP, TBEP, TDCP, and TCP there was sufficient information to identify sensitive end points; this was not the case for TPP, triisobutyl phosphate (TiBP), or tri-(2-chloroisopropyl) phosphate (TCPP).

TCEP induced brain lesions in rats in 16-week (175 mg/kg/day) and 2-year (88 mg/kg/day) studies; females appeared more sensitive than males. In the 16-week studies, the lesions were located in the hippocampus and thalamus, whereas dosing for 2 years involved primarily the brain stem and cerebral cortex. Cerebral ischemia and/or convulsive activity are potential mechanisms by which these lesions might occur. No such lesions were reported in studies with the other phosphate esters discussed in this profile. Decreased conduction velocity was reported in rats treated with 411 mg TnBP/kg/day for 14 days, and this was accompanied by morphological alterations in the nerve. Acute high doses of TBEP induced abnormal gait, piloerection, and tremors in rats. Several studies measured red blood cell cholinesterase activity and only in a study in rats dosed with TBEP was there a statistically significant decrease (although the magnitude was not specified) after 9 weeks of treatment, but not after 18 weeks of treatment. No clinical signs were associated with the decrease in cholinesterase activity in that study. TCP reduced hind-limb grip strength in mice (≥360 mg/kg/day) in a 16-day gavage study and in rats (≥400 mg/kg/day) in a 13-week gavage study. In the rat study, there were no morphological alterations in the brain, spinal cord, or sciatic nerve. However, gavage doses ≥100 mg TCP/kg/day for 13 weeks induced multifocal axonal degeneration in the spinal cord of female mice; reduced hind-limb grip strength was reported at higher doses (≥200 mg TCP/kg/day). TCP was not neurotoxic to rats or mice dosed with up to 15 or 37 mg/TCP/kg/day, respectively, for up to 2 years. Neither red blood cell nor brain cholinesterase were measured in the study of rats and mice exposed to TCP; however, serum cholinesterase was significantly reduced (41–80%) in rats and mice in the 13-week studies even with the

lowest doses tested (45–65 mg/kg/day). Reductions in the 2-year study did not exceed 50% in rats (15 mg/kg/day at 15 months), but were greater in mice (72–86%) at all time points measured (27–37 mg/kg/day at 3, 9, and 15 months).

The kidney and urinary tract from rats were targets for some of the subject phosphate ester flame retardants of this profile. Administration of TCEP to rats for 16 weeks resulted in increases in absolute and relative kidney weight without inducing histological alterations in doses of up to 350 mg/kg/day. However, treatment for 2 years with 88 mg/kg/day induced renal tubule epithelial hyperplasia in male and female rats. Effects were also reported in mice, but at higher dose levels. The kidney was also a sensitive target for TDCP in rats. Relatively low dietary doses of 20 mg/kg/day significantly increased the incidence of hyperplasia of the convoluted tubular epithelium in male rats; females appeared slightly less sensitive. For TnBP, the urinary bladder of rats was the most sensitive target in intermediate- and chronic-duration oral studies. Urinary bladder hyperplasia was found to be reversible during a 10-week period in a control diet that followed a 10-week exposure period. Interestingly, doses of TnBP that induced nearly 100% incidence of urinary bladder hyperplasia following intermediate-duration exposure induced a much lower incidence of this lesion in a 2-year study. This appeared to be due to the fact that in the 2-year study, rats with malignant bladder tumors usually did not have any remaining uninvolved epithelium to evaluate for the presence or absence of hyperplasia. The latter suggested that urinary bladder hyperplasia may be a precursor of bladder tumors.

The liver was not a particularly sensitive target for some of the phosphate ester flame retardants discussed in this document; in some cases the effects were limited to changes in organ weight. TCEP induced increases in liver weight without histological alterations in rats dosed with up to 350 mg TCEP/kg/day for 16 weeks. Extending the treatment for 2 years with doses of up to 88 mg TCEP/kg/day also resulted in only increases in organ weight. Similar findings were reported in rats dosed with TnBP in acute- and intermediate-duration studies and in intermediate- and chronic-duration studies in mice. TDCP induced histological alterations in the liver of rats (80 mg TDCP/kg/day) in a 2-year study and the same was reported in rats dosed with TBEP (173 mg/kg/day) for 18 weeks. In the single study available with TiBP, rats treated with up to 404 mg TiBP/kg/day for 13 weeks did not show gross or microscopic alterations in the liver. The liver was a sensitive target for TCP in male mice following chronic exposure. Exposure for 2 years, but not at interim kills, resulted in significant increased incidences of clear cell focus, fatty change, and ceroid pigmentation in males dosed with 13 mg TCP/kg/day; the no-observed-adverse-effect level (NOAEL) was 7 mg TCP/kg/day. No such effects were seen in female mice or in rats.

The adrenal cortex was a target for TCP in rats and mice. TCP induced cytoplasmic vacuolization of the adrenal cortex in all treated male and female rats in 13-week gavage and dietary studies. No NOAELs were identified in these studies; the lowest lowest-observed-adverse-effect levels (LOAELs) were in the 50–65 mg TCP/kg/day range. Similar findings were reported in the 13-week studies in mice: LOAELs also ranged from 50 to 65 mg TCP/kg/day. The severity of the lesion was generally dose-related and also exposure duration-related as shown in time-course studies. The 2-year study with three interim evaluations and a stop-exposure group showed that female rats are more sensitive than males and that the lesion in rats is reversible, since a group treated with a high dose for 22 weeks did not exhibit adrenal cortex lesions when evaluated on week 36. Almost all mice exposed for ≥9 months showed ceroid pigmentation in the adrenal cortex; this also occurred in controls. At the 3-month interim kill, only high-dose male mice (27 mg TCP/kg/day) had a significant increased incidence of the ceroid pigmentation. This suggests that in mice, the adrenal cortex lesion is a spontaneous lesion whose onset is accelerated by exposure to TCP. Studies conducted in rats suggested that the adrenocortical lipidosis induced by TCP might be caused by the inhibition of neutral cholesteryl ester hydrolase (nCEH), an enzyme that catalyzes the conversion of stored cholesteryl ester to free cholesterol, while acylcoenzyme A: cholesterol acyl transferase (ACAT), which is involved in the esterification of cholesterol, remained near normal levels.

Standard toxicity studies for several of the phosphate esters covered in this profile did not report morphological alterations in the reproductive organs of rats and mice. One exception was TCP. TCEP, TnBP, TPP, TDCP, and TCP were also tested for effects on fertility. TCEP in doses ≥350 mg/kg/day significantly reduced fertility in mice in a continuous breeding protocol study. Cross-mating experiments conducted to determine the affected sex showed that both sexes were adversely affected, but the males were relatively more sensitive, as all sperm end points examined (concentration, motility, and percent abnormal) were affected. In a 2-generation reproductive toxicity study in rats dosed with 217 mg TnBP/kg/day, there were no significant reproductive effects in either the F_0 or F_1 generations, including mating and fertility, and gross and microscopic appearance of the reproductive organs. TDCP was tested for its effects on fertility in male rabbits by dosing the rabbits with up to 200 mg TDCP/kg/day by gavage for 12 weeks and then mating the males with untreated females. Fertility was not affected and examination of sperm from the cauda epididymides for motility, morphology, and concentration did not show significant alterations. Fertility indices (number pregnant, corpora lutea, implantations, implantation efficiency, resorptions) were not affected in male or female rats dosed with up to 690 mg TPP/kg/day for 91 days before mating. TCP affected reproductive parameters in male and female rats and mice. Female rats were affected at lower doses than male rats. In males, TCP induced morphological alterations in the testes and affected sperm. The lowest LOAEL for significantly increased percent

abnormal sperm was 100 mg TCP/kg/day. A study showed that reduced fertility resulting from mating treated male rats with treated female rats was due to an effect of TCP on the males. In females, TCP affected the ovaries at relatively doses in intermediate- and chronic-duration studies; rats were more considerably more sensitive than mice. The lesion was characterized by hypertrophy and lipidosis in interstitial ovarian cells, which were likely due to inhibition of neutral cholesteryl ester hydrolase, a cytosolic enzyme that catalizes the conversion of stored cholesteryl ester to free cholesterol. As noted in the discussion of adrenal effects of TCP, the lesion in the ovaries also appeared to be reversible. The lowest LOAEL was 7 mg TCP/kg/day in female rats evaluated after 3 months of treatment in the NTP study; the NOAEL was 4 mg TCP/kg/day.

Studies in which animals have been exposed to various phosphate ester flame retardants only during pregnancy suggest that developmental end points are not particularly sensitive to these substances. Doses of TCEP that produced maternal toxicity in rats and mice did not affect fetal parameters. However, in a continuous breeding protocol study in mice, the lowest dose tested (175 mg TCEP/kg/day) significantly decreased the number of live male F_2 pups per litter. Studies conducted with TnBP also showed lack of developmental toxicity for this chemical even in the presence of frank maternal toxicity. However, in a 2-generation reproductive study in mice, exposure to TnBP produced a significant reduction in F_1 and F_2 pup weight per litter during postnatal days 0–21. Significant reductions in maternal body weight also occurred at this level, which may have contributed to the decrease in pup weight. Studies in rats exposed to TBEP or TDCP during pregnancy also reported no developmental effects at dose levels that significantly reduced weight gain in the dams. TPP was not a developmental toxicant in a study in which both male and female rats were dosed for 91 days before mating, and females continued being treated through gestation. A gestational exposure study with TCPP in rats also reported no significant developmental toxicity under the conditions of the study. Studies in which male and female rats were exposed to ≥200 mg TCP/kg/day showed decreased postnatal viability and reduced number of live pups per litter. In a continuous breeding study in mice, doses of approximately 124 mg TCP/kg/day resulted in a significant increase in the number of dead pups per litter at the fourth and fifth litter; the NOAEL was approximately 62.5 mg TCP/kg/day. There was no overt maternal toxicity in the TCP studies.

Very limited information is available regarding the effects of the phosphate esters covered in this profile on the immune system. Gross and microscopic examinations of the thymus, spleen, and lymph nodes conducted in many of the toxicity studies available did not reveal significant treatment-related alterations. Parameters of immunocompetence were evaluated in rats dosed with up to 711 mg TPP/kg/day for 120 days. The only effects noted were increases in the levels of α- and β-globulins at 6 months, which

suggested increased hepatic activity. Assessment of the humoral response to the T-lymphocyte-dependent antigen sheep red blood cell (SRBC) did not indicate alterations in immunocompetence due to treatment with TPP. A single study with TCP in rats reported that repeated doses ≥6 mg TCP/kg/day significantly reduced the antibody titers to tetanus toxoid and the cell-mediated immune response.

TCEP, TnBP, TDCP, and TCP have been tested for carcinogenicity in long-term oral bioassays. Doses of 88 mg TCEP/kg/day significantly increased the incidence of renal tubule adenoma or carcinoma in male Fischer-344 rats and renal tubule adenomas in female Fischer-344 rats. Based on these findings, NTP concluded that there was clear evidence of carcinogenic activity for male and female Fischer-344/N rats. TCEP (350 mg/kg/day) also induced a nonsignificant increase in the incidence of a rare renal tubule neoplasm in male $B6C3F_1$ mice, which led NTP to conclude that there was equivocal evidence of carcinogenic activity for male mice. TCEP increased, although not significantly, the incidence of tumors of the Harderian gland in female $B6C3F_1$ mice; based on this, NTP concluded that there was equivocal evidence of carcinogenic activity for female mice. In a dietary study in ddY mice, TCEP increased the incidences of renal (1,333 mg/kg/day) and liver (267 mg/kg/day) tumors in male mice and forestomach tumors (1,333 mg/kg/day) and leukemia (267 mg/kg/day) in female mice. In dermal assays, TCEP showed no significant carcinogenic, initiating, or promoting activity on the skin of female Swiss mice. IARC evaluated TCEP and concluded that the chemical is not classifiable as to its carcinogenicity to humans. Bioassays conducted for TCP in F344/N rats and $B6C3F_1$ mice showed no chemical-related increased incidences of neoplasms in either species. Rats and mice received doses of up to 15 and 37 mg TCP/kg/day, respectively, via the food.

TnBP significantly increased the incidence of combined papillomas, squamous cell carcinomas, and transitional cell carcinomas in the urinary bladder of male Sprague-Dawley rats at 143 mg/kg/day and of hepatocellular adenomas in male CD-1 mice at 585 mg/kg/day. TDCP significantly increased the incidence of neoplastic nodules in the liver of male and female Sprague-Dawley rats and the incidence of hepatocellular carcinomas in male rats dosed with 20 mg/kg/day. Doses of ≥20 mg TDCP/kg/day also increased the incidence of renal cortical tumors in male and female rats and interstitial cell tumors in the testes in males; the incidence of adrenocortical adenomas was also significantly increased in females dosed with 80 mg TDCP/kg/day.

The EPA has not evaluated the carcinogenicity of the phosphate ester flame retardants discussed in this profile.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for phosphate ester flame retardants. 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

Although some human data were available in two reports of occupational exposure to TDCP (Stauffer Chemical Co. 1983), a report of occupational exposure to TPP (Sutton et al. 1960), and two reports of occupational exposure to TCP (FMC 1981a, 1982a), the data were inadequate for derivation of inhalation MRLs.

Stauffer Chemical Co. (1983) conducted a retrospective cohort study to examine the mortality experience of 289 workers employed in the manufacture of TDCP. Exposure levels were <8 ppb. The overall mortality of the cohort was 75% of that expected in a comparable population of U.S. males. There were three deaths attributed to lung cancer, which was higher than the 0.8 expected. However, one case was found to have not been exposed to TDCP, a second case worked only 2 years before onset of the disease, and all three cases were cigarette smokers. The investigators concluded that there was insufficient evidence to establish a causal relationship between lung cancer and TDCP. ATSDR does not derive MRLs based on death or cancer; therefore, even if the exposure concentration of 8 ppb had been

considered a reliable NOAEL, an inhalation MRL based on this limited survey would have not been derived.

Stauffer Chem Co. (1983) also conducted a morbidity survey to identify adverse health effects among workers occupationally exposed to TDCP. The survey was based on an analysis of the physical examination reports of 93 exposed and 31 non-exposed workers examined in 1981 and found no apparent medical conditions related to exposure to TDCP. Time-weighted average breathing zone sampling conducted in 1978 and 1979 showed that the concentration in the process area or in other areas was ≤7–8 ppb (0.4–0.5 μg/m^3). The evaluation included tests for respiratory and cardiovascular functions, urinalyses and evaluation of hematology and clinical chemistry parameters. Limitations of the survey noted by the investigators included the fact that the number of non-exposed workers was only one third that of the exposed workers. Secondly, since payroll records were unavailable prior to 1975, some workers classified as non-exposed could have been exposed prior to 1975. Thirdly, since a higher percentage of exposed workers were employed before 1975 than non-exposed, and some of the exposed workers could have had potentially a long duration of exposure, the maximum effect of any harmful exposure should be observed among the exposed workers. These limitations, plus the lack of control for confounding, render the study inadequate for MRL derivation.

Sutton et al. (1960) reported that red blood cell cholinesterase activity was significantly reduced (18%) in a small group (n=6) of regular operators in a TPP production plant compared to unexposed subjects. They also noted that the variability both within and between individuals was great enough so that the small depressions in cholinesterase activity were not sufficient to identify individuals with TPP exposure. Health evaluations of this group and of others (the total number of workers examined was not specified) conducted over the years did not reveal any unusual frequency of symptoms, or physical or laboratory findings as compared to unexposed groups. Sutton et al. (1960) estimated that workers may have been exposed to a weighted average concentration of TPP vapor mist and dust of 3.5 mg/m^3. The lack of information regarding the total number of workers that participated in the health surveys, lack of detailed presentation of the results of the surveys, and uncertainty regarding the estimation of exposure levels make this report unsuitable for MRL derivation.

FMC (1981a, 1982a) conducted two studies on subjects who worked at a plant that manufactured phosphate esters in Nitro, West Virginia. One study (FMC 1981a) conducted neurological examinations of 113 participants; 60 of these participants had current or previous exposure to aryl phosphates (triaryl and other aryl phosphates). There was also exposure to alkyl phosphates including tributyl phosphate and

other organics. Exposure data were available from 1974 through 1981 from personal and general area samples. Prior to 1974, the aryl phosphate process was an open-batch process and significant exposure may have occurred. The results of the neurological examinations did not reveal significant differences between exposed and nonexposed subjects. FMC also conducted a mortality study among workers in the Nitro plant (FMC 1982a); a total of 737 individuals were studied. Workers were indentified in terms of the type of job performed and the products or processes with which they had direct contact. Twenty-one subjects were identified with Kronitex® (unidentified composition, but assumed to be mostly triaryl phosphates). The results of the analyses showed that the survival of employees of the Nitro plant compared favorable with the total employee group of FMC, with the U.S. population, and with the Charleston Standard Metropolitan Statistical Area. Since no adverse health effects were identified, these reports are inadequate for MRL derivation.

Toxicity information from animal studies available in the literature reviewed was limited to acute high-dose experiments aimed primarily at determining lethal concentrations, and is therefore inadequate for MRL derivation.

Oral MRLs

No reliable studies were located on health effects in humans exposed orally to the phosphate ester flame retardants discussed in this profile. Therefore, the discussion of derivation of MRLs for these compounds is based purely on results from animal studies. As previously mentioned, the information available from oral studies does not support treating these chemicals as a class for purposes of risk assessment based on the different toxicities exhibited by each one of them.

TCEP. An acute-duration oral MRL for TCEP was not derived due to inadequacies of the database. The few studies available did not identify a target for TCEP toxicity. The LOAEL in the studies available was 200 mg TCEP/kg/day for death of 7/30 pregnant Wistar rats (0/23 in the control group) in a developmental study in which the rats were exposed to TCEP by gavage on gestational days (Gd) 7–15 (Kawashima et al. 1983a). That dose level, however, did not produce developmental effects, including neurobehavioral evaluations in the pups. Other information available include LD_{50} data (Eldefrawi et al. 1977; Smyth et al. 1951), data from a developmental study of CD-1 mice in which the single dose level tested on Gd 6–13, 940 mg TCEP/kg/day, significantly reduced weight gain in the dams between Gd 6 and postnatal day (Pnd) 3, but produced no developmental effects in the progeny (Hardin et al. 1987), and a dose-range-finding study in which CD-1 mice treated by gavage with doses of up to

1,000 mg TCEP/kg/day for 14 days did not show clinical signs or significant alterations in body weight or water consumption (NTP 1991b). Adverse neurological effects were reported in two studies. Female Fischer-344 rats administered a single gavage dose of 275 mg TCEP/kg (only dose level tested) suffered seizures within 60–90 minutes of dosing (Tilson et al. 1990). This treatment resulted in mild impairment in the acquisition of a reference memory task in a water maze, and in performing a repeated acquisition task in a water maze. In a 16-day gavage study, B6C3F$_1$ mice given 350 or 700 mg TCEP/kg/day exhibited ataxia and convulsive movements during the first 3 days of dosing (NTP 1991a). These studies do not identify a clear target for TCEP, and the studies that provide information other than lethal doses are unsuitable for dose-response assessments.

- An MRL of 0.6 mg/kg/day was derived for intermediate-duration oral exposure (15–364 days) to TCEP based on necrosis of hippocampal neurons in female rats.

Although a limited number of intermediate-duration oral studies with TCEP were available for review, the data were sufficient for derivation of an intermediate-duration oral MRL. NTP (1991a) conducted studies in rats and mice administered TCEP by gavage 5 days/week for 16 days or 16 weeks, Anonymous (1977) conducted a 3-month dietary study in rats, and NTP (1991b) conducted a reproductive study in mice using a continuous breeding protocol; dosing was by daily gavage. The hippocampus from female rats was a target for TCEP toxicity in the 16-week gavage study in rats (NTP 1991a). Necrosis of neurons of the hippocampus was seen in 10/10 females and in 2/10 males treated with TCEP at 350 mg/kg/day and in 8/10 females treated with 175 mg/kg/day; no lesions were seen at ≤88 mg/kg/day. The affected neurons were mainly in the dorsomedial portion of the pyramidal row of the hippocampus. The more severe lesions showed mineral deposits in the affected areas. Females dosed with 350 mg/kg/day also showed neuronal necrosis in the thalamus. No brain lesions were seen in mice treated with up to 700 mg TCEP/kg/day for 16 weeks. It is worth noting that the unpublished 3-month dietary study in male and female rats administered up to 506 and 586 mg TCEP/kg/day, respectively, does not mention the occurrence of brain lesions, but it is unclear in the report available whether the brain was examined microscopically (Anonymous 1977).

In the NTP (1991a) study, treatment of rats and mice with TCEP also produced dose-related increases in absolute and relative liver and kidney weight in female rats dosed by gavage for 16 days or 16 weeks, in both cases without histological alterations; changes >10% relative to controls were generally achieved in the highest-dose groups. Mice dosed by gavage with 700 mg TCEP/kg/day for 16 weeks showed enlargement of the nuclei of epithelial cells in the renal tubules. In the absence of histopathology, the weight changes in the liver and kidneys from rats in the intermediate-duration studies could be considered

not adverse; however, results from a chronic-duration study suggest that in the kidneys, but not the liver, a progression into more severe effects takes place. Based on the latter observation, the increase in absolute kidney weight in rats in the 16-week gavage studies is considered a minimal LOAEL (175 mg/kg/day); the corresponding NOAEL is 88 mg/kg/day.

In the reproductive study using a continuous breeding protocol, mice were dosed by gavage with 0, 175, 350, or 700 mg TCEP/kg/day (NTP 1991b). Treatment with ≥350 mg TCEP/kg/day significantly decreased the number of F_1 litters produced by the parental generation. Only 2 out of 18 pairs delivered a third litter in the high-dose group versus 37/38 in the controls, and 13 out of 18 pairs delivered a fifth litter in the mid-dose group. Treatment with TCEP also induced significant and dose-related reductions in the number of live pups per litter at ≥350 mg TCEP/kg/day and in the number of live F_2 male pups/litter at ≥175 mg TCEP/kg/day (dose-related). Based on the effect on F_2 pups, a serious developmental LOAEL of 175 mg TCEP/kg/day was identified in this study; a developmental NOAEL was not defined.

Data sets for necrosis of hippocampal neurons and changes in absolute kidney weight in female rats reported in the NTP (1991a) study and decreased number of live F_2 pups reported in the NTP (1991b) study were analyzed using the benchmark dose (BMD) approach to determine the point of departure for MRL derivation. Models in the EPA Benchmark Software (BMDS version 2.1) were fit to the three data sets. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all of the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in kidney weight and number of male live pups, in the absence of a clear criteria as to what level of change in body/organ weight or body weight gain should be considered adverse, the BMR is defined as a change in weight or weight gain equal to 1 standard deviation (SD) from the control mean (EPA 2000). Using a BMR of 10%, the incidence data for necrosis in hippocampal neurons in female rats (NTP 1991a) were fit to the available BMD models. The data set for changes in absolute kidney weight in female rats in the NTP (1991a) proved not suitable for benchmark modeling even after dropping the two highest doses (out of five dose levels tested). Of the two data sets remaining, the best fit for the incidence of necrosis in hippocampal neurons in female rats (NTP 1991a) was obtained with the log-logistic model (BMD_{10} 143.41 mg/kg/day; $BMDL_{10}$

85.07 mg/kg/day), whereas the linear model provided the best fit for the decrease in live male F_2 pups in the continuous breeding protocol study (BMD_{10} 242.19 mg/kg/day; $BMDL_{10}$ 167.83 mg/kg/day) (NTP 1991b). Multiplying the $BMDL_{10}$ of 85.07 mg/kg/day by 5 days/7 days, to adjust for continuous exposure, results in a duration-adjusted $BMDL_{10}$ of 60.76 mg/kg/day. The lower $BMDL_{10}$ of 60.76 mg/kg/day is more health protective and was selected as the point of departure for MRL derivation. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the duration-adjusted $BMDL_{10}$ of 60.76 mg/kg/day results in an intermediate-duration oral MRL of 0.6 mg/kg/day for TCEP. A detailed description of the NTP (1991a) study and of the MRL derivation is presented in Appendix A.

If the changes in absolute kidney weight in female rats in the NTP (1991a) study had been used as a basis for MRL derivation using a NOAEL/LOAEL approach, the NOAEL would have been 88 mg TCEP/kg/day (<10% increase in kidney weight). The next highest dose, 175 mg/kg/day, induced a 16% increase in absolute kidney weight. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the duration-adjusted NOAEL of 62.85 mg/kg/day (88 mg/kg/day x 5 days/7 days) would have resulted in an MRL of 0.6 mg/kg/day for TCEP, which is identical to the MRL based on brain lesions in female rats derived using the BMD approach.

- An MRL of 0.2 mg/kg/day was been derived for chronic-duration oral exposure (365 days and longer) to TCEP based on renal tubule lesions in female rats.

The chronic-duration database for TCEP was limited to the NTP (1991a) 2-year bioassay in rats and mice. Fischer-344 rats were treated by gavage 5 days/week with 0, 44, or 88 mg TCEP/kg/day and $B6C3F_1$ mice were dosed similarly with 0, 175, or 350 mg TCEP/kg/day. Animals were monitored for clinical signs, body weight gain, hematology and clinical chemistry parameters (week 66 and at termination), and gross and microscopic changes in tissues and organs at week 66 and at termination. Nonneoplastic effects in mice were limited to an increased incidence of karyomegaly of the cells in the proximal convoluted tubules of the inner cortex and outer stripe of the outer medulla at ≥175 mg TCEP/kg/day. In rats, one of the principal nonneoplastic alterations attributed to administration of the test chemical was a significant increase in renal tubule epithelial hyperplasia in the convoluted tubules of the cortex in high-dose males and females; the respective incidences were 0/50, 2/50, and 24/50, and 0/50, 3/50, and 16/50. In addition to the kidney lesions, high-dose female rats showed degenerative lesions in the brain. The degenerative lesions were located in the cerebral cortex and brain stem, involved both the gray and white matter, and were focally distributed. Specifically, the lesions were in the thalamus, hypothalamus, basal ganglia, and frontal and parietal cortex. Other affected structures included the cingulate cortex, olfactory cortex,

superior colliculus, hippocampus, geniculate body, globus pallidus, ventral pallidum, and amygdaloid nuclear region. The lesions varied in severity from minimal to marked, and often involved extensive areas. Active lesions were characterized by degeneration and necrosis with hemorrhage, while resolving lesions exhibited loss of neurons and neuropil, proliferation of glial cells, capillary hyperplasia, hypertrophy of the tunica media of small vessels, and hemosiderin-laden macrophages. Brain lesions were already observed at the 66-month interim kill. Incidences of lesions in specific areas ranged from 24 to 38%. However, the reporting of the data (no individual animal data) in the NTP (1991a) study did not allow the determination of whether individual animals had more than one lesion type. The lesion with the highest incidence was cerebrum gliosis with an incidence of 19/50 (38%); the incidences in the control and low-dose groups were 0/50 and 0/49, respectively.

The incidences of cerebrum gliosis in female rats and of renal epithelial hyperplasia in both male and female rats reported in the NTP (1991a) study were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1) were fit to the three data sets. The best fit for the incidence of renal tubule hyperplasia in male rats was obtained with the LogLogistic model, which identified a BMD_{10} and $BMDL_{10}$ of 54.80 and 43.58 mg TCEP/kg/day, respectively. The Multistage (2-degree) model provided the best fit for the incidence of renal lesions in female rats; BMD_{10} and $BMDL_{10}$ values of 48.00 and 32.82 mg TCEP/kg/day, respectively, were identified. The data set for incidences of cerebrum gliosis in female rats was best fitted with the LogLogistic model, which defined a BMD_{10} and $BMDL_{10}$ of 80.04 and 59.86 mg TCEP/kg/day, respectively. The $BMDL_{10}$ of 32.82 mg TCEP/kg/day for renal tubular lesions in female rats is selected as the point of departure for MRL derivation on the basis of being more health protective. The slightly higher $BMDL_{10}$ obtained with the male rat data set does not seem to indicate that female rats are more sensitive than males. Multiplying the $BMDL_{10}$ of 32.82 mg/kg/day by 5/7, to adjust for continuous exposure, results in a duration-adjusted $BMDL_{10}$ of 23.44 mg/kg/day. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the duration-adjusted $BMDL_{10}$ of 23.44 mg/kg/day yields a chronic-duration oral MRL of 0.2 mg/kg/day for TCEP. A detailed description of the NTP (1991a) study and of the MRL derivation can be found in Appendix A.

TnBP

- An MRL of 1.1 mg/kg/day was derived for acute-duration oral exposure (14 days or less) to TnBP based on reduced body weight gain in pregnant rats.

Few acute-duration oral studies were available for review. One study conducted hematological and clinical chemistry tests and histological examinations of the brain, heart, kidneys, liver, lungs, spleen, ovaries, and testes from Sprague-Dawley rats following a 14-day gavage regime with 0, 137, or 411 mg TnBP/kg/day (Laham et al. 1984b). Significant findings in high-dose rats included decreased hemoglobin in females, increased absolute and relative liver weight in males and females, increased serum potassium in females, decreased absolute and relative spleen weight, and degenerative changes in the testes. Decreased nerve conduction velocity accompanied by morphological alterations in the sciatic nerve was also reported in Sprague-Dawley rats dosed with 411 mg TnBP/kg/day for 14 days; the NOAEL was 274 mg TnBP/kg/day (Laham et al. 1983). In a developmental study, pregnant Wistar rats were exposed to 0, 62.5, 125, 250, or 500 mg TnBP/kg/day on Gd 7–17 and were euthanized on Gd 20 (Noda et al. 1994). Rats exposed to 500 mg/kg/day showed piloerection, wetting of abdominal hair with urine, and salivation during the treatment, but these signs disappeared after the last treatment. Final maternal weight was reduced 6–9% in the two highest dose groups. Adjusted body weight gain (body weight gain minus gravid uterus weight) from Gd 0 to 20 was reduced 2.2% at 62.5 mg/kg/day, 13% at 125 mg/kg/day, 39% at 250 mg/kg/day, and 63% at 500 mg/kg/day. Food consumption was also reduced starting on Gd 7. Liver weight was increased 6% at 500 mg/kg/day and kidney weight was not significantly affected. Spleen weight was reduced 11% at 500 mg/kg/day. Gravid uterus weight was not affected. All pregnant rats had living fetuses on Gd 20. There was no significant difference between the groups in the number of corpora lutea, implants or living fetuses, incidence of dead or resorbed fetuses, sex ratio, or body weight of the living fetuses. There was only one malformation that occurred in the groups exposed to 125 mg/kg/day in which there were conjoined twins. No visceral anomalies attributed to treatment with TnBP were reported. Based on a significant reduction in maternal body weight gain at ≥125 mg/kg/day, a maternal NOAEL and LOAEL of 62.5 and 125 mg/kg/day, respectively, were defined in this study; the highest dose tested, 500 mg/kg/day, was a developmental NOAEL. Since the Noda et al. (1994) study identified the most sensitive end point, it was selected as the principal study for the derivation of an acute-duration oral MRL for TnBP.

Data from Noda et al. (1994) were analyzed using the BMD approach for MRL derivation. BMD models in the EPA BMDS (version 2.1) (linear, polynomial, power, and Hill models) were fit to the maternal body weight gain data to determine potential points of departure for the MRL (details of the modeling are presented in Appendix A). In the absence of a clear criteria as to what level of change in weight gain during pregnancy should be considered adverse, the BMR was defined as a change in mean body weight gain equal to 1 SD from the control mean (EPA 2000). The Linear model provided the best fit. The corresponding BMD_{1SD} was 130.32 mg/kg/day; the corresponding $BMDL_{1SD}$ was 111.47 mg/kg/day.

Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{1SD}$ results in an acute-duration oral MRL of 1.1 mg/kg/day for TnBP.

- An MRL of 0.08 mg/kg/day was derived for intermediate-duration oral exposure (15–364 days) to TnBP based on urinary bladder lesions in male rats.

Intermediate-duration oral studies with TnBP identified the urinary bladder as the most sensitive target for TnBP toxicity. Increased incidence of urothelial hyperplasia was reported in male Sprague-Dawley rats (females not tested) dosed via the diet with approximately 33 mg TnBP/kg/day for 10 weeks (Arnold et al. 1997), male Sprague-Dawley rats dosed with 68.1 mg TnBP/kg/day in the diet for 90 days (FMC 1985a), and in male and female F_0 and F_1 Sprague-Dawley rats dosed with 51 mg TnBP/kg/day in the diet for 10 weeks in a 2-generation reproductive study (Tyl et al. 1997). The NOAELs were in the range of 9–15 mg TnBP/kg/day. An additional study that also reported urothelial hyperplasia in rats used somewhat higher doses (200, or 333 mg/kg/day for 18 weeks) (Laham et al. 1985a). Mice appeared to be less sensitive than rats as evidenced by a NOAEL and LOAEL of 95 and 382 mg/kg/day, respectively, for urinary bladder hyperplasia in male mice (Auletta 1991). Arnold et al. (1997) also demonstrated that hyperplastic effects were reversible upon cessation of treatment and that acidification of the urine with ammonium chloride did not completely inhibit the proliferative changes, but the hyperplastic changes were milder when TnBP was coadministered with ammonium chloride. Also consistently reported in intermediate-duration oral studies with TnBP were increases in liver weight, generally with histological alterations observed only at the highest dose levels (FMC 1985a; Laham et al. 1985a; Oishi et al. 1982; Tyl et al. 1997). In a 2-generation reproductive study in rats dosed through the diet with up to 217 mg TnBP/kg/day, fertility indices were not significantly affected, but that dose level significantly decreased F_1 and F_2 pup weight during the preweaning periods (Tyl et al. 1997). In a 13-week gavage study, excessive salivation occurred frequently in rats after dosing with 100 mg TnBP/kg/day, and almost all the time in rats dosed with 325 mg TnBP/kg/day (Healy et al. 1995). In that study, neither motor activity nor functional observational battery (FOB) results obtained during the study were affected by treatment with up to 325 mg TnBP/kg/day. In addition, histological evaluations of unspecified nervous tissues were unremarkable (Healy et al. 1995).

As indicated above, urothelial hyperplasia was the most sensitive end point in the intermediate-duration studies with TnBP and will serve as the basis for the derivation of an intermediate-duration oral MRL for TnBP. Of the four studies that described the lesion in rats, only the studies by Arnold et al. (1997), FMC (1985a), and Tyl et al. (1997) are considered for further analysis on the basis that they identified a NOAEL; the lowest dose used by Laham et al. (1985a) induced hyperplasia in 100% of the rats. The data

are summarized in Table 2-1, which also includes the data set from the 2-year study of Auletta et al. (1998a). The data set from Tyl et al. (1997) corresponds to incidences in the parental generation (F_0).

Incidences in F_1 females were virtually the same as in F_0 females, whereas incidences in mid-dose F_1 males were slightly lower than in F_0 males.

Incidence data for urothelial hyperplasia in male rats from the Arnold et al. (1997) study, urothelial hyperplasia in F_0 males and females from the Tyl et al. (1997) study, and urothelial hyperplasia in male rats from the FMC (1985a) study were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1) were fit to urothelial hyperplasia data to determine potential points of departure for the MRL. For the Arnold et al. (1997) data set, the range of $BMDL_{10}$ values for adequately fitting models (by the chi-square goodness of fit measure) varied by >3-fold, but much of this variation was due to the relatively poor fit of the 1- and 2-degree multistage models. The range of $BMDL_{10}$ values from the remaining models was < 3-fold and the model with the lowest AIC (Gamma) was selected as the best fitting model, predicting BMD_{10} and $BMDL_{10}$ values of 19.74 and 8.03 mg/kg/day, respectively. For the urinary hyperplasia data in F_0 males in the Tyl et al. (1997) study, the best fitting model predicted BMD_{10} and $BMDL_{10}$ values of 21.43 and 13.03 mg TnBP/kg/day, respectively; the predicted values for F_0 female rats were 15.42 and 9.12 mg TnBP/kg/day, respectively. For the FMC (1985a) data set, the range of $BMDL_{10}$ values for adequately fitting models (by the chi-square goodness of fit measure) varied by >3-fold, but much of this variation was due to the relatively poor fit of the 1-degree multistage model. The range of $BMDL_{10}$ values from the remaining models was <2-fold and the model with the lowest AIC (Weibull) was selected as the best fitting model, predicting BMD_{10} and $BMDL_{10}$ values of 49.87 and 12.61 mg/kg/day, respectively. Comparing across the four intermediate-duration data sets, the lowest $BMDL_{10}$ of 8.03 mg/kg/day for urinary bladder hyperplasia (Arnold et al. 1997) is selected as the point of departure for the MRL. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ yields an intermediate-duration oral MRL of 0.08 mg/kg/day for TnBP. Details of the modeling are presented in Appendix A.

- The intermediate-duration oral MRL of 0.08 mg/kg/day for TnBP was adopted as chronic-duration (365 days or more) oral MRL for TnBP.

Only two chronic-duration oral studies were located for TnBP, one in Sprague-Dawley rats (Auletta et al. 1998a) and one in CD-1mice (Auletta et al. 1998b). As in the intermediate-duration studies, the urinary bladder from rats was the most sensitive target for TnBP toxicity. Rats were dosed via the diet for 2 years, whereas mice were treated for 18 months. Male rats received doses of 0, 9, 33, or 143 mg

Table 2-1. Incidence of Urinary Bladder Hyperplasia Induced by TnBP in Four Studies in Rats

				NOAEL	LOAEL		$BMDL_{10}$
Arnold et al. (1997)–10 weeks							
Dose (mg/kg/day)	0			9	33	143	
Incidence	0/10			0/10	8/10	10/10	**8.03**
FMC (1985a)–13 weeks							
Dose (mg/kg/day)	0.12	0.6	2.8	13.8	68.1	360	
Males	0/10	0/10	0/10	0/10	10/10	10/10	13.13
Tyl et al. (1997)–10 weeks							
Dose (mg/kg/day)	0			15	51	217	
Males	0/30			1/29	22/29	30/30	13.03
Females	0/30			2/29	21/30	30/30	12.61
Auletta et al. (1998a)–2 years							
Dose (mg/kg/day)	0			9	33	143	
Males	3/50			3/50	12/49	17/49	23.51
Females	1/50			1/50	5/49	29/49	53.59

$BMDL_{10}$ = The 95% lower confidence limit on the dose associated with a 10% extra risk; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

TnBP/kg/day, whereas females received doses of 0, 12, 42, or 182 mg TnBP/kg/day. The doses for male and female mice were 0, 28.9, 169, or 585 mg/kg/day and 0, 24.1, 206, or 711 mg/kg/day, respectively. At termination, the incidences of trace to severe urinary bladder hyperplasia in male rats were 3/50, 3/50, 12/49, and 17/49 with increasing doses. The corresponding incidences in female rats were 1/50, 1/50, 5/49, and 29/49. Urinary bladder hyperplasia was not observed in mice. Based on these findings, the increased incidence of urothelial hyperplasia in rats was used to determine the point of departure for derivation of a chronic-duration oral MRL for TnBP.

Incidence data for urinary bladder hyperplasia in male and female rats exposed to TnBP for 2 years (Auletta et al. 1998a) were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1) were fit to the urinary bladder lesion data to determine potential points of departure for the MRL. For the male data, the best fitting model (1-degree multistage) predicted BMD_{10} and $BMDL_{10}$ values of 35.41 and 23.51 mg/kg/day. For the female data, $BMDL_{10}$ values from models with adequate fit (by chi-square fit statistic) ranged close to 3-fold, but when the poor-fitting 1-degree form of the multistage model was ignored (the 2-degree form provided a much better fit), the range was about 2-fold. Thus the model with the lowest AIC (Probit) was selected as the best fitting model for the female data, predicting a $BMDL_{10}$ of 53.59 mg/kg/day. The $BMDL_{10}$ values for urinary bladder hyperplasia in chronically exposed male and female rats are higher than the $BMDL_{10}$ values for urinary bladder hyperplasia in the intermediate-duration studies (Arnold et al. 1997; Tyl et al. 1997). A likely explanation for this phenomenon is provided in the chronic study by the observation that rats with malignant bladder tumors usually did not have any remaining uninvolved epithelium to evaluate for the presence or absence of hyperplasia (Auletta et al. 1998a). Whether urinary bladder hyperplasia is a potential precursor of urinary bladder tumors is not known for certain, but the data are suggestive. The lower incidence of hyperplasia at the higher doses in the chronic-duration study may just be the result of the hyperplasia transforming into neoplasia. As shown in Table 10, dose levels that did not increase the incidence of urothelial hyperplasia in the intermediate-duration studies (NOAELs ranged from 9 to 15 mg/kg/day) also did not increase the incidence of urinary bladder hyperplasia in the chronic-duration study (NOAEL was 9 mg/kg/day) and did not increase the incidence of neoplastic lesions; thus, the $BMDL_{10}$ from intermediate-duration studies would be an adequately protective POD for the chronic MRL derivation. Therefore, the intermediate-duration oral MRL of 0.08 mg/kg/day based on a $BMDL_{10}$ of 8.03 mg/kg/day for urinary bladder hyperplasia is adopted also as chronic-duration oral MRL for TnBP.

TBEP

- An MRL of 4.8 mg/kg/day was derived for acute-duration oral exposure (14 days or less) to TBEP based on reduced body weight gain in pregnant rats.

Three acute-duration oral studies were located in the literature reviewed. In a gestational exposure study rats were administered 0, 250, 500, or 1,500 mg TBEP/kg/day on Gd 6–15 (Monsanto Co. 1985b). The highest dose tested induced overt toxicity in the dams, including wet haircoat matting or staining with urine, and brown material or blood on the face, neck, thorax, and/or anogenital area; this was observed in approximately half of the high-dose rats. Following dosing on Gd 6, two high-dose rats were ataxic, had reduced righting reflex, and/or were lethargic. Terminal body weight of high-dose dams (unadjusted for uterine content) was significantly reduced, but only by 6% relative to controls. In high-dose dams, weight gain was significantly reduced from Gd 6 on, and during treatment (Gd 6–15), weight gain was reduced 35%. Food consumption data were not provided. The maternal NOAEL in the study was 500 mg/kg/day and the developmental NOAEL was 1,500 mg/kg/day based on no evidence of fetotoxicity or teratogenicity. A single gavage dose study in Sprague-Dawley rats measured caudal nerve conduction velocity 3 weeks following exposure and also performed microscopic examination of the sciatic nerve (Laham et al. 1985b). During the week after dosing, females dosed with ≥1,750 mg/kg showed slight tremors and piloerection, whereas those treated with 3,200 mg/kg exhibited tremors and abnormal gait; males appeared to be somewhat less sensitive. Examination of the sciatic nerve showed nerve degeneration in females dosed with ≥2,000 mg/kg. The NOAEL for males and females was 3,200 and 1,500 mg/kg, respectively. In an additional acute-duration study, Sprague-Dawley rats (10/sex/dose) were treated with up to 100 mg TBEP/kg/day by gavage in corn oil for 14 days (Komsta et al. 1989). End points monitored included clinical signs, body weight, hematology and clinical chemistry at termination, organ weights (brain, heart, liver, kidneys, and spleen), microsomal liver enzyme activities, and gross and microscopic morphology of all major tissues and organs. The results did not show any significant differences between the treated and control groups for any of the parameters evaluated. However, because no adverse effects were reported, the Komsta et al. (1989) study is not a suitable basis for an MRL. The developmental study is a well-conducted study and the maternal changes in weight gain during the treatment period were used to determine the point of departure for MRL derivation.

Data from Monsanto Co. (1985b) were analyzed using the BMD approach for MRL derivation. BMD models in the EPA BMDS (version 2.1) (linear, polynomial, power, and Hill models) were fit to the maternal body weight gain data to determine potential points of departure for the MRL. The Multistage 3-degree polynomial model provided the best fit (details of the modeling are presented in Appendix A).

In the absence of a clear criteria as to what level of change in weight gain during pregnancy should be considered adverse, the BMR was defined as a change in mean body weight gain equal to 1 SD from the control mean (EPA 2000). The corresponding BMD_{1SD} was 824.97 mg/kg/day; the corresponding $BMDL_{1SD}$ was 477.25 mg/kg/day. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{1SD}$ results in an acute-duration oral MRL of 4.8 mg/kg/day for TBEP.

- An MRL of 0.09 mg/kg/day was derived for intermediate-duration oral exposure (15–365 days) to TBEP based on hepatocyte vacuolization in male rats.

Only one intermediate-duration oral study was located for TBEP. In that study, groups of Sprague-Dawley rats (20/sex/group) were fed a diet containing 0, 300, 3,000, or 10,000 ppm TBEP for approximately 18 weeks (Reyna and Thake 1987a). This corresponds to doses of approximately 0, 17.3, 173, or 578 mg/kg/day for males and 0, 21, 209, or 698 for females using food intake and body weight data from the study. End points monitored included clinical signs, body weight, food consumption, clinical chemistry and hematology (weeks 9 and 18), organ weights (brain, liver, kidneys, testes with epididymides), and gross and microscopic examination of all the major organs and tissues of controls and high-dose rats plus target tissues defined by the high-dose group and gross lesions from all necropsied animals. A detailed description of the study is provided in Appendix A. There were no treatment-related mortalities or adverse clinical signs throughout the study. Body weight was not significantly affected by treatment with the TBEP. Food consumption was lower in high-dose males and females and mid-dose males during the first week of the study, but was comparable to controls for the remainder of the study. The most sensitive organ was the liver. Absolute and relative liver weight was increased in high-dose males and females, but not significantly. Histopathology was restricted to the liver of males and consisted of increased incidence of periportal hepatocellular hypertrophy (0/10, 0/10, 3/10, 7/10 with increasing TBEP doses) and periportal vacuolization (1/10, 2/10, 6/10, 7/10). In the same study, although presented separately, the investigators measured tail nerve conduction velocity at the end of the treatment period (Reyna and Thake 1987b). Following these measurements, the sciatic, tibial, and plantar nerves were processed for light microscopy. A significant reduction in nerve conduction velocity was measured only in high-dose females. Since both the absolute and relative refractory periods were decreased (the opposite of what would be expected in the case of a reduction in conduction velocity), the effect was not seen in males, and morphology of the nerves was unremarkable, the decrease in conduction velocity in females appeared questionable.

Although the increased incidences of periportal hepatocyte hypertrophy and vacuolization may represent adaptive responses of the cell and not necessarily an adverse effect, the lack of chronic data makes it impossible to predict whether these changes may progress into more severe lesions under a longer exposure regime.

Incidence data for periportal hepatocyte hypertrophy and vacuolization in male rats exposed to TBEP (Reyna and Thake 1987a) were analyzed using the BMD approach for MRL derivation (further details of the modeling are presented in Appendix A). Models in the EPA BMDS (version 2.1) were fit to the hepatocyte hypertrophy and hepatocyte vacuolization reported in male rats to determine a point of departure for the MRL. For hepatocyte hypertrophy, the range of $BMDL_{10}$ values from adequately fitting models (by the chi-square statistic) was about 5-fold; thus the model predicting the lowest $BMDL_{10}$ value, 21.92 mg/kg/day, was selected. For hepatocyte vacuolization, the range of $BMDL_{10}$ values from adequately fitting models (by the chi-square statistic) was about 6-fold; thus, the model predicting the lowest $BMDL_{10}$ value, 8.88 mg/kg/day, was selected. The $BMDL_{10}$ value for hepatocyte vacuolization, 8.88 mg/kg-day, was selected as the point of departure. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ results in an intermediate-duration oral MRL of 0.09 mg/kg/day for TBEP. Details of the modeling are presented in Appendix A.

No chronic-duration oral studies with TBEP were located; therefore, a chronic-duration oral MRL was not derived for this compound.

TDCP. An acute-duration oral MRL was not derived for TDCP due to an insufficient database. Other than lethal dose studies, only one study, a developmental study in rats, was available for review for TDCP (Stauffer Chemical Co. 1981b). Pregnant rats were treated by gavage with 0, 25, 100, or 400 mg TDCP/kg/day on Gd 6–15 and were euthanized on Gd 19. Compound-related clinical signs were observed during treatment mainly in the high-dose group consisting of urine stains, hunched appearance, and salivation in almost all rats in this group, and alopecia in approximately half of the rats in the group. Final body weight of the high-dose group was significantly lower (16%) than in controls. During Gd 6–11, body weight gain of the mid-dose group was approximately 29% lower than controls and rats in the high-dose group lost weight. During the posttreatment days, weight gain was comparable among all groups. Food consumption during treatment days was significantly lower in the mid- and high-dose rats, but post-treatment values were comparable among groups. There was no significant effect on the numbers of corpora lutea or implantations. A statistically higher incidence of resorptions was found in high-dose rats, but the number per litter was not significantly affected. Fetal viability was significantly

decreased in high-dose rats. Mean fetal weight and length were significantly lower in high-dose rats. Decreased skeletal development (incomplete ossification of various bones) was noted in high-dose fetuses. This single study gives a very limited picture regarding the acute toxicity of TDCP since it provides virtually no information on maternal effects other than body weight changes. Acute-duration oral MRLs were derived for TnBP and TBEP based on effects on maternal body weight in gestational exposure studies (Monsanto Co. 1985b; Noda et al. 1994), but in both cases, there was additional information regarding the chemical from studies that evaluated gross and microscopic morphology of a number of organs and tissues and conducted hematological and clinical chemistry tests (Komsta et al. 1989; Laham et al. 1984b).

- An MRL of 0.05 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to TDCP based on increased absolute kidney weight in male rats.

Limited intermediate-duration studies were available. In a study in male rabbits, the animals were administered doses of 0, 2, 20, or 200 mg TDCP/kg/day by gavage for 12 weeks (Anonymous 1977). During the last week of treatment, male fertility was tested by mating the males with untreated females. Fertility was assessed by sacrificing the females at mid-gestation and evaluating their uteri. After the mating period, the males were euthanized and sperm from the cauda epididymides were analyzed for motility, morphology, and concentration. Blood was also collected for hematology and clinical chemistry tests. The pituitary, liver, kidneys, and reproductive tract were processed for microscopic examination. The treatment-related effects appeared to be a significant increase in relative liver weight (23%) and in absolute kidney weight (14%). Neither gross necropsy nor microscopic examinations revealed significant alterations in the organs examined. The fact that only a small number of organs were examined and no adverse effects were reported other than possibly minimal LOAELs for changes in liver and kidney weights, and the lack of information in female animals, limit the usefulness of the study for risk assessment. In the 2-year bioassay in rats conducted by Stauffer Chemical Co. (1981a), hematology and clinical chemistry tests, as well as urine analyses were conducted after 3 and 6 months of treatment; however, no gross or microscopic examination of the tissues was conducted at these times. Body weights were reduced in males and females 5–7% relative to controls at the 3- and 6-month time points. Body weight was reduced 12% in high-dose males on week 50. Hematology tests showed significant reductions in hemoglobin and hematocrit in high-dose males both at 3 and 6 months and of hemoglobin in females at 6 months. High-dose males also showed a reduction in red blood cell count at 6 months. At 12 months, there were significant reductions in hemoglobin in high-dose males (10.6%) and females (7.5%) and in red cell counts in high-dose males (10.7%). None of these alterations were observed after 24 months of treatment with TDCP. Prothrombin times and partial thromboplastin times showed

considerable variability from interval to interval and no consistent pattern of differences between treated and control rats were apparent during the study. Serum alkaline phosphatase levels were lower than controls in high-dose rats both at the 3- and 6-month intervals. Blood urea nitrogen (BUN) values in treated rats were not significantly different than in controls. Other clinical chemistry tests showed no consistent dose-related differences between controls and treated rats that could be attributed to treatment with TDCP. The most significant observations at 12 months were dose-related increases in absolute kidney and liver weights which achieved significance at the highest dose level; these changes in organ weights were not accompanied by histopathology. Changes in kidney weight were more marked than those in liver weight, 48% increase in high-dose males and 39% increase in high-dose females relative to controls. At the lowest dose, kidney weight was increased 12% in males relative to controls. In mid-dose males, absolute thyroid and liver weight were increased by 14 and 12%, respectively; the corresponding increases in high-dose males were 25 and 26%. Since the kidney was the most sensitive end point in rats exposed to TDCP for 24 months in the same study, it would appear that the increase in kidney weight observed at 12 months is a continuum of the same spectrum of health effects used to derive the chronic-duration MRL (see below) and may in fact be a precursor to the renal tubule hyperplasia seen in rats exposed to TDCP for 24 months. Since the hematological changes observed during the first year of the study are of questionable toxicological significance, it is appropriate to use the changes in absolute kidney weight at the 12-month time point as the basis for derivation of an intermediate-duration oral MRL for TDCP.

Although ATSDR typically defines intermediate duration to be from 15 to 364 days, using a 1-year (365 days) study seems justified based on the following. The kidney effects appear to be a progression of changes going from no effect to absolute kidney weight gain to renal tubule hyperplasia. When one looks at the 1-year time point, those effects are more in line with intermediate effects than they are at the 2-year time point. Therefore, ATSDR has considered this an intermediate-duration study.

Data from Stauffer Chemical Co. (1981a) were analyzed using the BMD approach for MRL derivation. BMD models in the EPA BMDS (version 2.1) were fit to the absolute kidney weight male and female datasets to determine potential points of departure for the MRL. In the absence of a clear criteria as to what level of change in kidney weight should be considered adverse, the BMR was defined as a change in mean kidney weight equal to 1 SD from the control mean (EPA 2000). For both data sets, constant variance models did not provide adequate fits. Selected non-constant variance models for male and female data predicted respective $BMDL_{1SD}$ values of 4.69 and 13.49 mg/kg/day; the lowest of these $BMDL_{1SD}$ values was selected as the point of departure. Applying an uncertainty factor of 100 (10 for

animal to human extrapolation and 10 for human variability) to the $BMDL_{1SD}$ of 4.69 mg/kg/day for increased kidney weights in male rats yields an intermediate-duration oral MRL of 0.05 mg/kg/day for TDCP. Using a database uncertainty factor does not seem necessary since the Stauffer Chemical Co. (1981a) study is a well-conducted study that tested an appropriate number of animals, evaluated a wide range of end points including hematology and clinical chemistry and conducted gross and microscopic examination of all major tissues and organs. Details of the modeling are presented in Appendix A.

- An MRL of 0.02 mg/kg/day has been derived for chronic-duration oral exposure (365 days and longer) to TDCP based on renal tubule hyperplasia in male rats.

A chronic-duration study with TDCP was available for review. In that study, groups of male and female Sprague-Dawley rats (60/sex/dose) were fed a diet that provided 0, 5, 20, or 80 mg TDCP/kg/day for 24 months (Stauffer Chemical Co. 1981a). End points monitored included lethality, clinical signs, body weight, food consumption, hematology, clinical chemistry and urinalysis (periodically throughout the study), gross necropsy, and histopathology at termination and at 12 months (10 rats/sex/dose). The most sensitive organs affected by treatment with TDCP appeared to be the liver and kidneys. At termination, gross observations revealed masses, nodules, and raised areas in the liver of high-dose rats; enlargement of the kidney in mid- and high-dose males and high-dose females plus higher incidence of discolorations, surface irregularities, masses, nodules, and cysts in treated rats than in controls; and higher incidence of small seminal vesicles and testicular enlargement, masses, nodules, flaccidity, and discolorations in mid- and high-dose males. Nonneoplastic lesions that were significantly increased in treated rats were foci/areas of hepatocellular alterations (high-dose males and females), dilation of liver sinusoids (high-dose males and females), hyperplasia of convoluted tubular epithelium of the kidney (high-dose males and females, mid-dose males), and chronic nephropathy (high-dose males and females). None of these alterations were seen at the 12-month interim kill. Hyperplasia of the renal convoluted tubular epithelium was the most sensitive effect and occurred with incidences of 2/45, 10/49, 28/48, and 24/46 in males as the doses increased; the corresponding incidences in females were 0/49, 1/48, 3/48, and 22/50. Based on the incidences of the lesion in males, a LOAEL of 20 mg TDCP/kg/day was defined; the NOAEL was 5 mg/kg/day. Examination of these incidences shows that males were clearly more sensitive than females. Therefore, the data set for hyperplasia of the renal convoluted tubular epithelium in males served as the basis for determining the point of departure for MRL derivation. A detailed description of the study and modeling of the data is provided in Appendix A.

Incidence data for renal tubule epithelial hyperplasia in male rats exposed to TDCP (Stauffer Chemical Co. 1981a) were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS

(version 2.1) (gamma, logistic, log-logistic, multi-stage, probit, log-probit, quantal linear, Weibull models) were fit to the renal tubular epithelial hyperplasia data in male rats to determine potential points of departure for the MRL. Since an adequate fit to the data set could not be obtained with any of the models, the high-dose was dropped, in accordance with EPA (2000) guidance. Comparing across models, the Multistage 1-degree polynomial model provided the best fit to the renal epithelial hyperplasia data after dropping the highest dose. From this model, the BMD_{10} was 2.60 mg TDCP/kg/day; the $BMDL_{10}$ was 1.94 mg TDCP/kg/day. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ of 1.94 mg/kg/day yields a chronic-duration oral MRL of 0.02 mg/kg/day for TDCP.

TCP. An acute-duration oral MRL was not derived for TCP due to an insufficient database. Acute-duration studies of TCP focused mainly in determining LD_{50} values in rodents (FMC 1976b, 1976c, 1978; Johannsen et al. 1977; FMC 1979b). NTP (1994) conducted 16-day studies in rats and mice, which could be considered acute since exceed only by 2 days the duration limit of 14 days that ATSDR considers acute-exposure. However, it is uncertain whether the ovaries and adrenal glands, two critical targets in intermediate- and chronic-duration studies, were examined microscopically. NTP (1994) states that the tissues examined microscopically are listed in Table 2 of the report; however, Table 2 lists all of the tissues examined in the 13-week (gavage and dietary) and 2-year studies, but not the 16-day studies.

- An MRL of 0.04 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to TCP based on ovarian lesions in rats.

Several intermediate-duration oral studies have been conducted with TCP in rats and mice. The most complete are the studies sponsored by NTP (1994), which include 13-week gavage and dietary studies in rats and mice and 3- and 9-month interim evaluations conducted as part of the 2-year study in rats and mice. These studies identified the ovary and adrenal cortex in female rats as the most sensitive target for TCP. TCP induced cytoplasmic vacuolization of the adrenal cortex and interstitial cell hyperplasia in the ovary in female rats. The LOAELs were 15 and 7 mg/kg/day, respectively; the corresponding NOAELs were 7 and 4 mg/kg/day and were established at the 3-month interim evaluation in the 2-year study. Female rats were more sensitive to the alterations in the adrenal gland than male rats. Male rats dosed with 3, 6, or 13 mg TCP/kg/day (75, 150, or 300 ppm in the diet) did not develop adrenal cortex lesions; however, in an additional group of males fed a diet containing 600 ppm TCP (a dose was not calculated by the investigators, but it can be estimated that it provided approximately 26 mg TCP/kg/day) and killed at 3 months, the incidence of adrenal lesions was 100% (10/10). Adrenal gland and ovarian lesions were also reported in other intermediate-duration studies in rats such as the 13-week gavage and dietary studies

conducted by NTP (1994) and studies conducted by Latendresse and coworkers (Latendresse et al. 1993, 1994b). However, these studies used relatively high doses of TCP. In addition, Latendresse et al. (1993, 1994b) used a single dose level of 400 mg TCP/kg/day and the NTP (1994) 13-week studies used doses ranging from 50 to 800 mg TCP/kg/day. In mice, adrenals lesions were seen in all groups of males and females, including controls with an incidence near/or 100% at 9, 15, and 24 months (NTP 1994). At the 3-month interim kill, only high-dose male mice (27 mg TCP/kg/day) showed a significant increase (6/10) relative to controls (0/8). This suggests that in mice, adrenal lesions occur spontaneously and TCP accelerates its onset.

Incidences of adrenal and ovarian lesions in rats at the 3- and 9-month interim kills are presented in Table 2-2. It should be mentioned that an intermediate-duration study of the effects of TCP on immune function in male Wistar rats reported that doses of approximately 6 mg TCP/kg/day significantly reduced humoral and cell-mediated immune response; the NOAEL was 2.4 mg TCP/kg/day (Banerjee et al. 1992). While that study suggests that the immune system might be a sensitive target for TCP, there is no support from other studies and replication of the findings would be useful. In addition, the TCP tested was a technical-grade formulation characterized only as a 90% mixture of isomers; the isomeric composition was not specified. For these reasons, the Banerjee et al. (1992) study was not considered for MRL derivation.

Incidence data (Table 2-2) for cytoplasmic vacuolization of the adrenal cortex in female rats and of hyperplasia of the interstitial ovarian cell in female rats exposed to TCP (NTP 1994) were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1.1) (Gamma, Logistic, Log-logistic, Multi-stage, Probit, Log-probit, Weibull models) were fit to the adrenal and ovarian lesion data to determine potential points of departure for the MRL. The best fit for the incidence data for the adrenal lesions at the 3-month time point was provided by a LogLogistic model with a BMD_{10} of 7.00 mg/kg/day and a corresponding $BMDL_{10}$ of 5.69 mg/kg/day. The best fit for the incidence data for adrenal lesions at the 9-month time point was provided also by a LogLogistic model; the BMD_{10} and $BMDL_{10}$ values were 6.49 and 4.58 mg/kg/day. The best fit for the incidence data for ovarian cell hyperplasia at the 3-month point was provided by a Weibull model; the BMD_{10} and $BMDL_{10}$ values were 6.21 and 3.72 mg/kg/day, respectively. The best fit for the incidence data for ovarian cell hyperplasia at the 9-month point was provided by a LogLogistic; the BMD_{10} and $BMDL_{10}$ values were 7.00 and 5.69 mg/kg/day, respectively. Applying uncertainty factors of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$s calculated above result in possible intermediate-duration oral MRLs ranging from 0.04 to 0.06 mg TCP/kg/day after rounding up. In order to be protective of human health, an intermediate-duration oral MRL of 0.04 mg/kg/day is derived for TCP based on a

Table 2-2. Adrenal Cortex and Ovarian Lesions in Female F344 Rats Exposed to TCP (NTP 1994)

Incidence of cytoplasmic vacuolization of the adrenal cortex				
Dose (mg/kg/day)	0	4	7	15
At 3 months	0/10	0/10	1/10	10/10
At 9 months	0/10	0/10	3/10	10/10
Incidence of hyperplasia of the interstitial ovarian cells				
At 3 months	0/10	0/10	6/10	10/10
At 9 months	0/10	0/10	1/10	10/10

$BMDL_{10}$ of 3.72 mg TCP/kg/day for ovarian lesions in rats at the 3-month time point. Further details of the modeling are presented in Appendix A.

- An MRL of 0.02 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to TCP based on ovarian lesions in rats.

Only one chronic-duration oral study is available for TCP and that is the NTP (1994) 2-year bioassay in F344/N rats and $B6C3F_1$ mice (95 rats and mice per sex per dose group) that also included interim evaluations. That study monitored clinical signs and body weight, assessed hematology parameters and measured serum cholinesterase activity at 3, 9, and 15 months, tested forelimb and hindlimb grip strength at 3, 9, and 15 months, and measured organ weights and conducted gross and microscopic examinations of all major organs and tissues at 3, 9, 15, and 24 months. Results of the 15-month interim evaluation and at termination provided adequate data to consider for derivation of a chronic-duration oral MRL for TCP. In addition to the adrenal gland and ovary of female rats, the liver of male mice was also a sensitive target for TCP. Significantly increased incidences of adrenal cortex vacuolization occurred in high-dose female rats (15 mg TCP/kg/day) at the 15-month time point and at termination. The same occurred with the incidences of hyperplasia of the interstitial cells in the ovary; the NOAEL was 7 mg TCP/kg/day. Male mice from the mid- and high-dose groups (13 and 27 mg TCP/kg/day) exposed to TCP for 2 years showed significantly increased incidences of clear cell foci, fatty change, and ceroid pigmentation in the liver; the NOAEL was 7 mg TCP/kg/day. Incidences of adrenal, ovarian, and liver lesions are shown in Table 2-3.

Incidence data for the data sets shown in Table 2-3 were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1.1) were fit to the adrenal, ovarian, and liver lesion data to determine potential points of departure for the MRL. Among the model that best fit the data, the lowest BMD_{10} ranged from 5.22 to 13.92 mg/kg/day with corresponding $BMDL_{10}$ ranging between 2.12 and 10.37 mg/kg/day. The lowest $BMDL_{10}$ of 2.12 mg/kg/day was obtained for the incidence data for hyperplasia of the interstitial cells of the ovary in female rats treated with TCP for 15 months. Adequate fits for the incidences of clear cell foci and ceroid pigmentation in male mice were obtained only after dropping the highest dose. In order to be protective of human health, the $BMDL_{10}$ of 2.12 mg/kg/day is selected as the point of departure for MRL derivation. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ of 2.12 mg/kg/day yields a chronic-duration oral MRL of 0.02 mg/ kg/day for TCP. Further details of the modeling are presented in Appendix A.

Table 2-3. Adrenal Cortex and Ovarian Lesions in Female F344 Rats and Liver Lesions in B6C3F$_1$ Male Mice Exposed to TCP (NTP 1994)

Incidence of cytoplasmic vacuolization of the adrenal cortex in rats				
Dose (mg/kg/day)	0	4	7	15
At 15 months	0/9	0/8	0/10	10/10
At 2 years	14/51	12/53	16/50	36/50
Incidence of hyperplasia of the interstitial ovarian cells in rats				
At 15 months	0/9	0/8	3/10	9/10
At 2 years	0/51	0/53	0/50	15/50
Incidence of liver lesions in mice after 2 years				
Dose (mg/kg/day)	0	7	13	27
Clear cell foci	5/52	8/49	17/49	12/50
Fatty change	6/52	10/49	23/49	22/50
Ceroid pigmentation	0/52	0/49	30/49	28/50

TPP. No MRLs were derived for TPP due to inadequacies of the database available for review; specifically, no toxicity was reported. Information regarding acute exposure to TPP was limited to lethal dose studies aimed mainly at determining LD_{50} values. Information regarding intermediate-duration exposure was limited to an early study by Sutton et al. (1960) who treated rats with up to 416 mg TPP/kg/day via the diet for 35 days and reported no hematological effects or alterations in body weight or in the weight of the liver and kidneys; no further end points were evaluated. In a 4-month dietary study, doses of 345 mg TPP/kg/day reduced weight gain of rats by 11%, but doses of up to 711 mg TPP/kg/day had no significant effect on the results of a battery of behavioral tests administered at monthly intervals during treatment (Sobotka et al. 1986). In a study in which male and female rats received doses of up to 690 mg TPP/kg/day for 90 days before mating and during gestation, there were no significant effects on reproductive parameters or on fetal parameters assessed on Gd 20 (Welsh et al. 1987). Indices of immunocompetence, including the humoral response to immunization with SRBC were also not significantly affected in rats exposed to up to 711 mg TPP/kg/day for 120 days (Hinton et al. 1996). No chronic-duration studies with TPP were located in the literature available for review.

TiBP. No MRLs were derived for TiBP due to lack of adequate information. Only one study with TiBP was available for review. In that study, male and female rats received doses of up to 346 and 404 mg TiBP/kg/day, respectively, for 13 weeks in the diet (Naylor and Ribelin 1990). End points evaluated included clinical signs, body weight, food consumption, hematology and clinical chemistry, selected organ weights, and gross and microscopic evaluation of all major organs and tissues. The only reported

effects were a statistically significant decrease in neutrophil count in high-dose males and an increase in mean corpuscular hemoglobin (MCH) in high-dose males and in mean corpuscular hemoglobin concentration (MCHC) in mid- (68 mg/kg/day) and high-dose males. Clinical chemistry tests also showed a statistically significant increase in serum cholesterol in high-dose males. In the absence of any other significant alterations, the toxicological significance of the reported effects is unknown and not suitable for MRL derivation.

TCPP. No MRLs were derived for TCPP due to lack of adequate information. Only one study was available for review (Kawasaki et al. 1982). That study determined a 96-hour LD_{50} of 1,500 mg TCPP/kg in female rats and reported that exposure to up to 1,000 mg TCPP/kg/day by gavage for 7 days had no significant effect on the relative weights of the brain, heart, lungs, liver, spleen, kidneys, or adrenals. In another experiment, exposure of pregnant rats to up to 893 mg TCPP/kg/day by gavage on Gd 0–20 and euthanized on Gd 20, did not result in fetotoxicity or teratogenicity. Some dams were allowed to give birth and their offspring were monitored for 4 weeks after weaning. Neonatal growth and viability during this period was comparable among groups. The information available is not suitable for MRL derivation.

2. RELEVANCE TO PUBLIC HEALTH

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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 phosphate ester flame retardants. 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 (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, 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 produce 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.

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.

This profile discusses the following phosphate ester flame retardants: tris(2-chloroethyl) phosphate (TCEP), tributyl phosphate (TnBP), tris(2-butoxyethyl) phosphate (TBEP), tris(1,3-dichloro-2-propyl) phosphate (TDCP), triphenyl phosphate (TPP), tris(2-chloroisopropyl) phosphate (TCPP), triisobutyl phosphate (TiBP), and tricresyl phosphate (TCP).

Although the industrial properties of the selected phosphate ester flame retardants have been known for many decades, there is relatively little information on their adverse health effects in the peer-review literature. In contrast, a significant amount of studies performed or sponsored by industry remain unpublished, although many of them can be obtained from the EPA. ATSDR has made an effort to include all of the relevant information in this profile for the chemicals mentioned above. However, it is important to note that the quality of the microfiche that contain the unpublished studies varied greatly; some are unreadable and others could not be used due to being “sanitized” by the manufacturer, thus making it impossible to determine the identity of the chemical being tested.

3.2.1 Inhalation Exposure

No studies were located regarding adverse health effects in the general population due to inhalation exposure to the subject phosphate ester flame retardants of this profile and very limited information was located regarding people occupationally exposed to these substances.

Data in animals were limited to brief summaries of exposures to high concentrations of the chemicals (vapors, aerosols, dusts) aimed primarily to estimate lethal concentrations. Therefore, only this information is presented in Section 3.2.1.

3.2.1.1 Death

No reports of death in humans following inhalation exposure to the subject phosphate ester flame retardants were located in the literature reviewed. FMC (1982a) conducted a mortality study among individuals who worked at a plant that manufactured phosphate esters since 1962 in Nitro, West Virginia. Prior to 1962, the plant had manufactured non-phosphate products. Included in the study were individuals who worked more than 3 months from January 1, 1950 through September 30, 1976. The cohort comprised 658 male employees and 79 female employees with an overall follow-up of 92.8%. Workers were identified in terms of the type of job performed and the products or processes with which they had direct contact. Operators could be identified with Kronitex® (cresyl phosphate esters of unspecified isomeric composition), aluminum chloride, or as involved with all other products or processes dealt with in the main plant. Of the 737 individuals studied, 21 were involved with Kronitex®. Mortality rates were made with comparable groups of the U.S. population, the Charleston (West Virginia) Standard Metropolitan Statistical Area, and with the total FMC employee group of both the Nitro and South Charleston plants. The results of the analyses showed that the survival of employees of the Nitro plants compared favorable with the total employee group of FMC, with the U.S. population, and with the Charleston Standard Metropolitan Statistical Area. Limitations of the study include the small number of workers involved with Kronitex® and lack of detailed reporting of the methodology.

See Section 3.2.1.7, Cancer, for information regarding cancer mortality among workers exposed to TDCP.

An LC_{50} of >5,000 mg/m^3 was estimated in rats exposed for 4 hours to an aerosol of TCEP (Anonymous 1977). All rats survived through the exposure and the observation period of 14 days, and gross necropsy did not reveal compound-related effects. FMC (1976a) reported that the lowest LC_{50} following a 1-hour exposure of rats to vapors of TnBP was 28,000 mg/m^3. Studies conducted by Eastman Kodak Co. (1968) reported that one out of three rats died following exposure to TnBP at a concentration of 41,382 mg/m^3; no deaths or clinical signs of toxicity occurred at 10.89 mg/m^3. MacKellar (1976) reported an LC_{50} of <200,000 mg/m^3 for TnBP in rats, as exposure to 200,000 mg/m^3 of TnBP killed 100% of the rats.

An LC_{50} of >9,800 mg/m^3 was reported for rats exposed for 1 hour to an aerosol of TDCP (Stauffer Chemical Co. 1981b). All rats survived through the exposure and 14-day observation period, and gross necropsy did not reveal compound-related effects. Exposure of rats for 4 hours to an aerosol of TBEP at a nominal concentration of 5,000 mg/m^3 resulted in the death of 4/5 males and 3/3 females at the end of a 14-day observation period (Mobil Oil Corporation 1981). Clinical signs of toxicity included lethargy, brown discharge from the mouth, and labored breathing.

An LC_{50} >200,000 mg/m^3 was described for TPP in rats in a summary of an acute inhalation study (FMC 1982b). Rats were exposed for 1 hour to dusts of TPP and were observed for 14 days. All rats survived through the exposure and observation period, and gross necropsy did not reveal compound-related effects. Exposure of rats to up to 83,350 mg/m^3 of vapors of TiBP for 6 hours induced gasping; prostration; yellow hair, ears, and feet; and red eyes during exposure, but no deaths occurred (Eastman Kodak Co. 1990). However, all rats exposed to this concentration died 48 hours following the exposure.

No deaths occurred in groups of rats, mice, and guinea pigs exposed to 3,530 mg/m^3 TCP vapors for 6 hours and observed for 14 days (Exxon Research 1975); therefore, the LC_{50} was estimated to be >3,530 mg/m^3. There were no adverse clinical signs during exposure or during the observation period, and gross examination at termination did not reveal treatment-related alterations. Exposure of rats to 200,000 mg/m^3 TCP aerosol for 2 hours induced prostration, ataxia, and ocular and nasal irritation and caused the death of three out of five males and five out of five females during the 14-day observation period (FMC 1976b). The LC_{50} in this study was estimated to be <200,000 mg/m^3. Conversely, exposure of rats to 200,000 mg/m^3 TCP aerosol for 1 hour did not cause any deaths, and gross necropsy did not reveal any remarkable findings (FMC 1976c). In another study in rats, one out of five males and one out of five females died before the end of a 14-day observation period following exposure to 20,000 mg/m^3 TCP aerosol for 1 hour (FMC 1979b). Slight depression was observed in some rats the first day of exposure and the LC_{50} was estimated to be >20,000 mg/m^3.

Additional information regarding LC_{50} values and lethal concentrations of the selected phosphate ester flame retardants can be found in IPCS (1990, 1991a, 1991b, 1998, 2000b).

Lethal exposure concentrations and LC_{50} values are presented in Table 3-1 and plotted in Figure 3-1.

Table 3-1 Levels of Significant Exposure to Selected Phosphate Esters - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
ACUTE EXPOSURE									
Death									
1	Rat	4 hr (NS)				5000	(LC50 is greater than 5000 mg/cubic meter/L)	Anonymous 1977 115-96-8	
2	Rat (NS)	6 hr (NS)				41382	(1/3 deaths)	Eastman Kodak Co. 1968 126-73-8	
3	Rat (NS)	6 hr (NS)				83350	(3/3 deaths 48 hours after exposure)	Eastman Kodak Co. 1990 126-71-6	
4	Rat (albino)	6 hr				3530	(the LC50 was greater than 3530)	Exxon Research 1975 1330-78-5	
5	Rat (Wistar)	1 hr (NS)				28000	(LC50)	FMC 1976a 126-73-8	
6	Rat (Wistar)	2 hr				200000	(3/5 males and 5/5 females died in 14 days)	FMC 1976b 1330-78-5	
7	Rat (Wistar)	1 hr				200000	(the LC50 was greater than 200000)	FMC 1976c 1330-78-5	

Table 3-1 Levels of Significant Exposure to Selected Phosphate Esters - Inhalation (continued)

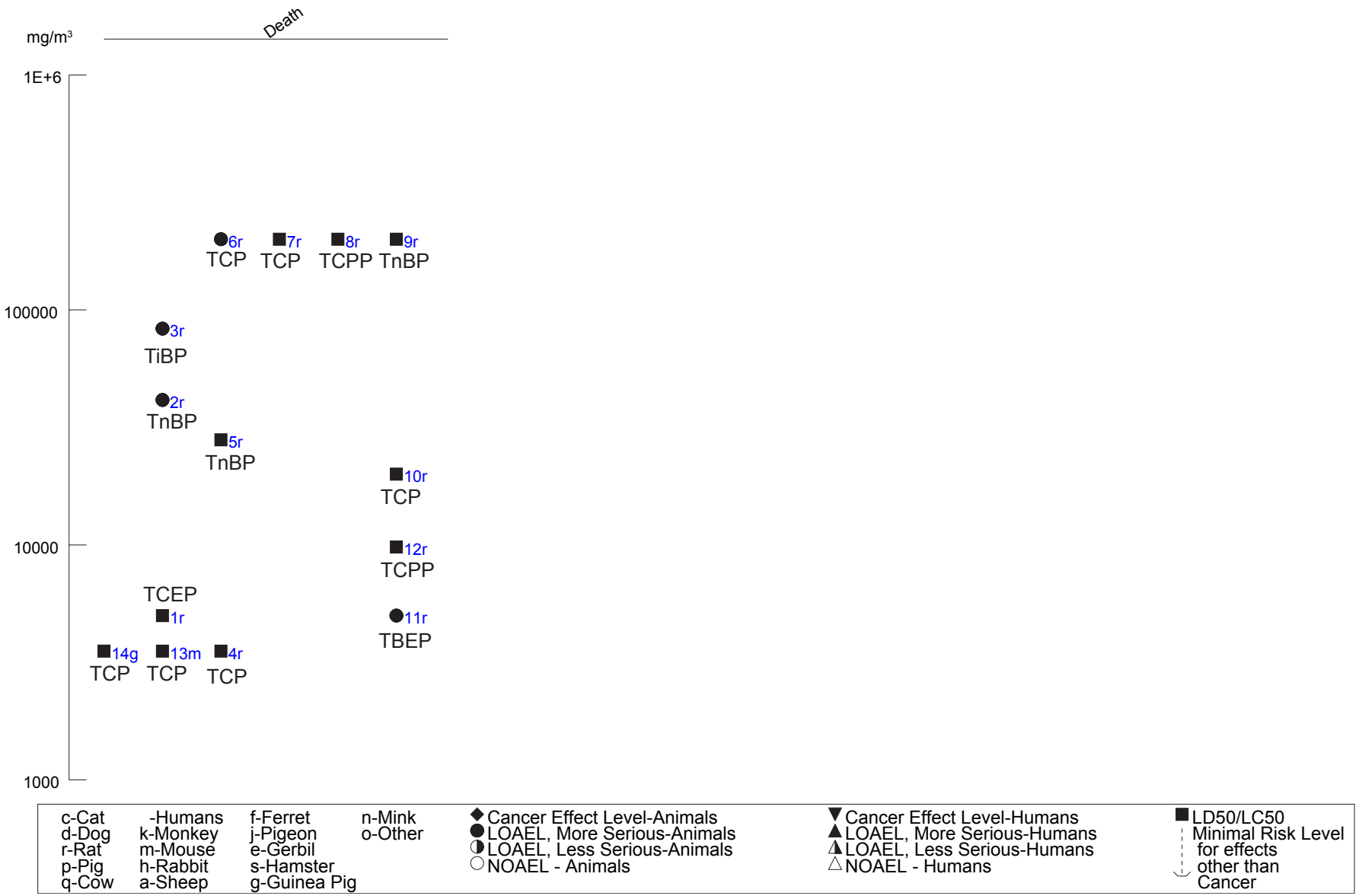
Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
8	Rat (Wistar)	1 hr (NS)				200000	(LC50 was greater than 200000 mg/cubic meter)	FMC 1982 115-86-6	
9	Rat (NS)	1 hr (NS)				200000	(LC50 is less than 200000 mg/m3)	MacKeller 1976 126-73-8	
10	Rat (albino)	1 hr				20000	(the LC50 was greater than 20000)	Mobil Oil Corporation 1978 1330-78-5	
11	Rat (Sprague-Dawley)	4 hr (NS)				5000	(7/8 deaths in 14 days)	Mobil Oil Corporation 1981 78-51-3	
12	Rat (Sprague-Dawley)	1 hr (NS)				9800	(1-hr LC50 is greater than 9800 mg/m3)	Stauffer Chemical Co. 1981b 13674-87-8	
13	Mouse (NS)	6 hr				3530	(the LC50 was greater than 3530)	Exxon Research 1975 1330-78-5	
14	Gn Pig (NS)	6 hr				3530	(the LC50 was greater than 3530)	Exxon Research 1975 1330-78-5	

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

hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified

Figure 3-1 Levels of Significant Exposure to Selected Phosphate Esters - Inhalation

Acute (≤14 days)



3.2.1.2 Systemic Effects

Respiratory Effects. Stauffer Chem Co. (1983) conducted a morbidity survey to identify adverse health effects among workers occupationally exposed to TDCP. The survey was based on an analysis of the physical examination reports of 93 exposed and 31 non-exposed workers examined in 1981. The evaluation included a self administered 175 item questionnaire, clinical studies including pulmonary function tests, a chest x-rays and electrocardiograms (EKG), and laboratory test including urinalyses, hematology and clinical chemistry parameters. Time-weighted average breathing zone sampling conducted in 1978 and 1979 showed that the concentration in the process area or in other areas was ≤7–8 ppb (0.4–0.5 μg/m^3). Analysis of alcohol consumption habits showed that there were significantly more non drinkers among non-exposed individuals and a higher daily alcohol consumption among exposed workers than non-exposed. There were no significant differences between the groups regarding smoking habits. In general, prevalence rates for positive responses to the questionnaire tended to be higher among non-exposed workers. From the respiratory section of the questionnaire, the main focus of the survey, exposed workers showed a 2-fold excess for bringing up phlegm first thing in the morning and for having a stuffy nose or post-nasal drip in the summer. Results from the chest x-rays showed no significant differences between exposed and non-exposed workers. Results from the pulmonary tests showed a six times greater percentage of abnormal pulmonary tests in non-exposed workers than in exposed workers; the impairment occurred primarily in FEV_1. Based on these findings, the investigators concluded that it was apparent that workers exposed to TDCP were not at increased risk for respiratory conditions. Limitations of the survey (which also apply to other end points mentioned below) noted by the investigators included the fact that the number of non-exposed workers was only one third that of the exposed workers. Secondly, since payroll records were unavailable prior to 1975, some of the workers classified as non-exposed could have been exposed prior to 1975. Thirdly, since a higher percentage of exposed workers were employed before 1975 than non-exposed, and some of the exposed workers could have had potentially a long duration of exposure, the maximum effect of any harmful exposure should be observed among the exposed workers.

Sutton et al. (1960) reported the results of health evaluations of men engaged in the manufacture and use of TPP. The workers could have been exposed to up to 29 mg/m^3 TPP mist and vapor or dust for short period of time, but the investigators estimated a weighted average exposure concentration of 3.5 mg/m^3. Although the total number of men evaluated was not indicated, review of medical records and chest x-ray

tests did not reveal respiratory alterations attributable to exposure to TPP. Review of the medical records, illnesses, and examinations of 11 plant operators found no cases of respiratory tract irritation.

Cardiovascular Effects. In the survey conducted by Stauffer Chem Co. (1983), workers exposed to TDCP had twice as many abnormal EKG tracings as non-exposed workers. The principal abnormalities observed were sinus bradycardia, sinus arrhythmias, left axis deviation and incomplete right bundle branch block. However, from the health questionnaire information, a lower percentage of these workers had a history of heart trouble than non-exposed workers, but a higher percent had a history of "other" chest trouble. In addition, exposed workers had a lower prevalence of diseases of the circulatory system. The review of medical evaluations of workers exposed to TTP conducted by Sutton et al. (1960) did not reveal electrocardiographic alterations attributable to occupational exposure to TPP.

Hematological Effects. Hematology tests (complete blood counts with differentials) carried out in the morbidity survey conducted by Stauffer Chem Co. (1983) showed no statistically significant differences between workers exposed to TDCP and non-exposed workers. Health evaluations of workers exposed to TPP that included hematology tests (hemoglobin, cell volume, white blood cell count, and differential) did not show deviations from the normal range attributable to exposure to TPP (Sutton et al. 1960).

Hepatic Effects. Results of the liver function tests performed on the workers studied by Stauffer Chem Co. (1983) showed that workers exposed to TDCP had a higher percentage of abnormal total bilirubin and total protein values than non-exposed workers. However, non-exposed workers had higher serum aspartate aminotransferase (AST) and alkaline phosphatase values. Health evaluations conducted in workers exposed to TPP did not reveal alterations in liver function as assessed by the cephalin cholesterol flocculation test (Sutton et al. 1960).

Renal Effects. In the morbidity survey conducted by Stauffer Chem Co. (1983), there was a considerably greater percentage of workers exposed to TDCP with abnormal BUN values than non-exposed workers, 14.1 versus 0.0%; creatinine values were similar for both groups. The results also showed that a greater percentage of non-exposed workers (25.8%) had abnormal urine results (unspecified) than exposed workers (6.7%). Examination of the urine of workers exposed to TPP did not reveal any abnormalities that could be attributed to exposure to the chemical (Sutton et al. 1960).

Dermal Effects. A higher prevalence of dermatitis was reported among TDCP workers compared with non-exposed workers in the morbidity survey conducted by Stauffer Chem Co. (1983); no further details were provided. No cases of dermatitis were observed among 11 workers exposed to TPP that were evaluated by Sutton et al. (1960).

3.2.1.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological and lymphoreticular effects in humans or animals following inhalation exposure to the phosphate ester flame retardants discussed in this profile.

3.2.1.4 Neurological Effects

FMC (1981a) conducted a cross-sectional study among workers at an aryl phosphates manufacturing plant in Nitro, West Virginia. The main objective was to determine whether exposure to these substances induced adverse neurological effects among the workers. Exposure appeared to have been mainly by the inhalation and dermal routes, but oral exposure could also have occurred. Some of the manufactured phosphates included tri-*m*-cresyl phosphate, tri-*p*-cresyl phosphate, trixylenyl phosphate, mixed isopropylphenyl triphenyl phosphate compounds, cresyl diphenyl phosphate, and tert-butylphenyl phosphate compounds. The study was conducted from July 1980 to December 1981 and involved 113 participants. Of these, 60 had current or previous exposure, 14 had plant assignment but were never exposed, and 39 were office workers who had never had plant assignments. Exposure duration varied from 1 to 25 years. Data on air and wipe samples were available between the period 1974 and 1981 as no industrial hygiene sampling was conducted before 1974. The highest air concentration of aryl phosphate was 4 ppb, measured in a general area. Some personal samples of other phosphates such as butyl phosphate were higher, reaching 15 ppb on one occasion. Qualitative analyses of wipe samples showed that aryl phosphate compounds entered the control room and even entered the lunchroom. All participants were interviewed, subjected to a clinical neurological examination, and tested for peripheral sensory and motor nerve conduction velocity. After adjusting for confounders such as sex, age, arm and foot temperature, and length of employment, the results showed no apparent detrimental effect of exposure to aryl phosphates. However, there were four cases in which the comparisons between exposed and control subjects approached the 0.05 level of significance (0.07–0.08). Two of these cases involved comparison of exposed with controls before 1974, when the aryl phosphate process was an open-batch process as opposed to a closed system put in operation after 1974. The differences in test results were small and were considered of questionable clinical significance by the investigators, who also suggested the conduct of follow-up studies.

Examination of 32 men who were assigned to jobs in which they occasionally handled bags of TPP and had a mean length of exposure of 7.4 years revealed no cases of neurological disease (Sutton et al. 1960). Examination of 11 of the men with the highest exposure who were working regularly at the time of the evaluations showed no evidence of neurological disease (Sutton et al. 1960). However, red blood cell cholinesterase activity was significantly reduced (18%) in this group of workers compared to unexposed subjects. Yet, Sutton et al. (1960) noted that the variability both within and between individuals was great enough so that the small depressions in cholinesterase activity were not sufficient to identify individuals with TPP exposure.

No studies were located regarding the following effects:

3.2.1.5 Reproductive Effects
3.2.1.6 Developmental Effects

3.2.1.7 Cancer

Stauffer Chemical Co. (1983) conducted a retrospective cohort study to examine the mortality experience of 289 workers employed in the manufacture of TDCP. The study period was established as January 1956 through December 1980. The cohort included active, terminated, retired, and deceased employees. Full-shift, time weighted average breathing zone sampling conducted from December, 1978 to May, 1979 showed that exposure levels were <8 ppb. Of the total cohort, only 42 workers had been employed ≥15 years. The overall mortality of the cohort was 75% of that expected in a comparable population of U.S. males, which probably reflected the healthy worker effect. There were three deaths attributed to lung cancer, which was higher than the 0.8 expected. However, based on the fact that one case was found to have not been exposed to TDCP, a second case worked only 2 years before onset of the disease, and all three cases were cigarette smokers, the investigators concluded that there was insufficient evidence to establish a causal relationship between lung cancer and TDCP. Considering the small size of the cohort, the investigators recommended continued surveillance of the group. Without providing further details, Stauffer Chem Co. (1983) stated that in the morbidity survey conducted among TDCP workers, there was an excess of benign neoplasms, primarily lipomas, relative to non-exposed workers.

3.2.2 Oral Exposure

3.2.2.1 Death

No reports of deaths of humans following oral exposure to the phosphate ester flame retardants subject of this profile were located in the reviewed literature.

Oral LD_{50} values between 46.4 and 100 mg/kg and between 46.4 and 1,000 mg/kg were reported for TCEP in male and female rats, respectively (Anonymous 1977). Other LD_{50} values reported for TCEP in rats were 1,230 and 1,410 mg/kg (Eldefrawi et al. 1977; Smyth et al. 1951). In a gestational exposure study, 7/30 rats dosed with 200 mg TCEP/kg/day died during the study; no deaths occurred in a group treated with 100 mg/kg/day (Kawashima et al. 1983a). In a 16-week duration study in which rats were treated with TCEP by gavage 5 days/week, 5/10 males and 3/10 females died on week 16 (NTP 1991a).

LD_{50} values and/or lethal doses ranging from 1,400 to 3,200 mg/kg were reported for TnBP in rats (Dow Chemical Co. 1956; Eastman Kodak Co. 1968; EI Dupont Denemours 1953a; Johannsen et al. 1977; Stauffer Chemical Co. 1973; Union Carbide Corp 1943). MacKellar (1976) reported that all rats (unspecified number) treated once with 20,000 mg TnBP/kg died. Eastman Kodak Co. (1968) also reported an LD_{50} between 400 and 800 mg/kg for TnBP in mice. In a gestational exposure study, all five pregnant rats dosed with 800 mg TnBP/kg/day died after five or six treatments (Noda et al. 1994). These rats showed marked reduction in body weight and food consumption, piloerection, wetting of abdominal hair with urine, and salivation. In a 13-week gavage study, 7/24 rats died at unspecified times before the end of the study (Healy et al. 1995). Gross examination of these rats showed a pale, frothy material in the trachea and/or lungs, suggesting that deaths may have been due to aspiration of saliva.

Oral LD_{50} values of 13,278 and 5,383 mg/kg were reported for TBEP in male and female rats, respectively (Mobil Oil Corporation 1976a). Clinical signs of toxicity observed included ataxia, labored breathing, red stains on the nose or eyes, rough coat, soft feces, urine stains, depression, prostration, and tremors. Gross necropsy of animals that died during the study revealed reddened intestines and/or reddened stomach linings. Without providing any details, Eldefrawi et al. (1977) reported an estimated oral LD_{50} of 2,830 mg/kg for TDCP in rats.

An oral LD_{50} of 10,800 mg/kg was described in rats administered TPP by capsule and observed for 14 days (Johannsen et al. 1977). Without providing further details, EF Houghton and Co. (1996) and FMC (1982b) reported LD_{50} values >6,400 and >20,000 mg/kg, respectively, for TPP in rats. Oral LD_{50}

values >3,200 and >6400 mg/kg were described for TiBP in rats and mice, respectively (Eastman Kodak Co. 1990). Mortality in rats occurred between 2.5 hours and 2 days following administration of TiBP and clinical signs of toxicity included ataxia, jerking, and white foam at the mouth. Mortality in mice occurred between 2 and 3 hours following administration of TiBP, and clinical signs of toxicity included ataxia. In a study conducted by Monsanto Co. (1989a, 1989b), a single dose of 5,000 mg/kg killed only 1/10 rats within a 14-day observation period. Clinical signs of toxicity observed 24 hours after dosing included dry rales, hypoactivity, and red nasal discharge.

Oral LD_{50} values of 2,000 and 1,260 mg/kg were reported for TCPP in male and female rats, respectively (Anonymous 1977). Spasm, salivation, ataxia, and spasmodic jumping were noticed in the rats. Kawasaki et al. (1982) reported a 96-hour oral LD_{50} of 1,500 mg/kg for TCPP in female rats. Tremors and wheezing were evident 30 minutes after dosing in rats that died. Rats that did not die after 5 hours did not do so later. In rats dosed once with 200, 500, or 2,000 mg TCPP/kg, all five high-dose females died (Stropp 1996). There were no other mortalities at any other dose level. Clinical signs observed in high-dose females included apathy, spasms, blood-crusted snout, and lateral position. No clinical signs of toxicity were observed in either sex at 200 or 500 mg/kg, and body weight was not affected. At necropsy, reddened lungs were observed in animals that died during the study; however, no surviving animals showed pathological changes at termination.

Two out of five males and two out of five female rats died following administration of a single dose of 20,000 mg/kg TCP and observed for 14 days (FMC 1976b). Autopsy revealed visceral hemorrhage. In rats dosed once with 17,400, 29,000 or 24,800 mg TCP/kg, 4/10 died in the mid-dose group and 6/10 died in the high-dose group (FMC 1976c). Gross necropsy revealed chromorhinorrhea and visceral hemorrhage and the 14-day LD_{50} was estimated to be 31,320 mg/kg. In another study, FMC (1978) reported a 14-day LD_{50} of 15,750 mg/kg for TCP in rats. Necropsy showed that most of the rats had reddened pyloric and intestinal mucosa. FMC (1979b) reported a 14-day LD_{50} of 16,100 mg/kg in rats receiving single doses of 0, 6,150, 9,600, 15,000, or 22,500 mg TCP/kg. All rats in the high-dose group and three females in the 15,000 mg/kg group died during the first 7 days after dosing. Diarrhea, oily body, and nasal secretion occurred in all treated groups. Without providing further details, Johannsen et al. (1977) reported a 14-day LD_{50} value of 15,800 mg/kg for TCP in rats. In a range-finding dietary study in mice fed 0, 1,604, 3,208, 6,416, or 12,833 mg TCP/kg/day for 14 days, all mice died in the three highest dose groups (Chapin et al. 1988). All mice in these dose groups showed piloerection, tremors, diarrhea, and lethargy. Reduced survival rates were observed in rats and mice administered daily doses of 0, 360, 730, 1,450, 2,900, or 5,800 mg/kg TCP by gavage in corn oil for a total of 13 or 14 doses in

16 days (NTP 1994). The only clinical signs were diarrhea in rats and rough hair coat in mice. A significant number of deaths occurred in male and female rats at 2,900 mg/kg, but not in the highest dose group of 5,800 mg/kg (no explanation was provided) and survival was significantly reduced in male and female mice at 1,450 mg/kg. Most of the deaths occurred during the first 14 days in rats and by the end of the second week of dosing in mice. In a 28-day dietary study in rats conducted by FMC (1976b), 4/10 males died following consumption of 938 mg TCP/kg and 5/10 females died after consuming 745 mg/kg. Most of the rats showed mild to severe enteritis. Gross necropsy conducted on all survivors showed no compound-related alterations in any organ examined; however, no information was provided regarding histopathology.

Additional information regarding LD_{50} values and lethal doses of phosphate ester flame retardants can be found in IPCS (1990, 1991a, 1991b, 1998, 2000b).

Oral LD_{50} values and oral lethal doses for the selected phosphate ester flame retardants are presented in Tables 3-2, 3-3, 3-4, 3-5, 3-6, and 3-7 and plotted in Figures 3-2, 3-3, 3-4, 3-5, 3-6, and 3-7.

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Tables 3-2, 3-3, 3-4, 3-5, 3-6, and 3-7 and plotted in Figures 3-2, 3-3, 3-4, 3-5, 3-6, and 3-7.

Respiratory Effects. The respiratory tract of animals has been examined in many repeated oral dose studies of the phosphate ester flame retardants discussed in this profile and no significant histological alterations have been reported. For example, no effects were noted in rats dosed daily with 350 mg TCEP/kg/day by gavage for up to 16 weeks (NTP 1991a) or in rats receiving dietary doses of up to 596 mg TCEP/kg/day for 3 months (Anonymous 1977). Similarly, mice dosed daily with up to 700 mg TCEP/kg/day for up to 16 weeks showed no alterations in the respiratory tract (NTP 1991a). No respiratory alterations were reported in rats or mice dosed with up to 88 or 350 mg TCEP/kg/day, respectively, for 2 years (NTP 1991a).

In studies with TnBP, treatment of rats with up to 411 mg/kg/day for 14 days (Laham et al. 1984b), 423 mg/kg/day for 90 days (FMC 1985a), 333 mg/kg/day for 18 weeks (Laham et al. 1985a), or 182 mg/kg/day for 2 years (Auletta et al. 1998a) did not result in alterations in the respiratory tract.

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (NS)				46.4 M (LD50 is between 46.4 and 100 mg/kg) 46.4 F (LD50 is between 46.4 and 1000 mg/kg)	Anonymous 1977 115-96-8	
2	Rat (albino)	once (G)				1230 (LD50)	Eldefrawi et al. 1977 115-96-8	
3	Rat (Wistar)	9 d Gd 7-15 1 x/d (GO)				200 F (7/30 pregnant rats died, 0/23 in controls)	Kawashima et al. 1983a 115-96-8	
4	Rat (albino)	once (G)				1410 (LD50)	Smyth et al. 1951 115-96-8	
Systemic								
5	Mouse (CD-1)	8 d Gd 6-13 1 x/d (G)	Bd Wt		940 F (12% reduced weight gain between Gd 6 and Pnd 3)		Hardin et al. 1987 115-96-8	Only one dose level was used.
6	Mouse (CD-1)	14 d 1 x/d (GO)	Bd Wt	1000			NTP 1991b 115-96-8	
Neurological								
7	Rat (Fischer- 344)	once (GO)				275 F (convulsions; loss of hippocampal cells)	Tilson et al. 1990 115-96-8	

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
8	Mouse (B6C3F1)	3 d 1 x/d (GO)		175		300	(ataxia, convulsions)	NTP 1991a 115-96-8	
Developmental									
9	Rat (Wistar)	9 d Gd 7-15 1 x/d (GO)		200 F				Kawashima et al. 1983a 115-96-8	NOAEL is for standard developmental indices.
10	Mouse (CD-1)	8 d Gd 6-13 1 x/d (G)		940 F				Hardin et al. 1987 115-96-8	NOAEL is for developmental indices in a preliminary assay.
INTERMEDIATE EXPOSURE									
Death									
11	Rat (Fischer- 344)	16 wk 5 d/wk 1 x/d (GO)				350	(5/10 males and 3/10 females died on week 16)	NTP 1991a 115-96-8	

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
12	Rat (Sprague-Dawley)	3 mo ad lib (F)	Resp	586 F			Anonymous 1977 115-96-8	NOAELs are for tissue or organ histopathology. Other refers to urinary bladder.
			Cardio	586 F				
			Gastro	586 F				
			Hemato	586 F				
			Musc/skel	586 F				
			Hepatic	586 F				
			Renal	586 F				
			Endocr	586 F				
			Dermal	586 F				
			Ocular	586 F				
			Bd Wt	192 M	506 M (13% reduction in final body weight)			
			Metab	586 F				
			Other	586 F				

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
13	Rat (Fischer- 344)	16 wk 5 d/wk 1 x/d (GO)	Resp	350			NTP 1991a 115-96-8	NOAELs are for organ or tissue histopathology. Other refers to urinary bladder.
			Cardio	350				
			Gastro	350				
			Musc/skel	350				
			Hepatic	88	175 (>10% increase in absolute liver weight)			
			Renal	88 F	175 F (>10% increased absolute and relative kidney weight)			
			Endocr	350				
			Dermal	350				
			Bd Wt	350				
			Other	350				

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
14	Rat (Fischer- 344)	16 d 5 d/wk 1x/d (GO)	Resp	350			NTP 1991a 115-96-8	NOAELs are for organ or tissue histopathology. Other refers to urinary bladder.
			Cardio	350				
			Gastro	350				
			Musc/skel	350				
			Hepatic	350				
			Renal	88 M	175 M (increased absolute and relative kidney weight)			
			Endocr	350				
			Dermal	350				
			Bd Wt	350				
			Other	350				

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
15	Mouse (B6C3F1)	16 wk 5 d/wk 1 x/d (GO)	Resp	700			NTP 1991a 115-96-8	NOAELs are for organ or tissue histopathology. Other refers to urinary bladder.
			Cardio	700				
			Gastro	700				
			Musc/skel	700				
			Hepatic	700				
			Renal	350 M	700 (nuclear enlargement of epithelial cells in renal tubules)			
			Endocr	700				
			Dermal	700				
			Bd Wt	700				
			Other	700				

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
16	Mouse (B6C3F1)	16 d 5 d/wk 1 x/d (GO)	Resp	700			NTP 1991a 115-96-8	NOAELs are for organ or tissue histopathology. Other refers to urinary bladder.
			Cardio	700				
			Gastro	700				
			Musc/skel	700				
			Hepatic	700				
			Renal	700				
			Endocr	700				
			Dermal	700				
			Bd Wt	700				
			Other	700				
Immuno/ Lymphoret								
17	Rat (Sprague-Dawley)	3 mo ad lib (F)		586 F			Anonymous 1977 115-96-8	NOAEL is for lymphoid tissues histopathology.
18	Rat (Fischer- 344)	16 d 5 d/wk 1 x/d (GO)		350			NTP 1991a 115-96-8	NOAEL is for histopathology of lymphoreticular organs and tissues.

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
19	Rat (Fischer- 344)	16 d 5 d/wk 1 x/d (GO)		350			NTP 1991a 115-96-8	NOAELs is for lymphoreticular tissues histopathology.
20	Mouse (B6C3F1)	16 wk 5 d/wk 1 x/d (GO)		700			NTP 1991a 115-96-8	The NOAEL is for histopathology of lymphoreticular organs.
21	Mouse (B6C3F1)	16 d 5 d/wk 1 x/d (GO)		700			NTP 1991a 115-96-8	NOAEL is for histopathology of lymphoreticular organs.
Neurological								
22	Rat (Sprague-Dawley)	3 mo ad lib (F)		586 F			Anonymous 1977 115-96-8	NOAEL is for brain histopathology.
23	Rat (Fischer- 344)	16 wk 5 d/wk 1 x/d (GO)		88[b] F		175 F (necrosis of hippocampal neurons)	NTP 1991a 115-96-8	
24	Rat (Fischer- 344)	16 d 5 d/wk 1 x/d (GO)		350			NTP 1991a 115-96-8	NOAEL is for brain histopathology.
25	Mouse (B6C3F1)	16 d 1 x/d (GO)		700			NTP 1991a 115-96-8	NOAEL is for brain histopathology.

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
26	Mouse (B6C3F1)	16 wk 5 d/wk 1 x/d (GO)		700			NTP 1991a 115-96-8	The NOAEL is for histopathology of the brain.
Reproductive								
27	Rat (Sprague-Dawley)	3 mo ad lib (F)		506 M 586 F			Anonymous 1977 115-96-8	NOAELs are for brain histopathology of reproductive organs.
28	Rat (Fischer- 344)	16 wk 5 d/wk 1 x/d (GO)		350			NTP 1991a 115-96-8	NOAEL is for histopathology of reproductive organs.
29	Rat (Fischer- 344)	16 d 5 d/wk 1 x/d (GO)		350			NTP 1991a 115-96-8	NOAEL is for reproductive organs histopathology.
30	Mouse (B6C3F1)	16 d 5 d/wk 1 x/d (GO)		700			NTP 1991a 115-96-8	NOAEL is for histopathology of reproductive organs.
31	Mouse (B6C3F1)	16 wk 5 d/wk 1 x/d (GO)		700			NTP 1991a 115-96-8	The NOAEL is for histopathology of reproductive organs.

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
32	Mouse (CD-1)	18 wk 1 x/d (GO)		175		350	(decreased number of F1 litters)	NTP 1991b 115-96-8	
Developmental									
33	Mouse (CD-1)	18 wk 1 x/d (GO)				175	(decreased number of live male F2 pups per litter)	NTP 1991b 115-96-8	

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
34	Rat (Fischer- 344)	104 wk 5 d/wk 1x/d (GO)	Resp	88			NTP 1991a 115-96-8	NOAELs are for organ or tissue histopathology. Other refers to urinary bladder.
			Cardio	88				
			Gastro	88				
			Hemato	88				
			Musc/skel	88				
			Hepatic	88				
			Renal	44[c]	88 (renal tubule epithelium hyperplasia)			
			Endocr	88				
			Dermal	88				
			Ocular	88				
			Bd Wt	88				
			Other	88				

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
35	Mouse (B6C3F1)	104 wk 5 d/wk 1 x/d (GO)	Resp	350			NTP 1991a 115-96-8	NOAELs are for organ or tissue histopathology. Other refers to urinary bladder.
			Cardio	350				
			Gastro	350				
			Hemato	350				
			Musc/skel	350				
			Hepatic	350				
			Renal		175 (nuclear enlargement in tubule cells)			
			Endocr	350				
			Dermal	350				
			Ocular	350				
			Bd Wt	350				
			Other	350				
36	Mouse (albino)	18 mo ad libitum (F)	Bd Wt	267		1333 (32% reduction in final body weight)	Takada et al. 1989 115-96-8	

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
37	Rat (Fischer- 344)	104 wk 5 d/wk 1x/d (GO)		88			NTP 1991a 115-96-8	The NOAEL is for histopathology of lymphoreticular organs and tissues.
38	Mouse (B6C3F1)	104 wk 5 d/wk 1 x/d (GO)		350			NTP 1991a 115-96-8	The NOAEL is for histopathology of lymphoreticular tissues.
Neurological								
39	Rat (Fischer- 344)	104 wk 5 d/wk 1x/d (GO)		44 F		88 F (degenerative lesions in cerebral cortex and brain stem)	NTP 1991a 115-96-8	
40	Mouse (B6C3F1)	104 wk 5 d/wk 1 x/d (GO)		350			NTP 1991a 115-96-8	The NOAEL is for histopathology of the brain.
Reproductive								
41	Rat (Fischer- 344)	104 wk 5 d/wk 1x/d (GO)		88			NTP 1991a 115-96-8	The NOAEL is for histopathology of reproductive organs.
42	Mouse (B6C3F1)	104 wk 5 d/wk 1 x/d (GO)		350			NTP 1991a 115-96-8	The NOAEL is for histopathology of the reproductive organs.

Table 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Cancer								
43	Rat (Fischer- 344)	104 wk 5 d/wk 1x/d (GO)				88 (CEL:renal tubule adenomas)	NTP 1991a 115-96-8	
44	Mouse (B6C3F1)	104 wk 5 d/wk 1x/d (GO)				350 M (CEL: renal adenoma and adenocarcinoma) 350 F (CEL: hardenian gland tumors)	NTP 1991a 115-96-8	Carcinogenic activity was considered equivocal by NTP.
45	Mouse (albino)	18 mo ad libitum (F)				267 M (CEL:hepatocellular adenoma/carcinoma) 267 F (CEL: leukemia)	Takada et al. 1989 115-96-8	

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

b Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.6 mg/kg/day; the MRL was derived by adjusting the BMDL10 of 85.07 mg/kg/day for continuous exposure (85.07 mg/kg/day 5/7) and dividing by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

c Used to derive a chronic-duration MRL of 0.2 mg/kg/day; the MRL was derived by adjusting the BMDL10 of 32.82 mg/kg/day for continuous exposure (32.82 x 5/7) and dividing by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; pnd = post-natal day; Resp = respiratory; wk = week(s); x = time(s)

Figure 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral

Acute (≤14 days)

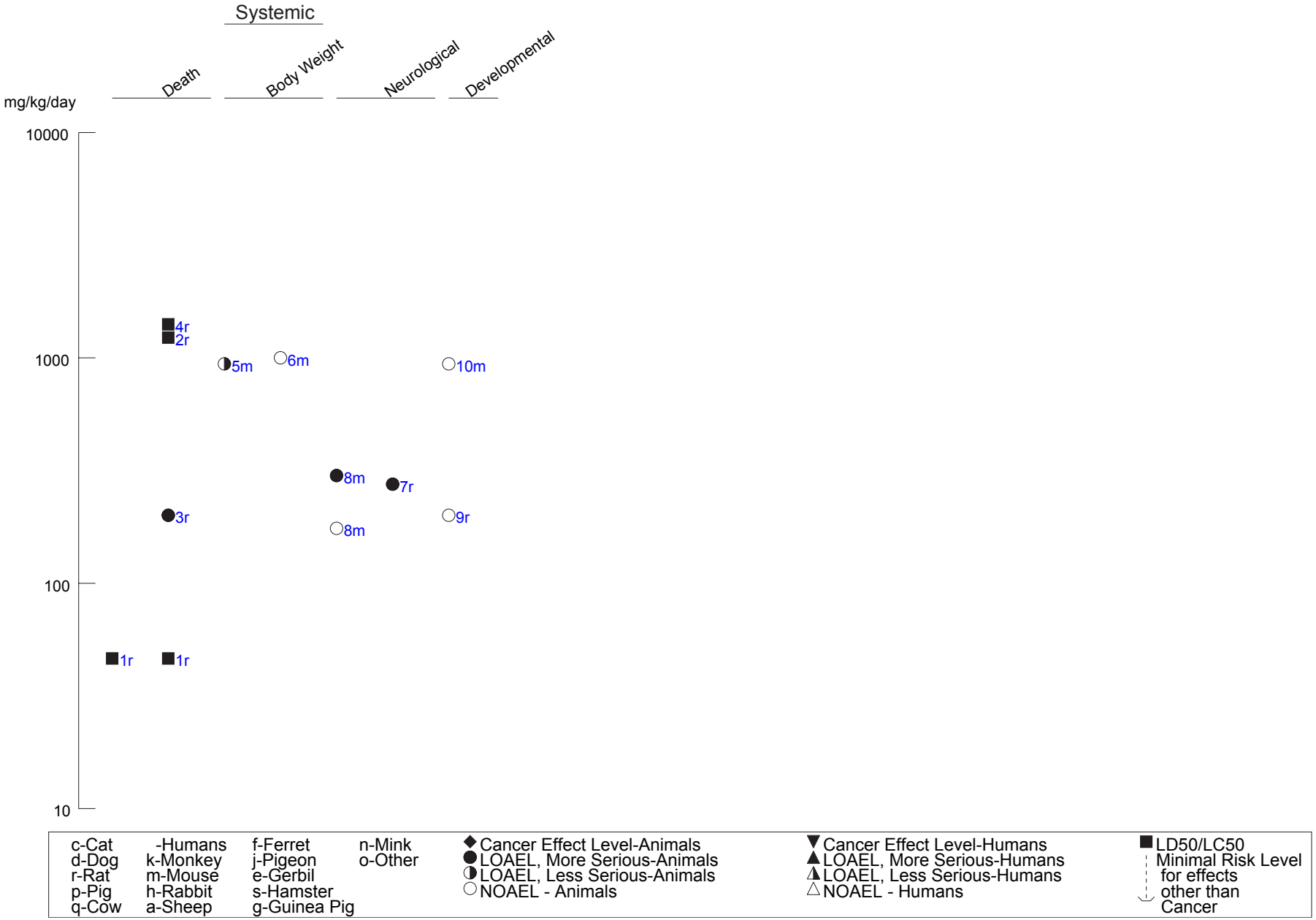


Figure 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral *(Continued)*

Intermediate (15-364 days)

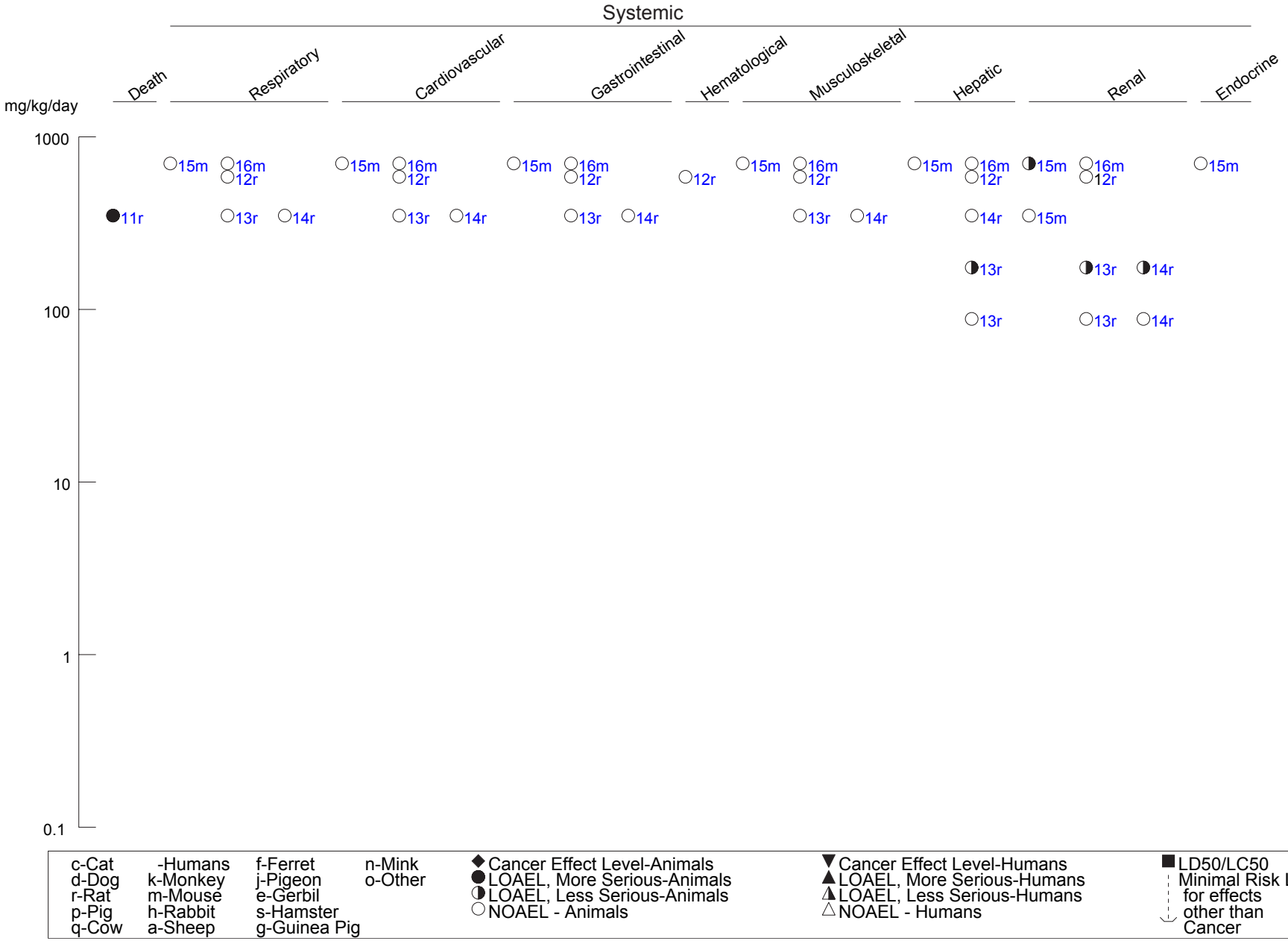


Figure 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral *(Continued)*

Intermediate (15-364 days)

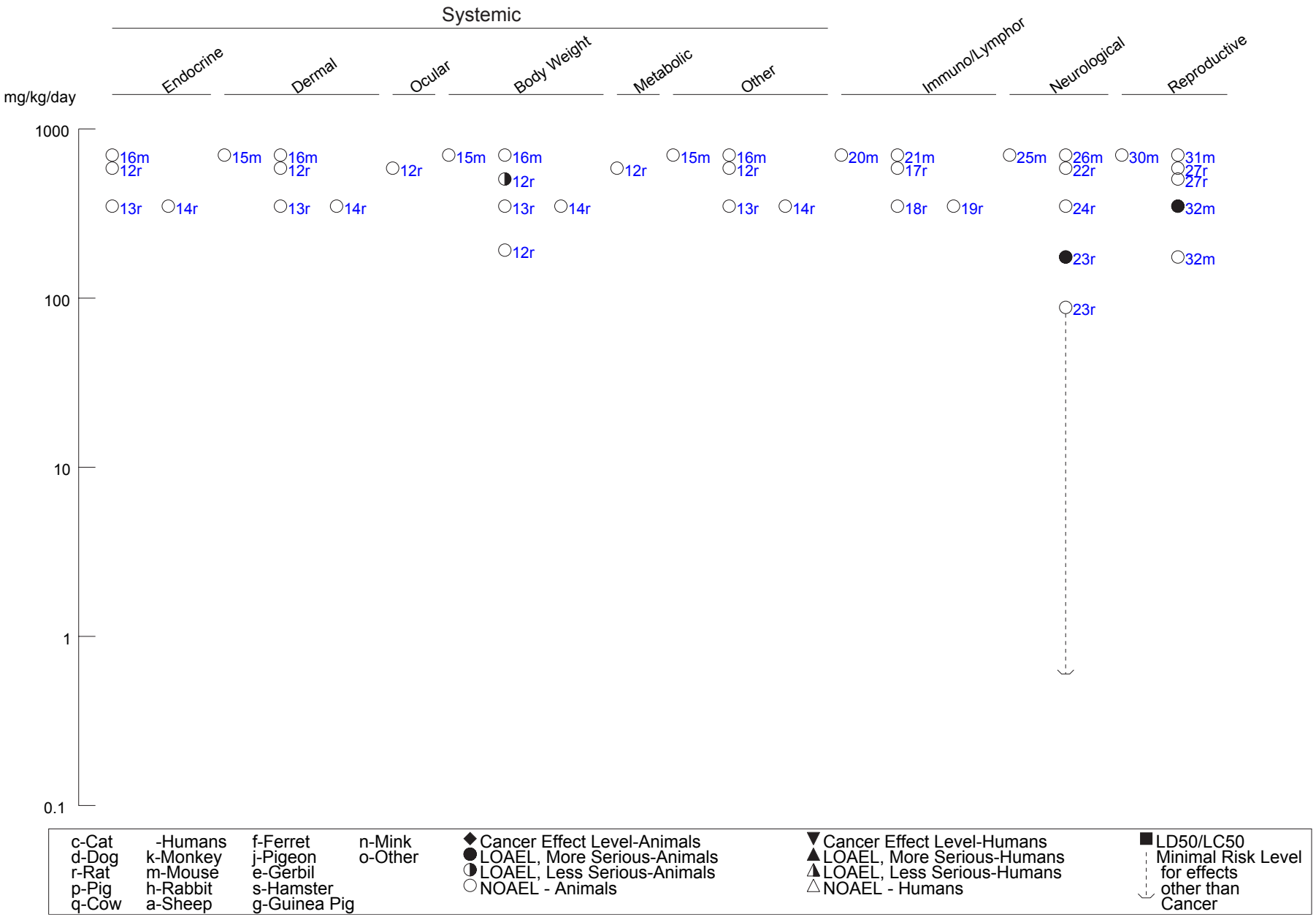


Figure 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral *(Continued)*

Intermediate (15-364 days)

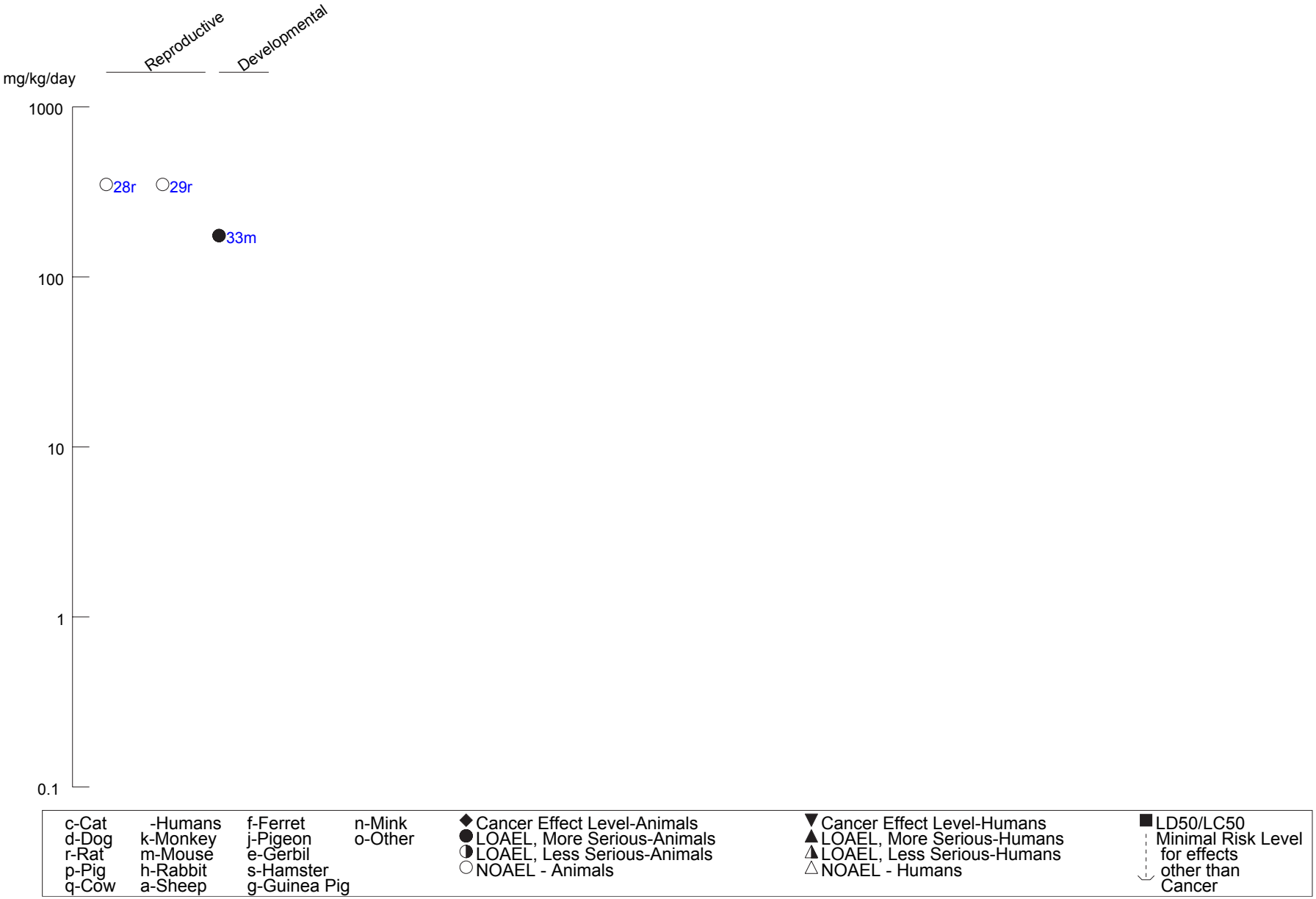


Figure 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral *(Continued)*

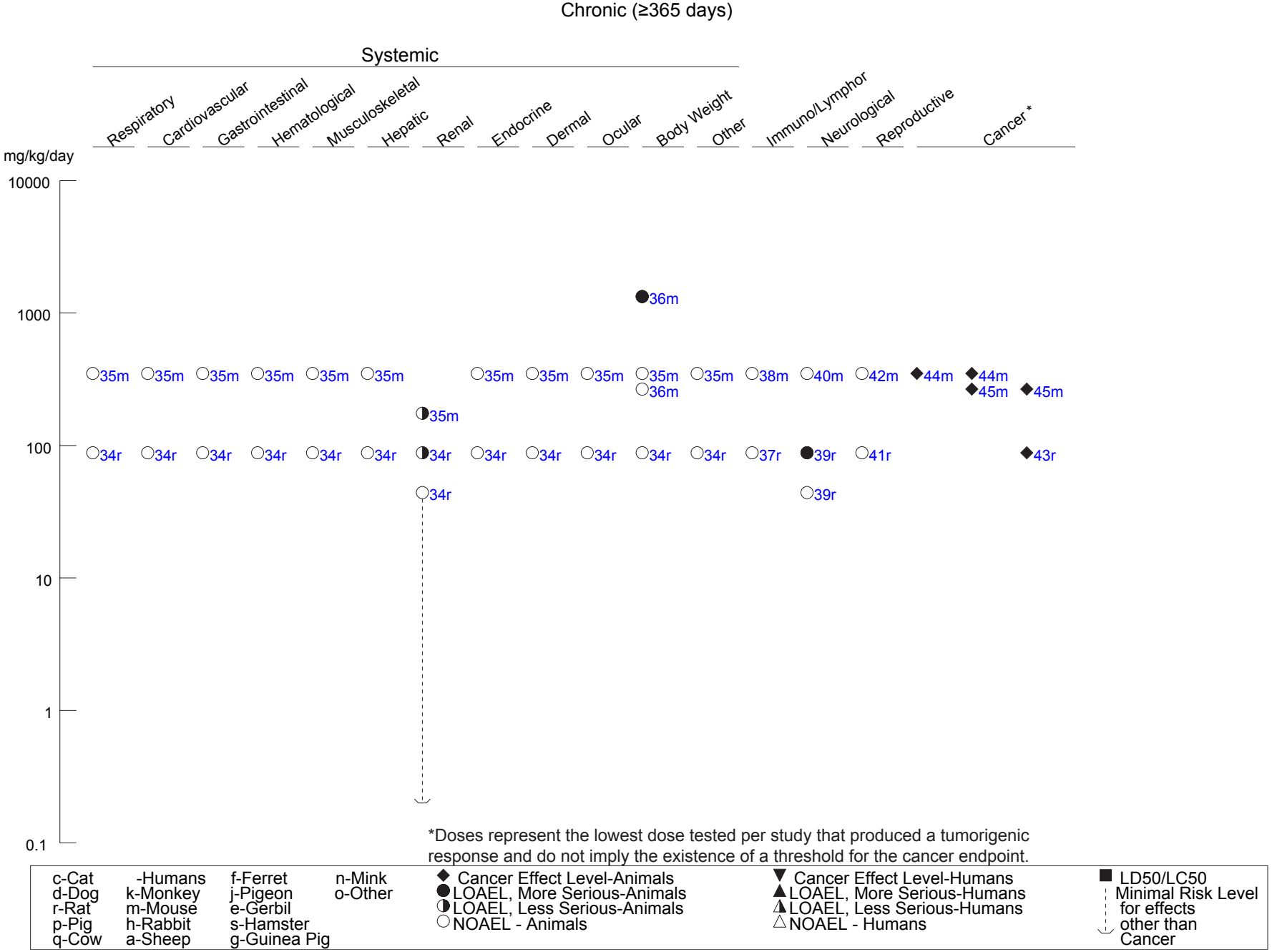


Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (NS)	once (GO)				2000 (2/2 died)	Dow Chemical Co. 1956 126-73-8	
2	Rat (NS)	once (NS)				1600 (LD50 is 1600-3200 mg/kg)	Eastman Kodak Co. 1968 126-73-8	
3	Rat (NS)	once (NS)				2250 (lethal dose)	El Dupont Denemours 1953a, 1953b 126-73-8	
4	Rat (Sprague-Dawley)	once (GO)				1400 (14-day LD50)	Johannsen et al. 1977 126-73-8	
5	Rat (NS)	once (NS)				20000 (all rats died)	MacKeller 1976 126-73-8	
6	Rat (Wistar)	11 d Gd 7-17 1 x/d (GO)				800 F (5/5 dead pregnant rats after 5 or 6 treatments)	Noda et al. 1994 126-73-8	
7	Rat (Sprague-Dawley)	once (G)				3160 M (LD50)	Stauffer Chemical Co. 1973 126-73-8	
8	Rat (NS)	once (G)				3200 (LD50)	Union Carbide Corp 1943 126-73-8	

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form	Comments
9	Mouse (NS)	once (NS)				400 (LD50 is 400-800 mg/kg)	Eastman Kodak Co. 1968 126-73-8	
Systemic								
10	Rat (Sprague-Dawley)	14 d 1x/d (G)	Bd Wt	411			Laham et al. 1983 126-73-8	
11	Rat (Sprague-Dawley)	14 d 1 x/d (G)	Resp	411			Laham et al. 1984b 126-73-8	NOAELs are for organ weight and histopathology.
			Cardio	411				
			Hemato	137 F	411 F (decreased hemoglobin)			
			Hepatic	137	411 (increased absolute and relative liver weight)			
			Renal	411				
			Bd Wt	411				
			Metab		137 F (increased serum potassium)			
12	Rat (Wistar)	11 d Gd 7-17 1 x/d (GO)	Bd Wt	100 F		200 F (37% reduced adjusted body weight gain on Gd 0-20)	Noda et al. 1994 126-73-8	

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
13	Rat (Wistar)	11 d Gd 7-17 1 x/d (GO)	Hepatic	500 F			Noda et al. 1994 126-73-8	Liver and kidneys NOAEL are for organ weight.
			Renal	500 F				
			Bd Wt	62.5 F[b]	125 F (13% reduced adjusted body weight gain on Gd 0-20)			
Immuno/ Lymphoret								
14	Rat (Sprague-Dawley)	14 d 1 x/d (G)		137 F	411 F (decreased absolute and relative spleen weight)		Laham et al. 1984b 126-73-8	
Neurological								
15	Rat (Sprague-Dawley)	once (GO)		325	1000 (decreased motor activity 11 hours postdosing)		Healy et al. 1995 126-73-8	
16	Rat (Sprague-Dawley)	14 d 1x/d (G)		274	411 (decreased nerve conduction velocity)		Laham et al. 1983 126-73-8	
17	Rat (Sprague-Dawley)	14 d 1 x/d (G)		411			Laham et al. 1984b 126-73-8	NOAEL is for weight and histopathology of the brain.
Reproductive								
18	Rat (Sprague-Dawley)	14 d 1 x/d (G)		137 M	411 M (degenerative changes in seminiferous tubules)		Laham et al. 1984b 126-73-8	

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Developmental								
19	Rat (Wistar)	11 d Gd 7-17 1 x/d (GO)		400 F			Noda et al. 1994 126-73-8	NOAEL is for standard developmental indices.
20	Rat (Wistar)	11 d Gd 7-17 1 x/d (GO)		500 F			Noda et al. 1994 126-73-8	NOAEL is for standard developmental indices.
INTERMEDIATE EXPOSURE								
Death								
21	Rat (Sprague-Dawley)	13 wk 1x/d (GO)				325 (7/24 deaths before end of the study)	Healy et al. 1995 126-73-8	
Systemic								
22	Rat (Sprague-Dawley)	10 wk ad lib (F)	Gastro	143 M			Arnold et al. 1997 126-73-8	NOAELs are for histopathology of stomach and kidneys.
			Renal	143 M				
			Bd Wt	33 M	143 M (final body weight reduced more than 10% relative to controls)			
			Other	9 M[c,d]	33 M (urothelial hyperplasia)			
23	Rat (Sprague-Dawley)	12 mo ad lib (F)	Hemato	182 F			Auletta et al. 1998a 126-73-8	

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
24	Rat (Sprague-Dawley)	90 d ad lib (F)	Resp	423 F			FMC 1985a 126-73-8	NOAELs are for organ histopathology.
			Cardio	423 F				
			Gastro	423 F				
			Hemato	68.1 M	360 M (increased activated partial thromboplastin time)			
			Musc/skel	423 F				
			Hepatic	13.8 M	68.1 M (increased absolute and relative liver weight)			
			Renal	423 F				
			Endocr	423 F				
			Dermal	423 F				
			Ocular	423 F				
			Bd Wt	68.1 M	360 M (14% reduction in final body weight)			
			Metab	68.1 M	360 M (increased serum calcium)			
			Other	13.8 M	68.1 M (urinary bladder epithelial cell hyperplasia)			

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
25	Rat (Sprague-Dawley)	13 wk 1x/d (GO)	Bd Wt	100	325 (final body weight reduced 15-20%)		Healy et al. 1995 126-73-8	
26	Rat (Sprague-Dawley)	18 wk 5 d/wk 1 x/d (G)	Resp	333			Laham et al. 1985a 126-73-8	NOAELs are for organ histopathology.
			Cardio	333				
			Gastro	333				
			Hemato	333				
			Hepatic	200 F	333 F (increase absolute and relative liver weight)			
			Renal	333				
			Endocr	333				
			Bd Wt	200 M	333 M (14% reduction in final body weight)			
			Metab	333				
			Other		200 (epithelial hyperplasia of the urinary bladder)			

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
27	Rat (Wistar)	10 wk ad lib (F)	Hemato		460 M (increased coagulation time)		Oishi et al. 1980 126-73-8	
			Renal		460 M (increased BUN)			
			Bd Wt		460 M (17% reduction in final body weight)	783 M (31% reduction in final body weight)		
28	Rat (Wistar)	9 wk ad lib (F)	Hemato	460 M			Oishi et al. 1982 126-73-8	
			Hepatic		460 M (increase in absolute and relative liver weight; slight histopathology)			
			Renal		460 M (increased BUN)			
			Bd Wt		460 M (11% decrease in final body weight)			
			Metab	460 M				

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Rat (Sprague-Dawley)	70-110 d Gd 1-20 Ld 1-20 ad lib (F)	Hepatic	51 F	217 F (hepatic centrilobular hypertrophy in F0 females)		Tyl et al. 1997 126-73-8	
			Renal	51 M	217 M (renal pelvic epithelial hyperplasia in F1 males)			
			Bd Wt	51	217 (greater than 10% reduction in body weight in F0 generation)			
			Other	15	51 (bladder hyperplasia in F0 generation)			

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
30	Mouse (CD-1)	13 wk ad lib (F)	Resp	1776 F			Auletta 1991 126-73-8	
			Cardio	1776 F				
			Gastro	1776 F				
			Hemato	382 M	1478 M (increased platelet counts)			
			Musc/skel	1776 F				
			Hepatic	95 M	382 M (hepatocyte hypertrophy)			
			Renal	1776 F				
			Endocr	1776 F				
			Ocular	1776 F				
			Bd Wt	1776 F				
			Metab	382 M	1478 M (increased serum calcium)			
			Other	95 M	382 M (urinary bladder epithelial hyperplasia)			
31	Mouse (CD-1)	12 mo ad lib (F)	Hemato	711 F			Auletta et al. 1998b 126-73-8	
Immuno/ Lymphoret								
32	Rat (Sprague-Dawley)	90 d ad lib (F)		423 F			FMC 1985a 126-73-8	NOAEL is for lymphoid organs histopathology.

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
33	Rat (Sprague-Dawley)	18 wk 5 d/wk 1 x/d (G)		333			Laham et al. 1985a 126-73-8	NOAEL is for spleen histopathology.
34	Rat (Wistar)	9 wk ad lib (F)		460 M			Oishi et al. 1982 126-73-8	NOAEL is for spleen histopathology.
35	Mouse (CD-1)	13 wk ad lib (F)		1776 F			Auletta 1991 126-73-8	NOAEL is for lymphoid tissues histopathology.
Neurological								
36	Rat (Sprague-Dawley)	90 d ad lib (F)		423 F			FMC 1985a 126-73-8	NOAEL is for histopathology of central and peripheral nervous tissues.
37	Rat (Sprague-Dawley)	13 wk 1x/d (GO)		32.5	100 (excessive salivation)		Healy et al. 1995 126-73-8	
38	Rat (Sprague-Dawley)	18 wk 5 d/wk 1 x/d (G)		333			Laham et al. 1985a 126-73-8	NOAEL is for clinical signs and brain histopathology.
39	Mouse (CD-1)	13 wk ad lib (F)		1776 F			Auletta 1991 126-73-8	NOAEL is for histopathology of the brain and spinal cord.

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
40	Rat (Sprague-Dawley)	90 d ad lib (F)		360 M 423 F			FMC 1985a 126-73-8	NOAEL is for histopathology of reproductive organs.
41	Rat (Sprague-Dawley)	18 wk 5 d/wk 1 x/d (G)		333			Laham et al. 1985a 126-73-8	NOAEL is weight and histopathology of ovaries or testes.
42	Rat (Sprague-Dawley)	70-110 d Gd 1-20 Ld 1-20 ad lib (F)		217			Tyl et al. 1997 126-73-8	NOAEL is for reproductive indices in 2-generation study.
43	Mouse (CD-1)	13 wk ad lib (F)		1478 M 1776 F			Auletta 1991 126-73-8	NOAEL is for histopathology of reproductive organs.
Developmental								
44	Rat (Sprague-Dawley)	70-110 d Gd 1-20 Ld 1-20 ad lib (F)		51	217 (reduced F1 and F2 pup weight during preweaning period)		Tyl et al. 1997 126-73-8	

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
45	Rat (Sprague-Dawley)	2 yr ad lib (F)	Resp	182 F			Auletta et al. 1998a 126-73-8	NOAELs are for tissue or organ histopathology.
			Cardio	182 F				
			Gastro	182 F				
			Hemato	182 F				
			Musc/skel	182 F				
			Hepatic	182 F				
			Renal	182 F				
			Endocr	182 F				
			Dermal	182 F				
			Ocular	182 F				
			Bd Wt	12 F	42 F (12% reduction in final body weight)	182 F (20% reduction in final body weight)		
			Other	9 M	33 M (urinary bladder hyperplasia)			

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
46	Mouse (CD-1)	18 mo ad lib (F)	Resp	711			Auletta et al. 1998b 126-73-8	NOAELs are for organ or tissue histopathology.
			Cardio	711 F				
			Gastro	711 F				
			Hemato	711 F				
			Musc/skel	711				
			Hepatic	28.9 M	169 M (increased absolute and relative liver weight)			
			Renal	711				
			Endocr	711 F				
			Dermal	711 F				
			Ocular	711				
			Bd Wt	711 F				
			Other	711				
Immuno/ Lymphoret								
47	Rat (Sprague-Dawley)	2 yr ad lib (F)		182 F			Auletta et al. 1998a 126-73-8	The NOAEL is for histopathology of lymphoreticular organs.
48	Mouse (CD-1)	18 mo ad lib (F)		711 F			Auletta et al. 1998b 126-73-8	NOAEL is for lymphoid organs histopathology.

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
49	Rat (Sprague-Dawley)	2 yr ad lib (F)		182 F			Auletta et al. 1998a 126-73-8	The NOAEL is for histopathology of central or peripheral nervous system.
50	Mouse (CD-1)	18 mo ad lib (F)		711 F			Auletta et al. 1998b 126-73-8	NOAEL is for nervous system tissues histopathology.
Reproductive								
51	Rat (Sprague-Dawley)	2 yr ad lib (F)		143 M 182 F			Auletta et al. 1998a 126-73-8	The NOAEL is for histopathology of the reproductive organs.
52	Mouse (CD-1)	18 mo ad lib (F)		585 M 711 F			Auletta et al. 1998b 126-73-8	NOAELs are for histopathology of reproductive organs.
Cancer								
53	Rat (Sprague-Dawley)	2 yr ad lib (F)				143 M (CEL: urinary bladder papillomas and carcinomas)	Auletta et al. 1998a 126-73-8	

Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
54	Mouse (CD-1)	18 mo ad lib (F)				585 M (CEL: hepatocellular adenomas)	Auletta et al. 1998b 126-73-8	

a The number corresponds to entries in Figure 3-3.

b Used to derive an acute-duration oral MRL of 1.1 mg/kg/day; the MRL was derived by dividing the BMDL1SD of 111.47 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

c Used to derive an intermediate-duration oral MRL of 0.08 mg/kg/day; the MRL was derived by dividing the BMDL10 of 8.03 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

d ATSDR adopted the intermediate-duration oral MRL also as chronic-duration oral MRL for TnBP.

ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; Hemato = hematological; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s); yr = year(s)

Figure 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral

Acute (≤14 days)

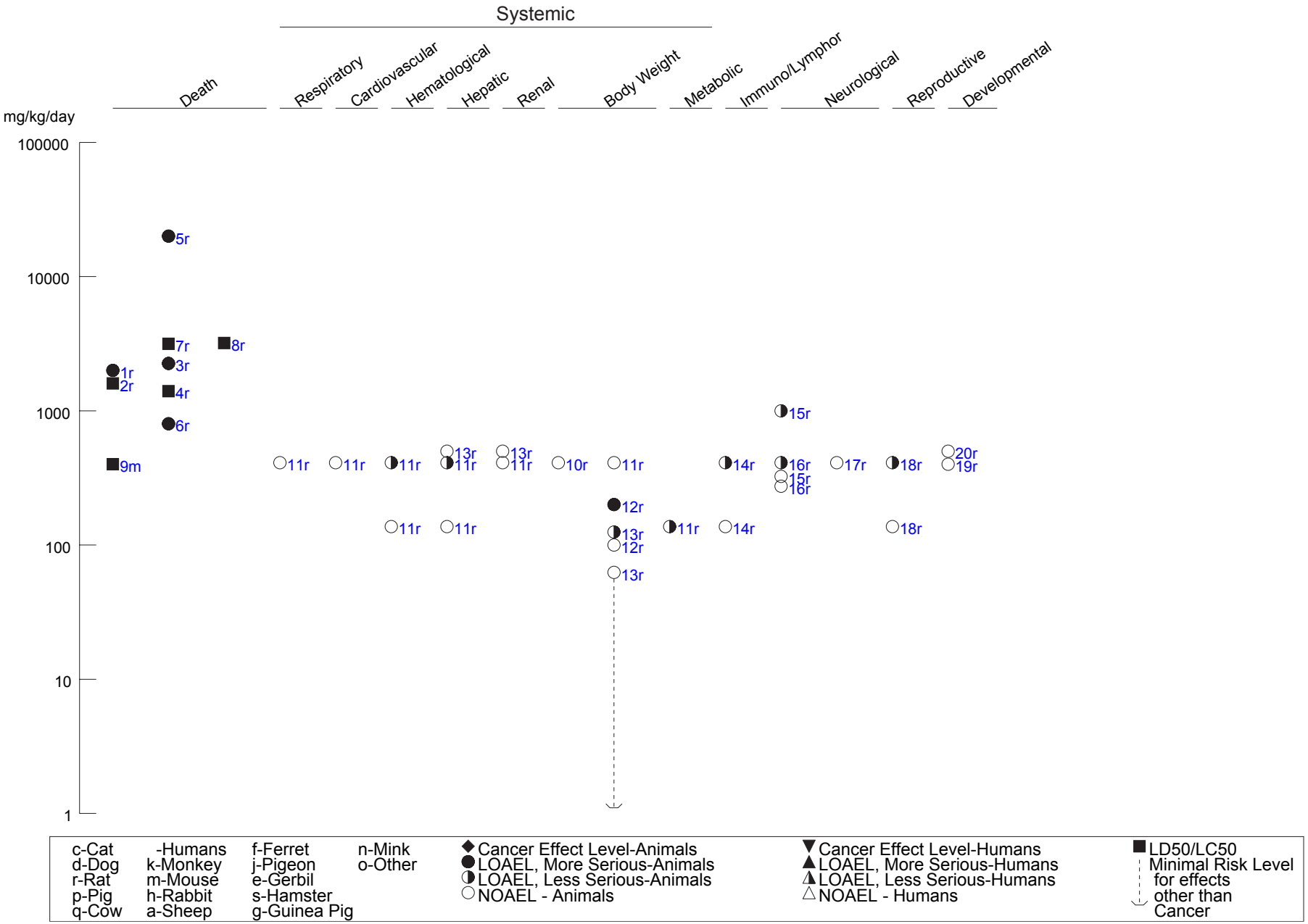


Figure 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral *(Continued)*

Intermediate (15-364 days)

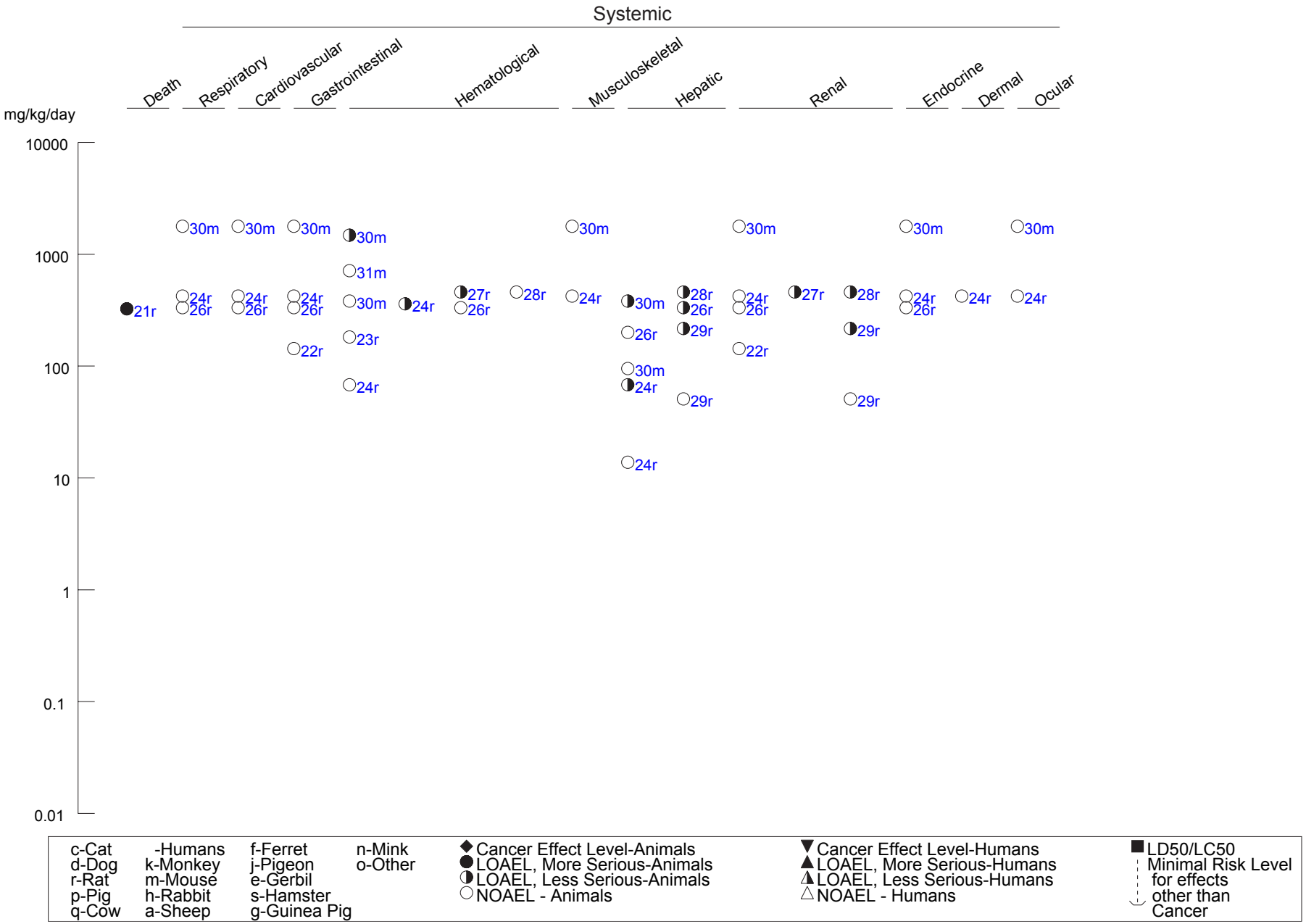


Figure 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral *(Continued)*

Intermediate (15-364 days)

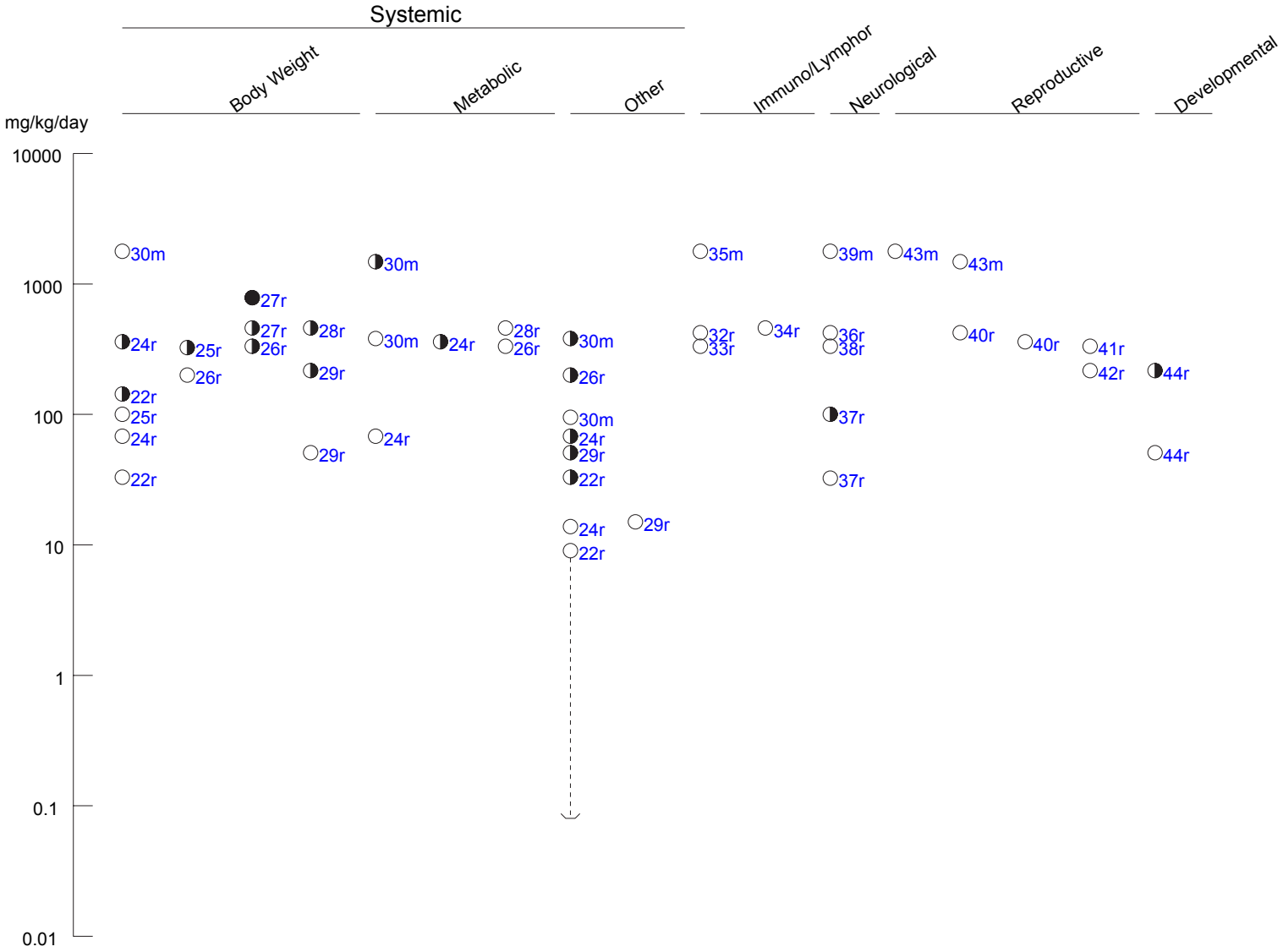
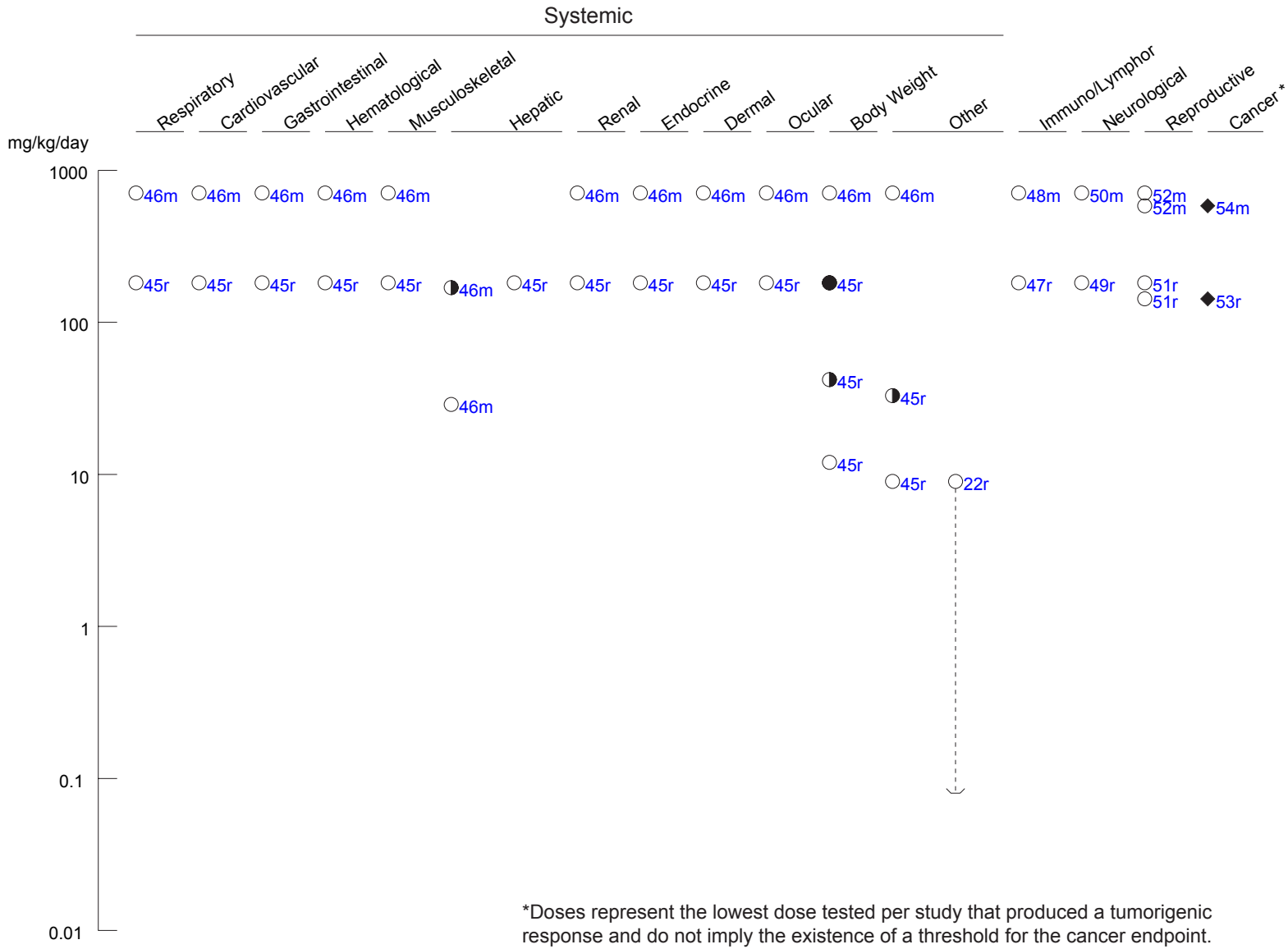


Figure 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral *(Continued)*

Chronic (≥365 days)



*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 endpoint.

c-Cat d-Dog r-Rat p-Pig q-Cow
-Humans k-Monkey m-Mouse h-Rabbit a-Sheep
f-Ferret j-Pigeon e-Gerbil s-Hamster g-Guinea Pig
n-Mink o-Other

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Table 3-4 Levels of Significant Exposure to Tris(2-butoxyethyl) Phosphate (TBEP) - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Fischer- 344)	Once (G)				13278 M (LD50) 5383 F (LD50)	Mobil Oil Corporation 1979a 78-51-3	
Systemic								
2	Rat (Sprague-Dawley)	14 d 1 x/d (GO)	Resp	100			Komsta et al. 1989 78-51-3	NOAELs are for organ weight and histopathology.
			Cardio	100				
			Gastro	100				
			Hemato	100				
			Musc/skel	100				
			Hepatic	100				
			Renal	100				
			Endocr	100				
			Dermal	100				
			Bd Wt	100				
			Metab	100				
3	Rat (CD)	10 d Gd 6-15 1 x/d (GO)	Bd Wt	500[b] F		1500 F (weight gain reduced 35% during Gd 6-15)	Monsanto Co. 1985b 78-51-3	

Table 3-4 Levels of Significant Exposure to Tris(2-butoxyethyl) Phosphate (TBEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
4	Rat (Sprague-Dawley)	14 d 1 x/d (GO)		100			Komsta et al. 1989 78-51-3	NOAEL is for lymphoid organ weights and histopathology.
Neurological								
5	Rat (Sprague-Dawley)	14 d 1 x/d (GO)		100			Komsta et al. 1989 78-51-3	NOAEL is for weight and histopathology of the brain.
6	Rat (Sprague-Dawley)	once (G)		1500 F	1750 F (slight tremors and piloerection)	3200 F (abnormal gait, tremors)	Laham et al. 1985b 78-51-3	
Reproductive								
7	Rat (Sprague-Dawley)	14 d 1 x/d (GO)		100			Komsta et al. 1989 78-51-3	NOAEL is for weight and histopathology of the testes and ovaries.
Developmental								
8	Rat (CD)	10 d Gd 6-15 1 x/d (GO)		1500 F			Monsanto Co. 1985b 78-51-3	NOAEL is for standard developmental indices.

Table 3-4 Levels of Significant Exposure to Tris(2-butoxyethyl) Phosphate (TBEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Systemic								
9	Rat (Sprague-Dawley)	18 wk ad lib (F)	Resp	698 F			Reyna and Thake 1987a 78-51-3	NOAELs are for tissue histopathology.
			Cardio	698 F				
			Gastro	698 F				
			Hemato	173 M	578 M (increased platelet counts)			
			Musc/skel	698 F				
			Hepatic	17.3[c] M	173 M (periportal hepatocelllar vacuolization)			
			Renal	698 F				
			Endocr	698 F				
			Dermal	698 F				
			Ocular	698 F				
			Bd Wt	698 F				
			Metab	698 F				
			Other	698 F				
Immuno/ Lymphoret								
10	Rat (Sprague-Dawley)	18 wk ad lib (F)		698 F			Reyna and Thake 1987a 78-51-3	NOAEL is for lymphoid tissues histopathology.
Neurological								
11	Rat (Sprague-Dawley)	18 wk ad lib (F)		698 M			Reyna and Thake 1987a 78-51-3	NOAEL is for brain and sciatic nerve histopathology.

Table 3-4 Levels of Significant Exposure to Tris(2-butoxyethyl) Phosphate (TBEP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
12	Rat (Sprague-Dawley)	18 wk ad lib (F)		209 F	698 F (reduced conduction velocity in tail nerve)		Reyna and Thake 1987b 78-51-3	
Reproductive								
13	Rat (Sprague-Dawley)	18 wk ad lib (F)		578 M 698 F			Reyna and Thake 1987a 78-51-3	NOAEL is for histopathology of reproductive organs.

a The number corresponds to entries in Figure 3-4.

b Used to derive an acute-duration oral MRL of 4.8 mg/kg/day; the MRL was derived by dividing the BMDL1SD of 477.25 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

c Used to derive an intermediate-duration oral MRL of 0.09 mg/kg/day; the MRL was derived by dividing the BMDL10 of 8.88 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s)

Figure 3-4 Levels of Significant Exposure to Tris(2-butoxyethyl) Phosphate (TBEP) - Oral

Acute (≤14 days)

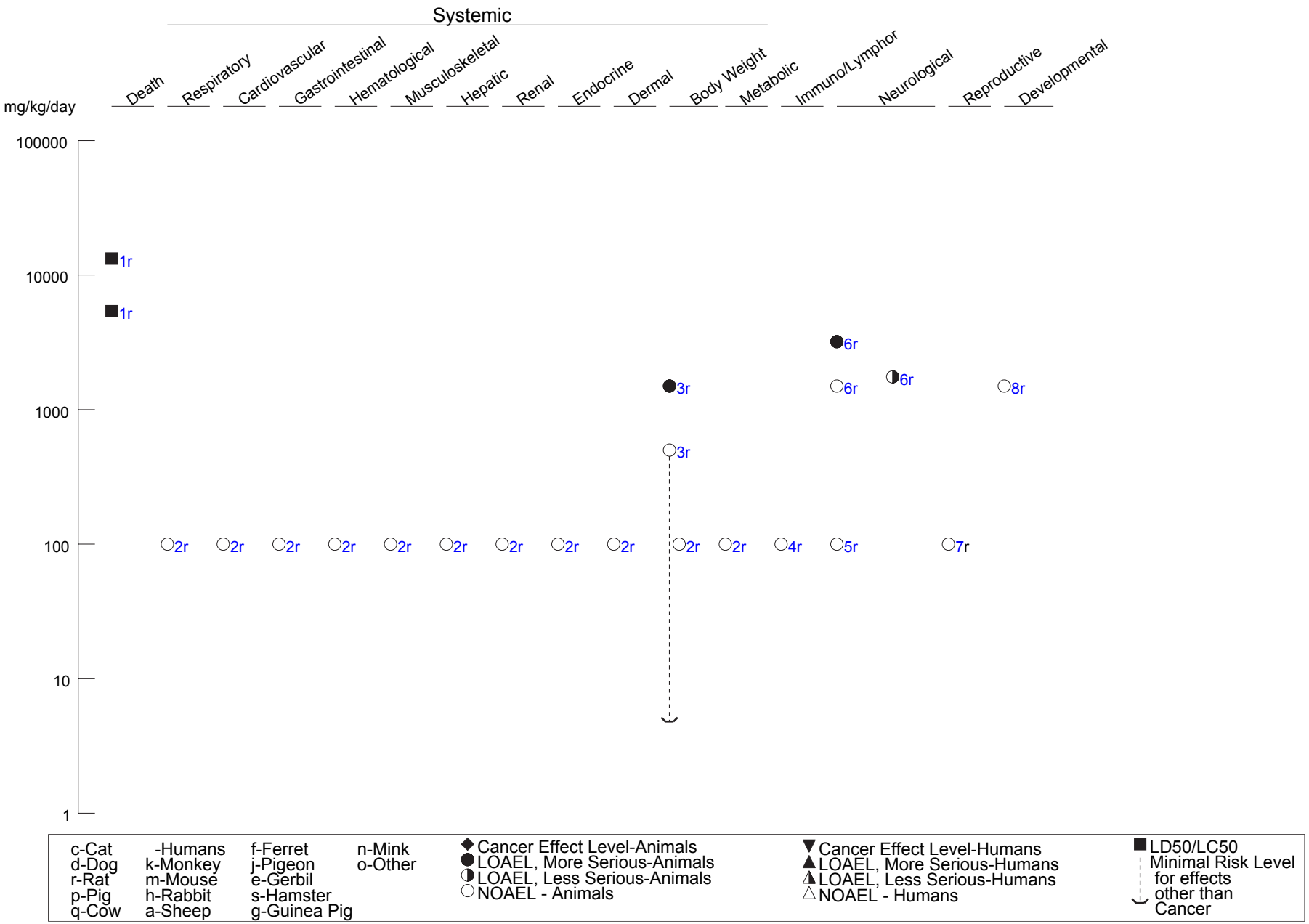


Figure 3-4 Levels of Significant Exposure to Tris(2-butoxyethyl) Phosphate (TBEP) - Oral *(Continued)*

Intermediate (15-364 days)

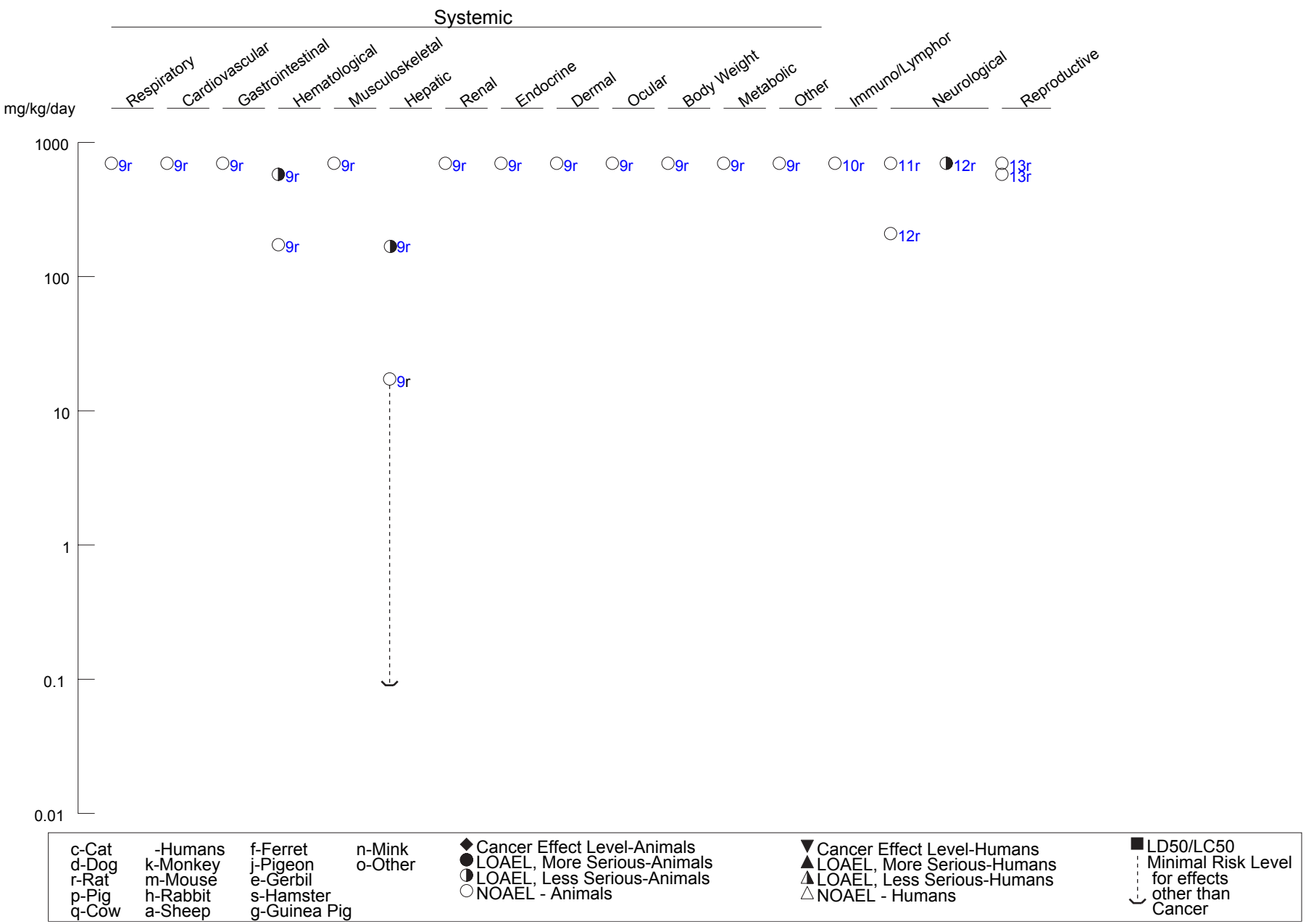


Table 3-5 Levels of Significant Exposure to Tris(1,3-dichloro-2-propyl) (TDCP) - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (albino)	once (G)				2830 (LD50)	Eldefrawi et al. 1977 13674-87-8	
Systemic								
2	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)	Bd Wt	25 F		100 F (29% decreased weight gain on Gd 6-11)	Stauffer Chemical Co. 1981b 13674-87-8	
Developmental								
3	Rat (Sprague-Dawley)	10 d Gd 6-15 1 x/d (GO)		100 F		400 F (reduced fetal viability)	Stauffer Chemical Co. 1981b 13674-87-8	

Table 3-5 Levels of Significant Exposure to Tris(1,3-dichloro-2-propyl) (TDCP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Systemic								
4	Rat (Sprague-Dawley)	12 mo ad lib (F)	Resp	80			Stauffer Chemical Co. 1981a 13674-87-8	
			Cardio	80				
			Gastro	80				
			Hemato	20 M	80 M (10.6% reduction in hemoglobin and red cell count at 12 months)			
			Musc/skel	80				
			Hepatic	5 M	20 M (12% increase in absolute liver weight)			
			Renal		5 M[b] (12% increase in absolute kidney weight)			
			Endocr	5 M	20 M (14% increase in absolute thyroid weight)			
			Dermal	80				
			Ocular	80				
			Bd Wt	20 M	80 M (12% reduction in body weight on week 50)			

Table 3-5 Levels of Significant Exposure to Tris(1,3-dichloro-2-propyl) (TDCP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
5	Rabbit (New Zealand)	12 wk 1 x/d (GO)	Hemato	200 M			Anonymous 1977 13674-87-8	Other is for urinary bladder histopathology.
			Hepatic	20 M	200 M (23% increase in relative liver weight)			
			Renal	20 M	200 M (14% increase in absolute kidney weight)			
			Endocr	200 M				
			Bd Wt	200 M				
			Other	200 M				
Immuno/ Lymphoret								
6	Rat (Sprague-Dawley)	12 mo ad lib (F)		80			Stauffer Chemical Co. 1981a 13674-87-8	NOAEL is for lymphoid tissues histopathology.
Neurological								
7	Rat (Sprague-Dawley)	12 mo ad lib (F)		80			Stauffer Chemical Co. 1981a 13674-87-8	NOAEL is for histopathology of the brain and spinal cord.
Reproductive								
8	Rat (Sprague-Dawley)	12 mo ad lib (F)		80			Stauffer Chemical Co. 1981a 13674-87-8	NOAEL is for histopathology of the reproductive organs.
9	Rabbit (New Zealand)	12 wk 1 x/d (GO)		200 M			Anonymous 1977 13674-87-8	NOAEL is for fertility parameters.

Table 3-5 Levels of Significant Exposure to Tris(1,3-dichloro-2-propyl) (TDCP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
10	Rat (Sprague-Dawley)	24 mo ad lib (F)	Resp	80			Stauffer Chemical Co. 1981a 13674-87-8	
			Cardio	80				
			Gastro	80				
			Hemato	20	80 (reduced hemoglobin, hematocrit, and total erythrocyte count)			
			Musc/skel	80				
			Hepatic	20	80 (foci/areas of hepatocellular alterations;dilation of sinusoids)			
			Renal	5 M[c]	20 M (hyperplasia of convoluted tubular epithelium)			
			Endocr	80				
			Dermal	80				
			Ocular	20	80 (accelerated development of sacculation along retinal arterioles)			
			Bd Wt	20		80 (21-24% reduction in final body weight)		

Table 3-5 Levels of Significant Exposure to Tris(1,3-dichloro-2-propyl) (TDCP) - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
11	Rat (Sprague-Dawley)	24 mo ad lib (F)		80			Stauffer Chemical Co. 1981a 13674-87-8	NOAEL is for lymphoid tissues histopathology.
Neurological								
12	Rat (Sprague-Dawley)	24 mo ad lib (F)		80			Stauffer Chemical Co. 1981a 13674-87-8	NOAEL is for histopathology of the brain and spinal cord.
Reproductive								
13	Rat (Sprague-Dawley)	24 mo ad lib (F)		80			Stauffer Chemical Co. 1981a 13674-87-8	NOAEL is for histopathology of the reproductive organs.
Cancer								
14	Rat (Sprague-Dawley)	24 mo ad lib (F)				20 M (CEL: testicular interstitial cell tumors)	Stauffer Chemical Co. 1981a 13674-87-8	
						20 (CEL: renal cortical tumors)		

a The number corresponds to entries in Figure 3-5.

b Used to derive an intermediate-duration oral MRL of 0.05 mg/kg/day; the MRL was derived by dividing the BMDL1SD of 4.69 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

c Used to derive a chronic-duration oral MRL of 0.02 mg/kg/day; the MRL was derived by dividing the BMDL10 of 1.94 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; wk = week(s); x = time(s)

Figure 3-5 Levels of Significant Exposure to Tris(1,3-dichloro-2-propyl) (TDCP) - Oral

Acute (≤14 days)

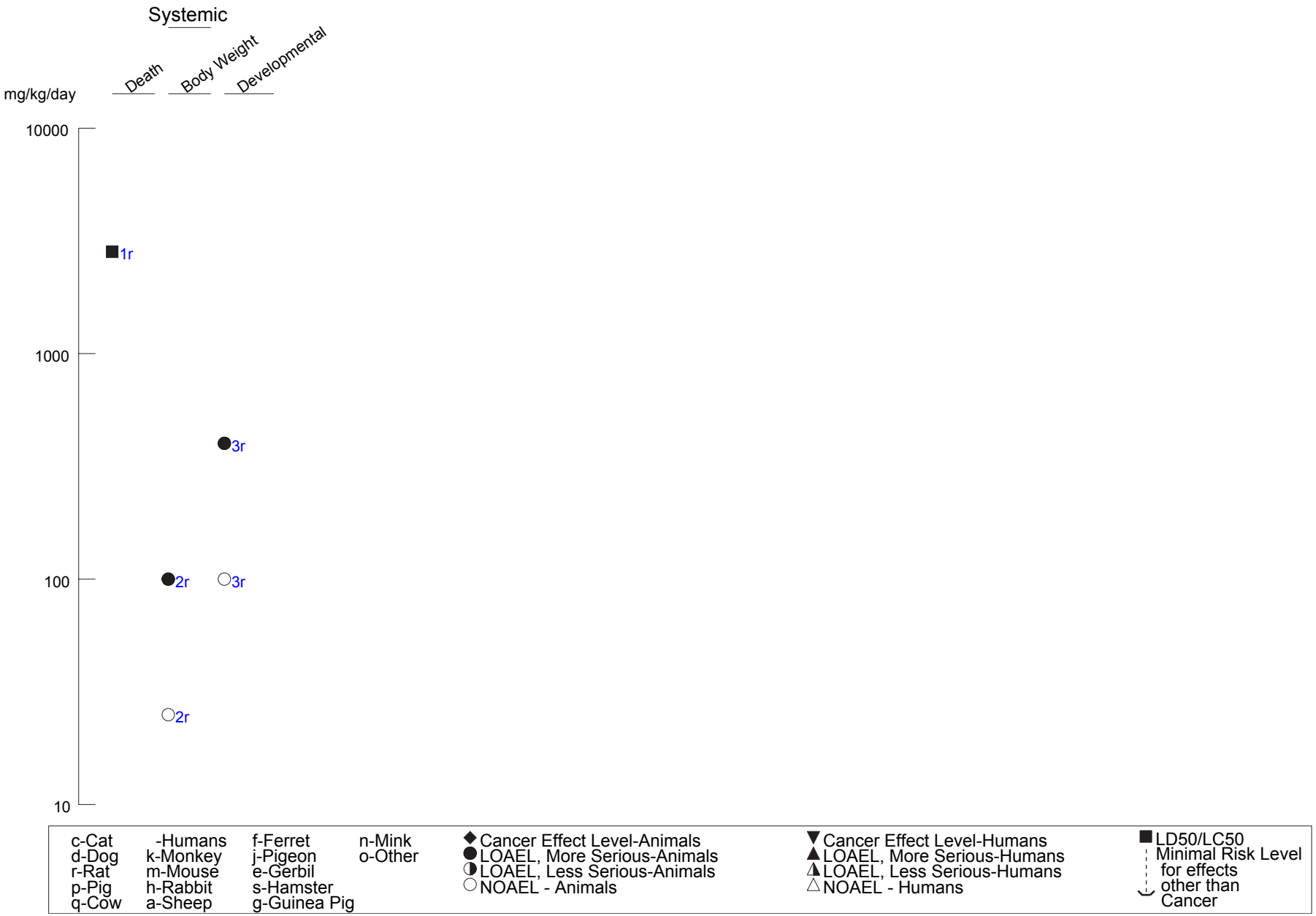


Figure 3-5 Levels of Significant Exposure to Tris(1,3-dichloro-2-propyl) (TDCP) - Oral *(Continued)*

Intermediate (15-364 days)

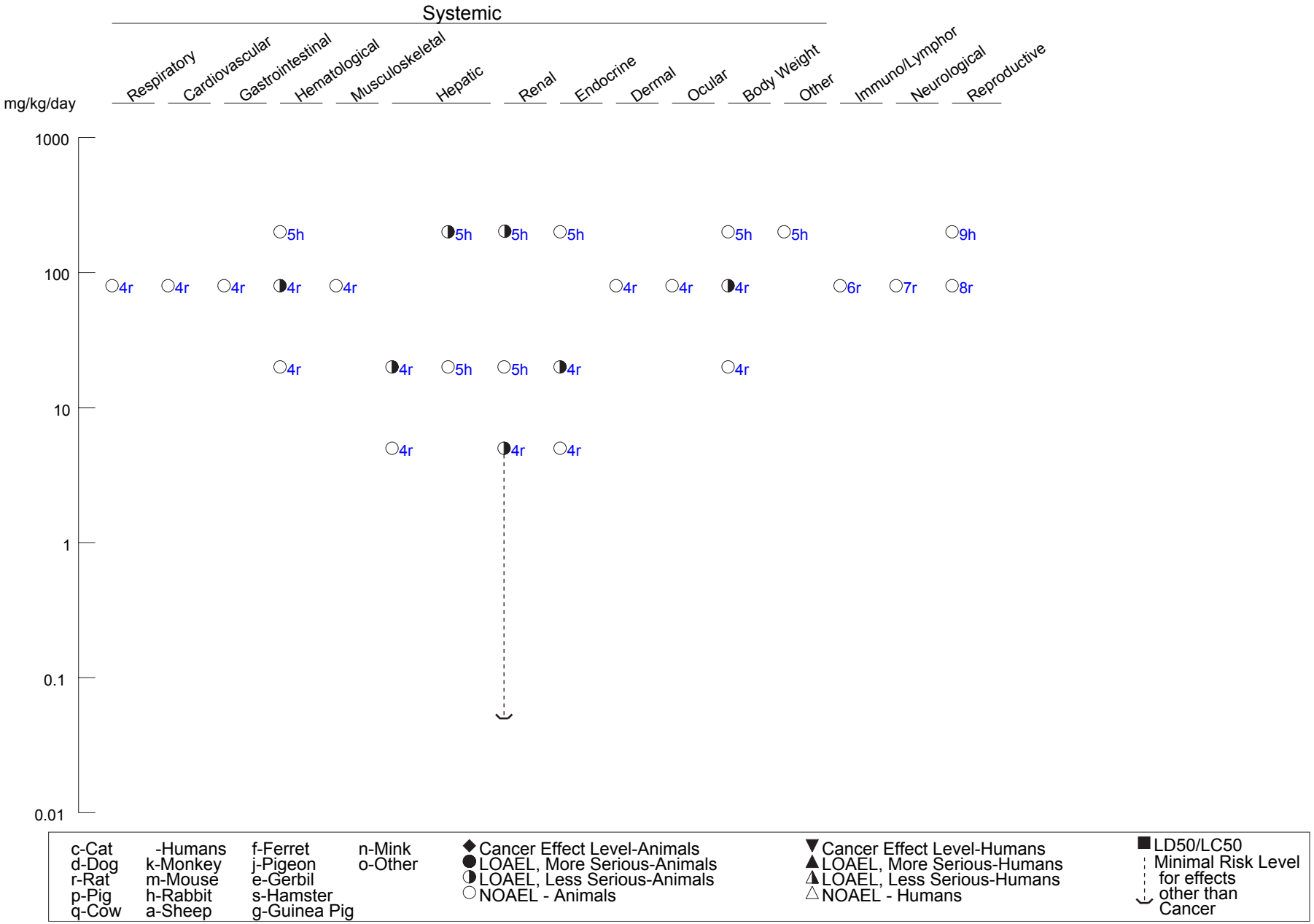


Figure 3-5 Levels of Significant Exposure to Tris(1,3-dichloro-2-propyl) (TDCP) - Oral *(Continued)*

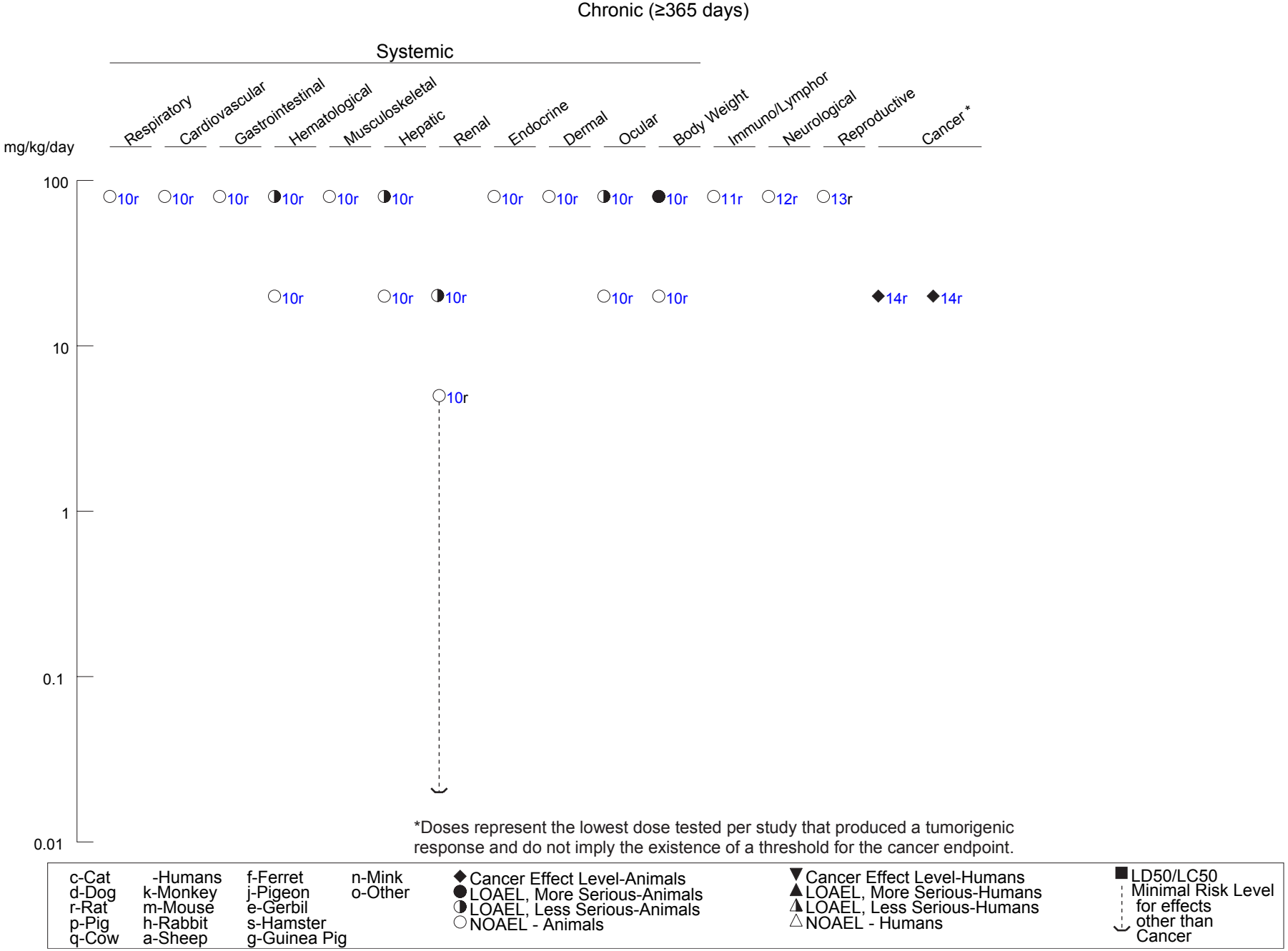


Table 3-6 Levels of Significant Exposure to TCP _ Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
ACUTE EXPOSURE									
Death									
1	Rat (Wistar)	once (G)				20000	(2/5 males and 2/5 females died in 14 days)	FMC 1976b 1330-78-5	
2	Rat (Wistar)	once (G)				31320	(14-day LD50)	FMC 1976c 1330-78-5	
3	Rat (Wistar)	once (G)				15750	(14-day LD50)	FMC 1978 1330-78-5	
4	Rat (Sprague-Dawley)	once (GO)				15800	(the LD50 was greater than 15800)	Johannsen et al. 1977 1330-78-5	
5	Rat (Wistar)	once (G)				16100	(14-day LD50)	Mobil Oil Corporation 1978 1330-78-5	
6	Rat (Fischer- 344)	16 d 1 x/d (GO)				2900	(reduced survival rate)	NTP 1994 1330-78-5	
7	Mouse (CD-1)	14 d ad lib (F)				3208	(16/16 dead in 14-day period)	Chapin et al. 1988 1330-78-5	
8	Mouse (B6C3F1)	16 d 5 d/wk 1 x/d (GO)				1450	(reduced survival rate)	NTP 1994 1330-78-5	

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
9	Mouse (CD-1)	14 d ad lib (F)	Gastro	1604	3208 (diarrhea)		Chapin et al. 1988 1330-78-5	
Neurological								
10	Mouse (CD-1)	14 d ad lib (F)		1604		3208 (tremors, lethargy)	Chapin et al. 1988 1330-78-5	
INTERMEDIATE EXPOSURE								
Death								
11	Rat (Sprague-Dawley)	28 d ad lib (F)				938 M (4/10 deaths) 745 F (5/10 deaths)	FMC 1976b 1330-78-5	
Systemic								
12	Rat (Sprague-Dawley)	28 d ad lib (F)	Hemato	938 M			FMC 1976b 1330-78-5	
			Hepatic	140 M				
			Renal	140 M				
			Bd Wt	140 M		938 M (36% reduced terminal body weight)		
13	Rat (Fischer- 344)	40 d 1 x/d (GO)	Endocr		400 F (adrenocortical hypertrophy and lipidosis)		Latendresse et al. 1993 1330-78-5	
			Bd Wt	400 F				

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
14	Rat (Fischer- 344)	20-60 d 1x/d (GO)	Endocr		400 (cytoplasmic vacuolization of adrenal cortical cells)		Latendresse et al. 1994a 1330-78-5	
15	Rat (Fischer- 344)	135 d 1 x/d (GO)	Hepatic		400 (30% increased in absolute liver weight)		Latendresse et al. 1994b 1330-78-5	
			Endocr		400 (2-3-fold increase in absolute adrenal gland weight)			
			Bd Wt	400				
16	Rat (Fischer- 344)	20-60 d 1 x/d (GO)	Hepatic		400 F (increased serum cholesterol and LDL)		Latendresse et al. 1995 1330-78-5	
			Endocr		400 F (lipidosis in adrenal cortical cells; increased serum estradiol)			

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
17	Rat (Fischer- 344)	16 d 5 d/wk 1 x/d (GO)	Resp	2900	5800 (18-21% decrease in absolute lung weight)		NTP 1994 1330-78-5	
			Cardio	360 M	730 M (14% decrease absolute heart weight)			
			Gastro	360 M	730 M (diarrhea in 6/10 males)			
			Hepatic		360 F (31% increase in absolute liver weight)			
			Renal	730	1450 (15-18% increased relative kidney weight)			
			Bd Wt	730 M	1450 M (17% decrease in final weight)	2900 M (24% decrease in final weight)		

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
18	Rat (Fischer- 344)	13 wk 5 d/wk 1 x/d (GO)	Resp	800			NTP 1994 1330-78-5	
			Cardio	800				
			Gastro	800				
			Hemato	800				
			Musc/skel	800				
			Hepatic	200 F	400 F (17% increased absolute and relative liver weight)			
			Renal	800				
			Endocr		50 (cytoplasmic vacuolization of adrenal cortex)			
			Dermal	800				
			Bd Wt	400 M	800 M (13% reduced final body weight)			

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
19	Rat (Fischer- 344)	13 wk ad lib (F)	Resp	770 F			NTP 1994 1330-78-5	NOAELs are for organ histopathology.
			Cardio	770 F				
			Gastro	770 F				
			Hemato	430 M	750 M (25% increased platelets)			
			Musc/skel	770 F				
			Hepatic	120 F	230 F (11% increase in relative liver weight)			
			Renal	230 F	430 F (edema and necrosis of renal papilla)			
			Endocr		55 M (cytoplasmic vacuolization of adrenal cortex)			
			Dermal	770 F				
			Bd Wt	230 F	430 F (11% reduction in final body weight)	750 M (33% reduced final body weight)		

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
20	Rat (Fischer- 344)	9 mo ad lib (F)	Resp	15 F			NTP 1994 1330-78-5	NOAELs are for organ histopathology.
			Cardio	15 F				
			Gastro	15 F				
			Hemato	15 F				
			Musc/skel	15 F				
			Hepatic	15 F				
			Renal	15 F				
			Endocr	7 F	15 F (cytoplasmic vacuolization of adrenal gland)			
			Dermal	15 F				
			Bd Wt	15 F				
21	Rat (Wistar)	9 wk ad lib (F)	Hemato	460 M			Oishi et al. 1982 1330-78-5	
			Hepatic		460 M (mild cytoplasmic vacuolization in liver; increased serum AST)			
			Bd Wt	460 M				

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
22	Mouse (CD-1)	105 d ad lib (F)	Hepatic	250			Chapin et al. 1988 1330-78-5	
			Renal	250				
			Endocr		62.5 M (hypertrophy and brown degeneration in adrenal cells of F1 offspring)			
			Bd Wt	124 F	250 F (14% reduced postpartum and terminal dam weight)			
23	Mouse (B6C3F1)	16 d 5 d/wk 1 x/d (GO)	Resp	5800			NTP 1994 1330-78-5	
			Cardio	360 F	760 F (21% reduced relative heart weight)			
			Hepatic		360 (increased absolute and relative liver weight)			
			Renal	5800				
			Bd Wt	730 M	1450 M (11% reduced final weight)			

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
24	Mouse (B6C3F1)	13 wk 5 d/wk 1 x/d (GO)	Resp	800			NTP 1994 1330-78-5	NOAEL are for organ histopathology.
			Cardio	800				
			Gastro	800				
			Hemato	800				
			Musc/skel	800				
			Hepatic	100 F	200 F (14% increase in absolute liver weight)			
			Renal	800				
			Endocr		50 (cytoplasmic vacuolization of adrenal cortex)			
			Dermal	800				
			Bd Wt	200	400 (12% reduction in final body weight)	800 M (24% reduced final body weight)		

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
25	Mouse (B6C3F1)	13 wk ad lib (F)	Resp	1050 F			NTP 1994 1330-78-5	NOAELs are for organ histopathology.
			Cardio	1050 F				
			Gastro	1050 F				
			Hemato	1050 F				
			Musc/skel	1050 F				
			Hepatic	1050 F				
			Renal	380 M	900 M (regeneration in renal tubules)			
			Endocr		65 F (cytoplasmic vacuolization in adrenal cortex)			
			Dermal	1050 F				
			Bd Wt	230 F	530 F (14% reduction in final body weight)			
			Other	130 F	230 F (hyperplasia in mucosal epithelium of gallbladder)			

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
26	Mouse (B6C3F1)	3 mo ad lib (F)	Resp	37 F			NTP 1994 1330-78-5	
			Cardio	37 F				
			Gastro	37 F				
			Hemato	37 F				
			Musc/skel	37 F				
			Hepatic	37 F				
			Renal	37 F				
			Endocr	13 M	27 M (ceroid pigmentation in adrenal cortex)			
			Dermal	37 F				
			Bd Wt	37 F				
Immuno/ Lymphoret								
27	Rat (Wistar)	6 wk ad lib (F)		2.4 M	6 M (reduced humoral and cell-mediated immune response)		Banerjee et al. 1992 1330-78-5	
28	Rat (Fischer- 344)	16 d 5 d/wk 1 x/d (GO)		730 F	1450 F (decrease absolute and relative thymus weight)		NTP 1994 1330-78-5	

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Rat (Fischer- 344)	13 wk 5 d/wk 1 x/d (GO)		800			NTP 1994 1330-78-5	NOAEL is for histopathology of lymphoreticular tissues.
30	Rat (Fischer- 344)	13 wk ad lib (F)		770 F			NTP 1994 1330-78-5	NOAELs are for organ histopathology of lymphoreticular tissues.
31	Rat (Wistar)	9 wk ad lib (F)		460 M			Oishi et al. 1982 1330-78-5	NOAEL is for spleen weight and histopathology.
32	Mouse (B6C3F1)	16 d 5 d/wk 1 x/d (GO)			1450 M (lymphoid depletion in thymus)		NTP 1994 1330-78-5	
33	Mouse (B6C3F1)	13 wk 5 d/wk 1 x/d (GO)		800			NTP 1994 1330-78-5	NOAEL are for organ histopathology of lymphoreticular organs.
34	Mouse (B6C3F1)	13 wk ad lib (F)		1050 F			NTP 1994 1330-78-5	NOAEL is for histopathology of lymphoreticular organs.

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
35	Mouse (B6C3F1)	3 mo ad lib (F)		37 F			NTP 1994 1330-78-5	NOAEL is for histopathology of lymphoreticular tissues.
Neurological								
36	Rat (Sprague-Dawley)	28 d ad lib (F)		120 F	745 F (lethargy)		FMC 1976b 1330-78-5	
37	Rat (Fischer- 344)	16 d 5 d/wk 1 x/d (GO)		730 M	1450 M (17% increase in relative brain weight)		NTP 1994 1330-78-5	
38	Rat (Fischer- 344)	13 wk 5 d/wk 1 x/d (GO)		200 F	400 F (reduced hindlimb grip strength)		NTP 1994 1330-78-5	
39	Rat (Fischer- 344)	13 wk ad lib (F)		430 M	750 M (19% reduction in hindlimb grip strength)		NTP 1994 1330-78-5	
40	Rat (Fischer- 344)	3 mo ad lib (F)		6 M	13 M (reduced hindlimb grip strength)		NTP 1994 1330-78-5	

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
41	Mouse (B6C3F1)	16 d 5 d/wk 1 x/d (GO)			360 M (reduced hindlimb grip strength)		NTP 1994 1330-78-5	
42	Mouse (B6C3F1)	13 wk 5 d/wk 1 x/d (GO)		50 F		100 F (multifocal axonal degeneration in spinal cord)	NTP 1994 1330-78-5	
43	Mouse (B6C3F1)	13 wk ad lib (F)		180 M	380 M (reduced forelimb grip strength)		NTP 1994 1330-78-5	
44	Mouse (B6C3F1)	3 mo ad lib (F)		18 F	37 F (reduced hindlimb grip strength)		NTP 1994 1330-78-5	
Reproductive								
45	Rat (Long- Evans)	66 d 1 x/d (GO)			100 M (increased percent abnormal sperm)		Carlton et al. 1987 1330-78-5	
					200 F (decreased fertility)			
46	Rat (Fischer- 344)	40 d 1 x/d (GO)			400 F (ovarian cell hypertrophy and lipidosis)		Latendresse et al. 1993 1330-78-5	

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
47	Rat (Fischer- 344)	20-60 d 1x/d (GO)			400 (lipidosis of ovarian interstitial cells; degeneration of seminiferous tubules)		Latendresse et al. 1994a 1330-78-5	
48	Rat (Fischer- 344)	135 d 1 x/d (GO)				400 M (decreased fertility)	Latendresse et al. 1994b 1330-78-5	
49	Rat (Fischer- 344)	20-60 d 1 x/d (GO)			400 F (lipidosis in ovarian interstitial cells)		Latendresse et al. 1995 1330-78-5	
50	Rat (Fischer- 344)	13 wk 5 d/wk 1 x/d (GO)		200 M	400 M (atrophy of seminiferous tubules) 50 F (interstitial cell hypertrophy in ovary)		NTP 1994 1330-78-5	
51	Rat (Fischer- 344)	13 wk ad lib (F)		220 M	430 M (atrophy of seminiferous tubule) 65 F (hypertrophy of interstitial cells in the ovary)		NTP 1994 1330-78-5	

Table 3-6 Levels of Significant Exposure to TCP - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
52	Rat (Fischer- 344)	9 mo ad lib (F)		13 M 7 F	15 F (ovarian interstitial cell hyperplasia)		NTP 1994 1330-78-5	
53	Rat (Fischer- 344)	3 mo ad lib (F)		13 M 4 F[b]	7 F (hyperplasia in ovarian interstitial cells)		NTP 1994 1330-78-5	
54	Rat (Wistar)	9 wk ad lib (F)		460 M			Oishi et al. 1982 1330-78-5	NOAEL is for testes weight.
55	Mouse (CD-1)	105 d ad lib (F)		62.5 M	124 M (reduced fertility of F1 offspring)		Chapin et al. 1988 1330-78-5	
56	Mouse (B6C3F1)	13 wk 5 d/wk 1 x/d (GO)		800 M	50 F (interstitial cell hypertrophy in the ovary)		NTP 1994 1330-78-5	
57	Mouse (B6C3F1)	13 wk ad lib (F)		900 M 230 F	530 F (cytoplasmic vacuolization of interstitial cells in the ovary)		NTP 1994 1330-78-5	

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
58	Mouse (B6C3F1)	3 mo ad lib (F)		27 M 37 F			NTP 1994 1330-78-5	NOAELs are for sex organs histopathology.
Developmental								
59	Rat (Long- Evans)	66 d 1 x/d (GO)				200 F (decreased postnatal viability)	Carlton et al. 1987 1330-78-5	
60	Rat (Fischer- 344)	135 d 1 x/d (GO)				400 (reduced number of live pups/litter)	Latendresse et al. 1994b 1330-78-5	
61	Mouse (CD-1)	105 d ad lib (F)		62.5		124 (increased dead F1 pups/litter)	Chapin et al. 1988 1330-78-5	

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
62	Rat (Fischer- 344)	2 yr ad lib (F)	Resp	15 F			NTP 1994 1330-78-5	NOAELs are for organ histopathology.
			Cardio	15 F				
			Gastro	15 F				
			Hemato	15 F				
			Musc/skel	15 F				
			Hepatic	15 F				
			Renal	15 F				
			Endocr	7 F	15 F (cytoplasmic vacuolization of adrenal gland)			
			Dermal	15 F				
			Bd Wt	15 F				

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
63	Mouse (B6C3F1)	2 yr ad lib (F)	Resp	37 F			NTP 1994 1330-78-5	NOAELs are for organ histopathology.
			Cardio	37 F				
			Gastro	37 F				
			Hemato	37 F				
			Musc/skel	37 F				
			Hepatic	7 M	13 M (cell foci, fatty change, ceroid pigmentation in liver)			
			Renal	37 F				
			Endocr	37 F				
			Dermal	37 F				
			Bd Wt	37 F				
Immuno/ Lymphoret								
64	Rat (Fischer- 344)	2 yr ad lib (F)		15 F			NTP 1994 1330-78-5	NOAEL is for histopathology of lymphoreticular organs and tissues.
65	Mouse (B6C3F1)	2 yr ad lib (F)		37 F			NTP 1994 1330-78-5	NOAEL is for organ histopathology of lymphoreticular tissues.

Table 3-6 Levels of Significant Exposure to TCP _ Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
66	Rat (Fischer- 344)	2 yr ad lib (F)		15 F			NTP 1994 1330-78-5	NOAEL is for grip strength and histopathology of nervous system
67	Mouse (B6C3F1)	2 yr ad lib (F)		37 F			NTP 1994 1330-78-5	NOAEL is for limb grip strength and histopathology of the nervous system.
Reproductive								
68	Rat (Fischer- 344)	2 yr ad lib (F)		7 F	15 F (ovarian interstitial cell hyperplasia)		NTP 1994 1330-78-5	NOAELs are for organ histopathology.
69	Rat (Fischer- 344)	15 mo ad lib (F)		7 F[c]	15 F (ovarian interstitial cell hyperplasia)		NTP 1994 1330-78-5	NOAELs are for organ histopathology.
70	Mouse (B6C3F1)	2 yr ad lib (F)		27 M 37 F			NTP 1994 1330-78-5	NOAELs are for sex organs histopathology.

a The number corresponds to entries in Figure 3-6

b Used to derive an intermediate-duration oral MRL of 0.04 mg/kg/day; the MRL was derived by dividing the BMDL10 of 3.72 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

c Used to derive a chronic-duration oral MRL of 0.02 mg/kg/day; the MRL was derived by dividing the BMDL10 of 2.12 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; wk = week(s); x = time(s)

Figure 3-6 Levels of Significant Exposure to TCP - Oral

Acute (≤14 days)

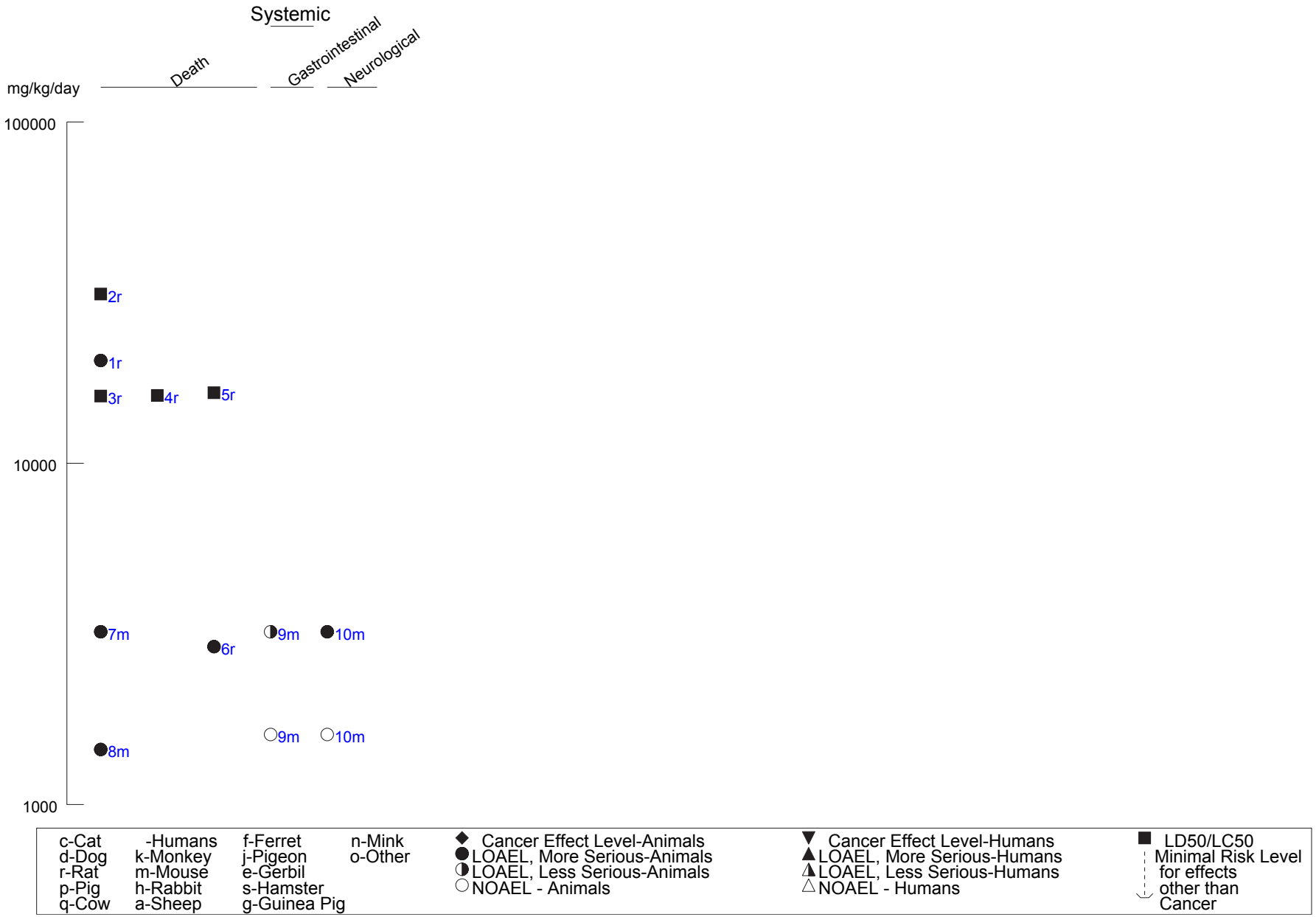


Figure 3-6 Levels of Significant Exposure to TCP - Oral *(Continued)*

Intermediate (15-364 days)

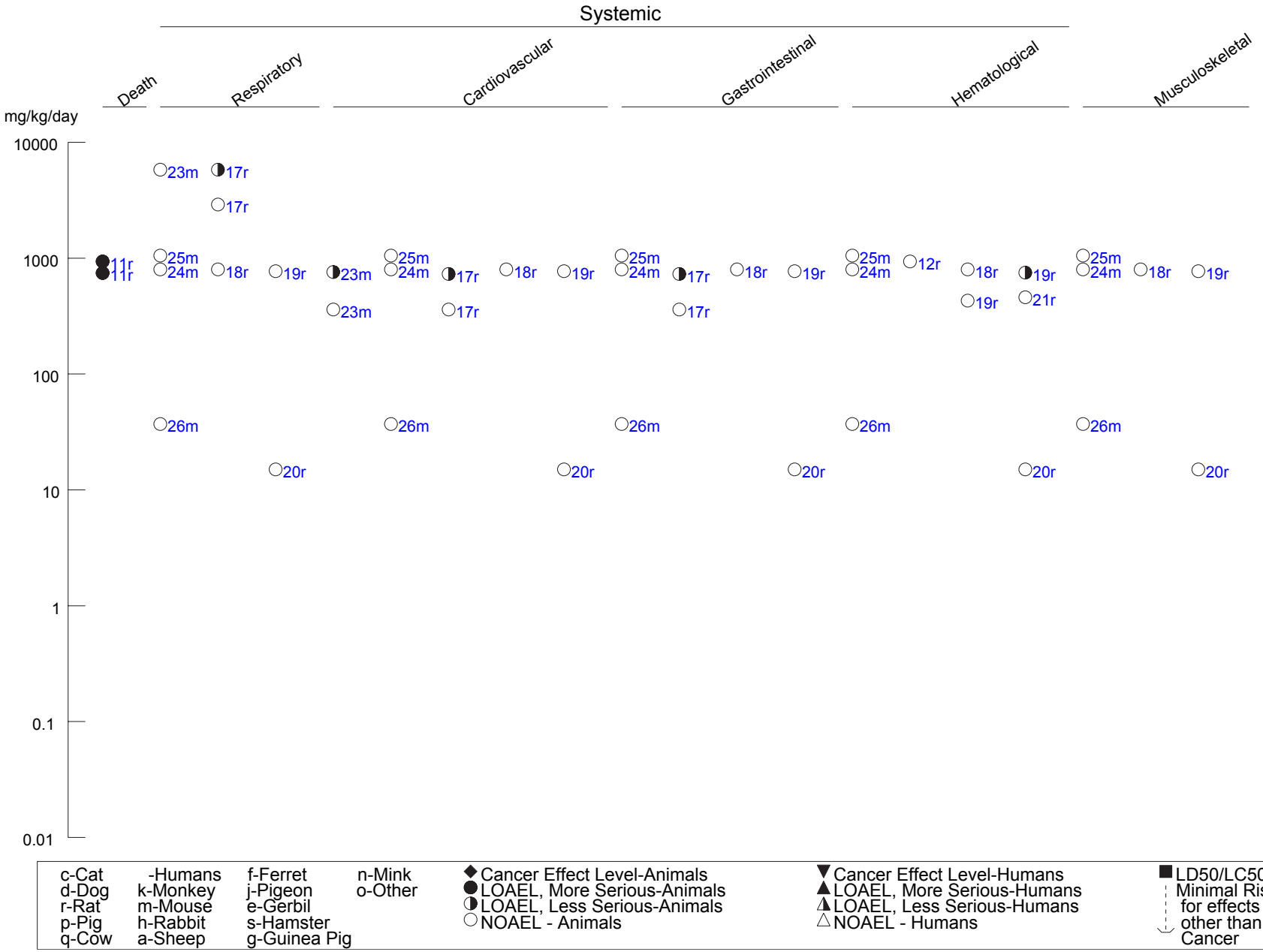


Figure 3-6 Levels of Significant Exposure to TCP - Oral *(Continued)*

Intermediate (15-364 days)

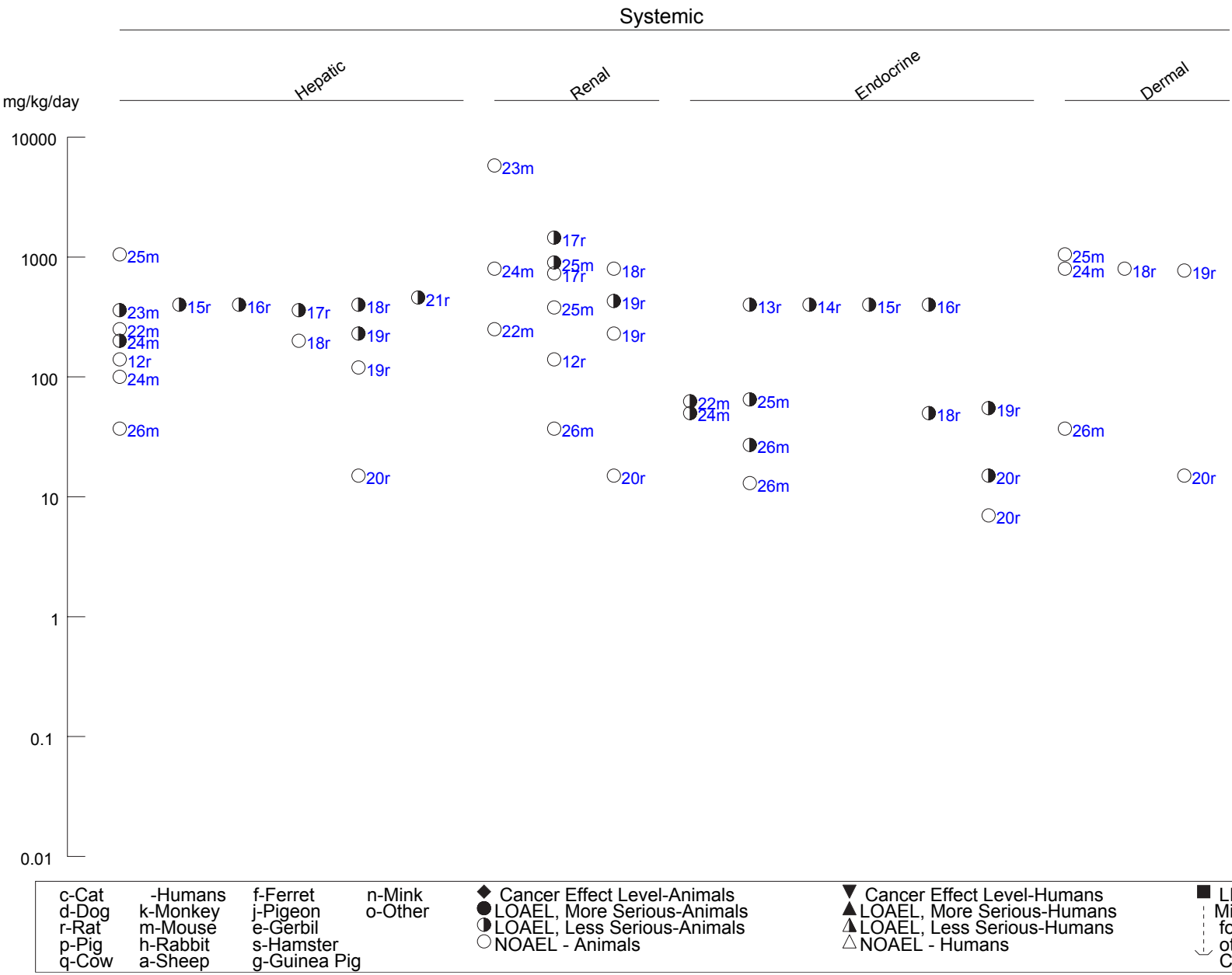


Figure 3-6 Levels of Significant Exposure to TCP - Oral *(Continued)*

Intermediate (15-364 days)

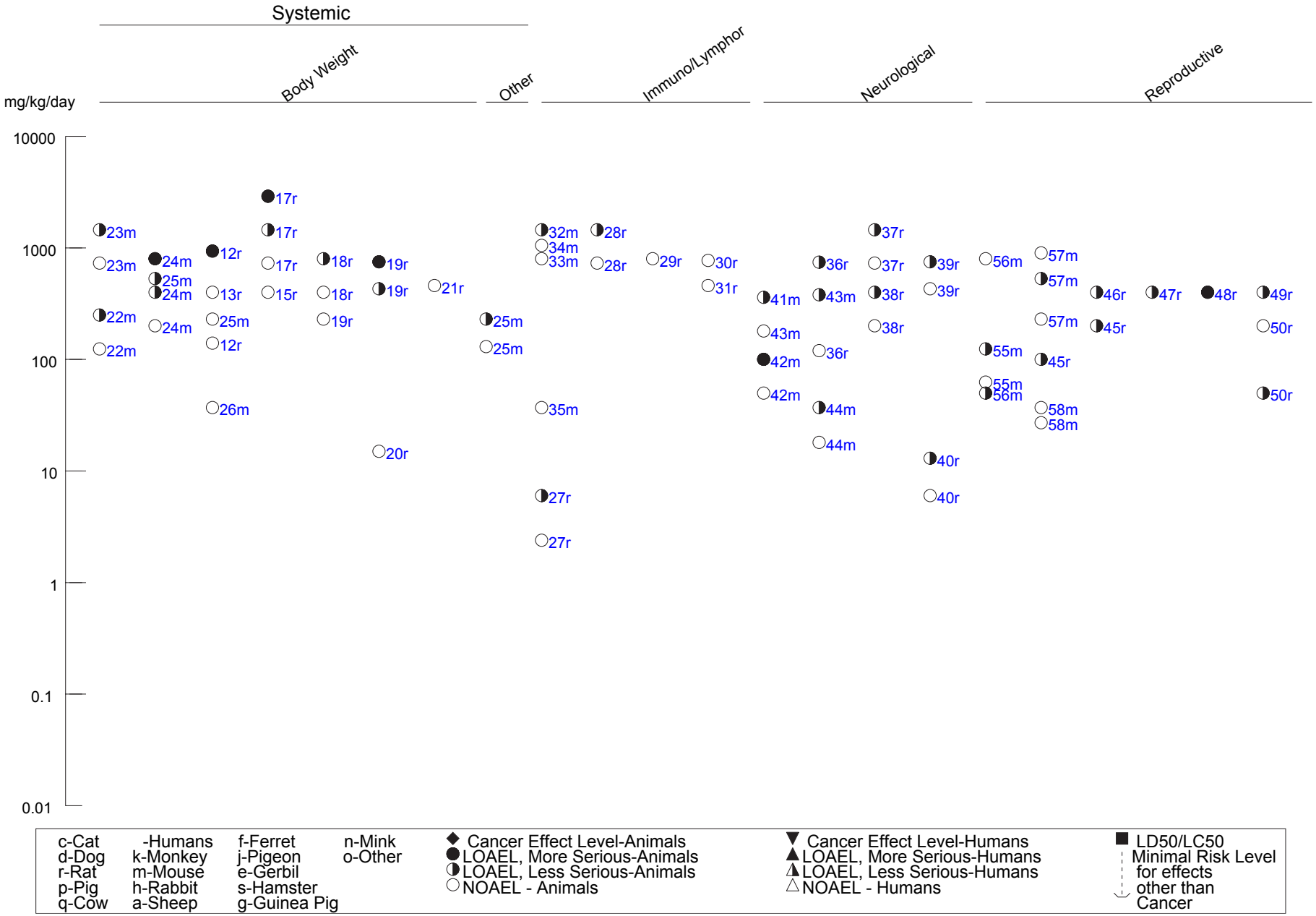
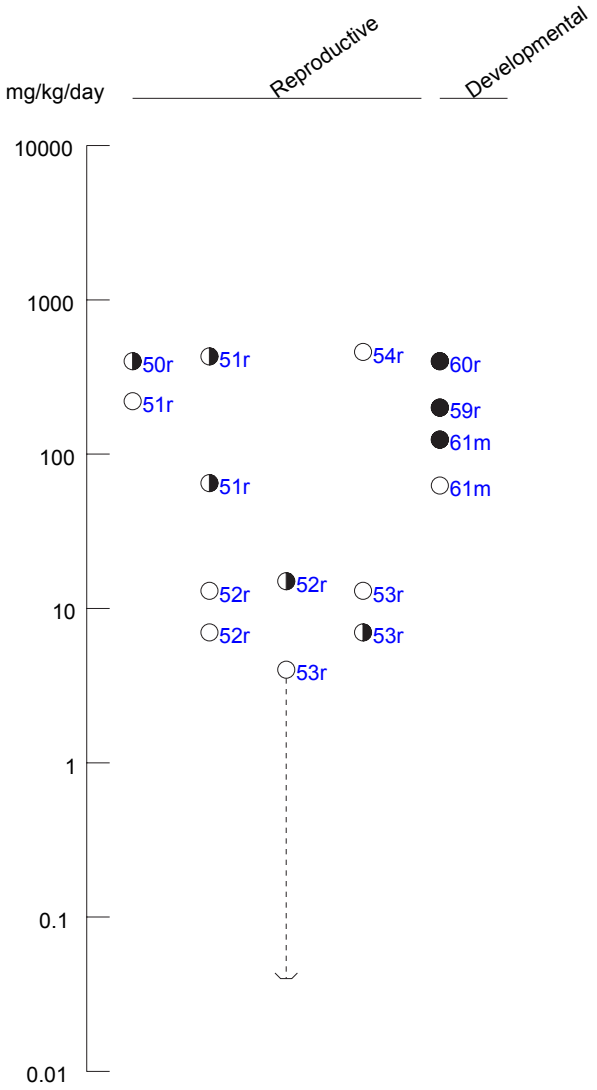


Figure 3-6 Levels of Significant Exposure to TCP - Oral *(Continued)*

Intermediate (15-364 days)



c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-6 Levels of Significant Exposure to TCP - Oral *(Continued)*

Chronic (≥365 days)

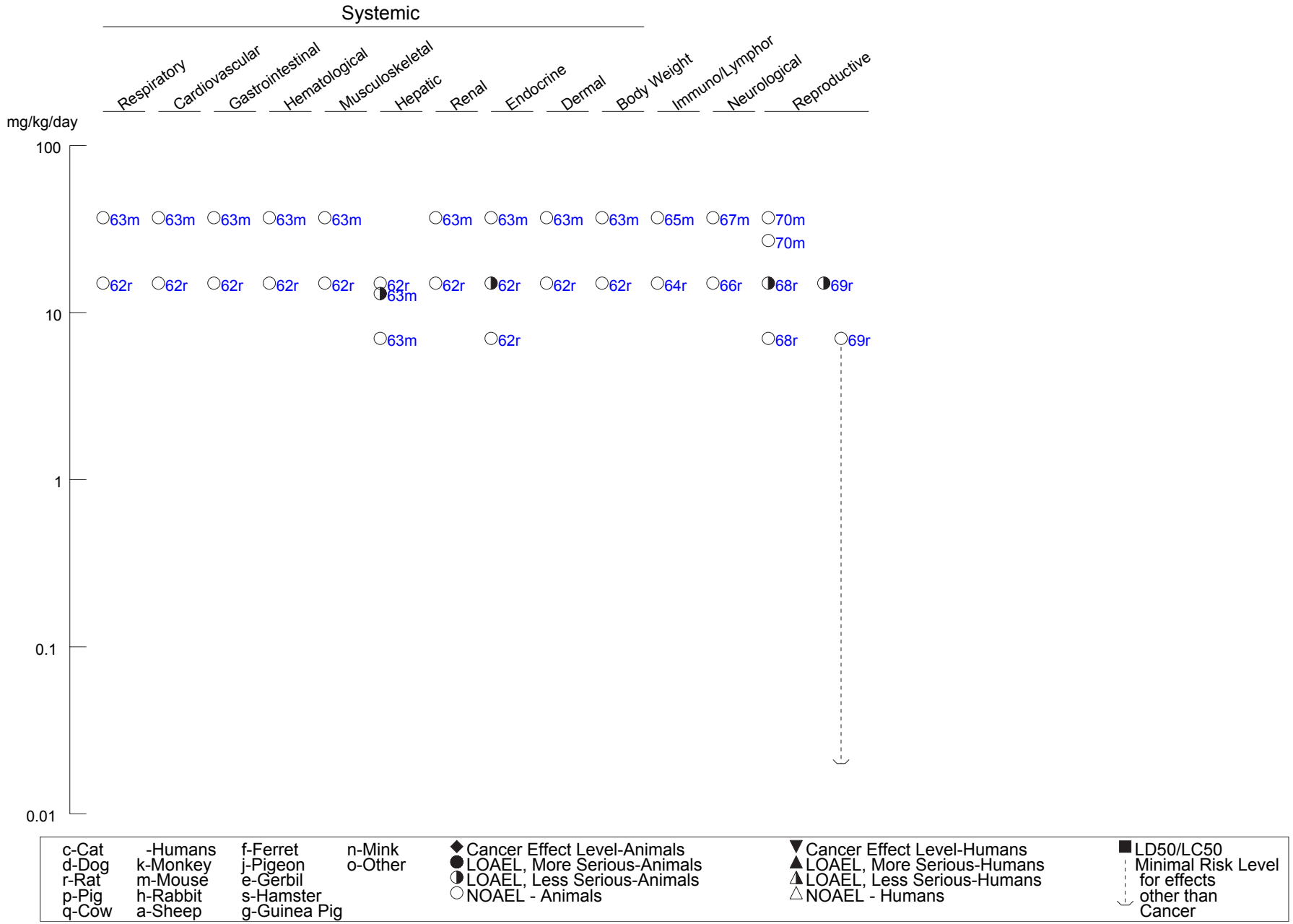


Table 3-7 Levels of Significant Exposure to TPP, TCPP, and TiBP - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (NS)				2000 M (4-6 hr LD50) 1260 F (5-hr LD50)	Anonymous 1977 13674-84-5	
2	Rat (NS)	once (G)				3200 (LD50s between 3200 and 6400 mg/kg were estimated)	Eastman Kodak Co. 1990 126-71-6	
3	Rat (NS)	once (NS)				6400 (LD50 is greater than 6400 mg/kg)	EF Houghton & Co. 1996 115-86-6	
4	Rat (Wistar)	once (GW)				20000 (LD50 is greater than 20000 mg/kg)	FMC 1982 115-86-6	
5	Rat (Sprague-Dawley)	once (C)				10800 (14-day LD50)	Johannsen et al. 1977 115-86-6	
6	Rat (Wistar)	once (GO)				1500 F (96-hr LD50)	Kawasaki et al. 1982 13674-84-5	
7	Rat (Sprague-Dawley)	once (G)				5000 (LD50 is greater than 5000 mg/kg)	Monsanto Co. 1989a, 1989b 126-71-6	

Table 3-7 Levels of Significant Exposure to TPP, TCPP, and TiBP - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
8	Rat (Wistar)	once (GO)				500 M (LD50 is greater than 500 mg/kg) 632 F (3-6 hr LD50)	Stropp 1996 13674-84-5	
9	Mouse (NS)	once (G)				6400 (LD50s between 6400 and 12800 mg/kg were estimated)	Eastman Kodak Co. 1990 126-71-6	
Systemic								
10	Rat (Wistar)	7 d 1 x/d (GO)	Bd Wt	1000 F			Kawasaki et al. 1982 13674-84-5	
INTERMEDIATE EXPOSURE								
Systemic								
11	Rat (Wistar)	20 d Gd 0-20 ad lib (F)	Bd Wt	893 F			Kawasaki et al. 1982 13674-84-5	

Table 3-7 Levels of Significant Exposure to TPP, TCPP, and TiBP - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
12	Rat (Sprague-Dawley)	13 wk ad lib (F)	Resp	404 F			Naylor and Ribelin 1990 126-71-6	NOAELs are for organ or tissue histopathology.
			Cardio	404 F				
			Gastro	404 F				
			Hemato	68 M	346 M (decreased neutrophil count; increased MCH and MCHC)			
			Musc/skel	404 F				
			Hepatic	68 M	346 M (increased serum cholesterol)			
			Renal	404 F				
			Endocr	404 F				
			Dermal	404 F				
			Ocular	404 F				
			Bd Wt	404 F				
			Metab	404 F				
			Other	404 F				
13	Rat (Sprague-Dawley)	4 mo ad lib (F)	Bd Wt	161 M	345 M (11% reduced body weight gain)		Sobotka et al. 1986 115-86-6	

Table 3-7 Levels of Significant Exposure to TPP, TCPP, and TiBP - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
14	Rat (Holtzman)	35 d ad lib (F)	Hemato	416 M			Sutton et al. 1960 115-86-6	Liver and kidney NOAELs are for organ weight.
			Hepatic	416 M				
			Renal	416 M				
			Bd Wt	416 M				
Immuno/ Lymphoret								
15	Rat (Sprague-Dawley)	120 d ad lib (F)		711			Hinton et al. 1996 115-86-6	NOAEL is for lymphoid tissue histopathology and humoral response to SRBC immunization.
16	Rat (Sprague-Dawley)	13 wk ad lib (F)		404 F			Naylor and Ribelin 1990 126-71-6	NOAEL is for lymphoid tissues histopathology.
Neurological								
17	Rat (Sprague-Dawley)	13 wk ad lib (F)		404 F			Naylor and Ribelin 1990 126-71-6	NOAEL is for histopathology of nervous tissues.
18	Rat (Sprague-Dawley)	4 mo ad lib (F)		711 M			Sobotka et al. 1986 115-86-6	NOAEL is for neuromotor function tests.
Reproductive								
19	Rat (Wistar)	20 d Gd 0-20 ad lib (F)		893 F			Kawasaki et al. 1982 13674-84-5	NOAEL is for number of implantations and resorptions.

Table 3-7 Levels of Significant Exposure to TPP, TCPP, and TiBP - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
20	Rat (Sprague-Dawley)	13 wk ad lib (F)		346 M 404 F			Naylor and Ribelin 1990 126-71-6	NOAELs are for histopathology of reproductive organs.
21	Rat (Sprague-Dawley)	111 d ad lib (F)		690 F			Welsh et al. 1987 115-86-6	NOAEL is for reproductive indices.
Developmental								
22	Rat (Wistar)	20 d Gd 0-20 ad lib (F)		893 F			Kawasaki et al. 1982 13674-84-5	NOAEL is for standard developmental indices.
23	Rat (Sprague-Dawley)	111 d ad lib (F)		690 F			Welsh et al. 1987 115-86-6	NOAEL is for embryo and fetotoxicity.

a The number corresponds to entries in Figure 3-7.

ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

Figure 3-7 Levels of Significant Exposure to TPP, TCPP, and TiBP - Oral

Acute (≤14 days)

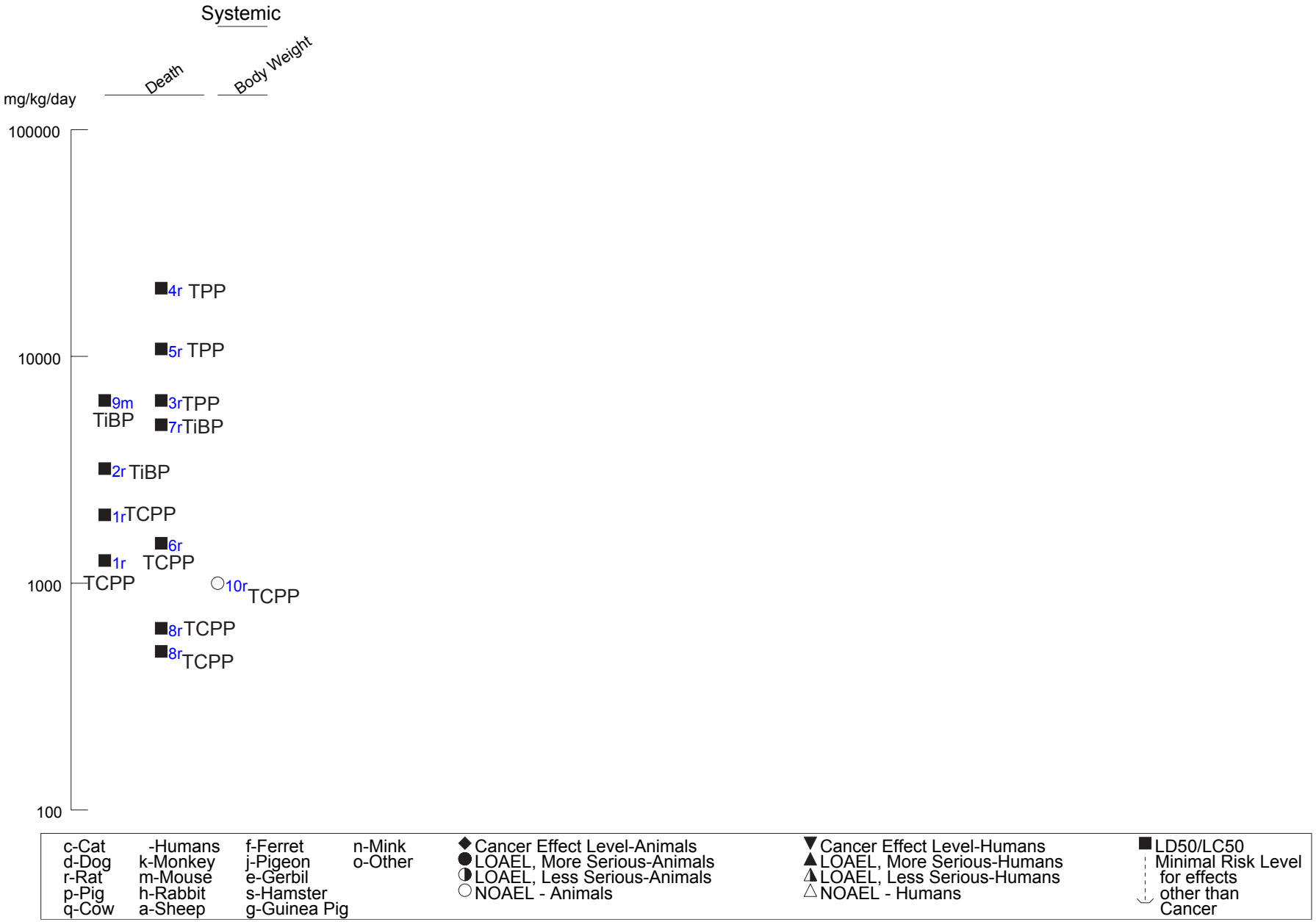
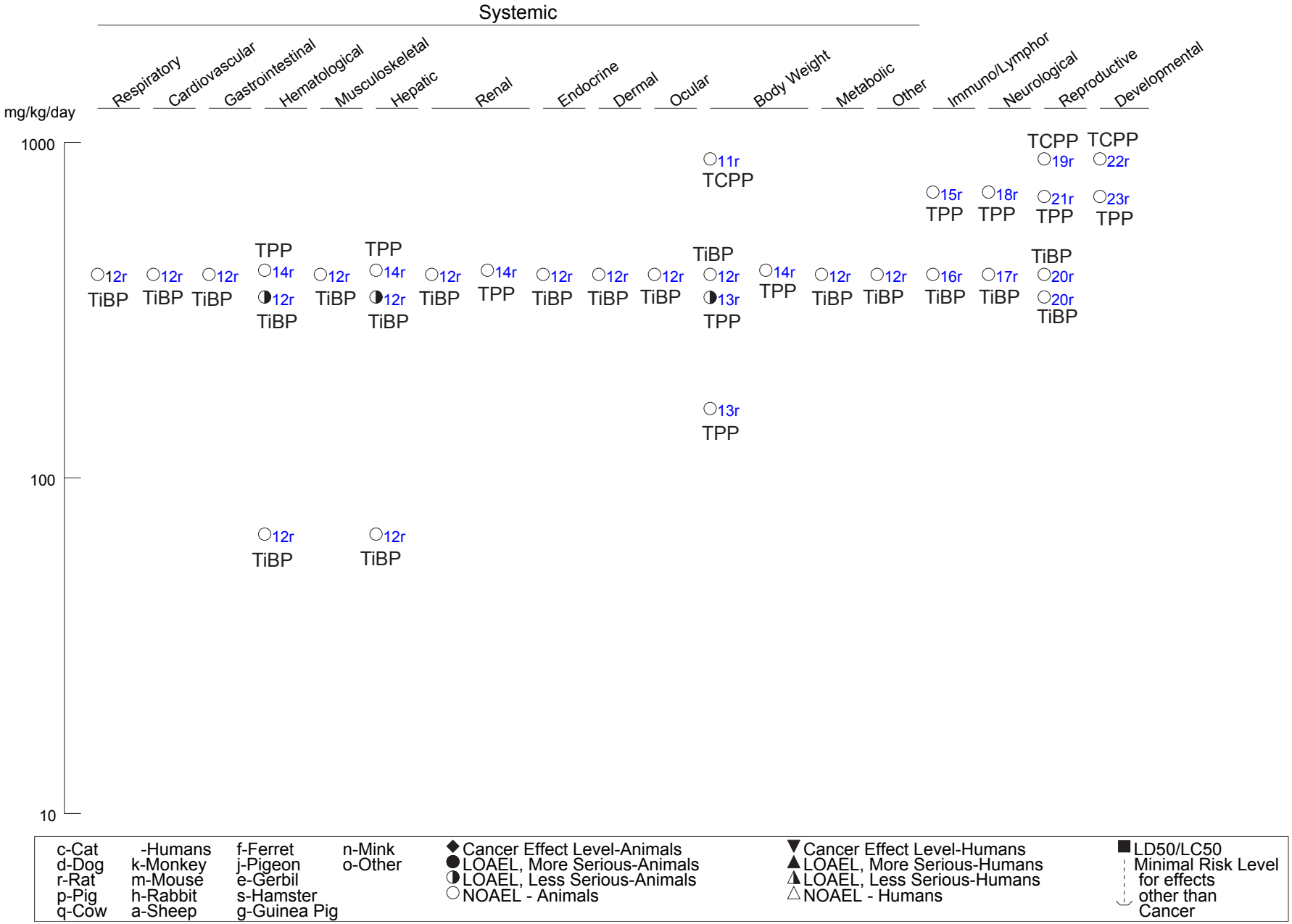


Figure 3-7 Levels of Significant Exposure to TPP, TCPP, and TiBP - Oral *(Continued)*

Intermediate (15-364 days)



Similar findings were reported in mice dosed with up to 1,776 mg/kg/day for 13 weeks (Auletta et al. 1991) or 711 mg/kg/day for 18 months (Auletta et al. 1998b).

Rats dosed with up to 100 mg TBEP/kg/day for 14 days (Komsta et al. 1989) or 698 mg TBEP/kg/day for 18 weeks (Reyna and Thake 1987a) showed no histological alterations in the respiratory tract. Doses of up to 404 mg TiBP/kg/day for 13 weeks also had no significant effect on the respiratory tract of rats (Naylor and Ribelin 1990). Administration of up to 80 mg TDCP/kg/day to rats for 2 years did not induce respiratory tract alterations (Stauffer Chemical Co. 1981a).

Rats administered by gavage 13 or 14 doses of 5,800 mg TCP/kg during a 16-day period had a 18–21% decrease in absolute lung weight, but there were no gross or histological alterations in the lungs (NTP 1994). Similar findings were reported in rats administered up to 800 mg TCP/kg/day by gavage for 13 weeks, up to 770 mg TCP/kg/day in the food for 13 weeks, or up to 15 mg TCP/kg/day in the food for 9 months (NTP 1994). In mice, 13 or 14 doses of up to 5,800 mg TCP/kg/day did not induce respiratory tract alterations (NTP 1994). Similar results were reported in mice receiving doses of up to 800 mg/kg/day by gavage, 1,050 mg TCP/kg/day in the food for 13 weeks, or 37 mg/kg/day for 9 months (NTP 1994). A similar lack of effects was reported in the respiratory tract of rats and mice dosed with up to 15 mg/TCP/kg/day or 37 mg/kg/day, respectively, for 2 years (NTP 1994). The TCP used in the NTP studies was a complex mixture consisting of 18% dicresyl phosphate esters and 79% tricresyl phosphate esters, two of which were identified as tri-*m*-cresyl phosphate (21%) and tri-*p*-cresyl phosphate (4%); no tri-*o*-cresyl phosphate was detected (0.1%).

Cardiovascular Effects. Evaluations of the cardiovascular system have been limited to monitoring the weight and gross and microscopic appearance of the heart of animals. No significant alterations in these parameters were reported in the studies mentioned above, except for a 14% decrease in absolute heart weight in male rats dosed intermittently with 730 mg TCP/kg/day for 16 days (the NOAEL was 360 mg/kg/day) and a 21% decrease in relative heart weight in female mice dosed similarly with 760 mg TCP/kg/day (the NOAEL was 360 mg/kg/day) (NTP 1994).

Gastrointestinal Effects. No alterations were observed in the gastrointestinal tract of rats dosed daily with 350 mg TCEP/kg/day by gavage for up to 16 weeks (NTP 1991a) or in rats receiving dietary doses of up to 596 mg TCEP/kg/day for 3 months (Anonymous 1977). Mice dosed daily with up to 700 mg TCEP/kg/day for up to 16 weeks showed no alterations in the gastrointestinal tract (NTP 1991a).

No apparent alterations were reported in rats or mice dosed with up to 88 or 350 mg TCEP/kg/day, respectively, for 2 years (NTP 1991a).

Rats dosed with up to 143 mg TnBP/kg/day in the diet for 10 weeks showed no significant alterations in the stomach (Arnold et al. 1997). Similar findings were reported in rats administered up to 423 mg TnBP/kg/day in the diet for 90 days (FMC 1985a) or 333 mg/kg/day by gavage for 18 weeks (Laham et al. 1985a). No alterations in the gastrointestinal tract were reported in mice treated with dietary doses of up to 1,776 mg TnBP/kg/day for 13 weeks (Auletta 1991). Longer-term studies also found a lack of significant alterations in the gastrointestinal tract of rats dosed with up to 182 mg TnBP/kg/day (Auletta et al. 1998a) for 2 years or mice dosed with up to 711 mg TnBP/kg/day for 18 months (Auletta et al. 1998b).

TBEP administered to rats by gavage in doses of up to 100 mg/kg/day for 14 days (Komsta et al. 1989) or in dietary doses of up to 698 mg/kg/day for 18 weeks (Reyna and Thake 1987a) did not induce gross or microscopic alterations in the gastrointestinal tract. TDCP in dietary doses of up to 80 mg/kg/day for 24 months also did not induce these alterations (Stauffer Chemical Co. 1981a). Administration of doses of up to 404 mg TiBP/kg/day to rats in the diet for up to 13 weeks did not result in alterations in the gastrointestinal tract (Naylor and Ribelin 1990).

In a 14-day range-finding study, dietary doses of approximately 3,208 mg TCP/kg/day induced diarrhea in male and female mice; no such effect was seen in mice dosed with approximately 1,604 mg/kg/day (Chapin et al. 1988) (the TCP contained <0.1% tri-*o*-cresyl phosphate). Administration by gavage of 730 mg TCP/kg/day, 5 days/week for a total of 13 or 14 doses in 16 days caused diarrhea in 6/10 male rats; the NOAEL was 360 mg/kg/day (NTP 1994). All 10 females dosed with 1,450 mg/kg/day suffered diarrhea (NTP 1994). Gross or microscopic examination of the gastrointestinal tract of rats and mice exposed to TCP for 13 weeks, 9 months, or 2 years in the NTP (1994) report did not reveal gastrointestinal alterations.

Hematological Effects. No significant alteration in hematological parameters were reported in rats fed diets that provided up to 586 mg TCEP/kg/day for 3 months (Anonymous 1977) or in rats treated by gavage with up to 88 mg TCEP/kg/day for 2 years (NTP 1991a). Similar results were reported in mice dosed by gavage with up to 350 mg TCEP/kg/day for 2 years (NTP 1991a).

More information is available for TnBP. Laham et al. (1984b) reported a significant decrease in hemoglobin in female rats, but not male rats, dosed with 411 mg TnBP/kg/day for 14 days. At 137 mg/kg/day, females also showed a decrease in mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC), but hemoglobin concentration was not elevated in high-dose females. A 90-day dietary study reported a significant increase in activated partial thromboplastin time in male rats dosed with 360 mg TnBP/kg/day at termination but not at the midpoint; this effect was not present in female rats that received doses of up to 423 mg TnBP/kg/day (FMC 1985a). The NOAEL in males was 68.1 mg/kg/day. Oishi et al. (1980) also reported an increase in coagulation time in rats dosed with 460 mg TnBP/kg/day (lowest dose tested) for 10 weeks. In a 2-year study in rats dosed via the diet with up to 182 mg TnBP/kg/day, interim evaluations conducted at 12 months showed no significant alterations in hematological parameters (Auletta et al. 1988a). Similar results were reported in an 18-week study in rats dosed with up to 333 mg TnBP/kg/day (Laham et al. 1985a). Evaluation of hematological parameters in mice showed an increase in platelet counts in males dosed with 1,478 mg TnBP/kg/day for 13 weeks (Auletta et al. 1991), but there was no evidence of hematological alterations at 9 months or at termination in mice dosed with up to 711 mg/kg/day in an 18-month study, although it appears that evaluations were limited to red blood cell and leukocyte total counts only (Auletta et al. 1988b).

Administration of up to approximately 948 mg TCP (Kronitex® TCP)/kg/day to male rats or 745 mg/kg/day to female rats in the diet for 28 days did not induce significant alterations in hematological parameters (FMC 1976b). In the 13-week gavage NTP (1994) study in rats, doses of up to 800 mg TCP/kg/day did not significantly alter hematological parameters, but doses of 750 and 770 mg/kg/day administered via the diet for 13 weeks to males and females, respectively, increased blood platelets 35 and 32%, respectively. Females in this group also exhibited a 57% increase in leukocytes. In another intermediate-duration study in rats, dietary doses of approximately 460 mg TCP/kg/day (only level tested) did not alter hematological parameters (Oishi et al. 1982). No hematological alterations were reported in mice in the intermediate-duration studies conducted by NTP (1994) (up to 800 mg/kg/day in the gavage study and 1,050 mg/kg/day in the dietary study) or in the chronic studies in rats (up to 15 mg TCP/kg/day) and mice (up to 37 mg/TCP/kg/day) conducted by NTP (1994).

Data for TDCP indicate that treatment of rabbits by gavage with up to 200 mg TDCP/kg/day for 12 weeks did not result in significant alterations in hematological parameters (Anonymous 1977). In the 2-year bioassay in rats, hemoglobin, hematocrit, and total erythrocyte values were often significantly lower than controls in high-dose rats (80 mg/kg/day), and the differences with the control group were usually more

pronounced in males (Stauffer Chemical Co. 1981a). Hemoglobin and hematocrit were significantly reduced in high-dose males both at 3 and 6 months and hemoglobin was reduced in high-dose females at 6 months. High-dose males also showed a reduction in red blood cell count at 6 months. At 12 months, there were significant reductions in hemoglobin in high-dose males (10.6%) and females (7.5%) and in red cell counts in high-dose males (10.7%). None of these alterations were observed after 24 months of treatment with TDCP. At 24 months, prothrombin times and partial thromboplastin times were significantly elevated in high-dose males; the NOAEL was 20 mg/kg/day.

Two studies were available that provided information for TBEP. No significant hematological alterations were reported in rats dosed daily by gavage with up to 100 mg TBEP/kg/day for 14 days (Komsta et al. 1989). In an 18-week study, dietary administration of TBEP resulted in statistically significant hematological changes that included decreased leukocyte counts (lymphocytes) in high-dose males (578 mg/kg/day) on week 9, increased platelet counts in high-dose males and females (698 mg/kg/day) on weeks 9 and 18, and increased platelet counts in mid-dose males (173 mg/kg/day) only on week 9 (Reyna and Thake 1987a).

Even less information is available for the remaining phosphate ester flame retardants discussed in this profile. Decreased neutrophil count and increased MCH and MCHC were reported in male rats treated with dietary doses of 346 mg TiBP/kg/day for 13 weeks; the NOAEL was 68 mg/kg/day (Naylor and Ribelin 1990). Sutton et al. (1960) reported that dietary doses of up to 416 mg TPP/kg/day for 35 days did not alter hematological parameters in rats (red blood cell and leukocyte counts, hemoglobin content, and cell volume).

Musculoskeletal Effects. No alterations in gross or microscopic morphology of bone or skeletal muscle have been reported in any of the studies of the phosphate ester flame retardants summarized in this profile. No effects were noted in rats dosed daily with 350 mg TCEP/kg/day by gavage for up to 16 weeks (NTP 1991a) or in rats receiving dietary doses of up to 596 mg TCEP/kg/day for 3 months (Anonymous 1977). Similarly, mice dosed daily with up to 700 mg TCEP/kg/day for up to 16 weeks showed no alterations in bone or muscle (NTP 1991a). No effects were reported in rats or mice dosed with up to 88 or 350 mg TCEP/kg/day, respectively, for 2 years (NTP 1991a).

Dietary administration of 423 mg TnBP/kg/day to rats for 90 days (FMC 1985a), 182 mg/kg/day to rats for 2 years (Auletta et al. 1998a), 1,776 mg TnBP/kg/day to mice for 13 weeks (Auletta 1991), or 711 mg/kg/day to mice for 18 months (Auletta et al. 1998b) did not result in alterations in bone or muscle.

Similar results were reported in rats treated with 80 mg TDCP/kg/day for 2 years (Stauffer Chemical Co. 1981a), rats treated with 100 mg TBEP/kg/day for 14 days (Komsta et al. 1989), rats treated with 698 mg TBEP/kg/day for 18 weeks (Reyna and Thake 1987a), or rats dosed with 404 mg TiBP/kg/day for 13 weeks (Naylor and Ribelin 1990).

Bone (unspecified) was examined in the intermediate- and chronic-duration studies conducted with TCP in rats and mice by NTP (1994); no histopathologic alterations were reported. The highest doses tested were 800 mg/kg/day in 13-week gavage study in rats and mice, 750–770 mg/kg/day in 13-week dietary study in rats, 900–1,050 mg/kg/day in the 13-week dietary study in mice, 13–15 in the 2-year study in rats, and 27–37 mg/kg/day in the 2-year study in mice.

Hepatic Effects. Administration of 350 mg TCEP/kg/day by gavage 5 days/week for 16 days to rats resulted in a significant increase (10%) in absolute and relative liver weight in females; doses of ≥175 mg/kg/day and 350 mg/kg/day produced similar effects in females and males, respectively, after 61 weeks of dosing; however, gross or microscopic examination of the liver did not show lesions (NTP 1991a). Dietary administration of up to 586 mg TCEP/kg/day for 3 months to rats did not produce significant changes in liver weight or in gross or microscopic appearance of the liver (Anonymous 1977). Mice administered up to 700 mg TCEP/kg/day for 16 days by gavage had no significant changes in liver weight or in gross or microscopic appearance of the liver, but similar dosing with ≥175 mg TCEP/kg/day for 16 weeks induced a significant increase in absolute and relative liver weight of females (NTP 1991a); the NOAEL was 88 mg/kg/day. No significant gross or microscopic alterations were reported in the liver in the latter experiment. In the 2-year bioassay, the liver did not appear to be a particularly sensitive target for TCEP. The only significant effect reported was an increase in absolute and relative liver weight in rats dosed with 88 mg TCEP/kg/day at week 66 interim kill; the NOAEL was 44 mg/kg/day (NTP 1991a). Clinical chemistry tests, as well as gross and microscopic examination of the liver, did not reveal significant chemical-related alterations. In mice, doses of up 350 mg TCEP/kg/day had no significant effect on liver parameters (NTP 1991a).

Treatment of male and female rats with 411 mg TnBP/kg/day by gavage for 14 days resulted in a significant increase in absolute and relative liver weight, and gross examination revealed slight liver enlargement; however, microscopic evaluation of liver tissue did not show significant alterations (Laham et al. 1984b). The NOAEL for liver weight was 137 mg/kg/day. In a developmental study, treatment of pregnant rats with up to 500 mg TnBP/kg/day on gestation days (Gd) 7–17 resulted in a 6% increase in

absolute liver weight on Gd 20; no other liver parameter was evaluated in this study (Noda et al. 1994). In a 90-day study in rats, consumption of a diet containing 1,000 ppm TnBP (68.1 mg/kg/day for males and 80.9 mg/kg/day for females) resulted in a significant increase in absolute and relative liver weight in males; the NOAEL was 13.8 mg/kg/day (FMC 1985a). Increases in serum transaminases were observed at the midpoint in the study and at termination mainly in rats that consumed 5,000 ppm TnBP in the diet (360 and 423 mg/kg/day in males and females, respectively); histological evaluation of the liver did not reveal lesions. In a similar study, dosing rats by gavage with 333 mg TnBP/kg/day for 18 weeks induced a significant increase in absolute and relative liver weight in females; the NOAEL was 200 mg/kg/day (Laham et al. 1985a). Clinical chemistry tests as well histological examination of the liver were unremarkable. In a 2-generation reproductive study in rats, dietary doses of approximately ≥51 mg TnBP/kg/day for 110 days induced a significant increase in the incidence of hepatic centrilobular hyperplasia only in parental females (Tyl et al. 1997); the NOAEL was 15 mg/kg/day. F_1 females treated similarly showed the lesion, but at a higher dose level of 217 mg TnBP/kg/day. In an intermediate-duration study in mice, dietary doses of ≥382 mg/kg/day significantly increased the incidence of centrilobular hepatocyte hypertrophy in males (Auletta et al. 1998b). Clinical chemistry tests showed significantly elevated serum alanine aminotransferase (ALT) and alkaline phosphatase (AP) activities in males dosed with 1,478 mg TnBP/kg/day and females dosed with 1,776 mg/kg/day. The NOAEL for hepatocyte hyperplasia in males was 95 mg/kg/day.

The liver was not a sensitive target in male or female rats dosed with up to 143 and 182 mg TnBP/kg/day, respectively, for 2 years, as judged by a lack of treatment-related gross or microscopic alterations in the liver at termination (Auletta et al. 1998a). In a similar 18-month study in mice, nonneoplastic effects were limited to significant increases in absolute and relative liver weight in males and females at dietary doses of ≥169 and ≥206 mg TnBP/kg/day, respectively (Auletta et al. 1998b).

The liver also did not seem to be a particularly sensitive target for TCP, at least in intermediate-duration studies. Increases in absolute and/or relative liver weight were reported in several intermediate-duration studies in rats and mice. Increases were generally moderate (≤30%) and were not accompanied by microscopic alterations. The LOAELs ranged from 200 mg/kg/day for a 14% increase in absolute liver weight in mice administered TCP by gavage for 13 weeks (NTP 1994) to 460 mg/kg/day (only dose tested) for a 16 and 23% increase in absolute and relative liver weight, respectively, in rats dosed with TCP (unidentified isomeric composition) in the food for 9 weeks (Oishi et al. 1982). The latter study also reported mild cytoplasmic vacuolization in the liver and increased serum AST. Significantly increased serum cholesterol and low-density lipoproteins were reported in rats dosed with 400 mg TCP/kg/day

(only dose tested; 62% *m*- and *p*-isomers, no *o*-isomers) for 20–60 days (Latendresse et al. 1995). No significant liver alterations were reported in rats dosed with up to 13–15 mg TCP/kg/day in the food for 2 years (NTP 1994). However, male mice dosed with 13 or 27 mg/TCP/kg/day for 2 years had significantly elevated incidences of clear cell focus, fatty change, and ceroid pigmentation in the liver (NTP 1994); the NOAEL was 7 mg/kg/day. Cells within foci were enlarged and contained one or more medium to large clear spaces in the cytoplasm. The fatty change consisted of small vacuoles in individual hepatocytes, randomly distributed throughout the liver; the severity was never greater than moderate. Ceroid pigmentation consisted of cells containing fine, yellow-brown granules in their cytoplasm. Female mice dosed with up to 37 mg TCP/kg/day did not exhibit increased incidences of these alterations.

Less information is available for the remaining phosphate ester flame retardants subject of this profile. Komsta et al. (1989) conducted liver function tests, measured microsomal enzyme activities, and evaluated the gross and microscopic appearance of the liver of rats dosed by gavage with up to 100 mg TBEP/kg/day for 14 days and reported no significant alterations in any of the parameters examined. However, in an 18-week dietary study in rats, treatment of males with ≥173 mg TBEP/kg/day resulted in a significant increase in periportal hepatocellular vacuolization (Reyna and Thake 1987a). At the next highest dose level, 578 mg/kg/day, the incidence of periportal hepatocellular hypertrophy was also significantly elevated. This was accompanied by elevations in serum gamma-glutamyl transferase (GGT) activity on weeks 9 and 18 of the study. No significant histopathology was reported in female rats. The hepatic NOAEL in males was 17.3 mg TBEP/kg/day. The increased incidence of hepatocyte hypertrophy in male rats in the Reyna and Thake (1987a) study was used to derive an intermediate-duration oral MRL for TBEP.

In a 12-week study with TDCP in rabbits, daily gavage doses of up to 200 mg/kg/day had no significant effect on clinical chemistry tests or on gross or microscopic morphology of the liver (Anonymous 1977). In the Stauffer Chemical Co. (1981a) bioassay, absolute liver weight was significantly increased in high-dose (80 mg/kg/day) males and females (26 and 23.5%, respectively) at the 12 month interval, but there were no significant histological alterations. In that study, extending the treatment to 24 months resulted in a significantly increased incidence of foci/areas of hepatocellular alterations and of dilated sinusoids in high-dose (80 mg/kg/day) males and females (Stauffer Chemical Co. 1981a). Gross observations revealed masses, nodules, and raised areas in the liver of rats in the 80 mg/kg/day groups. Clinical chemistry tests showed no consistent alterations throughout the study.

In a 13-week dietary study with TiBP in rats, clinical chemistry tests at termination showed a significant increase in serum cholesterol in males dosed with 346 mg/kg/day. The NOAEL was 68 mg/kg/day; no other clinical chemistry parameter was affected (Naylor and Ribelin 1990). Neither gross nor microscopic examination of the liver showed treatment-related effects. The NOAEL in females was 404 mg/kg/day. In an early study in rats, Sutton et al. (1960) reported that dietary administration of up to approximately 416 mg TPP/kg/day for 35 days had no significant effect on the weight of the liver; no other hepatic parameter was evaluated in this study.

Renal Effects. Treatment of male and female rats with 350 mg TCEP/kg/day by gavage 5 days/week for 16 days significantly increased the absolute and relative weight of the kidneys in males, whereas similar treatment with ≥175 mg TCEP/kg/day for 16 weeks increased absolute and relative kidney weight in both males and females (NTP 1991a); no kidney histopathology was reported in either case. In a 3-month dietary study in rats, doses of up to 586 mg TCEP/kg/day did not alter kidney weight or gross or microscopic morphology (Anonymous 1977). Treatment of mice with up to 700 mg TCEP/kg/day by gavage for 16 days did not produce alterations in the kidneys, but similar treatment with 700 mg/kg/day for 16 weeks significantly reduced absolute and relative kidney weight in males (NTP 1991a). Light microscopy showed enlargement of the nuclei of epithelial cells in the renal tubules in all males and females treated with 700 mg/kg/day. These lesions were observed primarily in the proximal convoluted tubules of the inner cortex and outer stripe of the outer medulla, and to a lesser extent, in the outer portion of the loops of Henle in the outer medulla. The NOAEL was 350 mg/kg/day.

In the 2-year bioassay in rats, the principal nonneoplastic alterations attributed to administration of TCEP were seen in the kidneys and consisted of focal hyperplasia of the renal tubule epithelium in high-dose (88 mg/kg/day) males and females; this occurred in the convoluted tubules of the cortex. The lesions were focal or multifocal and were characterized by stratification of the epithelial cells with partial to complete obliteration of the tubule lumens. The NOAEL was 44 mg/kg/day. In mice, the principal nonneoplastic effect associated with administration of TCEP also occurred in the kidneys. The incidence of karyomegaly (nuclear enlargement) of the cells in the proximal convoluted tubules of the inner cortex and outer stripe of the outer medulla was significantly increased in mid- (175 mg/kg/day) and high-dose (350 mg/kg/day) males and females (NTP 1991a). The increased incidence of renal tubule epithelial hyperplasia in female rats in the NTP (1991a) was used to derive a chronic-duration oral MRL for TCEP.

Daily gavage doses of up to 411 mg TnBP did not induce significant alteration in the weight or morphology of the kidneys (Laham et al. 1984b). Similar findings were reported in studies in rats dosed

with up to 143 mg TnBP/kg/day for 10 weeks (Arnold et al. 1997), 423 mg/kg/day for 90 days (FMC 1985a), or 333 mg/kg/day for 18 weeks (Laham et al. 1985a). Dose related increases in blood urea nitrogen (BUN) were reported in rats dosed via the diet with ≥460 mg TnBP/kg/day for 9–10 weeks (Oishi et al. 1980, 1982), but histopathologic evaluations apparently were not conducted. Increased incidence of renal pelvic epithelial hyperplasia was reported in F_1 males treated with 217 mg TnBP/kg/day in a 2-generation reproductive study (Tyl et al. 1997); the NOAEL was 51 mg/kg/day. No significant kidney alterations were reported in mice dosed with up to 1,776 mg TnBP/kg/day for 13 weeks (Auletta et al. 1991), in mice dosed with up to 711 mg/kg/day for 18 months (Auletta et al. 1998b), or in rats dosed with up to 182 mg/kg/day for 2 years (Auletta et al. 1998a).

Dosing of male rabbits by gavage with 200 mg TDCP/kg/day for 12 weeks induced a significant increase in absolute kidney weight, but did not induce gross or microscopic alterations in the kidneys (Anonymous 1977). In a 2-year bioassay in rats (0, 5, 20, or 80 mg/kg/day), the kidneys appeared to be the target for TDCP (Stauffer Chemical Co. 1981a). At the 12-month interval males and females exhibited dose-related increases in absolute kidney weight which achieved statistical significance in the high-dose groups. Relative to controls, absolute kidney weight increased 12, 17, and 48% in the low-, mid-, and high-dose males, respectively, the corresponding percentages in females were 7, 12, and 40%. However, no significant histological alterations were seen at this time point. Necropsy at 24 months revealed enlargement of the kidney in mid- and high-dose males and high-dose females, plus higher incidence of discolorations, surface irregularities, masses, nodules, and cysts in treated rats than in controls. Light microscopy revealed a significant increase in the incidence of hyperplasia of the convoluted tubular epithelium in males dosed with ≥20 mg TDCP/kg/day. High-dose females also exhibited this lesion and both high-dose males and females showed increased incidence of chronic nephropathy. BUN was significantly elevated in some mid- and high-dose rats at 18 and 24 months, which was consistent with the microscopic evidence of renal pathology. The increase in absolute kidney weight in female rats was used to derive an intermediate-duration oral MRL for TDCP. The increased incidence of renal tubular hyperplasia in male rats after 24 months of exposure to TDCP was used to derive a chronic-duration oral MRL for TDCP.

Significant renal effects of TCP were limited to rats and mice exposed to the chemical in the food for 13 weeks (NTP 1994). In female rats, increased incidence of renal papilla edema and necrosis occurred with doses ≥430 mg TCP/kg/day and increased nephropathy was seen at 770 mg/kg/day. Male rats dosed with 750 mg TCP/kg/day had increased incidence of edema and necrosis of the renal papilla and nephropathy. The corresponding NOAELs for renal effects in females and males were 230 and

430 mg/kg/day, respectively. In mice, a significant increased incidence of regeneration in the renal tubules was reported in males dosed with 900 mg TCP/kg/day; the NOAEL was 380 mg/kg/day. Renal lesions did not occur with comparable doses in the 13-week gavage studies conducted by NTP (1994); no explanation was offered for these apparent inconsistencies. No significant gross or microscopic alterations were reported in the kidneys of rats and mice dosed with up to 15 or 37 mg TCP/kg/day, respectively, for 2 years (NTP 1994).

Dosing of rats with up to 100 mg TBEP/kg/day for 14 days (Komsta et al. 1989) or 698 mg/kg/day for 18 weeks (Reyna and Thake 1987a) did not induce renal alterations and neither did administration of up to 404 mg TiBP/kg/day for 13 weeks (Naylor and Ribelin 1990). Sutton et al. (1960) reported that a 35-day dietary regime of up to 416 mg TPP/kg/day did not significantly alter the weight of the kidney in rats, but histological examinations were not conducted.

Endocrine Effects. Endocrine parameters evaluated in the toxicity studies available generally consisted of the weight and gross and microscopic morphology of endocrine glands (i.e., thyroid, pituitary, adrenals). As discussed below, except for TCP, no significant alterations were reported in endocrine glands following oral exposure to the phosphate ester flame retardants discussed in this profile.

The adrenal cortex was a target for TCP in rats. Studies conducted by Latendresse and coworkers (Latendresse et al. 1993, 1994a, 1994b, 1995) showed that exposure of rats to 400 mg TCP/kg/day (only dose level tested) for 20–60 days caused lipidosis in the adrenal cortical cells. After 20 days of exposure, lipidosis was present in all adrenal glands examined from treated rats. Adrenal glands were enlarged bilaterally in males and females and the cortex was markedly thickened. The cross-sectional area of the adrenal cortex was significantly increased. The degree of adrenocortical expansion was correlated with the severity of the cytoplasmic lipidosis. The lipid deposition was progressive with the duration of exposure. After 40 days, hypertrophy of adrenal cortical cells was more pronounced and after 60 days, cytoplasmic vacuolization became coarser. The ultrastructural changes correlated with light microscopic alterations of fatty change. Histochemical staining of the cells showed a marked increase in cytoplasmic lipid and cholesterol compared to controls. The accumulation of cholesterol-rich lipid appeared to be caused by the inhibition of neutral cholesteryl ester hydrolase (nCEH), an enzyme that catalyzes the conversion of stored cholesteryl ester to free cholesterol, while acylcoenzyme A: cholesterol acyl transferase (ACAT), involved in the esterification of cholesterol, remained near normal levels. Other intermediate-duration studies also described adrenal effects at lower doses. Treatment of rats with 50–65 mg TCP/kg/day (lowest doses tested) by gavage or through the diet for 13 weeks induced cytoplasmic

vacuolization of the adrenal cortex of males and females (10/10 vs. 0/10 in controls) (NTP 1994). In mice, gavage treatment with 50 mg TCP/kg/day (lowest dose tested) for 13 weeks induced cytoplasmic vacuolization in 10/10 males and females vs. 0/10 in controls. In the 13-week feed study, 10/10 female mice dosed with 65 mg TCP/kg/day (lowest dose tested) showed cytoplasmic vacuolization, whereas all males dosed with 110 mg TCP/kg/day showed vacuolization; 45 mg TCP/kg/day was a NOAEL. In the NTP (1994) 2-year feed study, no cytoplasmic vacuolization of the adrenal cortex was observed in males dosed with up to 13 mg TCP/kg/day at the 3-, 9-, 15-, or 24-month examinations. However, females dosed with 15 mg TCP/kg/day, but not 7 mg/kg/day, showed significant increases in the incidence of the lesion at all time points examined. The lesion was characterized by increased number of small, fine vacuoles in the cortical cells of the zona fasciculata resulting in a ground glass appearance and an increase in cell size. In the 2-year study in mice, ceroid pigmentation of the adrenal cortex was significantly increased in high-dose males (27 mg/kg/day) at the 3-month interim kills, and was present in almost all mice in all groups, including controls, exposed for ≥9 months. The lesion consisted of macrophages and/or epithelial cells in various stages of distension from the accumulation of yellow-brown cytoplasmic pigment. The severity of the lesion was dose-related. It should be noted that in a continuous breeding study in mice, F_1 offspring born to dams exposed perinatally to approximately 62.5 mg TCP/kg/day and then directly to the same dose until 74 days of age showed hypertrophy of the zona fasciculata and brown degeneration in the adrenals. This effect is listed in Table 3-6 as systemic rather than developmental because of the direct exposure of the F_1 offspring; it is unknown what the contribution of gestational and lactational exposure, if any, could have been. In addition to effects on the adrenal gland, TCP significantly increased the incidence of basophilic hypertrophy of the pituitary gland in male rats dosed ≥220 mg TCP/kg/day via the diet for 13 weeks (NTP 1994). Examination of other endocrine glands such as the thyroid and parathyroid in the NTP (1994) studies did not show treatment-related alterations.

No effects were noted in rats dosed daily with 350 mg TCEP/kg/day by gavage for up to 16 weeks (NTP 1991a) or in rats receiving dietary doses of up to 596 mg TCEP/kg/day for 3 months (Anonymous 1977). Similarly, mice dosed daily with up to 700 mg TCEP/kg/day for up to 16 weeks showed no alterations in the endocrine glands (NTP 1991a). No alterations in endocrine glands were reported in rats or mice dosed with up to 88 or 350 mg TCEP/kg/day, respectively, for 2 years (NTP 1991a).

No significant alteration in endocrine glands were noted in rats dosed with up to 423 mg TnBP/kg/day for 90 days (FMC 1985a) or 182 mg/kg/day for 2 years (Auletta et al. 1998a), or in mice dosed with up to 1,776 mg/kg/day for 13 weeks (Auletta et al. 1991) or 711 mg/kg/day for 18 months (Auletta et al. 1998b). Dosing of rabbits with up to 200 mg TDCP/kg/day for 12 weeks did not produce alterations in

the pituitary gland (Anonymous 1977). Significant increases in absolute thyroid weight were reported in rats dosed with up to 80 mg TDCP/kg/day for 12 or 24 months, but there were no significant histological alterations (Stauffer Chemical Co. 1981a). Rats dosed with 100 mg TBEP/kg/day for 14 days (Komsta et al. 1989) or rats dosed with 698 mg TBEP/kg/day for 18 weeks also showed no histological alterations in the thyroid gland (Reyna and Thake 1987a). A single study with TiBP reported no significant endocrine gland alterations in rats dosed with up to 404 mg/kg/day for 13 weeks (Naylor and Ribelin 1990).

Dermal Effects. Many of the oral toxicity studies described above conducted gross and microscopic examinations of the skin and none reported chemical-related alterations.

Ocular Effects. The eyes were examined in many toxicity studies with the phosphate ester flame retardants discussed in this profile and, with one exception, no significant alterations were reported. In the 24-month dietary study in rats dosed with 0, 20, or 80 mg TDCP/kg/day conducted by Stauffer Chemical Co. (1981a), ophthalmological examinations performed at 18 and 24 months revealed sacculations along the course of the retinal arterioles in one mid-dose male, four high-dose males, and four high-dose females, primarily at 24 months. Stauffer Chemical Co. (1981a) stated that this type of lesion is observed occasionally in old untreated rats and that, in this study, there appeared to have been an acceleration of this abnormal arteriolar process in some treated animals.

Body Weight Effects. Body weight was monitored in virtually all of the toxicity studies already described. Food consumption was not always reported, but when information was provided, it was usually in absolute terms (i.e., g/day); few studies also provided relative intake (i.e., g/kg body weight/day. It should also be noted that differences in food consumption, and consequently in body weight gain, between gavage and dietary studies may be due, in part, to poor palatability of the feed.

Body weight was not significantly affected in intermediate- and chronic duration gavage studies with TCEP in rats and mice conducted by NTP (1991a). In the intermediate-duration studies, rats and mice received doses of up to 350 and 700 mg TCEP/kg/day for 16 weeks; the corresponding doses in the 2-year study were 88 and 350 mg TCEP/kg/day. However, in a 3-month dietary study, male and female rats dosed with 506 and 586 mg TCEP/kg/day, respectively, had a final body weight 11–18% lower than controls (Anonymous 1977). The lower body weight was associated with a significant reduction in food consumption by the end of the study. In a gestational exposure study, Hardin et al. (1987) reported that pregnant rats dosed with 940 mg TCEP/kg/day on Gd 6–13 experienced a 12% reduction in body weight gain between Gd 6 and postnatal day 3 relative to controls; food consumption data were not available.

Administration of up to 411 mg TnBP/kg/day by gavage for 14 days to rats had no significant effect on body weight (Laham et al. 1984b), but administration of 125 mg/kg/day to pregnant rats on Gd 7–17 reduced adjusted body weight gain on Gd 0–20 by 13% relative to controls and 200 mg TnBP/kg/day reduced the same parameter by 37% (Noda et al. 1994). Food consumption was also significantly reduced. Final body weight was reduced between 10 and 20% relative to controls in rats dosed with 143 mg TnBP/kg/day in the diet for 10 weeks (Arnold et al. 1997), 217 mg/TnBP/kg/day in the diet for 70-110 days (Tyl et al. 1997), 360–423 mg TnBP/kg/day in the diet for 3 months (FMC 1985a), 460 mg TnBP/kg/day in the diet for 9 weeks (Oishi et al. 1980), 325 mg TnBP/kg/day by gavage for 13 weeks (Healy et al. 1995), 333 mg TnBP/kg/day by gavage for 18 weeks (Laham et al. 1985a), or 42 mg TnBP/kg/day in the diet for 2 years (Auletta et al. 1998a); some reduction in food consumption was reported in all of these studies except in Laham et al. (1985a), who did not provide information in that regard. Mice dosed via the diet with up to 1,776 mg TnBP/kg/day for 13 weeks (Auletta et al. 1991) or 711 mg TnBP/kg/day for 18 months (Auletta et al. 1998b) did not experience significant alterations in body weight compared to controls. The reduction in body weight in pregnant rats in the study by Noda et al. (1994) was used to derive an acute-duration oral MRL for TnBP.

Weight gain was significantly reduced (29%) on Gd 6–11 in pregnant rats dosed with 100 mg TDCP/kg/day; and on Gd 6–15, rats dosed with 400 mg/kg/day lost weight (Stauffer Chemical Co. 1981b). Food consumption during treatment days was significantly reduced relative to controls. Body weight gain was not affected in rabbits dosed by gavage with up to 200 mg TDCP/kg/day for 12 weeks (Anonymous 1977). In the 2-year bioassay, final body weight of male and female rats was reduced 21–24% relative to controls (Stauffer Chemical Co. 1981a). There was no consistent pattern of differences among groups over time regarding food consumption.

Terminal body weight was reduced 36% relative to controls in male rats dosed with approximately 938 mg TCP (Kronitex® TCP)/kg/day via the food for 28 days; this was associated with significantly reduced food intake (FMC 1976b). Body weight was reduced 17% in male rats and 11% in male mice dosed by gavage with 1,450 mg TCP/kg/day during a 16-day period (the NOAEL was 730 mg/kg/day); alterations in weight were less pronounced in females (NTP 1994). Significant reductions in final body weight were also reported in rats and mice that received the highest doses of TCP by gavage or through the food for 13 weeks in the NTP (1994) study (800 mg/kg/day in rats by gavage, 750 mg/kg/day in rats via food; 800 mg/kg/day in mice by gavage, 530 mg/kg/day in mice via the food). In the 2-year bioassay,

body weight of treated rats and mice was comparable to that of their respective controls throughout the study (NTP 1994). The highest doses in rats and mice were 13–15 and 27–37 mg/kg/day, respectively.

Studies with TBEP showed no significant alterations in body weight in rats treated with gavage doses of up to 100 mg/kg/day for 14 days (Komsta et al. 1989) or up to 698 mg/kg/day in the food for 18 weeks (Reyna and Thake 1987a). However, body weight gain was reduced 35% in pregnant rats during treatment with 1,500 mg TBEP/kg/day on Gd 6–15, the NOAEL was 500 mg/kg/day (Monsanto Co. 1985b). Reduced weight gain in pregnant rats from the Monsanto Co. (1985b) study was used to derive an acute-duration oral MRL for TBEP. TiBP did not alter weight gain in rats in dietary doses of up to 404 mg/kg/day for 13 weeks (Naylor and Ribelin 1990). TPP administered to rats in doses of up to 416 mg/kg/day in the food for 35 days had no significant effect on weight gain (Sutton et al. 1960), but 345 mg TPP/kg/day, also administered in the food, reduced weight gain by 11% (Sobotka et al. 1986); food consumption was not significantly altered in the latter study. TCPP administered to rats in gavage doses of up to 1,000 mg/kg/day for 7 days did not significantly affect weight gain (Kawasaki et al. 1982).

Metabolic Effects. Alterations in metabolic effects, principally in mean levels of serum electrolytes, have been reported in studies with some phosphate ester flame retardants subject of this profile. The toxicological significance of these effects is unknown. No significant alterations in serum electrolytes or glucose were reported in rats dosed with up to 586 mg TCEP/kg/day for 3 months (Anonymous 1977). Female rats dosed with ≥137 mg TnBP/kg/day for 14 days showed a dose-related increase in serum potassium levels, whereas no such effect was seen in males (Laham et al. 1984b); neither glucose nor other serum electrolytes were affected. In a 90-day study, male rats treated with 360 mg TnBP/kg/day had a significant increase in serum calcium levels at termination (FMC 1985a), but treatment of rats with up to 333 mg TnBP/kg/day for 18 weeks did not affect serum electrolytes, including calcium (Laham et al. 1985a). Neither sodium nor potassium levels were altered in rats dosed with 460 mg TnBP for 9 weeks (Oishi et al. 1982). Dosing of male and female mice with 1,478 and 1,776 mg TnBP/kg/day, respectively, for 13 weeks induced a significant increase in serum calcium at termination; the respective NOAELs were 382 and 461 mg/kg/day (Auletta et al. 1991). No significant alterations in serum electrolytes were reported in rats dosed with up to 100 mg TBEP/kg/day for 14 days (Komsta et al. 1989), 698 mg TBEP/kg/day for 18 weeks (Reyna and Thake 19897a), or 404 mg TiBP/kg/day for 13 weeks (Naylor and Ribelin 1990).

Other Systemic Effects. The urinary bladder of rats appears to be a sensitive target for TnBP. Treatment of male rats with TnBP in the diet for 10 weeks produced urothelial hyperplasia (Arnold et al.

1997). The incidence of simple hyperplasia was significantly increased at ≥33 mg TnBP/kg day, whereas the incidence of papillary and nodular hyperplasia was significantly increased at 143 mg/kg/day. Simultaneous administration of ammonium chloride (to acidify the urine and thus prevent the formation of magnesium ammonium phosphate crystals) did not prevent the proliferative changes in the bladder epithelium, but the hyperplastic effects were milder. Removing the rats from the experimental diet for 10 weeks after treatment led to healing, but the ulcer repair process was accompanied by submucosal fibrosis. The NOAEL was 9 mg TnBP/kg/day. FMC (1985a) also reported increased incidence of minimal to moderate hyperplasia of the transitional cell epithelium and males appeared more sensitive than females. The incidence of urinary bladder hyperplasia was significantly increased in males dosed with ≥68.1 mg TnBP/kg/day, and the NOAEL was 13.8 mg/kg/day; increased incidence in females occurred at 423 mg/kg/day. Laham et al. (1985a) also reported this lesion in an 18-week gavage study. All treated rats (6/6 compared with 0/6 in controls) showed diffuse hyperplasia of the bladder epithelium; severity appeared greater in males. The epithelium of treated rats showed a greater frequency of prominent nucleoli compared to controls and was thicker than in controls, particularly in males. The lowest dose of TnBP in this study was 200 mg/kg/day. Tyl et al. (1997) also reported bladder epithelial in male and female rats dosed with ≥51 mg TnBP/kg/day for 70–110 days via the diet; the NOAEL was 15 mg/kg/day. In the 2-year study, a significant increase in urinary bladder hyperplasia was seen in males dosed with ≥33 mg TnBP/kg/day; the NOAEL was 9 mg/kg/day. Rats with benign tumors also had hyperplasia present; however, rats with malignant bladder tumors usually did not have any remaining uninvolved epithelium to evaluate for the presence or absence of hyperplasia. This led Auletta et al. (1991a) to speculate that the bladder hyperplasia and papillomas could represent a progression of a hyperplastic lesion to neoplasia. Urinary bladder lesions were not seen in mice or in rats exposed to other phosphate ester flame retardants subject of this profile. The increased incidence of urinary hyperplasia in male rats in the study by Arnold et al. (1997) was used to derive an intermediate-duration oral MRL for TnBP. The intermediate-duration oral MRL for TnBP was also adopted as a chronic-duration oral MRL for TnBP.

3.2.2.3 Immunological and Lymphoreticular Effects

The information available does not suggest that the immunological system of rodents is especially sensitive to the effects of orally administered phosphate ester flame retardants discussed in this profile, although it should be mentioned that, for the most part, the testing has been limited to measurements of the weight of the thymus and spleen and gross and microscopic examinations of these organs and lymph nodes.

In studies with TCEP that evaluated the parameters mentioned above, no significant effects were noted in rats dosed daily with 350 mg TCEP/kg/day by gavage for up to 16 weeks (NTP 1991a) or in rats receiving dietary doses of up to 596 mg TCEP/kg/day for 3 months (Anonymous 1977). Similarly, mice dosed daily with up to 700 mg TCEP/kg/day for up to 16 weeks showed no alterations in lymphoreticular tissues (NTP 1991a). Similar findings were reported in rats or mice dosed with up to 88 or 350 mg TCEP/kg/day, respectively, for 2 years (NTP 1991a).

TnBP administered by gavage to rats in doses of 411 mg/kg/day for 14 days produced a significant decrease in absolute and relative spleen weight, but microscopic morphology was unremarkable (Laham et al. 1984b). Rats dosed with 423 mg/kg/day for 90 days (FMC 1985a), 333 mg/kg/day for 18 weeks (Laham et al. 1985a), or 182 mg/kg/day for 2 years (Auletta et al. 1998a) showed no significant alterations in lymphoid tissues. Similar findings were reported in mice dosed with up to 1,776 mg/kg/day for 13 weeks (Auletta et al. 1991) or 711 mg/kg/day for 18 months (Auletta et al. 1998b).

The same results were reported for TBEP given to rats by gavage in doses of up to 100 mg/kg/day for 14 days (Komsta et al. 1989) or in the diet in doses of up to 698 mg/kg/day for 18 weeks (Reyna and Thake 1987a). No significant alterations were observed in lymphoreticular organs of rats dosed via the diet with up to 404 mg TiBP/kg/day for 13 weeks (Naylor and Ribelin 1990) or up to 80 mg TDCP/kg/day for 12 or 24 months (Stauffer Chemical Co. 1981a).

Parameters of immunocompetence were evaluated in rats treated with dietary doses of up to 711 mg TPP/kg/day for 120 days (Hinton et al. 1996). Beginning on day 60, groups of rats were immunized with sheep red blood cells (SRBC). Secondary and tertiary immunizations were performed at successive 21-day intervals. Serum was analyzed for total and relative amount of proteins. At termination, the weights of the spleen and thymus were measured. Treatment with TPP did not significantly affect the weight or the microscopic appearance of the thymus or spleen. Separate evaluations of B- and T-lymphocyte regions in lymphoid organs showed no significant effects on distribution and proliferation. Total serum protein determination showed no significant effects of TPP, although there was a positive trend with increasing dose. At 6 months, all treated male groups had significantly increased β-globulins and females had increased α-globulins, but no significant differences were seen at termination. Assessment of the humoral response to the T-lymphocyte-dependent antigen SRBC did not indicate alterations in immunocompetence due to treatment with TPP.

Only one study was located that examined the effects of TCP (technical-grade) on immune parameters other than weight and morphology of lymphoreticular organs and tissues (Banerjee et al. 1992). In that study, rats were immunized with tetanus toxoid after 25 days on a diet containing TCP. The TCP used was characterized as technical-grade with 90% of a mixture of ortho, meta, and para isomers, but the proportion of each isomer was not specified. Tests conducted in blood collected after 6 weeks on the experimental diet showed that doses ≥6 mg TCP/kg/day significantly reduced the antibody titer to tetanus toxoid. Serum IgM and IgG were significantly reduced in rats dosed with 12 mg TCP/kg/day. In addition, the cell-mediated immune response was also significantly reduced in rats dosed with ≥6 mg TCP/kg/day. The gross and microscopic appearance of the thymus, spleen, and lymph nodes of rats and mice exposed to TCP were examined by NTP (1994) and only in the 16-day gavage studies were alterations reported. In female rats, administration of 1,450 mg TCP/kg/day induced a significant decrease in absolute (40%) and relative (36%) thymus weight; this dose reduced absolute thymus weight in males by 25%. A higher dose of 2,900 mg TCP/kg/day, which was lethal to males and females, induced diffuse necrosis of the thymus in males and females and diffuse lymphoid depletion of the thymus in females. In mice, doses of 1,450 mg TCP/kg/day, which also caused deaths in males and females, induced lymphoid depletion of the thymus in males. Higher doses (≥2,900 mg/kg/day) also affected spleen and lymph nodes in male and female mice. No significant effects were reported in rats and mice dosed with 730 mg TCP/kg/day. No alterations in lymphoreticular tissues from rats or mice were reported in the 13-week or 2-year studies conducted by NTP (1994).

The highest NOAEL values and all LOAEL values from each reliable study for immunological and lymphoreticular effects in each species and duration category are recorded in Tables 3-2, 3-3, 3-4, 3-5, 3-6, and 3-7 and plotted in Figures 3-2, 3-3, 3-4, 3-5, 3-6, and 3-7.

3.2.2.4 Neurological Effects

Acute-, intermediate-, and chronic-duration exposure of rats to TCEP has produced adverse neurological effects including morphological and behavioral effects. Tilson et al. (1990) administered a single dose of 275 mg TCEP/kg by gavage to female rats and reported that the animals suffered seizures within 60–90 minutes of dosing, characterized by facial twitching, myoclonic motions of the jaw, forelimb clonus, and whole body jerks. Necropsy conducted 7 days after dosing showed severe damage to the CA1 and CA3 regions of the hippocampus. TCEP also produced some necrosis in the lateral and medial thalamic nuclei. In a separate experiment, treated rats were trained on a spatial memory task in a water maze 3 weeks after dosing and were killed 2 days after training for histological evaluation. The results showed

that the treated rats were mildly impaired in the acquisition of a reference memory task in the water maze, and were consistently impaired in performing a repeated acquisition task in the water maze. In a 16-day study in mice dosed daily by gavage, mice given 350 or 700 mg TCEP/kg/day exhibited ataxia and convulsions during the first 3 days of dosing; the NOAEL was 175 mg/kg/day (NTP 1991a). Neither gross nor microscopic examination of the brain at termination showed significant alterations, but it was not specifically indicated whether the hippocampus was examined.

In a 16-week study, administration of ≥175 mg TCEP/kg/day, 5 days/week to male and female rats induced ataxia, convulsions, excessive salivation, and gasping in some females and reduced serum cholinesterase activity by 25–41% (NTP 1991a). Examination of the hippocampus at termination revealed necrosis in 10/10 females and 2/10 males dosed with 350 mg/kg/day (the highest dose tested) and in 8/10 females dosed with 175 mg/kg/day; the NOAEL for these effects was 88 mg/kg/day. None of these effects were observed in rats dosed by gavage with the same doses for 16 days (NTP 1991a). Dietary doses of up to 586 mg TCEP/kg/day for 3 months did not induce alterations in the brain and did not affect the activity of red blood cell cholinesterase (Anonymous 1977). The increased incidence of necrosis in the hippocampus from female rats in the NTP (1991a) study was used to derive an intermediate-duration oral MRL for TCEP.

In the 2-year NTP (1991a) study (0, 44, or 88 mg/kg/day by gavage 5 days/week), there were no clinical signs in rats attributable to administration of TCEP, but treatment with TCEP resulted in degenerative lesions in the brain, mainly in high-dose females. The degenerative lesions were located in the cerebral cortex and brain stem, involved both the gray and white matter and were focally distributed. Specifically, the lesions were in the thalamus, hypothalamus, basal ganglia, and frontal and parietal cortex. Other affected structures included the cingulate cortex, olfactory cortex, superior colliculus, hippocampus, geniculate body, globus pallidus, ventral pallidum, and amygdaloid nuclear region. The lesions varied in severity from minimal to marked and often involved extensive areas. Active lesions were characterized by degeneration and necrosis with hemorrhage, while resolving lesions exhibited loss of neurons and neuropil, proliferation of glial cells, capillary hyperplasia, hypertrophy of the tunica media of small vessels, and hemosiderin-laden macrophages. Mice treated similarly with up to 350 mg TCEP/kg/day did not exhibit brain lesions.

Studies with TnBP showed that a single gavage dose of 1,000 mg/kg/day induced a significant reduction in motor activity in rats 11 hours postdosing, but that was comparable to controls on days 7 and 14 postdosing (Healy et al. 1995); the NOAEL was 325 mg/kg/day. A FOB performed at various time

points during the 14-day study occasionally revealed differences between high-dose rats and controls (data not shown), which the investigators attributed to nonspecific toxicity rather than to neurotoxicity. In another acute-duration study, Laham et al. (1983) reported decreased caudal nerve conduction velocity in rats dosed with 411 mg TnBP/kg/day 2 days after a 14-day daily dosing. Two weeks after the last dose, light and electron microscopy of the nerve showed retraction of Schwann cell processes surrounding unmyelinated fibers. The NOAEL was 274 mg/kg/day. This dosing protocol did not alter brain weight or the gross or microscopic appearance of the brain, and red blood cell acetylcholinesterase activity was not significantly reduced (Laham et al. 1984b). There were no signs of toxicity in any of the 14-day studies.

Dosing male and female rats with up to 360 and 423 mg TnBP/kg/day, respectively, for 90 days had no significant effect on the gross or microscopic morphology of the brain, spinal cord, or sciatic nerve, or on red blood cell or brain cholinesterase activities measured on day 45 and at termination (FMC 1985a). In another 90-day study in rats treated daily by gavage with TnBP, Healy et al. (1995) reported that postdosing salivation occurred rarely at 32.5 mg/kg/day, frequently at 100 mg/kg/day, and almost all the time at 325 mg/kg/day. An FOB conducted at various times during the dosing period showed no significant alterations, and light microscopy of unspecified tissues of the nervous system was unremarkable. In yet another intermediate-duration study, gavage doses of up to 333 mg TnBP/kg/day for 18 weeks reduced red blood cell cholinesterase only by 9% in females and had no significant effect on brain weight or morphology (Laham et al. 1985a). Dietary treatment of rats with up to 182 mg TnBP/kg/day for 2 years (Auletta et al. 1998b) or mice with up to 711 mg/kg/day for 18 months did not induce clinical signs or produce histopathology in the brain, spinal cord, or sciatic nerve.

As stated previously in Chapter 2, there are many reports of neurotoxic effects in humans attributed to exposure to food items contaminated with tri-*o*-cresyl phosphate (TOCP) ranging from single cases to episodes involving thousands of individuals (IPCS 1990). TOCP occurs as a contaminant in commercial TCP mixtures, usually in low concentrations (<0.1%) (NAS 2000). TOCP is not a subject of this profile as an individual isomer; however, it is a subject to the extent that it contributes to the overall toxicity of currently used TCP mixtures.

Tremors and lethargy were described in mice before dying after receiving doses ≥3,208 mg TCP/kg/day via the food in a 14-day study (Chapin et al. 1988). Lethargy was also described in rats fed a diet that provided doses ≥745 mg TCP/kg/day in a 28-day study (FMC 1976b). In the 16-day gavage study conducted by NTP (1994), a number of significant alterations occurred in neurobehavioral tests; however, because they occurred at dose levels that caused mortality and/or reduction in body weight, it was not

possible to determine whether the effects were due to a direct effect on the nervous system or to general toxicity. In the 16-day study in mice, 360 mg TCP/kg/day, the lowest doses tested, significantly reduced hindlimb grip strength in males, but had no significant effect on motor activity or forelimb grip strength (NTP 1994). Significant reduction in hindlimb grip strength was also reported in rats in the 13-week gavage study (400 mg/kg/day) and 13-week feed study (750 mg/kg/day) (NTP 1994). No significant alterations were seen in other tests such as motor activity, forelimb strength, startle response, and paw-lick latency, and microscopic examinations of the brain, spinal cord, and sciatic nerve were unremarkable. Mice appeared to be more sensitive than rats in the 13-week studies (NTP 1994). In the gavage study, histologic examination of the spinal cord and sciatic nerve showed significantly elevated multifocal axonal degeneration in the spinal cord and sciatic nerve in males and females from the 200 mg/kg/day group and also multifocal axonal degeneration in the spinal cord of females at 100 mg/kg/day; the NOAEL was 50 mg/kg/day. Since the TCP mixture contained <1% TOCP, NTP (1994) suggested that this effect may have been due to the presence of *o*-cresol groups in the mixed triester fraction. Hindlimb weakness and tremors were reported in males and females in the 800 mg/kg/day group starting about day 60. Significant reduction in hindlimb grip strength occurred in males and females at ≥200 mg/kg/day. In the dietary study, tremors occurred in 2/10 males dosed with 900 mg/kg/day and 3/10 females dosed with 1,050 mg/kg/day starting on day 86. Significant decreases in forelimb and hindlimb grip strength occurred in the two highest dose groups. In males, forelimb grip strength was reduced 16 and 30% at 380 and 900 mg/kg/day, respectively; hindlimb grip strength was reduced 54% at 900 mg/kg/day. In females, forelimb grip strength was reduced 33 and 35% at 530 and 1,050 mg/kg/day, respectively; in these same groups, hindlimb grip strength was reduced 31 and 88%. Significant axonal degeneration in the sciatic nerve and spinal cord occurred in males at 900 mg/kg/day and in females at 530 and 1,050 mg/kg/day. The only significant alterations (>10% difference with controls) in neurobehavioral tests in the 2-year NTP (1994) bioassay was an 11% reduction in hindlimb grip strength in male rats dosed with 13 mg TCP/kg/day at the 3-month evaluation. No gross or microscopic alterations were reported in the brain, spinal cord, or sciatic nerve from rats or mice in the 2-year studies. Serum cholinesterase was measured in rats and mice in the 13-week and 2-year studies. In the 13-week studies, decreases in activity were dose-related and already significant with the lowest doses tested (range: 41–44% in male rats, 68–72% in female rats, 67–76% in male mice, and 71–81% in female mice). The lowest doses in these studies ranged from 55 to 65 mg TCP/kg/day in rats and from 45 to 65 mg TCP/kg/day in mice. In the 2-year studies, reductions in serum cholinesterase activity did not exceed 49% in rats (high-dose females at the 15-month time point). In mice, reductions in enzyme activity were greater and comparable across time points (3, 9, and 15 months) ranging from 72 to 86% in the highest dose groups (27–37 mg TCP/kg/day).

Less information is available for other phosphate ester flame retardants. Female rats administered a single gavage dose of ≥3,200 mg TBEP/kg showed abnormal gait, piloerection, and tremors during the first week after dosing; these signs were also seen in some females dosed with 1,750 mg/kg (Laham et al. 1985b). Males exhibited similar signs at ≥8,000 mg/kg. Exposure of rats to up to 100 mg TBEP/kg/day by gavage for 14 days did not produce alterations in the weight or histology of the brain (Komsta et al. 1989). In the only long-term studies available with TBEP, 18-week dosing of male and female rats with up to 578 and 698 mg TBEP/kg/day, respectively, did not produce adverse clinical signs or induce gross or microscopic alterations in the brain or sciatic nerve (Reyna and Thake 1987a), but induced a reduction in nerve conduction velocity in females (Reyna and Thake 1987b). Red blood cell cholinesterase activity was significantly reduced in all treated groups of females at week 9, but not at week 18; the magnitude of the reduction was not provided (Reyna and Thake 1987a).

The only information available for TDCP is that from a 24-month bioassay in which rats received dietary doses of 0, 20, or 80 mg TDCP/kg/day (Stauffer Chemical Co. 1981a). TDCP did not induce clinical signs or morphological alterations in the brain or spinal cord. Changes in red blood cell cholinesterase measured throughout the study were inconsistent.

Administration of dietary doses of up to 346 and 404 mg TiBP/kg/day to male and female rats, respectively, for 13 weeks did not induce clinical signs or produce morphological alterations in the brain, spinal cord, or sciatic nerve (Naylor and Ribelin 1990). A 4-month study with TPP in rats receiving up to 711 mg TPP/kg/day via the diet reported no treatment-related effects in a battery of behavioral tests administered at various intervals, which included assessment of motility, balance, coordination, and muscular strength (Sobotka et al. 1986).

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Tables 3-2, 3-3, 3-4, 3-5, 3-6, and 3-7 and plotted in Figures 3-2, 3-3, 3-4, 3-5, 3-6, and 3-7.

3.2.2.5 Reproductive Effects

No significant alterations were noted in the weight or gross or microscopic appearance of the reproductive organs of male or female rats dosed daily with 350 mg TCEP/kg/day by gavage for up to 16 weeks (NTP 1991a) or of rats receiving dietary doses of up to 596 mg TCEP/kg/day for 3 months (Anonymous 1977).

Similarly, mice dosed daily with up to 700 mg TCEP/kg/day for up to 16 weeks showed no alterations in the reproductive organs (NTP 1991a). No alterations were reported in the reproductive organs of rats or mice dosed by gavage with up to 88 or 350 mg TCEP/kg/day, respectively, for 2 years (NTP 1991a).

The effects of TCEP on fertility of CD-1 mice were examined in a continuous breeding protocol study (NTP 1991b). Pairs of mice were administered TCEP in doses of 0, 175, 350, or 700 mg/kg/day by gavage in corn oil for 1 week during cohabitation, 14 weeks postmating, and 3 additional weeks. End points evaluated included clinical signs, body weight, fertility, litters per pair, live pups per litter, proportion of pups born alive, sex ratio, and neonatal pup weight. The last F_1 litter was reared by the dam until weaning, after which time the F_1 rats were treated as were the F_0 generation. The F_1 rats were used to assess second generation fertility. Dosing with TCEP significantly reduced the number of litters produced by mid- and high-dose F_0 mice. Only 2/18 pairs delivered a third litter in the high-dose group versus 37/38 in the controls. The number of pairs that delivered a fifth litter in the mid-dose group was also significantly reduced. Cumulative days to litter were also significantly increased in the high-dose group starting with the second litter. Cross-mating experiments conducted with controls and high-dose mice to determine the affected sex showed that both sexes were adversely affected, but the males were relatively more sensitive, as all sperm end points examined (concentration, motility, and percent abnormal) were affected. Mating of the F_1 generation showed no significant effect on pregnancy or fertility indices.

Daily administration of 411 mg TnBP/kg/day by gavage for 14 days to male and female rats induced degenerative changes in about 50% of the seminiferous tubules in one out of four males examined (Laham et al. 1984b). The tubules showed varying degrees of aspermatogenesis; spermatocytes and spermatids were the cells most frequently affected. The NOAEL was 137 mg/kg/day. No significant alterations were reported in the ovaries. No significant gross or microscopic alterations were reported in the reproductive organs of male and female rats that received dietary doses of up to 423 mg TnBP/kg/day for 90 days (FMC 1985a) or 333 mg/kg/day by daily gavage for 18 weeks (Laham et al. 1985a), or in mice dosed with up to 1,776 mg/kg/day in the diet for 90 days (Auletta et al. 1991). In a 2-generation reproductive toxicity study in rats dosed with up to 217 mg TnBP/kg/day, there were no significant reproductive effects in either the F_0 or F_1 generations, including mating and fertility, and no effects on gross and microscopic appearance of the reproductive organs (Tyl et al. 1997). In rats dosed for 2 years with up to 182 mg TnBP/kg/day (Auletta et al. 1998a) or mice dosed with up to 711 mg TnBP/kg/day for 18 months (Auletta et al. 1998b), examination of the reproductive organs showed no significant gross or microscopic alterations.

Several intermediate- and chronic-duration studies have examined the effects of TCP on reproductive parameters in animals. These studies have provided information on gross and microscopic morphology of reproductive organs, fertility, and sperm parameters. Treatment by gavage of female rats with to 200 mg TCP/kg/day (TCP contained <9% tri-*o*-cresyl phosphate) and males with 100 mg TCP/kg/day before and during breeding resulted in significantly reduced fertility in the females, although the mating index was not affected (Carlton et al. 1987). Examination of males revealed a significantly increased percent (~20-fold) of morphologically abnormal sperm in the cauda epididymis. Males dosed with 200 mg TCP/kg/day showed minimal-to-mild necrosis and degeneration of seminiferous tubules, hypospermia in the epididymis, increases in degenerate and immature spermatids, and early sperm granulomas in the seminiferous tubules. Females showed diffuse vacuolar cytoplasmic alterations in ovarian interstitial cells and an impression of increased follicular and luteal activity. In a similar experiment in rats dosed by gavage with 400 mg TCP/kg/day (only dose tested), only 9/20 treated pairs delivered a litter compared to 40/40 controls; no treated pair delivered a second litter compared to 39/40 in controls (Latendresse et al. 1994b). To determine which sex was affected, the investigators paired treated males with untreated females and reported that no litters were produced, although all females with an estrous detected were bred by the treated males. In contrast, the reproductive efficiency of treated females was comparable to controls, which indicated that reduced fertility was due to an effect on males. In a continuous breeding study in mice, fertility of F_0 males and females exposed to approximately 250 mg TCP/kg/day was significantly reduced (Chapin et al. 1988). The results of a crossover mating experiment indicated that the fertility of both male and females was affected by TCP exposure. However, the number of live pups/litter and the proportion of pups born alive were more affected when the males were treated. Sperm analysis of male F_0 showed a significant reduction in percent motile sperm (59%) and sperm concentration (71%) and an increased percent abnormal sperm (83%). Histopathology of F_0 animals showed no treatment-related effects on prostate, seminal vesicles, ovaries, uterus, or vagina, but the testes of males exposed to 250 mg TCP/kg/day showed atrophy of seminiferous tubules. Direct exposure of the last litter of F_0 mice and mating at 74 days of age showed reduced fertility at 124 mg/kg/day, but not at 62.5 mg/kg/day. Histopathology of F_1 mice did not show pathology in the reproductive organs of males or females. Sperm analysis in males in the 124 mg/kg/day group showed significant reduction in percent motility (44%). Testicular alterations were reported in rats treated with 400 mg TCP/kg/day for 20–60 days (Latendresse et al. 1994a). All exposed rats had altered morphology of seminiferous tubule epithelium. The tubular alterations were usually mild and found in cellular profiles in the seminiferous tubules in Stages IX-XI. The germinal epithelium was characterized by mild degeneration and exfoliation of spermatocytes and spermatids and retained basally located Step 19 spermatids. Rats exposed for 40–

60 days occasionally showed more severe degeneration. Leydig and other interstitial cells appeared normal.

Latendresse and coworkers conducted a series of studies that examined the effects of TCP on the ovaries of rats (Latendresse et al. 1993, 1994a, 1994b, 1995). These studies, which tested one dose level, 400 mg TCP/kg/day, showed that exposure to TCP induced hypertrophy and lipidosis in interstitial ovarian cells, which did not appear to be due to inhibition of steroidogenesis because serum concentrations of corticosterone, androstenedione, and progesterone were similar to controls. Alternatively, the effect was likely due to inhibition of nCEH, a cytosolic enzyme that catalyzes the conversion of stored cholesteryl ester to free cholesterol. Ovaries in treated rats were characterized macroscopically by a relative increase in the interstitial tissue between follicles and corpora lutea of the cortex and also the medulla. The interstitial compartment was composed of a prominent, uniform population of vacuolated cells arranged in sheets and nests surrounded by anastomosing bands of fibrovascular stroma. Ovarian interstitial cell were increased in size compared to controls. The difference was correlated with the severity of lipidosis. Histochemical staining of ovarian cells showed a marked increase in cytoplasmic lipid and cholesterol. These studies also showed that the accumulation of cholesteryl ester in the ovarian cells appears unrelated to reproductive performance since treated female rats had normal estrous cycles and fertility. Both the 13-week gavage and 13-week dietary studies in rats conducted by NTP (1994) reported hypertrophy of the interstitial cells in the ovary at the lowest dose levels used (50 and 65 mg/kg/day, respectively). Atrophy of the seminiferous tubules was reported at 400 and 430 mg/kg/day; the NOAELs were 200 and 220 mg/kg/day. In the 13-week studies in mice, 50 mg TCP/kg/day, the lowest dose tested in the gavage study, significantly increased the incidence of interstitial cell hypertrophy in the ovary. However, in the 13-week dietary study in mice, doses considerably higher (230 mg/kg/day) had no significant effect on the ovary; doses ≥530 mg/kg/day induced cytoplasmic vacuolization in the ovarian interstitial cells. In the 2-year bioassay, there were no significant morphological alterations in the reproductive organs of male rats (high dose was 13 mg/kg/day) or of male or female mice (high doses were 27 and 37 mg/kg/day, respectively) at the 3-, 9-, 15-, or 24-month time points. However, significant dose-related increased incidence of hyperplasia of the ovarian interstitial cell occurred in the mid- (7 mg/kg/day) and high-dose (15 mg/kg/day) groups of female rats at 3 months, in the high-dose groups at 9 and 15 months, and also in the high-dose group at the 2-year terminal examination. The increased incidence in hyperplasia of the interstitial cells in the ovary in the NTP (1994) study was used to derive an intermediate- and a chronic-duration oral MRL for TCP.

Daily administration of up to 100 mg TBEP/kg/day to rats by gavage for 14 days did not significantly affect the weight or gross or microscopic morphology of the testes or ovaries (Komsta et al. 1989). Similar findings were reported in rats that consumed doses of up to 698 mg TBEP/kg/day via the diet for 18 weeks (Reyna and Thake 1987a).

TDCP was tested for its effects on fertility in male rabbits (Anonymous 1977) by dosing the rabbits by gavage with up to 200 mg TDCP/kg/day for 12 weeks. During the last week of treatment, male fertility was tested by mating the males with untreated females. Fertility was assessed by euthanizing the females at mid-gestation and evaluating their uteri. After the mating period, the males were euthanized and sperm from the cauda epididymides were analyzed for motility, morphology, and concentration. The results showed no alterations in mating behavior, fertility, or sperm quantity and quality. Neither gross necropsy nor microscopic examinations revealed significant alterations in the reproductive tract. In the 2-year bioassay with TDCP, dietary doses of up to 80 mg TDCP/kg/day had no significant effect on the gross or microscopic morphology of the reproductive organs of males or females (Stauffer Chemical Co. 1981a).

Fertility indices (number pregnant, corpora lutea, implantations, implantation efficiency, resorptions) were not affected in male or female rats dosed with up to 690 mg TPP/kg/day through the diet for 91 days before mating (Welsh et al. 1987). Feeding rats a diet that provided up to 404 mg TiBP/kg/day for 13 weeks also did not affect the gross or microscopic anatomy of the reproductive organs. Dietary administration of up to 893 mg TCPP/kg/day to rats on Gd 0–20 had no significant effect on the number of implantations or resorptions (Kawasaki et al. 1982).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Tables 3-2, 3-3, 3-4, 3-5, 3-6, and 3-7 and plotted in Figures 3-2, 3-3, 3-4, 3-5, 3-6, and 3-7.

3.2.2.6 Developmental Effects

The developmental effects of TCEP have been studied in rats and mice. In rats, administration of up to 200 mg TCEP/kg/day by gavage in oil on Gd 7–15 did not significantly affect the number of live fetuses, sex ratio, or fetal weight measured on Gd 20 (Kawashima et al. 1983a). In addition, treatment with TCEP had no significant effect on the incidence of skeletal malformations or on postnatal viability monitored up to postnatal week 10. Behavioral and motor tests conducted on the offspring, including open field activity, performance in a water maze, balance, pain reflexes, and hearing reflexes, did not reveal

significant differences between treated and control rats. Hardin et al. (1987) conducted a preliminary assay of developmental toxicity of TCEP in mice dosed by gavage with 940 mg TCEP/kg/day (only dose level tested) on Gd 6–13. At delivery, the number of live pups was recorded and live pups were weighed as a litter. Neither live pups nor dead pups were systematically examined for malformations. Dosing with TCEP had no significant effects on the number of viable litters, number of live pups born per litter, percent survival of pups, birth weight, or pup weight gain. In the continuous breeding protocol study conducted by NTP (1991b), treatment of the F_0 generation with ≥350 mg TCEP/kg/day significantly reduced the number of live pups per litter. In addition, the number of F_2 male pups per litter born to the treated F_1 generation was significantly lower than in controls in the groups dosed with ≥175 mg TCEP/kg/day, the lowest dose level tested; a developmental NOAEL was not identified in the study.

Studies conducted by Noda et al. (1994) with TnBP showed lack of developmental toxicity for this chemical even in the presence of frank maternal toxicity. Treatment of pregnant female rats by gavage on Gd 7–17 with up to 500 mg/kg/day resulted in piloerection, wetting of abdominal hair with urine, and salivation during the treatment, but these effects disappeared after the last treatment. Adjusted body weight gain from Gd 0–20 was reduced 13% at 125 mg/kg/day, 39% at 250 mg/kg/day, and 63% at 500 mg/kg/day. Gravid uterus weight was not affected. All pregnant rats had living fetuses on Gd 20. There was no significant difference between groups in the number of corpora lutea, implants or living fetuses, incidence of dead or resorbed fetuses, sex ratio, or body weight of the living fetuses. There was only one malformation that occurred in the 125 mg/kg/day group in which there were conjoined twins. No increases in visceral anomalies were reported. In a 2-generation reproduction study, the only significant developmental effect attributed to treatment with TnBP was a reduction in F_1 and F_2 pup weight per litter measured 5 times from postnatal days 0–21 at maternal doses of approximately 217 mg/kg/day; the number of pups per litter was comparable among groups (Tyl et al. 1997). Significant reductions in maternal body weight also occurred at this level, which may have contributed to the decrease in pup weight.

Monsanto (1985b) conducted a gestational exposure study with TBEP. Pregnant rats were treated with up to 1,500 mg TBEP/kg/day by gavage on Gd 6–15 and were euthanized on Gd 20. Immediately after kill, the uterus and ovaries were exposed and the number and location of viable and nonviable fetuses, early and late resorptions, and number of total implantations and corpora lutea were recorded. Fetuses were weighed, sexed, and examined for external malformations and variations. Fetuses were then prepared for visceral and skeletal examinations. No significant alterations were reported in any of the developmental

parameters evaluated. Some dams in the 1,500 mg/kg/day group occasionally exhibited signs of toxicity after dosing such as ataxia and lethargy, and gained significantly less weight than control rats.

A study with TDCP evaluated litter data, and fetal development (visceral abnormalities and skeletal anomalies) following exposure of pregnant rats to up to 0, 25, 100, or 400 mg TDCP/kg/day on Gd 6–15 and euthanized on Gd 19 (Stauffer Chemical Co. 1978f). There was no effect on number of corpora lutea or implantations. A statistically higher incidence of resorptions was found in rats dosed with 400 mg/kg/day, but the number per litter was not statistically increased. Fetal viability was significantly decreased in high-dose rats (86.6 vs. 93.3% in controls). Mean fetal weight and length were lower in high-dose rats, but the difference with controls was <10%. Decreased skeletal development (incomplete ossification of various bones) was noted in high-dose fetuses. Maternal final body weight of the high-dose group was significantly lower (16%) than in controls. During Gd 6–11, body weight gain of the mid-dose group was significantly lower (30%) than controls, and high-dose rats lost weight. A developmental NOAEL of 100 mg/kg/day was defined in this study; the maternal NOAEL was 25 mg/kg/day.

Three studies were located that provide information regarding developmental effects of TCP in animals. Rat pups produced from the mating of males exposed daily to 100 mg TCP/kg/day by gavage for 56 days before mating and during mating, and females exposed similarly to 200 mg TCP/kg/day for 12 days before breeding and during gestation and lactation showed significantly decreased postnatal viability (Carlton et al. 1987). However, exposure to TCP did not affect pup body weight, or day of eye opening or of vaginal patency. In another study, exposure of male and female rats to 400 mg TCP/kg/day by daily gavage through a 63-day breeding period and females for a 28-day postbreeding period resulted in a significantly reduced number of live pups per litter, but there was no significant effect on proportion of pups born alive or total and mean weight of pups per litter within 18 hours of birth (Latendresse et al. 1994b). In a continuous breeding study in mice, exposure of the parental generation to approximately 250 mg TCP/kg/day in the diet for 7 days before mating followed by 98 days of breeding exposure resulted in a significantly increased number of dead pups per litter at the first, second, and third litters (Chapin et al. 1988). Exposure to 124 mg TCP/kg/day resulted in a significantly increased number of dead pups per litter at the fourth and fifth litters.

Information regarding developmental effects of TPP is available in a study by Welsh et al. (1987). Male and female rats were fed a diet containing TPP for 91 days before mating and the females continued in the experimental diets during gestation and lactation. Cesarean sections were performed on Gd 20. The

investigators estimated that during Gd 0–20, the females consumed up to 690 mg TPP/kg/day. Treatment with TPP had no significant effect on fetal parameters (viability, early or late deaths, fetal weight, length or distribution) or skeletal anomalies. Although the incidence of some specific soft-tissue variations seemed higher in treated rats than in controls, Welsh et al. (1987) stated that because the baseline incidence in controls was also high and there was no clear dose-response, the significance of the finding was unclear. Dietary administration of up to 893 mg TCPP/kg/day to rats on Gd 0–20 had no significant effects on fetal weight or incidences of external malformations (Kawasaki et al. 1982). Cervical ribs, missing ribs, and delayed ossification of sternebrae were more frequent in the treated groups but the difference with controls was not significant. Neonatal growth and viability during the 4 weeks after weaning was comparable among groups.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Tables 3-2, 3-3, 3-4, 3-5, 3-6, and 3-7 and plotted in Figures 3-2, 3-3, 3-4, 3-5, 3-6, and 3-7.

3.2.2.7 Cancer

Information regarding the carcinogenic potential of TCEP, TnBP, TDCP, and TCP was available in the literature reviewed.

NTP (1991a) conducted 2-year bioassays in Fischer-344/N rats and B6C3F$_1$ mice. Rats were dosed by gavage once per day, 5 days/week for 104 weeks with 0, 44, or 88 mg TCEP/kg/day. Survival was reduced in high-dose males and females. Females that died early frequently had brain lesions, while males did not. Interim kills (10/sex/group) on week 66 revealed an adenoma of the renal tubule in one high-dose male; no other neoplastic lesions were reported at this time point. Treatment with TCEP resulted in the following significant increased incidences of neoplastic lesions (overall rates): (1) renal tubule adenomas (1/50, 5/50, 24/50) renal tubule adenoma or carcinomas (2/50, 5/50, 25/50) in high-dose males; and renal tubule adenomas (0/50, 2/50, 5/50) in high-dose females (the adenomas occurred in the cortex and consisted of cells morphologically similar to those in foci of renal tubule epithelial hyperplasia); (2) benign granular cell tumors of the brain in high-dose males (0/50, 0/50, 3/50); and (3) follicular cell adenoma or carcinoma of the thyroid in high-dose females (0/50, 3/50, 4/50). Mononuclear cell leukemia was also elevated in treated rats, but the incidences were within the range of historical controls. NTP (1991a) concluded that there was clear evidence of carcinogenic activity for male and female rats based on the increased incidence of renal tubule adenomas.

Mice were treated in the same manner with doses of 0, 175, or 350 mg TCEP/kg/day (NTP 1991a). Survival rate in mice was not significantly affected by treatment with TCEP. An initial analysis of the kidneys showed adenomas of the renal tubule in one control male, one high-dose male, and one low-dose female, and a carcinoma in a second high-dose male. Because of the rare occurrence of renal tubule neoplasms in male $B6C3F_1$ mice, the remaining portions of the kidneys were processed to produce additional sections per mouse for light microscopy examination. The results of a combined initial and second analysis of incidences of renal neoplasms yielded the following results: male adenomas 1/50, 1/50, 3/50; male adenocarcinoma, 0/50, 0/50, 1/50; and female adenoma, 0/50, 1/49, 0/50. Based on these results, NTP (1991a) concluded that there was equivocal evidence of carcinogenic activity for male mice. Female mice showed an increased incidence of tumors of the Harderian gland (3/50, 8/50, 7/50, not significant) which became significant at the high-dose if data for the interim evaluation and termination were combined (3/59, 8/60, 10/60). Based on these results, NTP (1991a) concluded that there was equivocal carcinogenic activity for female mice.

Takada et al. (1989) also conducted a bioassay with TCEP in ddY mice. Mice were fed TCEP in the diet at 0, 0.012, 0.06, 0.3, and 1.5% for 18 months. Assuming a mean body weight of 0.045 kg and daily food consumption of 0.004 kg/day from graphs in the paper, the diet provided approximately 0, 11, 53, 267, and 1,333 mg TCEP/kg/day. Treatment with TCEP significantly increased the incidences of renal cell adenomas and carcinomas in high-dose males (2/50, 0/49, 2/49, 5/47, and 41/50), hepatocellular adenoma/carcinoma in the two highest male groups (4/50, 5/49, 7/49, 12/47, and 19/50), forestomach papillomas/squamous cell carcinomas in high-dose females (0/49, 0/49, 0/50, 1/49, and 7/50), and leukemia in the two highest female groups (1/49, 3/49, 6/50, 9/49, and 9/50).

Auletta et al. (1998a; 1998b) examined the carcinogenicity of TnBP in Sprague-Dawley rats and CD-1 mice. TnBP was administered in the diet to rats at levels that provided 0, 9, 33, or 143 mg TnBP/kg/day to males and 0, 12, 42, or 182 mg TnBP/kg/day to females. Treatment with TnBP did not affect survival. Neoplastic lesions were restricted to the urinary bladder. The incidence of urinary bladder papillomas was significantly increased in high-dose males and females; transitional cell carcinomas were also significantly increased in males. The incidences of combined papillomas, squamous cell carcinoma, and transitional cell carcinomas was 0/50, 0/50, 2/49, and 30/49 in males and 0/50, 0/50, 0/49, and 2/49 in females. Most of the hyperplastic and neoplastic lesions were not associated with calculi, but when calculi were present, they were usually associated with hyperplasia and/or neoplasia. Rats found to have papillomas (benign tumors) often had hyperplasia present. In contrast, rats

with malignant bladder tumors usually did not have any remaining uninvolved epithelium to evaluate for the presence or absence of hyperplasia.

In mice, the experimental diets provided doses of 0, 28.9, 169, or 585 mg TnBP/kg/day to males and 0, 24.1, 206, or 711 mg TnBP/kg/day to females. Survival was not affected by treatment with TnBP. Increased incidence of neoplasms was seen only in the liver of male mice. The incidences of hepatocellular adenomas in males were 3/50, 6/50, 7/50, and 10/50 with increasing doses; the highest dose level achieved statistical significance. The incidence of malignant liver tumors was comparable between controls and treated males. In females, there was no significant association between tumor incidences and treatment with TnBP.

TDCP was tested only in rats (Stauffer Chemical Co. 1981a). Male and female Sprague-Dawley rats were fed a diet that provided 0, 20, or 80 mg TDCP/kg/day for 2 years. Mortality was comparable among groups during the first year of the study, but it increased in high-dose males during the second year and was significantly higher than controls at termination. The incidence of neoplastic nodules in the liver of high-dose males and females was significantly increased (2/45, 7/48, 1/48, 13/46 in males and 1/49, 1/47, 4/46, 8/50 in females) and the incidence of hepatocellular carcinomas was also increased in high-dose males (1/45, 2/48, 3/48, 7/46). In the kidney, both mid- and high-dose males and females had significantly increased incidence of renal cortical tumors (1/45, 3/49, 9/48, 22/36 in males; 0/49, 1/48, 8/48, 25/50 in females). In the testes, interstitial cell tumors were significantly increased in mid- and high-dose males (7/43, 8/48, 23/47, 32/45), whereas adrenocortical adenomas were significantly increased in high-dose females (8/48, 5/27, 2/33, 19/49).

NTP (1994) conducted a 2-year oral bioassay with TCP in F344/N rats and B6C3F_1 mice. Groups of rats (95/sex/dose) were fed a diet that provided 0, 3, 6, or 13 mg TCP/kg/day to males and 0, 4, 7, or 15 mg TCP/kg/day to females. The mice (95/sex/dose) were fed a diet that provided 0, 7, 13, or 27 mg TCP/kg/day to males and 0, 8, 18, or 37 mg TCP/kg/day to females. Interim kills (up to 15 animals/sex/dose) were conducted at 3, 9, and 15 months. The results showed no chemical-related increased incidences of neoplasms in rats or mice.

3.2.3 Dermal Exposure

3.2.3.1 Death

No reports of deaths in humans following dermal exposure to the selected phosphate ester flame retardants were located in the reviewed literature.

No deaths occurred among an unspecified number of rabbits applied a dose of 5,000 mg TCEP/kg and observed for 14 days (Anonymous 1977). Application of 10–20 mL TnBP/kg to guinea pigs for 24 hours under occluded conditions resulted in an estimated dermal LD_{50} between 9,727 and 19,454 mg/kg (Eastman Kodak Co. 1968). Other studies reported dermal LD_{50} values >3,100, >10,000, and >4,640 mg/kg for TnBP in rabbits (Johannsen et al. 1977; MacKellar 1976; Stouffer Chemical Co. 1973).

No deaths were reported in rabbits applied a dose of 4,640 mg TDCP/kg to the skin for 24 hours and observed for 14 days (Stauffer Chemical Co. 1981b). Application of 23,700 mg TDCP/kg also did not cause lethality among rabbits, but induced signs of cholinergic stimulation (Stauffer Chemical Co. 1981b). Dermal LD_{50} values >5,000 and >10,000 mg/kg were estimated for TiBP in guinea pigs and rabbits, respectively (Eastman Kodak Co. 1990; Monsanto Co. 1989a, 1989b). Johannsen et al. (1977) reported that the dermal LD_{50} for TPP in rabbits was >7,900 mg/kg, whereas FMC (1982b) estimated a dermal LD_{50} >10,000 mg/kg for TPP in rabbits. No deaths were reported in rabbits applied a dose of 5,000 mg/kg TCP to the skin for 24 hours and observed for 14 days; however, some of the rabbits in this study had diarrhea and became emaciated (FMC 1979b). Application of 7,900 mg/kg TCP also did not cause lethality among rabbits and the LD_{50} was estimated to be >7,900 mg/kg (Johannsen et al. 1977). Application of 10,000 mg TCP/kg to the intact or abraded clipped back of rabbits resulted in no deaths during a 14-day observation period (FMC 1976b). However, FMC (1978) reported that the dermal LD_{50} for TCP was <20,000 mg/kg in rabbits, as all animals in the study were dead by day 6 following a single application of 20,000 mg TCP/kg. Most of the rabbits in this study were reported to have loose feces, although necropsy revealed no gross internal changes except in one rabbit that had a fluid-distended stomach. Additional information regarding acute lethal doses or LD_{50} values of dermally-applied phosphate ester flame retardants can be found in IPCS (1990, 1991a, 1991b, 1998, 2000b).

Dermal lethal doses and/or dermal LD_{50} values are presented in Table 3-8.

Table 3-8 Levels of Significant Exposure to Selected Phosphate Esters - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
ACUTE EXPOSURE								
Death								
Gn Pig (NS)	24 hr (NS)					9727 mg/kg (LD50 is 9727-19454 mg/kg)	Eastman Kodak Co. 1968 126-73-8	
Gn Pig (NS)	once (NS)					10000 mg/kg (the LD50 was greater than 10000 mg/kg)	Eastman Kodak Co. 1990 126-71-6	
Rabbit (New Zealand)	(NS)					5000 mg/kg/day (LD50 is greater than 5000 mg/kg)	Anonymous 1977 115-96-8	
Rabbit (albino)	once					10000 mg/kg (the LD50 was greater than 10000)	FMC 1976b 1330-78-5	
Rabbit (New Zealand)	24 hr					20000 B mg/kg (6/6 deaths in 6 days)	FMC 1978 1330-78-5	
Rabbit (NS)	once (NS)					10000 mg/kg (LD50 is greater than 10000 mg/kg)	FMC 1982 115-86-6	
Rabbit (New Zealand)	once (GO)					7900 B mg/kg (the LD50 was greater than 7900)	Johannsen et al. 1977 1330-78-5	
Rabbit (New Zealand)	24 hr					7900 B mg/kg (The LD50 was greater than 7900 mg/kg)	Johannsen et al. 1977 115-86-6	

Table 3-8 Levels of Significant Exposure to Selected Phosphate Esters - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Rabbit (New Zealand)	24 hr				3100 B mg/day	(the LD50 was greater than 3100 mg/kg)	Johannsen et al. 1977 126-73-8	
Rabbit (NS)	(NS)				10000 mg/kg	(LD50 is greater than 10000 mg/kg)	MacKeller 1976 126-73-8	
Rabbit (New Zealand)	once				5000 B mg/kg	(the LD50 was greater than 5000)	Mobil Oil Corporation 1978 1330-78-5	
Rabbit (NS)	NS (NS)				5000 mg/kg	(the LD50 was greater than 5000 mg/kg)	Monsanto Co. 1989a, 1989b 126-71-6	
Rabbit (New Zealand)	24 h (NS)				4640 mg/kg	(LD50 is greater than 4640 mg/kg)	Stauffer Chemical Co. 1973 126-73-8	
Rabbit (New Zealand)	24 h (NS)				4640 mg/kg	(LD50 is greater than 4640 mg/kg)	Stauffer Chemical Co. 1981b 13674-87-8	
Rabbit (NS)	once (NS)				23700 mg/kg/day	(LD50 is greater than 23700 mg/kg)	Stauffer Chemical Co. 1981b 13674-87-8	
Systemic								
Rat (NS)	(NS)	Dermal	750 mg/kg				Akzo Chemical Inc 1991 126-73-8	

Table 3-8 Levels of Significant Exposure to Selected Phosphate Esters - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Gn Pig (NS)	24 hr (NS)	Dermal		20 g/kg	(severe skin irritation)		Eastman Kodak Co. 1968 126-73-8	
Gn Pig (NS)	once (NS)	Dermal		5000 mg/kg	(moderate edema)		Eastman Kodak Co. 1990 126-71-6	
Gn Pig (Hartley)	(NS)	Dermal	0.3 B mg				Socma 1990 126-73-8	
Rabbit (New Zealand)	once (NS)	Ocular	10 mg				Anonymous 1977 115-96-8	
Rabbit (NS)	(NS)	Ocular		100 Percent (%)	(moderate immediate pain with slight conjunctival irritation)		Dow Chemical Co. 1956 126-73-8	
Rabbit (NS)	(NS)	Dermal		10 Percent (%)	(slight hyperemia and moderate necrosis)		Dow Chemical Co. 1956 126-73-8	
Rabbit (albino)	once	Dermal	0.5 ml				FMC 1976b 1330-78-5	NOAEL is for skin irritation.

Table 3-8 Levels of Significant Exposure to Selected Phosphate Esters - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Rabbit (albino)	once	Ocular	0.1 ml				FMC 1976b 1330-78-5	NOAEL is for eye irritation.
Rabbit (New Zealand)	24 hr	Dermal	0.5 B ml				FMC 1978 1330-78-5	NOAEL is for skin irritation.
Rabbit (New Zealand)	4 hr	Dermal	0.5 B ml				FMC 1978 1330-78-5	NOAEL is for skin corrosion.
Rabbit (New Zealand)	24 hr	Ocular	0.1 B ml				FMC 1978 1330-78-5	NOAEL is for eye irritation.
Rabbit (New Zealand)	24 hr (NS)	Dermal		0.5 B ml	(mild skin irritation)		FMC 1979, 1981 126-73-8	
Rabbit (NS)	once (NS)	Dermal	0.5 ml				FMC 1982 115-86-6	
Rabbit (NS)	once (NS)	Ocular		0.1 ml	(mild eye irritation)		FMC 1982 115-86-6	
Rabbit (New Zealand)	once	Ocular	0.1 B ml				Mobil Oil Corporation 1978 1330-78-5	NOAEL is for eye irritation.

Table 3-8 Levels of Significant Exposure to Selected Phosphate Esters - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Rabbit (New Zealand)	once	Dermal	0.3 B ml				Mobil Oil Corporation 1978 1330-78-5	NOAEL is for primary dermal irritation.
Rabbit (New Zealand)	4 hr (NS)	Dermal		0.5 ml	(mild skin irritation)		Mobil Oil Corporation 1979b 126-73-8	
Rabbit (New Zealand)	4 hr (NS)	Dermal		0.5 B ml	(slight erythema)		Monsanto Co. 1989a, 1989b 126-71-6	
Rabbit (New Zealand)	once (NS)	Ocular	0.1 ml				Stauffer Chemical Co. 1973 126-73-8	
Rabbit (NS)	once (NS)	Ocular		0.02 ml	(necrosis)		Union Carbide Corp 1943 126-73-8	
Immuno/ Lymphoret								
Gn Pig (Hartley)	(NS)	Dermal	0.3 B mg				Socma 1990 126-73-8	
Neurological								
Rabbit (NS)	once (NS)			23700 mg/kg	(diarrhea, pupillary constriction, depressed RBC cholinesterase)		Stauffer Chemical Co. 1981b 13674-87-8	

Table 3-8 Levels of Significant Exposure to Selected Phosphate Esters - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
INTERMEDIATE EXPOSURE							
Systemic							
Rabbit (New Zealand)	3 wk 5 d/wk 1 x/d	Resp	1000 B mg/kg/day			Monsanto Co. 1979 115-86-6	NOAELs are for organ or tissue histopathology.
		Cardio	1000 B mg/kg/day				
		Gastro	1000 B mg/kg/day				
		Hemato	1000 B mg/kg/day				
		Musc/skel	1000 B mg/kg/day				
		Hepatic	1000 B mg/kg/day				
		Renal	1000 B mg/kg/day				
		Endocr	1000 B mg/kg/day				
		Dermal	1000 B mg/kg/day				
		Ocular	1000 B mg/kg/day				
		Bd Wt	1000 B mg/kg/day				

Table 3-8 Levels of Significant Exposure to Selected Phosphate Esters - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
		Metab	1000 B mg/kg/day				
Rabbit (New Zealand)	3 wk 5 d/wk 1 x/d	Hemato	1000 B mg/kg/day			Monsanto Co. 1985d 78-51-3	
		Hepatic	1000 B mg/kg/day				
		Renal	1000 B mg/kg/day				
		Dermal		10 B mg/kg/day (slight edema, atonia, desquamation)			
		Bd Wt	1000 B mg/kg/day				
Immuno/ Lymphoret							
Rabbit (New Zealand)	3 wk 5 d/wk 1 x/d		1000 B mg/kg/day			Monsanto Co. 1979 115-86-6	NOAEL is lymphoid tissues histopathology.
Neurological							
Rabbit (New Zealand)	3 wk 5 d/wk 1 x/d		1000 B mg/kg/day			Monsanto Co. 1979 115-86-6	NOAEL is for histopathology of central and peripheral nervous tissues.
Rabbit (New Zealand)	3 wk 5 d/wk 1 x/d		1000 B mg/kg/day			Monsanto Co. 1985d 78-51-3	NOAEL is for brain weight and RBC and brain cholinesterase.

Table 3-8 Levels of Significant Exposure to Selected Phosphate Esters - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
Reproductive							
Rabbit (New Zealand)	3 wk 5 d/wk 1 x/d		1000 B mg/kg/day			Monsanto Co. 1979 115-86-6	NOAEL is for histopathology of the reproductive organs.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; ; F = Female; Gastro = gastrointestinal; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

3.2.3.2 Systemic Effects

With the exception of dermal and ocular effects, most of the information summarized below is derived from two 3-week studies of TBEP and TPP in rabbits (Monsanto Co. 1979, 1985d).

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 3-8.

Respiratory Effects. The only relevant information is that application of up to 1,000 mg TPP/kg/day onto a clipped intact or abraded area of the back of rabbits 5 days/week for 3 weeks did not result in gross or microscopic alterations in the lungs (Monsanto Co. 1979).

Cardiovascular Effects. A 3-week study reported that daily applications of up to 1,000 mg TPP/kg/day onto the clipped intact or abraded area of the back of rabbits had no effect on the gross or microscopic morphology of the heart (Monsanto Co. 1979).

Gastrointestinal Effects. No gross or microscopic alterations were reported in the gastrointestinal tract of rabbits that received daily applications of up to 1,000 mg TPP/kg/day on a clipped intact or abraded area on the back 5 days/week for 3 weeks (Monsanto Co. 1979).

Hematological Effects. Hematology tests done on blood collected at termination from rabbits treated dermally with up to 1,000 mg TBEP/kg/day 5 days/week for 3 weeks did not reveal any significant deviation from normal limits (Monsanto Co. 1985d). Similar results were reported in rabbits exposed to TPP (Monsanto Co. 1979).

Musculoskeletal Effects. There were no gross or microscopic alterations in skeletal muscle from rabbits that received daily application of up to 1,000 mg TPP/kg/day 5 days/week for 3 weeks onto the clipped intact and abraded area of the back (Monsanto Co. 1979).

Hepatic Effects. Application of up to 1,000 mg TBEP/kg/day to the unabraded clipped skin of rabbits 5 days/week for 3 weeks did not result in alterations in liver weight, liver function tests, or the gross or microscopic appearance of the liver (Monsanto Co. 1985d). The same results were obtained in rabbits exposed to up to 1,000 mg TPP/kg/day (Monsanto Co. 1979).

Renal Effects. Application of up to 1,000 mg/kg/day of TBEP or TPP to the clipped skin on the back of rabbits 5 days/week for 3 weeks did not result in alterations in kidney weight or the gross or microscopic appearance of the kidney (Monsanto Co. 1985d).

Endocrine Effects. Application of up to 1,000 mg TPP/kg/day to a clipped intact or abraded area of the skin of rabbits 5 days/week for 3 weeks had no significant effect on the gross or morphological appearance of the adrenal, thyroid, and pituitary (Monsanto Co. 1979).

Dermal Effects. Without providing any further details, IPCS (1991a, 1991b) stated that there have been reports of skin irritation among subjects occupationally exposed to TnBP. Several studies provide information regarding dermal effects of TnBP in animals. Application of 750 mg TnBP/kg to the skin of rats did not produce irritation (Akzo Chemical Inc 1991). In guinea pigs, application of a dose of 20,000 mg TnBP/kg for 24 hours produced severe skin irritation (Eastman Kodak Co. 1968), but application of 0.3 mg once per week for 3 weeks did not produce skin irritation (SOCMA 1990). Application of TnBP as a 10% emulsion for 20 times on the ear and 6 times on the abdomen produced moderate exfoliation on the ear and slight hyperemia and slight exfoliation on the abdomen (Dow Chemical Co. 1956). Similar application of TnBP neat produced slight hyperemia and moderate necrosis on the ear after the 5th application. All signs of toxicity were reversed within 2–3 weeks after treatment (Dow Chemical Co. 1956). Both FMC (1979a, 1981b) and Mobil Oil Corporation (1979b) reported that application of 0.5 mL TnBP for 4–24 hours produced mild skin irritation in rabbits. Moderate edema was reported in guinea pigs that received an application of 5,000 mg TiBP/kg to the skin (Eastman Kodak Co. 1990) and mild, reversible skin irritation was reported in rabbits applied 0.5 mL TiBP and observed for 7–14 days (Monsanto Co. 1989a, 1989b). Application of 0.5 mL TPP to the clipped, intact, or abraded skin of rabbits did not result in the formation of erythema or edema (FMC 1982b).

TCP did not cause dermatitis when applied as a 10% solution in olive oil to the skin of workers (Alomar et al. 1985). Application of 0.3–0.5 mL TCP to the intact or abraded skin of rabbits for up to 24 hours did not cause corrosion or skin irritation (FMC 1976b, 1978; FMC 1979b).

In the 3-week study with TBEP in rabbits (Monsanto Co. 1985d), the undiluted test material was applied to the unabraded dorsal skin clipped of hair in doses of 0, 10, 100, or 1,000 mg/kg/day; the area was covered for 6 hours after each application. Gross necropsy showed slight to moderate erythema in the treated rabbits during the study; the incidence and severity was dose-related during the second and third week of the study. Atonia and desquamation were also more pronounced in treated rabbits (incidence and

severity were dose-related). Slight fissuring became evident over time in some mid-dose and most high-dose rabbits. Eschar formation was also seen in treated rabbits. Exfoliation also occurred in mid- and high-dose animals. Microscopic evaluation of sites from high-dose rabbits showed squamous cell hyperplasia, hyperkeratosis, erosions-ulcers, acute-subacute inflammation, and congestion and hemorrhage, in various combinations.

In the 3-week study with TPP, there were no treatment-related alterations in the intact or abraded skin of rabbits applied up to 1,000 mg TPP/kg/day for 3 weeks (Monsanto Co. 1979).

Ocular Effects. Application of 10 mg or 0.1 mL of TCEP into the lower eyelid of rabbits did not produce significant eye irritation (Anonymous 1977). Application of neat TnBP to the eye of rabbits induced slight conjunctival irritation which subsided within 24 hours (Dow Chemical Co. 1956). Union Carbide (1943) reported that application of 0.02 mL TnBP to the eye of rabbits induced necrosis, but a report by Stauffer Chemical Co. (1973) indicates that application of 10 mg or 0.1 mL TnBP to the eye of rabbits did not induce signs of eye irritation. There is not enough information in either report to explain this apparent discrepancy. Instillation of 0.1 mL TPP into the eye of rabbits produced mild irritation only when the eye remained unwashed after application (FMC 1982b). No ocular effects were reported in rabbits that received daily skin applications of up to 1,000 mg TPP/kg/day 5 days/week for 3 weeks (Monsanto Co. 1979). Instillation of 0.1 mL of TCP (unspecified concentration) into the eyes of rabbit for up to 24 hours did not cause eye irritation (FMC 1978; FMC 1979b).

Body Weight Effects. Application of up to 1,000 mg/kg/day of TBEP or TPP to a clipped area of intact or abraded the dorsal skin of rabbits 5 days/week for 3 weeks did not affect food consumption, body weight, or body weight gain (Monsanto Co. 1979, 1985d).

Metabolic Effects. Application of up to 1,000 mg TPP/kg/day to a clipped area of intact or abraded dorsal skin of rabbits 5 days/week for 3 weeks had no significant effect on serum levels of glucose, calcium, or inorganic phosphorus (Monsanto Co. 1979).

3.2.3.3 Immunological and Lymphoreticular Effects

Limited data were located regarding immunological and lymphoreticular effects in humans following dermal exposure to the selected phosphate ester flame retardants. Tarvainen (1995) reported that neither TPP nor TCP were allergens when patch-tested among 839 patients in a dermatologic clinic in Finland.

Schlede et al. (2003) collected and evaluated data on humans and animals from the literature regarding the allergenic potency of TCP and concluded that TCP is an insignificant contact allergen or has questionable contact allergenic effects.

A study in which 0.3 mg TnBP was applied to the skin of guinea pigs once per week for 3 weeks showed that under the conditions of the study, TnBP was nonsensitizing (SOCMA 1990). A 3-week study in which rabbits were applied up to 1,000 mg TPP/kg/day 5 days/week to an area of intact or abraded dorsal skin did not report gross or microscopic changes in the spleen, thymus, or lymph nodes (Monsanto Co. 1979).

These two values are presented in Table 3-8.

3.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans following dermal exposure to the subject phosphate ester flame retardants of this profile.

Application of up to 1,000 mg TEBP/kg/day to the clipped unabraded dorsal skin of rabbits 5 days/week for 3 weeks did not induce clinical signs nor did it alter the activities of red blood cell (RBC) or brain cholinesterase or affect brain weight (Monsanto Co. 1985d). In the study with TPP, there were no alterations in brain weight or in gross and microscopic morphology of the brain, spinal cord, or sciatic nerve (Monsanto Co. 1979). However, at termination, there was a dose-related decrease in RBC and brain cholinesterase activities, which achieved statistical significance in the high-dose group (1,000 mg/kg/day, other groups were 10 and 100 mg/kg/day), but there were no clinical signs of increased cholinergic activity.

The doses of 1,000 mg/kg/day of TBEP and TPP are presented as NOAELs for neurological effects in Table 3-8.

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans exposed to the selected phosphate ester flame retardants by any route of exposure.

The only relevant information regarding reproductive effects in animals is that in a 3-week study in rabbits applied up to 1,000 mg TPP/kg/day to the dorsal skin 5 days/week, there were no morphological alterations in the ovaries, uterus, prostate, or testes (Monsanto Co. 1979). This value is presented as a NOAEL in Table 3-8.

3.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following dermal exposure to the subject phosphate ester flame retardants of this profile.

3.2.3.7 Cancer

Only information regarding TCEP was located in the literature. Sala et al. (1982) studied the initiation/promotion properties of TCEP in female Swiss mice. In the initiation study, mice received a single application of 71 mg of TCEP to the dorsal clipped skin and then repeated applications of 12-O-tetra-decanoyl-phorbol-13-acetate (TPA). In the promotion studies, mice received, for 78 weeks, twice weekly applications of TCEP (21 mg) in acetone onto the area of dorsal skin after initiation with 7,12-dimethyl-benz(a)anthracene (DMBA). TCEP was also tested for complete carcinogenicity by treating the mice twice weekly without any initiation treatment. TCEP was negative as an initiator, promoter, and complete skin carcinogen. However, TCEP by itself increased the incidence (not significantly) of lung adenomas in mice relative to a group initiated with DMBA and promoted with TCEP. The investigators had no explanation for the role of DMBA in decreasing the incidence of lung tumors.

3.3 GENOTOXICITY

For the most part, the phosphate ester flame retardants subject of this profile have provided negative evidence of mutagenicity in *in vitro* tests with prokaryotic organisms (i.e., *Salmonella typhimurium*) and mammalian cell systems. *In vivo* studies have, for the most part, also provided negative results. Tables 3-9 and 3-10 provide a summary of genotoxicity data for these test systems.

In vitro Exposure Studies. *In vitro* studies with phosphate ester flame retardants have provided mixed results. In general, TBEP, TCEP, TCP, TCPP, TiBP, TnBP, and TPP have been found to be nonmutagenic in *S. typhimurium* with and without metabolic activation (Abe and Urano 1994; Brusick et al. 1979; FMC 1978, 1979b; Föllmann and Wober 2006; Gee et al. 1998; Monsanto Co. 1985e; NTP 1994; Segeman et al. 1992; Søderlund et al. 1985; Stauffer Chemical Co. 1981b; Tennant and Ashby

Table 3-9. Genotoxicity of Phosphate Ester Flame Retardants *In Vitro*

Species (test system)	Compound	End point	Results		Reference
			With activation	Without activation	
Prokaryotic organisms:					
Salmonella typhimurium, TA98	TBEP	Gene mutation	–	–	Abe and Urano 1994
S. typhimurium, TA09, TA100, TA1535, and TA1537	TBEP	Gene mutation	–	–	Monsanto Co. 1985e
S. typhimurium, TA97a, TA98, TA100, TA104, TA1535, TA1537, and TA1538	TCEP	Gene mutation	–	–	Föllmann and Wober 2006
S. typhimurium, TA1535, TA1537, TA98, and TA100	TCEP	Gene mutation	–	No data	Haworth et al. 1983
S. typhimurium, TA98	TCEP	Gene mutation	–	–	Abe and Urano 1994
S. typhimurium, TA100, TA1535, TA1537, and TA98	TCEP	Gene mutation	±	±	Nakamura et al. 1979; NTP 1991a
S. typhimurium, TA98, TA100, TA1535, TA1537, and/or TA97	TCEP	Gene mutation	–	–	Tennant and Ashby 1991
S. typhimurium, TA1535, TA1537, TA1538,TA98, and TA100/*Saccharomyces cerevisiae* strain D4	TCP	Gene mutation	–	–	FMC 1979b
S. typhimurium, TA98, TA100, TA1535, TA1537, TA1538	TCP	Gene mutation	–	–	FMC 1978
S. typhimurium, TA98, TA100, TA1535, TA1537, TA1538	TCP	Gene mutation	–	–	FMC 1979b
S. typhimurium, TA98, TA100, TA1535, TA1537	TCP	Gene mutation	–	–	NTP 1994
S. typhimurium, TA100, TA98, TA1535, TA1537, TA97, TA102, TA104	TCP	Gene mutation	–	–	Gee et al. 1998
S. typhimurium, TA97a, TA98, TA100, TA104, TA1535, TA1537, TA1538	TCPP	Gene mutation	–	–	Föllmann and Wober 2006

Table 3-9. Genotoxicity of Phosphate Ester Flame Retardants *In Vitro*

Species (test system)	Compound	End point	Results		Reference
			With activation	Without activation	
S. typhimurium, TA98	TCPP	Gene mutation	–	–	Abe and Urano 1994
S. typhimurium, TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, and TA1538	TCPP	Gene mutation	–	–	Zeiger et al. 1992
S. typhimurium, strain n/a	TDCP	Gene mutation	+	No data	NTP 1983
S. typhimurium, TA100	TDCP	Gene mutation	+	No data	Gold et al. 1978
S. typhimurium, TA100	TDCP	Gene mutation	–	–	Søderlund et al. 1985
S. typhimurium TA1535, TA1537, TA97, TA98, and TA100	TDCP	Gene mutation	+	+	Mortelmans et al. 1986
S. typhimurium, TA100	TDCP	Gene mutation	±	–	Lynn et al. 1981
S. typhimurium, TA100	TDCP	Gene mutation	±	±	Brusick et al. 1979
S. typhimurium, TA11535	TDC	Gene mutation	–	–	Brusick et al. 1979
S. typhimurium, TA100	TDCP	Gene mutation	–	No data	Dybing et al. 1983
S. typhimurium, TA98, TA100, TA1535, TA1537, and TA1538/ *Saccharomyces cerevisiae* strain D4	TDCP	Gene mutation	–	–	Stauffer Chemical Co. 1981b
S. typhimurium, TA98, TA100, TA1535, TA1537	TiBP	Gene mutation	–	–	Stegeman et al. 1992
S. typhimurium, TA98	TnBP	Gene mutation	–	No data	Abe and Urano 1994
S. typhimurium, TA102 and TA2638	TnBP	Gene mutation	–	–	Watanabe et al. 1996
Escherichia coli, Wp2/pKM1010 and WP2 *uvr*A/pKM101	TnBP	Gene mutation	–	–	Watanabe et al. 1996
S. typhimurium, strain n/a	TPP	Gene mutation	–	No data	NTP 1982
S. typhimurium, TA98, TA100, TA1535, TA1537, and/or TA97	TPP	Gene mutation	–	–	Zeiger et al. 1987
Mammalian cells:					
CHO cells (HGPRT)	TBEP	Forward gene mutation	–	–	Monsanto Co. 1985c
Mouse L5178Y Lymphoma cells	TBEP	Gene mutation	–	–	Mobil Oil Corporation 1991

Table 3-9. Genotoxicity of Phosphate Ester Flame Retardants *In Vitro*

Species (test system)	Compound	End point	Results		Reference
			With activation	Without activation	
Chinese hamster V79 cells	TCEP	Cytotoxicity, neutral red uptake assay	+	–	Föllmann and Wober 2006
Chinese hamster V79 cells	TCEP	DNA damage, Comet analysis,	–	–	Föllmann and Wober 2006
CHO cells	TCEP	Chromosomal aberrations	–	–	Galloway et al. 1987; NTP 1991a
CHO cells	TCEP	Chromosomal aberrations, sister chromatid exchange	±	–	Galloway et al. 1987; NTP 1991a
Chinese hamster V79 cells	TCEP	Forward gene mutation	–	–	Sala et al. 1982
Chinese hamster V79 cells	TCEP	Sister chromatid exchange	+	+	Sala et al. 1982
Mouse C3H10T1/2 cells	TCEP	Transformation assay	–	–	Sala et al. 1982
Syrian hamster embryo cells	TCEP	Transformation assay	+	+	Sala et al. 1982
CHO cells	TCP	Sister chromatid exchange	–	–	NTP 1994
CHO cells	TCP	Chromosomal aberrations	–	–	NTP 1994
Chinese hamster V79 cells	TCPP	Cytotoxicity, neutral red uptake assay	+	–	Föllmann and Wober 2006
Chinese hamster V79 cells	TCPP	DNA damage, Comet analysis,	–	–	Föllmann and Wober 2006
Chinese hamster V79 cells	TDCP	Gene mutation	–	No data	Søderlund et al. 1985
Syrian hamster cells	TDCP	Transformation assay	No data	+	Søderlund et al. 1985
Mouse L5178Y Lymphoma cells	TDCP	Gene mutation	–	–	Brusick et al. 1979
Mouse L5178Y lymphoma cells	TDCP	Sister chromatid exchange	±	±	Brusick et al. 1979
Mouse L5178Y lymphoma cells	TDCP	Chromosomal aberrations	+	+	Brusick et al. 1979

Table 3-9. Genotoxicity of Phosphate Ester Flame Retardants *In Vitro*

Species (test system)	Compound	End point	Results		Reference
			With activation	Without activation	
Mouse BALB/3T3 cells	TDCP	Transformation assay	–	–	Brusick et al. 1979
Chinese hamster V79 cells	TDCP	Gene mutation	–	No data	Dybing et al. 1983
Mouse L5178Y lymphoma cells	TDCP	Gene mutation	±	–	Stauffer Chemical Co. 1981b
CHO cells	TnBP	Gene mutation	–	–	Batt et al. 1992
CHO cells	TnBP	Chromosomal aberrations	–	–	Batt et al. 1992

+ = positive result; — = negative result; ± = weak or equivocal result; CHO = Chinese hamster ovary; TBEP = tributoxyethyl phosphate; TCEP = tris-(2-chloroethyl)-phosphate; TCP = tricresyl phosphate; TCPP = tri-(2-chloroisopropyl) phosphate; TDCP = tris(1,3 dichloro-2-propyl) phosphate; TiBP = triisobutyl phosphate; TnBP = tributyl phosphate; TPP = triphenyl phosphate

Table 3-10. Genotoxicity of Phosphate Ester Flame Retardants *In Vivo*

Species (test system)	Compound	End point	Results	Reference
Chinese hamster (male/female, 2/sex/dose)	TCEP	Chromosomal aberrations, micronucleus assay	±	Sala et al. 1982
Drosophila melanogaster	TCEP	Gene mutation, spot test	–	Vogel and Nivard 1993
Mouse (male, Charles River CD; eight per treatment)	TDCP	Chromosomal aberrations, bone marrow cytogenic assay	–	Brusick et al. 1979
D. melanogaster (modifed Muller five stock)	TDCP	Gene mutation, sex-linked recessive lethal assay	–	Brusick et al. 1979
D. melanogaster (males, 25/dose)	TDCP	Gene mutation, sex-linked recessive lethal assay	–	Stauffer Chemical Co. 1981b
Mouse (Male CD-1; 6/dose)	TDCP	Chromosomal aberrations, bone marrow cytogenic assay	–	Stauffer Chemical Co. 1981b
Mouse (male/female CD1; 15/sex/dose)	TiBP	Chromosomal aberrations, micronucleus assay	–	Flowers and Garrett 1992
Rat (male/female, strain and number not reported)	TnBP	Chromosomal aberrations	–	Batt et al. 1992

+ = positive result; — = negative result; ± = equivocal result; TCEP = tris-(2-chloroethyl)-phosphate; TDCP = tris(1,3-dichloro-2-propyl) phosphate; TiBP = triisobutyl phosphate; TnBP = tributyl phosphate

1991; Watanabe et al. 1996; Zeiger et al. 1987, 1992). Additionally, in a study conducted by Watanabe et al. (1996), TnBP was found to be nonmutagenic in *Escherichia coli*. Studies of TCEP conducted by Nakamura et al. (1979) provided weak evidence of mutagenicity for this compound. Studies with TDCP have demonstrated mixed results in *S. typhimurium,* probably reflecting differences in methodology. Positive results were determined for an unreported strain with metabolic activation (NTP 1983), for strain TA100 with metabolic activation (Gold et al. 1978; Lynn et al. 1981), and for strains TA1535, TA1537, TA97, TA98, and TA100 with and without metabolic activation (Mortelmans et al. 1986). Conversely, negative results were determined for strain TA100 with and without metabolic activation in a study conducted by Søderlund et al. (1985), and equivocal results were noted in studies conducted with and without metabolic activation by Brusick et al. (1979).

Studies with mammalian cells *in vitro* have also provided mixed results. TBEP and TnBP were not genotoxic in Chinese hamster ovary cells and TBEP produced negative results for genotoxicity in mouse L5178Y lymphoma cells in assays conducted with and without metabolic activation (Batt et al. 1992; Mobil Oil Corporation 1991; Monsanto Co. 1985c). In addition, TnBP and TCP produced negative results in tests for chromosomal aberrations and/or sister chromatid exchanges in Chinese hamster ovary cells with and without metabolic activation (Batt et al. 1992; NTP 1994). Results for TCEP, TCPP, and TCDP were mixed.

In a neutral red uptake assay in Chinese hamster V79 cells, Föllmann and Wober (2006) reported positive results for TCEP and TCPP in the presence of metabolic activation only. Negative results were also reported in this study for TCEP and TCPP in a comet analysis of V79 cells both in the presence and absence of metabolic activation. TCEP did not induce chromosomal aberrations in Chinese hamster ovary cells in tests with and without metabolic activation (Galloway et al. 1987; NTP 1991a). However, in studies conducted by Sala et al. (1982), TCEP was found to be positive for sister chromatid exchange in Chinese hamster V79 cells as well as in a transformation assay in Syrian hamster embryo cells. Although a positive result was obtained in the sister chromatid exchange assay, no clear concentration-response was evident. Results from studies conducted by Sala et al. (1982) also showed TCEP to be negative in a test for forward gene mutation in Chinese hamster V79 cells, and negative in a transformation assay in mouse C3H10T1/2 cells. Sala et al. (1982) speculated that the negative result seen in mouse C3H10T1/2 cells in comparison with the positive result in Syrian hamster cells could have been due to the high metabolic activity known to occur naturally in hamster cells.

In vitro studies with TDCP in mammalian cells provided negative results for gene mutation in Chinese hamster V79 cells, mouse L5178Y lymphoma cells, and mouse BALB/3T3 cells (Brusick et al. 1979; Dybing et al. 1983; Søderlund et al. 1985). In a chromosomal aberration study conducted on mouse L5178Y lymphoma cells, positive results were demonstrated with and without metabolic activation (Brusick et al. 1979). Søderlund et al. (1985) also provided positive results in a gene mutation study in Syrian hamster cells in the absence of metabolic activation only. Equivocal results were obtained in a gene mutation assay (Stauffer Chemical Co. 1981b) and in a chromosomal aberration study (Brusick et al. 1979) in mouse L5178Y lymphoma cells. The classification of equivocal was based on the variability of the results and on weak positive results.

In vivo Exposure Studies. The relatively few studies available for review that examined the potential *in vivo* genotoxicity of the phosphate ester flame retardants discussed in this profile were negative (Table 3-10). In a micronucleus assay conducted on Chinese hamsters with TCEP, study results were equivocal (Sala et al. 1982). This result was due to a difference in response between sexes and dose variations which made analysis difficult. TDCP was negative for gene mutations in sex-linked recessive studies conducted on *Drosophila melanogaster* (Brusick et al. 1979; Stauffer Chemical Co. 1981b), as well as in a gene mutation spot test (Bruisck et al. 1979). Results for chromosomal aberrations in rats were negative in a study conducted with TnBP (Batt et al. 1992). Chromosomal aberration studies were also negative in CD-1 mice for TDCP (Brusick et al. 1979; Stauffer Chemical Co. 1981b) and TiBP (Flowers and Garrett 1992).

3.4 TOXICOKINETICS

Almost all of the information regarding toxicokinetics of the subject phosphate ester flame retardants is derived from studies with TDCP, TCEP, TCP, and TnBP in animals. TDCP, TCEP, TnBP, and TCP isomers were well absorbed in rats following oral dosing. Significant amounts of TDCP and TnBP were also absorbed through rat skin; however, TnBP was poorly absorbed through pig skin. Oral and dermal absorption of the remaining phosphate ester flame retardants covered in this profile can be inferred from toxicity studies, but rates are not available. None of these substances showed preferential accumulation in specific tissues or organs. Analyses of excreta, mostly from rats, indicated that TDCP, TCEP, and TnBP undergo extensive metabolism by Phase I and Phase II enzymatic systems and the metabolic products are rapidly excreted, principally in the urine. Tri-*p*-cresyl phosphate was extensively metabolized in the rat. The route of excretion of TCP isomers appeared to be dose-dependent and isomer-specific. Species and gender differences in metabolism and excretion were reported for TCEP. Female rats excreted less of a

high-dose of TCEP than did males, and mice eliminated TCEP faster than did male or female rats. An *in vitro* study showed that both liver slices and microsomes from humans and male rats metabolized TCEP to the same main metabolites; female liver microsomes did not appear to metabolize TCEP. No physiologically based pharmacokinetic (PBPK) models have been developed for any of the phosphate ester flame retardants covered in this profile.

As indicated previously, TOCP is not a subject of this profile as an individual isomer since it is present only in very small amounts in commercial TCP mixtures currently being used. However, there is a considerable number of studies dealing with the toxicokinetics of this isomer, likely triggered by the numerous reports of neurotoxic effects in humans who used products or consumed food items contaminated with this substance. Original references regarding the toxicokinetics of TOCP can be found in IPCS (1990).

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

The only relevant information available in humans regarding the phosphate ester flame retardants discussed in this profile is that male volunteers who inhaled small particles of TPP at a flow rate of 18 L/second retained a mean of 41% of the inhaled TPP in the lungs (Landhal et al. 1951, 1952). Retention increased as particle size and flow rate increased. No pertinent information was found from studies in animals.

3.4.1.2 Oral Exposure

No information was located regarding absorption of phosphate ester flame retardants in humans following oral exposure. The fact that TDCP was detected in adipose tissue and seminal fluid from members of the general population (Hudec et al. 1981; LeBel and Williams 1986) suggests that this substance was absorbed, most likely through consumption of contaminated food or water, the main sources of exposure for the general population.

TDCP. A study in which male Sprague-Dawley rats were administered 0.2, 2, or 20 µmol TDCP/kg (0.086, 0.86, or 8.6 mg/kg) showed that better than 90% of the administered dose was absorbed from the gastrointestinal tract within 24 hours after dosing, regardless of the dose (Nomeir et al. 1981).

TCEP. Administration of a single gavage dose of 175 mg ^{14}C-TCEP/kg to male and female Fischer-344 rats resulted in rapid absorption from the stomach (Herr et al. 1991). Analysis of radioactivity in plasma over a 4-hour period showed that unmetabolized TCEP accounted for an average of 43.6% of the total radioactivity across time points and sexes. The concentration of TCEP in plasma reached a maximum early and did not vary significantly from 5 minutes to 4 hours after dosing. It appeared that at early time points plasma from female rats had twice as much TCEP than that from males, but because only three rats per sex were used, it was not possible to determine whether the difference was statistically significant.

TnBP. Analysis of the urine, expired air, and tissues of male and female Sprague-Dawley rats following gavage administration of single or repeated doses of 10 or 350 mg ^{14}C-TnBP/kg yielded a maximum combined radioactivity of approximately 90% of the administered dose in females dosed repeatedly with 350 mg TnBP/kg/day (SOCMA 1992). Approximately 6% of the administered ^{14}C was found in the feces, but it is not possible to determine whether this amount correspond to unabsorbed parent compound or absorbed material secreted in the bile. The half-life for the ^{14}C-TnBP-derived radioactivity in blood was estimated to be approximately 25 hours for both dosing regimes.

TCP. NTP (1994) reported that all three isomers of TCP were well absorbed when administered individually to rats as ^{14}C-TCP in doses of 0.5–200 mg/kg by gavage in corn oil, but the basis for this conclusion was not stated (NTP 1994). Rats administered a single dose of 7.8 mg/kg ^{14}C-tri-*p*-cresyl phosphate by gavage excreted 41% of the administered dose in the urine in 7 days, indicating that at least that amount was absorbed (Kurebayashi et al. 1985).

3.4.1.3 Dermal Exposure

TDCP. Measurements of ^{14}C-TDCP-derived radioactivity in tissues from male Sprague-Dawley rats 4 hours after application of the compound in methanol to a shaved area of 4 cm^2 in the back showed that the chemical was readily absorbed through the skin (Nomeir et al. 1981). The rate of absorption was not estimated.

TnBP. Application of 10 or 350 mg ^{14}C-TnBP/kg to a 2 cm^2 shaved area of the skin of male and female Sprague-Dawley rats for 6 hours followed by washing with soap and water resulted in absorption of at least 53% (high-dose females) of the applied dose, which was the radioactivity recovered in combined urine, feces, expired air, and tissues (SOCMA 1992).

In a study in Yucatan® minipigs, males and females were applied a dose of 10 or 350 mg ^{14}C-TnBP to a lightly clipped area of the skin for 6 hours after which time the area was washed with soap and water (SOCMA 1992). Excreta were collected for up to 168 hours after dosing. Analysis of urine and feces samples showed only ≤4% of the applied dose in excreta. In low-dose animals, 57–64% of the applied dose of ^{14}C was recovered at the dosing site (includes dosed site plus dose wash plus dose wrappings). In high-dose minipigs, 87–92% of the applied ^{14}C was recovered at the dosing site. Compared to rats, minipigs absorbed about 10 times less TnBP than rats.

3.4.1.4 Other Routes of Exposure

TDCP. Hughes et al. (2001) studied the dermal absorption of TDCP in an *in vitro* preparation of skin from adult hairless mice mounted on a flow-through diffusion cell. ^{14}C-TDCP in acetone in concentrations of 20, 100, or 200 pmol were applied to the skin and receptor fluid was collected over a 24-hour period. At this time, the skin was washed with ethanol to remove unabsorbed TDCP. For all doses, the greatest percent of the dose was absorbed between 6 and 12 hours. The 24-hour cumulative percent of the dose in the receptor fluid was 57, 45, and 39% for the 20, 100, and 200 pmol solutions, respectively. Washing with ethanol removed 11–25% of the applied radioactivity, whereas 28–35% of the applied radioactivity remained in the skin. Analysis of homogenates of the skin and receptor fluid showed the presence of parent compound and a minor unknown peak.

TnBP. Marzulli et al. (1965) studied the *in vitro* dermal absorption of a series of organic phosphates using sheets of anterior forearm stratum corneum conjunctum from humans mounted in diffusion cells. The chemicals comprised TnBP and other organic phosphates with shorter alkyl chain. TnBP was found to penetrate the skin at a maximum steady state rate of 0.18 μg/cm^2/minute, which was slower than the rates determined for the other organic phosphates tested, indicating that chain length was an important factor in dermal absorption of organic phosphates.

Intravenous administration of a single dose on 5 mg ^{14}C-TnBP/kg to male or female Sprague-Dawley rats showed that ^{14}C declined in plasma during the first 4 hours and then increased to reach a plateau between 4 and 24 hours; this was followed by a gradual decline of radioactivity in plasma that reached about 5% of the peak at 96 hours after dosing (SOCMA 1992). No significant differences were noted between males and females. The investigators suggested that ^{14}C during the first 4 hours may reflect unchanged TnBP with a short half-life in blood of approximately 1.3 hours. The mean terminal half-life of ^{14}C

estimated from urinary excretion data was approximately 29 hours, suggesting that the TnBP metabolites rapidly disappear from plasma due to tissue uptake followed by slower excretion into the urine.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No relevant information was located regarding distribution of the selected phosphate ester flame retardants in humans or animals following inhalation exposure.

3.4.2.2 Oral Exposure

As mentioned previously, TDCP was detected in adipose tissue and seminal fluid from members of the general population (Hudec et al. 1981; LeBel and Williams 1986); no further relevant information was located.

The tissue distribution of an equimolar dose of ^{14}C-labeled TCPP, TCEP, and TDCP was studied in male Wistar rats (Minegishi et al. 1988). The rats received a single dose of 50 μmol/kg (~14 mg/kg) by gavage and were euthanized at various times during a 7-day period. Elimination half-lives from blood appeared to have two phases. The first phase ranged from 12 to 14 hours, whereas the second phase ranged from 42 to 59 hours for the three chemicals. The average times at which each chemical reached the maximum concentration in various tissues were 5.7 hours for TCPP, 6 hours for TCEP, and 9.6 hours for TDCP. In general, low tissue/blood ratios were recorded in the brain, heart, muscle, and testes. Moderate ratios were obtained in adipose tissue, the spleen, and lung; high ratios were recorded in the liver and kidneys. The highest amounts of radioactivity in the liver and kidney were detected during the first 12 hours after dosing. Seven days after dosing, for the three flame retardants, the highest amount of radioactivity was found in the liver. The longest elimination half-lives from any tissue corresponded to adipose tissue and ranged from 87 hours for TCEP to 103 hours for TCPP.

TCEP. The distribution of ^{14}C-TCEP into seven brain regions from male and female Fischer-344 rats was studied by Herr et al. (1991). The brain areas analyzed were: cerebellum, brainstem, caudate, hypothalamus, cortex, hippocampus, and midbrain. Two hours after administration of single doses of 175, 350 or 700 mg TCEP/kg, all brain areas had dose-related TCEP-derived radioactivity. No preferential distribution was found across brain regions, sexes, or doses. Twenty-four hours after dosing, all brain areas had similar amounts of radioactivity; at this time, mean brain/blood ratios of 0.3 and

0.7 were determined for the 175 and 350 mg/kg dose groups, respectively, providing no evidence of bioaccumulation. Twenty-four hours after 14 days of dosing with 175 mg TCEP/kg/day, radioactivity could be quantified in blood and in all brains areas. Again, no preferential accumulation was observed in any specific brain area. At this time, the average brain/blood ratio was only 0.4, indicating that no accumulation occurred even after repeated dosing. Analysis of blood and brain tissues 72 hours after a single dose of TCEP showed brain/blood ratios of approximately 0.5, indicating that no differential elimination of radioactivity existed among the various brain areas. Extraction of cortical tissue 2 hours after a single dose of ^{14}C-TCEP showed that the radioactivity was primarily parent compound. However, when cortical tissues from selected treatment groups were pooled to maximize detection of ^{14}C, a metabolite could be detected, and there was evidence that the parent compound/metabolite ratio was greater in cortical tissue of female rats than of male rats.

TnBP. Administration of a single dose of 10 or 350 mg ^{14}C-TnBP/kg or eight consecutive doses of 10 or 350 mg ^{14}C-TnBP/kg/day to male or female Sprague-Dawley rats by gavage in corn oil resulted in only ≤1% of the administered radioactivity detected in tissues 168 hours after dosing (SOCMA 1992), suggesting little or no accumulation of parent compound or metabolites at the time of tissue analysis.

TDCP. A study in which male Sprague-Dawley rats were administered a single oral dose of 0.2, 2, or 20 µmol TDCP/kg (0.086, 0.86, or 8.6 mg/kg) showed that distribution of radioactivity to tissues, determined 24 hours after dosing, was unaffected by the size of the dose and that the liver and kidneys had the highest concentration of radioactivity (Nomeir et al. 1981).

TCP. The distribution of ^{14}C-TCP-derived radioactivity was studied in male Wistar rats for up to 168 hours after administration of a single dose of 89.6 mg/kg ^{14}C-tri-*p*-cresyl phosphate by gavage in corn oil (Kurebayashi et al. 1985). At 24 hours, radioactivity was widely distributed in the tissues. Relatively high concentrations of label were found in adipose tissue, liver, and kidneys, in addition to the intestine and stomach, whereas the lungs, testes, spleen, thymus, and blood had intermediate amounts of label. At 24 hours, the lowest concentrations of radioactivity were found in the heart, muscle, and brain. At 72 hours, the concentration of radioactivity in tissues had diminished to approximately 25% of that detected at 24 hours. At 168 hours, the radioactivity in tissues had further decreased to approximately 10% of the values reported at 24 hours. To identify metabolites in liver, kidney, and adipose tissue, the acetone-extractable fraction was methylated with ethereal diazomethane and analyzed by gas chromatography. Parent compound and *p*-cresyl *p*-carboxyphenyl phosphate were present in the fraction

of liver at 24 hours after administration. A trace of parent compound was detected in the liver and kidneys at 72 hours. Parent compound was also detected in adipose tissue at 24 and 72 hours.

3.4.2.3 Dermal Exposure

No relevant information was found in human studies.

TDCP. Application of 0.86 mg ^{14}C-TDCP/kg to a 4-cm^2 shaved area of the skin of rats resulted in tissue/blood ratios similar to those estimated in an experiment in which rats were injected TDCP intravenously (see Section 3.4.2.4 below), suggesting that tissue distribution is independent of the route of administration (Nomeir et al. 1981). Four hours after the application, the concentration in tissues, in decreasing order was: liver > lung > skin > blood > kidneys > adipose > muscle.

TnBP. Application for 6 hours of 10 or 350 mg ^{14}C-TnBP/kg to a 2-cm^2 area of the back of male or female Sprague-Dawley rats followed by washing with soap and water resulted in ≤1% of the applied radioactivity in tissues 168 hours after dosing (SOCMA 1992).

3.4.2.4 Other Routes of Exposure

TDCP. The distribution of ^{14}C-TDCP-derived radioactivity was studied in male Sprague-Dawley rats administered a single intravenous injection of ^{14}C-TDCP (Lynn et al. 1981). Tissue samples (all major tissues and organs) were collected at five time intervals up to 120 hours after dosing. TDCP disappeared rapidly from plasma with a half-life of <5 minutes. This was paralleled by a rapid rise in the concentration of the major metabolite of TDCP, bis(1,3-dichloro-2-propyl) phosphate (BDCP, see Section 3.4.3). After 2 hours, the concentration of BDCP declined with a half-life of approximately 4–6 hours. In most tissues, the concentrations of TDCP were initially (at 5 minutes) high, but declined considerably by 30 minutes; 8 hours after dosing, TDCP was detected only in fat tissue. No TDCP was detected in any tissues studied ≥24 hours after dosing. BDCP was also quantified in each of the tissues studied. The highest concentration of the metabolite was observed in the lung, liver, blood, and kidneys. BDCP could be detected in tissues within 5 minutes of dosing and up to 24 hours later, but not in quantifiable amounts 5 days after dosing. The highest concentrations of radiolabel were measured in the kidneys, lung, and liver. Five minutes after dosing, 46.4% of the administered TDCP had been metabolized and 16% of the phosphate was recovered as BDCP. By 30 minutes, 82% of the whole-body radiolabel was present as metabolite and 27% of the administered phosphate was recovered as BDCP. At

8, 24, and 120 hours after dosing, 55.7, 59, and 63% of the administered phosphate was recovered as BDCP, respectively.

A similar study was conducted by Nomeir et al. (1981). Intravenous injection of ^{14}C-TDCP to male Sprague-Dawley rats resulted in initially high concentrations of radioactivity in the lung, liver, kidneys, and blood, whereas the lowest concentrations were found in muscle, skin, and adipose tissue. The relatively high concentration of radioactivity in the lung was thought to be the product of a first-pass effect. Except for the skin, radioactivity decreased in most tissues by 7 hours after dosing. By day 10, the remaining radioactivity was only 1–5% of that measured 15 minutes after dosing. Tissue fractioning studies showed that radiolabel derived from the parent compound significantly decreased in most tissues within the first 2 hours following apparent exponential decay rates with half-lives of 3–4 hours; elimination half-lives from the lung and adipose tissues were 1.5 and 5.4 hours, respectively. One day after dosing, only 20–30% of the radioactivity remaining in tissues was the parent compound. The clearance of the remaining radioactivity followed a single exponential decay with a half-life much longer than that observed for TDCP.

Morales and Matthews (1980) studied the subcellular distribution of TDCP in male CD-1 mice. Mice received a single intravenous injection of ^{14}C-TDCP and 6 hours later, the covalent binding of radioactivity to DNA, RNA, and protein from liver, muscle, and kidney was monitored. The highest concentration of radioactivity was found in the liver. In each tissue in which it was measured, the concentration of TDCP-derived bound radioactivity was highest in low molecular weight RNA followed in decreasing concentration by protein, rRNA, and DNA.

TnBP. Administration of a single intravenous dose of 5 mg ^{14}C-TnBP/kg into the tail vein of male or female Sprague-Dawley rats resulted in ≤1% of the applied radioactivity in tissues 168 hours after dosing (SOCMA 1992).

TCP. NTP (1994) studied the distribution of radioactivity in male F344/N rats following intravenous administration of each one of the pure ^{14}C-TCP isomers at doses of 2 or 30 mg/kg. Without providing further details, the report stated that all three isomers were rapidly distributed to muscle and liver, and then redistributed to adipose tissue and skin. NTP (1994) also stated that the parent compounds were rapidly cleared with no tendency to bioaccumulate in specific organs or tissues.

3.4.3 Metabolism

TDCP. Lynn et al. (1981) studied the metabolism of TDCP in male Sprague-Dawley rats. Analysis by high-pressure liquid chromatography (HPLC)/liquid scintillation counting of the urine of rats following an intraperitoneal dose of ^{14}C-TDCP showed a major component (approximately 69% of the radioactivity) identified as BDCP. A second component was identified as the dimethyl derivative of 1,3-dichloro-2-propyl phosphate. Analysis without derivatization of chloroform extracts of the urine of rats by gas chromatography/mass spectrometry (GC/MS) showed that the major component was 1,3-dichloro-2-propanol. Analysis over a 5-day period of excreta from rats injected intravenously with ^{14}C-TDCP also showed BDCP to be a major component of the urine, feces, and bile. A metabolic scheme was not proposed, but Lynn et al. (1981) noted that the formation of the mono- and diester-metabolites was likely to proceed by either mixed function oxidase reactions, hydrolase reactions, and/or glutathione S-alkyltransferase reactions. Similar studies in rats conducted by Nomeir et al. (1981) also showed that the major metabolite excreted in the urine was BDCP, which accounted for 67.2% of the total radioactivity in the urine. Approximately 32% of the ^{14}C-TDCP-derived radioactivity in the urine was an unidentified polar metabolite, whereas only 0.29% was 1,3-dichloro-2-propyl phosphate and 0.45% was unchanged parent compound.

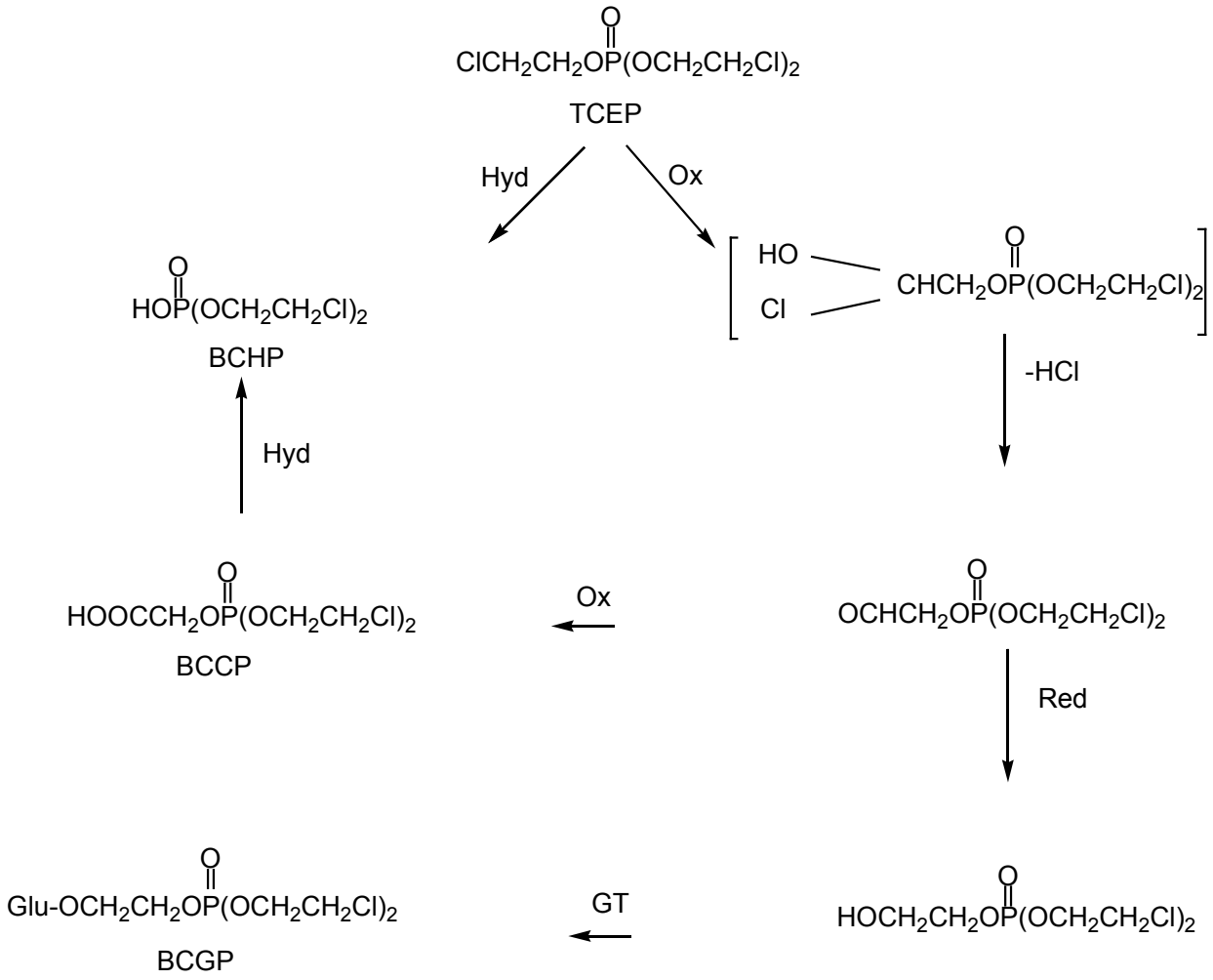
In vitro studies with rat liver fractions showed that TDCP was metabolized by enzymes located in the microsomal and soluble fractions, and to a lesser extent, by enzymes in the mitochondrial fraction (Nomeir et al. 1981). It appeared that TDCP was metabolized via oxidative and conjugation reactions. Experiments using the 10,000 g supernatant in the presence and absence of various cofactors showed that little metabolism (6.4%) occurred in the absence of cofactors. In contrast, addition of GSH or NADPH markedly increased metabolism (28 and 26%, respectively), with the highest rate being observed in the presence of both cofactors (34.7%). Metabolism also increased steadily for up to 2 hours. Experiments with the isolated microsomal fraction showed that this fraction metabolized TDCP to 1,3-dichloro-2-propanol, 3-chloro-1,2-propanediol, BDCP, and at least one unidentified metabolite. In the soluble fraction, TDCP was metabolized to one metabolite, which was probably a glutathione conjugate formed with the intact TDCP molecule.

TCEP. HPLC analyses of the cumulative 24-hour urine of male and female Fischer-344 rats and male B6C3F$_1$ mice following a gavage dose of 175 mg ^{14}C-TCEP/kg showed the presence of up to six peaks (Burka et al. 1991). Although qualitatively similar, the profiles showed quantitative differences between rats and mice and between male and female rats. The major peak in both species accounted for 70% of

the total radioactivity in urine from male mice, but only 50% in both male and female rats. In contrast, both male and female rat urine contained approximately 2 times more of a peak eluting at 9.7 minutes than did urine from mice, whereas urine from female rats contained more of a peak eluted at 12.9 minutes (12%) than either male rats (4%) or male mice (7%). Characterization of urinary metabolites by nuclear magnetic resonance and MS showed that the major metabolite in female rat urine was bis(2-chloroethyl) carboxymethyl phosphate (BCCP). This metabolite co-chromatographed with the major metabolite found in both male rats and mouse urine. Two additional metabolites that were identified in female rat urine were bis(2-chloroethyl) hydrogen phosphate (BCHP) and the glucuronide of bis(2-chloroethyl) 2-hydroxyethyl phosphate (BCGP); both BCHP and BCGP also co-chromatographed with metabolites found in mouse and male rat urine. Experiments pretreating male rats with inhibitors of the enzyme aldehyde dehydrogenase showed increased TCEP-induced toxicity, whereas preadministration of SK 525A, a mixed-function oxidase inhibitor, slowed elimination of ^{14}C in urine and inhibited production of BCCP, but did not increase neurotoxicity. Burka et al. (1991) took these observations to imply that a metabolite rather than unmetabolized TCEP produces neurotoxicity. This, however, seems to conflict with results of studies of distribution of ^{14}C in brains of rats that reported that at the time of seizures, most of the TCEP-derived radioactivity present in brain tissue was in the form of parent compound (Herr et al. 1991). A metabolic scheme proposed by Burka et al. (1991) is shown in Figure 3-8.

Differences in the metabolism of TCEP between male and female Fischer-344 rats have also been reported in *in vitro* studies. In a study that also included liver preparations from humans, Chapman et al. (1991) reported that both liver slices and microsomes from humans and male rats metabolized TCEP to bis(2-chloroethyl) hydrogen phosphate, 2-chloroethanol, and three unidentified metabolites. TCEP was metabolized by liver slices from female rats, but liver microsomes from female rats did not appear to metabolize TCEP. Additional experiments suggested that a substantial TCEP-hydrolyzing activity in rat liver was localized in the cytosol. The overall rate of TCEP metabolism by male rat liver slices was 1.7 times greater than for female rat liver slices. TCEP was metabolized by rat plasma, without sex differences, but not by human plasma or whole blood. In all studies, the major metabolites were bis(2-chloroethyl) hydrogen phosphate and 2-chloroethanol. Since BCCP and BCGP were produced *in vivo* in rats (Burka et al. 1991), but no significant amounts were produced *in vitro*, Chapman et al. (1991) suggested that *in vivo* α-oxidation of TCEP may occur extrahepatically. Studies with enzyme inhibitors (male rats only) suggested that cytochrome P-450 was responsible for approximately 38% of the total microsomal TCEP hydrolytic activity. The remaining microsomal TCEP hydrolytic activity appeared to be associated with a B-esterase. Chapman et al. (1991) noted that B-esterases are present in rat serum,

Figure 3-8. Proposed Scheme for TCEP Metabolism in Rats and Mice



BCCP = bis(2-chloroethyl) carboxymethyl phosphate; BCGP =bis(2-chloroethyl) 2-hydroxyethyl phosphate; BCHP = bis(2-chloroethyl) hydrogen phosphate; GT = glucuronyl transferase; Hyd = hydrolysis; Ox = oxidation; Red = reduction; TCEP = tris(2-chloroethyl) phosphate

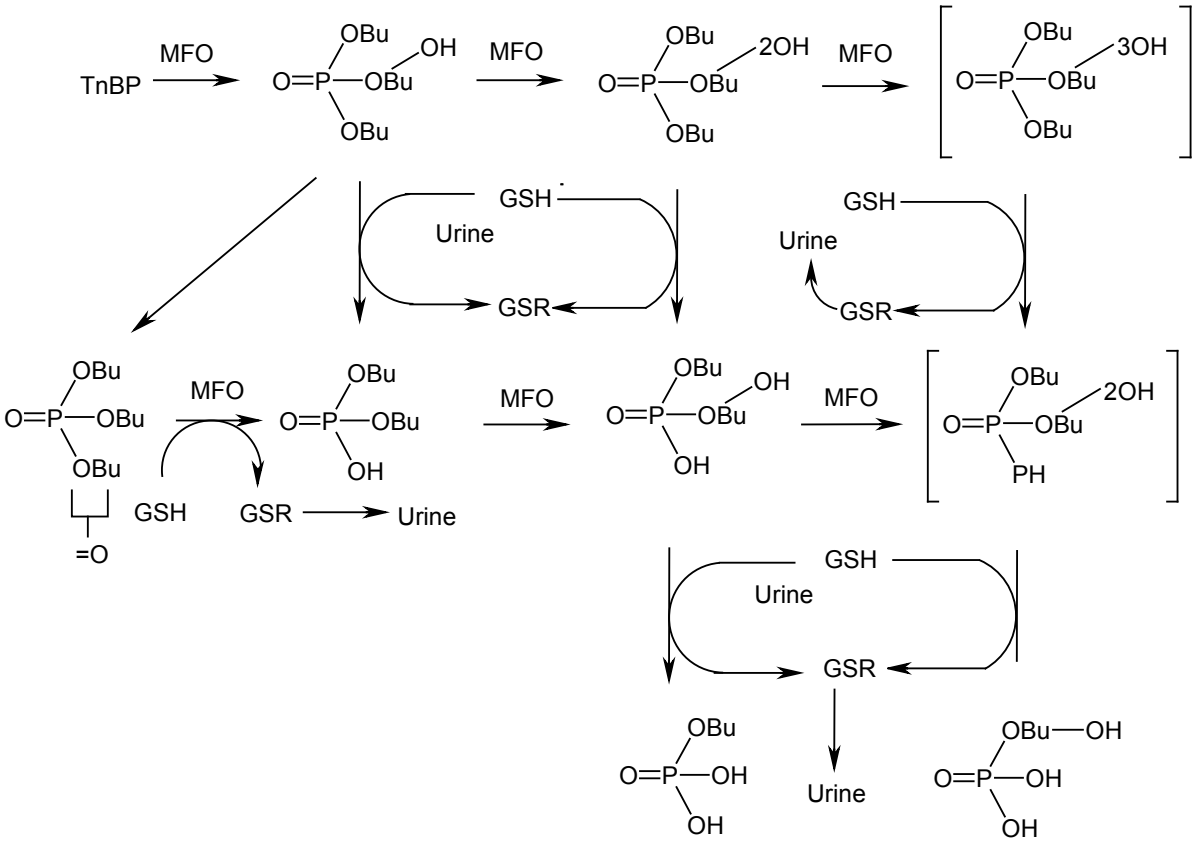
Source: Burka et al. 1991

but not human serum, which would be consistent with the finding in their study of hydrolysis of TCEP by rat serum, but not human plasma.

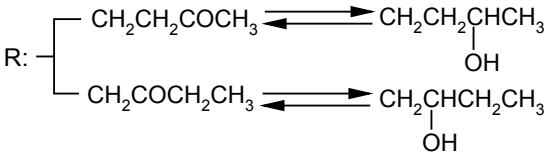
TnBP. Analyses of urine samples from male Wistar rats administered a single intraperitoneal dose of 250 mg ^{14}C-TnBP revealed 11 phosphorus-containing metabolites (Suzuki et al. 1984a). The major metabolites were dibutyl hydrogen phosphate, butyl dihydrogen phosphate, and butyl bis(3-hydroxybutyl) phosphate; no glucuronide or cysteine conjugates could be detected, which suggested that biotrans-formation of TnBP in rats is carried out mainly by phase I reactions. However, in a subsequent study, Suzuki et al. (1984b) detected several S-containing metabolites in crude extracts of urine from rats treated with TnBP intraperitoneally. The main metabolites were (3-oxobutyl) and (3-hydroxybutyl) mercapturic acids, and traces of (2-oxobutyl)- and (2-hydroxybutyl) mercapturic acids. The results also suggested that TnBP undergoes transalkylation of 3-hydroxybutyl or 3-oxobutyl moieties after oxidation of the original butyl moieties. Based on these findings, Suzuki et al. (1984b) proposed a metabolic scheme for TnBP shown in Figure 3-9. Recently, Neerathilingam et al. (2010), using high-resolution ^{1}H NMR-based metabonomics, identified dibutyl phosphate, *N*-acetyl-(S-3-hydroxybutyl)-L-cysteine, and N-acetyl-(S-3-oxobutyl)-L-cysteine as the main metabolites in the urine collected from rats during 24 hours after the administration of a single gavage dose of TnBP. These investigators also found that TnBP induced variations of endogenous urinary metabolites such as benzoate, urea, and trigonelline along with metabolites involved in the Krebs cycle including citrate, cis-aconitate, trans-aconitate, 2-oxoglutarate, succinate, and fumarate and suggested that this could be used as a biomarker of TnBP exposure.

SOCMA (1992) also studied the metabolism of TnBP in male and female Sprague-Dawley rats following administration of intravenous, dermal, or oral (single or repeated doses of 10 or 350 mg/kg) doses. Urine, feces, and expired air were collected at various times up to 168 hours after dosing (rats killed); blood was collected at termination. Because blood at collection contained <5% of the administered dose, blood samples were not chromatographed. HPLC analyses of urine showed the presence of 10 radioactive peaks, and 6 of them contained radioactivity ≥5% of the administered dose. None of the fecal samples contained >5% of the administered radioactivity. In general, the chromatographic profiles of all samples were similar, with differences only in the relative concentration of the peaks. Usually, the majority of the radioactivity in the urine was contained in the more polar peaks. Incubation of urine with β-glucuronidase produced no changes in the profile, suggesting that phase II metabolism was not a significant biotransformation route for TnBP. Differences in chromatographic profiles from rats in the various groups appeared greater between individual animals than among treatment groups or between male and female rats. However, profiles from female rats treated with multiple doses or a single high

Figure 3-9. Proposed Metabolic Pathway of TnBP in Rats



G: gluathione or N-acetyl-L-cysteine



MFO = mixed function oxidase; GSH = glutathione; GSR = reduced glutathione; TnBP = tributyl phosphate

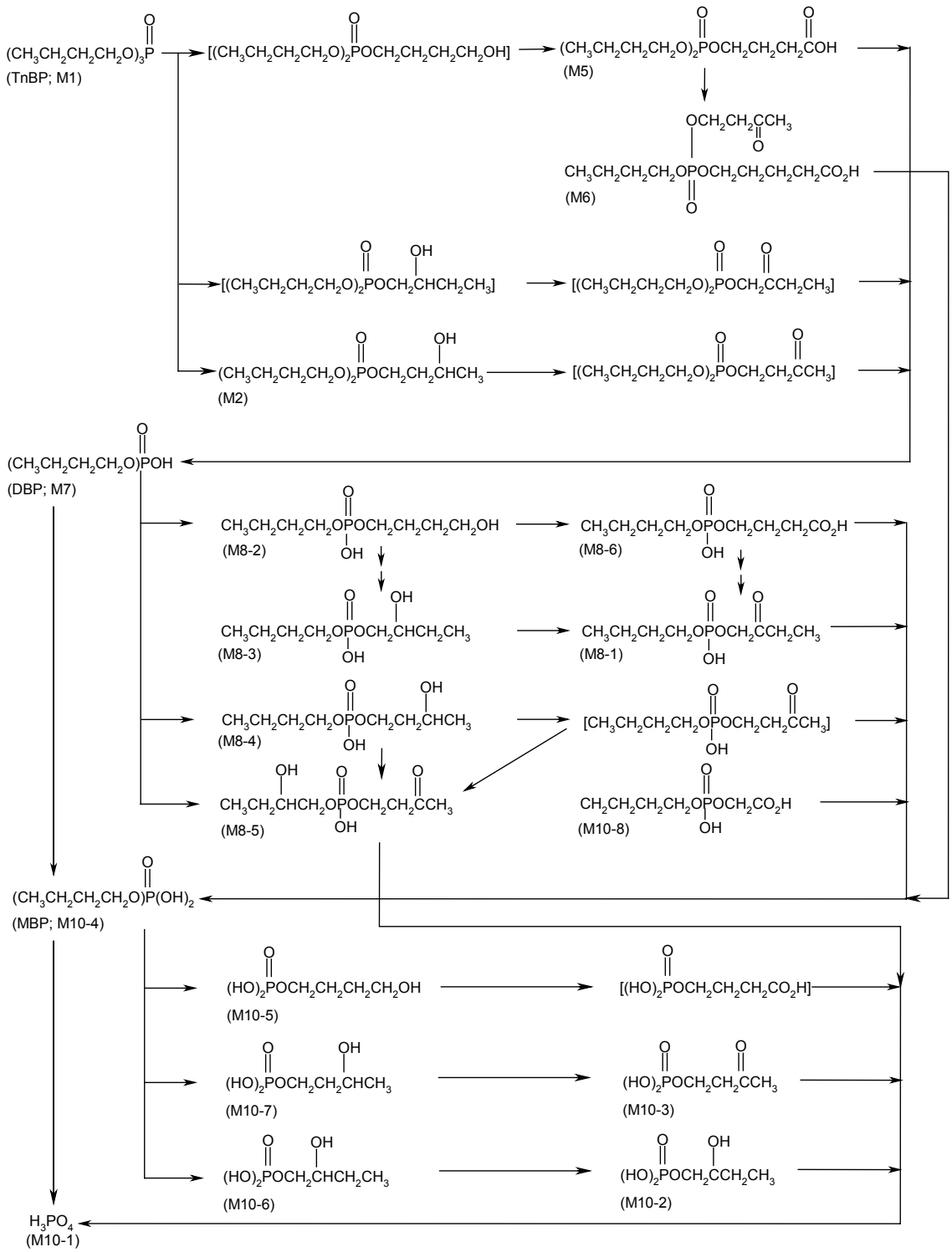
Source: Suzuki et al. 1984b

dose of TnBP showed higher concentrations of less polar metabolites than profiles from similarly treated males. From the 10 detected radioactive peaks, 18 metabolites were characterized. The three metabolites present in the highest concentrations in most of the samples were butyl 3-hydroxybutyl hydrogen phosphate (M8-4 in Figure 3-10), dibutyl hydrogen phosphate (M7), and butyl butanoic acid hydrogen phosphate (M8-6). Other metabolites were phase I metabolites produced by oxidation (acid, keto, hydroxylated) or enzymatic hydrolysis of the butyl chains of TnBP. SOCMA (1992) proposed a scheme in which the butyl groups of TnBP are oxidized metabolically to alcoholic, ketonic, and acidic groups. The oxidized butyl groups are then enzymatically hydrolyzed with sequential loss proceeding from the tri-substituted to the di-, mono-, and finally to unsubstituted phosphoric acid. The degree of oxidation or extent of hydrolysis of the detected metabolites was found to be independent on dosing, treatment, or sex of the animal. The metabolic scheme is presented in Figure 3-10.

SOCMA et al. (1994) also studied the metabolism of TnBP in Yucatan® minipigs following administration of ^{14}C-TnBP in a single intravenous injection (5 mg/kg) or after application of chemical (10 or 350 mg/kg) to the skin for 6 hours, as done in the rat experiments. Excreta were collected for up to 168 hours after dosing. Only urine samples from animals dosed intravenously were analyzed for metabolites since fecal samples from pigs treated intravenously or dermally, or urine samples from pigs treated dermally contained <5% of the administered dose. HPLC profiles of urine showed four major peaks, which were characterized as two diasteromeric pairs of glucuronides of two precursor metabolites, a monohydroxy and a dihydroxy dibutyl phosphate. Neither time of sample collection or gender appeared to qualitatively change the distribution or type of the excreted metabolites. Unchanged TnBP was found at ≤0.4% of the administered dose. Hydrolysis of urine samples with β-glucuronidase followed by derivatization reactions and GC analysis showed that two peaks with mass spectra corresponding to 2-hydroxybutyl dibutyl phosphate and dibutyl phosphate. Based on these results, SOCMA (1994) proposed a metabolic scheme, shown in Figure 3-11, that involves phase I and phase II reactions. The parent chemical is assumed to be oxidized by mixed function oxidases to produce the monohydroxyl and dihydroxyl species, which are substrates for glucuronide formation.

TPP. Sasaki et al. (1984) provided some information regarding the *in vitro* metabolism of TPP by a rat liver preparation. Rat liver microsomes were able to metabolize TPP in the presence (91% of substrate) and absence (66% of substrate) of NADPH. This suggested that an arylesterase in the microsomes also contributed to the metabolism of TPP. Sasaki et al. (1984) also reported that the soluble fraction from rat liver also metabolized (15%) TPP. Experiments to identify metabolites of TPP were not conducted.

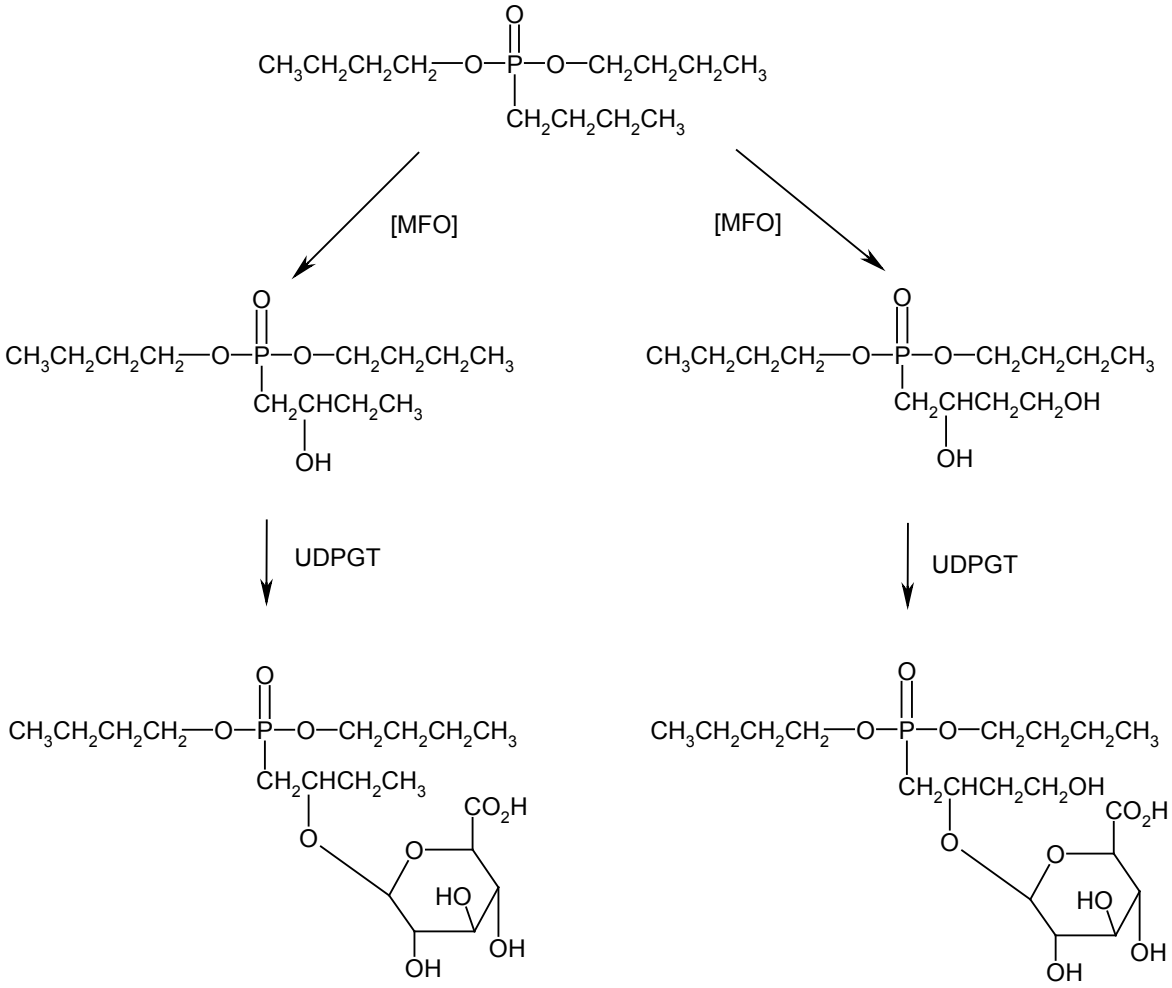
Figure 3-10. Suggested Biotransformation Scheme of TnBP in Rats



[ ] = not observed; DBP = dibutyl phosphate; MBP = monobutyl phosphate; TnBP = tributyl phosphate

Source: SOCMA 1992

Figure 3-11. Proposed Metabolic Pathway of TnBP in Yucatan® Minipigs



MFO = mixed function oxidase; TnBP = tributyl phosphate; UDPGT = uridine diphosphate glucuronyl transferases

Source: SOCMA 1994

TCP. Kurebayashi et al. (1985) studied the metabolism of tri-*p*-cresyl phosphate in male Wistar rats. Metabolites were identified in blood, urine, feces, and tissues of rats at various times (up to 72 hours) following administration of 7.8 or 89.6 mg/kg ^{14}C-tri-*p*-cresyl phosphate by gavage in corn oil. Metabolism involved a series of successive oxidations (in the liver) and hydrolysis (in the intestine) that resulted in *p*-hydroxybenzoic acid, di-*p*-cresyl phosphate, and *p*-cresyl *p*-carboxyphenyl phosphate as the major urinary metabolites. In the bile, the major metabolites were di-*p*-cresyl phosphate, *p*-cresyl *p*-carboxyphenyl phosphate, and the oxidized triesters di-*p*-cresyl *p*-carboxyphenyl phosphate, and *p*-cresyl *p*-carboxyphenyl phosphate. Analysis of the feces revealed metabolites very similar to those monitored in the bile; at the high dose, the main fecal metabolite was the unchanged tri-*p*-cresyl phosphate, probably due to incomplete absorption. Analysis of expired air showed $^{14}CO_2$ that appeared to be formed by decarboxylation of *p*-hydroxybenzoic acid by intestinal microbes. NTP (1994) proposed metabolic pathways for tri-*p*-cresyl phosphate based on the results of Kurebayashi et al. (1985); these are shown in Figure 3-12.

3.4.4 Elimination and Excretion

No studies were located regarding elimination and excretion of the selected phosphate ester flame retardants or metabolites in humans following any route of exposure.

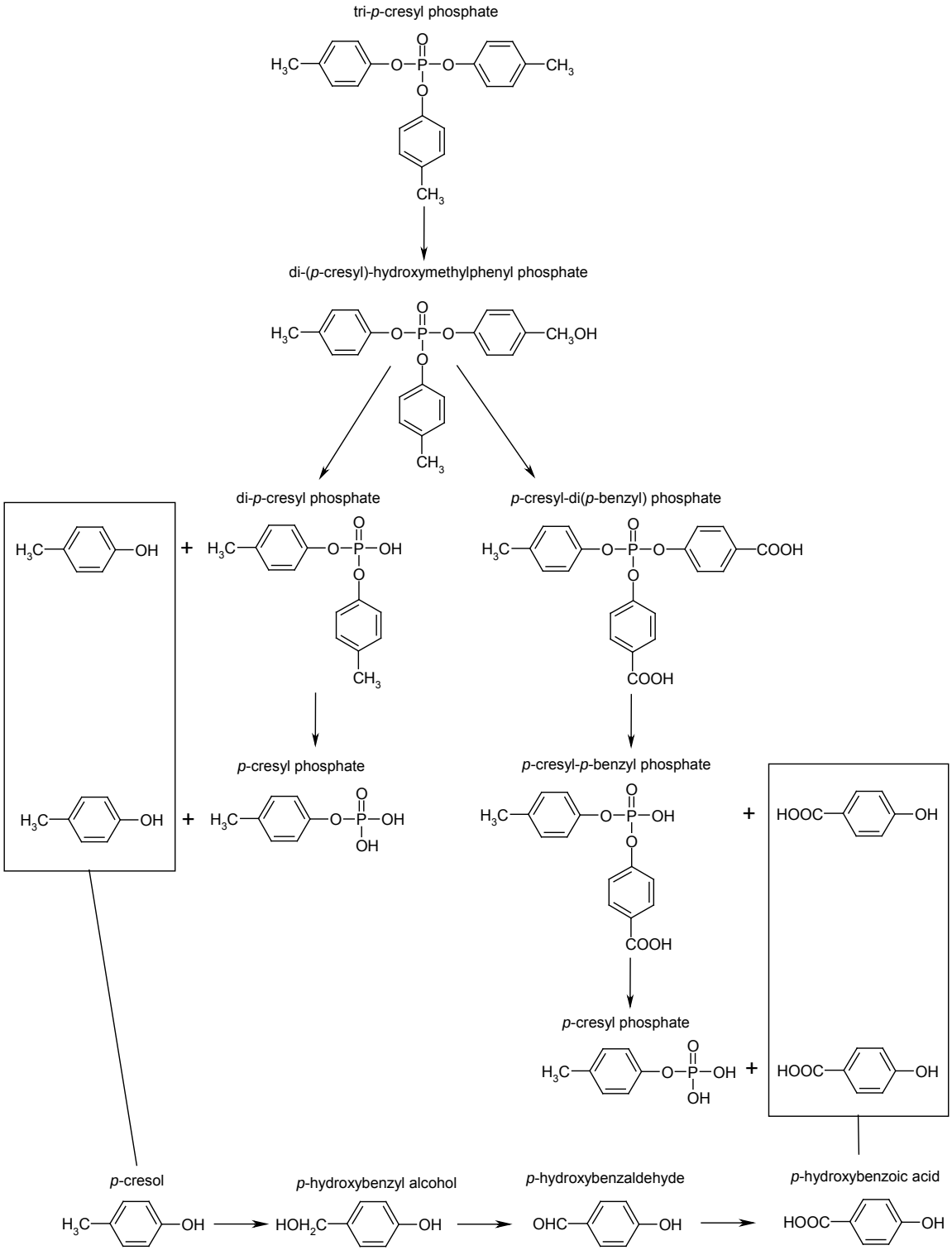
3.4.4.1 Inhalation Exposure

No pertinent information was located regarding excretion of phosphate ester flame retardants in animals following inhalation exposure.

3.4.4.2 Oral Exposure

Minegishi et al. (1988) compared the excretion of TDCP, TCPP, and TCEP in male Wistar rats during a 7-day period following gavage administration of a single equimolar dose of 50 µmol/kg of ^{14}C-labeled compound. During the 7-day period, the cumulative excretion of radiolabel in urine followed the order TCEP > TCPP > TDCP. Almost all (~90%) of the administered TCEP was excreted in the urine, whereas ~60% of TCPP and ~40% of TDCP were excreted in the urine. The order of excretion was TDCP (~40%) > TCPP > TCEP in feces, and TDCP (~18%) > TCPP > TCEP in expired air. For the three compounds, recovery within the 7 days was almost 100%. Experiments in rats with cannulated bile ducts showed that peak biliary excretion occurred approximately 2 hours after dosing with TCPP and TCEP, whereas the peak for TDCP was reached at approximately 6 hours after dosing. As a percent of the

Figure 3-12. Proposed Metabolic Pathways for Tri-*p*-Cresyl Phosphate



Adapted from: NTP 1994

administered dose, 45% of TCPP, 40% of TDCP, and 25% of TCEP were excreted in the bile in 48 hours. Since the biliary/fecal excretion ratios for TCEP and TCPP exceeded 1, it appeared that enterohepatic circulation occurred for these two compounds.

TCEP. Excretion of ^{14}C was studied in female Fischer-344 rats by collecting urine, feces, exhaled volatiles, and CO_2 over a 3-day period following gavage administration of 175 or 350 mg ^{14}C-TCEP/kg (Herr et al. 1991). The major portion of either dose was excreted in the urine within 24 hours. Only ≤1% of the radioactivity was excreted in expired air or as ^{14}C-CO_2 in 72 hours. Less than 10% of the radiolabel was excreted in feces over 3 days. Additional experiments were conducted to compare excretion between male and female rats over a 24-hour period. No significant differences were seen between males and females administered 175 mg TCEP/kg. However, females dosed with 350 mg TCEP/kg excreted significantly less cumulative ^{14}C in urine than males at the 8- and 24-hour time points. Also, high-dose female rats excreted less cumulative ^{14}C in urine than low-dose females at the 4-, 12-, and 24-hour time points. High-dose females also excreted less cumulative ^{14}C in feces over the 24-hour period than males.

Further studies of the metabolism and excretion of TCEP were conducted by Burka et al. (1991). In that study, cumulative 24-hour excretion of ^{14}C-TCEP-derived radioactivity was measured in the urine and feces of male and female Fischer-344 rats and male B6C3F_1 mice following a gavage dose of 175 mg TCEP/kg. In rats, >75% of the administered ^{14}C was eliminated in the urine and <10% was eliminated in the feces over 24 hours; no significant differences were seen between males and females. However, male mice eliminated ^{14}C 3 times faster than rats during the first 8 hours. Administration of nine consecutive oral doses to rats did not change the elimination rate of ^{14}C in urine. The elimination of ^{14}C in urine of female rats followed first-order kinetics with mean half-lives of 6.2, 6.1, and 6.5 hours after one, four, and seven doses, respectively. The corresponding half-lives in male rats were 7.6, 7.8, and 7.1 hours. The difference between males and females was statistically significant after one and four doses, but not after seven doses.

TnBP. Administration of a single dose of 14 mg ^{14}C-TnBP by gavage to male Wistar rats resulted in 50% of the ^{14}C recovered in the urine, 10% in exhaled air, and 6% in feces within 1 day (Suzuki et al. 1984a). This was compared with corresponding values of 70, 7, and 7% after administration of the same dose by intraperitoneal injection (Suzuki et al. 1984a).

The excretion of ^{14}C-TnBP-derived radioactivity was also studied in male and female Sprague-Dawley rats over a 168-hour period following administration by gavage of a single dose of 10 or 350 mg TnBP/kg or eight consecutive doses of 10 or 350 mg/kg/day (SOCMA 1992). Analyses of excreta showed that the major portions of the administered doses were eliminated within 48 hours in urine and feces. The ratio of radioactivity urine/feces ranged from about 4 in single- low-dose males to 14 in repeated-high-dose females. Excretion of radioactivity in expired was low ranging from 3.6% in repeated-high-dose females to 8.3% in single-high-dose males.

TCP. Kurebayashi et al. (1985) studied the excretion of radioactivity derived from ^{14}C-tri-*p*-cresyl-phosphate in urine and feces from male Wistar rats following the administration of a single dose of 7.8 or 89.6 mg/kg of the compound by gavage in corn oil. Urine and feces were collected daily for 7 days. With both doses, most of the radioactivity was excreted within 24 hours. At the low dose, 41% of the radioactivity was excreted in the urine and 44% in the feces in 7 days. Expired air accounted for 19% of the administered dose. In rats with cannulated bile ducts, about 28% of the administered radioactivity was excreted into the bile during 24 hours. At the high dose, 12% of the radioactivity was excreted in the urine and 77% in the feces, and 6% in expired air in 7 days.

NTP (1994) examined the excretion of radioactivity derived from ^{14}C-labeled pure TCP isomers administered to male F344/N rats by gavage in corn oil in doses of 0.5, 2, 20, or 200 mg/kg. Approximately 70% of tri-*o*-cresyl phosphate-derived label was excreted in the urine and 20% in feces within 24 hours for all dose levels administered. Tri-*m*-cresyl phosphate was excreted mainly in the feces, and as the dose increased, the percentage of fecal excretion increased while urinary excretion decreased. The urine was the main route of excretion of ^{14}C derived from tri-*p*-cresyl phosphate when the compound was administered in low doses while fecal excretion was predominant at higher doses (20 and 200 mg/kg).

3.4.4.3 Dermal Exposure

TnBP. SOCMA (1992) studied the excretion of ^{14}C-TnBP-derived radioactivity in Sprague-Dawley rats over a 168-hour period after application of 10 or 350 mg TnBP/kg to a 2-cm^2 area of the skin for 6 hours followed by washing with soap and water. The major portion of the recoverable dose was excreted in the urine and feces within 48 hours. In males, over the 168-hour period, approximately 29 and 40% of the applied low- and high-dose, respectively, was recovered in urine and 3 and 7% in feces. In females, approximately 32 and 44% of the applied low- and high-dose, respectively, was recovered in urine and

3 and 7% in feces. In both the low- and high-dose groups, between 24% (high-dose females) and 43% (low-dose females) of the applied ^{14}C was recovered in the wash. Radioactivity in expired air comprised ≤2% of the applied dose. No significant differences in excretion were seen between males and females.

Yucatan® minipigs excreted in the urine and feces ≤4% of a dermal dose of 10 or 350 mg of ^{14}C-TnBP/kg applied to the skin for 6 hours, indicating that dermal absorption of TnBP in this species is about 10 times lower than in rats under similar experimental conditions (SOCMA 1992).

3.4.4.4 Other Routes of Exposure

TDCP. In male Sprague-Dawley rats administered a single intravenous injection of ^{14}C-TDCP, the primary route of excretion of radiolabel was the urine with significantly lesser amounts being excreted in the feces and in expired CO_2 (Lynn et al. 1981). Approximately 62% of the radiolabel in the composite urine and 51% in composite feces over a 5-day period was found to be BDCP. On a molar basis, BDCP excreted in the urine and feces accounted for approximately 63% of the administered dose of TDCP. Only trace amounts of the parent compound were detected in the urine and feces. Experiments in rats with cannulated bile ducts showed that approximately one third of the administered radiolabel was excreted via the bile in 24 hours. Comparison of rats with cannulated bile ducts with normal rats showed that at least 67% of the radiolabel excreted in the bile was reabsorbed.

Similar results were reported by Nomeir et al. (1981) who also administered ^{14}C-TCDP to male Sprague-Dawley rats intravenously. In their study, approximately 47 and 21% of the administered radiolabel was excreted in the urine and feces, respectively, within 10 days of administration. The major metabolite excreted in the urine was BDCP. Experiments with bile duct-cannulated rats suggested that a portion of the radioactivity excreted in the bile was reabsorbed from the gastrointestinal tract and excreted in the urine. Nomeir et al. (1981) also showed that approximately 20% of an intravenous dose of TDCP was exhaled as CO_2 during the first 24 hours after dosing; the radioactivity was primarily metabolites rather than parent compound.

TnBP. Administration of a single intraperitoneal dose of 14 mg ^{14}C-TnBP to male Wistar rats resulted in 70% of the ^{14}C recovered in the urine, 7% in exhaled air, and 4% in feces within 1 day (Suzuki et al. 1984a). The detection of radiolabel in the feces after an intraperitoneal injection suggested that some metabolites were excreted via the bile duct.

SOCMA (1992) studied the excretion of ^{14}C-TnBP-derived radioactivity in Sprague-Dawley rats over a 168-hour period after a single intravenous injection of 5 mg TnBP/kg into the tail vein. The major portion of the recoverable dose was excreted in the urine and feces within 48 hours. Over the 168-hour period, approximately 69 and 80% of the injected dose was recovered in urine of males and females, respectively; in the same period, 17 and 7% was recovered in feces from males and females, respectively. Cumulative recovery of ^{14}C in expired air accounted for 4–6% of the administered dose of TnBP. Only ≤1% of the administered dose was recovered in tissues. In total, approximately 90% of the administered dose of radioactivity was recovered in excreta.

SOCMA (1992) also studied the excretion of ^{14}C-TnBP-derived radioactivity in Yucatan® minipigs by analyzing excreta collected for up to 168 hours after administration of a single intravenous dose of 5 mg TnBP/kg. About 82% of the administered dose was excreted in the urine and 2–3% in the feces. The majority of the urinary excretion occurred during the first 6 hours after dosing. There was no difference between males and females.

TCP. Intravenous administration of 2 or 20 mg/kg ^{14}C-labeled tri-*o*-cresyl phosphate or tri-*m*-cresyl phosphate to male F344/N rats resulted in 40–60% of the label excreted in the bile within 6 hours (NTP 1994). However, in the case of tri-*p*-cresyl phosphate, increasing the dose from 2 to 20 mg/kg approximately doubled biliary excretion. For the three isomers, the percentage of the dose excreted in the feces was less than that excreted in the bile, suggesting that considerable enterohepatic recycling occurred. For the three isomers, almost all of the label had been excreted within 3 days of dosing.

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.

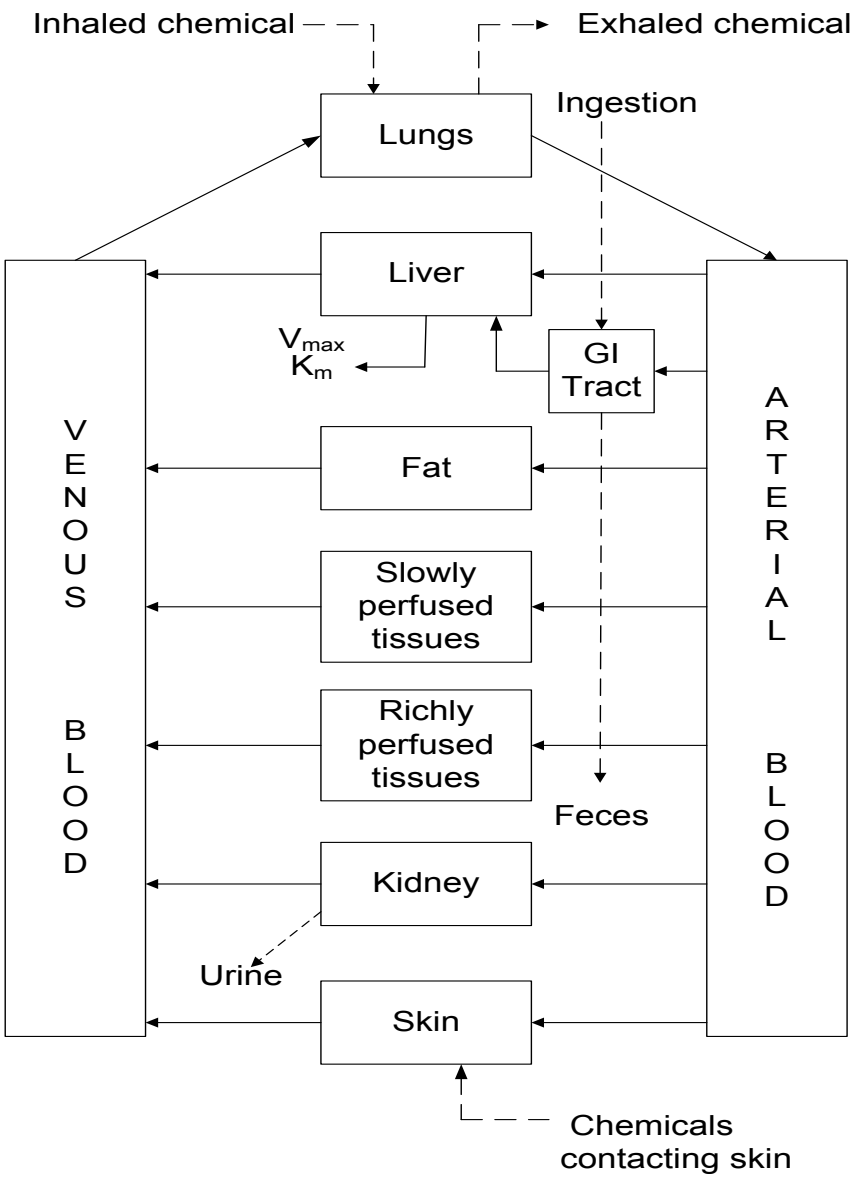
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 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. If the uptake and disposition of the chemical substance(s) are adequately described, however, 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 3-13 shows a conceptualized representation of a PBPK model.

Figure 3-13. 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: adapted from Krishnan and Andersen 1994

If PBPK models for phosphate ester flame retardants 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 have been developed for the phosphate ester flame retardants discussed in this profile.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Studies with TCEP, TDCP, TCP, and TnBP in animals showed that these substances are rapidly and extensively absorbed through the gastrointestinal tract (Herr et al. 1991; Nomeir et al. 1981; NTP 1994; SOCMA 1992). However, the mechanisms involved in the absorption of these compounds have not been studied. Given the fast absorption, it seems reasonable to assume that the process occurs through passive diffusion. TDCP was also rapidly absorbed through the skin of rats, but a rate of absorption was not estimated (Nomeir et al. 1981). A study with TnBP showed significant differences in dermal absorption between rats and minipigs; that rats absorbed about 10 times more of ^{14}C-TnBP-derived radioactivity than did minipigs (SOCMA 1992). No mechanism for dermal absorption was proposed, but a study with isolated human skin showed that for a group of alkyl phosphate ester flame retardants, chain length was an important factor in dermal absorption; the shorter the alkyl chain length, the faster the compound was absorbed (Marzulli et al. 1965). It was also observed that substances with benzene/water partition ratios closest to 1 had the highest penetration rates, and compounds with the lower boiling points penetrated the skin better than those with the highest boiling points.

Distribution. No specific mechanisms of distribution were apparent for the phosphate ester flame retardants for which there are distribution data (i.e., TCEP, TnBP, TDCP, TCPP, tri-*p*-cresyl phosphate). In general, oral studies with radiolabeled compounds showed no preferential accumulation in tissues. A study in which three dose levels of TDCP (0.086, 0.86, or 8.6 mg/kg) were administered to rats showed linear increases in distribution to tissues over the dose range tested 24 hours after dosing, indicating independence from dose size (Nomeir et al. 1981). That study also provided evidence of distribution independent from the route of exposure as tissue/blood ratios of radioactivity after dermal exposure to TDCP were similar to ratios calculated after intravenous administration of the compound. A study of distribution of ^{14}C-TCEP-derived radioactivity to various brain areas from rats also showed almost linear distribution of radioactivity over the dose range tested 2 hours after dosing (Herr et al. 1991). That study also showed that distribution to the areas monitored was sex-independent.

Metabolism. The metabolism of TDCP, TCEP, TnBP, and tri-*p*-cresyl phosphate has been fairly well studied and involves both phase I and phase II reactions. In rats, metabolism was the main form of elimination of TDCP (Lynn et al. 1981). The role that metabolism may play in the toxicity and/or carcinogenicity of TDCP is unknown.

Studies in rats aimed at identifying the chemical entity responsible for the seizure activity and brain lesions in rats exposed to TCEP showed quantitative differences in metabolism between rats and mice and between female and male rats (Burka et al. 1991). Pretreatment of the rats with the mixed function oxidase inhibitor SK 525A, which should have led to accumulation of parent compound, did not result in increased neurotoxicity, which led Burka et al. (1991) to suggest that a metabolite rather than TCEP produces neurotoxicity. This, however, seems to be in conflict with the observation that at the time of seizure activity, only unmetabolized TCEP was detected in extractions of brain cortical tissues from individual rats. In addition, further experiments showed some evidence that in pooled tissues, the unmetabolized TCEP/metabolite ratio was greater for cortical tissues of female rats (the more sensitive gender) than male rats (Herr et al. 1991). *In vitro* studies with liver preparations from humans and rats also showed differences in the metabolism of TCEP between species and between male and female rats (Chapman et al. 1991). For example, both liver slices and microsomes from humans and male rats metabolized TCEP to bis(2-chloroethyl) hydrogen phosphate, 2-chloroethanol, and three unidentified metabolites. However, TCEP was metabolized by liver slices from female rats, but not by liver microsomes from female rats. In addition, TCEP was metabolized by rat plasma, without sex differences, but not by human plasma or whole blood.

The metabolism of TnBP has been studied in rats and minipigs. SOCMA (1992, 1994) conducted studies in both species and reported that phase II metabolism appeared to be a much more significant biotransformation route in minipigs than in rats. In neither species did there appear to be significant differences in the metabolic profile between males and females. The role of metabolism of TnBP in the toxicity of this substance is not known. Intermediate- and chronic-duration toxicity studies with TnBP in rats showed the urinary bladder to be the most sensitive tissue, as it caused urinary bladder hyperplasia, which appeared to develop into urinary bladder tumors after chronic-duration exposure (Arnold et al. 1997; Auletta et al. 1998a; FMC 1985a; Tyl et al. 1997). The mechanism by which this occurs is not known, but it has been suggested that it may involve one or more metabolites, particularly dibutyl phosphate (Arnold et al. 1997).

TCP induced adrenal gland and ovarian lesions in rats and liver lesions in male mice (NTP 1994). The TCP mixture used consisted of 18% dicresyl phosphate esters and 79% tricresyl phosphate esters. Two of the tricresyl phosphate esters were identified as tri-*m*-cresyl phosphate (21%) and tri-*p*-cresyl phosphate (4%) with no detectable tri-*o*-cresyl phosphate (<0.1%). What the role of metabolism may have been in the induction of the adrenal, ovarian, and liver lesions reported in the NTP (1994) and other studies is unknown. However, the multifocal axonal degeneration observed in the spinal cord of mice treated with ≥100 mg TCP/kg/day in the 13-week gavage study (NTP 1994) was likely due to the generation of a potent delayed neurotoxic saligenin cyclic phosphate metabolite as a result of the metabolism of *o*-methylphenyl compounds present in the mixed triester fraction. This has been studied in detail for tri-*o*-cresyl phosphate (e.g., Abou-Donia and Nomair 1986; Eto et al. 1962).

Excretion. Studies of elimination of some of the selected phosphate ester flame retardants indicate that for most of them the urine is the main route of elimination and that, for some of them, there are differences between species and between male and female animals. For example, a comparative study of TDCP, TCPP, and TCEP reported that in rats, approximately 90% of the administered TCEP was excreted in the urine, whereas 60% of TCPP and 40% of TDCP were excreted in the urine (Minegishi et al. (1988). It also appeared that enterohepatic circulation occurred for TCEP and TCPP, but not TDCP. A study with TCEP reported that at high doses, female rats excreted less cumulative TCEP-derived radioactivity in urine and feces than males over a 24-hour period (Herr et al. 1991). It was also shown that male mice eliminated TCEP-derived radioactivity significantly faster than male or female rats during an 8-hour period after a single gavage dose (Burka et al. 1991). A study with TCP showed differences between the isomers (NTP 1994). Biliary excretion of ^{14}C derived from tri-*p*-cresyl phosphate doubled when an intravenous dose increased from 2 to 20 mg/kg; however, no such dose dependency was reported following injections of tri-*o*-cresyl phosphate or tri-*m*-cresyl phosphate. All three isomers seemed to undergo considerable enterohepatic recycling. Studies with TnBP in rats and minipigs applied the same doses of the chemical onto the skin showed that rats eliminated considerably more TnBP-derived radioactivity in the urine (up to 40% of the applied dose) than minipigs (≤4% of the applied dose) over the same period of time (SOCMA 1992). This reflected reduced absorption in minipigs compared to rats, since rats and minipigs excreted similar percentages of radioactivity in the urine following intravenous administration of the chemical.

3.5.2 Mechanisms of Toxicity

Few studies were located that explored possible mechanisms of action for the most sensitive end points affected by the phosphate ester flame retardants discussed in this profile. The rat kidney was a sensitive target for TCEP, as chronic treatment resulted in increased incidence of renal tubule hyperplasia (NTP 1991a). The mechanism by which this occurred is not known. However, a recent study suggested that TCEP might alter the levels of cell cycle regulatory proteins in the kidney (Ren et al. 2008). The investigators incubated primary cultured rabbit renal proximal tubule cells with TCEP and reported that TCEP decreased cell viability, inhibited the expression of some regulatory proteins (CDK4, cyclin D1, CDK2, cyclin E), increased the expression of others ($p21^{WAF/Cip1}$, $p27^{Kip1}$), and decreased DNA synthesis and cell numbers. Whether or not this also occurs *in vivo* in rats is not known, but further research in this area would be valuable.

TCEP also induced brain lesions in rats in acute-, intermediate-, and chronic-duration studies; this was observed mostly in females (NTP 1991a, Tilson et al. 1990). The lesions occurred mostly in the hippocampus following acute- and intermediate-duration exposure and in the cerebral cortex and brain stem following chronic-duration exposure. In the acute study, the rats also exhibited seizure activity, and rats in the highest dose groups in the intermediate-duration study experienced occasional periods of hyperactivity after dosing; no clinical signs were reported in the chronic-duration study (NTP 1991a). Since in the acute study, the seizure activity and neurohistological damage were attenuated by pretreatment with atropine or chlordiazepoxide, Tilson et al. (1990) suggested that the morphological damage was related to the seizures produced by TCEP. What triggers the seizures is not known for certain, but a study of the effects of TCEP on ambulatory activity in mice suggested that TCEP may act as a GABA antagonist (Umezu et al. 1998). Through the use of various pharmacological manipulations with cholinergic antagonists and GABA agonists, the investigators determined that the TCEP-induced increased ambulatory activity was not a result of inhibition of acetylcholinesterase, but of an action as GABA antagonist. It would be useful to try to replicate these results in rats.

A characteristic effect of TnBP was the induction of urinary bladder hyperplasia in rats in intermediate- and chronic-duration studies (Arnold et al. 1997; Auletta et al. 1998a; FMC 1985a; Tyl et al. 1991). The hyperplasia was the consequence of focal urothelial necrosis. In one of the intermediate-duration studies, it was shown that the effects were reversible upon cessation of treatment and that acidification of the urine with ammonium chloride did not prevent, but attenuated, the proliferative changes (Arnold et al. 1997). The mechanism by which the urinary bladder changes occur is not known, but scanning electron

microscopy showed that the epithelial necrosis was not due to the presence of urinary calculi, microcrystalluria, or precipitate formation. Since TnBP is extensively metabolized, Arnold et al. (1997) speculated that the cytotoxicity may be due to one or more metabolites, possibly dibutyl phosphate.

TPP was one of several triaryl phosphates that were tested for effects on human nuclear receptors (Honkakoski et al. 2004). Nuclear receptors control a wide range of cellular processes and alterations in their functions can result in also a wide range of clinical manifestations. Experiments were conducted with HEK293 cells transfected with mouse or human nuclear constitutively active receptor (CAR) or pregnane X receptor (PXR) and their reported genes; the cells were incubated with vehicle, reference substances, or triaryl phosphates. The results showed TPP to be a weak activator of mouse CAR and PXR, but a greater activator of human CAR (5.5-fold) and PXR (3-fold). Additional experiments with COS-1 cells transfected with human glucocorticoid receptor (GR), progesterone receptor (PR), androgen receptor (AR), and estrogen receptor (ER) showed TPP to inhibit GR and AR in the absence of any added agonist and to inhibit testosterone-induced AR-activity by 30–40%. The significance of these findings to *in vivo* exposure situations remains to be determined. The few toxicity studies available with TPP in animals did not identify significant health effects.

Sensitive targets for TCP were the adrenal gland and ovary of rats and the liver of male mice (NTP 1994). The mechanisms by which these effects occur have not been elucidated, but some studies have provided some insight. TCP induced hypertrophy and cholesteryl lipidosis in adrenocortical interstitial cells of rats (females were more sensitive than males) and in ovarian interstitial cells of rats. Latendresse and coworkers (Latendresse et al. 1993, 1994a, 1995) discussed several potential mechanisms that could explain the elevated cholesterol in adrenocortical and ovarian interstitial cells including (1) inhibition of steroidogenesis, (2) increased *de novo* synthesis of cholesterol in target cells, and (3) increased synthesis by the liver and target cell uptake of cholesterol, and/or cholesterol storage. Of these possibilities, the most plausible seemed an alteration in the storage pathway resulting from the inhibition by TCP of nCEH, an enzyme that catalyzes the conversion of stored cholesteryl ester to free cholesterol (Latendresse et al. 1993). Such an action would result in accumulation of cholesteryl esters in adrenocortical and ovarian interstitial cells. TCP also inhibited ACAT in the adrenals. ACAT is involved in the esterification of cholesterol to form cytoplasmic lipid droplets of cholesteryl ester, a mechanism by which the cells store and conserve cholesterol in excess of that required for steroidogenesis (Latendresse et al. 1993). Male $B6C3F_1$ mice showed increased incidences of fatty change, clear foci, and ceroid pigmentation in hepatocytes after exposure to TCP for 2 years, which could indicate a disruption in lipid metabolism. However, since no such effects were reported in females, additional mechanisms are probably involved.

High doses of some phosphate flame retardants, such as TCP and TCEP, inhibit acetyl cholinesterase (AChE) by phosphorylating a serine hydroxyl group at the active esteric site of the enzyme (Abou-Donia 1995). Inhibition of AChE results in accumulation of the neurotransmitter acetylcholine in nicotinic and muscarinic receptors that triggers a series of typical signs and symptoms, the severity of which depend of the amount of organophosphorus compound absorbed (Abou-Donia 1995). Acute mild poisoning results in fatigue, giddiness, and sweating, which may be accompanied by anorexia, headache, weakness, anxiety, tremors of tongue and eyelids, miosis, impairment of visual acuity, and tightness of the chest. If exposure continues, mild poisoning may be followed by salivation, lacrimation, abdominal cramps, vomiting, sweating, slow pulse, bradycardia, fall in blood pressure, and muscular tremors. High amounts of organophosphorus compounds results in diarrhea, pinpoint and nonreactive pupils, muscular twitching, wheezing, increase in bronchial secretion, respiratory difficulty, cough, pulmonary edema, cyanosis, loss of sphincter and urinary bladder control, tachycardia, elevated blood pressure, convulsions, coma, heart block, and possibly death (Abou-Donia 1995).

Some triaryl phosphates also cause organophosphorus pesticide neurotoxicity (OPIDN), a neurodegenerative disorder characterized by a delayed onset of prolonged ataxia and upper motor neuron spasticity (Abou-Donia 1995; Abou-Donia and Lapadula 1990; Johnson 1975). The lesion is a central-peripheral distal axonopathy caused by a wallerian-type degeneration of the axon, followed by myelin degeneration of the central and peripheral nervous system (Jorner et al. 1989). The presence of the ortho-methyl group in the aromatic series seems to be essential for aromatic chemicals to be neurotoxic, which seems to be related to the metabolism of the *o*-methyl phenyl derivative to the saligenin *o*-tolyl cyclic phosphate. Neurotoxic esterase (NTE), the enzymatic activity that hydrolyzes phenyl phenylvalerate, has been proposed as a possible target for OPIDN mainly because of a good correlation established between inhibition of the enzyme by organophosphorus compounds and their ability to produce OPIDN. However, the involvement of NTE in the mechanism of OPIDN has not been established. Alternatively, evidence has emerged that supports the possibility that delayed neurotoxic organophosphorus compounds may interfere with protein kinases by competing with ATP as phosphoryl group donor and phosphorylating their serine or threonine hydroxyl residues. Such action would alter the regulation of normal neuronal processes and result in axonal degeneration (Abou-Donia 1990; Abou-Donia and Lapadula 1995).

3.5.3 Animal-to-Human Extrapolations

An animal model that can be used to predict health effects in humans resulting from exposure to any of the selected phosphate ester flame retardants has not been identified largely because there is very limited information regarding health effects of these substances in humans. Trying to predict what would happen to humans exposed to any of these chemicals based on the results from the available animal studies may be inappropriate at this time given that several studies identified significant differences in susceptibility between species for some toxic effects. For example, rats were more sensitive to the effects of TCP on the adrenal gland and ovary than mice (NTP 1994). Male mice were more sensitive to the liver effects of TCP than female mice and both sexes of rats (NTP 1994). Rats were significantly more sensitive to the effects of TnBP on the urinary bladder than mice (Arnold et al. 1997; Auletta 1991; Auletta et al. 1998a, 1998b; FMC 1985a; Tyl et al. 1997). Also, treatment of rats and mice with TCEP resulted in brain lesions only in rats, even though mice received higher doses of TCEP (NTP 1991a). The mechanisms of these differential susceptibilities have not been elucidated, but may be related to differences in pharmacokinetics between species. Some evidence for this was presented by Chapman et al. (1991) in studies of the metabolism of TCEP by liver slices and microsomes, and plasma from male and female rats and humans.

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 1997). 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 after exposure to the phosphate ester flame retardants subject of this profile.

The information available from studies in animals does not suggest that these substances have endocrine disrupting properties. Toxicity studies summarized in Section 3.2.2.2, Systemic Effects, did not find alterations in gross or microscopic appearance of endocrine glands. It should be noted, however, that except for a study of TCP, none of the studies available examined endocrine gland function as judged, for example, by levels of hormones in serum (i.e., thyroid hormones, sex hormones). Exposure of female rats to 400 mg TCP/kg/day for 20 days did not significantly affect serum levels of androstenedione or progesterone, but significantly increased serum levels of estradiol (Latendresse et al. 1995). The effect on estradiol appeared to be the result of TCP-induced alteration in liver metabolism increasing the protein-bound fraction of estradiol or nonpolar conjugated estradiol.

TCEP decreased fertility in mice in a continuous breeding protocol study following exposure of the parental generation to ≥350 mg/kg/day by gavage for approximately 14 weeks (NTP 1991b). Reduced fertility appeared to have been due primarily to alterations in sperm parameters such as concentration, motility, and abnormal forms, but a specific mechanism was not apparent. TCP reduced fertility in mice dosed with approximately 250 mg/kg/day in a continuous breeding study due to alterations in the seminiferous tubules and in sperm parameters (Chapin et al.1988). TCP also reduced fertility in male rats dosed with 400 mg/kg/day by apparently inducing abnormal Sertoli cell function (Latendresse et al. 1994b). A study by Laham et al. (1984b) reported that administration of 411 mg TnBP/kg/day to rats by gavage for 14 days induced degenerative changes in the seminiferous tubules in the testes. However, this

was based on the examination of only 4 male rats out of 10, and only one presented the lesions. A study of TDCP in which rabbits were administered up to 200 mg TDCP/kg/day by gavage for 12 weeks and then mated with untreated females showed no effect on fertility when the females were euthanized at mid-gestation and their uteri were examined (Anonymous 1977). Examination of sperm from the rabbits showed no significant alterations in quantity or quality.

Little information is available regarding tests that evaluate potential endocrine disrupting properties *in vitro*. TCEP, TnBP, and TBEP tested negative for estrogenic activity in a reporter gene expression assay using yeast cells (Nishihara et al. 2000). A substance was considered positive when its activity was >10% of the activity of 10^{-7} M 17β-estradiol. TPP was inactive (nonbinder) in a binding assay to the estrogen receptor from uteri from ovariectomized Sprague-Dawley rats (Blair et al. 2000). TPP was characterized as a moderate binder to the androgen receptor (AR) in a competitive binding assay that used a commercially obtained recombinant rat protein expressed in *E. coli* (Fang et al. 2003). The relative binding affinity of TPP was four orders of magnitude lower than that of the standard AR ligand used in the assay. TPP was also shown to inhibit the AR in COS-1 cells transfected with human AR in the absence of any added agonist to the incubation medium and also to inhibit testosterone-induced AR-activity by 30–40% (Honkakoski et al. 2004). Föllman and Wober (2006) examined the estrogenic or anti-estrogenic effects of TCEP and TCPP with the recombinant yeast reporter gene assay and in human endometrial cancer cells and reported that neither compound showed hormonal activity. No information was located for the remaining phosphate ester flame retardants discussed in this profile.

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 all 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 hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to 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, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage 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). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). 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 who all have a low glomerular filtration rate and have not 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).

No studies were located that described health effects in children following exposure to the phosphate ester flame retardants discussed in this profile. Also, no studies were located that compared the health effects of these compounds in young and adult animals to ascertain potential age-related differences in susceptibility.

A limited number of studies in animals suggest that developmental indices, especially in studies of gestational exposure alone, are not particularly sensitive to exposure to these compounds. For example, rats exposed to 200 mg TCEP/kg/day on Gd 7–15 showed piloerection, general weakness, and reduced food consumption, and 7 out of 30 died (Kawashima et al. 1983a). However, fetal parameters recorded in survivors on Gd 20 were not affected and gestational exposure did not affect neonatal viability monitored up to week 10. Pregnant mice dosed with 940 mg TCEP/kg/day on Gd 6–13 suffered a significant reduction in body weight gain, yet at delivery, there were no significant effects on the number of viable litters, number of live pups born per litter, percent survival of pups, pup birth weight, or pup weight gain (Hardin et al. 1987). Similar results were reported with TBEP (Monsanto 1985b) and TnBP (Noda et al. 1994) in rats. Doses of TBEP that induced frank signs of toxicity in the dams such as ataxia and lethargy, and reduced weight gain did not induce embryotoxicity or teratogenicity. Doses of TnBP that induced a significant reduction in adjusted weight gain on Gd 0–20 did not produce a significant difference between groups in the number of corpora lutea, implants or living fetuses, incidence of dead or resorbed fetuses, sex ratio, or body weight of the living fetuses. In a study with TDCP, doses that significantly decreased weight gain in pregnant rats did not significantly affect fetal viability or mean fetal weight or length (Stauffer Chemical Co. 1981b). TCP was not teratogenic in rats but decreased postnatal viability at doses ≥250 mg/kg/day (Carlton et al. 1987). Higher doses of 400 mg/kg/day in rats and 250 mg/kg/day in mice decreased the number of live pups per litter (Chapin et al. 1988; Latendresse et al. 1994b). These doses are considerably higher than those that induce alterations in the adrenals, ovary, or liver (NTP 1994). No developmental effects were reported in a gestational exposure study with TCPP (Kawasaki et al. 1982) or in a study with TPP administered to male and female rats in doses of up to approximately 690 mg/kg/day for 91 days before mating and continuing during gestation (Welsh et al. 1987).

In a continuous breeding protocol study conducted by NTP (1991b), treatment of the F_0 generation with ≥350 mg TCEP/kg/day significantly reduced the number of live pups per litter. In addition, the number of F_2 male pups per litter born to the treated F_1 generation was significantly lower than in controls in the groups dosed with ≥175 mg TCEP/kg/day, the lowest dose level tested; a developmental NOAEL was not identified in the study. In the absence of clear signs of parental toxicity, the mechanism of action for these effects is unknown. In a 2-generation reproduction study, the only significant developmental effect

was a significant reduction in F_1 and F_2 pup weight per litter measured 5 times from postnatal days 0 to 21 at maternal doses of approximately 217 mg/kg/day; the number of pups per litter was comparable among groups (Tyl et al. 1997). Significant reductions in maternal body weight also occurred at this level, which may have contributed to the decrease in pup weight.

No information was located regarding the pharmacokinetics of these compounds in children or regarding biomarkers of exposure or effect for these compounds in children.

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 phosphate ester flame retardants 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 phosphate ester flame retardants 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 Phosphate Ester Flame Retardants

There are no specific biomarkers that can be used to identify exposure to the subject phosphate ester flame retardants flame retardants of this profile other than the chemical themselves. TDCP was detected in adipose tissue from members of the general Canadian population (LeBel and Williams 1986) and also in seminal fluid from the U.S. general population (Hudec et al. 1981), indicating that exposure to this substance had occurred or was ongoing.

TPP was found to inhibit human blood monocyte carboxylesterase (Saboori et al. 1991), but so did a variety of organophosphorus compounds. Thus, reductions in the activity of this enzyme are not specific for TPP. No studies were located of the metabolism of these substances in humans that could have provided information regarding metabolic products in urine.

Recently, Neerathilingam et al. (2010), reported that administration of a single gavage dose of TnBP to rats induced variations of endogenous urinary metabolites such as benzoate, urea, and trigonelline along with metabolites involved in the Krebs cycle including citrate, cis-aconitate, trans-aconitate, 2-oxoglutarate, succinate, and fumarate and suggested that this could be used as a biomarker of TnBP exposure.

3.8.2 Biomarkers Used to Characterize Effects Caused by Phosphate Ester Flame Retardants

The few studies available of workers exposed to the phosphate ester flame retardants discussed in this profile did not identify any specific medical condition related to exposure (FMC 1981a, 1982a; Stouffer Chemical Company 1983a). Sutton et al. (1960) reported that red blood cell cholinesterase activity was

significantly reduced (18%) in a small group of regular operators in a TPP production plant compared to unexposed subjects. However, exposure to other chemicals, particularly organophosphate pesticides, can also reduce the activity of red blood cell cholinesterase; therefore, a reduction in red blood cell cholinesterase activity may be used as biomarker for a class of chemicals, but not for any one of the chemicals discussed in this profile. Although red blood cell acetylcholinesterase better reflects levels of acetylcholinesterase in the central nervous system, nonspecific cholinesterase (also known as pseudocholinesterase or butyrylcholinesterase) is commonly used to determine exposure to organophosphorus compounds. Plasma cholinesterase activity can be reduced 75–80% after exposure to organophosphorus compounds without significant physiological consequences (Abou-Donia 1995).

As indicated in Section 3.5.2, Mechanism of Toxicity, inhibition of acetylcholinesterase results in accumulation of acetylcholine in nicotinic and muscarinic receptors that triggers a series of typical signs and symptoms, the severity of which depend of the amount of organophosphorus compound absorbed and duration of exposure (Abou-Donia 1995). Acute mild poisoning results in fatigue, giddiness, and sweating, which may be accompanied by anorexia, headache, weakness, anxiety, tremors of tongue and eyelids, miosis, impairment of visual acuity, and tightness of the chest. If exposure continues, mild poisoning may be followed by salivation, lacrimation, abdominal cramps, vomiting, sweating, slow pulse, bradycardia, fall in blood pressure, and muscular tremors. High amounts of organophosphorus compounds results in diarrhea, pinpoint and nonreactive pupils, muscular twitching, wheezing, increase in bronchial secretion, respiratory difficulty, cough, pulmonary edema, cyanosis, loss of sphincter and urinary bladder control, tachycardia, elevated blood pressure, convulsions, coma, heart block, and possibly death (Abou-Donia 1995).

3.9 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding interactions of the phosphate ester flame retardants discussed in this profile with other unrelated chemicals or with other phosphate esters. The mechanisms of action for some of the most sensitive effects of the selected phosphate ester flame retardants have not been elucidated. For example, the mechanisms by which TCEP induces brain damage in rats, TnBP induces urinary bladder hyperplasia in rats, or TCP adrenal gland and ovarian lesions in rats and liver lesions in male mice are not known; therefore, it is difficult to anticipate the type of response that might occur following simultaneous exposure to any of these chemicals and other substances. In addition to chemical-specific effects that occurred at low doses, such as those mentioned above, phosphate esters have also shown common effects. For instance, TCEP, TnBP, and TDCP induced increases in liver weight in rodents in

long-term studies, but in the absence of information on a possible mechanism of action, any prediction of what the response would be to exposure to a mixture would be pure speculation.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to phosphate ester flame retardants than will most persons exposed to the same level of phosphate ester flame retardants in the environment. Reasons 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 phosphate ester flame retardants, or compromised function of organs affected by phosphate ester flame retardants. Populations that are at greater risk due to their unusually high exposure to phosphate ester flame retardants are discussed in Section 6.7, Populations with Potentially High Exposures.

There is no adequate information from studies in humans to determine whether there are populations unusually susceptible to the selected phosphate ester flame retardants discussed in this profile. Studies in animals have described species and gender differences in susceptibility to some of these chemicals. For example, male rats were more susceptible than females to the liver effects of TBEP (Reyna and Thake 1987a); female rats were more susceptible to brain lesions produced by exposure to TCEP than males, and rats were more susceptible than mice (NTP 1991a). Female rats were more susceptible to TCP-induced adrenal lesions than male rats and male mice were more susceptible to TCP-induced liver lesions than female mice (NTP 1994). However, making inferences into potential differences in humans based on the effects reported in studies in animals would be purely speculative at this time.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to phosphate ester flame retardants. However, 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 phosphate ester flame retardants. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to organophosphorus compounds:

Goldfrank LR, Flomenbaum NE, Lewin NA et al., eds. 2002. Goldfrank's toxicologic emergencies. 7th ed. New York, NY: McGraw-Hill, 1346-136.5.

Ellenhorn MJ, Barceloux DG. 1988. Medical toxicology: Diagnosis and treatment of human poisoning. New York, NY: Elsevier, 1617-1621.

Viccellio P, Bania T, Brent J, et al., 1988. Insecticides and pesticides. In: Emergency toxicology. 2nd ed. Philadelphia, PA; Lippincott-Raven Press, 401-413.

3.11.1 Reducing Peak Absorption Following Exposure

There have been no reports of health effects in humans induced by exposure to phosphate ester flame retardants other than reports of skin irritation and contact dermatitis in subjects exposed to TnBP, TBEP, and TPP (ACGIH 2001; Camarasa and Serra-Baldrich 1992; Carlsen et al. 1986; IPCS 1991a, 1991b). Skin irritation can be relieved by applying general measures such as removing the contaminated clothing and washing the exposed area thoroughly with soap and water (HSDB 2009). If contact with the eyes occurs, irrigation with copious amounts of water at room temperature for at least 15 minutes is recommended (HSDB 2009). In case of ingestion, emesis is not recommended because of the potential for gastrointestinal irritation. The use of activated charcoal is of unproven value in patients ingesting irritant chemicals where it may obscure the endoscopic findings when the procedure is justified (HSDB 2009). If used, it is recommended that it be administered as slurry (240 mL water per 30 g of charcoal). The usual dose is 25–100 g in adults and adolescents, 25–50 g in children (1–12 years), and 1 g/kg in infants <1 year old (HSDB 2009).

3.11.2 Reducing Body Burden

No information was located regarding reducing body burden following exposure to phosphate ester flame retardants.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The phosphate ester flame retardants discussed in this profile are not potent anticholinesterase agents, but cases of accidental or intentional acute exposure to high amounts may occur. If cholinergic signs and symptoms develop, appropriate treatment may be warranted. The following information has been extracted from HSDB (2009). Suction of oral secretions is recommended until atropine can be administered. Atropine should be administered intravenously until atropinization is achieved. Adults should receive 2–5 mg every 5–10 minutes, and children should receive 0.05 mg/kg every 10–15 minutes. This may be necessary for hours or days depending on the severity of the intoxication. Patients with moderate to severe poisoning should be treated with 2-PAM (Pralidoxime) in addition to atropine;

2-PAM is most effective if given within 48 hours for 24 hours after cholinergic manifestations have ceased. The initial recommended dose is 30 mg/kg followed by an infusion of >8 mg/kg/hour. Alternatively, adults may receive 1–2 g 2-PAM in 100 mL of 0.9% saline over 15–30 minutes follow by infusion of 500–1,000 mg/hour as a 2.5% solution. The initial dose may be repeated 1 hour and then every 3–8 hours if muscle weakness or fasciculations persist. Children may be treated with 20–50 mg/2-PAM/kg infused over a 2-hour period (maximum 2 g) as a 5% solution in 0.9% saline followed by a continuous infusion of 10–20 mg/kg/hour. Alternatively, the initial dose may be repeated in 1 hour and then every 3–6 hours if muscle weakness or fasciculations persist.

3.12 ADEQUACY OF THE DATABASE

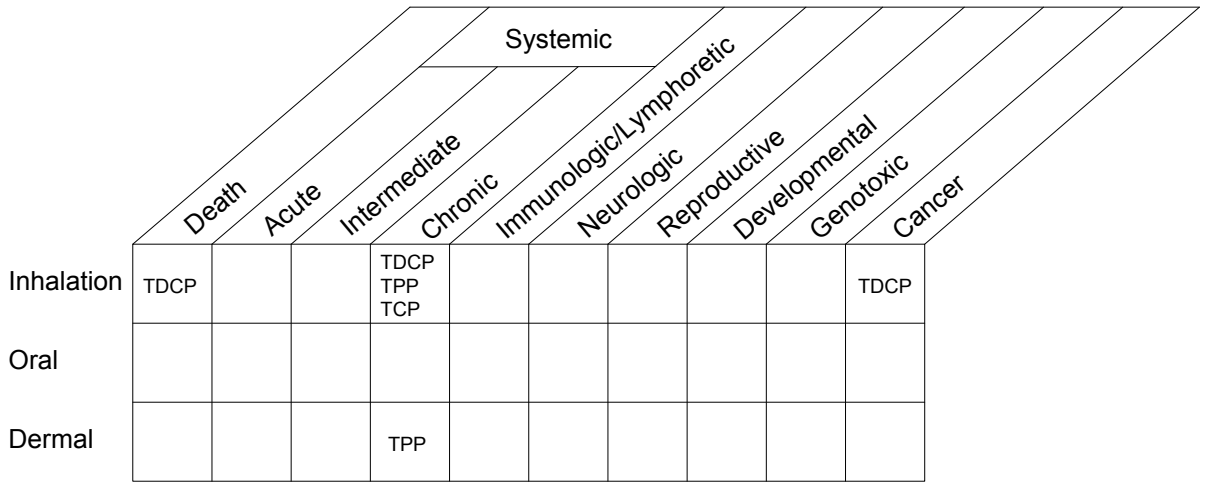
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of phosphate ester flame retardants is available. Where adequate 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 health effects (and techniques for developing methods to determine such health effects) of phosphate ester flame retardants.

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.

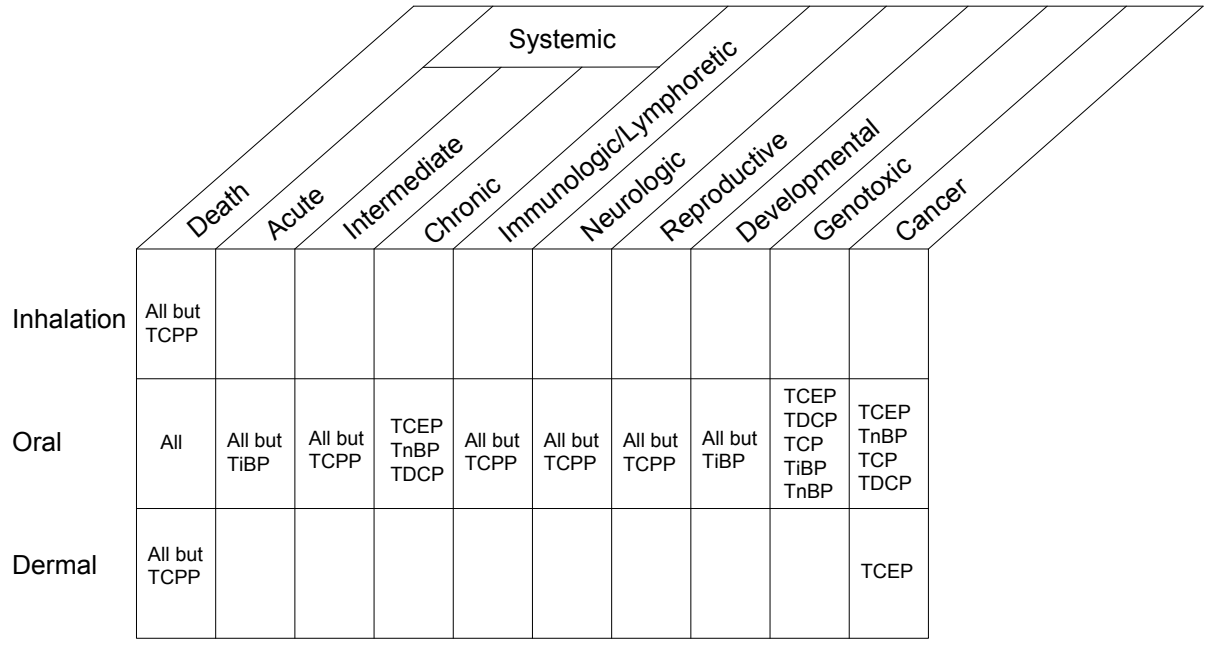
3.12.1 Existing Information on Health Effects of Phosphate Ester Flame Retardants

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to phosphate ester flame retardants are summarized in Figure 3-14. The purpose of this figure is to illustrate the existing information concerning the health effects of phosphate ester flame retardants. The presence of the acronym in a square indicates that one or more studies provide information associated with that particular effect for that particular phosphate ester. The presence of the acronym in the square 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

Figure 3-14. Existing Information on Health Effects of Phosphate Ester Flame Retardants



Human



Animal

TCEP = tris-(2-chloroethyl)-phosphate; TCP = tricresyl phosphate; TCPP = tri-(2-chloroisopropyl) phosphate; TDCP = tris(1,3-dichloo-2-propyl) phosphate; TiBP= triisobutyl phosphate; TnBP = tributyl phosphate

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.

As shown in Figure 3-14, there was very limited information on the effects in humans of the phosphate ester flame retardants discussed in this profile. The available information was derived from only a few occupational studies in which exposure was assumed to have been primarily by inhalation of vapor mists and dust. These studies provided information on morbidity and mortality of workers exposed to TDCP, TPP, and TCP. A few studies were also available that provide information on dermal effects of TPP on members of the general population.

Most of the studies available in animals were conducted by the oral route of exposure, although information on lethality due to acute high inhalation and dermal exposures was also available. Sufficient information on health effects of oral exposure to TCEP, TnBP, TBEP, TDCP, and TCP was available to derive oral MRLs for these substances, although not for all exposure durations. In general, information was available for systemic, neurological, reproductive, developmental effects, genotoxicity, and cancer; less data were located for immunological effects. Limited information was available for TPP and even less information was available for TiBP and TCPP.

The information available from animal studies was insufficient to conclusively determine whether or not the effects of the selected phosphate ester flame retardants are route-dependent; however, the toxicokinetics data for a few of these chemicals suggested that, other than portal-of-entry effects such as skin or gastrointestinal irritation, the toxicity of these substances is probably not route-dependent. In addition, the environmental monitoring data available suggested that the levels of some of these substances to which the general population might be exposed through contact or use of consumer products (including food and water), or that are commonly found in environmental media are generally orders of magnitude lower than those used in studies with experimental animals.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. No data were located regarding health effects in humans following acute exposure by any route to the phosphate ester flame retardants discussed in this profile. However, it should be clarified that there is extensive information on the effects of TOCP, one of the isomers of TCP, in humans resulting from the consumption of contaminated food items or alcohol (Abou-Donia 1995;

Abou-Donia and Lapadula 1990). As previously mentioned, TOCP, which may be found in very small concentrations in technical TCP mixtures currently being used, is not a subject of this toxicological profile. The acute inhalation studies in animals provide information mostly on lethal doses and are not adequate for derivation of acute-duration inhalation MRLs. The dermal studies available in animals were also designed to estimate lethal doses. However, it would be useful to determine whether dermal exposure to these substances results in sufficient material being absorbed to be of concern. The selection of an appropriate animal model for human dermal exposure is important; limited data with TnBP indicate that Yucatan® minipigs absorbed 10 times less TnBP through the skin than rats (SOCMA 1992). Sufficient data were available to derive acute-duration oral MRLs for TnBP and TBEP; both studies were gestational exposure studies in rats (Monsanto Co. 1985b; Noda et al. 1994). No MRLs were derived for TCEP, TDCP, TCP, TCPP, TiBP, or TPP due to either lack of studies, the studies available did not identify clear adverse effects, or did not monitor end points shown to be sensitive end points in longer-term studies. In general, and this applies also to the subsequent sections, the decision to recommend additional studies by any route for any one of phosphate ester flame retardants selected for this profile should take into account information regarding environmental monitoring, potential routes of exposure for the population, and information on levels of these substances in biological fluids from a representative sample of the population. While recognizing that it would be useful for health assessors to have MRLs for all of these chemicals, this information should help prioritize the need for additional studies.

Intermediate-Duration Exposure. No specific information was located regarding health effects in humans following intermediate-duration exposure to the selected phosphate ester flame retardants, although some workers exposed to TDCP, TPP, or TCP in the studies conducted by Stauffer Chemical Co. (1983a), Sutton et al. (1960), and FMC (1981a, 1982a) may have been exposed for <1 year. No intermediate-duration inhalation studies in animals were located. Intermediate-duration dermal studies in rabbits were available for TPP (Monsanto Co. 1979) and TBEP (Monsanto Co. 1985d). These studies evaluated systemic toxicity end points as well as effects at the application site. The only effects reported were dermal effects in rabbits treated with ≥10 mg TBEP/kg/day. Intermediate-duration oral studies, adequate for use as the basis for MRL derivation, were available for TCEP, TnBP, TBEP, TCP and TDCP. The MRL for TCEP was based on necrosis of hippocampal neurons in female rats in a 16-week gavage study (NTP 1991a). That study also provided information on a wide range of systemic end points. In addition, a continuous breeding protocol study in mice was available (NTP 1991b). Several intermediate-duration studies in rats exposed to TnBP in the diet were available (Arnold et al. 1997; FMC 1985a; Laham et al. 1985a; Tyl et al. 1997). These studies identified the urinary bladder of rats as a sensitive target for TnBP and the intermediate-duration oral MRL for this chemical was based on this end

point (Arnold et al. 1997). Information on reproductive and neurological effects of TnBP was also available (Arnold et al. 1997; Healy et al. 1995). The intermediate-duration oral MRL for TBEP was based on hepatic effects in rats exposed to TBEP in the diet in the only wide scope study available for this chemical (Reyna and Thake 1987a). The intermediate-duration oral MRL for TCP was based on ovarian effects in rats in a comprehensive dietary study (NTP 1994). An intermediate-duration oral study that evaluated reproductive parameters in male rabbits was available for TDCP (Anonymous 1977). The limited scope of this study precluded its use for MRL derivation. However, data from the interim assessment of rats after 12 months of treatment in the 24-month bioassay conducted by Stauffer Chemical Co (1981a) were used to derive an intermediate-duration oral MRL for TDCP. Intermediate-duration oral studies with TPP provided information regarding organ weights in rats (Sutton et al. 1960), neurobehavioral effects in rats (Sobotka et al. 1986), reproductive and developmental effects in rats (Welsch et al. 1987), and immunological effects in rats (Hinton et al. 1996). However, no MRL was derived for TPP based on no clear evidence of toxicity provided in these studies. Only one intermediate-duration study that reported effects of unknown toxicological significance in rats was located for TiBP (Naylor and Ribelin 199). No intermediate-duration oral studies were available for TCPP. As indicated above, monitoring data as well as potential for exposure should be considered in the decision to recommend conducting studies to fill the data gaps for individual triphosphate ester flame retardants. Since these chemicals are usually found as mixtures at hazardous waste sites and in environmental media, there is a need to conduct toxicity studies for mixtures to determine how these chemicals interact with each other and how this affects their toxicity.

Chronic-Duration Exposure and Cancer. Studies by Stauffer Chemical Co. (1983a), Sutton et al. (1960), and FMC (1981a, 1982a) provide data on workers exposed chronically to TDCP, TPP, and TCP respectively. Neither study found significant associations between exposure to these substances and adverse health effects. In both cases, the primary route of exposure is assumed to have been inhalation, but dermal exposure probably also occurred. No information was located regarding health effects in humans following chronic exposure to the other phosphate ester flame retardants discussed in this profile. No chronic inhalation or dermal studies were identified for any of the phosphate ester flame retardants discussed in this profile. Chronic data were available for TCEP in an NTP (1991a) bioassay that examined a wide range of end points in rats and mice treated with the chemical by gavage. The most sensitive effects identified in that study were brain lesions in female rats and renal tubule lesions in male and female rats. A chronic-duration oral MRL was derived for TCEP based on the renal lesions in female rats; additional chronic studies for this chemical do not seem necessary. Long-term studies were also available for TnBP in rats and mice (Auletta et al. 1998a, 1998b). The urinary bladder from rats was the

target for TnBP toxicity; treated rats showed an increased incidence of urinary bladder hyperplasia. Because the incidences were lower than those seen in intermediate-duration studies at comparable doses, the intermediate-duration oral MRL was also adopted as the chronic-duration MRL (a detailed explanation can be found in Section 2.3). A chronic-duration study in rats treated with TDCP in the diet was available (Stauffer Chemical Co. 1981a). Liver and kidneys effects occurred at the lowest dose tested and the latter served as the basis for derivation of a chronic-duration oral MRL for TDCP. Additional studies for TDCP do not seem necessary. A 2-year bioassay in rats and mice was available for TCP (NTP 1994); histological alterations in the ovary of rats served as the basis for derivation of a chronic-duration oral MRL for TCP. No chronic-duration oral studies were identified for TBEP, TPP, TiBP, or TCPP. It seems reasonable that before conducting chronic-duration studies with these chemicals, a more or less complete intermediate-duration database be available in which the most sensitive end points have been identified in well-conducted studies. As previously mentioned, studies of the toxicity of mixtures of phosphate esters flame retardants would be valuable since these substances are generally found as mixtures at hazardous waste sites and other environmental media.

No associations between exposure to TDCP and cancer were reported in a retrospective cohort study that examined the mortality experience of workers employed in the manufacture of TDCP (Stauffer Chemical Co. 1983a). Similar findings were reported for workers involved in the manufacture of TCP (FMC 1982a). No further information was located regarding exposure to the selected phosphate ester flame retardants and cancer in humans. TCEP, TnBP, TDCP, and TCP have been tested for carcinogenicity in long-term oral bioassays. Treatment of rats with TCEP by gavage increased the incidence of renal tubule adenoma or carcinoma in males and renal tubule adenomas in females (NTP 1991a). TCEP also induced a nonsignificant increase in the incidence of a rare renal tubule neoplasm in male $B6C3F_1$ mice. TCEP increased, although not significantly, the incidence of tumors of the Harderian gland in female $B6C3F_1$ mice. In another study, dietary treatment of mice with TCEP increased the incidences of renal and liver tumors in male mice and forestomach tumors and leukemia in female mice (Takada et al. 1989). In dermal assays, TCEP showed no significant carcinogenic, initiating, or promoting activity on the skin of female mice (Sala et al. 1982). TnBP increased the incidence of urinary bladder cancer in male rats (Auletta et al. 1998a) and hepatocellular adenomas in male mice (Auletta et al. 1998b). TDCP increased the incidence of neoplastic nodules in the liver of male and female rats and the incidence of hepatocellular carcinomas in male rats (Stauffer Chemical Co. 1981a). TDCP also increased the incidence of renal cortical tumors in male and female rats, interstitial cell tumors in the testes in male rats, and adrenocortical adenomas in female rats. TCP was not carcinogenic in oral bioassays in rats and mice (NTP 1994). Additional standard cancer studies for these chemicals seem unnecessary, but mechanistic

studies are lacking. For example, further research is needed to elucidate the mechanism by which TnBP induces urinary bladder cancer in rats, which does not seem to be related to changes in urine pH and composition or to physical agents such as calculi, microcrystals, or precipitate (Auletta et al. 1998a). It would be valuable to determine also whether or not urinary bladder hyperplasia is a precursor of bladder cancer. The mechanisms of carcinogenicity for TCEP or TDCP also are not known. Studies of subcellular distribution of radioactivity derived from phosphate ester flame retardants, such as those conducted by Morales and Matthews (1980) with TDCP can provide information on the possible formation of adducts with cellular macromolecules that may be involved in carcinogenicity. No information was located regarding cancer effects in animals exposed to TBEP, TPP, TiBP, or TCPP. Knowing the extent of exposure of the general population to these substances may be a factor to consider in deciding whether or not to conduct cancer studies with these chemicals.

Genotoxicity. No information was located regarding genotoxic effects of the selected phosphate ester flame retardants in humans. All of the selected phosphate ester flame retardants have been tested for genotoxic effects in *in vitro* assays in various strains of *S. typhimurium.* With a few exceptions, the results have been mostly negative. Positive results were reported for TDCP in the presence of metabolic activation in two studies (Gold et al. 1978; NTP 1983) and in one study both in the presence and absence of metabolic activation (Mortelmans et al. 1986). It is unclear what the value would be of conducting additional mutagenicity studies in prokaryotic organisms. *In vitro* assays in mammalian cells yielded negative results for TBEP (Mobil Oil Corporation 1991; Monsanto Co. 1985c), TnBP (Batt et al. 1992), and TCP (NTP 1994). Mixed results were reported for TCEP (Föllmann and Wober 2006; Galloway et al. 1987; NTP 1991a; Sala et al. 1982), TCPP (Föllmann and Wober 2006), and TDCP (Brusick et al. 1979; Dybing et al. 1983; Søderlund et al. 1985; Stauffer Chemical Co. 1981b); no studies were located for TPP or TiBP. It is difficult to determine whether the different results with a specific test among the phosphate ester flame retardants represent true mechanistic differences or reflect methodological differences. Additional tests will probably not resolve the issue. However, as mentioned above, additional studies of the potential binding of phosphate ester flame retardants or their metabolites, particularly of those that have shown to induce cancer in animals, to cellular macromolecules could provide valuable information regarding mechanisms of carcinogenicity. TDCP, TCEP, TiBP, and TnBP yielded negative results in tests for clastogenicity *in vivo* (Batt et al. 1992; Brusick et al. 1979; Flowers and Garrett 1992; Sala et al. 1982; Stauffer Chemical Co. 1981b; Vogel and Nivard 1993). *In vivo* studies with TCPP, TBEP, and TPP would be valuable.

Reproductive Toxicity. No information was located regarding reproductive effects in human exposed to the selected phosphate ester flame retardants. TCEP, TnBP, TPP, TDCP, and TCP have been tested for effects on fertility in oral studies. TCEP reduced fertility in mice in a continuous breeding protocol study (NTP 1991b). Both sexes were adversely affected, but the males appeared to be more sensitive than females, as all sperm end points examined (concentration, motility, and percent abnormal) were affected. In a 2-generation reproductive toxicity study in rats, TnBP had no significant effect on mating and fertility rates, or on gross and microscopic appearance of the reproductive organs in the F_0 or F_1 generations (Tyl et al. 1997). TDCP did not affect fertility in male rabbits treated by gavage for 12 weeks and then mated with untreated females (Anonymous 1977). Fertility indices (number pregnant, corpora lutea, implantations, implantation efficiency, resorptions) were not affected in male or female rats dosed with TPP for 91 days before mating (Welsh et al. 1987). TCP reduced fertility in rats (Carlton et al. 1987; Latendresse et al. 1994b) and mice (Chapin et al. 1988); males were principally affected. In addition, TCP induced histological alterations in the ovary of rats and this occurred at low doses of TCP (NTP 1994). TBEP has not been tested for effects on fertility, but acute- and intermediate-duration studies in rats reported no gross or microscopic alterations in the reproductive organs of males and females (Komsta et al. 1989; Reyna and Thake 1987a). Exposure of rats to TiBP in the diet for 13 weeks also did not result in gross or microscopic alterations in the reproductive organs (Naylor and Ribelin 1990). In the absence of any evidence indicating that the reproductive organs are sensitive targets for TBEP or TiBP, fertility testing does not appear necessary at this time. No relevant data were located for TCPP; acute and intermediate oral studies that might be conducted with this chemical should include examination of the reproductive organs to determine potential reproductive effects.

Developmental Toxicity. No information was located regarding developmental effects in humans exposed to the phosphate ester flame retardants discussed in this profile. The developmental effects of TCEP (Hardin et al. 1987; Kawashima et al. 1983a), TnBP (Noda et al. 1994), TBEP (Monsanto 1985b), TDCP (Stauffer Chemical Co. 1981b), TPP (Welsch et al. 1987), TCPP (Kawasaki et al. 1982), and TCP (Carlton et al. 1987; Chapin et al. 1988; Latendresse et al. 1994b) have been examined in oral studies that included exposure during gestation. In general, these studies did not report fetotoxicity or teratogenicity even at doses that produced maternal toxicity. However, in a continuous breeding protocol study in mice exposed to TCEP, there was a decrease in the number of live male F_2 pups per litter (NTP 1991b). Also, in a 2-generation reproductive study in mice exposed to TnBP, there was reduction in F_1 and F_2 pup weight per litter during postnatal days 0–21 (Tyl et al. 1997). TCP reduced postnatal viability in rats (Carlton et al. 1987) and reduced the number of rat pups per litter (Latendresse et al. 1994b) and mice (Chapin et al. 1988). Additional developmental studies for these seven phosphate ester flame retardants

do not seem necessary at this time. However, since no relevant information was located for TiBP, conducting a preliminary test in mice, as done for TCEP by Hardin et al. (1987), may be appropriate.

Immunotoxicity. No studies were located that examined immunological effects in humans following exposure to the selected phosphate ester flame retardants discussed in this document. However, there have been reports of allergic dermal reactions to products containing TPP (Camarasa and Serra-Baldrich 1992; Carlsen et al. 1986). Oral toxicity studies conducted with the selected phosphate ester flame retardants, except TCPP, did not report significant alterations in the gross or microscopic appearance of lymphoreticular tissues. However, immunocompetence was examined only in studies in rats exposed to TPP (Hinton et al. 1996) and TCP (Banerjee et al. 1992). No significant alterations in the humoral response to immunization with SRBC were reported in the study with TPP. However, exposure to TCP reduced the humoral and cell-mediate immune response in rats. Any extrapolation to what might occur in humans based on this limited information in animals would be purely speculative at this time. Since very limited information is available regarding the immunotoxicity of the remaining phosphate ester flame retardants, studies performing a Tier I battery of tests would help evaluate the possibility that exposure to these chemicals might cause subtle alterations in immune parameters.

Neurotoxicity. With the exception of a study of workers exposed to TCP (FMC 1981a), no relevant information was located regarding neurological effects in humans exposed to the selected phosphate ester flame retardants. FMC (1981a) reported that workers exposed to triaryl phosphates did not exhibit adverse clinical neurological alterations or significant alterations in peripheral sensory and motor nerve conduction velocities. It is worth noting that there are many reports of neurotoxic effects in humans attributed to exposure to food items contaminated with TOCP ranging from single cases to episodes involving thousands of individuals (IPCS 1990). TOCP occurs as a contaminant in commercial TCP mixtures, usually in low concentrations (<0.1%). Studies in animals have provided information regarding the effects of TCEP, TnBP, TBEP, TDCP, TCP, TiBP, and TPP on the nervous system. No relevant data were located for TCPP, but before conducting neurotoxicity studies for this chemical, it may be desirable first to determine whether there is any indication of neurotoxicity in a general toxicity study. The nervous system did not seem to be a particularly sensitive target for this group of chemicals except for TCEP. While effects were reported in some studies, they tended to occur at the highest dose levels. Some of the data available were limited to reports of lack of clinical signs and histopathological effects in the brain and spinal cord of rats in a 24-month study with TDCP (Stauffer Chemical Co. 1981a) or of similar observations in rats dosed with TiBP for 13 weeks (Naylor and Ribelin 1990). TPP was evaluated for neurobehavioral effects in rats in a 4-month dietary study; no significant effects were reported (Sobotka et

al. 1986). TnBP reduced nerve conduction velocity and altered the morphology of the nerve in rats (Laham et al. 1983), but did not significantly alter parameters of a functional observation battery in acute- or intermediate-duration studies (Healy et al. 1995). TBEP was also reported to cause a reduction in nerve conduction velocity in rats in an intermediate-duration study (Reyna and Thake 1987b). TCP induced spinal cord degeneration in mice in an intermediate-duration study (NTP 1994) and reduced hindlimb grip strength in rats and mice also in intermediate-duration studies (NTP 1994), but no significant neurological alterations were reported in rats or mice in chronic-duration studies (NTP 1994). Since the TCP mixture used contained <1% TOCP, the spinal cord degeneration observed in mice may have been due to the presence of *o*-cresol groups in the mixed trimester fraction; studies aimed at identifying the isomeric contaminants responsible for the neuropathy would be valuable. TCEP affected the nervous system in acute-, intermediate-, and chronic-duration studies. Treatment with TCEP caused morphological damage to the hippocampus of rats in acute- (Tilson et al. 1990) and intermediate-duration (NTP 1991a) studies and to the cortex and brain stem in a chronic-duration study (NTP 1991a); rats were considerably more sensitive than mice, and female rats appeared more sensitive than males. In the acute study, rats suffered seizures 60–90 minutes after dosing and showed mildly impaired learning behavior 3 weeks after dosing (Tilson et al. 1990). Pharmacokinetics studies have been conducted that tried to identify the chemical entity responsible for the physiological and morphological effects of TCEP as well as provide an explanation for the differential susceptibility between rats and mice and between female and male rats (Burka et al. 1991; Herr et al. 1991). These issues have not been resolved and continued research seems necessary. The mechanism by which TCEP or a metabolite induces seizures in rats has not been elucidated, although there is some evidence indicating that it acts as a GABA antagonist (Umezu et al. 1998). Further research on this specific issue would also be valuable.

Epidemiological and Human Dosimetry Studies. Information on health effects in humans exposed specifically to the selected phosphate ester flame retardants (not to mixtures) was derived from a study of workers employed in the manufacture of TDCP (Stauffer Chemical Co. 1983a), a study of operators in a TPP production plant (Sutton et al. 1960), and studies of workers exposed to triaryl phosphates (FMC 1981a, 1982a). In none of these studies were there associations found between exposure to the phosphate ester flame retardants and adverse health conditions. In addition, there are some reports of allergic dermal reactions to products containing TPP (Camarasa and Serra-Baldrich 1992; Carlsen et al. 1986). Follow-up evaluations of individuals who may have been occupationally exposed to any of these substances would provide valuable information. No specific group from the general population that may have been subjected to unusually high concentrations of these chemicals was identified. Studies in animals have identified sensitive targets for some of the phosphate ester flame

retardants discussed in this profile (i.e., brain areas for TCEP, urinary bladder for TnBP, liver for TBEP, adrenal gland and ovary for TCP). Studies have also shown differences in susceptibility between species. Therefore, there is no basis to speculate, based on studies in animals, what health effects might be observed (or what health effects one should look for) in subjects who might experience repeated exposure to these compounds.

Biomarkers of Exposure and Effect.

Exposure. There are no specific biomarkers that can be used to identify exposure to the phosphate ester flame retardants flame retardants subject of this profile other than the chemicals themselves. Studies of levels of phosphate ester flame retardants in blood and urine of workers who are exposed to higher levels of these substances than the general population would be helpful to characterize potential biomarkers, which could be the parent compound and/or metabolites. These biomarkers could then be looked for in biological fluids of members of the general population, particularly children, to ascertain the prevalence and magnitude of exposure to these chemicals, if the existing analytical methods are sensitive enough to do so.

Effect. There are no biomarkers of effect specific for the selected phosphate ester flame retardants. Exposure to high amounts of some of these chemicals, may reduce the activity of plasma and red blood cell cholinesterase, but this can also occur following exposure to organophosphorus compounds in general. Research to identify reliable biomarkers for exposure to these chemicals would be useful.

Absorption, Distribution, Metabolism, and Excretion. There were no data regarding the toxicokinetics of the selected phosphate ester flame retardants in humans except for a study that investigated the metabolism of TCEP in human liver preparations *in vitro* (Chapman et al. 1991) and a study that investigated the pulmonary retention of TPP in volunteers exposed to an aerosol of this chemical (Landahl et al. 1951, 1952). There are no data regarding the toxicokinetics of these chemicals in animals following inhalation exposure, but this information would likely do little to further our understanding of the pharmacokinetics processes of these substances. There are studies in animals that provide information regarding the oral absorption of TCEP (Herr et al. 1991), TDCP (Nomeir et al. 1981), TCP (NTP 1994), TnBP (SOCMA 1992), and dermal absorption of TDCP (Nomeir et al. 1981) and TnBP (SOCMA 1992). Tissue distribution data are available for TCPP, TCEP, TDCP, TCP, and TnBP following oral exposure (Herr et al. 1991; Minegishi et al. 1988; NTP 1994; SOCMA 1992), for TDCP and TnBP following dermal exposure (Nomeir et al. 1981; SOCMA 1992), and for TDCP following

intravenous administration (Lynn et al. 1981). The metabolism of TCEP, TDCP, TnBP, and tri-*p*-cresyl phosphate has been well studied (Burka et al. 1991; Chapman et al. 1991; Kurebayashi et al. 1985; Lynn et al. 1981; Nomeir et al. 1981; SOCMA 1992, 1994; Suzuki et al. 1984a, 1984b). These studies were able to identify and quantify metabolites in excreta and propose metabolic pathways for these phosphate ester flame retardants. The excretion routes for TDCP, TCPP, TCEP, TCP, and TnBP (Burka et al. 1991; Herr et al. 1991; Kurebayashi et al. 1985; Minegishi et al. 1988; Suzuki et al. 1984a) have been studied in animals following oral exposure and for TnBP following dermal exposure (SOCMA 1992). It would be useful to have information on the toxicokinetics of TBEP, TPP, and TiBP. Since phosphate ester flame retardants are usually found as mixtures in the environment, it would be valuable to have information on toxicokinetic interactions among these chemicals and how these interactions can potentially affect their toxicity.

Comparative Toxicokinetics. Relevant information is available for TCEP and TnBP. Herr et al. (1991) studied the distribution of radioactivity in the brain of male and female rats following oral administration of ^{14}C-TCEP and reported no significant differences between the sexes, although there was suggestive evidence that the parent compound/metabolite ratio in cortical tissues was greater in females than in males 2 hours after a single dose of TCEP. Herr et al. (1991) also reported slower excretion of metabolic products in females than in males. Burka et al. (1991) investigated the metabolism and excretion of TCEP-derived radioactivity in female and male rats and in male mice. The results showed quantitative differences in metabolic products between rats and mice and between male and female rats and slower elimination of radioactivity in the urine in rats than in mice. A study of the metabolism of TCEP by *in vitro* liver preparations and plasma from humans and male and female rats also showed differences between the rat sexes and between rats and humans (Chapman et al. 1991). Studies with TnBP showed that rats absorb about 10 times less TnBP through the skin than minipigs and that there are also differences in the metabolic disposition of TnBP between rats and minipigs (SOCMA 1992, 1994). No comparative data were located for other phosphate ester flame retardants. If the metabolism of any of the selected phosphate ester flame retardants can be elucidated in humans, for example, through the analysis of blood and urine samples from workers exposed to these compounds, it would be valuable to have data in more than one animal species to identify the best possible animal model for human risk assessment.

Methods for Reducing Toxic Effects. Acute exposure to high amounts of phosphate ester flame retardants may inhibit cholinesterase activity to the extent that clinical signs and symptoms indicative of cholinergic stimulation may occur. If such situation arises, there are well-established treatment

procedures. Since no population has been identified as having been subjected or currently undergoing exposure to excessive amounts of phosphate ester flame retardants, attempts to propose studies of specific methods to reduce possible adverse effects do not appear warranted at this time.

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.

There are no studies that specifically address exposure to phosphate ester flame retardants in children. There have been some case reports of allergic dermatitis in subjects exposed to products containing TPP (Camarasa and Serra-Baldrich 1992; Carlsen et al. 1986). It is reasonable to assume that this may also occur in children. There is no information on whether exposure to phosphate ester flame retardants alters the developmental process in humans. Gestational exposure studies have been conducted with six out of the eight selected phosphate ester flame retardants discussed in this profile, the exception being TiBP. In general, these studies showed that developmental end points are not particularly sensitive. The possibility that phosphate ester flame retardants may have endocrine-disrupting ability in mammals has not been systematically studied.

There are no data to evaluate whether pharmacokinetics of phosphate ester flame retardants in children are different from adults. There is no information on whether these substances can cross the placenta and there are no studies on whether they can be transferred from mother to offspring through maternal milk. Cross-fostering studies can provide important information regarding the role of *in utero* vs. lactation exposure to phosphate ester flame retardants in normal development.

Research into the development of sensitive and specific biomarkers of exposures and effects for phosphate ester flame retardants would be valuable for both adults and children. There are no data on the interactions of phosphate ester flame retardants with other chemicals in children. There are no pediatric-specific methods to reduce peak absorption, reduce body burdens, or to interfere with the mechanisms of action of these compounds. Based on the information available, it is reasonable to assume that the supportive methods recommended for maintaining vital functions in adults will also be applicable to children.

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 pertaining to the phosphate ester flame retardants subject of this profile were identified in the Federal Research in Progress (FEDRIP 2009) database.

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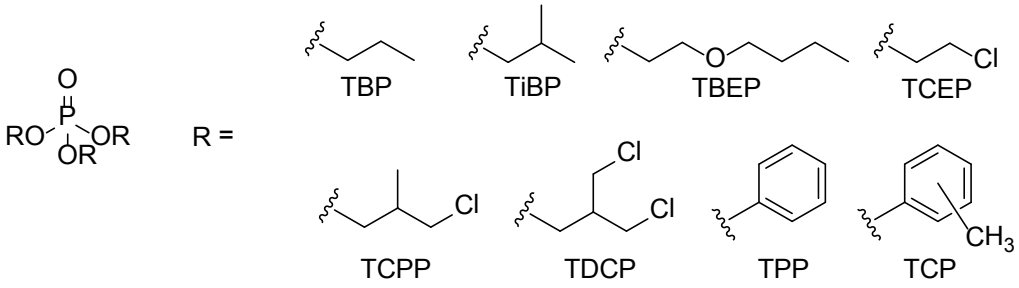
4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Phosphate esters are considered derivatives of the tri protic acid, phosphoric acid $O=P(OH)_3$, with the general formula of $R_xH_{3-x}PO_4$ where x=1 for mono, x=2 for di, and x=3 for triesters. Phosphorus has a high affinity for oxygen due to the difference in electronegativity (1.4), and consequently, the P=O bond possesses more σ character than π character. Therefore, the P=O bond, which dominates phosphate chemistry, can be more accurately depicted as a coordinate bond, P→O, or as $P^+–O^-$. These phosphoric acid esters are often referred to as organophosphates. Trialkyl, triaryl, and trihaloalkyl/aryl, and mixed phosphate esters possess a central phosphorus atom with an oxidation state of +5 and an approximate tetrahedral geometry (Fee 2005; Gard 2005).



A wide array of substituents can occur as esters of phosphates. In many cases, all of the substituents are identical, as is the case for this profile; however, variable, mono-, di-, or tri-substituted as well as mixed substituents are common. The selected compounds, shown above, are trisubstituted, contain identical substituents, and fall into the following categories: alkyl (TnBP, TiBP), alkyl ether (TBEP), chloroalkyl (TCEP, TCPP, TDCP), and aryl (TPP, TCP) phosphate esters. Although the majority of selected compounds are discrete chemicals, commercial formulations of TCPP may contain minor amounts of structural isomers (NAS 2000). In addition, the commercial mixture of TCP as described here is an unspecified mixture of isomers, but commercial mixtures are predominantly meta and para isomers with less than 1% ortho (Winder and Balouet 2002). Table 4-1 lists common synonyms, trade names, and other pertinent information to identify the selected phosphate esters for this profile.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 4-2 lists important chemical and physical properties of the selected phosphate esters.

Table 4-1. Chemical Identity of Selected Phosphate Ester Flame Retardants[a]

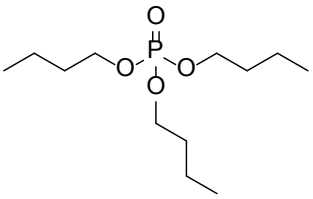
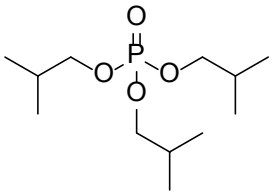
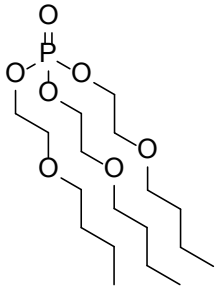
Characteristic	Tributyl phosphate	Triisobutyl phosphate	Tris(2-butoxyethyl) phosphate
Synonym(s)	TnBP; butyl phosphate; phosphoric acid tributyl ester; tri-n-butyl phosphate; tributoxyphosphine oxide	TiBP; isobutyl phosphate; phosphoric acid, tris(2-methylpropyl) ester	TBEP; tri(2-butoxyethyl) phosphate; tributoxyethyl phosphate; 2-butoxyethanol, phosphate; ethanol, 2-butoxy-, phosphate (3:1); phosphoric acid, tributoxyethyl ester; tributyl cellosolve phosphate
Registered trade name(s)	Disflamoll TB; Celluphos 4; Phosflex 4[b]; Skydrol LD-4[b]	No data	Kronitex KP-140; KP 140; Phosflex T-bep
Chemical formula	$C_{12}H_{27}O_4P$	$C_{12}H_{27}O_4P$	$C_{18}H_{39}O_7P$
Chemical structure			
Identification numbers:			
CAS registry	126-73-8	126-71-6	78-51-3
RTECS[c]	TC7700000	No data	KJ9800000
EPA hazardous waste	No data	No data	No data
EPA/OPP pesticide Code	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	1678	No data	2564
EINECS	204-800-2	204-798-3	201-122-9
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Selected Phosphate Ester Flame Retardants[a]

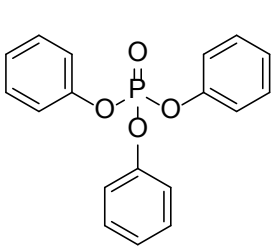
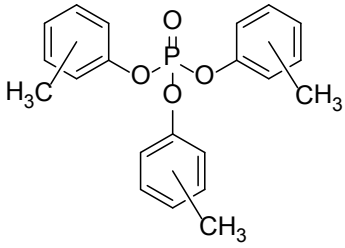
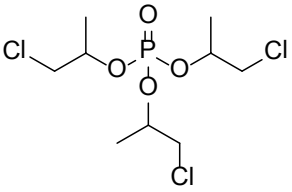
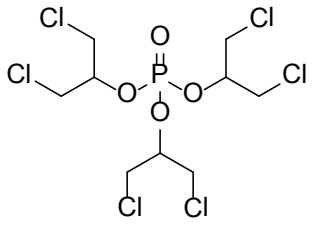
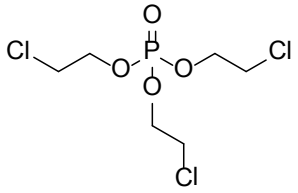
Characteristic	Triphenyl phosphate	Tricresyl phosphate	Tri-(2-chloroisopropyl) phosphate
Synonym(s)	TPP; phosphoric acid, triphenyl ester; triphenoxyphosphine oxide	TCP; phosphoric acid, tris(methylphenyl) ester; phosphoric acid, tritolyl ester; tris(methylphenyl) phosphate	TCPP; tris(1-chloro-2-propyl) phosphate; tris(2-chloroisopropyl) phosphate[d]; phosphoric acid, tris(2-chloro-1-methyl) ether[e]
Registered trade name(s)	Celluflex TPP; Disflamoll TP; Phosflex TPP	Kronitex TCP[b]; Phosflex 179A; Disflamoll TKP; Lindol; Celluflex 179C	Hostaflam OP 820; Amgard TMCP; Fyrol PFC[d]; Antiblaze 80[f]
Chemical formula	$C_{18}H_{15}O_4P$	$C_{21}H_{21}O_4P$	$C_9H_{18}Cl_3O_4P$
Chemical structure			
Identification numbers:			
CAS registry	115-86-6	1330-78-5	13674-84-5
RTECS[c]	TC8400000	TD0175000	TC9000000
EPA hazardous waste	No data	No data	No data
EPA/OPP Pesticide Code	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	IMO 9.0	UN 2574; IMO 6.1	No data
HSDB	2536	6774	No data
EINECS	204-112-2	215-548-8	237-158-7
NCI	No data	C61041	No data

Table 4-1. Chemical Identity of Selected Phosphate Ester Flame Retardants[a]

Characteristic	Tris(1,3-dichloro-2-propyl) phosphate	Tris(2-chloroethyl) phosphate
Synonym(s)	TDCP; tris(1,3-dichloroisopropyl) phosphate; tris(1-chloromethyl-2-chloroethyl)phosphate; 2-propanol, 1,3-dichloro-, phosphate (3:1)	TCEP; trichlorethyl phosphate; phosphoric acid; tris(2-chloroethyl)-ester; tri(2-chloroethyl) phosphate; ethanol, 2-chloro-, phosphate (3:1); tris(2-chloroethyl) orthophosphate
Registered trade name(s)	Fyrol FR-2; Antiblaze 195[f]	Antiblaze 100; Celluflex CEF; Disflamoll TCA; Fyrol CEF; Niax 3CF, Tolgard TCEP; Genomoll P; Hostaflam UP810; Levagard EP
Chemical formula	$C_9H_{15}Cl_6O_4P$	$C_6H_{12}Cl_3O_4P$
Chemical structure		
Identification numbers:		
CAS registry	13674-87-8	115-96-8
RTECS[c]	No data	KK2450000
EPA hazardous waste	No data	No data
EPA/OPP Pesticide Code	No data	No data
OHM/TADS	No data	No data
DOT/UN/NA/IMDG shipping	No data	UN: 3082[g]
HSDB	4364	2577
EINECS	237-159-2	204-118-5
NCI	No data	C60128

[a]All information obtained from HSDB 2009, 2011 and ChemIDplus 2009, 2011, except where noted.
[b]IPCS 1990,1991a, 2000b.
[c]RTECS 2009.
[d]Ashford 1994.
[e]Lewis 2000.
[f]Weil 2001.
[g]NIOSH 2007.

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/Intergovernmental Maritime Dangerous Goods Code; EINECS = European Inventory of Existing Chemical Substances; 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; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Selected Phosphate Ester Flame Retardants[a]

Property	Tributyl phosphate (TnBP)	Triisobutyl phosphate (TiBP)	Tris(2-butoxyethyl) phosphate (TBEP)
Molecular weight	266.31	266.31[c]	398.48
Physical description	Colorless to pale-yellow liquid	Clear, colorless, low viscosity liquid[c]	Slightly yellow, oily liquid
Melting point	-80 °C	No data	-70 °C
Boiling point	289 °C; decomposes[b]	264 °C[d]	215–228 °C at 4 mm Hg
Density	0.9727 g/cm^3 at 25 °C	0.9681 g/cm^3 at 20 °C[d]	1.020 g/cm^3 at 20 °C
Odor	Odorless	Specific odor[c]	Sweetish, butyl-like
Solubility:			
Water	0.28 g/L at 25 °C	Very soluble in water[c]; 0.05% in water[c] and 6.3% water in TnBP[c]	1.1 g/L at 25 °C
Organic solvent(s)	Soluble in diethyl ether, benzene, carbon disulfide; miscible with ethanol	Very soluble in benzene, ether, and ethanol[d]	Soluble in most organic liquids; soluble in mineral oil; insoluble or limited solubility in glycerol, glycols, certain amines
Other	Miscible with most solvents and diluents	No data	No data
Log K_{ow}	4.00	3.60 (estimated)[e]	3.75
Vapor pressure	1.13x10^{-3} mm Hg at 25 °C	0.0128 mm Hg at 25 °C (estimated)[e]	0.03 mm Hg at 150 °C
Autoignition temperature	>482 °C[b]	No data	No data
Flashpoint	146 °C	175 °C (Cleveland)[c]	223 °C
Flammability limits in air	Combustible	No data	Combustible
Conversion factors	1 ppm=10.89 mg/m^3[b]	No data	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Selected Phosphate Ester Flame Retardants[a]

Property	Triphenyl phosphate (TPP)	Tricresyl phosphate (TCP)	Tri-(2-chloroisopropyl) phosphate (TCPP)
Molecular weight	326.28	368.36	327.57
Physical Description	Colorless, crystalline powder; white platelets, crystals from absolute alcohol-ligroin, prisms from alcohol, needles from ether-ligroin	Colorless liquid[f]; Oily flame resistant liquid[g]	Colorless liquid[f]
Melting point	49–50 °C	-33 °C[h]	-40 °C
Boiling point	245 °C at 11 mm Hg	265 °C at 10 mm Hg[g]	>270 °C; gradually decomposes when heated over 200°C[f]
Density	1.2055 g/cm^3 at 50 °C	1.162 g/cm^3 at 25 °C	1.29 g/cm^3 at 25 °C[f]
Odor	Slightly aromatic odor resembling phenol	Odorless; very slightly aromatic[h]	Mild odor[f]
Solubility:			
Water	0.0019 g/L at 25 °C	0.00036 g/L at 25 °C	1.2 g/L at 25 °C
Organic solvents	Very soluble in carbon tetrachloride; soluble in alcohol, benzene, ether, chloroform and acetone; insoluble in petroleum	Miscible with all the common solvents and thinners	Soluble in most organic solvents; insoluble in water[f]
Other	Soluble in most lacquers, solvents thinners, and oils	Miscible with vegetable oil; Miscible with lindseed oil, china wood oil, castor oil[g]	No data
Log K_{ow}	4.59	5.11	2.59
Vapor pressure	6.28x10^{-6} mm Hg at 25 °C	6.00x10^{-7} mm Hg at 25 °C (extrapolated)[i]	2.02x10^{-5} mm Hg at 25 °C
Autoignition temperature	No data	No data	No data
Flashpoint	220 °C	257 °C[h]	No data
Flammability limits in air	Noncombustible	No data	No data
Conversion factors	1 ppm=13.32 mg/m^3	No data	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Selected Phosphate Ester Flame Retardants[a]

Property	Tris(1,3-dichloro-2-propyl) phosphate (TDCP)	Tris(2-chloroethyl) phosphate (TCEP)
Molecular weight	430.88	285.50
Physical Description	Viscous, clear liquid	Clear, transparent, Low viscosity liquid
Melting point	27 °C	-55 °C
Boiling point	236–237 °C at 5 mm Hg	330 °C at 1 atm
Density	1.48 g/cm^3 at 25 °C	1.425 g/cm^3 at 20 °C
Odor	Mild odor	Slight odor
Solubility:		
Water	7 mg/L at 24 °C	7.0 g/L (temperature not specified)
Organic solvents	Soluble in most organic solvents	Soluble in most organic solvents; soluble in carbon tetrachloride, alcohols, esters, ketones, and aromatic hydrocarbons; very slightly soluble in aliphatic hydrocarbons; insoluble in benzene
Other	No data	No data
Log K_{ow}	3.65	1.44
Vapor pressure	5.2 x10^{-2} mm Hg at 25 °C (estimated)[e]	6.125x10^{-2} mm Hg at 25 °C
Autoignition temperature	No data	1,115 °C
Flashpoint	252 °C	216 °C
Flammability limits in air	No data	Combustible
Conversion factors	No data	1 ppm=11.65 mg/m^3
Explosive limits	No data	No data

[a]All information obtained from HSDB 2009, 2011 and ChemIDplus 2009, 2011, except where noted.
[b]NIOSH 2005a.
[c]LANXESS 2005.
[d]Lide 2008.
[e]EPA 2009h.
[f]Ashford 1994.
[g]O'Neil et al. 2006.
[h]IPCS 1990.
[i]Boethling and Cooper 1985.

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

5.1 PRODUCTION

Phosphate esters are a class of anthropogenic organic compounds found in the environment as a result of release from commercial and industrial products (Watts and Linden 2009). Phosphate esters, TnBP, TiBP, TBEP, and TCEP are produced by chemical synthesis via condensation of phosphorus oxychloride and an alkyl or aryl alcohol (Davis and Richardson 1980; HSDB 2009; Kelly 2006; Muir 1984) at low temperatures and pressures to avoid formation of alkyl chlorides (Muir 1984). TPP and TCP are made by heating either phosphorus pentachloride or phosphorus oxychloride with phenol and cresol, respectively. (HSDB 2011). Cresol is often derived from petroleum refining or coal tar and is consequently available in various grades containing a mixture of ortho-, meta-, and para- isomers. The resulting TCP produced commercially is generally a complex mixture (HSDB 2011). TDCP is produced via the epoxide opening of epichlorohydrin in the presence of phosphorus oxychloride (Weil 2001), and TCPP is similarly produced with propylene oxide and sometimes TCEP with ethylene oxide (Muir 1984).

Worldwide production of flame retardants in 1992 was estimated at 600,000 metric tons with 102,000 metric tons representing phosphate ester-derived flame retardants. In 2001, estimates increased to 1,217,000 and 186,000 metric tons, respectively (Hartmann et al. 2004). Use of flame retardants in the United States totaled an estimated 622,000 metric tons in 2007 (Fink et al. 2008). This represents an increase of 58 thousand metric tons, or 10% over the 2004 level. The value of these products rose from $844 million in 2004 to $1,126 million in 2007, a 33% increase, (Fink et al. 2008) and U.S. flame retardant demand is expected to grow at a 2–3% average annual rate through 2012 (Fink et al. 2008) due to an increase in restrictions for competing polybrominated diphenyl ethers (PDBE) (Hartmann et al. 2004; Quintana and Reemtsma 2006).

TnBP production in 1975 was > 908 kg (1 metric ton) (HSDB 2009) and is currently estimated by the 2006 Inventory Update Reporting (IUR) to be in the range of 1–10 million pounds (EPA 2010).

TiBP production is not listed with the EPA or other agencies as it appears that this chemical is produced predominantly outside of the United States.

TBEP production is estimated by the 2006 IUR in the range of 1–10 million pounds (EPA 2010).

TPP production in 1975 was > 908 kg (1 metric ton) (HSDB 2009) and is currently estimated by the 2006 IUR to be in the range of 10–50 million pounds (EPA 2010).

TCP production is estimated by the 2006 IUR in the range of 1–10 million pounds (EPA 2010).

TCEP production in 1975 was estimated to be > 908 kg (1 metric ton) (HSDB 2009) and is currently estimated by the 2006 IUR to be in the range of 500,000–1 million pounds (EPA 2010).

TCPP annual worldwide demand exceeded 40,000 metric tons in 1997 (IPCS 1998) and currently is estimated by the 2006 IUR to be produced in the range of 10–50 million pounds (EPA 2010).

TDCP annual worldwide demand was 8,000 metric tons in 1997 (IPCS 1998) and is currently estimated by the 2006 IUR to be produced in the range of 10–50 million pounds (EPA 2010).

No information is available in the TRI database on facilities that manufacture or process phosphate ester flame retardants because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 1998a).

5.2 IMPORT/EXPORT

Imports of TBEP and TCEP were reported to be negligible in 1972, while all other selected phosphate esters were not listed as being imported (HSDB 2009). No export data were available for the selected phosphate ester compounds discussed in this profile.

5.3 USE

Trialkyl, triaryl, and trihaloalkyl/aryl, and mixed phosphate esters have been used since the 1940s in industrial consumer products (Muir 1984). Phosphate esters represent an important class of commercial additives used as flame retardants, plasticizers, hydraulic fluids, solvents, extraction agents, antifoam agents, adhesives, and coatings for electronic devices (Andresen and Bester 2006; Ashford 1994; Lewis 2007; Lide 2008; Owens et al. 2007; Watts and Linden 2009; Weil 2001; Wolf and Kaul 2005). A summary of applications of the selected phosphate ester flame retardants is shown in Table 5-1.

Table 5-1. Applications of Phosphate Ester Flame Retardants

Compound Name	Flame retardant	Plasticizer	Hydraulic fluid	Floor finish, wax	Lacquer, paint, glue	Anti-foam agent	Industrial processes
Tributyl phosphate (TnBP)		X	X	X	X	X	X
Triisobutyl phosphate[a] (TiBP)		X			X	X	
Tris(2-butoxy-ethyl) phosphate (TBEP)	X	X		X	X	X	
Triphenyl phosphate (TPP)	X	X	X		X		
Trecresyl phosphate[b] (TCP)	X	X	X		X		
Tri-(2-chloro-isopropyl) phosphate (TCPP)	X	X					
Tris(1,3-di-chloro-2-propyl) phosphate (TDCP)	X	X			X		
Tris(2-chloro-ethyl) phosphate (TCEP)	X	X			X		X

[a]TiBP Datasheet, Anderson et al. 2004, 2006.
[b]IPCS 1990.

Source: Marklund et al. 2003

Flame retardants generally function in the vapor phase, where the enthalpy-generating combustion occurs, and serve to slow or hinder the ignition or growth of a fire (Gann and Gilman 2003). There are five specific mechanisms by which flame retardancy may occur: physical dilution, chemical interaction, inert gas dilution, thermal quenching, or protective coatings (Mack 2004). Phosphate ester flame retardation mechanisms vary based on structure and properties, but generally function by suppressing flammability of pyrolysis products (vapor-phase mechanism) or by chemical interaction through changing the nature of the decomposition products (Weil 2001). In general, the effectiveness of a particular phosphorus compound depends strongly on the nature of the matrix polymer but, for chemically similar compounds, the flame-retardant effectiveness often increases with increasing phosphorus content (Granzow 1978). Halogens play an important part in contributing to flame retardancy, although this contribution is offset by the lower phosphorus content. The halogens reduce vapor pressure and water solubility, thus aiding retention of these additives (Weil 2001).

Due to an increased demand for fire safety in commercial products, flame retardant use substantially increased during the 1960s and 1970s (Muir 1984). In particular, products made from synthetic polymers are treated with phosphate esters (Weil 2001). The chlorinated haloalkyl phosphates, TCPP, TDCP, and TCEP, are most commonly used as flame retardants in both rigid and flexible polyurethane foam, and some textiles (Anderson et al. 2004).

The nonderivatized alkyl and aryl phosphates, TnBP, TiBP, TBEP, TCP and TPP, all function predominantly as industrial plasticizers in polymers, rubbers, plastics, and vinyl resins, as well as flame retardants (Anderson et al. 2004, 2006). Phosphate esters are added to flexible plastics such as polyvinyl chloride (PVC) and polyurethane foams in low part per hundred concentrations (Muir 1984). Addition of phosphate esters often effects the flammability of rigid plastics such as PVC by dilution of the highly flammable chlorinated plasticizers (Green 1992). Phosphate esters can, however, change polymer decomposition chemistry when combusted (Gann and Gilman 2003). Advantages of phosphate esters over traditional plasticizers include low corrosivity of the combustion gases, lack of effect on polymer transparency, and suppression of afterglow. Disadvantages include volatility, sensitivity to hydrolysis, and negative effects on the heat distortion temperatures of plastics (Wolf and Kaul 2005). When used as flame retardants in polymers, phosphate esters typically represent 1–30% of the composition of the polymer with an average of 5–15% (Hartmann et al. 2004).

TnBP, TPP and TCP are used as hydraulic fluids with flame retardant properties predominantly present as mixtures of various alkyl- and aryl-substituted phosphate esters (Anderson et al. 2004; Batt et al. 1992;

IPCS 1990). They are recognized as replacements to polychlorinated biphenyls (PCBs) (Gomez-Belinchon et al. 1988; Muir 1984). Phosphate esters generally have better fire resistance than mineral oils and are less hazardous than PCBs. The lubricating properties are generally good; however, the high temperature stability is fair. Decomposition products, such as phosphoric acid, can be corrosive, deteriorate paints and finishes, and cause swelling of many seal materials in hydraulic systems (Denniston 1995).

TnBP is used as a solvent for cellulose esters, lacquers, natural gums, herbicide solutions, and carbonless copying systems and as an extractant in the nuclear fuel reprocessing and other metals (Anderson et al. 2004; Thomas and Macaskie 1996). Some trialkyl phosphates, $O=P(OR)_3$, are outstanding solvents for nitrates, especially $(UO_2)(NO_3)_2$, and are therefore important in uranium processing (Fee 2005). TnBP forms weak complexes with the neutral metal nitrates, affecting the solubilizing of the actinides in the organic phase (Godfrey et al. 1996). TnBP is the most frequently used solvent in liquid-liquid extraction for fuel reprocessing via a process known as the PUREX process (Plutonium Uranium Refining by EXtraction) (Dodi and Verda 2001; Godfrey et al. 1996; Stevens et al. 2007). This method enables recycling of extracted uranium and plutonium from an aqueous nitric acid phase (Dodi and Verda 2001) and is considered the most convenient method to retreat spent fuel (Lamouroux et al. 2000). Due to the acidic nature of the process, some decomposition of TnBP to dibutyl phosphate (DBP) and monobutyl phosphate (MBP) occurs via dealkylation of one or two butoxy groups, respectively (Dodi and Verda 2001).

TiBP is used as a pore size regulator for concrete, while TnBP shows excellent antifoam properties in concrete (Anderson et al. 2004; Andresen and Bester 2006). TBEP is also found in some floor polishes. TCEP was phased out due to toxicity issues (EPA 2010). Electronic equipment can contain various phosphate esters (Carlsson et al. 2000; Marklund et al. 2003).

5.4 DISPOSAL

No data are available on the disposal of specific phosphate ester flame retardants; however, hydraulic fluids containing phosphate esters do have recommended disposal methods. Used phosphate ester hydraulic fluids are not listed as hazardous wastes and can be recycled or burned for energy recovery. In general, the newer phosphate ester hydraulic fluids do not contain known chemicals or other materials that are listed in 40 CFR 261 (Resource Conservation and Recovery Act [RCRA]). Recycling of some

flame retardant-containing products, including some plastics, has been found possible (Lorenz and Bahadir 1993; Mayer et al. 1993).

With the exception of TnBP, the selected phosphate ester flame retardants are regulated under the Toxic Substances Control Act (TSCA) of 1976, requiring the reporting of record-keeping, testing, and restrictions to the EPA. The High Production Volume Challenge (HPV) program, administered by the EPA, challenges companies to report health and environmental effects data publicly for chemicals produced or imported in the United States in quantities of 1 million pounds or more per year. All of the selected chemicals except TiBP appear on this list.

6. POTENTIAL FOR HUMAN EXPOSURE

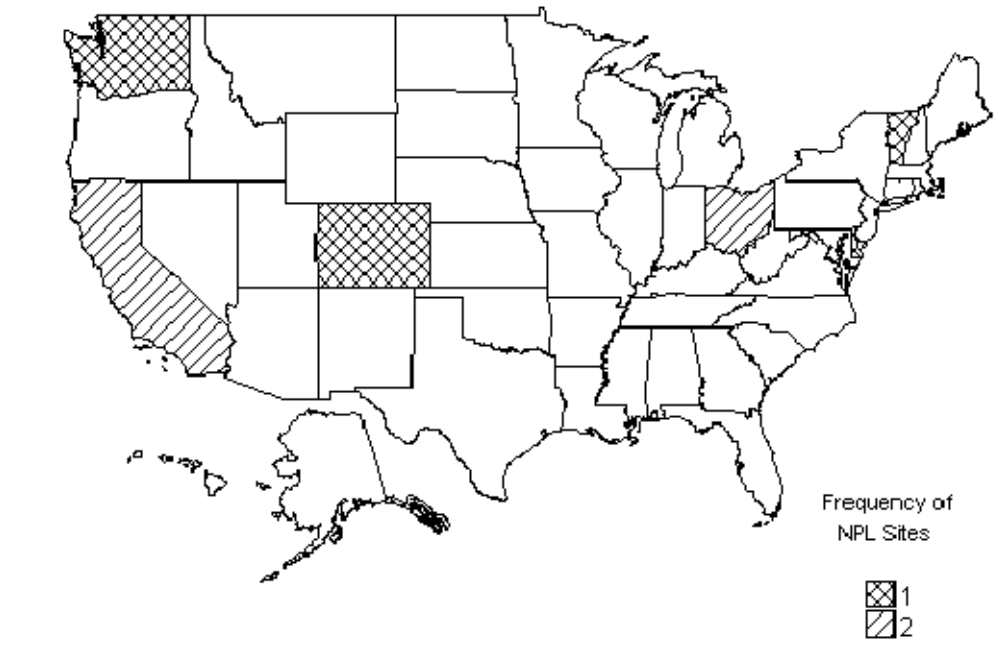
6.1 OVERVIEW

Phosphate ester flame retardants have been identified in at least 8 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for phosphate ester flame retardants is not known. The frequency of these sites can be seen in Figure 6-1.

Phosphate ester flame retardants are released to the environment through their use in industrial and consumer products. Since their introduction in the 1940s and popularization in the 1970s, these anthropogenic compounds have been frequently detected in water, soil, and air (Muir 1984). Trialkyl, triaryl and trihaloalkyl/aryl, and mixed phosphate esters represent an important class of commercial additives used as flame retardants, plasticizers, hydraulic fluids, solvents, extraction agents, antifoam agents, adhesives, and coatings for electronic devices (Ashford 1994; Andresen and Bester 2006; IPCS 1990; Lide 2008; Lewis 2007; Owens et al. 2007; Watts and Linden 2009; Weil 2001; Wolf and Kaul 2005).

Water is the most common medium in which phosphate ester flame retardants are detected in the environment. Phosphate ester flame retardant presence is widespread in surface water and groundwater of the United States and other foreign countries, primarily due to landfill leaching of PVC plastics and polyurethane foams, effluent from industrial sources, and spills of hydraulic fluids. Many hydraulic fluids are composed of mixtures of phosphate esters and are consequently released into the environment as a mixture as indicated, for example, in the Toxicological Profile for Hydraulic Fluids (ATSDR 1997). Ultimately, these primary contaminated waters are transported to secondary sources, such as drinking water, by treated sewage, agricultural runoff, and deposition from snow and rain (Andresen et al. 2004; Fries and Puttmann 2001; Gomez-Belinchon et al. 1988; Ishikawa et al. 1985; Lee and Rasmussen 2006; Meyer and Bester 2004; Muir 1984; Peterman et al. 1980; Reemtsma et al. 2006; Watts and Liden 2008, 2009). Hydrolysis, although slow due to poor solubility and pH dependence, is the most important abiotic fate process for phosphate esters (Boethling and Cooper 1985). Biodegradation via hydrolysis from microbial esterases in river water, lake water, sewage, and sludge takes place in <10 days (Howard and Deo 1979; Mayer et al. 1981; Muir et al. 1980; Saeger et al. 1979).

Figure 6-1. Frequency of NPL Sites with Phosphate Ester Flame Retardants



Derived from HazDat 2007

In soil and sediment, phosphate ester flame retardants are considered persistent as they have a tendency to adsorb strongly, thus limiting the availability of these substances to microorganisms (Boethling and Cooper 1985; Muir 1984). Phosphate esters generally have a low water solubility and relatively high octanol/water partition coefficient (K_{ow}), which results in high soil adsorption coefficients (K_{oc}). Muir (1984) reported K_{oc} values ranging from 151 to 14,350 for several of the selected phosphate esters with the highest for TCP. Reports from soil analyses at military bases and airports have confirmed the presence of some phosphate esters, particularly TnBP, as it represents a major component in hydraulic fluid Skydrol 500B, Skydrol LD, and Hyjet IV (Monsanto Co. 1980). In addition, sediments of rivers and lakes have been shown to contain these compounds (Ishikawa et al. 1985; Muir et al. 1989). Volatilization and biodegradation are potential fate processes for phosphate esters adsorbed to soils (Anderson 1993; Muir 1984, 1989).

Diffusion into air from plastics, textiles, adhesives, and electronics accounts for numerous reports of phosphate esters in indoor air (Carlsson et al. 2000; Garcia et al. 2007; Hutter et al. 2006; Ingerowski et al. 2001, 2003; Otake et al. 2004, 2001; Owens et al. 2007; Sjodin et al. 2001). Outdoor air sampled near places where hydraulic fluids are used, such as at airports and outside of newly constructed homes and buildings, have indicated the presence of these phosphate esters (Haraguchi et al. 1985; Monsanto Co. 1980; Saito et al. 2007).

Ingestion of food or water is the primary exposure pathway that humans have to the phosphate ester flame retardants discussed in this profile. Exposure to phosphate esters via direct or indirect dermal adsorption from treated matricies is also possible, but unlikely due to the chemical and physical properties that make flame retardants useful. Young children are at an increased exposure risk due to the potential for oral exposure via dissolution of phosphate esters from repeated sucking on treated materials (NRC 2000). Inhalation is also a potential route of exposure primarily in indoor air from PVC plasticizers, floor polishes, electronics, and textiles.

Average daily intakes (ADIs) have been estimated for the U.S. population for TnBP, TPP, TBEP, TCPP, and TCEP (Gunderson 1988, 1995a, 1995b). The estimated ADI values are generally in the ng/kg body weight/day range. Additional sources of exposure for the general population include inhalation of air and ingestion of drinking water containing these phosphate esters. Occupational exposure may be greater than exposure to the general population for employees in industries where significant quantities of phosphate esters are manufactured or used.

The selected phosphate esters indicated in Table 4-1 have been frequently detected in the environment due to their commercial production, use, and disposal. However, other compounds that were not selected are also reported in the environmental monitoring literature. Mixtures of several phosphate esters present in a single monitoring sample are commonplace. According to the surveyed literature, the most prevalent phosphate esters in all environmental and dietary samples appear to be TnBP and TPP. Consequently, a significant portion of the noted studies pertain to these compounds. TCP and TPP are commonly used together in hydraulic fluids and lubricants and are detected together in environmental media (IPCS 1990). TBEP is also quite prevalent due to its presence in floor polishes, while the chlorinated phosphate esters, TCEP, TCPP, and TDCP, all appear much less frequently in the literature. TiBP appears the most infrequently in published monitoring studies of the environment or food.

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 2005). 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 2005).

6.2.1 Air

There is no information on releases of phosphate ester flame retardants to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 1997).

Phosphate ester flame retardants are generally liquids in their pure form at 25 °C and have moderate Henry's Law constants (10^{-4}–10^{-8} atm-m^3/mol) and vapor pressures (10^{-2}–10^{-7} mm Hg); therefore, if

aerosolized, they should exist in the vapor phase or vapor phase and particulate phase (Muir 1984). Halogenated phosphate esters have a reduced vapor pressure and solubility, which generally aid in retention of these compounds as additives. Releases to the air likely occur from industrial sources, such as the manufacture, production, and transportation of pure phosphate esters, as well as diffusion from products containing phosphate esters.

Semi-volatile flame retardant hydraulic fluids could account for aerosolized phosphate esters lost from seal leakage, plastics, or vinyl car seats (EPA 1979). Skydrol 500B, a hydraulic fluid, contains 65–75% TnBP. In 1979, TnBP was detected in airport air over Vancouver, British Colombia at concentrations of 0.01–0.3 mg/m^3 (Monsanto Co. 1980).

6.2.2 Water

There is no information on releases of phosphate ester flame retardants to the water from manufacturing and processing facilities because these releases are not required to be reported (EPA 1997).

Phosphate ester flame retardants are released to environmental surface water and groundwater primarily from leaching of hydraulic fluid spills and discarded or landfilled PVC, polyurethane foam, electronic wall coverings, and other flame retardant materials (Muir 1984).

6.2.3 Soil

There is no information on releases of phosphate ester flame retardants to the soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 1997).

Phosphate ester flame retardants are released to soil from the use of waste water for irrigation, the disposal of flame retardant plastics in landfills, the leakage of hydraulic fluids, or the deposition of aerosolized phosphate esters (Muir 1984).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Phosphate esters are synthetic compounds that are present in the air, water, and soil due to their use primarily as flame retardants, hydraulic fluids, and plasticizers. The ability of phosphate esters to enter

the atmosphere as vapors depends greatly upon the vapor pressure of the individual compound. Therefore, phosphate esters can be present in the vapor phase or particulate phase (EPA 1979; Muir 1984).

Phosphate esters generally have low water solubilities and relatively high K_{ow} values, which result in high K_{oc} values. Muir (1984) reported the K_{oc} values for TPP, TCP, TnBP, TBEP, TCEP, and TDCP as 7,850, 14,350, 3,592, 2,311, 151, and 2,591, respectively, using data from Kenaga and Goring (1980). TCEP, as apparent from the K_{oc} values, is particularly mobile in soil and has the greatest potential to leach into groundwater. Relative to pesticides, the high K_{oc} of the other phosphate esters indicate relatively low leaching potential. The fate and distribution of several phosphate esters were studied in laboratory experiments using river water, pond water, and sediment mesocosms (Muir et al. 1989). Following addition of each compound to the water column, rapid partitioning into the sediment was observed in each case. Volatilization of phosphate esters from dry soils is unlikely given the vapor pressures and adsorption coefficients; however, volatilization from moist soil is possible given the range of Henry's Law constants (10^{-4}–10^{-8} atm-m^3/mol) and vapor pressures (10^{-2}–10^{-7} mm Hg) (Muir 1984).

TnBP, TPP, TCEP, and TDCP have been reported to have a moderate potential to bioaccumulate in aquatic organisms based on their K_{ow} values (Sasaki et al. 1981). Bioconcentration of phosphate esters requires assessment by using not only the K_{ow} or water solubility, but also the capacity of absorption and metabolic behavior (Sasaki et al. 1981, 1982). Bioaccumulation ratios in fish (rainbow trout) are reported to range from 133 to 2,807 (Muir et al. 1981). Phosphate esters have been detected in fish, sediment, and water at or near the site of hydraulic fluid use (Mayer et al. 1981).

Uptake or degradation of TCEP in water was nearly nonexistent, resulting in very low bioaccumulation for this compound as analyzed for bioconcentration in killifish and goldfish using both a static water system and a continuous flow test system. Muir et al. (1983a) calculated the bioconcentration factors (BCFs) for TPP as 573 and 561 for rainbow trout and fathead minnows, respectively, using ^{14}C-labeled TPP. The results from the same study determined that meta- and para-TCP had BCFs of 1,420 and 784 in rainbow trout and 928 and 596 in fathead minnows, respectively (Muir et al. 1983a). It was found that, in general, the hydrolysis rate of the phosphate ester had a greater effect on bioconcentration than the hydrophobicity of the compound (Muir et al. 1983a).

6.3.2 Transformation and Degradation

6.3.2.1 Air

These compounds are capable of degrading through reaction with hydroxyl radicals, which is the main route of atmospheric degradation for most organic substances. Predicted hydroxyl radical rate constants range from 10^{-12} to 10^{-11} cm^3/molecule-second and corresponding atmospheric half-lives are on the order of 1–12 hours for the selected phosphate esters assuming a constant atmospheric hydroxyl radical concentration of $1.5x10^6$ hydroxyl radicals per cm^3 (Meylan and Howard 1993). Particulate-phase phosphate esters are subject to wet and dry deposition, while semi-volatile phosphate esters have the potential to hydrolyze to diesters, monoesters, and phosphoric acid (Ishikawa et al. 1992). Phosphate esters maintain oxidative stability at isothermal or room temperature conditions; however, thermal decomposition of these substances predominates at high temperature in the presence of air (Shankwalkar and Placek 1992).

6.3.2.2 Water

Hydrolysis is the most important abiotic fate process for phosphate esters proceeding stepwise to release alkyl and aryl alcohols (Boethling and Cooper 1985). The rate of hydrolysis is highly dependent on pH, temperature, presence of catalytic reagents, and stability of the conjugate acid or base, as well as the dielectric constant of the solvent (Katagi 2002). Phosphate esters are highly pH-dependent and generally are resistant to hydrolysis in neutral or acidic water (pH 5.0–7.0), but readily degrade in more alkaline conditions (pH 9.0–9.5) (Howard and Deo 1979; Mayer et al. 1981; Muir 1984). Half-lives of TPP at pH 8.2, 9.0, and 9.5 were 7.5, 3.0, and 1.3 days, respectively, indicating much faster hydrolysis as alkalinity increases. TPP hydrolysis was measured in distilled, lake, and river water. The results showed that the pseudo first-order rate constants for distilled water, Lake Ontario water, and Seneca River water were 0.93, 0.64, and 0.34 $days^{-1}$, corresponding to half-lives of 0.75, 1.0, and 2.0 days, respectively (Howard and Deo 1979).

Comparatively, dialkyl and diaryl phosphate esters have been found to be far less susceptible to hydrolysis than the corresponding triesters, likely due to the primary species being an anion. Dichloroalkyl phosphate esters such as TDCP are more labile than monochloroalkyl phosphate esters such as TCEP and TCPP (Hartley 1959; Muir 1984). Therefore, once the first ester substituent is hydrolyzed, removal of the second and third ester becomes much more difficult.

Aqueous base-catalyzed hydrolysis occurs via an S_N2-like nucleophilic attack on the phosphorus atom by OH^- on one of the tetrahedral faces, forming a transient tetracoordinate trigonal bipyramidal intermediate, followed by departure of the leaving group to form a phosphate diester. This mechanism and structure are evidenced by ^{18}O labeling and crystallographic data, respectively (Davis and Richardson 1980; Katagi 2002; Vernon 1959). Given this mechanism, electron-withdrawing substituents, such as halogens, increase the electrophilicity of the phosphorus, whereas electron-donating substituents are stabilizing (Davis and Richardson 1980). Through coordination, certain metal ions such as Ir, Rh, Co, Cu, Zn, and Mn have shown to facilitate phosphate ester hydrolysis. Low environmental concentrations of dissolved transition metals in the aquatic environment do, however, make this an unlikely mechanism. Heterogeneous reactions with suspended or sedimentary mineral phases have been shown to hydrolyze some phosphate esters (Baldwin et al. 1995).

Nonhalogenated phosphate esters are degraded by microorganisms in activated sludge; however, the halogenated phosphate esters are resistant to biodegradation. Standard biodegradation tests indicated that TnBP, TCP, and TPP are readily biodegradable, but TCPP is not. TPP achieved 83–94% of its theoretical biochemical oxygen demand (BOD) and TnBP achieved 89–91% of its theoretical BOD in 28 days using an activated sludge as inoculum and the modified MITI (OECD 301C) test (IPCS 2004, 2006). TCP achieved primary biodegradation in excess of 97% using a 4-week-long, semi-continuous activated sludge test and 100% in a river die-away study. In a CO_2 evolution study with TCP, 78.6% of theoretical CO_2 was evolved in 7 days and 82.1% was evolved in 28 days (Saeger 1979). In a 48-hour waste water treatment simulation, 40–60% of TCP was degraded (Ishikawa et al. 1985). TCPP achieved 0% of its theoretical BOD in 28 days using the same test (IPCS 2000a) and showed no decrease in concentration in landfill leachate after 80 days under aerobic conditions (Kawagoshi et al. 2002). Biodegradation is generally initiated by hydrolysis of the ester bond by microbial esterases (Yamada 1987). The hydrolysis product of TnBP, butanol, can be used as a carbon source (Thomas and Macaskie 1996, 1998). Consequently, several naturally isolated *Pseudomonas* cultures were found to substantially degrade TnBP by metabolizing and growing on minimal TnBP media as the feedstock (Thomas et al. 1997). Ninety-six percent of both TnBP and TPP was degraded upon addition of activated sludge (Saeger et al. 1979). Takahashi et al. (2008) isolated a mixed bacterial culture capable of degrading previously nonbiodegradable chlorinated phosphate esters TCEP and TCPP. A mixed culture primarily composed of *Acidovorax* spp., *Aquabacterium* spp., and *Sphingomonas* spp. degraded TCEP, while a mixed culture of *Acidovorax* spp. and *Sphingomonas* spp. was found to degrade TCPP.

Efforts to enhance the degradation of halogenated phosphate esters such as TCPP at water treatment facilities have been investigated (Watts and Linden 2008, 2009). The addition of ozone and hydrogen peroxide to produce photochemically generated hydroxyl radicals in aqueous solution was shown to be an effective method of increasing the oxidation of TCEP and TCPP in bench scale experiments. High initial levels of hydrogen peroxide are used in conjunction with a powerful ultraviolet light source to initiate the formation of hydroxyl radicals (Watts and Linden 2009).

Removal of phosphate esters from waste water can require additional processing. Halogenated phosphate esters, including TCEP, are particularly biorecalcitrant and are emerging as significant contaminants from waste water pollution into freshwater resources (Watts and Linden 2008). Ishikawa and Baba (1988) recognized the pH dependence of hydrolysis while attempting to hydrolyze phosphate esters with aqueous chlorine. Chlorination had little effect on TCEP and TCPP at all pHs and only achieved 50% degradation at pH 7 for TnBP and TPP.

6.3.2.3 Sediment and Soil

Muir et al. (1989) studied the fate and degradation of four phosphate esters, including TPP, in sediment/water systems and observed rapid degradation of these substances. The average half-lives of TPP in pond sediments were 2.8 days at 25 °C, 2.8 days at 10 °C, and 11.9 days at 2 °C; in river sediments, the average half-life was 7.0 days. Comparatively, in the same study, meta-TCP had average half-lives in pond sediments of 3.2 days at 25 °C, 4.1 days at 10 °C, and 16.3 days at 2 °C; in river sediments, the average half-life was 10.1 days. Under anaerobic soil conditions, TPP had a half-life of 32 days (Anderson 1993), while sterile soil produced nearly quantitative recovery of TPP after 101 days. TCEP soil attenuation was <33% from waste waters passed through soil columns for 1 month (Watts and Linden 2008).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to phosphate ester flame retardants depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of phosphate ester flame retardants 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 phosphate ester flame retardants 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 phosphate ester flame retardants in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Several phosphate esters were detected in the ambient air of Kitakyushu, Japan and measured by gas chromatography-mass spectrometry (GC-MS) at concentrations ($\mu g/m^3$) of 0.0023 (TnBP), 0.0053 (TCPP), 0.0047 (TDCP), and 0.0022 (TPP) in 1983 (Haraguchi et al. 1985). Several phosphate esters were detected in outdoor air from eight sites in Tokyo, Japan including TnBP (0–1.7 ng/m^3), TCPP (0–3.1 ng/m^3), and TBEP (0–1.1 ng/m^3) (Saito et al. 2007). TCP was not detected in this study. Atmospheric samples collected near heavily industrialized areas in Japan contained TCP at concentrations ranging from 11.5 to 70.3 ng/m^3 (IPCS 1990). TCP was qualitatively identified in fly ash and stack emissions from refuse combustion (Junk and Ford 1980). TCP was detected in air samples near production sites in West Virginia at levels of 0.01–2 ng/m^3 (Boethling and Cooper 1985).

TnBP is a component of two formulations of hydraulic fluid, Skydrol 500B and Skydrol LD. Consequently, TnBP was detected in the air at the CP air test facility at Vancouver International Airport at a concentration of 0.04–0.3 mg/m^3 (Monsanto Co. 1980), indicating that phosphate ester hydraulic fluids may be released during aircraft maintenance operations from equipment using phosphate ester hydraulic fluids.

The use of phosphate esters as an additive to flexible plastics, such as PVC and polyurethane foams, and their ability to leach from the polymer matrix often leads to their detection in indoor air at low levels. Phosphate esters have been found in indoor air from both homes and offices (Carlsson et al. 2000; Garcia et al. 2007; Hutter et al. 2006; Ingerowski et al. 2001, 2003; Otake et al. 2004, 2001; Owens et al. 2007; Sjodin et al. 2001). PVC plasticizers, floor polishes, and flame retardants for electronics and textiles are the primary contributors of phosphate esters to indoor air. PVC-containing plasticizer is a stiff resin but softens and expands upon heating and remains this way when cooled due to the molecular changes that take place (Otake et al. 2001, 2004). Phosphate esters are not chemically bound to host materials and consequently, can be emitted to the surrounding air as vapor or particulates depending on the vapor pressure of the compound (Carlsson et al. 2000; Garcia et al. 2007).

Recognition that phosphate esters, particularly TCEP and TCPP, were impacting indoor air took place in 1993 in Japan. TCEP was used in wall coverings and television sets in Japan until its carcinogenic

properties were suspected and it was replaced with TCPP (Saito et al. 2007). In Tokyo, Japan, several phosphate esters were detected in indoor air environments. In 18 houses sampled, concentration ranges (ng/m^3) were 0–30.6 (TnBP), 0–1,260 (TCPP), 0–136 (TCEP), 0–13.7 (TBEP), and 0–0.60 (TDCP). In addition, 14 office buildings had concentration ranges (ng/m^3) of 0.46–21.7 (TnBP), 0–0.86 (TPP), 0–57.6 (TCPP), 0–42.1 (TCEP), 0–118 (TBEP), and 0–8.7 (TDCP) (Saito et al. 2007). In a newly constructed home in Tokyo, Japan, indoor air concentrations (ng/m^3) were 36.6 (TnBP), 5.5 (TCPP), 1.2 (TCEP), 71.0 (TBEP), and 1.3 (TDCP). TBEP was determined to originate from the floor polishing agent, while TnBP originated from the polyolefin wall and ceiling coverings (Saito et al. 2007). Migration rates of TDCP and TCP were measured as 0.28 and 5.9 $\mu g/m^2$-hour, respectively, from computer monitors, and migration rates of TCPP and TCEP were measured as 1.7 and 13.0 $\mu g/m^2$-hour, respectively, from TV sets using an interior surface to solid extraction disk (Saito et al. 2007). This indicates that migration from electronic devices to air is occurring at ambient temperatures.

6.4.2 Water

Phosphate esters are commonly detected in surface water, groundwater, sewage, waste water, and drinking water due to their presence in many commercial products and the ability to leach or diffuse from their anthropogenic source (Watts and Linden 2009). These contaminants are widely distributed in the aquatic environment (Ishikawa et al. 1985; Muir 1984). In the United States, the presence of phosphate esters has been reported in waters from the Delaware River, the Great Lakes region, and several Midwest rivers; phosphate esters have also been detected in water at foreign locations such as Japan, the Netherlands, Germany, and Canada (Muir 1984). Conventional treatment of drinking water in the United States showed that removal of TnBP, TBEP, TCEP, and TDCP was incomplete (Andresen and Bester 2006). In particular, TCEP is resistant to conventional potable water and waste water treatments (Meyer and Bester, 2004; Reemtsma et al. 2006; Watts and Liden 2008, 2009). Several studies have measured phosphate esters in surface waters from Wisconsin (Peterman et al. 1980), Kansas (Lee and Rasmussen 2006), and Germany (Andresen et al. 2004; Fries and Puttmann 2001). Phosphate esters have also been detected in coastal waters from Spain (Gomez-Belinchon et al. 1988) and Japan (Ishikawa et al. 1985). Pedersen et al. (2005) detected TCEP, TCPP, TBEP, and TDCP flame retardants in agricultural runoff from fields irrigated with treated effluent in Ventura County, California.

Waters from waste water treatment facilities (WWTF) discharged into lakes, rivers, streams, and tributaries of various watersheds are known to contain phosphate esters. A number of studies indicate influent and effluent of WWTF testing positive for phosphate esters (Jackson and Sutton 2008; Marklund

2005b; Pedersen et al. 2005; Reemtsma et al. 2006; Thruston et al. 1991). Therefore, introduction of these anthropogenic compounds into the environment is augmented if an effective purification is not performed to remove or degrade phosphate esters at the WWTF.

Analysis of several streams in Johnson County, Kansas in 2002–2003 revealed the presence of phosphate ester flame retardants. On average, concentrations of 0.5 μg/L of TnBP, TPP, TBEP, TCEP, and TDCP were reported in these streams. In addition, several water samples collected and analyzed near a WWTF in the same area contained TBEP and TDCP. The mean concentrations of TBEP and TCDP in the effluent were 4.4 and 0.4 μg/L, respectively, and 2.0 and 0.4 μg/L <500 m downstream from the treatment plant. Maximum concentrations of 15 and 0.6 μg/L for TBEP and TDCP, respectively, were measured in the immediate effluent, and maximum levels of 6.2 and 0.6 μg/L, respectively, were measured <500 m downstream (Lee and Rasmussen 2006). A comprehensive study conducted by the U.S. Geological Survey from 1999 to 2000 analyzed surface water samples from 139 streams obtained in 30 states across the continental United States (Kolpin et al. 2002). TCEP, TDCP, and TPP were detected in 57.6, 12.9, and 14.1% of the surface water samples tested over this 2-year period, respectively. The maximum concentrations of TCEP, TDCP, and TPP were reported as 0.54, 0.16, and 0.22 μg/L, respectively, with median levels of 0.1, 0.1, and 0.04 μg/L, respectively (Kolpin et al. 2002).

Municipal waste water effluent collected from a treatment plant leading to the Oder River, Germany, contained mean levels of 622, 352, and 2,955 ng/L of TnBP, TCEP, and TBEP, respectively, in specimens obtained during a 2002–2003 sampling period (Fries and Puttmann 2003). Mean levels of TnBP, TCEP, and TBEP measured in the influent to the plant were 15,404, 986, and 12,835 ng/L, respectively. The concentration of TnBP, TCEP, and TBEP in river water at various sampling points in the river downstream from the plant ranged from 69 to 1,044 ng/L (TnBP), from not detected to 1,036 ng/L (TCEP), and from 121 to 952 ng/L (TBEP). Groundwater samples obtained from areas adjacent to the river contained TnBP, TCEP, and TBEP at ranges from not detected to 1,120, from not detected to 312, and from 154 to 410 ng/L, respectively.

Phosphate esters are widely used as incombustible plasticizers in Japan and, as a consequence, have been detected in the environment. Samples collected and analyzed in 1989–1990 from the Yodo River, Osaka City Rivers, Osaka Bay, and Yamato River in Japan indicated the presence of phosphate ester flame retardants. The most prevalent phosphate ester detected was TCPP at 13.1 μg/L in the Yamato River; however, TCEP, TnBP, TDCP, and TPP were also detected at lower concentrations (Fukushima et al. 1992).

Three volcanic lakes located in Central Italy were examined for the presence of phosphate esters (Bacaloni et al. 2008). Due to their location, the lakes lack emissaries and tributaries and sewage treatment plant inputs. Therefore, contamination can occur only via local anthropogenic activities or long-range transport and deposition from rainfall or runoff processes. The results of this study indicated the presence of TCEP, TCPP, TDCP, TPP, TiBP, TnBP, and TBEP in all three of these lakes at the parts per trillion (ng/L) level, with a noticeable seasonal variation for several of the compounds. For each of the three lakes, maximum concentrations of the phosphate esters tended to occur during the late summer to autumn months, which coincide with heavy tourist activity and increased vehicular traffic at all three locations. The mean monthly range of concentrations at all three lakes were as follows: TCEP, not detected to 64 ng/L; TCPP, 2–62 ng/L; TDCP, 2–60 ng/L; TPP 2–21 ng/L; TiBP, 1–380 ng/L; TnBP, 3–784 ng/L; and TBEP, 8–127 ng/L.

Aerosolized phosphate esters are subject to wet deposition. TPP and TnBP were identified, but not quantified, in rainwater samples obtained from Los Angeles, California (Kawamura and Kaplan 1983), and snowfall samples from various areas of Northern Sweden (Marklund 2005a). TnBP was detected in the snowfall at an airport in Sweden at levels as high as 23,000 ng/kg, likely as a consequence of its use in aircraft hydraulic fluids. TnBP, TCEP, and TBEP were detected in rainwater samples collected in Bahnbrucke, Germany at levels of 911, 121, and 394 ng/L, respectively (Fries and Puttmann 2003).

TnBP is frequently used as a solvent in liquid-liquid extraction for uranium and plutonium fuel reprocessing. Consequently, it has been detected in storage ponds and waste streams at nuclear fuel reprocessing sites. TnBP and uranium concentrations in a typical fuel rod storage pond were 300 and 142 μM, respectively (Thomas and Macaskie 1996).

TCEP, TDCP, and TPP were analyzed in groundwater samples from 47 sites in 18 different states as part of a national reconnaissance program of water quality in the United States (Barnes et al. 2008). TCEP was detected in 29.8% of the samples tested at a maximum concentration of 0.737 μg/L. TDCP and TPP were detected in 2.1 and 4.3% of the groundwater samples tested, respectively; however, all detections were below the reporting level. Focazio et al. (2008) studied the frequency of detection of phosphate esters and 96 other compounds in 25 ground- and 49 surface-water sources used for public drinking water systems from 25 different states and Puerto Rico. TCEP, TDCP, TnBP, and TPP were detected in 20.3, 12.2, 8.1, and 1.35% of the samples tested, respectively. The maximum concentration of TnBP was 0.74 μg/L; however, all of the other compounds were detected below the reporting limit of 0.5 μg/L.

TPP was identified, but not quantified, in water samples collected from groundwater and treated water obtained from 31 wells in the Piedmont and Highlands regions of Northern New Jersey (Stiles et al. 2008). In a 1979 survey of treated potable drinking water from 29 municipalities across Canada, the presence of TnBP, TCEP, TDCP, TPP, TCP, and TBEP was frequently observed. TBEP was the most commonly detected phosphate ester with levels as high as 560 ng/L (Williams et al. 1981). TCP was detected at levels of 0.4–1.8 ng/L in 5 of 12 samples of municipal drinking water collected at treatment plants in the Great Lakes region of Canada (Williams et al. 1982). Phosphate esters were detected in untreated surface water from the Ruhr River in Germany; reported concentrations of TCPP, TCEP, and TDCP were 50–150, 10–130, and 10–40 ng/L, respectively (Andresen and Bester 2006). Following treatment of the water, the concentrations were all reduced to 0.3–3 ng/L (Andresen and Bester 2006).

6.4.3 Sediment and Soil

Available literature suggests that halogenated phosphate esters are somewhat persistent organic compounds when adsorbed to soils and sediments (Boethling and Cooper 1985; Muir 1984). However, Muir et al. (1989) found that nonhalogenated phosphate esters, particularly TPP, are degraded in <3 days. In general, partitioning of phosphate esters provides potential for contact with sediments in lakes, rivers, and sea floors.

A national survey conducted in 1977–1978 in Japan resulted in the detection of TnBP at concentrations of 8–130 ng/g in rivers sediments, 3–24 ng/g in estuary sediments, and 2–240 ng/g in sea sediments (Ishikawa et al. 1985). TCP was detected in 2 of 75 sea sediment samples at concentrations of 1.06 and 2.16 µg/g (Ishikawa et al. 1985). Phosphate ester levels of 0.1–1 µg/g have been detected in river sediments of industrial areas contaminated with triaryl-based hydraulic fluids (Ishikawa et al. 1985; Muir et al. 1989). Commercial and military use of phosphate ester hydraulic fluid is estimated to result in up to 80% of the consumption of these to be lost to unrecovered leakage. Consequently, air force bases have reported detection of several phosphate esters, including TPP, in soils (David and Seiber 1999b; Monsanto Co. 1980). TCP was reported in sediments collected from the Detroit river (0.23–1.3 mg/kg) and Sparrows Point in the Baltimore Harbor (0.4–0.6 mg/kg) (Boethling and Copper 1985). Due to the high sedimentation coefficient of TCP, several studies in Japan have detected TCP in sediments with levels ranging from 4 to 2,160 ng/g (IPCS 1990). In Glil-Yam, Israel, Muszkat et al. (1993) reported the presence of TnBP at 25 ppb in effluent used for crop irrigation. A national survey in 1977–1978 resulted in the detection of TCEP in sea sediments at a concentration of 90 ng/g (Ishikawa et al. 1985).

6.4.4 Other Environmental Media

In 1982, the Food and Drug Administration (FDA) found detectable levels of phosphate esters present in food samples during a portion of the annual Pesticide Screening program. The presence of these phosphate esters in foodstuffs presumably arose from the diffusion of these substances through the wrapping material used to package the food (Daft 1982). Since 1982, phosphate ester flame retardants are regularly tested for in various foods by the FDA's Total Diet Study. The results obtained are summarized in Table 6-1. No data were available for TiBP, TCP, or TDCP from this study (FDA 2006). The most frequently identified phosphate ester flame retardant was TPP, which also had the highest reported content. TPP was found in caramels and margarine at approximately 0.04 ppm. In baby foods, turkey and vegetables contained the highest level of TPP at approximately 0.02 ppm. TnBP was the second most frequently detected phosphate ester, but most levels measured were below 0.004 ppm, with baby cereal (prepared with water) and applesauce being the highest (FDA 2006).

In a study based in the United Kingdom, similar to the U.S. based FDA Total Diet Study, the most prevalent of the selected phosphate esters were TnBP and TPP, occurring in meats, cereals, nuts, and some vegetables (Gilbert et al. 1986).

House dust has been found to contain phosphate esters such as TCEP and TCPP (Garcia et al. 2007; Hutter et al. 2006; Ingerowski et al. 2001; Marklund 2003). TBEP was measured at levels of 4,300–7,800 mg/kg in house dust prior to removal of the cleaning polish on the floor. Once a wet cleaning was performed, the level of TBEP dropped to 410 mg/kg after 3 months and to 90 mg/kg after 6 months (Hutter et al. 2006). Dust samples obtained from different private residences (houses) located in the northwest of Spain were found to contain levels of TBEP as high as 18.5 µg/g. Other phosphate esters were also detected in the dust samples at average concentrations (µg/g) of 0.21 (TiBP), 0.25 (TnBP), 1.7 (TCEP), 3.9 (TCPP), 0.35 (TDCP), 2.6 (TPP), and 9.9 (TBEP) (Garcia et al. 2007).

Phosphate esters were detected in soft polyurethane foam samples at levels of 0.4–0.7 µg/g for TnBP, 0.8–3.1 µg/g for TCEP, 0.9–3.1 µg/g for TCPP, 4.5–10.2 µg/g for TDCP, 4.7–23.3 µg/g for TPP, and 1.6 µg/g for TBEP (Nagase et al. 2003). TCP was detected on the inside surface of automobile windows, presumably due to its use as a plasticizer in interior automobile plastics (Boethling and Cooper 1985).

Table 6-1. Phosphate Ester Flame Retardant Levels in Food

Food item	Level (ppm)
Tributyl phosphate (TnBP)	
Rice, white, enriched, cooked	0.00011
Oatmeal, plain, cooked	0.00014
Cream of wheat (farina), enriched, cooked	0.00200
Corn flakes cereal	0.00314
Fruit-flavored cereal, presweetened	0.00018
Shredded wheat cereal	0.00123
Raisin bran cereal	0.00018
Crisped rice cereal	0.00086
Oat ring cereal	0.00034
Apple (red), raw (with peel)	0.00043
Applesauce, bottled	0.00430
Orange juice, frozen concentrate, reconstituted	0.00045
Grapefruit juice, frozen concentrate, reconstituted	0.00091
Prune juice, bottled	0.00089
Dill cucumber pickles	0.00023
Sugar, white, granulated	0.00045
Peach, canned in light/medium syrup	0.00045
Tomato juice, bottled	0.00018
Baby food, cereal, mixed, dry, prepared with water	0.00432
Tris(2-butoxyethyl) phosphate (TBEP)	
Oatmeal, plain, cooked	0.00368
Bread, whole wheat	0.00114
Candy, caramels	0.00075
BF, juice, apple	0.00018
Peach, canned in light/medium syrup	0.00039
Popsicle, fruit-flavored	0.00225
Tri-(2-chloroisopropyl) phosphate (TCPP)	
Apple (red), raw (with peel)	0.00082
Pear, raw (with peel)	0.00009
Prunes, dried, uncooked	0.00015
Apple juice, bottled	0.00005
Tomato catsup	0.00030
Tomato juice, bottled	0.00032
Baby food, arrowroot cookies	0.00018

Table 6-1. Phosphate Ester Flame Retardant Levels in Food

Food item	Level (ppm)
Triphenyl phosphate (TPP)	
Peas, green, frozen, boiled	0.00023
Rolls, white, soft, enriched	0.00075
Bread, whole wheat	0.00036
Tortilla, flour	0.00050
Bread, rye	0.00039
Strawberries, raw/frozen	0.00028
Lemonade, frozen concentrate, reconstituted	0.00041
Sauerkraut, canned	0.00025
Broccoli, fresh/frozen, boiled	0.00023
Asparagus, fresh/frozen, boiled	0.00023
Tomato, raw	0.00341
Mashed potatoes with margarine and milk, prepared from instant	0.0025
Scalloped potatoes, homemade	0.00023
Soup, vegetable beef, canned, condensed prepared with water	0.00068
White sauce homemade	0.00285
Margarine, regular (salted)	0.04068
Butter, regular (salted)	0.00175
Cream substitute, non-dairy, liquid/frozen	0.00102
Candy, caramels	0.04503
Fruit drink, from powder	0.00023
Wine, dry table, red/ white	0.00068
Bread, cracked wheat	0.00057
Crackers, graham	0.00045
Sweet cucumber pickles	0.00025
Beef and vegetable stew, canned	0.00975
Baby food, juice, apple-banana	0.00295
Baby food, zwieback toast	0.00400
Baby food, vegetables and turkey	0.02175

Table 6-1. Phosphate Ester Flame Retardant Levels in Food

Food item	Level (ppm)
Tris(2-chloroethyl) phosphate (TCEP)	
Peas, green, frozen, boiled	0.00182
Oatmeal, plain, cooked	0.00002
Cream of wheat (farina), enriched, cooked	0.00259
Rolls, white, soft, enriched	0.00008
Broccoli, fresh/frozen, boiled	0.00014
Green beans, fresh/frozen, boiled	0.00159
Baby food, turkey and rice	0.00048
Baby food, peas	0.00002
Bread, cracked wheat	0.00002
Eggplant, fresh, peeled, boiled	0.00175
Candy, hard, any flavor	0.00002
Sweet cucumber pickles	0.00005
Baby food, teething biscuits	0.00006
Soup, Oriental noodles (ramen noodles), prepared with water	0.00725
Baby food, pears and pineapple	0.00002

Source: FDA Total Diet Study Market Baskets 1991–2003 (FDA 2006)

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure to phosphate esters can occur through ingestion of food and water containing phosphate esters or inhalation of vapors or particulates released from flame retardant materials. Dermal exposure can occur through direct contact with flame-retarded textiles occurs; however, these substances are not highly absorbed through dermal routes. As fabrics and foams treated with phosphate ester flame retardants wear, they can shed small fibers and produce particles that could be ingested or inhaled if ≤10 μm (NRC 2000). The most significant route of exposure to the general population is via ingestion of food or water contaminated with phosphate ester flame retardants (Fiserova-Bergerova and Pierce 1990; Hartmann et al. 2004; Hughes et al. 2001; IPCS 1997).

Data regarding dietary intake of phosphate ester flame retardants in children and adults in the United States are available only for select compounds and years. In 1980 and 1981–1982, ADI values of TCEP for adults were 0.041 and 0.055 μg/kg, respectively. In 1981–1982, the ADI for TnBP was found to be 0.025 μg/kg. This value was determined by measuring of TnBP in meats and fruits, and TCEP in cereals (Gantrell 1986). The ADI was calculated by Gunderson (1988, 1995a, 1995b) from the reported FDA Total Diet Study and these data are summarized in Table 6-2. Mean daily intakes for male and female teenagers aged 14–16 were highest for TPP ranging from 1.6 to 18.2 ng/kg/day. For male and female adults aged 25–30, TPP also had the highest mean daily intakes, ranging from 0.8–18.4 ng/kg/day. Both male and female adults aged 60–65 showed the highest mean daily intake for TBEP, ranging from 0.2 to 16.8 ng/kg/day. TPP was also quite prevalent for this age group. No data were reported for TiBP, TCP, or TDCP (Gunderson 1988, 1995a, 1995b).

In the United Kingdom, a diet study modeled after the U.S. Total Diet Study determined a total daily intake of 0.075–0.105 mg/day for trialkyl/aryl phosphates. The most prevalent of the selected phosphate esters were TnBP and TPP, found in meats, cereals, nuts, and some vegetables (Gilbert et al. 1986).

In Canada, TDCP was detected in human adipose tissue by LeBel and Williams (1983, 1986) in concentrations that ranged from not detectable (<0.001 μg/kg) to 257 μg/kg. In later studies, samples from four out of six cities showed no detectable TDCP; however, two concentrations ranged up to 32 μg/kg. (LeBel and Williams, 1983, 1986; LeBel et al. 1989). Using negative chemical ionization mass spectrometry (LC-MS-NCI) with a limit of detection of 0.01 μg, Hudec et al. (1981) found concentrations of TDCP in the seminal fluid of 34 out of 123 student donors ranging from 5 to 50 μg/L.

Table 6-2. Dietary Phosphate Ester Flame Retardant Intake

	Mean (ng/kg body weight/day)		
Age group	1982–1984[a]	1984–1986[b]	1986–1991[c]
Tributyl phosphate (TnBP)			
6–11 months	38.9	42.5	3.0
2 years	27.7	33.1	2.5
14–16 years, females	3.5	4.5	0.5
14–16 years, males	5.0	6.6	0.7
25–30 years, females	3.3	4.0	0.3
25–30 years, males	2.7	3.1	0.3
60–65 years, males	5.4	6.2	0.4
60–65 years, females	6.2	7.1	0.4
Triphenyl phosphate (TPP)			
6–11 months	0.3	1.8	15.7
2 years	4.4	16.0	34.8
14–16 years, females	1.6	5.8	16.3
14–16 years, males	1.2	5.0	18.2
25–30 years, females	0.8	3.3	12.8
25–30 years, males	1.6	5.5	18.4
60–65 years, males	0.5	2.4	11.4
60–65 years, females	0.5	2.4	15.8
Tris(2-butoxyethyl) phosphate (TBEP)			
6–11 months	2.9	0.2	5.2
2 years	14.4	1.5	3.7
14–16 years, females	8.4	0.7	1.2
14–16 years, males	7.7	1.1	1.1
25–30 years, females	12.9	0.4	2.0
25–30 years, males	10.7	0.8	0.9
60–65 years, males	16.8	0.2	3.4
60–65 years, females	13.7	0.2	2.8
Tri-(2-chloroisopropyl) phosphate (TCPP)			
6–11 months	No data	No data	0.1
2 years	No data	No data	0.2
14–16 years, females	No data	No data	0.1
14–16 years, males	No data	No data	0.1
25–30 years, females	No data	No data	0.1
25–30 years, males	No data	No data	0.1
60–65 years, males	No data	No data	0.1
60–65 years, females	No data	No data	

Table 6-2. Dietary Phosphate Ester Flame Retardant Intake

	Mean (ng/kg body weight/day)		
Age group	1982–1984[a]	1984–1986[b]	1986–1991[c]
Tris(2-chloroethyl) phosphate (TCEP)			
6–11 months	No data	4.9	No data
2 years	No data	6.5	No data
14–16 years, females	No data	2.1	No data
14–16 years, males	No data	1.1	No data
25–30 years, females	No data	1.8	No data
25–30 years, males	No data	1.3	No data
60–65 years, males	No data	3.1	No data
60–65 years, females	No data	2.6	No data

[a]Gunderson 1988 (ADI 1982–1984).
[b]Gunderson 1995a (ADI 1984–1986); expressed as μg/kg body weight/day in source.
[c]Gunderson 1995b (ADI 1986–1991); expressed as μg/kg body weight/day in source.

Morgan and Hughes (1981) tested workers manufacturing triaryl phosphate esters, including TPP, for cholinesterase activity to determine its efficacy as a biomarker for absorption. The results showed that it is not adequately sensitive to be used as a biomarker for phosphate ester absorption.

Three primary uses that account for the greatest potential worker exposure include aircraft manufacturing, hydraulic system component manufacturing, and commercial airline operations (Batt et al. 1992). In addition, workers in industries that manufacture plastics, floor polishes, wall coverings, and electronics may have a greater-than-average potential for exposure. Since TnBP and TCP are widely used in hydraulic and turbine oils, a study by Solbu and Daae et al. (2011) investigated exposures to pilots by measuring air and surface samples in various aircrafts following a recent flight. TCP was detected in 39% of the wipe samples but only 4% of the air samples, while TnBP was detected in all of the samples.

A survey conducted by NIOSH from 1981 to 1983 collected data on potential occupational exposures to chemical agents. These data provided estimates that indicated that the numbers of workers potentially exposed to TPP, TCP, TnBP, TBEP, TCEP, and TCPP were 91,754, 239,503, 109,402, 257,421, 5,073, and 120 respectively (NIOSH 1990).

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. 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 spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Exposure of children to phosphate ester flame retardants is likely to occur primarily through diet, indoor air, or by contact with flame retardant-treated plastics or fabrics. Young children are likely to have an increased oral exposure risk. Children may repeatedly suck on furnishing fabrics, plastics, or polished

surfaces, presenting potential dissolution of leachable flame retardants. Effective phosphate ester flame retardants are dependent upon retention in the applied matrix, and are therefore likely chosen based upon their ability to resist extraction from the matrix (NRC 2000). Children and infants may be exposed to phosphate ester flame retardants through ingestion of dust in homes where plastics, foams, floor polishes, or wall covering products containing phosphate esters are used (Hutter et al. 2006).

In 1980, the ADIs of TnBP for infants and toddlers were 0.051 and 0.132 μg/kg, respectively. In 1979 and 1980, TCEP was found to have an ADI of 0.016 and 0.004 μg/kg, respectively, in infants and 0.009 μg/kg and none detected, respectively, in toddlers. These were determined by measuring TnBP in cereals and TCEP in fruits (Gantrell 1985). Mean daily intakes for 6–11-month-old children were highest for TnBP between 1982 and 1986, ranging from 38.9 to 42.5 ng/kg//day. This number dropped significantly to 0.3 ng/kg/day in the last study published in 1986–1991. The next greatest exposure of 6–11-month-old children via diet appears to be TPP, with an ADI of 15.7 ng/kg/day in 1986–1991. The exposure data indicated that 2-year-old children could have exposures >30 ng/kg/day of TnBP and TPP (Gunderson 1988, 1995a, 1995b).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Phosphate esters do not occur naturally in the environment; therefore, potential high exposures are limited to occupational or indoor environments. Occupational exposure to phosphate ester flame retardants may occur during the manufacture, use, transport, processing, or disposal/recycling of flame retardants. Due to the presence of phosphate esters in turbine and hydraulic fluids, particularly TCP and TnBP, pilots may have a high risk of exposure (Solbu and Daae 2011). Routes of exposure could include inhalation, dermal contact, or ingestion. Living or working in an environment where there is an excess of flame retardant-treated products such as wall coverings, plastics, or electronics could contribute to a higher-than-average exposure. Additionally, living in an area where phosphate ester-contaminated effluent is used for drinking water or crop irrigation could contribute to a higher-than-average exposure (Fiserova-Bergerova and Pierce 1990; IPCS 1997).

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 phosphate ester flame retardants 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 phosphate ester flame retardants.

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. Table 4-2 summarizes many of the relevant physical and chemical properties of the selected phosphate ester flame retardants. The only data need is for measured Log K_{ow} and vapor pressures for TiBP.

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 2006, became available in February of 2008. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Current data on the use of each selected phosphate ester flame retardants are available and displayed in Table 5-1. Production, import, and export data are scarce and difficult to find, but estimates are provided by the EPA High Production Volume (HPV) Challenge Program or the Hazardous Substance Data Bank (HSDB) for all selected phosphate ester flame retardants. No data were available for manufacturers for TCPP, TCP, and TiBP as indicated in Table 5-1 (EPA 2006; HSDB 2009). A data need exists for release and disposal of phosphate ester flame retardants.

Environmental Fate. The environmental entry mechanism of phosphate esters, as well as transport and partitioning, is highly dependent on the specific compound. The environmental fate mechanisms of groups within the selected compounds (e.g., halogenated, alkyl, and aryl phosphate esters) are well understood (Muir 1984). Hydrolysis and adsorption are the primary forces that influence phosphate ester environmental fate and are well documented (Howard and Deo 1979; Kenaga and Goring 1980; Mayer et al. 1981; Muir 1984). No data needs are identified.

Bioavailability from Environmental Media. A data need exists for bioavailability of phosphate ester flame retardants from various media. Minimal data exist in the form of human monitoring, but several studies suggest that absorption of phosphate esters can occur via ingestion of foods and water contaminated with effluent or landfill leachate, inhalation of indoor and some outdoor air near airports and military installations, or dermal contact with contaminated soils or water (Fiserova-Bergerova and Pierce 1990; IPCS 1997; Monsanto Co. 1980; Saito et al. 2007).

Food Chain Bioaccumulation. Sufficient bioaccumulation data are available for TnBP, TPP, TCP, TCEP, and TDCP (Muir 1980, 1983a; Sasaki et al. 1981, 1982); however, a data need exists for bioaccumulation of TiBP, TBEP, and TCPP.

Exposure Levels in Environmental Media. **R**eliable monitoring data for the levels of phosphate ester flame retardants in contaminated media at hazardous waste sites are needed so that the information obtained on levels of phosphate ester flame retardants in the environment can be used in combination with the known body burden of phosphate ester flame retardants to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Extensive reports are available regarding quantifiable levels of phosphate ester flame retardants detected in the environment. More specifically, extensive monitoring data exist on phosphate ester flame retardants in water (Andresen et al. 2004; Fries and Puttmann 2001; Gomez-Belinchon et al. 1988; Ishikawa et al. 1985; Lee and Rasmussen 2006; Meyer and Bester 2004; Muir 1984; Peterman et a 1980; Reemtsma et al. 2006; Watts and Liden 2008, 2009) and indoor air (Carlsson et al. 2000; Garcia et al. 2007; Hutter et al. 2006; Ingerowski 2001, 2003; Otake et al. 2004, 2001; Owens et al. 2007; Sjodin et al. 2001). Studies detecting phosphate ester flame retardants in outdoor air are more sparse (Haraguchi et al. 1985; Monsanto Co. 1980; Saito et al. 2007). Additional data of phosphate ester flame retardants in soil and in food, as well as more recent average daily intake data, would be useful for estimating human exposure. In particular, there is a data need for environmental concentrations of TiBP.

Exposure Levels in Humans. Given that these compounds are considered emerging pollutants in some of the literature, there are relatively little data concerning levels of phosphate ester flame retardants in humans. There are, however, studies that reported levels of TDCP in human adipose tissue (Lebel and Williams 1983, 1986) and in the seminal fluid of student donors (Hudec et al. 1981). A data need exists for additional information regarding levels of these substances in blood, and urine from individuals with

potentially high exposures such as children and infants. A data need exists for studies addressing biomarkers as a method for determining exposure to mixtures of phosphate esters.

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

Exposures of Children. Children are exposed to phosphate ester flame retardants by the same routes as adults. In addition, oral exposure can occur from dissolution of phosphate ester treated materials since children are more likely to repeatedly suck on these materials (NRC 2000). A data need exists for levels of phosphate esters in blood and urine from children with known environmental exposure, as well as concentrations present in breast milk or infant formula to better estimate total exposure. Gantrell (1985) and Gunderson (1988, 1995a, 1995b) addressed only TnBP, TPP, TCEP, TCPP, and TBEP over a limited number of years (1982–1991). A data need exists for updated exposure in the form of ADI for children with the aforementioned compounds as well as new data regarding of TiBP and TDCP exposures.

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

Exposure Registries. No exposure registries for phosphate ester flame retardants were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is 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.

6.8.2 Ongoing Studies

No ongoing studies pertaining to the environmental fate of phosphate ester flame retardants were identified in a search of the Federal Research in Progress database (FEDRIP 2009).

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring phosphate ester flame retardants, their metabolites, and other biomarkers of exposure and effect to phosphate ester flame retardants. 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 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

Methods for the determination of phosphate ester flame retardants in biological materials are summarized in Table 7-1. There is virtually no information regarding the toxicokinetics of these chemicals in humans, including information on possible metabolites; consequently, there are no methods for determining metabolites. Thus far, detection of the parent compound is the only method available for detecting exposure to phosphate ester flame retardants.

There are very few published articles regarding bioanalytical methods for phosphate ester flame retardants, but interest in these compounds as emerging pollutants has stimulated development of a select few (Shah et al. 2006). The bioanalytical methods presented are preliminary and are not accepted methods of accurately determining phosphate ester flame retardants in biological materials.

Alkyl and aryl phosphate ester flame retardants were measured in blood using a method developed by Jonsson and Nilsson (2003). The sample preparation from blood plasma consisted of a hollow fibre-based XT-tube extractor to perform the liquid-liquid microextraction in hexane/methyl tert-butyl ether 2:1 (v/v). A top gas chromatograph equipped with a TS-2 nitrogen-phosphorus detector (NPD) was employed to analyze the phosphate esters. The detection limits were 0.3 ng/mL for TPP and 36 ng/mL for TBEP. Recoveries varied between 40 and 80% with a relative standard deviation (RSD) around 4%

Table 7-1. Analytical Methods for Determining Phosphate Ester Flame Retardants in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Analyte	Percent recovery	Reference
Urine	MISPE >80% recovery	LC-ESI-MS	0.025 ng/µL	TPP	72–75 RSD: 11–12%	Moller et al. 2004
			No data	TnBP	No data	
Blood plasma	Liquid-liquid microextraction	GC-MS-NPD	0.3 ng/mL	TPP	40–80 RSD: 4%	Jonsson and Nilsson 2003
			36 ng/mL	TnBP	40–80 RSD: 4%	
			No data	TBEP, TCEP, TCPP	40–80 RSD: 4%	
Blood Plasma	Methanol extraction, acetonitrile precipitation, then SPME	GC-ICP-MS	17 ng/L	TnBP	43 RSD 11%	Shah et al. 2006
			240 ng/L	TCEP	49 RSD 7%	
			24 ng/L	TPP	66 RSD 14%	
Tissue	Extract with benzene or acetone/hexane; fractionation by GPC	GC-MS-NPD	No data	TPP, TnBP, TBEP, TDCP, TCEP *o*-TCP *m*-TCP	2.5 ng: 78–96 10 ng: 52–100 25 ng: 88–105	LeBel and Williams 1983
Seminal fluid	Steam distillation; continuous liquid-liquid extraction	LC-MS-NCI	0.01 µg	TDCP	No data	Hudec et al. 1981

ESI = electronspray; GC = gas chromatography; GPC = gel permeation chromatography; ICP = inductively coupled plasma; LC = liquid chromatography; MISPE = molecularly imprinted polymer solid-phase extraction; MS = mass spectrometry; *m*-TCP = *meta*-tricresyl phosphate; NCI = negative chemical ionization; NPD = nitrogen-phosphorus detection; *o*-TCP = *ortho*-tricresyl phosphate; RSD = relative standard deviation; SPME = solid phase microextraction; TBEP = tris(2-butoxyethyl) phosphate; TCEP = tris(2-chloroethyl) phosphate; TCPP = tri-(2-chloro-isopropyl) phosphate; TiBP = triisobutyl phosphate; TnBP = tributyl phosphate; TOF = time of flight; TPP = triphenyl phosphate

for most compounds. The method was also able to detect and quantify other phosphate ester flame retardants such as TnBP, TCEP, and TCPP, although the detection limit was not sufficiently low.

Another analytical method to determine phosphorus-specific compounds in human plasma was published by Shah et al. (2006). This technique uses solid-phase microextraction (SPME) followed by gas chromatography (GC) inductively coupled plasma (ICP) mass spectrometry (MS) and high resolution GC time of flight (TOF) MS. The detection limits from blood plasma were 17 ng/L for TnBP, 240 ng/L for TCEP, and 24 ng/L for TPP.

In urine, Moller et al. (2004) detected and quantified TnBP and TPP hydrolysis products. The method is capable of extracting the corresponding diesters of TnBP and TPP via molecularly imprinted polymer solid-phase extraction (MISPE) and liquid chromatography (LC) electrospray (ESI) MS method using a Hypercarb LC column with a graphitized carbon stationary phase. The detection limit was 0.025 ng/µL for diphenyl phosphate, the hydrolysis product of TPP.

In Canada, TDCP was detected in human adipose tissue by LeBel and Williams (1983, 1986) in concentrations that ranged from not detectable (<0.001 µg/kg) to 257 µg/kg. In later studies, samples from four out of six cities showed no detectable TDCP; however, two concentrations ranged up to 32 µg/kg (LeBel and Williams 1983, 1986; LeBel et al. 1989). Using LC negative chemical ionization (NCI) MS with a limit of detection of 0.01 µg, Hudec et al. (1981) found TDCP in the seminal fluid of 34 out of 123 student donors. The TDCP concentrations ranged from 5 to 50 µg/L.

7.2 ENVIRONMENTAL SAMPLES

Methods for the determination of phosphate ester flame retardants in environmental samples are summarized in Table 7-2.

Standard environmental analysis methods are available for several of the selected phosphate ester flame retardants from the U.S. Geological Survey (USGS) and NIOSH (NIOSH 1994a, 1994b; USGS 2001). All standardized methods, as well as literature methods available, utilize either liquid- or gas-based chromatography with predominantly GC flame photometric detection (FPD) being employed. Methods for analyzing phosphate ester flame retardants in air, water, soil, and other environmental media are prevalent throughout the literature.

Table 7-2. Analytical Methods for Determining Phosphate Ester Flame Retardants in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Analyte(s)	Reference
Air (indoor)	Collection on filter, extract with ethyl ether, filter	NIOSH 5034 GC-FPD	2 µg/sample	No data	TnBP	NIOSH 1994a
Air (indoor)	Collection on filter, extract with ethyl ether, filter	NIOSH 5034 GC-FPD	0.05 µg/sample	101.3%	*o*-TCP	NIOSH 1994c
Air (indoor)	Absorbed on a filter, extracted with dichloromethane	GC-MS	3 ng/mL or 13 ng/m^3	92–109	TnBP, TiBP, TCP, TPP	Solbu et al. 2007
Air (outdoor)	Trap with glycerol-Florisil column, elute with MeOH/water, extract with hexane	GC-FPD	1 ng/m^3	No data	Trialkyl/aryl phosphates	IPCS 1991b (EHC-111)
Water, sediments, solid wastes, sludges	Collection on filter, extract with ethyl ether, filter	NIOSH 5038 GC-FPD	10 µg/sample	No data	TPP	NIOSH 1994b
Water, sediments, solid wastes, sludges	Extracted with CH_2Cl_2 or MeCN, gel permeatation, SPE	GC-FPD EPA-8141a; EPA-1618	Not specified	No data	TCP	EPA 1989, 1994
Filtered waste water and water	Filtered, extracted with an SPE cartridge containing a polystyrene divinylbenzene phase, dried, rinsed with DCM/ether, and concentrated	USGS-NWQL O-1433-01 GC-MS	TnBP 0.1 µg/L	TnBP: 110[a], 5.97% RSD	TnBP, TBEP, TPP, TDCP, TCEP	USGS 2001
			TBEP 0.2 µg/L	TBEP: 103.4[a], 12.52% RSD		
			TPP 0.06 µg/L	TPP: 90[a], 4.5% RSD		
			TDCP: 0.08 µg/L	TDCP: 96.4[a], 5.29% RSD		
			TCEP: 0.08 µg/L	TCEP: 100[a], 5.04% RSD		
Water (drinking)	Adsorb resin, elute	GC-NPD	1 ng/L	No data	Trialkyl/aryl phosphates	LeBel et al. 1979

Table 7-2. Analytical Methods for Determining Phosphate Ester Flame Retardants in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Analyte(s)	Reference
Sediments (sea or river)	Extract with MeCN or acetone, Florisil column	GC-FPD	TnBP: 2 ng/g TCPP: 5 ng/g TCEP: 5 ng/g TPP: 5 ng/g TCP: 20 ng/g	83–98	TnBP, TCEP, TPP, TCPP, TCP	Ishikawa et al. 1985

[a]Percent recovery and relative standard deviation were reported by NEMI (2009).

DCM = dichloromethane; FPD = flame photometric detection; GC = gas chromatography; MS = mass spectrometry; *m*-TCP = *meta*-tricresyl phosphate; NIOSH = National Institute for Occupational Safety and Health; NPD = nitrogen-phosphorus detection; *o*-TCP = *ortho*-tricresyl phosphate; RSD = relative standard deviation; SPE = solid phase extraction; TBEP = tris(2-butoxyethyl) phosphate; TCEP = tris(2-chloroethyl) phosphate; TCPP = tri-(2-chloroisopropyl) phosphate; TiBP = triisobutyl phosphate; TnBP = tributyl phosphate; TPP = triphenyl phosphate; USGS = U.S. Geological Survey

Drinking water has been analyzed for TPP using a modified version of EPA method 525.5 using C-18 bonded solid phase extraction columns (Stiles et al. 2008) and also using GC-MS with NPD (LeBel et al. 1979). TPP adsorbed to sediments and soils can also be analyzed using a method developed by Degeus et al. (1994) using thermionic detection (TID) with supercritical fluid chromatography (SFC).

An alternative method for testing for phosphate ester flame retardants was developed by Lombardo and Egry (1979) based on an AOAC method developed for analysis of pesticide residues in fatty foods. The method extracted the hydraulic fluid from contaminated fish samples and analyzed them by gas-liquid chromatography (GLC) with phosphorus selective detection. The analysis yielded concentrations of TPP concentrations of 0.06 and 0.12 ppm in carp and 0.15 ppm in goldfish collected from Waukegan Harbor, Illinois.

Several other methods were developed for detection of phosphate esters in various types of media. Lamouroux et al. (2000) report an LC-MS method for determining degradation products of TnBP used in nuclear fuel processing. The TnBP content affects the performance of the extracting solvent; therefore, determining the diester and monoester content is desired.

Nagase et al. (2003) used GC-FPD to detect phosphate ester flame retardants in polyurethane foam cushions. The detection limits were 0.3–0.9 μg/g. The recoveries from a 0.05 g sample of soft polyurethane foam were 80–90%, when the spiked amounts were 0.25–1 μg. The compounds were detected from soft polyurethane foam at a level of 0.4–23.3 μg/g.

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 phosphate ester flame retardants 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 phosphate ester flame retardants.

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. *In vitro* analytical methods have shown to detect TnBP, TPP, TCEP, TCPP, and TBEP in bodily fluids using GC-MS (Moller et al. 2004; Jonsson and Nilsson 2003). It is not documented whether these methods could be applied to analysis of TiBP or TDCP in bodily fluids. TDCP is the only analyte of the selected phosphate esters reported to be analyzed in human tissue and seminal fluid (Hudec et al. 1981; Lebel and Williams 1983, 1986). There are no specific biomarkers of exposure other than the phosphate esters themselves. A data need exists for additional bioanalytical methods for TiBP and TDCP. As information becomes available regarding the metabolism of these chemicals in humans, appropriate methods need to be developed for the detection and quantification of metabolites in tissues and biological fluids.

Effect. No significant health effects have been reported in humans exposed to the phosphate ester flame retardants discussed in this profile in the limited studies available of workers exposed to TDCP or TPP (Stauffer Chem Co. 1983; Sutton et al. 1960). Consequently, no associations have been established between body burdens of phosphate esters and health effects. More information is needed regarding the toxicity and toxicokinetics of these substances to determine whether the existing analytical methods reported in Table 7-1 are adequate in selectivity and sensitivity to measure phosphate esters in biological materials at levels associated with adverse health effects.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. GC coupled with various detection methods (MS, FPD, or NPD) provide sufficiently accurate, precise, and repeatable methods for determining phosphate ester concentrations in the environment (Ishikawa et al. 1985; LeBel et al. 1979; NIOSH 1994a, 1994b; Solbu et al. 2007; USGS 2001; IPCS 1991a, 1991b). These analytical methods can adequately measure phosphate esters in air, water, soil, and sediments at concentrations in the ng/L or ng/m^3 range.

7.3.2 Ongoing Studies

No ongoing studies pertaining to analytical methods for phosphate ester flame retardants were identified in a search of the Federal Research Progress database (FEDRIP 2009).

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, 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.

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

ATSDR has derived an intermediate-duration oral MRL of 0.6 mg/kg/day for TCEP based on an increased incidence of brain lesions in female Fischer-344 rats dosed by gavage 5 days/week for 16 weeks (NTP 1991a). The MRL was derived using benchmark modeling of incidence data for brain lesions in female rats. The predicted dose associated with a 10% extra risk (BMD_{10}) for brain lesions was 143.41 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 85.07 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived a chronic-duration oral MRL of 0.2 mg/kg/day for TCEP based on an increased incidence of renal tubule epithelial hyperplasia in female Fischer-344 rats dosed by gavage 5 days/week for 2 years (NTP 1991a). The MRL was derived using benchmark modeling of incidence data for renal lesions in female rats. The BMD_{10} for renal lesions was 48.00 mg/kg/day; the $BMDL_{10}$ was 32.82 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived an acute-duration oral MRL of 1.1 mg/kg/day for TnBP based on decreased body weight gain in Wistar rats during pregnancy (Noda et al. 1994). The MRL was derived using benchmark modeling of the decrease in body weight gain. The BMD_{1SD} was 130.32 mg/kg/day; the corresponding $BMDL_{1SD}$ was 111.47 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived an intermediate-duration oral MRL of 0.08 mg/kg/day for TnBP based on an increased incidence of urinary bladder hyperplasia in male Sprague-Dawley rats dosed via the diet for 10 weeks (Arnold et al. 1997). The MRL was derived using benchmark modeling of incidence data for urinary bladder lesions in male rats. The BMD_{10} for urinary bladder lesions was 19.74 mg/kg/day; the

Table 8-1. Regulations, Advisories, and Guidelines Phosphate Ester Flame Retardants

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 3[a]	IARC 2009
	Tris-(2-chloroethyl)-phosphate		
WHO	Air quality guidelines	No	WHO 2000
	Drinking water quality guidelines	No	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2008
	Tributyl phosphate	2.5 mg/m^3 (0.19 ppm)	
	Triphenyl phosphate	3.0 mg/m^3 (0.22 ppm)	
	TLV Basis		
	Tributyl phosphate	Nausea, headache, eye and upper respiratory irritation	
	Triphenyl phosphate	Cholinesterase inhibitor	
AIHA	ERPG values	No	AIHA 2008
EPA	AEGL values	No	EPA 2009a
	Hazardous air pollutant	No	EPA 2009b 42 USC 7412
NIOSH	REL (10-hour TWA)		NIOSH 2005b
	Tributyl phosphate	2.5 mg/m^3 (0.19 ppm)	
	Triphenyl phosphate	3.0 mg/m^3 (0.22 ppm)	
	IDLH		
	Tributyl phosphate	327 mg/m^3 (30 ppm)	
	Triphenyl phosphate	1,000 mg/m^3 (75 ppm)	
	Target organs		
	Tributyl phosphate	Eyes, skin, and respiratory system	
	Triphenyl phosphate	Blood and peripheral nervous system	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2009 29 CFR 1910.1000, Table Z-1
	Tributyl phosphate	5.0 mg/m^3 (0.46 ppm)	
	Triphenyl phosphate	3.0 mg/m^3 (0.22 ppm)	

Table 8-1. Regulations, Advisories, and Guidelines Phosphate Ester Flame Retardants

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
b. Water			
EPA	Drinking water standards and health advisories	No	EPA 2006a
	National primary drinking water standards	No	EPA 2003
	National recommended water quality criteria	No	EPA 2006b
c. Food			
FDA	EAFUS[b]	No	FDA 2008
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2008
	Tributyl phosphate	No	
	Triphenyl phosphate	A4[c]	
EPA	Inert ingredients are permitted for use in nonfood use pesticide products		EPA 2009c
	Tributyl phosphate, tributoxyethyl phosphate, and triphenyl phosphate	Yes	
	Inert ingredients are no longer permitted for use in nonfood use pesticide products		EPA 1998b 63 FR 34834
	Tricresyl phosphate	Yes	
	Carcinogenicity classification	No	IRIS 2009
	RfC	No	
	RfD	No	
	MTL		EPA 2009
	Triphenyl phosphate	Yes[d]	
	Tricresyl phosphate	Yes[d]	
	Tri-(2-chloroisopropyl) phosphate	Yes[e]	
	Tris-(2-chloroethyl)-phosphate	Yes[e]	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	No	EPA 2009d 40 CFR 302.4
	Effective date of toxic chemical release reporting	No	EPA 2009e 40 CFR 372.65

Table 8-1. Regulations, Advisories, and Guidelines Phosphate Ester Flame Retardants

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	TSCA chemical lists and reporting periods		EPA 2009f 40 CFR 712.30
	Tributyl phosphate, triisobutyl phosphate, and tributoxyethyl phosphate		
	Effective date	10/29/1990	
	Reporting date	12/27/1990	
	TSCA health and safety data reporting		EPA 2009g 40 CFR 716.120
	Tributyl phosphate		
	Effective date	06/18/1986	
	Sunset date	06/18/1996	
	Tricresyl phosphate		EPA 2009g 40 CFR 716.120
	Effective date	10/04/1982	
	Sunset date	10/04/1992	
	Trisobutyl phosphate		
	Effective date	10/29/1990	
	Sunset date	11/09/1993	
	Tributoxyethyl phosphate		
	Effective date	10/29/1990	
	Sunset date	12/19/1995	
	Triphenyl phosphate		
	Effective date	10/04/1982	
	Sunset date	10/04/1992	
	TSCA chemical lists and reporting periods		EPA 2009f 40 CFR 712.30
	Tri-(2-chloroisopropyl) phosphate and tris-(2-chloroethyl)-phosphate		
	Effective date	12/16/1988	
	Sunset date	11/09/1993	
	Tris(1,3-dichloro-2-propyl) phosphate		
	Effective date	12/16/1988	
	Sunset date	12/19/1995	

Table 8-1. Regulations, Advisories, and Guidelines Phosphate Ester Flame Retardants

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NTP	Carcinogenicity classification	No data	NTP 2005
	Nominated for in-depth toxicological evaluation	Tricresyl phosphate	NTP 2011

[a]Group 3: not classifiable as to carcinogenicity to humans
[b]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[c]A4: not classifiable as a human carcinogen
[d]Triphenyl phosphate and tricresyl phosphate were added to the MTL in 1992 and the testing action development is underway. The testing needs include health effects, ecological effects, and chemical fate.
[e]Tri-(2-chloroisopropyl) phosphate and tris-(2-chloroethyl)-phosphate were added to the MTL in 1992 and the chemical testing program is underway.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MTL = Master Testing List; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

$BMDL_{10}$ was 8.03 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

ATSDR has adopted the intermediate-duration oral MRL of 0.08 mg/kg/day for TnBP also as the chronic-duration oral MRL for TnBP. A detailed explanation can be found in Section 2.3.

ATSDR has derived an acute-duration oral MRL of 4.8 mg/kg/day for TBEP based on decreased body weight gain in CD rats during Gd 6–15 (Monsanto Co. 1985b). The MRL was derived using benchmark modeling of the decrease in body weight gain. The BMD_{1SD} was 824.97 mg/kg/day; the corresponding $BMDL_{1SD}$ was 477.25 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived an intermediate-duration oral MRL of 0.09 mg/kg/day for TBEP based on an increased incidence of periportal hepatocyte vacuolization in male Sprague-Dawley rats dosed via the diet for 18 weeks (Reyna and Thake 1987a). The MRL was derived using benchmark modeling of incidence data for hepatocyte vacuolization in male rats. The BMD_{10} for hepatocyte vacuolization was 22.02 mg/kg/day; the $BMDL_{10}$ was 8.88 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived an intermediate-duration oral MRL of 0.05 mg/kg/day for TDCP based on increased absolute kidney weight in male Sprague-Dawley rats dosed via the diet for 12 months (Stauffer Chemical Co. 1981a). The MRL was derived using benchmark modeling of the increase in kidney weight. The BMD_{1SD} was 13.36 mg/kg/day; the corresponding $BMDL_{1SD}$ was 4.69 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived a chronic-duration oral MRL of 0.02 mg/kg/day for TDCP based on an increased incidence of renal tubular epithelial hyperplasia in male Sprague-Dawley rats dosed via the diet for 2 years (Stauffer Chemical Co. 1981a). The MRL was derived using benchmark modeling of incidence data for renal lesions in male rats. The BMD_{10} for renal tubular hyperplasia was 2.60 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 1.94 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived an intermediate-duration oral MRL of 0.04 mg/kg/day for TCP based on an increased incidence of hyperplasia of the interstitial cell in the ovary in female F344/N rats dosed via the diet for

3 months (NTP 1994). The MRL was derived using benchmark modeling of incidence data for ovarian lesions. The BMD_{10} for ovarian lesions was 6.21 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 3.72 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived a chronic-duration oral MRL of 0.02 mg/kg/day for TCP based on an increased incidence of hyperplasia of the interstitial cell in the ovary in female F344/N rats dosed via the diet for 15 months (NTP 1994). The MRL was derived using benchmark modeling of incidence data for ovarian lesions. The BMD_{10} for ovarian lesions was 5.22 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 2.12 mg/kg/day. An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 for human variability).

EPA (IRIS 2009) has not established an oral reference dose (RfD) or inhalation reference concentration (RfC) for phosphate ester flame retardants.

The International Agency for Research on Cancer (IARC) has classified TCEP as a Group 3 carcinogen (*not classifiable as to carcinogenicity to humans*) (IARC 2009). The American Conference of Governmental Industrial Hygienists (ACGIH) has classified TPP as an A4 carcinogen (*not classifiable as a human carcinogen*) (ACGIH 2008). Neither the National Toxicology Program (NTP) nor the EPA has classified the phosphate ester flame retardants discussed in this profile for human carcinogenicity (IRIS 2009; NTP 2005).

OSHA has required employers of workers who are occupationally exposed to TnBP and TPP to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs) (OSHA 2009). The employer must use engineering and work practice controls to reduce exposures to not exceed 5 and 3 mg/m^3 at any time for TnBP and TPP, respectively (OSHA 2009).

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), TnBP, TBPE, and TPP are permitted for use in nonfood pesticide products (EPA 2009c).

All of the phosphate ester flame retardants subject of this profile are required under Section 4(a) of the Toxic Substances Control Act (TSCA) to submit copies of health and safety studies (EPA 2009f). TnBP,

TiBP, and TBEP are required to report production, use, and exposure-related information on chemical substances listed under TSCA (EPA 2009g).

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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-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without 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 of a substance that should not be exceeded, even instantaneously.

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 assessment.

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

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

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)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

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 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 chemical.

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) allowable exposure level in workplace air averaged over an 8-hour 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.

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 air/blood 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 chemical. 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 chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, 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)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

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 most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

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 chemical 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 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 chemical-induced end point 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 (proposed), 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 (proposed), Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tris(2-chloroethyl) phosphate (TCEP)
CAS Numbers: 115-96-8
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 23
Species: Rat

Minimal Risk Level: 0.6 [X] mg/kg/day [ ] ppm

Reference: NTP. 1991a. NTP toxicology and carcinogenesis studies of tris(2-chloroethyl) phosphate (CAS No. 115-96-8) in F344/N rats and B6C3F$_1$ mice (gavage studies). Program NT. TR 391. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr391.pdf. May 6, 2009.

Experimental design: Groups of Fischer-344 rats (10/sex/dose) were administered 0, 22, 44, 88, 175, or 350 mg TCEP by gavage in corn oil 5 days/week for 16 weeks (females) or 18 weeks (males). End points examined included clinical signs, body weight, serum cholinesterase activity, organ weight, gross necropsy, and histopathology of tissues and organs (control and highest dose group). The brain and kidneys of mid-dose (88 mg/kg/day) females were also examined microscopically.

Effect noted in study and corresponding doses: Two females in each the 175 and 350 mg/kg/day groups died on week 4 due to overdosing that week; others in these groups showed ataxia, convulsions, excessive salivation, and gasping. Females receiving 175 and 350 mg/kg/day experienced occasional periods of hyperactivity after dosing. High-dose females showed periodic convulsions during week 12. At termination, serum cholinesterase was reduced by 25 and 41% in females treated with 175 and 350 mg/kg/day, respectively; serum cholinesterase activity in males was comparable among groups. Final absolute and relative (to body weight or brain weight) weight of the liver and kidney of treated males and females were increased relative to controls (>10% at 175 mg/kg/day). At termination, serum cholinesterase was reduced by 25 and 41% in females treated with 175 and 350 mg/kg/day, respectively; cholinesterase in males was comparable among groups. There were no gross lesions due to treatment. However, necrosis of neurons of the hippocampus was seen in 10/10 females and in 2/10 males treated with 350 mg/kg/day, and in 8/10 females treated with 175 mg/kg/day. The affected neurons were mainly in the dorsomedial portion of the pyramidal row of the hippocampus. The more severe lesions showed mineral deposits in the affected areas. High-dose females also showed neuronal necrosis in the thalamus. The dose of 88 mg TCEP/kg/day is a NOAEL for brain lesions in female rats.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 85.07 mg/kg/day for brain lesions in female rats.

[ ] NOAEL [ ] LOAEL [X] $BMDL_{10}$

Uncertainty Factors used in 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? Yes, the test chemical was administered 5 days/week; therefore, the $BMDL_{10}$ of 85.07 mg/kg/day was adjusted for continuous exposure by multiplying by 5 and dividing by 7 yielding a duration-adjusted $BMDL_{10}$ of 60.76 mg/kg/day.

Other additional studies or pertinent information that lend support to this MRL: Only three studies were available for review. NTP (1991a) also conducted studies in $B6C3F_1$ mice and reported that no brain lesions were observed in mice treated with up to 700 mg TCEP/kg/day for 16 weeks. Similar doses were tested in CD-1 mice in a reproductive study that used a continuous breeding protocol, and no brain lesions were reported in that study (NTP 1991b). In the reproductive study, the lowest dose tested, 175 mg TCEP/kg/day, caused a significant reduction in the number of live F_2 male pups per litter. In a 90-day study in male and female Sprague-Dawley rats administered up to 586 mg TCEP/kg/day via the diet, no brain lesions were reported (Anonymous 1977). However, it is unclear in the report available whether the brain was examined microscopically. No adverse effects were reported in that study, including hematology and clinical chemistry parameters, and histopathology of organs and tissues.

Modeling of the changes in absolute kidney weight in female rats proved unsuccessful as an adequate fit could not be obtained with any model. However, if the changes in absolute kidney weight in female rats in the NTP (1991a) study had been used as basis for MRL derivation using a NOAEL/LOAEL approach, the NOAEL would have been 88 mg TCEP/kg/day (<10% increase in kidney weight). The next highest dose, 175 mg/kg/day induced a 16% increase in absolute kidney weight. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the duration-adjusted NOAEL of 62.86 mg/kg/day (88 mg/kg/day x 5/7) would have resulted in an MRL of 0.6 mg/kg/day for TCEP, which supports the MRL derived using the BMD approach using the data set for brain lesions.

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APPENDIX A

BENCHMARK MODELING OF BRAIN LESIONS IN FEMALE RATS

Incidence data for brain lesions in female rats exposed to TCEP (NTP 1991a) were analyzed using the BMD approach for MRL derivation (Table A-1). Models in the EPA BMDS (version 2.1) were fit to the brain lesions data to determine a potential point of departure for the MRL. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in body weight, in the absence of a clear criteria as to what level of change in body/organ weight or body weight gain should be considered adverse, the BMR is defined as a change in weight or weight gain equal to 1 SD from the control mean (EPA 2000).

Table A-1. Incidence of Hippocampal Necrosis in Female Rats Exposed to TCEP for 16 Weeks

Dose (mg/kg/day)	Total number of rats	Number of rats with lesions
0	10	0
22	10	0
44	10	0
88	10	0
175	10	8
350	10	10

Source: NTP 1991a

Table A-2. Model Predictions for Necrosis of Hippocampal Neurons in Female Rats Exposed to TCEP for 16 Weeks

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	5	0.28	1.00	-0.49	0.20	-0.49	12.52	106.78	80.41
Logistic	4	0.00	1.00	0.00	0.00	0.00	14.01	160.02	88.23
LogLogistic[d,e]	**5**	**0.00**	**1.00**	**-0.013**	**0.00**	**-0.013**	**12.01**	**143.41**	**85.07**
LogProbit[d]	4	0.00	1.00	0.00	0.00	0.00	14.01	140.11	84.26
Multistage (1-degree)[f]	5	13.21	0.02	-1.1	-1.52	-2.3	33.31	ND(LS)	ND(LS)
Multistage (2-degree)[f]	5	5.08	0.41	-0.81	-1.70	-1.70	20.35	56.58	41.38
Multistage (3-degree)[f]	5	2.35	0.80	-0.42	-1.28	-1.28	16.02	77.77	59.06
Multistage (4-degree)[f]	5	1.12	0.95	-0.96	0.37	0.96	14.04	91.96	69.76
Multistage (5-degree)[f]	5	0.54	0.99	-0.70	0.19	0.19	13.04	103.04	76.30
Probit	4	0.00	1.00	0.00	0.00	0.00	14.01	147.06	85.11
Weibull[c]	4	0.00	1.00	-0.01	0.00	-0.01	14.01	149.30	84.03

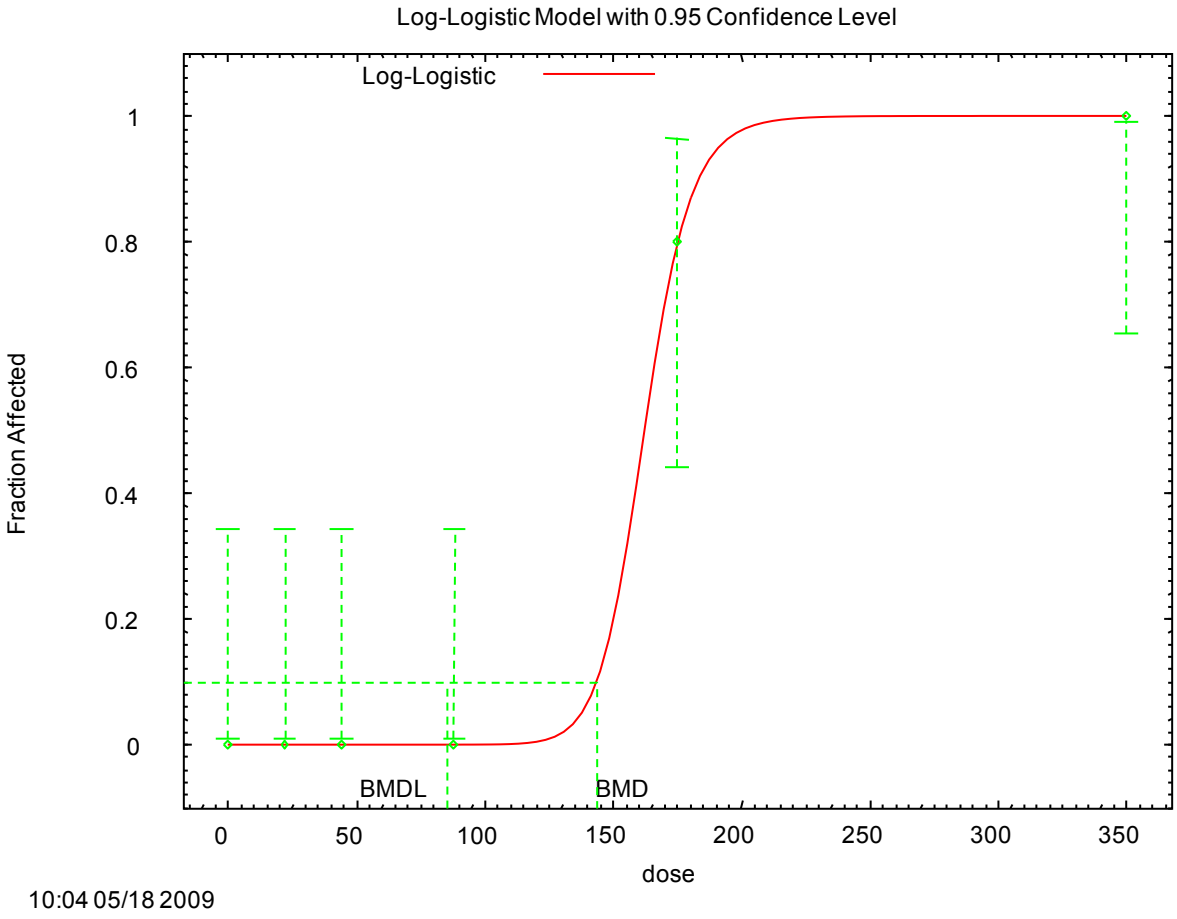
[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. All models (except for the Multistage 1-degree) provided adequate fit to the data. Since the range of BMDLs was <3-fold, the model with the lowest AIC was selected.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); BMR = benchmark response; DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND(LS) = not determined; largest scaled residual >2

Source: NTP 1991a

Based on these criteria, a Log-logistic model provided the best fit to the data (Table A-2). From this model, the predicted doses associated with a 10% extra risk (BMD_{10}) for brain lesions in female rats was 143.41 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 85.07 mg/kg/day (Figure A-1). Modeling the decrease in the number of live F_2 male pups per litter reported in the NTP (1991b) study resulted in the Linear (constant variance) model providing the best fit with a BMD_{10} and $BMDL_{10}$ of 242.19 and 167.83 mg/kg/day, respectively, considerably higher than the values obtained in the analysis of the brain lesions in female rats.

Figure A-1. Predicted and Observed Incidence of Brain Lesions in Female Rats Exposed to TCEP for 16 Weeks



APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tris(2-chloroethyl) phosphate (TCEP)
CAS Numbers: 115-96-8
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 34
Species: Rat

Minimal Risk Level: 0.2 [X] mg/kg/day [ ] ppm

Reference: NTP. 1991a. NTP toxicology and carcinogenesis studies of tris(2-chloroethyl) phosphate (CAS No. 115-96-8) in F344/N rats and B6C3F_1 mice (gavage studies). Program NT. TR 391. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr391.pdf. May 6, 2009.

Experimental design: Groups of Fischer-344 rats (60 rats/sex/dose) were administered 0, 44, or 88 mg TCEP/kg/day by gavage in corn oil 5 days/week for 104 weeks. End points examined included clinical signs, body weight, organ weight, gross necropsy, and histopathology of all major tissues and organs at interim kill (week 66, 10 rats/sex/group) and at termination. Hematology and clinical chemistry tests were conducted at interim kill.

Effect noted in study and corresponding doses: There were no clinical signs attributable to administration of TCEP or effects on body weight. Survival was reduced in high-dose males and females. Females that died early frequently had brain lesions, males did not. There were no chemical-related alterations in clinical chemistry and hematology parameters at week 66. Interim necropsy revealed a significant increase in absolute and relative liver and kidney weights in high-dose males. At termination, one of the principal nonneoplastic alterations attributed to administration of TCEP was a significant increase in renal tubule epithelial hyperplasia in the convoluted tubules of the cortex in high-dose males and females. The lesions were focal or multifocal and were characterized by stratification of the epithelial cells with partial to complete obliteration of the tubule lumens. In addition to the kidneys lesions, high-dose female rats showed degenerative lesions in the brain. The degenerative lesions were located in the cerebral cortex and brain stem, involved both the gray and white matter, and were focally distributed. Specifically, the lesions were in the thalamus, hypothalamus, basal ganglia, and frontal and parietal cortex. Other affected structures included the cingulate cortex, olfactory cortex, superior colliculus, hippocampus, geniculate body, globus pallidus, ventral pallidum, and amygdaloid nuclear region. The lesions varied in severity from minimal to marked, and often involved extensive areas. Active lesions were characterized by degeneration and necrosis with hemorrhage, while resolving lesions exhibited loss of neurons and neuropil, proliferation of glial cells, capillary hyperplasia, hypertrophy of the tunica media of small vessels, and hemosiderin-laden macrophages. Brain lesions were already observed at the 66-month interim kill. Incidences of lesions in specific areas ranged from 24 to 38%. The lesion with the highest incidence was cerebrum gliosis with an incidence of 19/50 (38%); the incidences in the control and low-dose groups were 0/50 and 0/49, respectively. A NOAEL of 44 mg/kg/day was defined for renal tubule epithelial hyperplasia in male and female rats and for cerebrum gliosis in female rats.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 32.82 mg/kg/day for renal tubule epithelial hyperplasia in female rats.

[ ] NOAEL [ ] LOAEL [X] $BMDL_{10}$

Uncertainty Factors used in 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? Yes, the test chemical was administered 5 days/week; therefore, the $BMDL_{10}$ of 32.82 mg/kg/day was adjusted for continuous exposure by multiplying by 5 and dividing by 7 yielding a duration-adjusted $BMDL_{10}$ of 23.44 mg/kg/day.

Other additional studies or pertinent information that lend support to this MRL: The NTP (1991a) study was the only chronic-duration oral study available for TCEP. The $BMDL_{10}$ for cerebrum gliosis in female rats was somewhat higher (59.86 mg/kg/day) than that obtained for the renal tubular hyperplasia in both male and female rats; therefore, the MRL derived based on renal lesion is protective of brain lesions.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

BENCHMARK MODELING OF RENAL TUBULE HYPERPLASIA IN FEMALE RATS

Incidence data for renal tubule epithelial hyperplasia in female rats exposed to TCEP (NTP 1991a) were analyzed using the BMD approach for MRL derivation (Table A-3). Models in the EPA BMDS (version 2.1) were fit to the brain lesions data to determine a potential point of departure for the MRL. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in body/organ weight or weight gain, in the absence of a clear criteria as to what level of change should be considered adverse, the BMR is defined as a change equal to 1 SD from the control mean (EPA 2000).

Table A-3. Incidence of Renal Tubule Epithelial Hyperplasia in Rats Exposed to TCEP for 2 Years

Dose (mg/kg/day)	Total number of rats	Males with lesions	Females with lesions
0	50	0	0
44	50	2	3
88	50	24	16

Source: NTP 1991a

Based on the criteria mentioned above, the Multistage (2-degree) model best fit the data. From this model, the predicted doses associated with a 10% extra risk (BMD_{10}) for renal tubule hyperplasia in female rats was 48.00 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 32.82 mg/kg/day (Figure A-2). Modeling the data set for renal tubule hyperplasia in male rats resulted in the Log logistic model providing the best fit with a BMD_{10} and $BMDL_{10}$ of 54.80 and 43.58 mg/kg/day, respectively, only slightly higher than the values obtained in the analysis of the lesions in female rats. Modeling the data set for cerebrum gliosis in female rats resulted in the Log logistic model providing the best fit with a BMD_{10} and $BMDL_{10}$ of 80.04 and 59.86 mg/kg/day, respectively. Therefore, the MRL based on renal lesions is protective of brain lesions.

Table A-4. Model Predictions for Incidence of Renal Tubule Epithelial Hyperplasia in Female Rats Exposed to TCEP for 2 Years

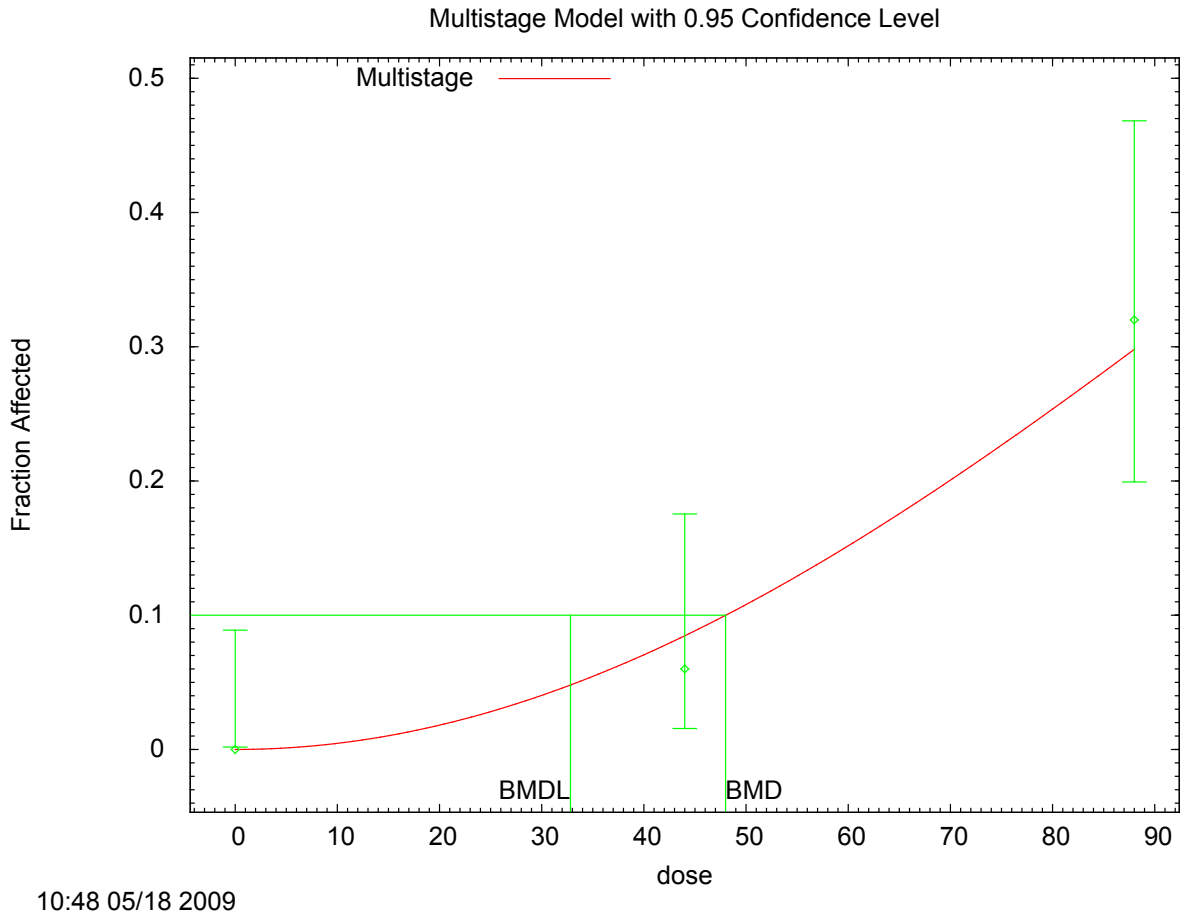
Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	1	0.00	1.00	0.00	0.00	0.00	89.38	53.09	36.09
Logistic	1	0.41	0.52	0.36	-0.08	-0.53	90.06	60.16	49.51
LogLogistic[d]	1	0.00	1.00	0.00	0.00	0.00	89.38	53.33	36.29
LogProbit[d]	1	0.00	1.00	0.00	0.00	0.00	89.38	52.37	37.59
Multistage (1-degree)[e]	2	3.66	0.16	0.00	-1.54	-1.54	91.51	32.13	22.50
Multistage (2-degree)[e,f]	**2**	**0.51**	**0.78**	**-0.63**	**0.34**	**-0.63**	**87.93**	**48.00**	**32.82**
Probit	1	0.20	0.66	0.24	-0.08	-0.36	89.71	57.32	46.59
Weibull[c]	1	0.00	1.00	0.00	0.00	0.00	89.38	53.83	35.90

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided adequate fit to the data. Since the range of BMDLs was <3-fold, the model with the lowest AIC was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); BMR = benchmark response; DF = degrees of freedom

Source: NTP 1991a

Figure A-2. Predicted and Observed Incidence of Renal Tubule Hyperplasia in Female Rats Exposed to TCEP for 2 Years



APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tributyl phosphate (TnBP)
CAS Numbers: 126-76-8
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 13
Species: Rat

Minimal Risk Level: 1.1 [X] mg/kg/day [ ] ppm

Reference: Noda T, Yamano T, Shimizu M, et al. 1994. Effects of tri-n-butyl phosphate on pregnancy in rats. Food Chem Toxicol 32(11):1031-1036.

Experimental design: Groups of Wistar rats (20 rats/sex/dose level) were administered 0, 62.5, 125, 250, or 500 mg TnBP/kg/day by gavage in corn oil on Gd 7–17. Clinical signs, body weight, and food consumption were monitored. The rats were euthanized on Gd 20. The gravid uterus, the position and number of living and dead fetuses in the uterus, including resorbed fetuses in the uterus, the number of corpora lutea, and maternal liver, kidneys, and spleen weights were recorded. The living fetuses were examined for their sex and external malformation, and then weighed. Skeletal abnormalities were evaluated in half of the fetuses, whereas the other half was evaluated for visceral abnormalities.

Effect noted in study and corresponding doses: Rats exposed to 500 mg TnBP/kg/day showed piloerection, wetting of abdominal hair with urine, and salivation during treatment, but these signs disappeared after the last treatment. Final maternal weight was reduced 6–9% in the two highest dose groups. Adjusted body weight gain (weight gain from Gd 0 to 20 minus gravid uterus weight) was reduced 13% at 125 mg/kg/day, 39% at 250 mg/kg/day, and 63% at 500 mg/kg/day. Absolute liver and kidney weight in treated rats was not affected (<10% change relative to controls). Spleen weight was reduced 11% at 500 mg/kg/day. Gravid uterus weight was not affected by treatment. All pregnant rats had fetuses on Gd 20. There were no significant differences between the groups in any of the developmental parameters evaluated. There was only one malformation occurring in the 125 mg/kg/day dose group and consisted of conjoined twins. No visceral anomalies were reported. Based on a significant reduction in maternal body weight gain at ≥125 mg/kg/day, a maternal NOAEL and LOAEL of 62.5 and 125 mg/kg/day, respectively, were defined in this study; the highest dose tested, 500 mg/kg/day was a developmental NOAEL.

Dose and end point used for MRL derivation: $BMDL_{1SD}$ of 111.47 mg/kg/day for decrease weight gain in pregnant rats on Gd 0–20.

[ ] NOAEL [ ] LOAEL [X] BMDL

Uncertainty Factors used in 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 MRL: Only one additional study was a potential source of data for MRL derivation. In that study, groups of Sprague-Dawley rats (10/sex/group) were administered 0, 137, or 411 mg TnBP/kg/day by gavage on 14 consecutive days (Laham et al. 1984b). End points examined included clinical signs, body weight, hematological and clinical chemistry tests, and histological examinations of the brain, heart, kidneys, liver, lungs, spleen, ovaries, and testes. Significant findings in high-dose rats included decreased hemoglobin in females, increased absolute and relative liver weight in males and females, increased serum potassium in females, decreased absolute and relative spleen weight, and degenerative changes in the testes. A study of limited scope reported decreased nerve conduction velocity accompanied by morphological alterations in the sciatic nerve of rats dosed with 411 mg TnBP/kg/day for 14 days; the NOAEL was 274 mg TnBP/kg/day (Laham et al. 1983).

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

APPENDIX A

BENCHMARK MODELING OF REDUCED WEIGHT GAIN IN PREGNANT RATS

Data from Noda et al. (1994) were analyzed using the BMD approach for MRL derivation. BMD models in the EPA BMDS (version 2.1) to determine potential points of departure for the MRL (Table A-5).

Table A-5. Data for the Change in Adjusted Body Weight Gain on Gestation Days 0–20 Exposed to TnBP on Gestation Days 7–17

Dose (mg/kg/day)	Number of animals tested	Body weight gain (g)	SD
0	20	38.0	7.46
62.5	20	37.2	8.27
125	20	33.2	8.98
250	20	23.0	6.51
500	20	9.4	8.56

Source: Noda et al. 1994

Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in body/organ weight or weight gain, in the absence of a clear criteria as to what level of change should be considered adverse, the BMR is defined as a change equal to 1 SD from the control mean (EPA 2000). Based on the criteria for model selection, the Linear model provided the best fit (Table A-6 and Figure A-3).

Table A-6. Model Predictions for TnBP, Change in Body Weight Gain on Gestation Days 0–20

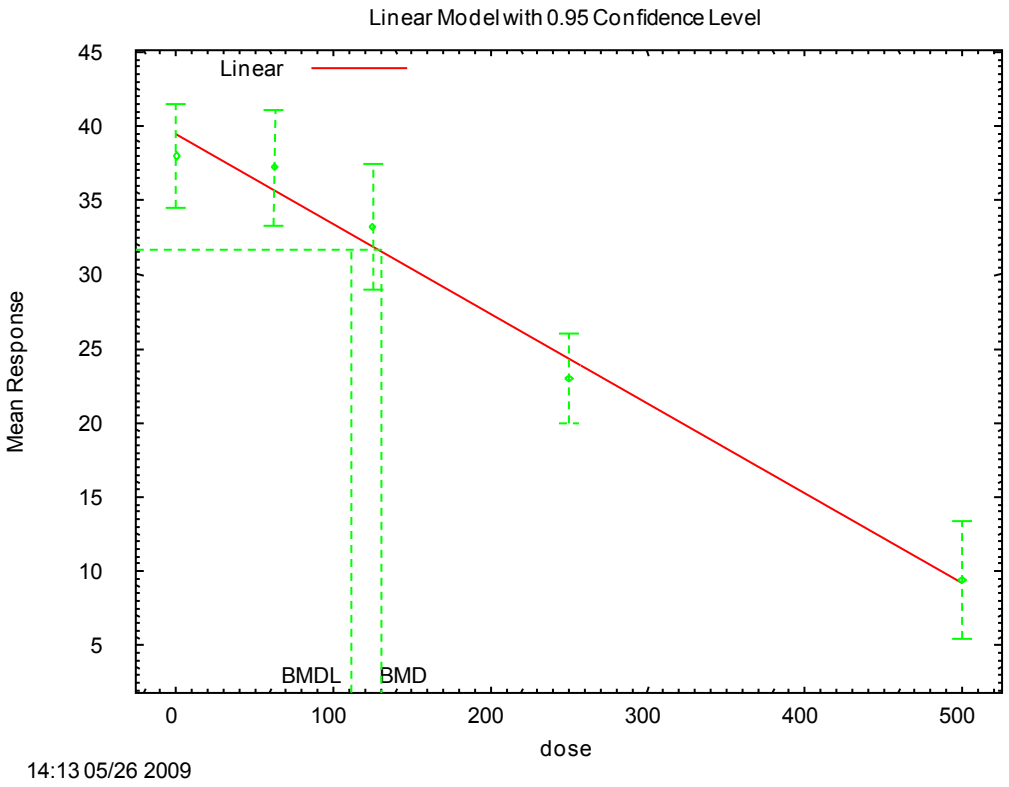
Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Constant variance									
Hill[d]	<0.0001	0.65	0.86	-0.08	0.02	0.13	520.89	162.91	113.67
Linear[e,f]	**<0.0001**	**0.65**	**0.46**	**0.71**	**-0.78**	**-0.87**	**519.44**	**130.32**	**111.47**
Polynomial (2-degree)[e]	<0.0001	0.65	0.28	0.66	-0.86	-0.86	521.43	133.85	111.53
Power[d]	<0.0001	0.65	0.31	0.52	-1.01	-1.01	521.19	145.15	112.27

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model. Constant variance model provided adequate fit to variance data. With constant variance model applied, all models (except for the Hill) provided adequate fit to means. Since the range of BMDLs was <3-fold, the model with lowest AIC was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 1 SD = change is 1 standard deviation from the control mean); BMR = benchmark response; DF = degrees of freedom

Source: Noda et al. 1994

Figure A-3. Fit of Linear Model (Constant Variance) to Data on Body Weight Gain on Gestation Days 0–20 in Rats Exposed to TnBP on Gestation Days 7–17



APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tributyl phosphate (TnBP)
CAS Numbers: 126-76-8
Date: April 2012
Profile Status: Draft 2, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 22
Species: Rat

Minimal Risk Level: 0.08 [X] mg/kg/day [ ] ppm

Reference: Arnold LL, Christenson WR, Cano M, et al. 1997. Tributyl phosphate effects on urine and bladder epithelium in male Sprague-Dawley rats. Fundam Appl Toxicol 40(2):247-255.

Experimental design: Groups of male Sprague-Dawley rats (20 in the control and high-dose group, 10 in the low- and mid-dose groups) were fed a diet containing 0, 200, 700, or 3,000 ppm TnBP for 10 weeks. This corresponds to doses of approximately 0, 9, 33, or 143 mg TnBP/kg/day based on a similar study in male Sprague-Dawley rats exposed to the same dietary concentrations of TnBP (Auletta et al. 1998a). End points examined included clinical signs, body weight, food consumption, urinalysis, and histological examination (10 rats per group at termination) of the stomach, kidneys, and urinary bladder. To evaluate the effect of urine acidification, an additional group of rats received 3,000 ppm TnBP plus 12,300 ppm ammonium chloride. Yet another group received ammonium chloride alone. Reversibility of the effects of TnBP was examined in a group of 10 rats kept on a control diet for 10 weeks after the 10-week treatment period.

Effect noted in study and corresponding doses: There were no clinical signs attributable to TnBP. Mean final weight of the high-dose group was reduced >10% relative to controls; food consumption was not significantly affected. During the recovery period, body weight of the high-dose recovered to control levels. Urinary parameters on week 11 among treated groups were comparable to controls except for osmolality and creatinine, which were significantly lower in the high-dose group than in controls, indicating a dilutional effect. Urinary pH in the groups receiving ammonium chloride was 6.0 compared to $\geq$ 7.5 in the other groups. There was no evidence of an amorphous precipitate, abnormal microcrystals, or calculi in the urine from individual rats. Crystals were present in the control and TnBP-treated rats. Treatment with TnBP caused urinary bladder hyperplasia in mid-and high-dose rats, with severity that was dose-related, reversible, and less severe in the rats dosed also with ammonium chloride. Incidences were 0/10, 0/10, 8/10, and 10/10 with increasing doses (see also Table A-7 below). There were no histological alterations in the stomach or kidneys. A NOAEL of 9 mg TnBP/kg/day for urothelial hyperplasia was defined in this study; the LOAEL was 33 mg/kg/day.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 8.03 mg/kg/day for urinary bladder hyperplasia in male rats dosed in the diet for 10 weeks.

[ ] NOAEL [ ] LOAEL [X] $BMDL_{10}$

Uncertainty Factors used in 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? Yes, doses were estimated based on a similar study in male Sprague-Dawley rats exposed to the same dietary concentrations of TnBP (Auletta et al. 1998a).

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 MRL: The urinary bladder was also the most sensitive tissue in two additional intermediate-duration studies. Increased incidence of urinary bladder hyperplasia was reported in male and female rats in a 3-month dietary study (FMC 1985a); the NOAEL was 13.8 mg TnBP/kg/day and the LOAEL was 68.1 mg TnBP/kg/day. Tyl et al. (1997) reported similar results in F_0 and F_1 male and female rats dosed with approximately 51 mg TnBP/kg/day in a 2-generation reproductive study; the NOAEL was 15 mg TnBP/kg/day (see Table A-7).

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

BENCHMARK MODELING OF URINARY BLADDER HYPERPLASIA IN RATS

Incidence data for urothelial hyperplasia in male rats from the Arnold et al. (1997) study, for urothelial hyperplasia in F_0 males and females from the Tyl et al. (1997) study, and for urothelial hyperplasia in males from the FMC 1985a) study were analyzed using the BMD approach for MRL derivation. Incidences are shown in Table A-7. The results form the Arnold et al. (1997) model fit are shown in Table A-8; the FMC (1985a) and Tyl et al. (1997) model fit results are not shown. The data set from Tyl et al. (1997) corresponds to incidences in the parental generation (F_0). Incidences in F_1 females were virtually the same as in F_0 females, whereas incidences in mid-dose F_1 males were slightly lower than in F_0 males. Also included in Table A-7 is the data set from the 2-year study of Auletta et al. (1998a). The results from fitting the Auletta (1998a) data to various BMDL models are shown in Table A-9 (male rats) and Table A-10 (female rats) on pages A-24 and A-25, respectively, with the chronic MRL worksheet. Only the best fit $BDML_{10}$ value from each of the various studies is included in the summary Table A-7.

Table A-7. Incidence of Urinary Bladder Hyperplasia Induced by TnBP in Four Studies in Rats

				NOAEL	LOAEL		$BMDL_{10}$
Arnold et al. (1997)–10 weeks							
Dose (mg/kg/day)	0			9	33	143	
Males	0/10			0/10	8/10	10/10	**8.03**
FMC (1985a)–13 weeks							
Dose (mg/kg/day)	0.12	0.6	2.8	13.8	68.1	360	
Males	0/10	0/10	0/10	0/10	10/10	10/10	12.61
Tyl et al. (1997)–10 weeks							
Dose (mg/kg/day)	0			15	51	217	
Males	0/30			1/29	22/29	30/30	13.03
Females	0/30			2/29	21/30	30/30	9.12
Auletta et al. (1998a)–2 years							
Dose (mg/kg/day)	0			9	33	143	
Males	3/50			3/50	12/49	17/49	23.51
Females	1/50			1/50	5/49	29/49	53.59

$BMDL_{10}$ = The 95% lower confidence limit on the dose associated with a 10% extra risk; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Table A-8. Model Predictions for Incidence of Urinary Bladder Hyperplasia in Male Rats Exposed to TnBP for 10 weeks

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day
Gamma[c,d]	**3**	**0.00**	**1.00**	**-0.02**	**0.001**	**-0.02**	**12.01**	**19.74**	**8.03**
Logistic	2	0.00	1.00	0.00	0.00	0.00	14.01	28.80	10.49
LogLogistic[e]	2	0.00	1.00	0.00	0.00	0.00	14.01	26.21	8.27
LogProbit[e]	2	0.00	1.00	0.00	0.00	0.00	14.01	21.67	8.24
Multistage (1-degree)[f]	3	4.41	0.22	0.00	-1.83	-1.83	19.03	3.30	1.96
Multistage (2-degree)[f]	3	1.23	0.75	-1.03	0.40	-1.03	14.21	9.17	4.46
Multistage (3-degree)[f]	3	0.33	0.95	-0.56	0.12	-0.56	12.65	13.52	6.10
Probit	2	0.00	1.00	0.00	0.00	0.00	14.01	25.25	9.61
Weibull[c]	2	0.00	1.00	-0.013	0.00	-0.013	14.01	23.96	7.89

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Selected model. All models provided adequate fit to the data. The range of $BMDL_{10}$ values was >3-fold across all models, but much of this variation was due to the poorest fitting model, the 1-degree multistage. Ignoring the $BMDL_{10}$ from the 1-degree multistage model, the range of $BMDL_{10}$ values was <3-fold; thus, the model with the lowest AIC was selected (Gamma).
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

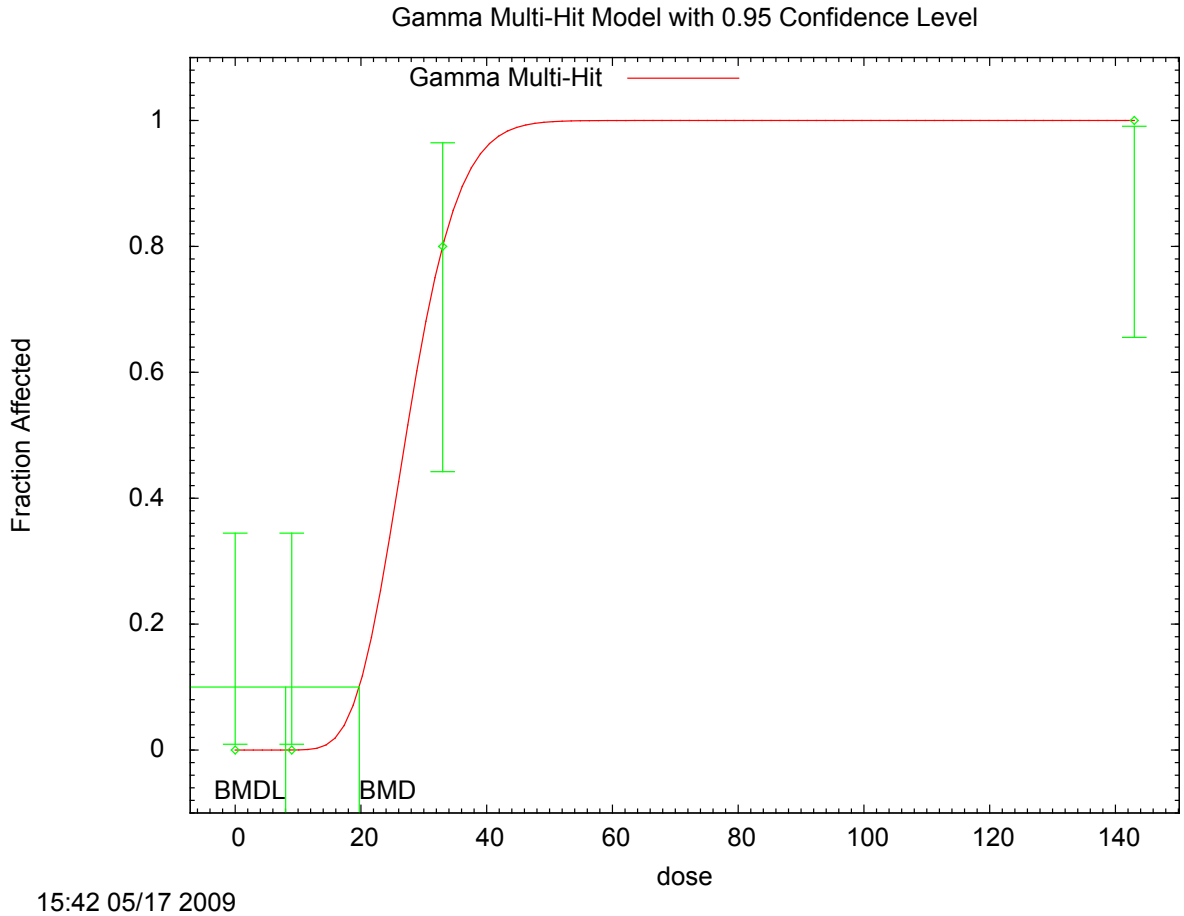
AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); BMR = benchmark response; DF = degrees of freedom

Source: Arnold et al. 1997

Incidence data for urothelial hyperplasia in male rats from the Arnold et al. (1997) study, urothelial hyperplasia in F_0 males and females from the Tyl et al. (1997) study, and urothelial hyperplasia in male rats from the FMC (1985a) study were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1) were fit to urothelial hyperplasia data to determine potential points of departure for the MRL. For the Arnold et al. (1997) data set, the range of $BMDL_{10}$ values for adequately fitting models (by the chi-square goodness of fit measure) varied by > 3-fold, but much of this variation was due to the relatively poor fit of the 1- and 2-degree multistage models. The range of $BMDL_{10}$ values from the remaining models was <2-fold and the model with the lowest AIC (Gamma) was selected as the best fitting model, predicting BMD_{10} and $BMDL_{10}$ values of 19.74 and 8.03 mg/kg/day. For the urinary hyperplasia data in F_0 males in the Tyl et al. (1997) study, the best fitting model predicted BMD_{10} and $BMDL_{10}$ values of 21.43 and 13.03 mg TnBP/kg/day, respectively; the predicted values for F_0 female rats were 15.42 and 9.12 mg TnBP/kg/day, respectively. For the FMC (1985a) data set, the range of $BMDL_{10}$ values for adequately fitting models (by the chi-square goodness of fit measure) varied by >3-fold, but much of this variation was due to the relatively poor fit of the 1-degree multistage model. The range of $BMDL_{10}$ values from the remaining models was <3-fold and the model with the lowest AIC (Weibull) was selected as the best fitting model, predicting BMD_{10} and $BMDL_{10}$ values of 49.87 and 12.61 mg/kg/day, respectively. Comparing across the four intermediate-duration data sets, the lowest $BMDL_{10}$ of 8.03 mg/kg/day for urinary bladder hyperplasia (Arnold et al. 1997) is selected as the point of departure for the MRL (Table A-8). Applying an uncertainty factor of 100 (10 for animal to human

extrapolation and 10 for human variability) to the $BMDL_{10}$ yields an intermediate-duration oral MRL of 0.08 mg/kg/day for TnBP. The model fit is shown in Figure A-4.

Figure A-4. Fit of Gamma Model to Data on Incidence of Urinary Bladder Hyperplasia in Male Sprague-Dawley Rats Exposed to TNBP for 10 Weeks



Source: Arnold et al. 1997

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tributyl phosphate (TnBP)
CAS Numbers: 126-76-8
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Species: Rat

Minimal Risk Level: 0.08 [X] mg/kg/day [ ] ppm

Reference: Arnold LL, Christenson WR, Cano M, et al. 1997. Tributyl phosphate effects on urine and bladder epithelium in male Sprague-Dawley rats. Fundam Appl Toxicol 40(2):247-255.

It is recommended that the intermediate-duration oral MRL of 0.08 mg/kg/day for TnBP also be adopted as chronic-duration oral MRL, as explained below.

Only two chronic-duration oral studies were located for TnBP, one in rats (Auletta et al. 1998a) and one in mice (Auletta et al. 1998b). As in the intermediate-duration studies, the urinary bladder from rats was the most sensitive target for TnBP toxicity. Rats were dosed via the diet for 2 years, whereas mice were treated for 18 months. Male rats received doses of 0, 9, 33, or 143 mg TnBP/kg/day, whereas females received doses of 0, 12, 42, or 182 mg TnBP/kg/day. The doses for male and female mice were 0, 28.9, 169, or 585 mg/kg/day and 0, 24.1, 206, or 711 mg/kg/day, respectively. At termination, the incidences of trace to severe urinary bladder hyperplasia in male rats were 3/50, 3/50, 12/49, and 17/49 with increasing doses (see Table A-7 in the derivation of the intermediate-duration oral MRL). The corresponding incidences in female rats were 1/50, 1/50, 5/49, and 29/49. Urinary bladder hyperplasia was not observed in mice. Based on these findings, the increased incidence of urothelial hyperplasia in rats was used to determine a point of departure for derivation of a chronic-duration oral MRL for TnBP.

Incidence data for urinary bladder hyperplasia in male and female rats exposed to TnBP (Auletta et al. 1998a) were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1) were fit to the urinary bladder lesion data to determine potential points of departure for the MRL. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >2–3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. Comparing across models using these criteria showed that the Multistage 1-degree model was the only model with an adequate fit for the incidence data in male rats, whereas the Probit model provided the best fit for the incidence data in female rats. This analysis yielded respective $BMDL_{10}$ values of 23.51 and 53.59 mg TnBP/kg/day (Tables A-9 and A-10).

Table A-9. Model Predictions for Incidence of Urinary Bladder Hyperplasia in Male Rats Exposed to TnBP for 2 Years

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b]: Dose below BMD	Scaled residuals[b]: Dose above BMD	Scaled residuals[b]: Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Logistic	2	6.84	0.03	2.19	-0.32	2.19	173.60	ND(LS)	NS(LS)
LogLogistic[d,e]	1	20.68	0.00	-2.16	-2.16	-2.16	190.72	ND(LS)	NS(LS)
LogProbit[d]	2	20.68	0.00	-2.16	-2.16	-2.16	188.72	ND(LS)	NS(LS)
Multistage (1-degree)[c]	**2**	**4.10**	**0.13**	**1.75**	**-0.63**	**1.75**	**171.02**	**35.41**	**23.51**
Probit	2	6.55	0.04	2.16	-0.36	2.16	173.30	ND(LS)	NS(LS)

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Selected model.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); BMR = benchmark response; DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND(LS) = not determined; largest scaled residual >2

Source: Auletta et al. 1998a

Table A-10. Model Predictions for Incidence of Urinary Bladder Hyperplasia in F_0 Female Rats Exposed to TnBP for 2 Years

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b]: Dose below BMD	Scaled residuals[b]: Dose above BMD	Scaled residuals[b]: Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	1	0.11	0.74	0.12	-0.03	-0.26	124.28	47.67	28.56
Logistic	2	1.42	0.49	0.92	-0.09	0.92	123.59	73.30	59.41
LogLogistic[d]	1	0.09	0.76	0.09	-0.02	-0.24	124.27	47.03	28.66
LogProbit[d]	1	0.01	0.91	0.02	-0.01	-0.08	124.18	45.90	33.21
Multistage (1-degree)[e,]	2	4.00	0.14	-1.13	-1.17	-1.17	126.67	26.26	19.85
Multistage (2-degree)[e]	1	0.31	0.58	0.27	-0.04	-0.44	124.50	50.93	28.07
Multistage (3-degree)[e]	1	0.31	0.58	0.27	-0.04	-0.44	124.50	50.93	27.98
Probit[f]	**2**	**0.97**	**0.62**	**0.76**	**-0.10**	**0.76**	**123.14**	**65.64**	**53.59**
Weibull[c]	1	0.17	0.68	0.16	-0.03	-0.32	124.34	48.48	28.42

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided adequate fit to the data. Since the range of BMDLs was <3-fold, the model with the lowest AIC was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); BMR = benchmark response; DF = degrees of freedom

Source: Auletta et al. 1998a

As seen in Tables A-9 and A-10, and also in Table A-7, these values are higher than the $BMDL_{10}$ values obtained in the analyses of the incidences of urinary bladder hyperplasia reported in the intermediate-duration studies (Arnold et al. 1997; Tyl et al. 1997). As the data show, the incidences of urinary bladder hyperplasia at comparable high doses are higher in the intermediate-duration studies than in the chronic-duration study. A likely explanation for this phenomenon is provided in the chronic study by the observation that rats with malignant bladder tumors usually did not have any remaining uninvolved epithelium to evaluate for the presence or absence of hyperplasia (Auletta et al. 1998a). Whether urinary bladder hyperplasia is a potential precursor of urinary bladder tumors is not known for certain, but the data are suggestive. The lower incidence of hyperplasia at the higher dose levels in the chronic-duration study may just be the result of the hyperplasia transforming into neoplasia. As shown in Table A-7, dose levels that did not increase the incidence of urothelial hyperplasia in the intermediate-duration studies (NOAELs ranged from 9 to 15 mg/kg/day) also did not increase the incidence of urinary bladder hyperplasia in the chronic-duration study (NOAEL was 9 mg/kg/day) and did not increase the incidence of neoplastic lesions; thus, the NOAEL from intermediate-duration studies would also be protective for chronic exposure. Therefore, the intermediate-duration oral MRL of 0.08 mg/kg/day based on a $BMDL_{10}$ of 8.03 mg/kg/day is adopted also as chronic-duration oral MRL for TnBP.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tris(2-butoxyethyl) phosphate (TBEP)
CAS Numbers: 78-51-3
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 3
Species: Rat

Minimal Risk Level: 4.8 [X] mg/kg/day [ ] ppm

Reference: Monsanto Co. 1985b. Tributoxyethyl phosphate: Teratology study in rats with attachments and cover letter dated 083085. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA96-910000298. OTS0528528.

Experimental design: Groups of female Sprague-Dawley rats (25/dose group) were administered 0, 250, 500, or 1500 mg TBEP/kg/day by gavage in corn oil on Gd 6–15. End points monitored included mortality, clinical signs, and body weight. The rats were euthanized on Gd 20. Immediately after kill, the uterus and ovaries were exposed and the number and location of viable and nonviable fetuses, early and late resorptions, and number of total implantations and corpora lutea were recorded. Fetuses were weighed, sexed, and examined for external malformations and variations. Fetuses were then prepared for visceral and skeletal examinations.

Effect noted in study and corresponding doses: There was one early death in the high-dose group, but the cause of death could not be determined. Chemical-related clinical signs included wet haircoat matting or staining with urine, brown material or blood on the face, neck, thorax, and/or anogenital area; this was observed in approximately half of the high-dose rats. Following dosing on Gd 6, two high-dose rats were ataxic, had reduced righting reflex, and/or were lethargic. Terminal body weight of the dams (unadjusted for uterine content) was significantly reduced, but only 6% relative to controls. Weight gain in high-dose rats was significantly reduced from Gd 6 on; during treatment (Gd 6–15), weight gain in this group was reduced 35%. Fetal body weight and sex ratios were not affected and neither were other developmental parameters. Treatment with TBEP did not affect the incidence of external, visceral, or skeletal anomalies. A maternal NOAEL and LOAEL of 500 and 1500 mg TBEP/kg/day, respectively, were defined in this study. The highest dose tested, 1500 mg/kg/day, was a developmental NOAEL based on no evidence of fetotoxicity or teratogenicity.

Dose and end point used for MRL derivation: BMDL of 477.25 mg/kg/day for decrease weight gain in pregnant rats on Gd 6–15.

[ ] NOAEL [ ] LOAEL [X] BMDL

Uncertainty Factors used in 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 MRL: Only one additional study was a potential source of data for MRL derivation. In that study, Sprague-Dawley rats (10/sex/dose level) were treated with up to 100 mg TBEP/kg/day by gavage in corn oil for 14 days (Komsta et al. 1989). End points monitored included clinical signs, body weight, hematology and clinical chemistry at termination, organ weights (brain, heart, liver, kidney, and spleen), microsomal liver enzyme activities, and gross and microscopic morphology of all major tissues and organs. The results did not show any significant differences between the treated and control groups for any of the parameters evaluated. However, because no adverse effects were reported, the Komsta et al. (1989) study was not considered a suitable basis for an MRL. An additional study that used considerably higher doses reported that 1 week after administration of a single gavage dose of ≥1,750 mg TBEP/kg, female rats showed slight tremors and piloerection, whereas those treated with 3,200 mg/kg exhibited tremors and abnormal gait; males appeared to be somewhat less sensitive. Examination of the sciatic nerve showed nerve degeneration in females dosed with ≥2,000 mg/kg. The NOAEL for males and females was 3,200 and 1,500 mg/kg, respectively.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

BENCHMARK MODELING OF REDUCED WEIGHT GAIN IN PREGNANT RATS

Data from Monsanto Co. (1985b) were analyzed using the BMD approach for MRL derivation. BMD models in the EPA BMDS (version 2.1) were fit to the maternal body weight gain data to determine potential points of departure for the MRL (Table A-11). Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in body/organ weight or weight gain, in the absence of a clear criteria as to what level of change should be considered adverse, the BMR is defined as a change equal to 1 SD from the control mean (EPA 2000).

Table A-11. Data for the Change in Body Weight Gain in Pregnant Rats Exposed to TBEP on Gestation Days 6–15

Dose (mg/kg/day)	Number of animals tested	Body weight gain (g)	SD
0	25	55	5.5
250	25	53	8.4
500	25	52	7.6
1,500	25	36	11.1

Source: Monsanto Co. 1985b

As seen in Table A-12, using the criteria for model selection mentioned above, the Polynomial 3-degree polynomial model provided the best fit. The corresponding BMD_{1SD} was 824.97 mg/kg/day; the corresponding benchmark dose limit ($BMDL_{1SD}$) was 477.25 mg/kg/day. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{1SD}$ of 477.25 mg/kg/day results in an acute-duration oral MRL of 4.8 mg/kg/day for TBEP. The model fit is shown in Figure A-5.

Table A-12. Model Predictions for Change in Maternal Body Weight Gain in Pregnant Rats Exposed to TBEP on Gestation Days 6–15

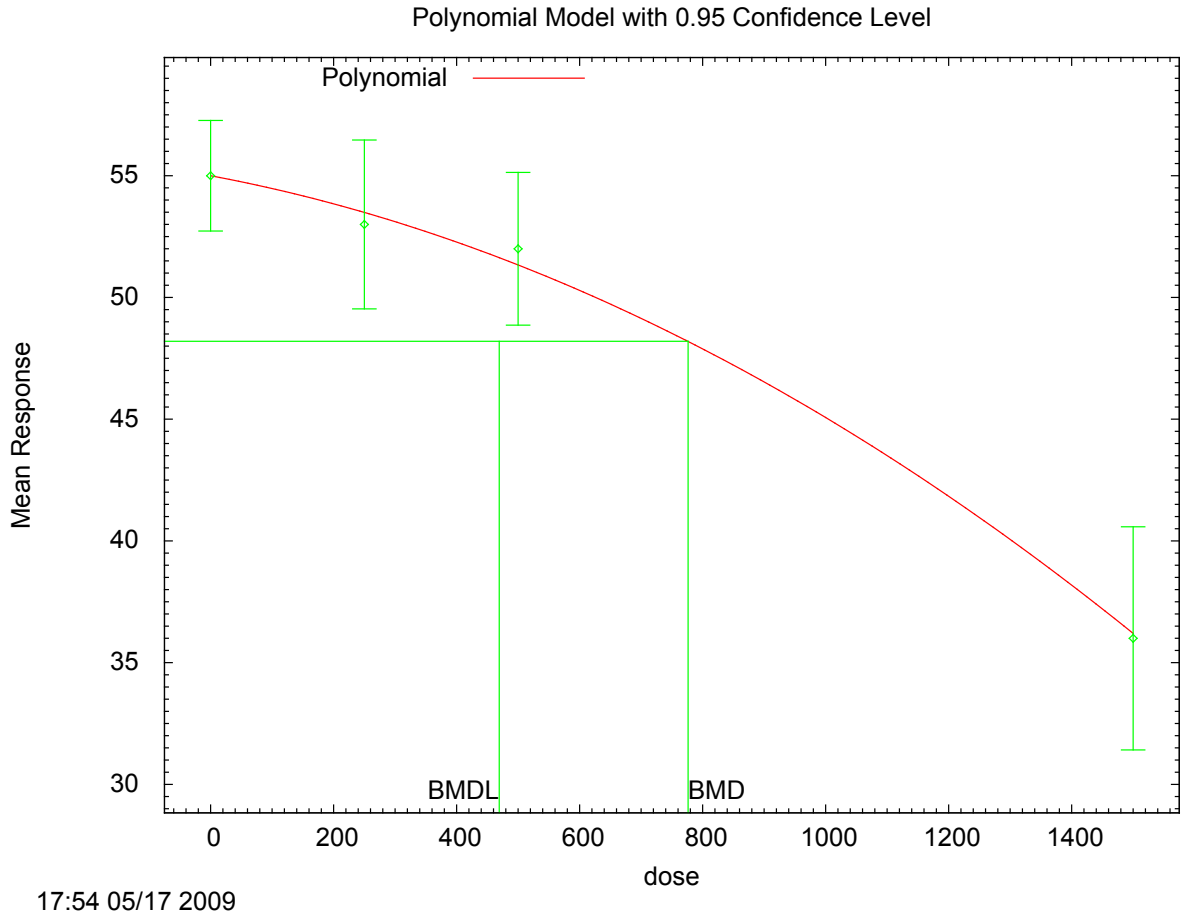
Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Constant variance									
Linear[d]	<0.0001	0.007	0.27	1.31	-0.43	1.31	530.01	635.60	521.84
Nonconstant variance									
Hill[e]	<0.0001	0.18	NA	0.47	-0.094	-0.47	525.61	766.47	NA
Linear[d]	<0.0001	0.18	0.27	1.37	-0.70	1.37	523.40	533.99	418.71
Polynomial (2-degree)[d]	<0.0001	0.18	0.42	0.44	-0.094	0.44	523.41	776.36	469.34
Polynomial (3-degree)[d,f]	**<0.0001**	**0.18**	**0.50**	**0.35**	**-0.07**	**0.35**	**523.23**	**824.97**	**477.25**
Power[e]	<0.0001	0.18	0.36	0.47	-0.094	0.47	523.60	766.71	461.90

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model. Constant variance model did not fit variance data, but non-homogenous variance model did. With non-homogenous variance model applied, all models (except for the Hill model) provided adequate fit to means. Since the range of BMDLs was <3-fold, the model with the lowest AIC was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 1 SD = change is 1 standard deviation from the control mean); BMR = benchmark response; NA = not applicable (p-value did not generate or BMDL computation failed)

Source: Monsanto Co. 1985b

Figure A-5. Fit of Polynomial Model (Nonconstant Variance) to Data on Body Weight Gain in Rats Exposed to TBEP on Gestation Days 6–15



APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tris(2-butoxyethyl) phosphate (TBEP)
CAS Numbers: 78-51-3
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 9
Species: Rat

Minimal Risk Level: 0.09 [X] mg/kg/day [ ] ppm

Reference: Reyna MS, Thake DG. 1987a. Eighteen week feeding study of tributoxyethyl phosphate (TBEP) administered to Sprague-Dawley rats. Monsanto Agricultural Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0530087.

Experimental design: Groups of Sprague-Dawley rats (20/sex/group) were fed a diet containing 0, 300, 3,000, or 10,000 ppm TBEP for approximately 18 weeks (Reyna and Thake 1987a). This corresponds to doses of approximately 0, 17.3, 173, or 578 mg/kg/day for males and 0, 21, 209, or 698 mg/kg/day for females using food intake and body weight data from the study. End points monitored included clinical signs, body weight, food consumption, clinical chemistry and hematology (weeks 9 and 18), organ weights (brain, liver, kidneys, testes with epididymides), and gross and microscopic examination of all the major organs and tissues of controls and high-dose rats plus target tissues defined by the high-dose group and gross lesions from all necropsied animals.

Effect noted in study and corresponding doses: There were no treatment-related mortalities or adverse clinical signs. Body weight was not significantly affected by treatment with the test material. Food consumption was lower in high-dose males and females and mid-dose males during the first week of the study, but was comparable to controls the remainder of the study. Ophthalmological examinations at termination were unremarkable. Statistically significant hematological changes included decreased leukocyte (lymphocyte) in high-dose males on week 9, and increased platelet counts in high-dose males and females on week 9 and 18 and in mid-dose males on week 9. Significant clinical chemistry changes consisted of increased serum cholesterol in high-dose males on week 18 and on mid- and high-dose females on week 9, increased serum GGT activity in high-dose males on week 9 and 18 and in high-dose females on week 9, decreased serum cholinesterase in high-dose males and females on weeks 9 and 18, and decreased erythrocyte cholinesterase in all treated females only on week 9; brain cholinesterase activity was not affected. Absolute and relative liver weights were increased in high-dose males and females, but not significantly. Histopathological lesions were restricted to the liver of male rats and consisted of increased incidence of periportal hepatocellular hypertrophy (0/10, 0/10, 3/10, 7/10) and periportal vacuolization (1/10, 2/10, 6/10, 7/10).

Dose and end point used for MRL derivation: $BMDL_{10}$ of 8.88 mg/kg/day for hepatocyte vacuolization in male rats dosed in the diet for 18 weeks.

[ ] NOAEL [ ] LOAEL [X] $BMDL_{10}$

Uncertainty Factors used in 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? Yes, ppm in food were converted to doses using mean food intake and body weight from the study.

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 MRL: The study by Reyna and Thake (1987a) was the only intermediate-duration oral study that examined a wide range of end points available for review. In the same study, although presented separately, the investigators measured tail nerve conduction velocity at the end of the treatment period (Reyna and Thake 1987b). Following these measurements, the sciatic, tibial, and plantar nerves were processed for light microscopy. A significant reduction in nerve conduction velocity was measured only in high-dose females. Since both the absolute and relative refractory periods were decreased (the opposite of what would be expected in the case of a reduction in conduction velocity), the effect was not seen in males, and morphology of the nerves was unremarkable, the decrease in conduction velocity in females appeared questionable.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

APPENDIX A

BENCHMARK MODELING OF HEPATOCYTE HYPERTROPHY AND VACUOLIZATION IN MALE RATS

Incidence data for periportal hepatocyte hypertrophy and vacuolization in male rats exposed to TBEP (Reyna and Thake 1987a) were analyzed using the BMD approach for MRL derivation (Tables A-13 and A-14).

Table A-13. Incidence of Periportal Hepatocyte Hypertrophy in Male Rats Exposed to TBEP for 18 Weeks

Dose (mg/kg/day)	Total number of rats	Number of rats with lesions
0	10	0
17.3	10	0
173	10	3
578	10	7

Source: Reyna and Thake 1987a

Table A-14. Incidence of Periportal Hepatocyte Vacuolization in Male Rats Exposed to TBEP for 18 Weeks

Dose (mg/kg/day)	Total number of rats	Number of rats with lesions
0	10	1
17.3	10	2
173	10	6
578	10	7

Source: Reyna and Thake 1987a

Models in the EPA BMDS (version 2.1) were fit to the hepatocyte hypertrophy and hepatocyte vacuolation reported in male rats to determine a point of departure for the MRL. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models.

Based on the criteria for model selection, comparing across models (Tables A-15 and A-16), the best fit for the hepatocyte hypertrophy data was provided by the Log Logistic model; the BMD_{10} and $BMDL_{10}$ were 80.62 and 21.92 mg TBEP/kg/day, respectively. The best fit for the incidence of hepatocyte vacuolization was provided also by the Log Logistic model, which estimated a BMD_{10} and $BMDL_{10}$ of 22.02 and 8.88 mg TBEP/kg/day, respectively. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ of 8.88 mg/kg/day results in an intermediate-duration oral MRL of 0.09 mg/kg/day for TBEP. The model fit for hepatocyte vacuolization is shown in Figure A-6.

Table A-15. Model Predictions for Incidence of Hepatocyte Hypertrophy in Male Rats Exposed to TBEP for 18 Weeks

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	2	0.28	0.87	-0.37	0.34	-0.37	28.85	78.52	32.71
Logistic	2	3.01	0.22	-0.77	1.33	1.33	32.18	168.20	104.90
LogLogistic[d,e]	**2**	**0.15**	**0.93**	**-0.31**	**0.20**	**-0.31**	**28.68**	**80.62**	**21.92**
LogProbit[d]	3	0.09	0.99	-0.13	0.20	-0.18	26.54	88.23	54.34
Multistage (1-degree)[f]	3	0.37	0.95	-0.59	0.05	-0.59	27.14	52.73	31.87
Multistage (2-degree)[f]	2	0.36	0.84	-0.54	0.26	-0.54	29.07	63.10	32.07
Probit	2	2.72	0.26	-0.70	1.30	1.30	31.71	156.18	100.50
Weibull[c]	2	0.31	0.86	-0.43	0.33	-0.43	28.92	74.28	32.50

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data. Since the range of BMDLs was >3-fold, the model with lowest $BMDL_{10}$ was selected.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); BMR = benchmark response; DF = degrees of freedom

Source: Reyna and Thake 1987a

Table A-16. Model Predictions for Incidence of Hepatocyte Vacuolization in Male Rats Exposed to TBEP for 18 Weeks

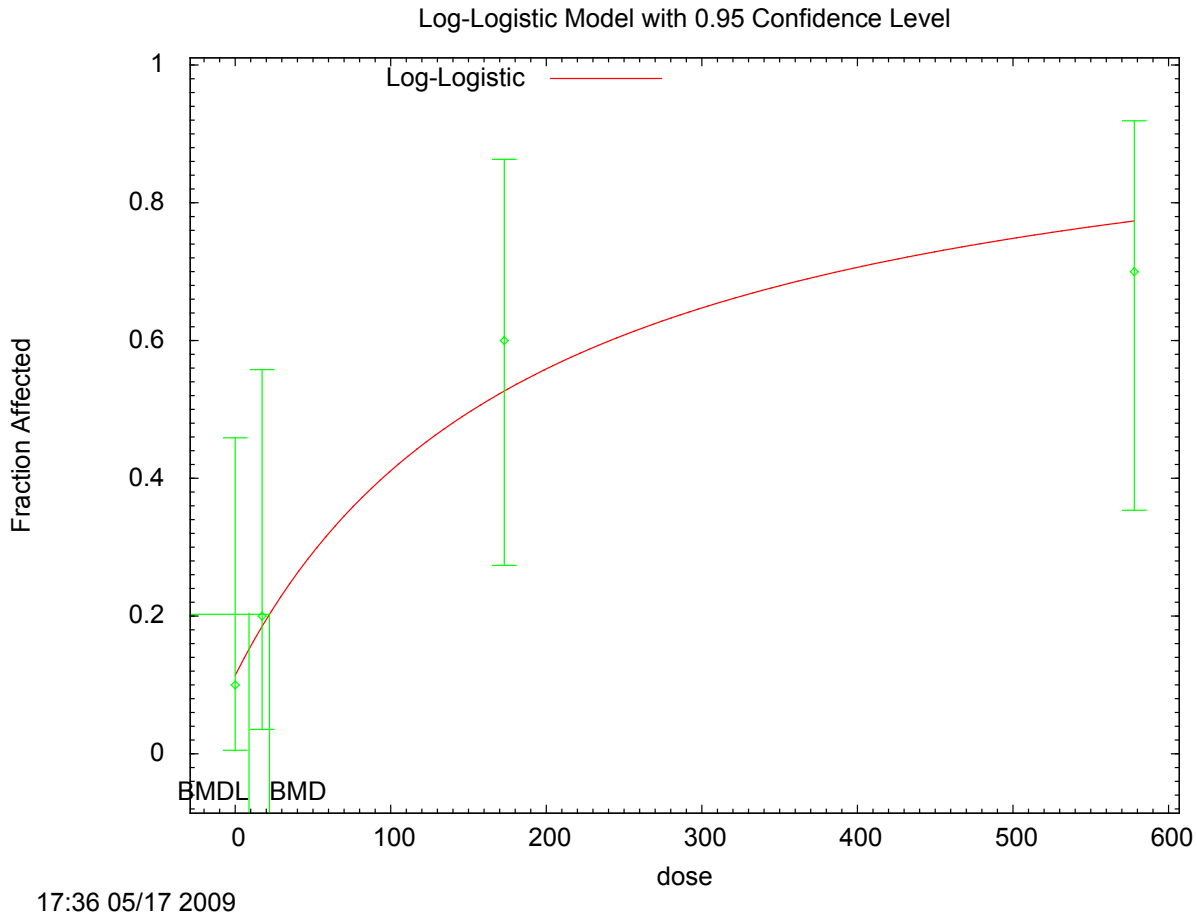
Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Logistic	2	3.39	0.18	-0.27	1.48	1.48	49.64	95.80	60.25
LogLogistic[c]	**2**	**0.56**	**0.76**	**0.12**	**0.46**	**0.46**	**46.73**	**22.02**	**8.88**
LogProbit[d]	2	2.29	0.32	0.27	0.99	0.99	48.40	73.86	40.22
Multistage (1-degree)[e]	2	1.73	0.42	0.12	1.02	1.02	47.89	43.84	24.80
Probit	2	3.35	0.19	-0.24	1.50	1.50	49.59	93.91	62.31

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Selected model. All models provided adequate fit to the data. Since the range of BMDLs was >3-fold, the model with the lowest $BMDL_{10}$ was selected.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); BMR = benchmark response; DF = degrees of freedom

Source: Reyna and Thake 1987a

Figure A-6. Fit of Log Logistic Model to Data on the Incidence of Periportal Hepatocyte Vacuolization in Male Rats Exposed to TBEP for 18 Weeks



APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tris(1,3-dichloro-2-propyl) phosphate (TDCP)
CAS Numbers: 13674-87-8
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 4
Species: Rat

Minimal Risk Level: 0.05 [X] mg/kg/day [ ] ppm

Reference: Stauffer Chemical Co. 1981a. A two year oral toxicity/carcinogenicity study of fyrol FR-2 in rats. In: A two-year oral toxicity/carcinogenicity study of fyrol FR-2 in rats (volume I-IV) (final reports) with attachments, cover sheets and letter dated 093081. Stauffer Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. EPA88-8100282. OTS0204911.

Experimental design: Groups of Sprague-Dawley rats (60/sex/dose level) were fed a diet that provided 0, 5, 20, or 80 mg/kg/day of TDCP for 24 months. End points monitored included lethality, clinical signs, body weight, food consumption, hematology, clinical chemistry and urinalysis (at 3, 6, 12, 18, and 24 months, 9–10 rats/sex/sampling), gross necropsy, and histopathology at termination and at 12 months (10 rats/sex/dose).

Effect noted in study and corresponding doses: Mortality was comparable among groups during the first year of the study. Clinical signs were comparable among groups. Body weights were reduced in males and females 5–7% relative to controls at the 3- and 6-month time points. At week 50, mean body weight of males was 12% lower than controls, whereas mean body weight of females was 8% lower than controls. Hematology tests showed significant reductions in hemoglobin and hematocrit in high-dose males both at 3 and 6 months and of hemoglobin in females at 6 months. High-dose males also showed a reduction in red blood cell count at 6 months. The differences in mean hematological parameters between treated and control rats seen at 3 and 6 months were ≤5%. At 12 months, there were significant reductions in hemoglobin in high-dose males (10.6%) and females (7.5%) and in red cell counts in high-dose males (10.7%). None of these alterations were observed after 24 months of treatment with TDCP. Prothrombin times and partial thromboplastin times showed considerable variability from interval to interval and no consistent pattern of differences between treated and control rats were apparent during the study. Serum alkaline phosphatase levels were lower than controls in high-dose rats both at the 3- and 6-month intervals. BUN values in treated rats were not significantly different than in controls. Other clinical chemistry tests showed no consistent dose-related differences between controls and treated rats that could be attributed to treatment with TDCP. The most significant observations at 12 months were dose-related increases in absolute kidney and liver weights which achieved significance at the highest dose level; these changes in organs weight were not accompanied by histological alterations. Changes in kidney weight were more marked than those in liver weight, 48% increase in high-dose males and 39% increase in high-dose females relative to controls. At the lowest dose, kidney weight was increased 12% in males relative to controls. In mid-dose males, absolute thyroid and liver weight were increased by 14 and 12%, respectively; the corresponding increases in high-dose males were 25 and 26%. Since the kidney was the most sensitive end point in rats exposed to TDCP for 24 months in the same study, it would appear that the increase in kidney weight observed at 12 months is on the continuum of the same spectrum of health effects used to derive the chronic-duration MRL and may, in fact, be a precursor to the renal tubule hyperplasia seen in rats exposed to TDCP for 24 months. Since the hematological changes observed during the first year of the study are of questionable toxicological significance, it is appropriate

to use the changes in absolute kidney weight at the 12-month time point as basis for derivation of an intermediate-duration oral MRL for TDCP. Changes in absolute kidney weight in male and female rats were analyzed using the BMD approach for MRL derivation as detailed below.

Dose and end point used for MRL derivation: $BMDL_{1SD}$ of 4.69 mg/kg/day for increase absolute kidney weight in male rats.

[ ] NOAEL [ ] LOAEL [X] $BMDL_{1SD}$

Uncertainty Factors used in 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 MRL: Only one addition intermediate-duration study is available for TDCP (Anonymous 1977). In that study, male rabbits were administered doses of 0, 2, 20, or 200 mg TDC/kg/day by gavage for 12 weeks. During the last week of treatment, male fertility was tested by mating the males with untreated females. Fertility was assessed by sacrificing the females at mid-gestation and evaluating their uteri. After the mating period, the males were euthanized and sperm from the cauda epididymides were analyzed for motility, morphology, and concentration. Blood was also collected for hematology and clinical chemistry tests. The pituitary, liver, kidneys, and reproductive tract were processed for microscopic examination. The treatment-related effects appeared to be a significant increase in relative liver weight (23%) and in absolute kidney weight (14%) at 200 mg/kg/day. Neither gross necropsy nor microscopic examinations revealed significant alterations in the organs examined.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

APPENDIX A

BENCHMARK MODELING OF CHANGES IN KIDNEY WEIGHT IN RATS

Data from Stauffer Chem Co. (1981a) were analyzed using the BMD approach for MRL derivation. BMD models in the EPA BMDS (version 2.1) were fit to the absolute kidney weight male and female datasets (Tables A-17 and A-18) to determine potential points of departure for the MRL.

Table A-17. Data for the Change in Absolute Kidney Weight in Male Rats Exposed to TDCP for 1 Year

Dose (mg/kg/day)	Number of animals tested	Kidney weight (g)	Standard deviation
0	9	3.185	0.488
5	10	3.571	0.311
20	10	3.736	0.654
80	10	4.703	0.853

Source: Stauffer Chem Co. 1981a

Table A-18. Data for the Change in Absolute Kidney Weight in Female Rats Exposed to TDCP for 1 Year

Dose (mg/kg/day)	Number of animals tested	Kidney weight (g)	Standard deviation
0	10	2.031	0.193
5	10	2.179	0.198
20	10	2.271	0.269
80	10	2.836	0.443

Source: Stauffer Chem Co. 1981a

Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in body/organ weight or weight gain, in the absence of a clear criteria as to what level of change should be considered adverse, the BMR is defined as a change equal to 1 SD from the control mean (EPA 2000). Data from Stauffer Chemical Co. (1981a) were analyzed using the BMD approach for MRL derivation. BMD models in the EPA BMDS (version 2.1) were fit to the absolute kidney weight male and female datasets to determine potential points of departure for the MRL. For both data sets, constant variance models did not provide adequate fits (Tables A-19 and A-20). Selected non-constant variance models for male and female data predicted $BMDL_{1SD}$ values of 4.69 and 13.49 mg/kg/day, respectively; the lowest of these $BMDL_{1SD}$ was selected as the point of departure. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{1SD}$ of 4.69 mg/kg/day for increased kidney weights in male rats yields an intermediate-duration oral MRL of 0.05 mg/kg/day for TDCP. The model fit of the male data set is shown in Figure A-7.

Table A-19. Model Predictions for Change in Absolute Kidney Weight in Male Rats Exposed to TDCP for 1 Year

Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Constant variance									
Linear[d]	<0.0001	0.02	0.52	0.21	-0.097	-0.86	3.98	34.6	25.79
Nonconstant variance									
Hill[e,f]	**<0.0001**	**0.11**	**0.48**	**0.98**	**-0.55**	**-0.98**	**1.70**	**13.36**	**4.69**
Linear[d]	<0.0001	0.11	0.48	0.24	-0.21	-1.06	0.67	24.86	16.31

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model. Constant variance model did not fit variance data, but non-homogenous variance model did. With non-homogenous variance model applied, all models provided adequate fit to means. The constant variance model did not fit variance data, but the non-homogenous variance models did. With the non-homogenous variance model applied, two models provided adequate fit to means. The algorithms for the 2- and 3-degree polynomial and the Power models fit a linear model. Because range of $BMDL_{1SD}$ values from adequately fitting models was >3-fold, the model with the lowest $BMDL_{1SD}$ was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 1 SD = change is 1 standard deviation from the control mean); BMR = benchmark response

Source: Stauffer Chem Co. 1981a

Table A-20. Model Predictions for Change in Absolute Kidney Weight in Female Rats Exposed to TDCP for 1 Year

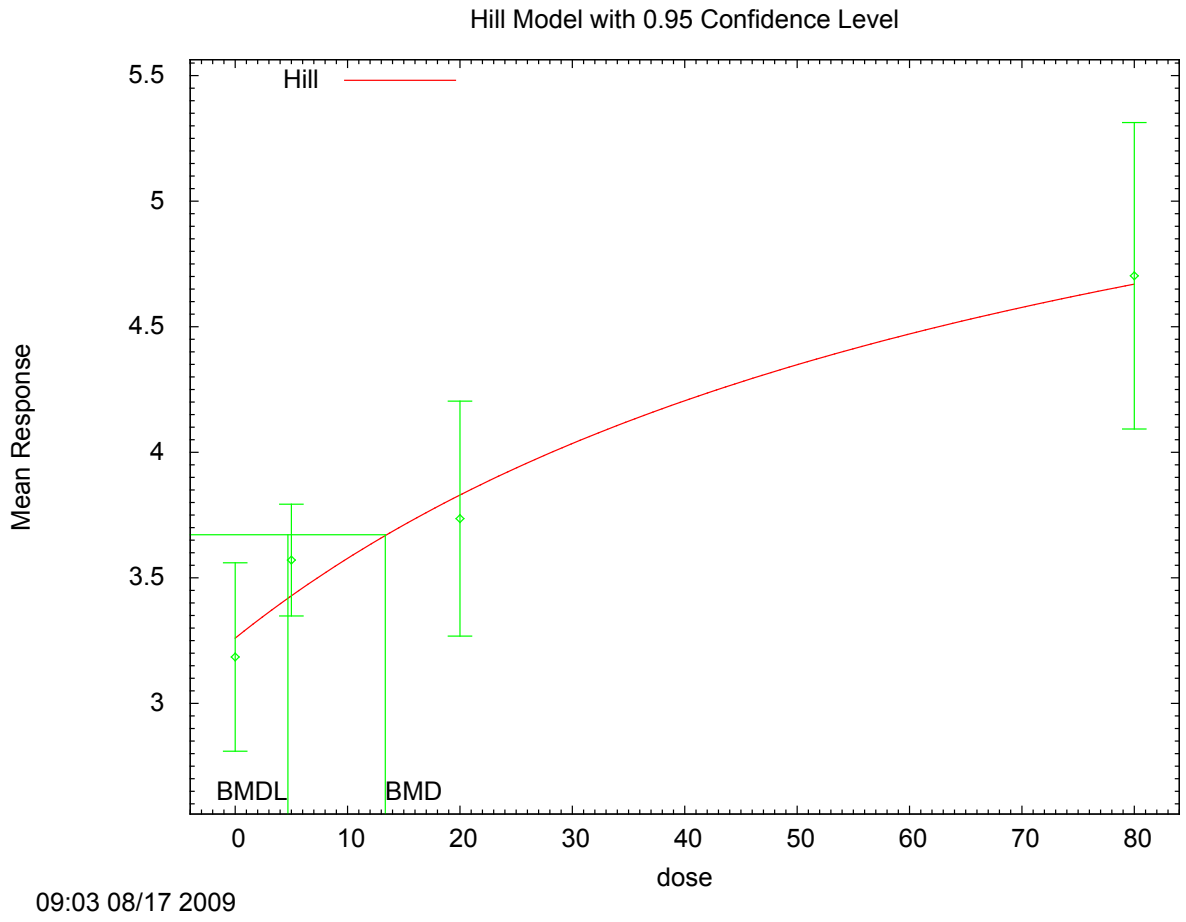
Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Constant variance									
Linear[d]	<0.0001	0.02	0.72	0.012	-0.039	0.58	-55.58	29.59	22.67
Nonconstant variance									
Hill[e]	<0.0001	0.83	0.35	0.84	-0.42	0.84	-60.81	14.80	5.79
Linear[d,f]	**<0.0001**	**0.83**	**0.56**	**0.84**	**0.00092**	**0.84**	**-62.53**	**19.73**	**13.49**

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model. Constant variance model did not fit variance data, but non-homogenous variance model did. With non-homogenous variance model applied, all models provided adequate fit to means. The constant variance model did not fit variance data, but the non-homogenous variance model did. With the non-homogenous variance model applied, two models provided adequate fit to means The algorithms for the 2- and 3-degree polynomial and the Power models fit a linear model. Because range of $BMDL_{1SD}$ values from adequately fitting models was <3-fold, the model with the lowest AIC was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 1 SD = change is 1 standard deviation from the control mean); BMR = benchmark response

Source: Stauffer Chem Co. 1981a

Figure A-7. Fit of the Hill Model to Data on TDCP, Changes in Absolute Kidney Weight in Male Rats Exposed to TDCP for 1 Year



Source: Stauffer Chemical Co. 1981a

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tris(1,3-dichloro-2-propyl) phosphate (TDCP)
CAS Numbers: 13674-87-8
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 10
Species: Rat

Minimal Risk Level: 0.02 [X] mg/kg/day [ ] ppm

Reference: Stauffer Chemical Co. 1981a. A two year oral toxicity/carcinogenicity study of fyrol FR-2 in rats. In: A two-year oral toxicity/carcinogenicity study of fyrol FR-2 in rats (volume I-IV) (final reports) with attachments, cover sheets and letter dated 093081. Stauffer Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. EPA88-8100282. OTS0204911.

Experimental design: Groups of Sprague-Dawley rats (60/sex/dose level) were fed a diet that provided 0, 5, 20, or 80 mg/kg/day of TDCP for 24 months. End points monitored included lethality, clinical signs, body weight, food consumption, hematology, clinical chemistry and urinalysis (periodically throughout the study), gross necropsy, and histopathology at termination and at 12 months (10 rats/sex/dose).

Effect noted in study and corresponding doses: Mortality was comparable among groups during the first year of the study, but increased in high-dose males during the second year and was significantly higher than controls at termination. Clinical signs were comparable among groups. Ophthalmological examinations at 18 and 24 months suggested that treatment with TDCP may have accelerated the development of sacculations along the course of the retinal arterioles in high-dose rats. In general, body weights of mid- and high-dose rats were lower than controls throughout the study. At termination, final body weights of high-dose males and females were 24 and 21% lower than controls, respectively. At week 50, body weights of mid-dose males and females were 12 and 8% lower than controls, respectively. There was no consistent pattern of differences among groups over time regarding food consumption. Hemoglobin, hematocrit, and total erythrocyte values were often significantly lower than controls in high-dose rats and the differences were usually more pronounced in males. This was observed throughout the study. At 24 months, prothrombin times and partial thromboplastin times were significantly elevated in high-dose males. Serum alkaline phosphatase values were lower than controls in high-dose males throughout the study; the biological significance of this is unclear. BUN was markedly elevated in a few mid- and high-dose rats at 18 and 24 months, which was consistent with microscopic evidence of renal pathology. Other clinical chemistry parameters were not consistently altered by treatment. Plasma cholinesterase was lower in high-dose females at 18 months (34%, significant) and 24 months (30%, not significant); changes at other times or in red blood cell cholinesterase were inconsistent. Urinalyses were unremarkable. Significant changes in organ weight consisted of increase absolute and relative liver, kidney, and thyroid weights in high-dose males and females at 12 and 24 months. At termination, gross observations revealed masses, nodules, and raised areas in the liver of high-dose rats; enlargement of the kidney in mid- and high-dose males and high-dose females plus higher incidence of discolorations, surface irregularities, masses, nodules, and cysts in treated rats than in controls; higher incidence of small seminal vesicles and testicular enlargement, masses, nodules, flaccidity, and discolorations in mid- and high-dose males. Nonneoplastic lesions that were significantly increased in treated rats were foci/areas of hepatocellular alterations (high-dose males and females), dilation of liver sinusoids (high-dose males and females), hyperplasia of convoluted tubular epithelium of the kidney (high-dose males and females, mid-dose males), and chronic nephropathy (high-dose males and females). None of these alterations were

seen at the 12-month interim kill. Hyperplasia of the renal convoluted tubular epithelium was the most sensitive effect and occurred with incidences of 2/45, 10/49, 28/48, and 24/46 in males as the doses increased; the corresponding incidences in females were 0/49, 1/48, 3/48, and 22/50. A NOAEL and LOAEL of 5 and 20 mg TDCP/kg/day, respectively, for renal epithelial hyperplasia in male rats was defined in this study.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 1.94 mg/kg/day for renal tubular epithelial hyperplasia in male rats dosed in the diet for 2 years.

[ ] NOAEL [ ] LOAEL [X] $BMDL_{10}$

Uncertainty Factors used in 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? Yes, ppm in food were converted to doses by the investigators.

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 MRL: The study by Stauffer Chemical Co. (1981a) was the only chronic-duration oral study available for review.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

APPENDIX A

BENCHMARK MODELING OF RENAL TUBULE HYPERPLASIA IN RATS

Incidence data for renal tubule epithelial hyperplasia in male rats exposed to TDCP (Stauffer Chemical Co. 1981a) were analyzed using the BMD approach for MRL derivation (Table A-21).

Table A-21. Incidence of Renal Tubule Epithelial Hyperplasia in Rats Exposed to TDCP for 2 Years

Dose (mg/kg/day)	Total number of males	Males with lesions	Total number of females	Females with lesions
0	45	2	49	0
5	49	10	48	1
20	48	28	48	3
80	46	24	50	22

Source: Stauffer Chemical Co. 1981a

A glance at these incidences shows that males were clearly more sensitive than females. Therefore, the data set for hyperplasia of the renal convoluted tubular epithelium in males served as the basis for determining a point of departure for MRL derivation. Models in the EPA BMDS (version 2.1) were fit to the renal tubular epithelial hyperplasia data in male rats to determine potential points of departure for the MRL (Table A-22).

Table A-22. Model Predictions for Incidence of Renal Tubular Epithelial Hyperplasia in Male Rats

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	0	0.00	NA	0.00	0.00	0.00	137.16	3.04	1.95
Logistic	1	1.84	0.18	0.94	-0.18	-0.96	137.11	6.07	4.86
LogLogistic[d]	0	0.00	NA	0.00	0.00	0.00	137.16	3.22	1.46
LogProbit[d]	1	0.64	0.43	-0.26	0.62	0.62	135.78	4.40	3.35
Multistage (1-degree)[e,f]	**1**	**0.08**	**0.78**	**0.073**	**-0.23**	**-0.23**	**135.23**	**2.60**	**1.94**
Multistage (2-degree)[e]	0	0.00	NA	0.00	0.00	0.00	137.16	2.94	1.95
Probit	1	1.52	0.22	0.88	-0.19	0.88	136.74	5.59	4.53
Weibull[c]	0	0.00	NA	0.00	0.00	0.00	137.16	3.02	1.95

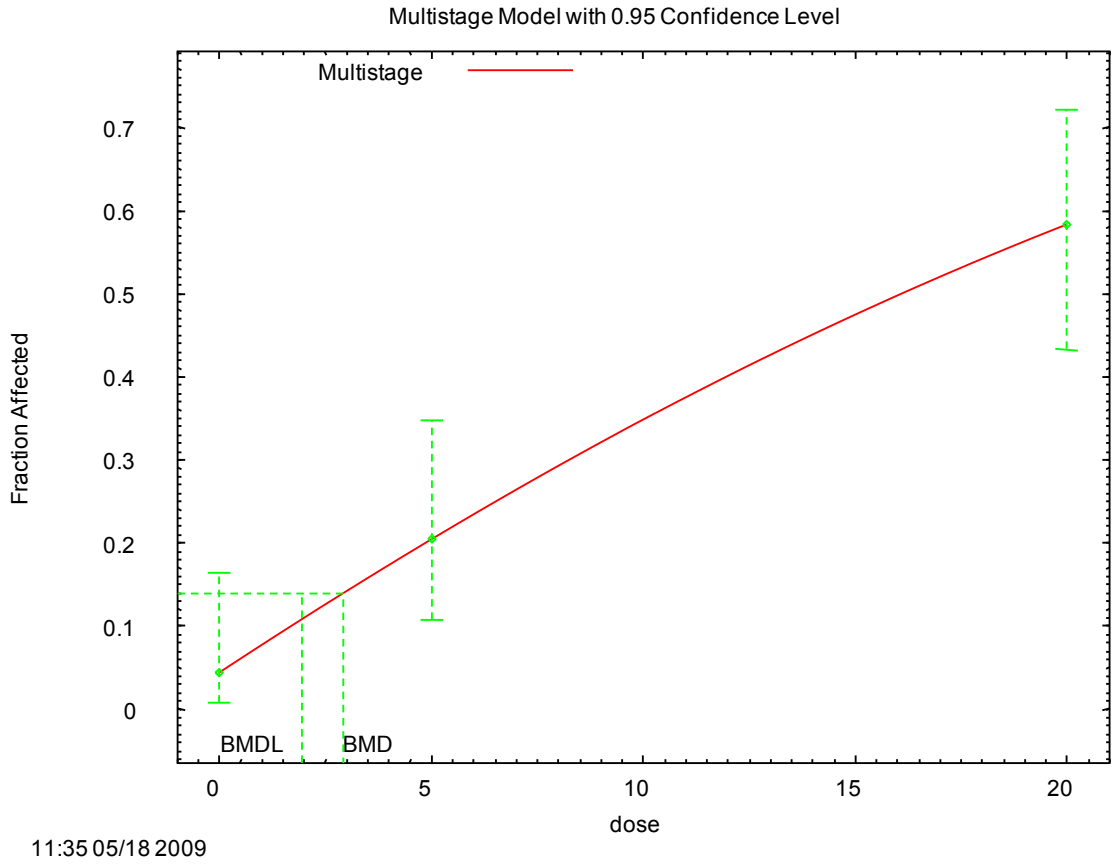
[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. No models provided adequate fit to the data with all doses, but adequate fits were achieved after dropping the highest dose. Since the range of BMDLs was <3-fold, the model with the lowest AIC was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = dose associated with 10% extra risk); BMR = benchmark response; DF = degrees of freedom; NA = not applicable (p-value not generated)

Source: Stauffer Chem Co. 1981a

Adequate model fit is judged by three criteria: goodness-of-fit (p>0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. Since an adequate fit to the data set could not be obtained with any of the models, the high-dose was dropped, in accordance with EPA (2000) guidance. Comparing across models (Table A-22) using the selection criteria mentioned above shows that the Multistage (1-degree polynomial) model provided the best fit to the renal epithelial hyperplasia. From this model, the predicted dose associated with a 10% extra risk (BMD_{10}) was 2.60 mg TDCP/kg/day and the ($BMDL_{10}$ was 1.94 mg TDCP/kg/day. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ of 1.94 mg/kg/day yields a chronic-duration oral MRL of 0.02 mg/kg/day for TDCP. The model fit is shown in Figure A-8.

Figure A-8. Fit of Multistage (1-Degree Polynomial) Model to Incidence of Renal Tubular Epithelia Hyperplasia in Male Rats Exposed to TDCP for 2 Years



Source: Stauffer Chemical Co. 1981a

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tricresyl phosphate (TCP)
CAS Numbers: 1330-78-5
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 53
Species: Rat

Minimal Risk Level: 0.04 [X] mg/kg/day [ ] ppm

Reference: NTP. 1994. Toxicology and carcinogenesis studies of tricresyl phosphate (CAS No. 1330-78-5) in F344/N rats and B6C3F$_1$ mice (gavage and feed studies). Program NT. TR 433.

Experimental design: Groups of Fischer-344 rats (95/sex/dose) were fed a diet containing 0 (control), 75, 150, or 300 ppm TCP for 104 weeks. This diet supplied doses of 0, 3, 6, or 13 mg TCP/kg/day to males and 0, 4, 7, or 15 mg/kg/day to females (estimated by the investigators). The TCP used in the NTP studies was a mixed isomer preparation of 79% tricresyl phosphate esters consisting of 21% tri-*m*-cresyl phosphate, 4% tri-*p*-cresyl phosphate, <1% tri-*o*-cresyl phosphate, and other unidentified tricresyl phosphate esters. Fifteen rats per sex per dose group were euthanized after 3, 9, and 15 months of the diet. Additional 95 rats per sex were fed a diet with 600 ppm TCP (dose not provided) for 22 weeks and then were place on the control diet; of these, thirty rats per sex were examined at 9 and 15 months. Ten rats per sex in the 600 ppm group were also euthanized at 3 months. All rats were observed twice daily. Clinical findings and body weight were recorded weekly for 13 weeks, then monthly and at the interim evaluations. Food consumption was measured once per month. Neurobehavioral assessments were conducted before exposure and at 3, 9, and 15 months (forelimb and hindlimb grip strength). Blood was collected at 3, 9, and 15 months for hematology tests and serum cholinesterase activity. At interim kills the adrenal, brain, kidney, liver, and testes were weighted. All rats were necropsied and a complete histopathologic examination was conducted in all rats.

Effects noted in study and corresponding doses: Survival was not significantly affected by exposure to TCP. Mean body weight was comparable among groups throughout the study. Food consumption was not significantly affected. There were no chemical-related clinical signs. The only significant alteration in organ weight was an increase in absolute (25%) and relative (23%) weight of the left adrenal in females at the 3 month interval at 15 mg/kg/day; the corresponding increases in adrenal weight in the 600 ppm females were 37% and 38%. There were no significant chemical-related changes in hematological values. Serum cholinesterase was reduced at the 3, 9, and 15 month interval, more severely in females (23% at 7 mg/kg at 3 months, 35% at 7 mg/kg at 9 months; 32% at 4 mg/kg at 15 months). Results of the neurological tests showed a significant reduction (11%) in hindlimb grip strength in male rats dosed with 13 mg/kg/day at the 3 month evaluation. Chemical-related non-neoplastic lesions were restricted to the adrenal cortex of both sexes and the ovary of females. Cytoplasmic vacuolization of the adrenal gland occurred in males only at the 3 months examination in the 600 ppm group (10/10 vs 0/10 in other groups). In females, incidences were significantly elevated at all intervals examined except in the 600 ppm group beyond 3 months, suggesting reversibility of the lesion if treatment ceased. At 3 months the incidences were 0/10, 0/10, 1/10, 10/10 and 9/10 in the 0, 75, 150, 300, and 600 ppm groups, respectively; in the same groups, at 9 months the incidences were 1/10, 0/10, 3/10, 10/10, and 0/10. The lesion was characterized by increased number of small, fine vacuoles in the cortical cells of the zona fasciculata resulting in a ground glass appearance and an increase in cell size. Minimal to mild interstitial cell hyperplasia in the ovaries occurred at 3 months in females dosed 7 and 15 mg/kg/day (0/10, 0/10, 6/10,

10/10, and 10/10 in the 0, 75, 150, 300, and 600 ppm groups, respectively). However, the incidence of ovarian lesions in the 600 ppm group at the 9-month evaluation (this group terminated exposure at 22 weeks) was only 40% (4/10), again suggesting reversibility once treatment ceased. The lesion was characterized by an increase in size and possibly number of interstitial cells without any particular alteration of ovarian architecture. No significant lesions were found in other tissues.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 3.72 mg/kg/day for ovarian lesions in female rats.

[ ] NOAEL [ ] LOAEL [X] $BMDL_{10}$

Uncertainty Factors used in 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? Doses were estimated by the investigators based on body weight and food consumption data.

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? No.

Other additional studies or pertinent information that lend support to this MRL: Adrenal gland and ovarian lesions were also reported in other intermediate-duration studies in rats such as the 13-week gavage and dietary studies conducted by NTP (1994) and studies conducted by Latendresse and coworkers (Latendresse et al. 1993, 1994b). However, these studies used relatively high doses of TCP. In addition, Latendresse et al. (1993, 1994b) used a single dose level of 400 mg TCP/kg/day, whereas the NTP (1994) 13-week studies used doses ranging from 50 to 800 mg TCP/kg/day. In the 2-year NTP (1994) study in mice, adrenal lesions were seen in all groups of male and female mice, including controls, with an incidence near or at 100% at 9, 15, and 24 months (NTP 1994). At the 3-month interim kill, only high-dose male mice (27 mg TCP/kg/day) showed a significant increase (6/10) relative to controls (0/8).

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

BENCHMARK MODELING OF ADRENAL AND OVARIAN LESIONS IN RATS

Incidences of adrenal and ovarian lesions in rats at the 3- and 9-month interim kills are presented in Table A-23.

Table A-23. Incidences of Adrenal Cortex and Ovarian Lesions in Female F344 Rats Exposed to TCP for 3 or 9 Months

Incidence of cytoplasmic vacuolization of the adrenal cortex				
Dose (mg/kg/day)	0	4	7	15
At 3 months	0/10	0/10	1/10	10/10
At 9 months	0/10	0/10	3/10	10/10
Incidence of hyperplasia of the interstitial ovarian cells				
At 3 months	0/10	0/10	6/10	10/10
At 9 months	0/10	0/10	1/10	10/10

Source: NTP 1994

Incidence data for cytoplasmic vacuolization of the adrenal cortex in female rats and of hyperplasia of the interstitial ovarian cell in female rats exposed to TCP (NTP 1994) were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1.1) were fit to the adrenal and ovarian lesion data to determine potential points of departure for the MRL. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. Using these criteria, the best fitting model for each of the four data sets were selected and the results are summarized in Table A-24.

Table A-24. Summary of Modeling of Intermediate-Duration Data for Tricresyl Phosphate in Female Rats

	Best fitting model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Adrenal lesions at 3 months	LogLogistic	7.00	5.69
Adrenal lesions at 9 months	LogLogistic	6.49	4.58
Ovarian lesions at 3 months	**Weibull**	**6.21**	**3.72**
Ovarian lesions at 9 months	LogLogistic	7.00	5.69

As shown in Table A-24, among the models selected as providing the best fit for each of the four data sets, the lowest $BMDL_{10}$ value is 3.72 mg TCP/kg/day and was obtained with the fit of the Weibull model for increased incidence of hyperplasia of the interstitial ovarian cells at the 3-month time point. To be protective of human health, this value is used as point of departure for MRL derivation. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ of 3.72 mg TCP/kg/day results in an intermediate-duration oral MRLs of 0.04 mg/kg/day for TCP. Further details of the modeling of this data set are shown in Table A-25. The model fit of the data is shown in Figure A-9. It should be noted that the Multistage (2-degree) model, that provided a lower

$BMDL_{10}$ of 1.53 mg/kg/day, was not considered the best fitting model because it has relatively high residuals and the highest AIC and lowest goodness-of-fit p-value among the models that fit the data.

Table A-25. Model Predictions for Incidence of Hyperplasia of the Interstitial Cells in the Ovary of Female F344 Rats Fed TCP in the Diet for 3 Months

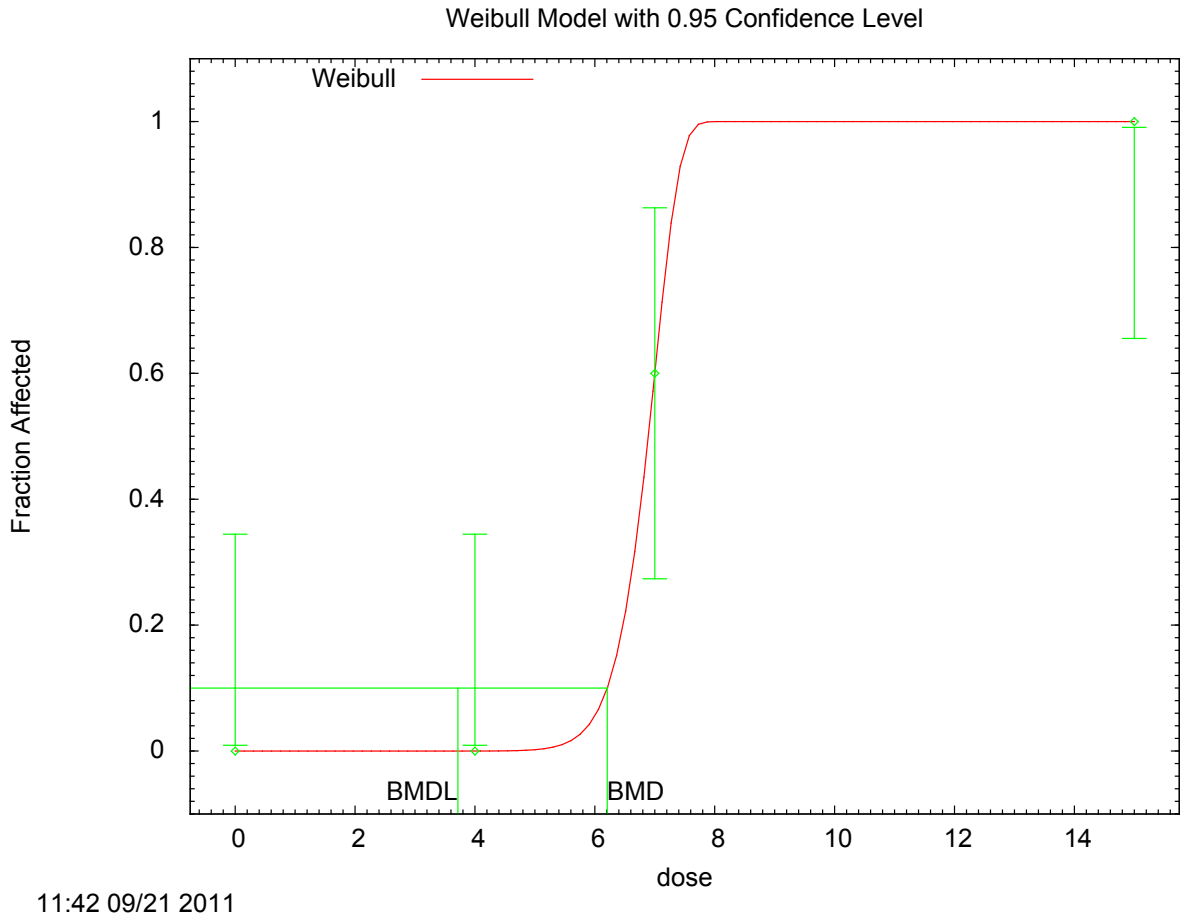
Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	3	0.26	0.97	-0.48	0.18	-0.48	15.95	4.87	3.62
Logistic	2	0.00	1.00	0.00	0.00	0.00	17.46	6.59	3.80
LogLogistic[d]	3	0.00	1.00	-0.03	0.00	-0.03	15.46	6.06	3.91
LogProbit[d]	2	0.00	1.00	0.00	0.00	0.00	17.46	6.06	3.86
Multistage (1-degree)[e]	3	8.08	0.04	0.00	-2.40	-2.40	28.67	ND(LS)	ND(LS)
Multistage (2-degree)[e]	3	3.32	0.34	0.00	-1.64	-1.64	21.21	2.66	1.53
Multistage (3-degree)[e]	3	1.76	0.62	0.00	-1.19	-1.19	18.47	3.70	2.01
Probit	2	0.00	1.00	0.00	0.00	0.00	17.46	6.22	3.73
Weibull[c,f]	**3**	**0.00**	**1.00**	**-0.02**	**0.00**	**-0.02**	**15.46**	**6.21**	**3.72**

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models (except the Multistage 1-degree) provided an adequate fit of the data. Since the range of BMDLs was <3-fold, the model with the lowest AIC was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = dose associated with 10% extra risk); BMR = benchmark response; DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND(LS) = not determined; largest scaled residual >2

Source: NTP 1994

Figure A-9. Fit of Weibull Model to Incidence of Hyperplasia of Ovarian Interstitial Cells in Female Rats Exposed to TCP for 3 Months



APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tricresyl phosphate (TCP)
CAS Numbers: 1330-78-5
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [] Intermediate [X] Chronic
Graph Key: 69
Species: Rat

Minimal Risk Level: 0.02 [X] mg/kg/day [ ] ppm

Reference: NTP. 1994. Toxicology and carcinogenesis studies of tricresyl phosphate (CAS No. 1330-78-5) in F344/N rats and B6C3F$_1$ mice (gavage and feed studies). Program NT. TR 433.

Experimental design: Groups of Fischer-344 rats (95/sex/dose) were fed a diet containing 0 (control), 75, 150, or 300 ppm TCP for 104 weeks. This diet supplied doses of 0, 3, 6, or 13 mg TCP/kg/day to males and 0, 4, 7, or 15 mg/kg/day to females (estimated by the investigators). Fifteen rats per sex per dose group were euthanized after 3, 9, and 15 months of the diet. Additional 95 rats per sex were fed a diet with 600 ppm TCP (dose not provided) for 22 weeks and then were place on the control diet; of these, thirty rats per sex were examined at 9 and 15 months. Ten rats per sex in the 600 ppm group were also euthanized at 3 months. All rats were observed twice daily. Clinical findings and body weight were recorded weekly for 13 weeks, then monthly and at the interim evaluations. Food consumption was measured once per month. Neurobehavioral assessments were conducted before exposure and at 3, 9, and 15 months (forelimb and hindlimb grip strength). Blood was collected at 3, 9, and 15 months for hematology tests and serum cholinesterase activity. At interim kills the adrenal, brain, kidney, liver, and testes were weighted. All rats were necropsied and a complete histopathologic examination was conducted in all rats.

Groups of B6C3F$_1$ mice (95/sex/group) were fed a diet containing 0, 75, 150, or 300 ppm TCP for 104 weeks. This diet supplied doses of 0, 7, 13, or 27 mg TCP/kg/day to males and 0, 8, 18, or 37 mg/kg/day to females. Fifteen mice per sex per group were euthanized after 3, 9, and 15 months of the diet. All mice were observed twice daily. Clinical findings and body weight were recorded weekly for 13 weeks, then monthly and at the interim evaluations. Food consumption was measured once per month. Feed consumption was measured once per month. Neurobehavioral assessments were conducted before exposure and at 3, 9, and 15 months (forelimb and hindlimb grip strength). Blood was collected at 3, 9, and 15 months for hematology tests and serum cholinesterase activity. At interim kills the adrenal, brain, kidney, liver, and testes were weighted. All mice were necropsied and subjected to a complete histopathologic examination.

Effect noted in study and corresponding doses: Survival of rats was not significantly affected by exposure to TCP. Mean body weight was comparable among groups throughout the study. Food consumption was not significantly affected. There were no chemical-related clinical signs. The only significant alteration in organ weight was an increase in absolute (25%) and relative (23%) weight of the left adrenal in females at the 3 month interval at 15 mg/kg/day; the corresponding increases in adrenal weight in the 600 ppm females were 37% and 38%. There were no significant chemical-related changes in hematological values. Serum cholinesterase was reduced at the 3, 9, and 15 month interval, more severily in females (23% at 7 mg/kg at 3 months, 35% at 7 mg/kg at 9 months; 32% at 4 mg/kg at 15 months). Results of the neurological tests showed a significant reduction (11%) in hindlimb grip strength in male rats dosed with 13 mg/kg/day at the 3 month evaluation. Chemical-related non-

neoplastic lesions were restricted to the adrenal cortex of both sexes and the ovary of females. Cytoplasmic vacuolization of the adrenal gland occurred in males only at the 3 months examination in the 600 ppm group (10/10 vs 0/10 in other groups). In females, incidences were significantly elevated at all intervals examined except in the 600 ppm group beyond 3 months, suggesting reversibility of the lesion if treatment ceased. At 3 months the incidences were 0/10, 0/10, 1/10, 10/10 and 9/10 in the 0, 75, 150, 300, and 600 ppm groups, respectively; in the same groups, at 9 months the incidences were 1/10, 0/10, 3/10, 10/10, and 0/10. The lesion was characterized by increased number of small, fine vacuoles in the cortical cells of the zona fasciculata resulting in a ground glass appearance and an increase in cell size. Minimal to mild interstitial cell hyperplasia in the ovaries occurred at 3 months in females dosed 7 and 15 mg/kg/day (0/10, 0/10, 6/10, 10/10, and 10/10 in the 0, 75, 150, 300, and 600 ppm groups, respectively). However, the incidence of ovarian lesions in the 600 ppm group at the 9-month evaluation (this group terminated exposure at 22 weeks) was only 40% (4/10), again suggesting reversibility once treatment ceased. The lesion was characterized by an increase in size and possibly number of interstitial cells without any particular alteration of ovarian architecture. No significant lesions were found in other tissues.

Survival of mice was not significantly affected by exposure to TCP. Mean body weight was comparable among groups throughout the study. Food consumption was not significantly affected. There were no chemical-related clinical signs. There were no significant chemical-related changes in hematological values. Serum cholinesterase values were significantly reduced in all treated groups (20–35% with the low dose). The only significant neurological effect was a reduction (7%) of hindlimb grip strength in high-dose females at the 3-month interim examination. Significant alterations in organ weight were limited to the adrenal glands and consisted in a decrease in absolute weight in high-dose males (33%) and increase (40%) in high-dose females, both at the 15-month evaluation. Histopathology was limited to the adrenal gland and liver. High-dose males had a significant increased incidence of ceroid pigmentation in the gland (0/8, 3/10, 3/30, 6/10) at the 3-month examination. At 2 years almost all mice had ceroid pigmentation but the severity increased with dose. The lesion consisted of macrophages and/or epithelial cells in various stages of distension from the accumulation of yellow-brown cytoplasmic pigment. Male mice from the mid- and high-dose groups had significantly elevated incidences of clear cell focus (5/52, 8/49, 17/49, 12/50), fatty change (6/52, 10/49, 23/49, 22/50), and ceroid pigmentation (0/52, 0/49, 30/49, 28/50) in the liver at termination (2 years). Cells within foci were enlarged and contained one or more medium to large clear spaces in the cytoplasm. The fatty change consisted of small vacuoles in individual hepatocytes, randomly distributed throughout the liver; the severity was never greater than moderate. Ceroid pigmentation consisted of cells containing fine, yellow-brown granules in their cytoplasm. There were no significant histological alterations in other organs.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 2.12 mg/kg/day for ovarian lesions in female rats.

[ ] NOAEL [ ] LOAEL [X] $BMDL_{10}$

Uncertainty Factors used in 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? Doses were estimated by the investigators based on body weight and food consumption data.

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? No.

Other additional studies or pertinent information that lend support to this MRL: Adrenal gland and ovarian lesions were also reported in other intermediate-duration studies in rats such as the 13-week gavage and dietary studies conducted by NTP (1994) and studies conducted by Latendresse and coworkers (Latendresse et al. 1993, 1994b). However, these studies used relatively high doses. In addition, Latendresse et al. (1993, 1994b) used a single dose level of 400 mg TCP/kg/day, whereas the NTP (1994) 13-week studies used doses ranging from 50 to 800 mg TCP/kg/day.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

BENCHMARK MODELING OF ADRENAL AND OVARIAN LESIONS IN RATS AND LIVER LESIONS IN MICE

Incidences of adrenal and ovarian lesions in rats and liver lesions in mice at the 15-month and 2-year interim kills are presented in Table A-26.

Table A-26. Adrenal Cortex and Ovarian Lesions in Female F344 Rats and Liver Lesions in B6C3F$_1$ Male Mice Exposed to TCP

Incidence of cytoplasmic vacuolization of the adrenal cortex in rats				
Dose (mg/kg/day)	0	4	7	15
At 15 months	0/9	0/8	0/10	10/10
At 2 years	14/51	12/53	16/50	36/50
Incidence of hyperplasia of the interstitial ovarian cells in rats				
At 15 months	0/9	0/8	3/10	9/10
At 2 years	0/51	0/53	0/50	15/50
Incidence of liver lesions in mice after 2 years				
Dose (mg/kg/day)	0	7	13	27
Clear cell foci	5/52	8/49	17/49	12/50
Fatty change	6/52	10/49	23/49	22/50
Ceroid pigmentation	0/52	0/49	30/49	28/50

Incidence data for cytoplasmic vacuolization of the adrenal cortex and of hyperplasia of the interstitial ovarian cell in female rats and of liver lesions in male mice exposed to TCP (NTP 1994) were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1.1) were fit to the adrenal and ovarian lesion data to determine potential points of departure for the MRL. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. Using these criteria, the best fitting model for each of the four data sets were selected and the results are summarized in Table A-27.

Table A-27. Summary of Modeling of Chronic-Duration Data for Tricresyl Phosphate

		Best fitting model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Adrenal lesions at 15 months (rats)		Weibull	11.44	6.73
Adrenal lesions at 2 years (rats)		Multistage 3-degree	7.11	3.73
Ovarian lesions at 15 months (rats)		**Multistage 3-degree**	**5.22**	**2.12**
Ovarian lesions at 2 years (rats)		LogLogistic	13.92	10.37
Liver lesions at 2 years (mice)	Clear foci	Multistage 2-degree	7.46	3.25
	Fatty change	LogLogistic	3.91	2.59
	Ceroid pigmentation	LogLogistic	11.22	8.64

As shown in Table A-27, among the models selected as providing the best fit for each of the four data sets, the lowest $BMDL_{10}$ value is 2.12 mg TCP/kg/day and was obtained with the fit of the Multistage 3-degree model for increased incidence of hyperplasia of the interstitial ovarian cells at the 15-month time point. To be protective of human health, this value is used as point of departure for MRL derivation. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ of 2.12 mg TCP/kg/day results in a chronic-duration oral MRL of 0.02 mg/kg/day for TCP. Further details of the modeling of this data set are shown in Table A-28. The model fit of the data is shown in Figure A-10.

Table A-28. Model Predictions for Incidence of Hyperplasia of the Interstitial Cells in the Ovary of Female F344 Rats Fed TCP in the Diet for 15 Months

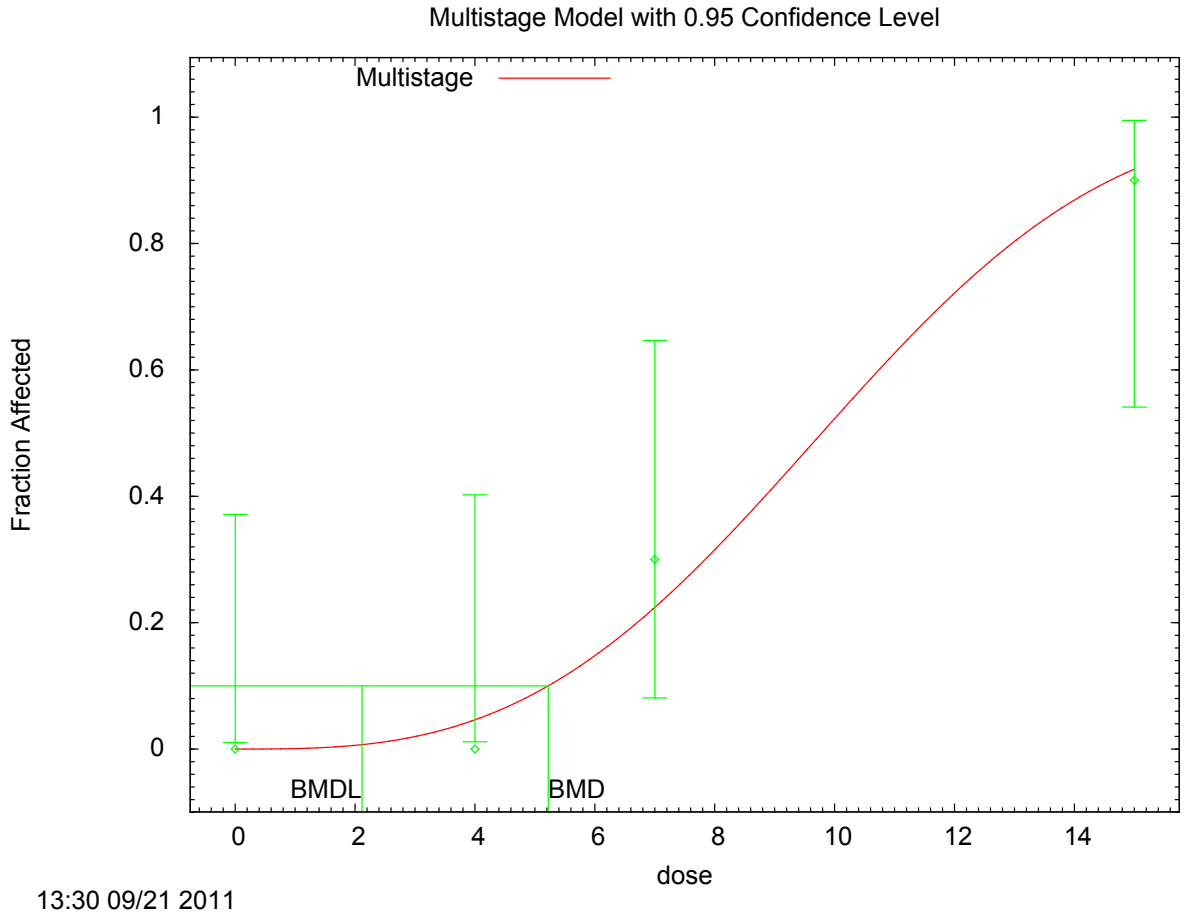
Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	2	0.41	0.81	-0.49	0.37	-0.49	23.35	5.37	3.22
Logistic	2	1.13	0.57	-0.73	0.65	-0.73	24.39	5.29	3.31
LogLogistic[d]	2	0.34	0.84	-0.48	0.28	-0.48	23.28	5.41	3.46
LogProbit[d]	2	0.24	0.89	-0.38	0.27	-0.38	23.10	5.47	3.61
Multistage (1-degree)[e]	3	5.59	0.13	0.00	-1.67	-1.67	28.84	1.41	0.89
Multistage (2-degree)[e]	3	1.42	0.70	0.00	-1.05	-1.05	23.14	3.61	1.96
Multistage (3-degree)[e,f]	**3**	**0.76**	**0.86**	**-0.62**	**0.58**	**-0.62**	**21.82**	**5.22**	**2.12**
Probit	2	0.96	0.62	-0.68	0.64	-0.68	24.10	5.25	3.18
Weibull[c]	2	0.69	0.71	-0.66	0.48	-0.66	23.81	5.07	2.79

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided an adequate fit of the data. The range of $BMDL_{10}$ values from adequately fitting models was >3-fold mainly due to the poor fitting of the Multistage 1-degree model (highest AIC value, largest scaled residuals, and worst goodness-of-fit p-value). $BMDL_{10}$ values from the remaining models were <3-fold, thus; the model with the lowest AIC value was selected (Multistage 3-degree).

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

Source: NTP 1994

Figure A-10. Fit of Multistage 3-Degree Polynomial Model to Incidence of Hyperplasia of the Interstitial Cells in the Ovary of Female F344 Rats Fed TCP in the Diet for 15 Months



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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 nontechnical 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 chemical 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 judgment, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgment 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 are 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 harmful 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 an 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 a harmful 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 an 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 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

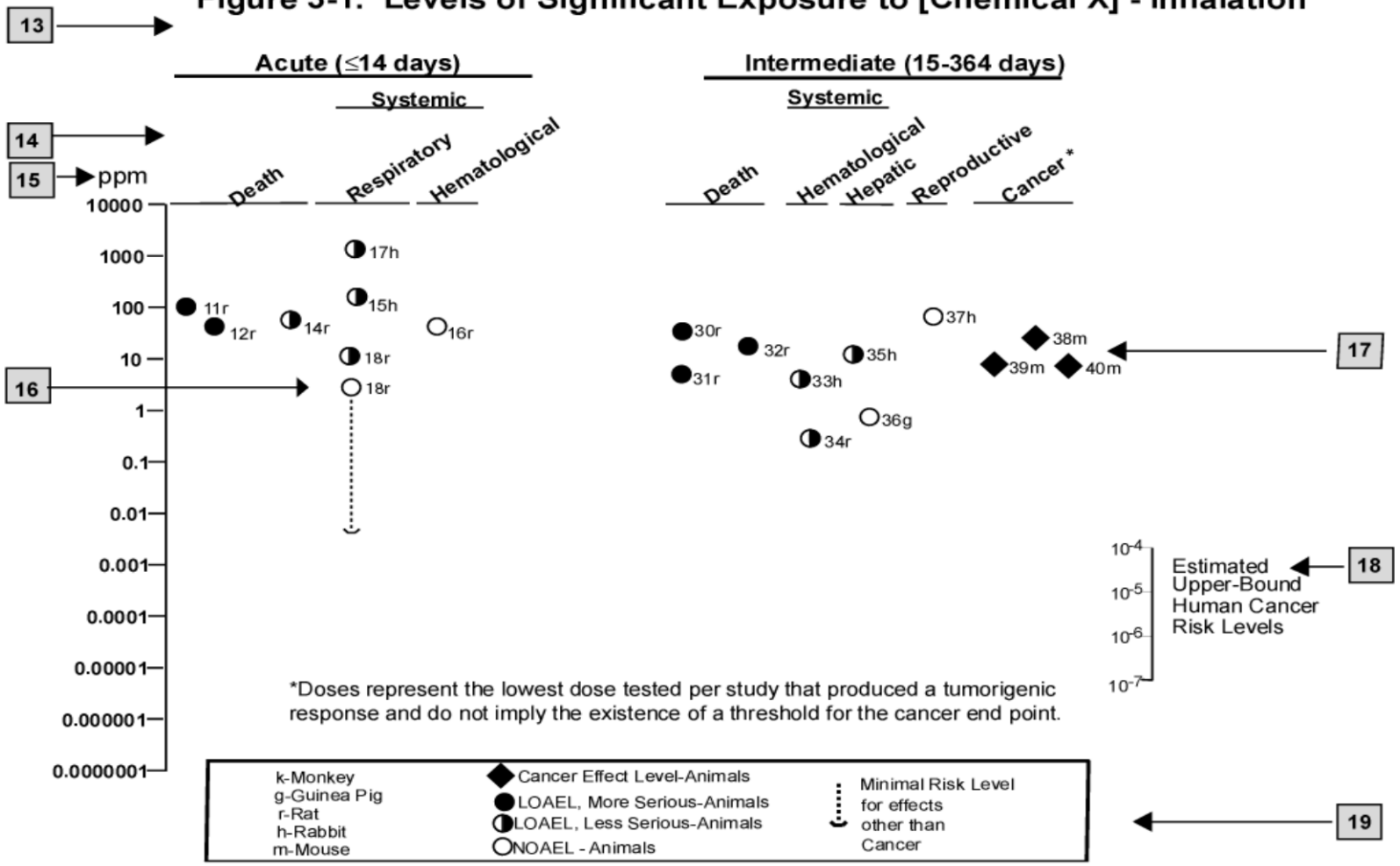
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	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 an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ 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



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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
CL	ceiling limit value
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

APPENDIX C

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	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
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
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
RfC	reference concentration
RfD	reference dose
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
SGPT	serum glutamic pyruvic transaminase
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
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

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APPENDIX D. INDEX