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)

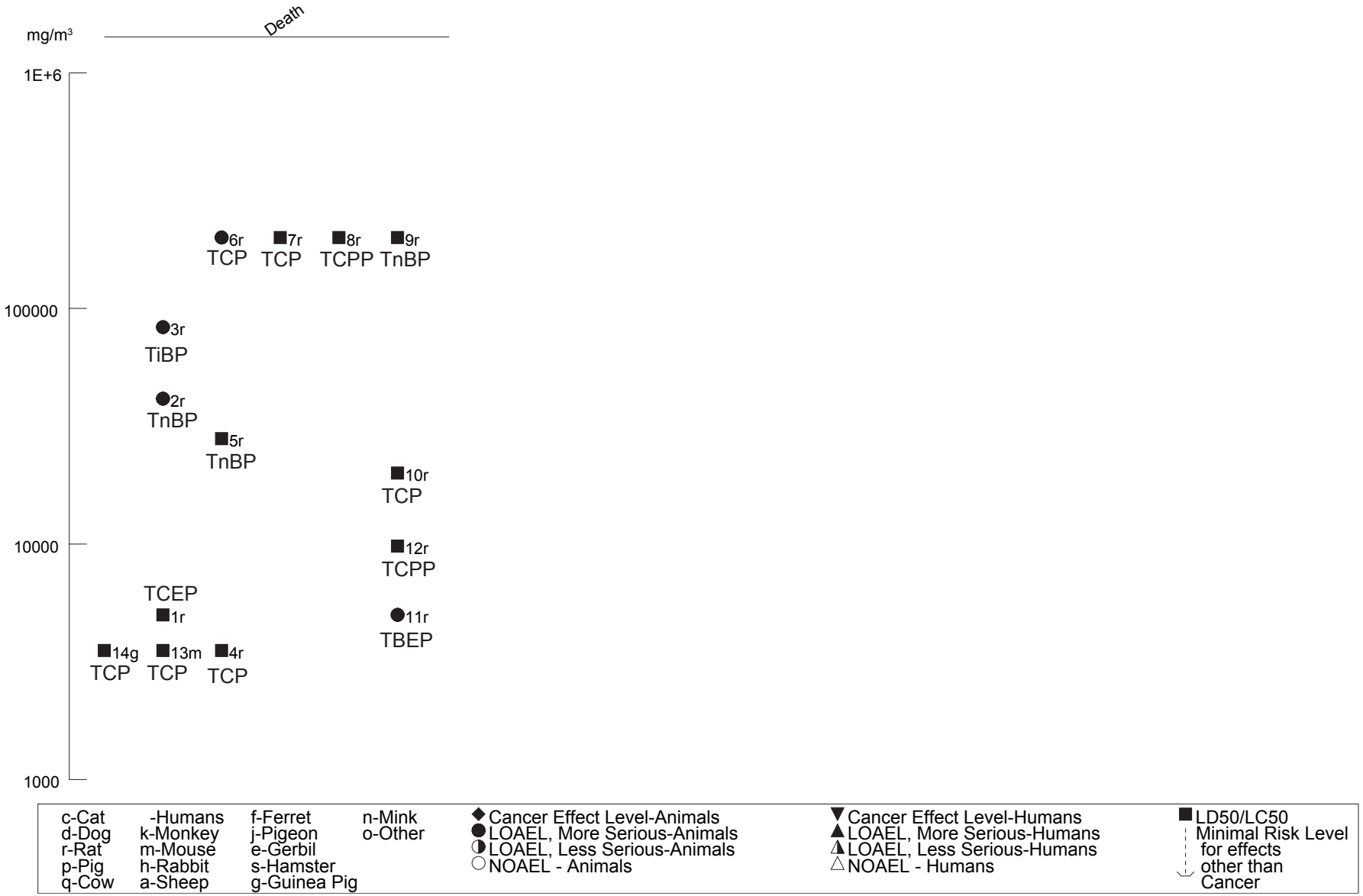
Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)		Reference Chemical Form	Comments
8	Rat (Wistar)	1 hr (NS)				200000	(LC50 was greater than 200000 mg/cubic meter)	FMC 1982 115-86-6	
9	Rat (NS)	1 hr (NS)				200000	(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)

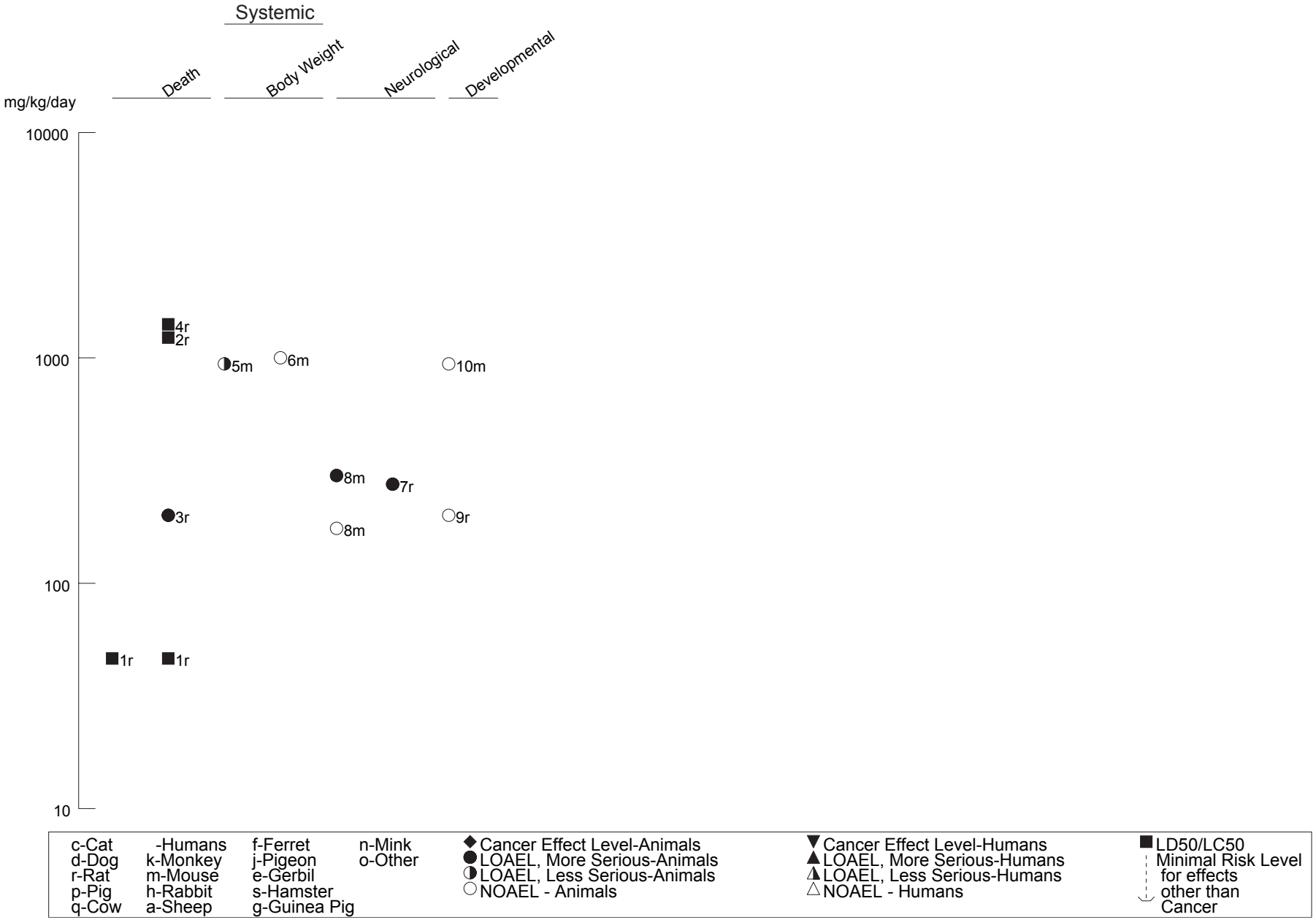


Figure 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral *(Continued)*

Intermediate (15-364 days)

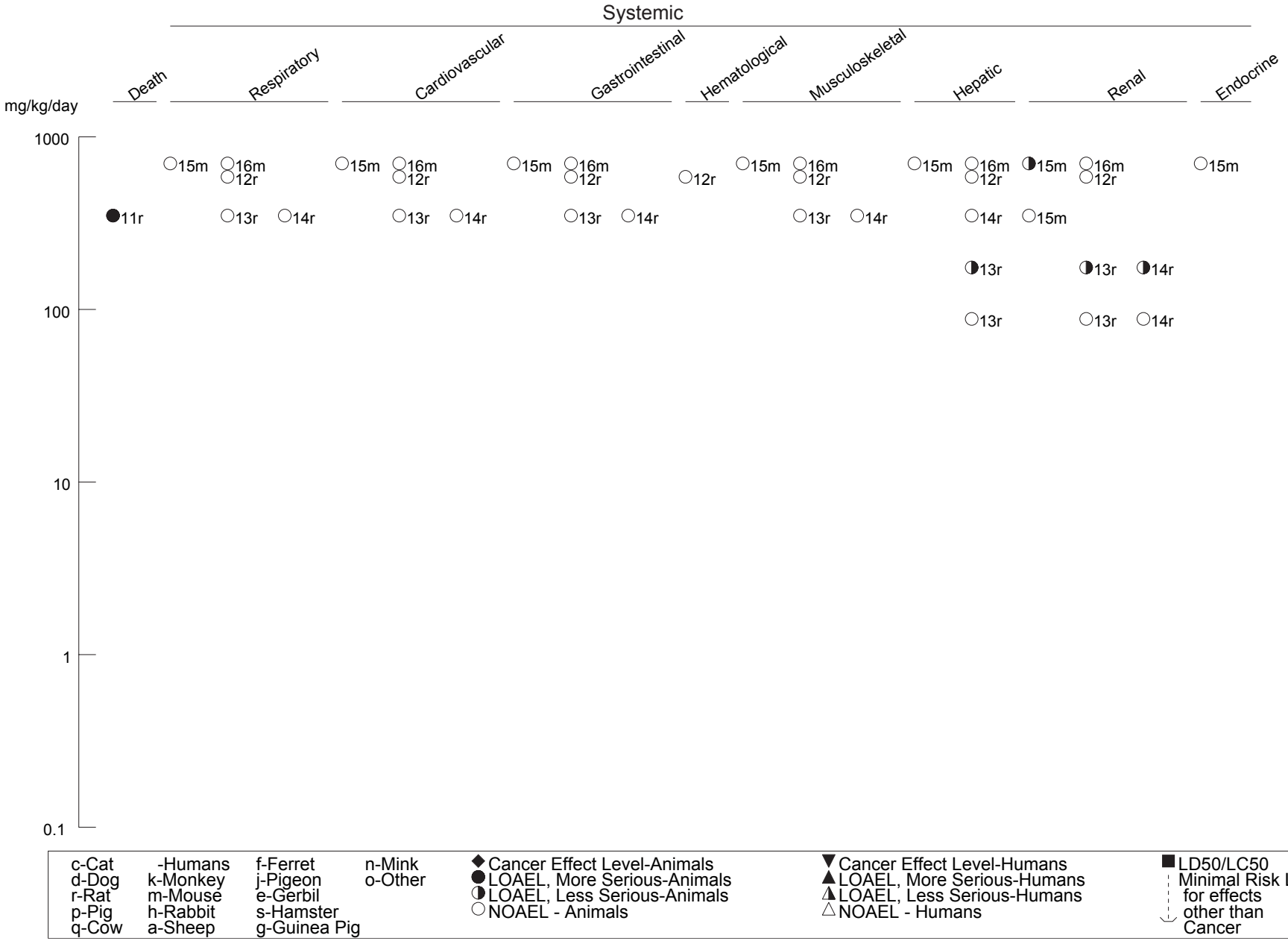


Figure 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral *(Continued)*

Intermediate (15-364 days)

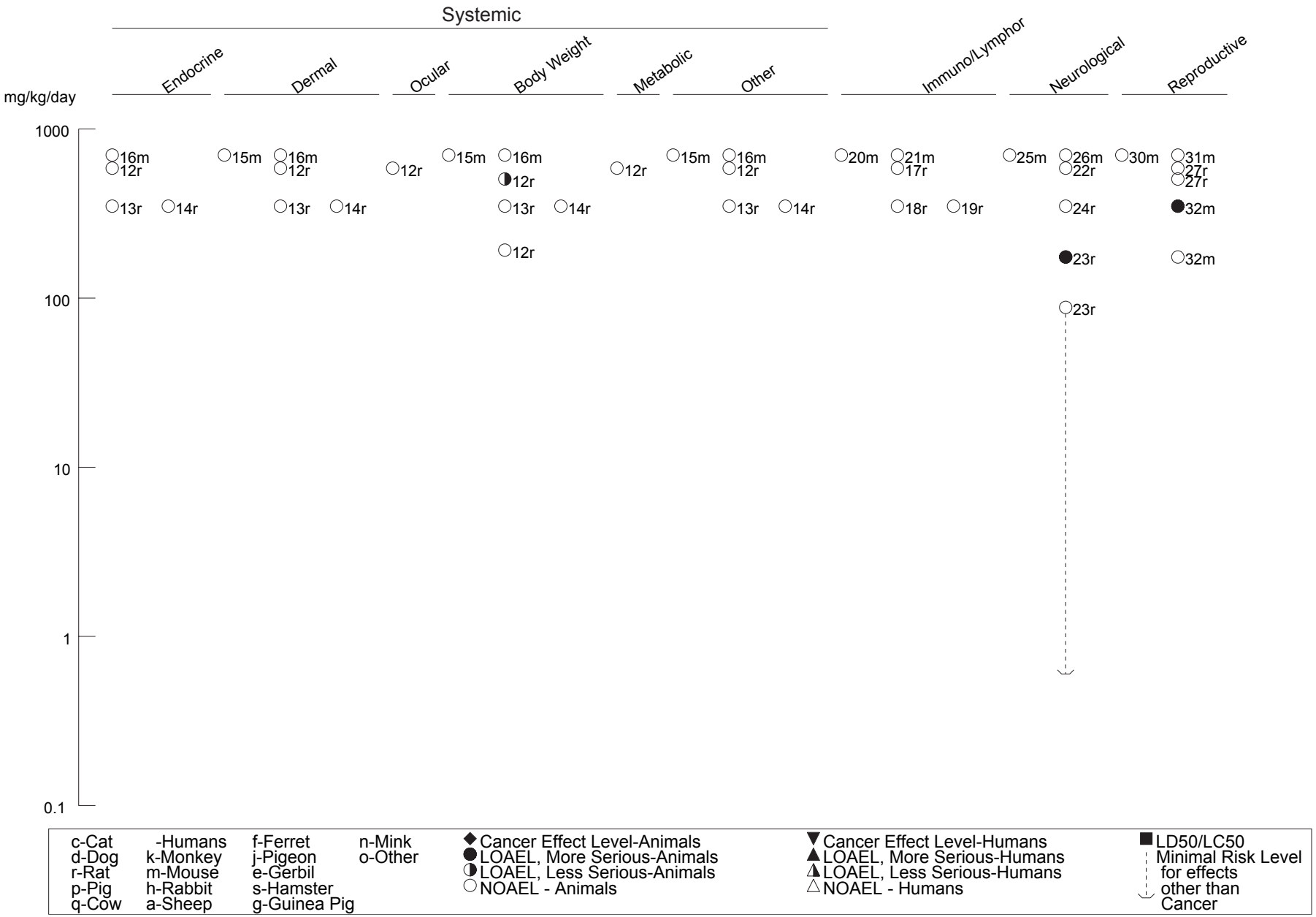


Figure 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral *(Continued)*

Intermediate (15-364 days)

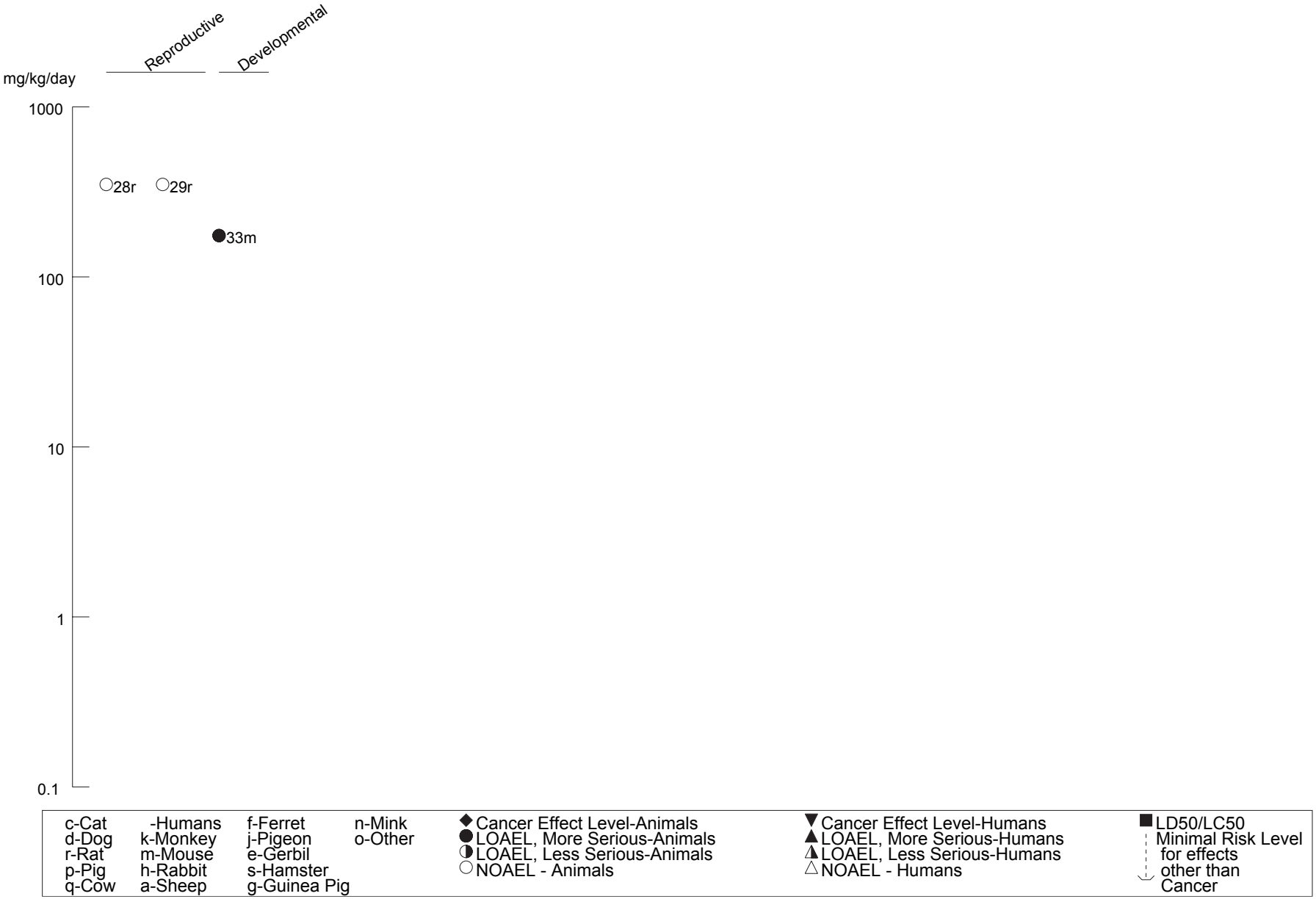


Figure 3-2 Levels of Significant Exposure to Tris(2-chloroethyl) Phosphate (TCEP) - Oral *(Continued)*

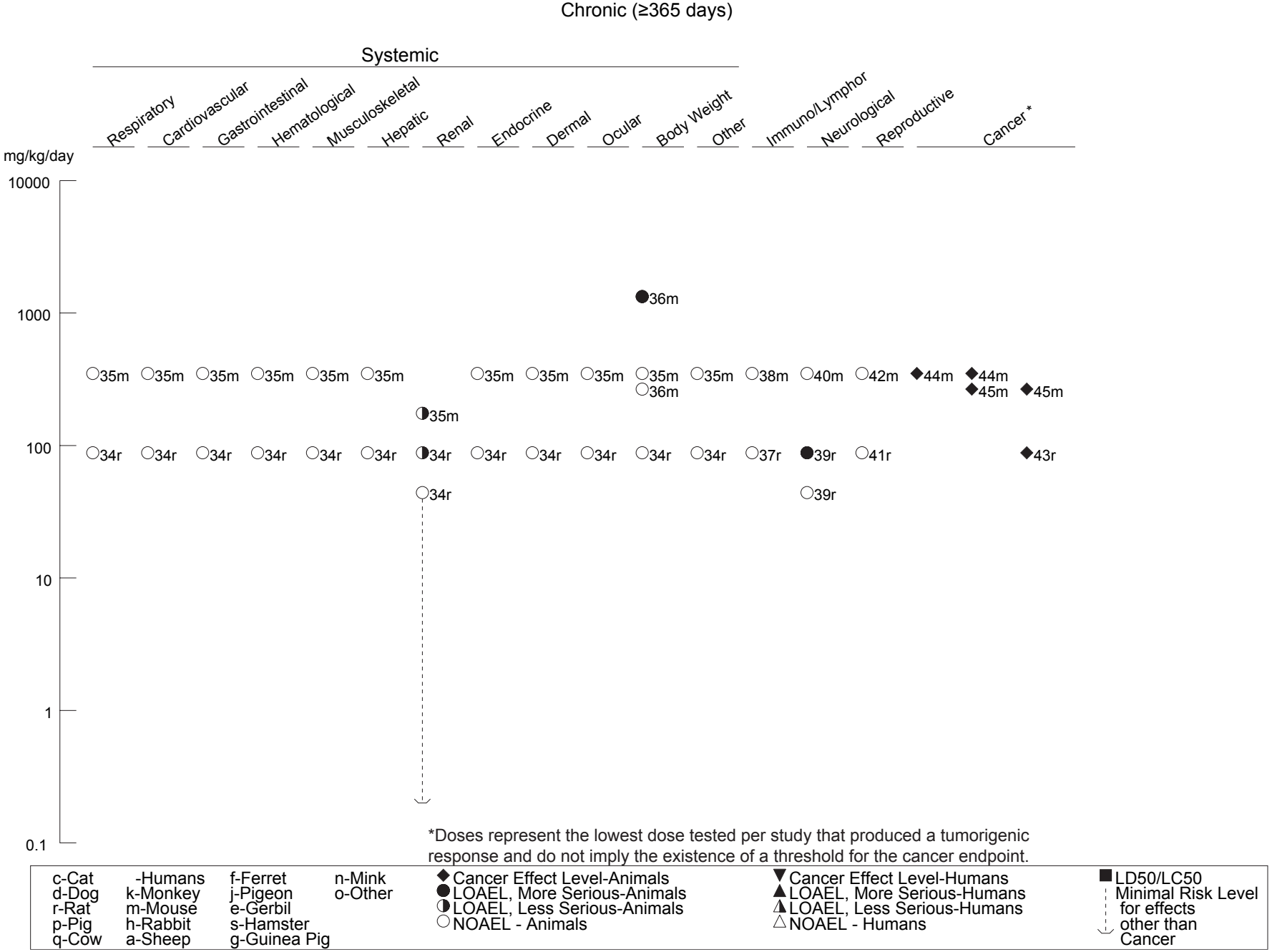


Table 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral

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)	EI 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[c] M	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)

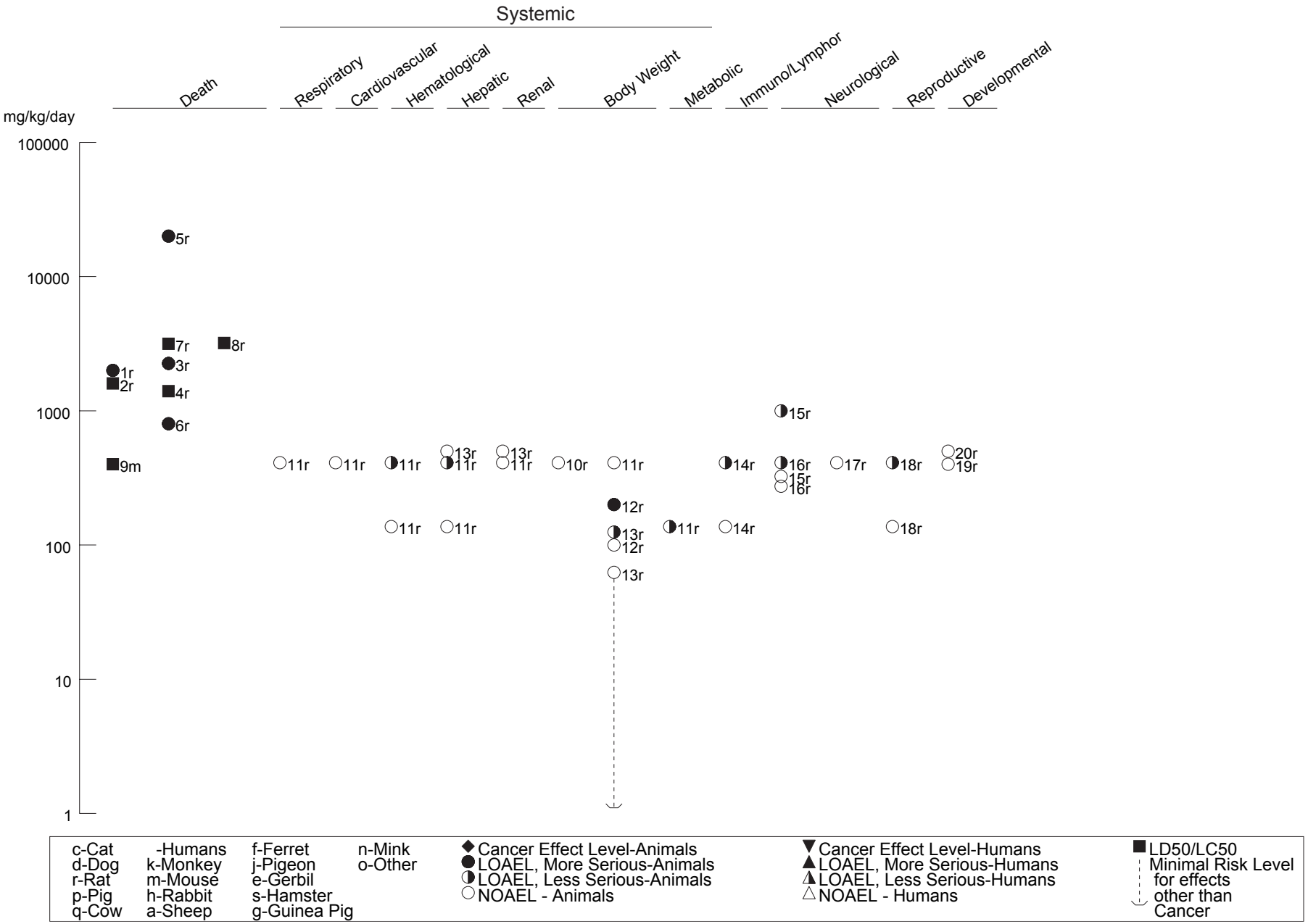


Figure 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral *(Continued)*

Intermediate (15-364 days)

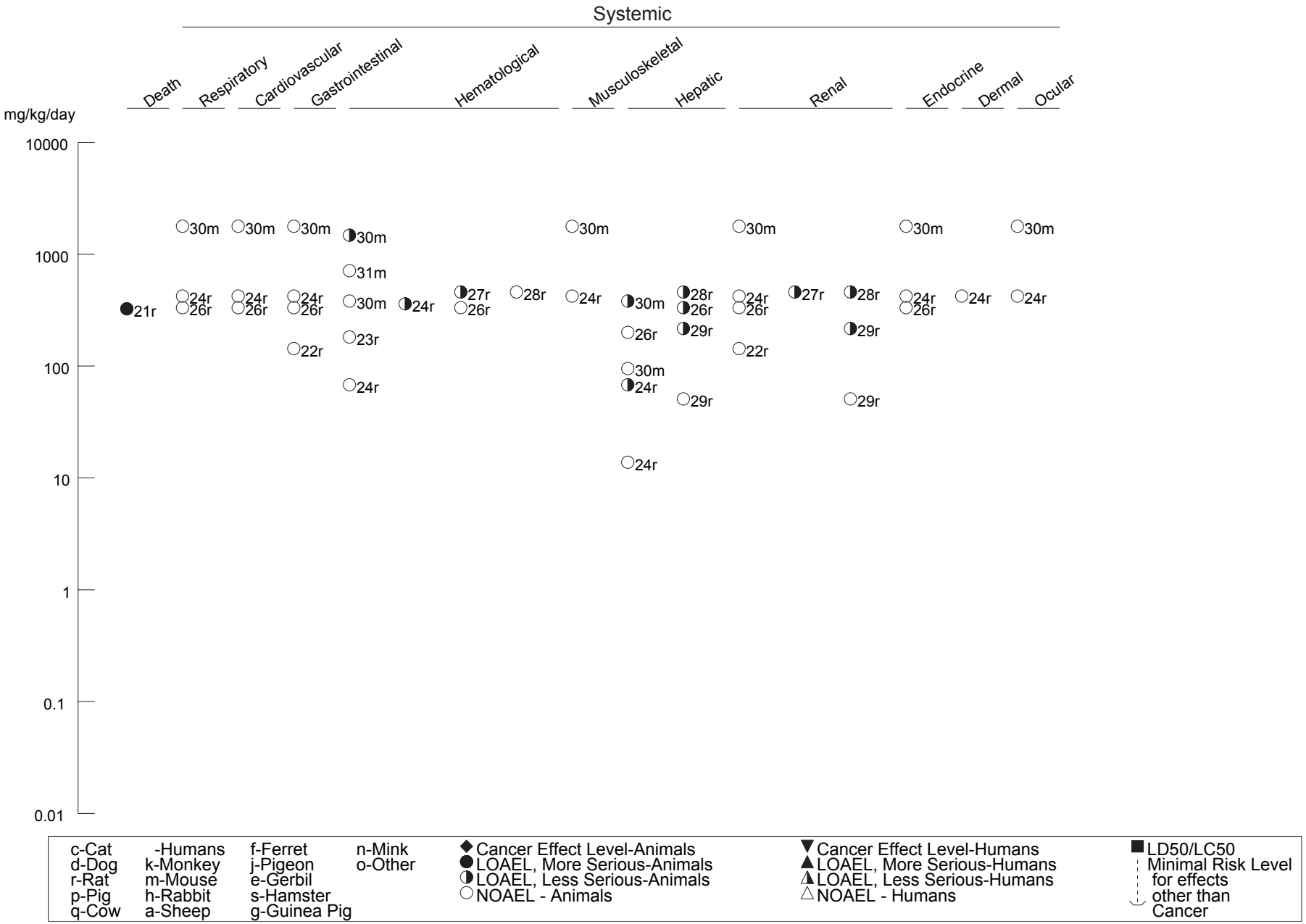


Figure 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral *(Continued)*

Intermediate (15-364 days)

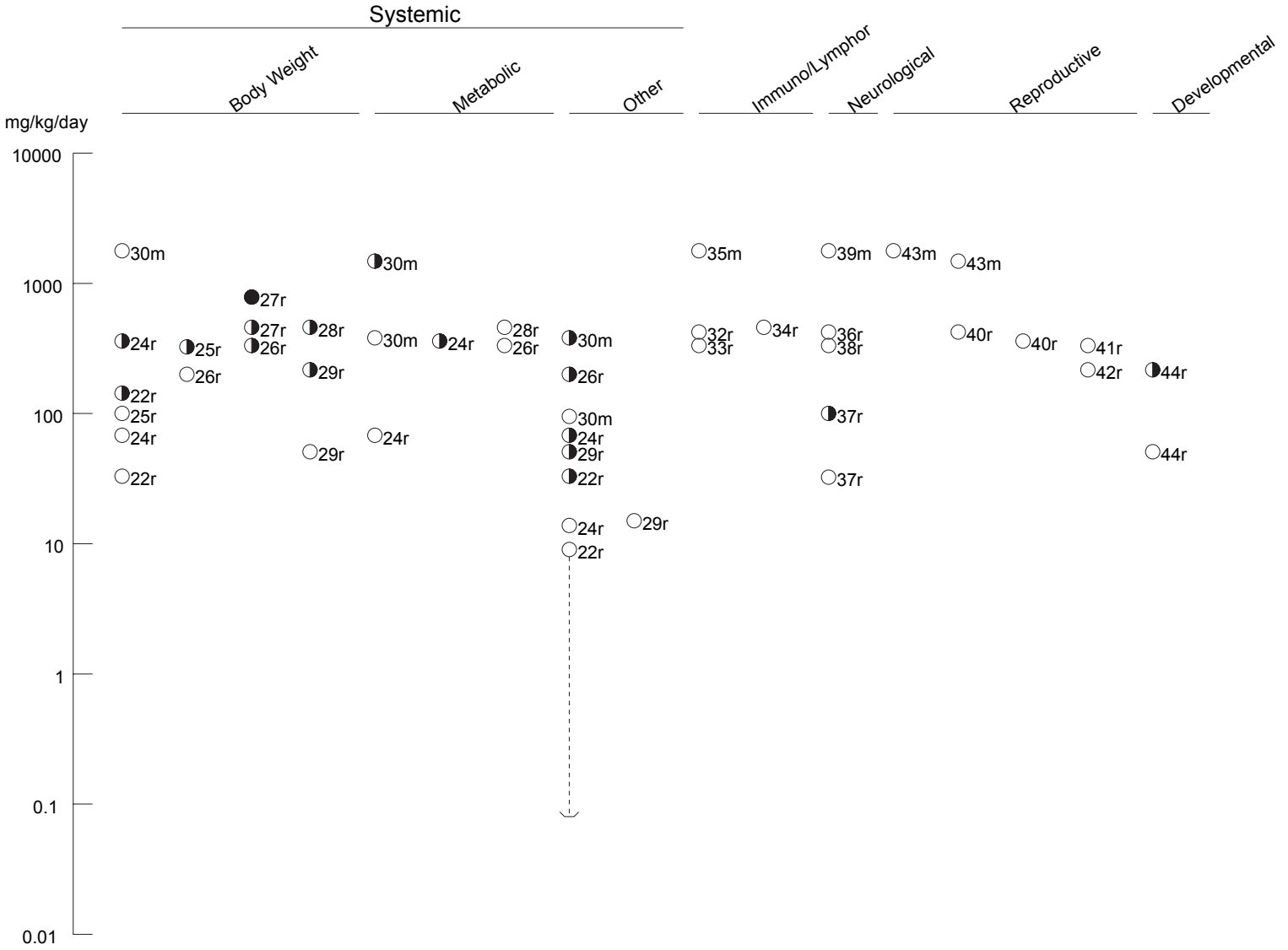
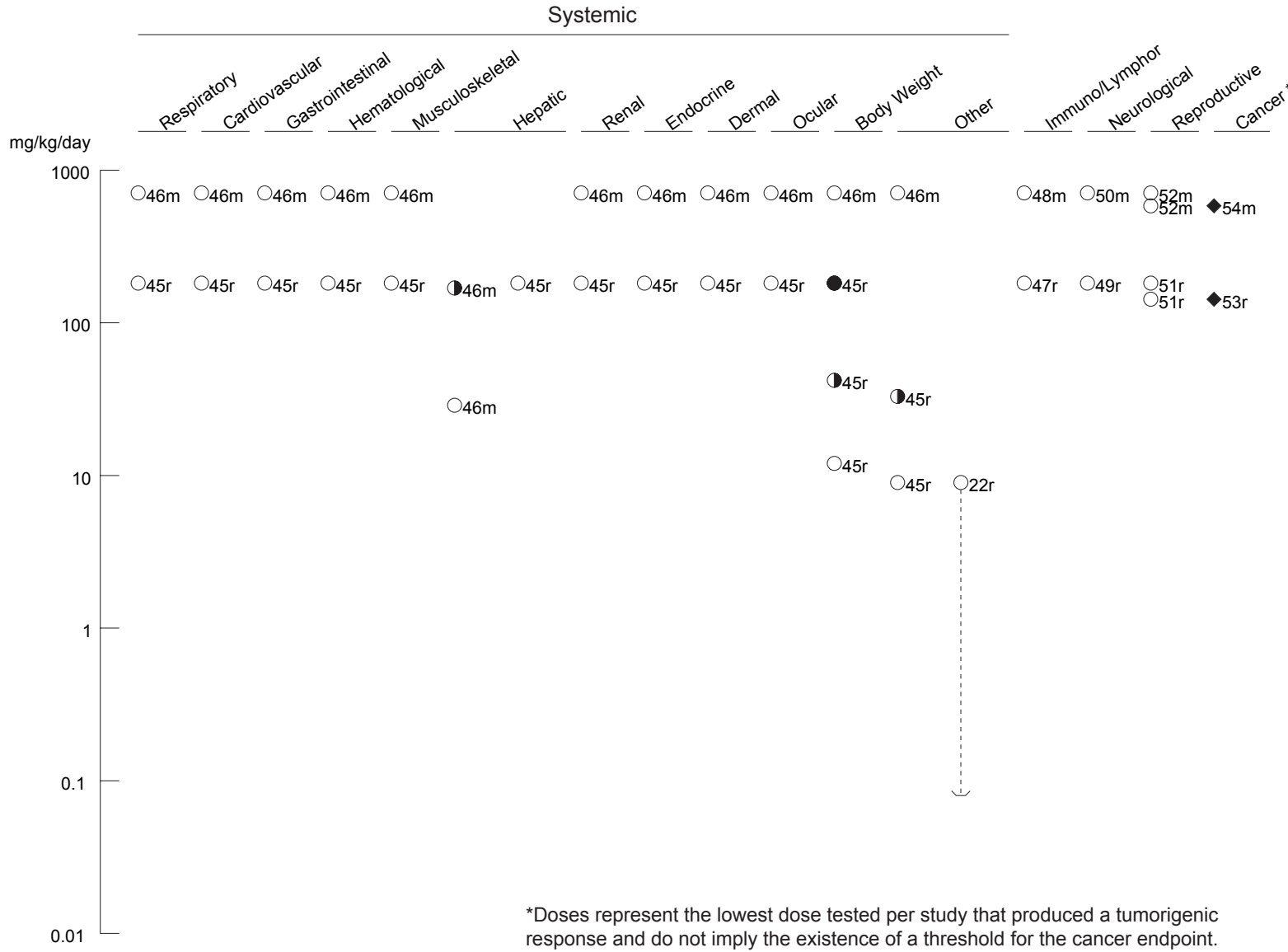


Figure 3-3 Levels of Significant Exposure to Tri-n-butyl Phosphate (TnBP) - Oral *(Continued)*

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	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

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)

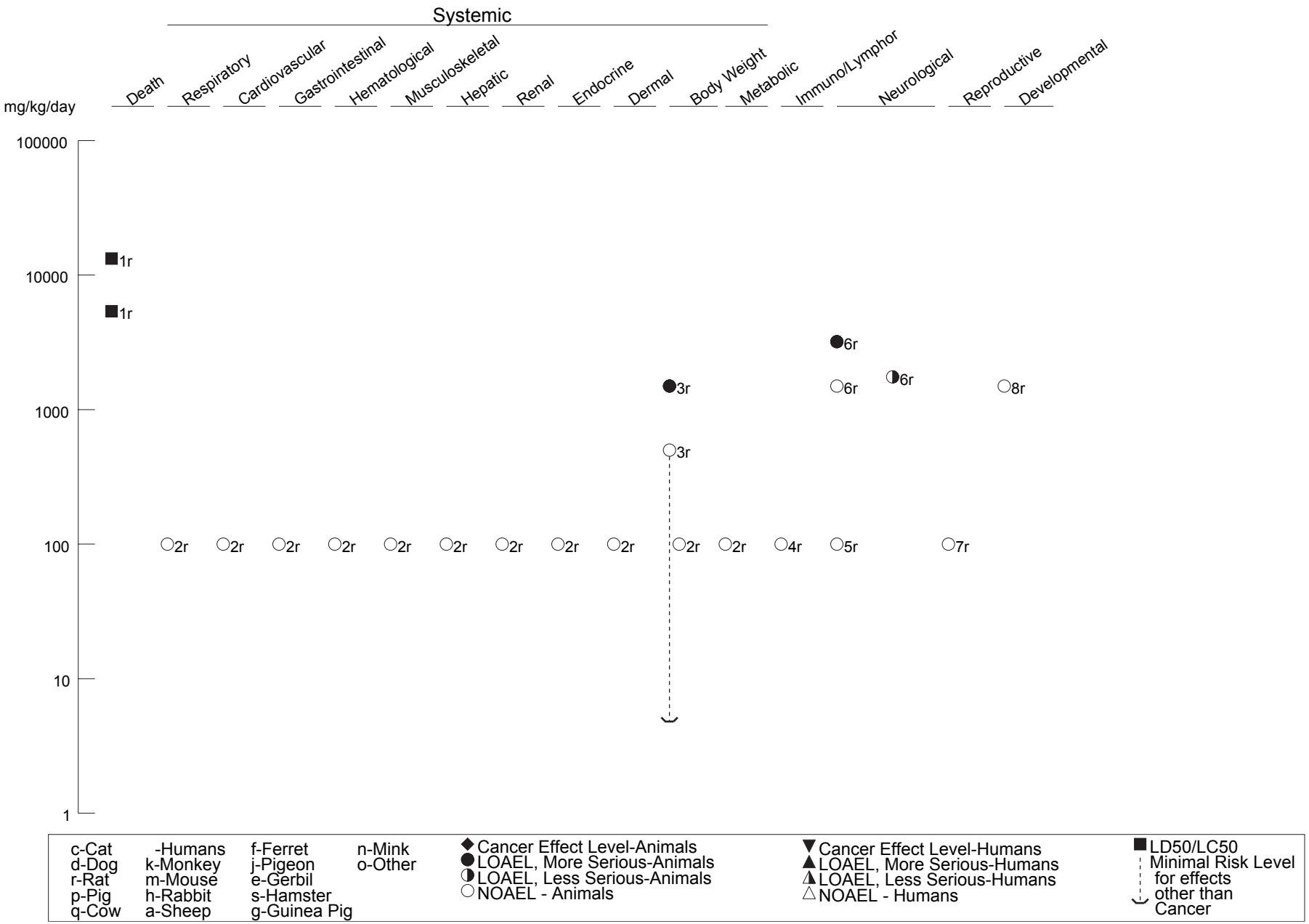


Figure 3-4 Levels of Significant Exposure to Tris(2-butoxyethyl) Phosphate (TBEP) - Oral *(Continued)*

Intermediate (15-364 days)

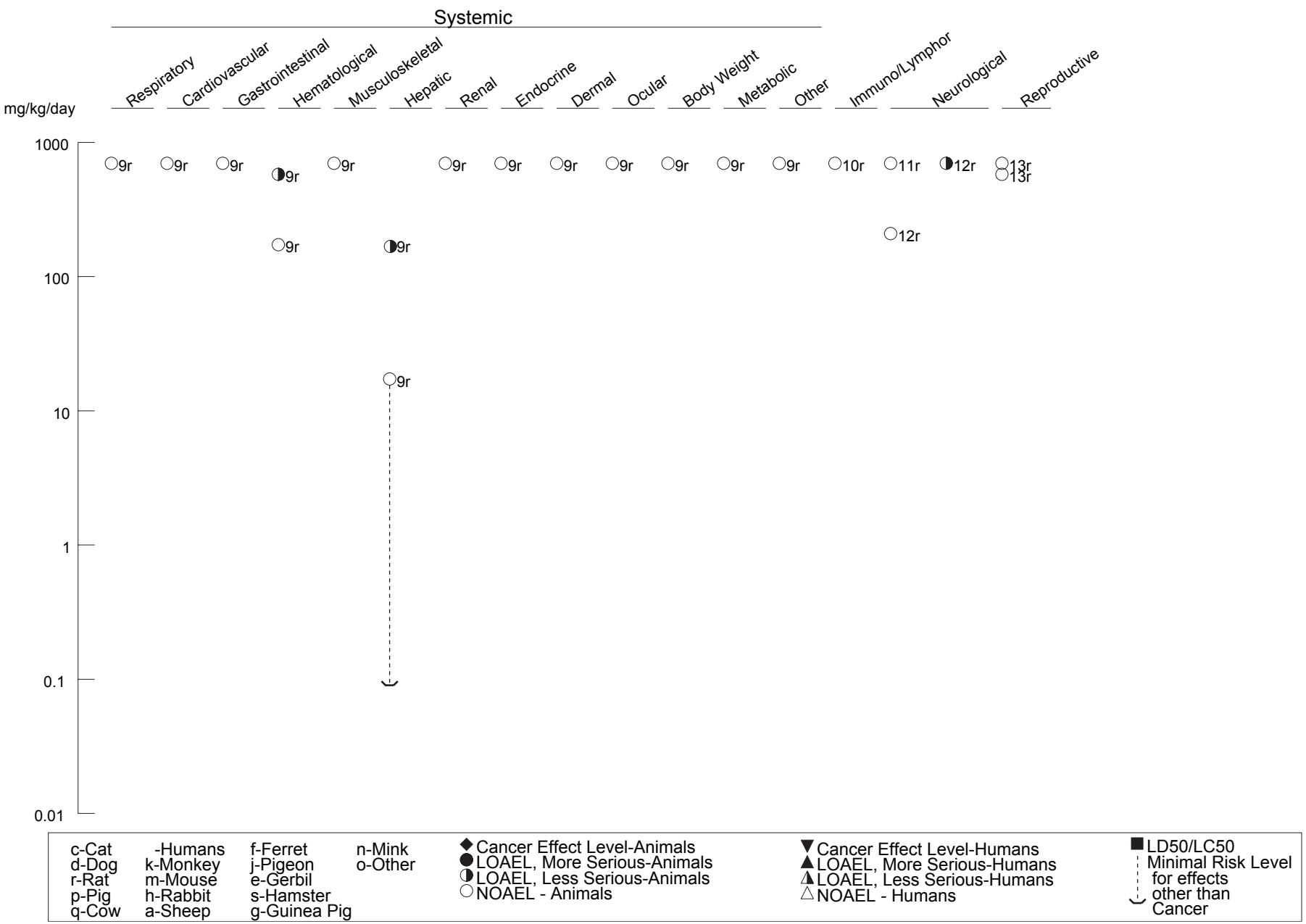


Table 3-5 Levels of Significant Exposure to Tris(1,3-dichloro-2-propyl) (TDCP) - Oral

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)

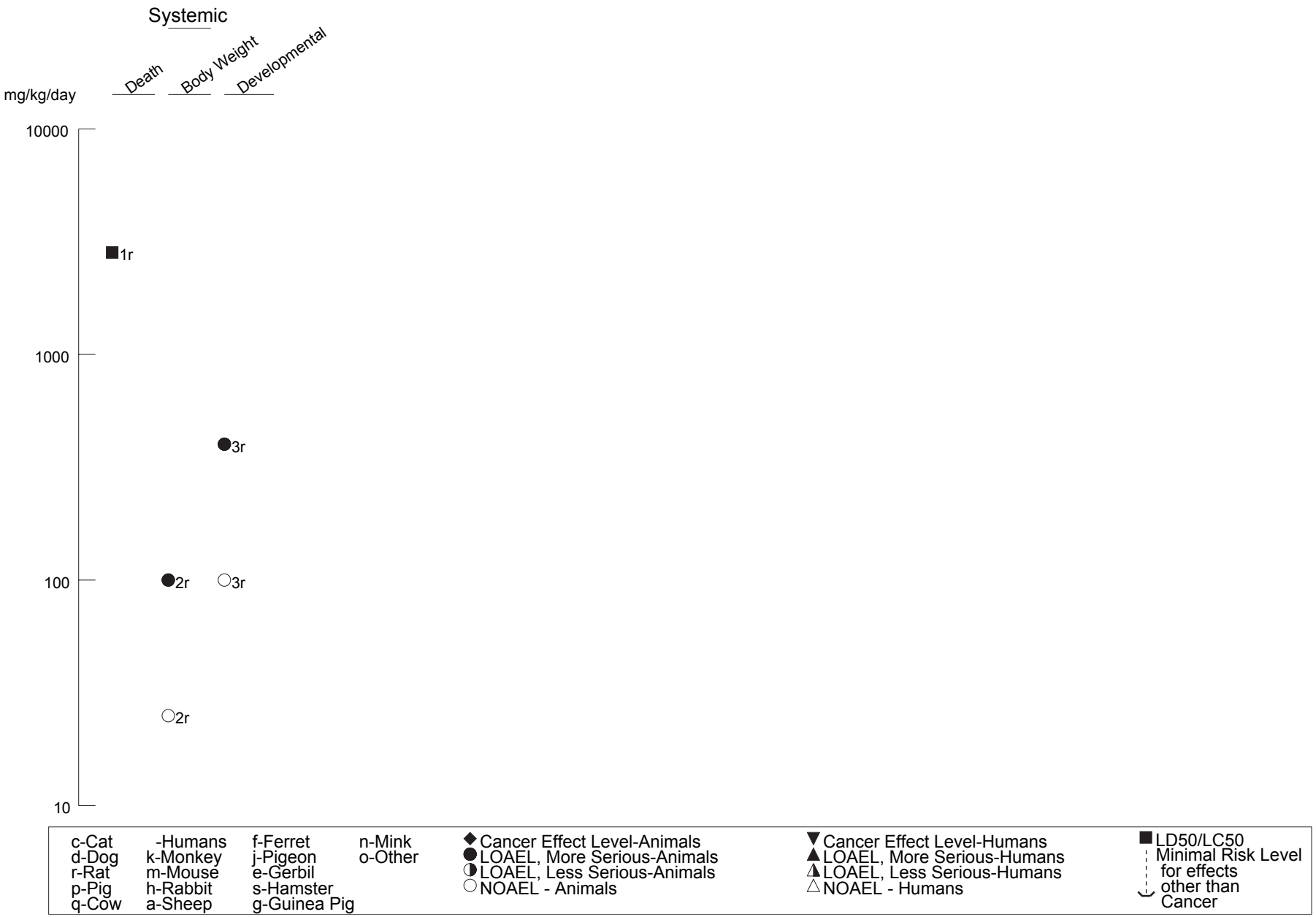


Figure 3-5 Levels of Significant Exposure to Tris(1,3-dichloro-2-propyl) (TDCP) - Oral *(Continued)*

Intermediate (15-364 days)

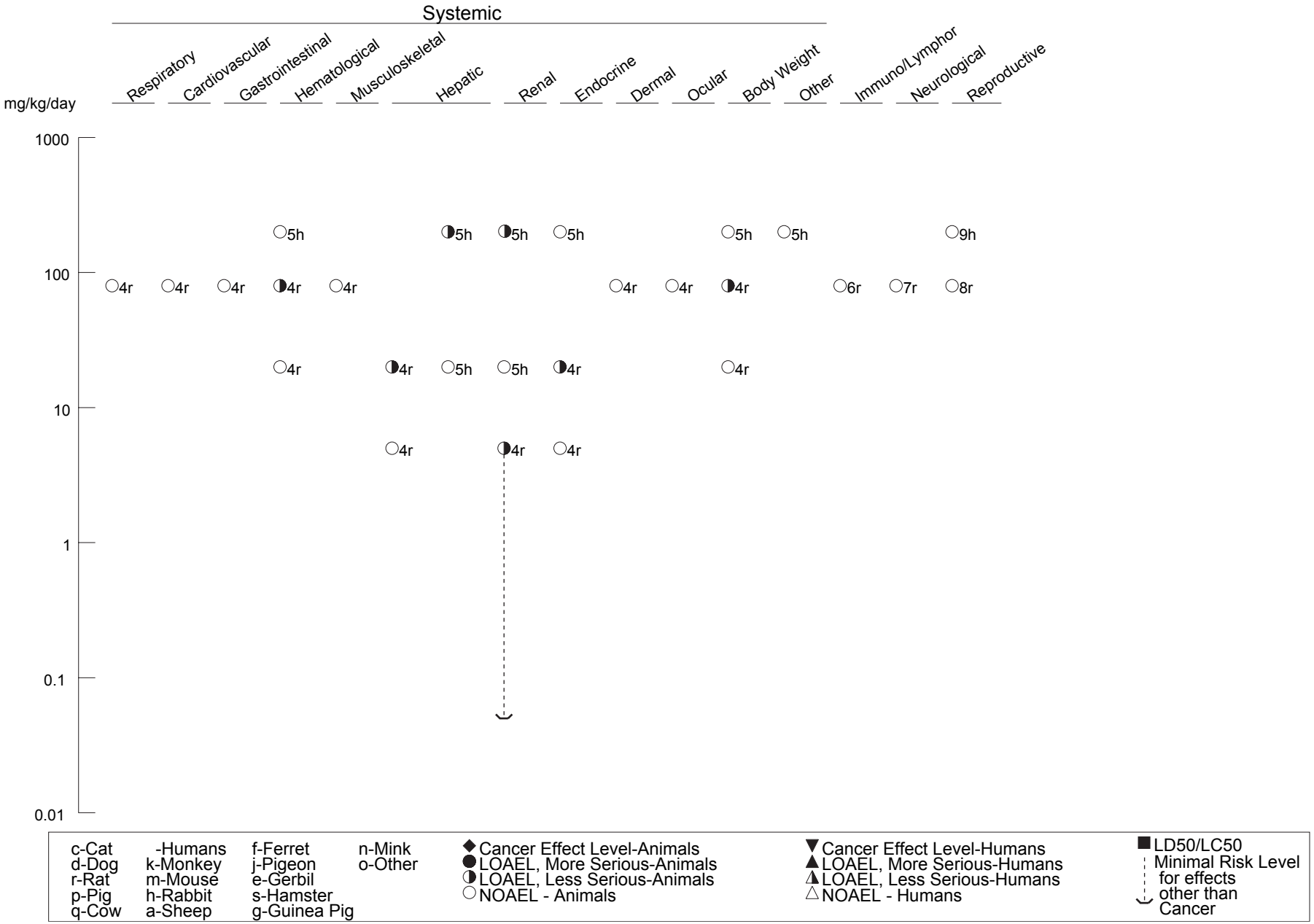


Figure 3-5 Levels of Significant Exposure to Tris(1,3-dichloro-2-propyl) (TDCP) - Oral *(Continued)*

Chronic (≥365 days)

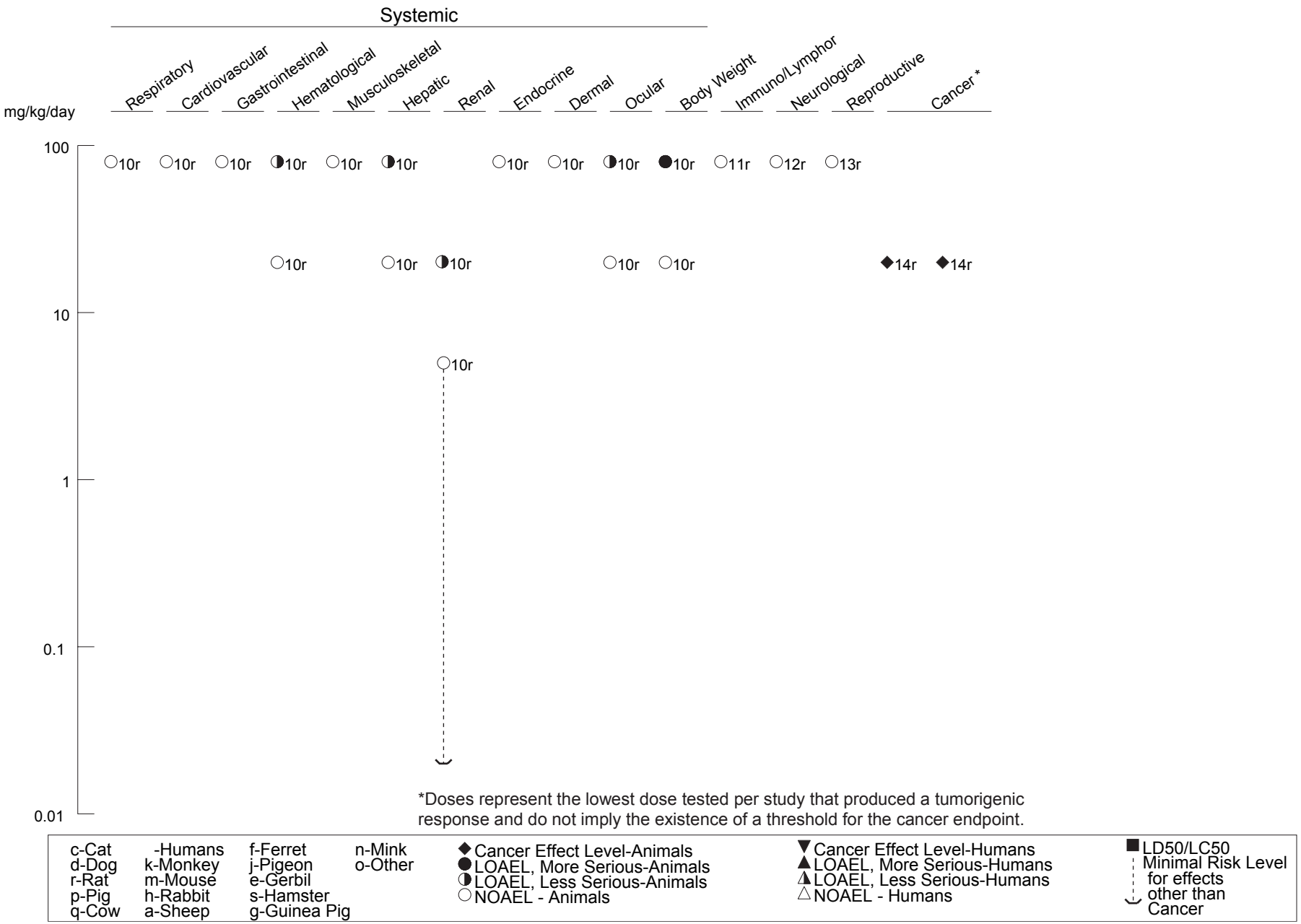


Table 3-6 Levels of Significant Exposure to TCP - Oral

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)

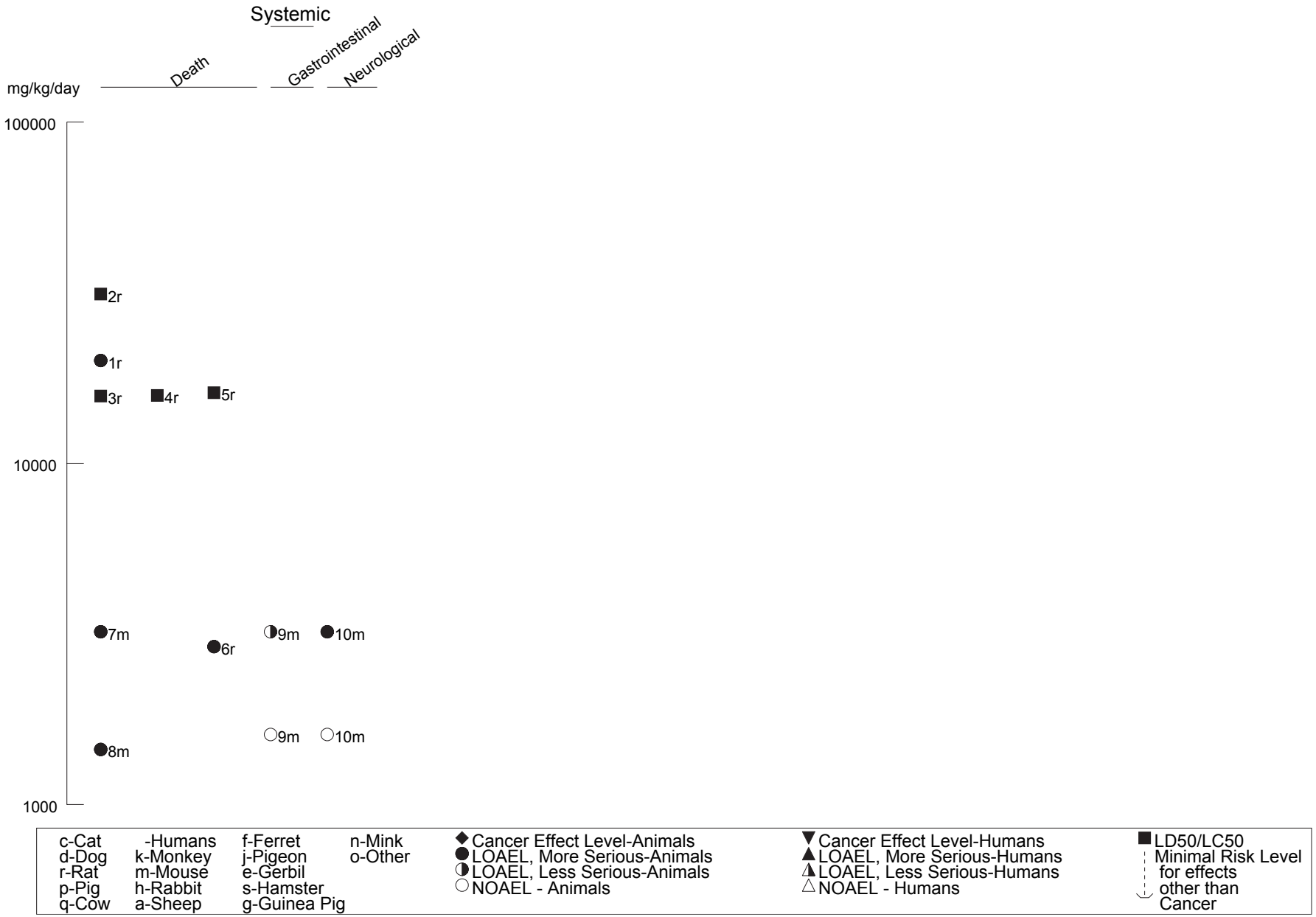


Figure 3-6 Levels of Significant Exposure to TCP - Oral *(Continued)*

Intermediate (15-364 days)

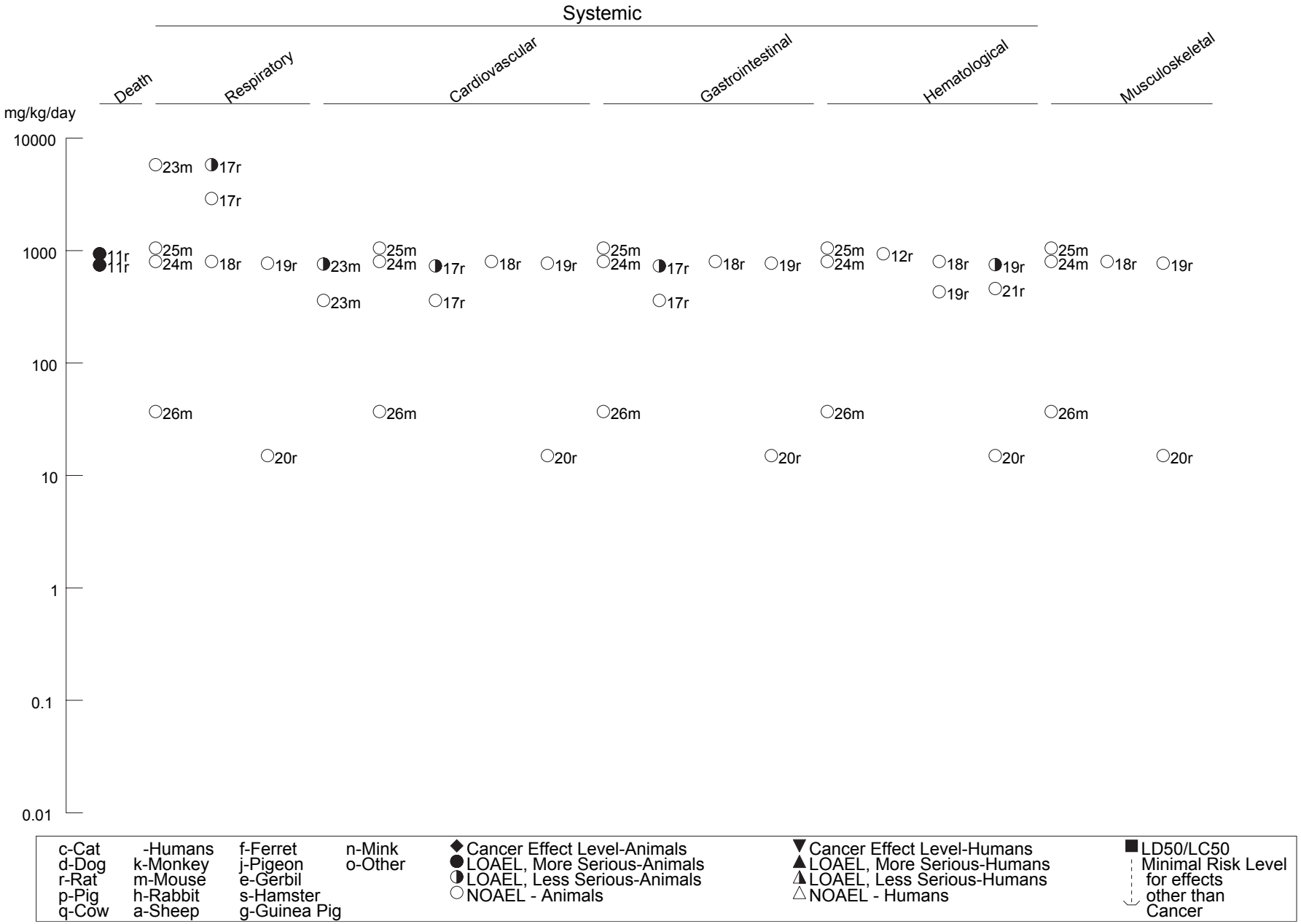


Figure 3-6 Levels of Significant Exposure to TCP - Oral *(Continued)*

Intermediate (15-364 days)

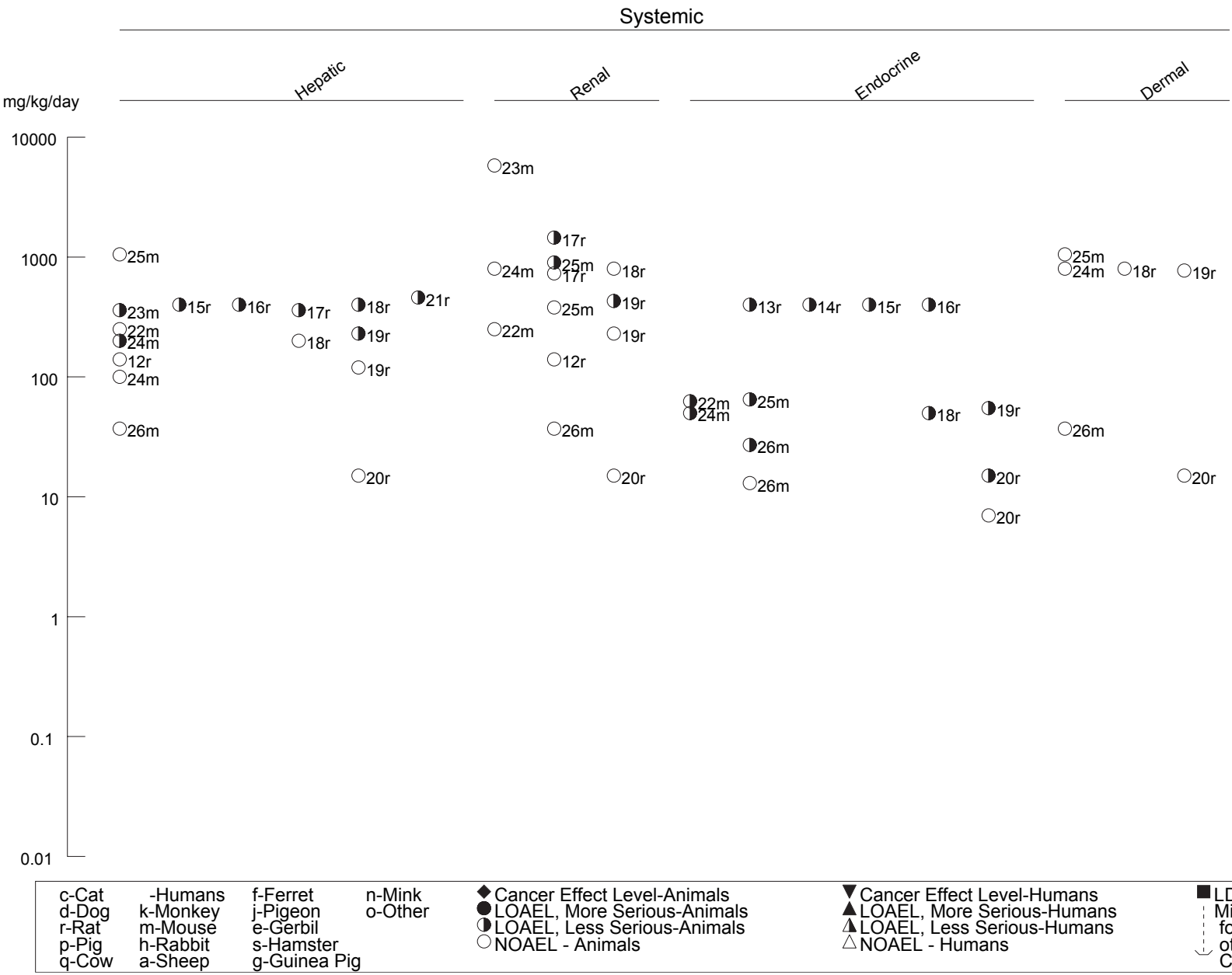


Figure 3-6 Levels of Significant Exposure to TCP - Oral *(Continued)*

Intermediate (15-364 days)

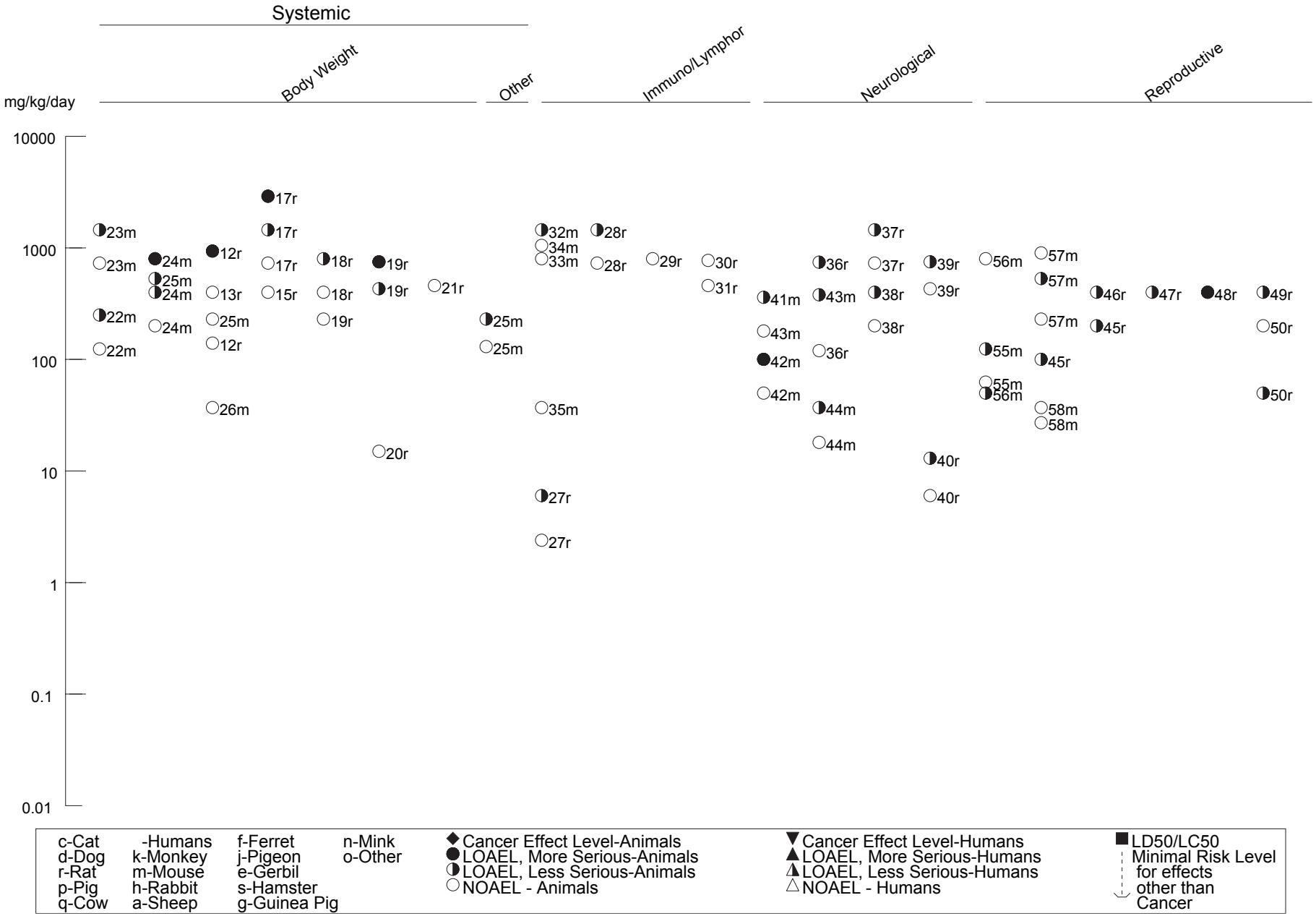


Figure 3-6 Levels of Significant Exposure to TCP - Oral *(Continued)*

Intermediate (15-364 days)

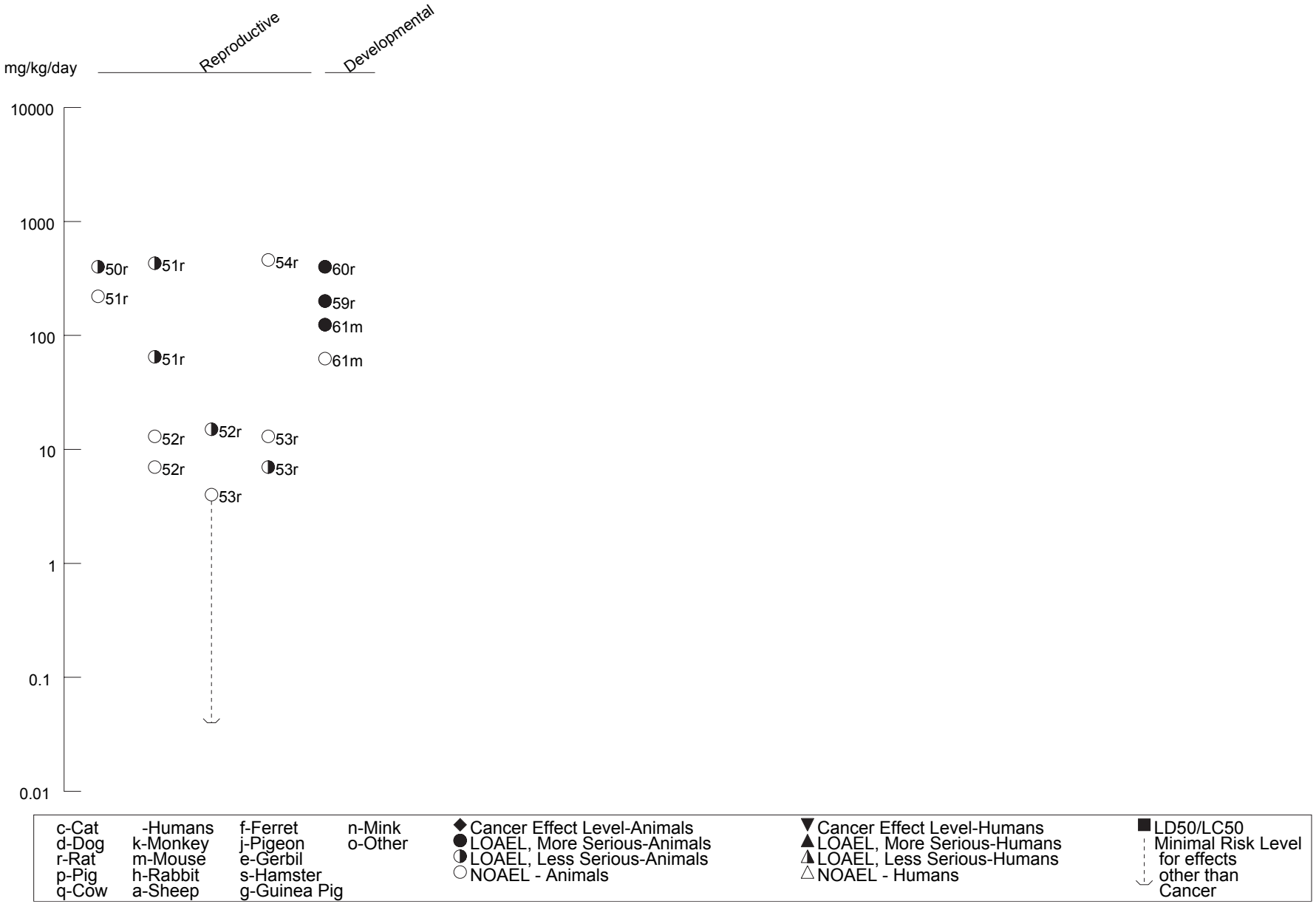


Figure 3-6 Levels of Significant Exposure to TCP - Oral *(Continued)*

Chronic (≥365 days)

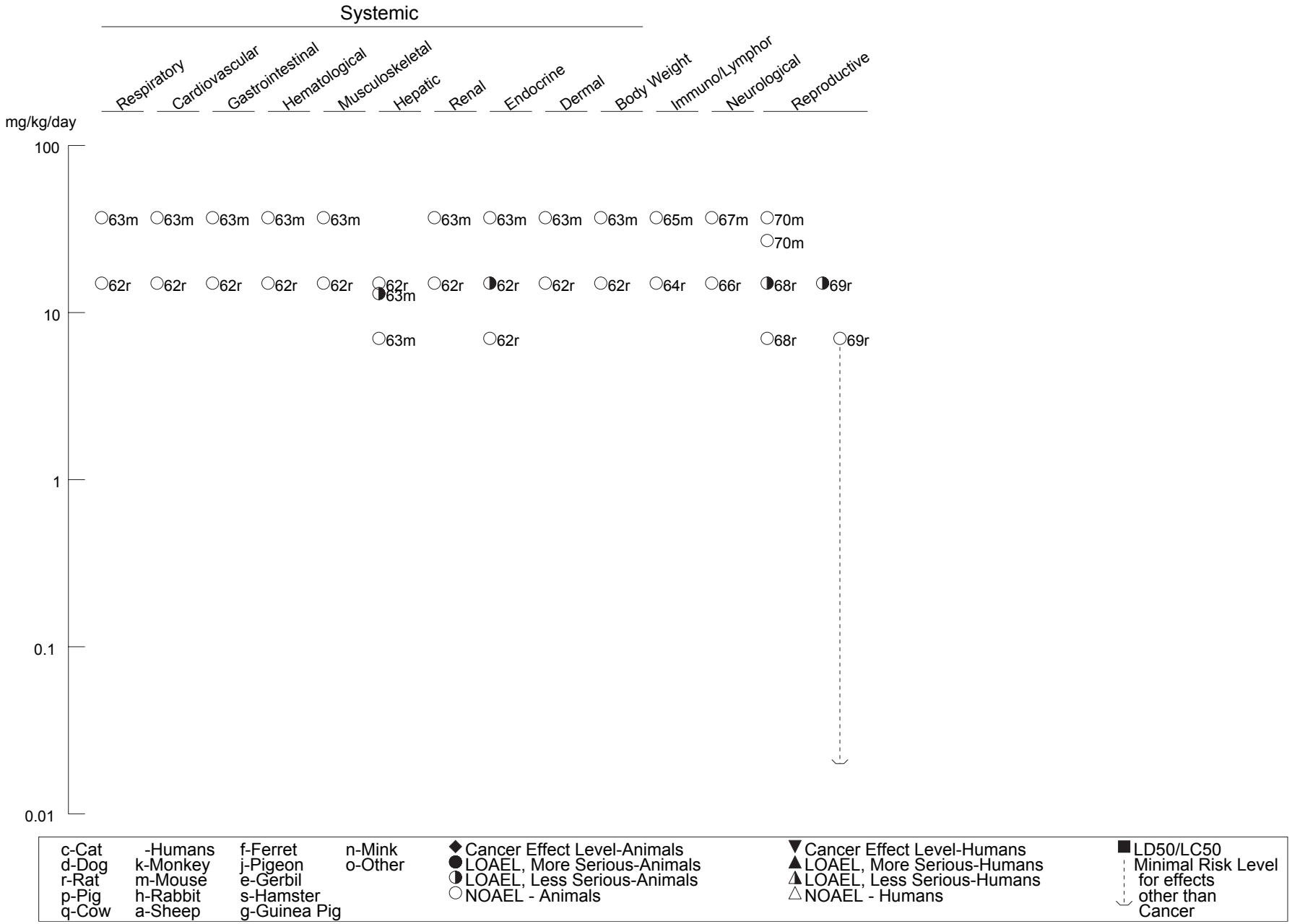


Table 3-7 Levels of Significant Exposure to TPP, TCPP, and TiBP - Oral

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)

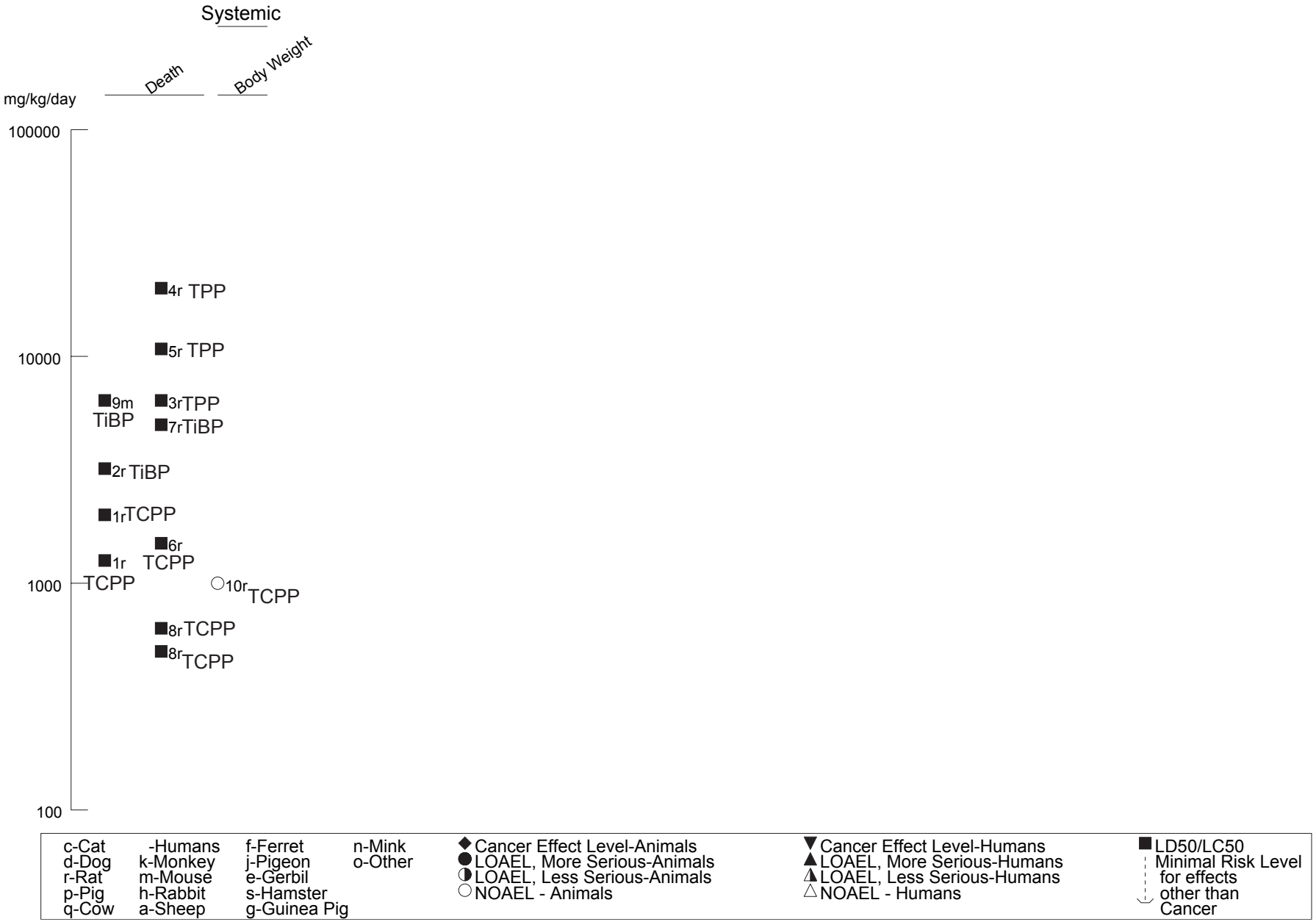
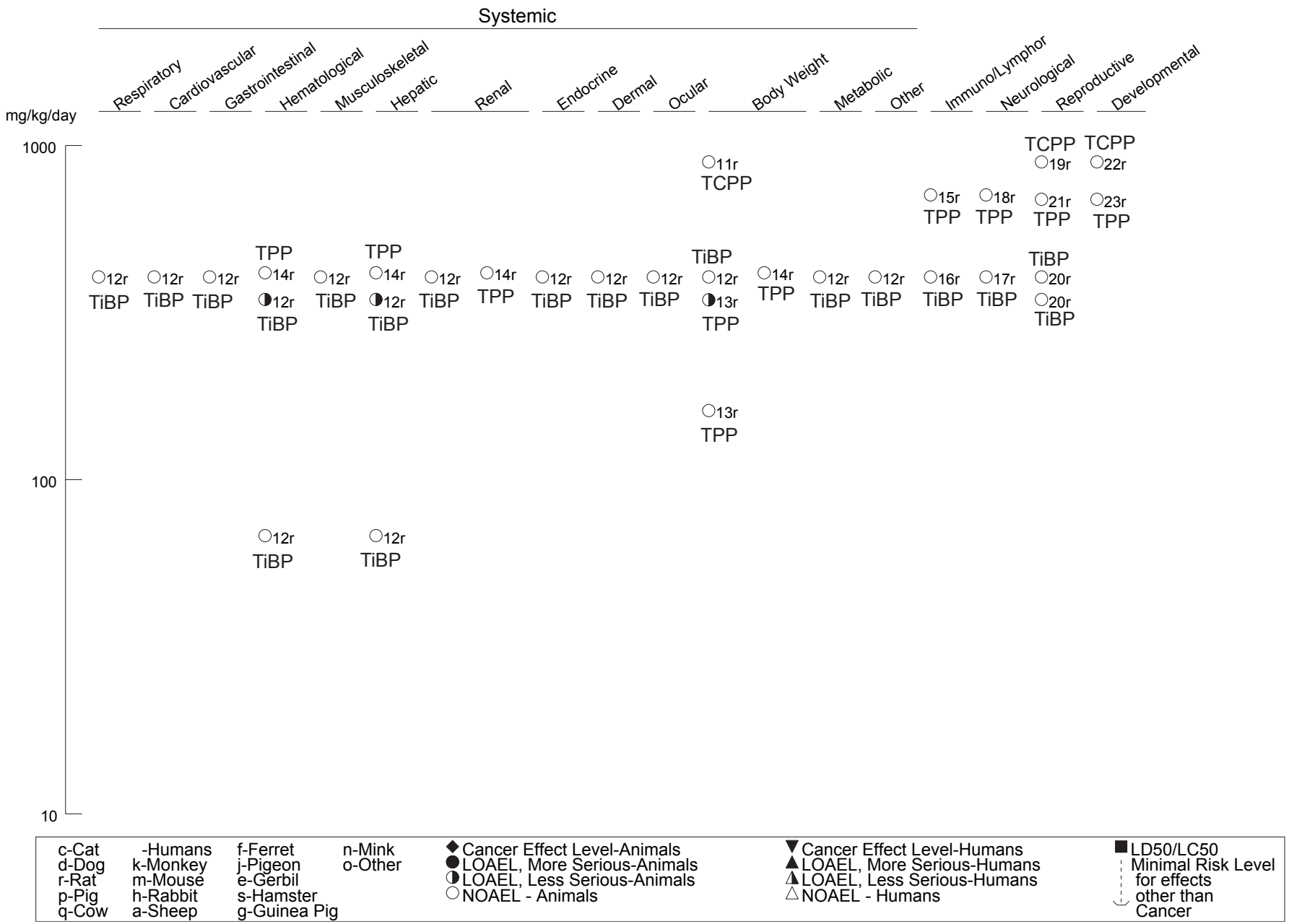


Figure 3-7 Levels of Significant Exposure to TPP, TCPP, and TiBP - Oral *(Continued)*

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 Less Serious	LOAEL Serious	Reference Chemical Form	Comments
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 5^{th} 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.

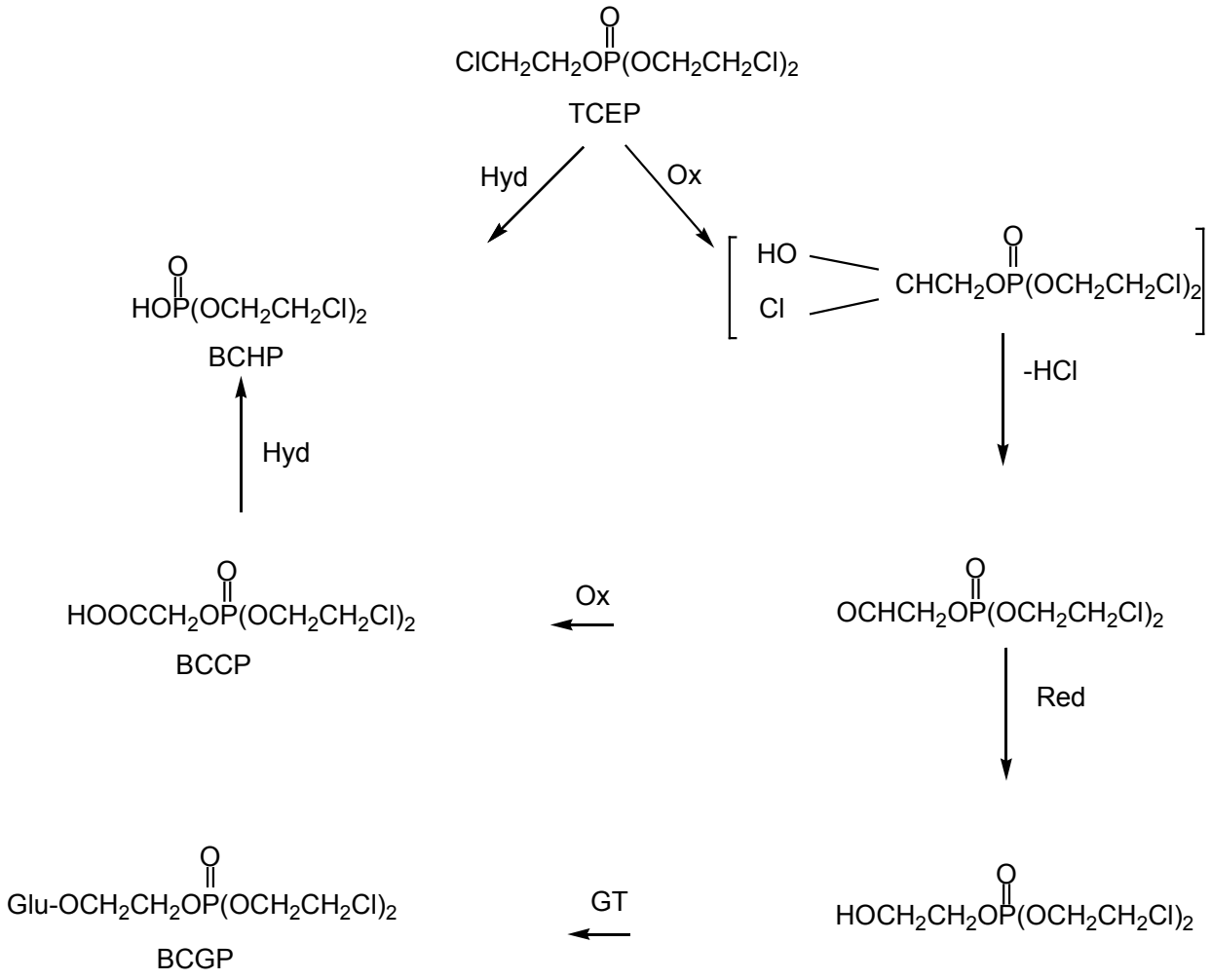
In vitro studies with rat liver fractions showed that TDCP was metabolized by enzymes located in the microsomal and soluble fractions, and to a lesser extent, by enzymes in the mitochondrial fraction (Nomeir et al. 1981). It appeared that TDCP was metabolized via oxidative and conjugation reactions. 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

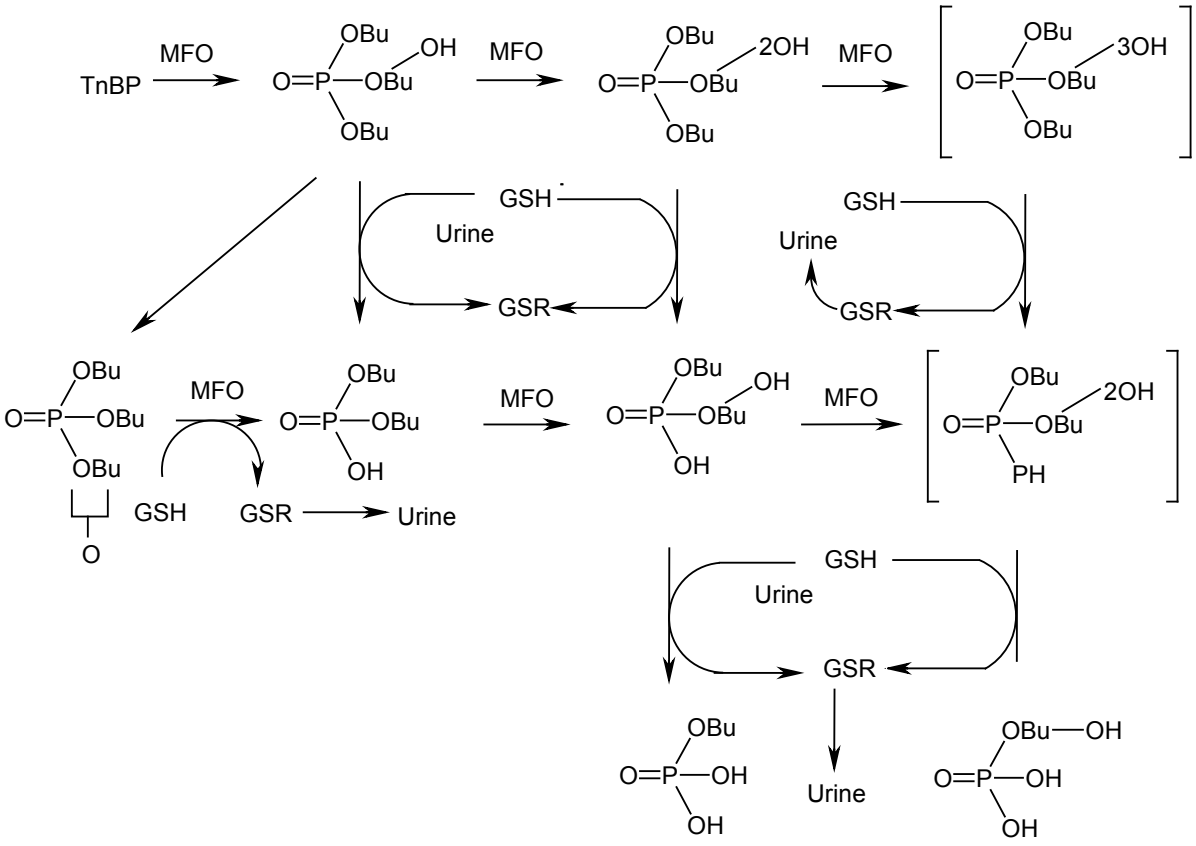
Source: Burka et al. 1991

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.

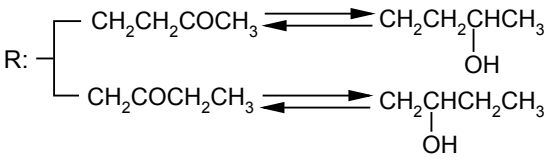
TnBP. Analyses of urine samples from male Wistar rats administered a single intraperitoneal dose of 250 mg ^{14}C-TnBP revealed 11 phosphorus-containing metabolites (Suzuki et al. 1984a). The major metabolites were dibutyl hydrogen phosphate, butyl dihydrogen phosphate, and butyl bis(3-hydroxybutyl) phosphate; no glucuronide or cysteine conjugates could be detected, which suggested that biotransformation 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

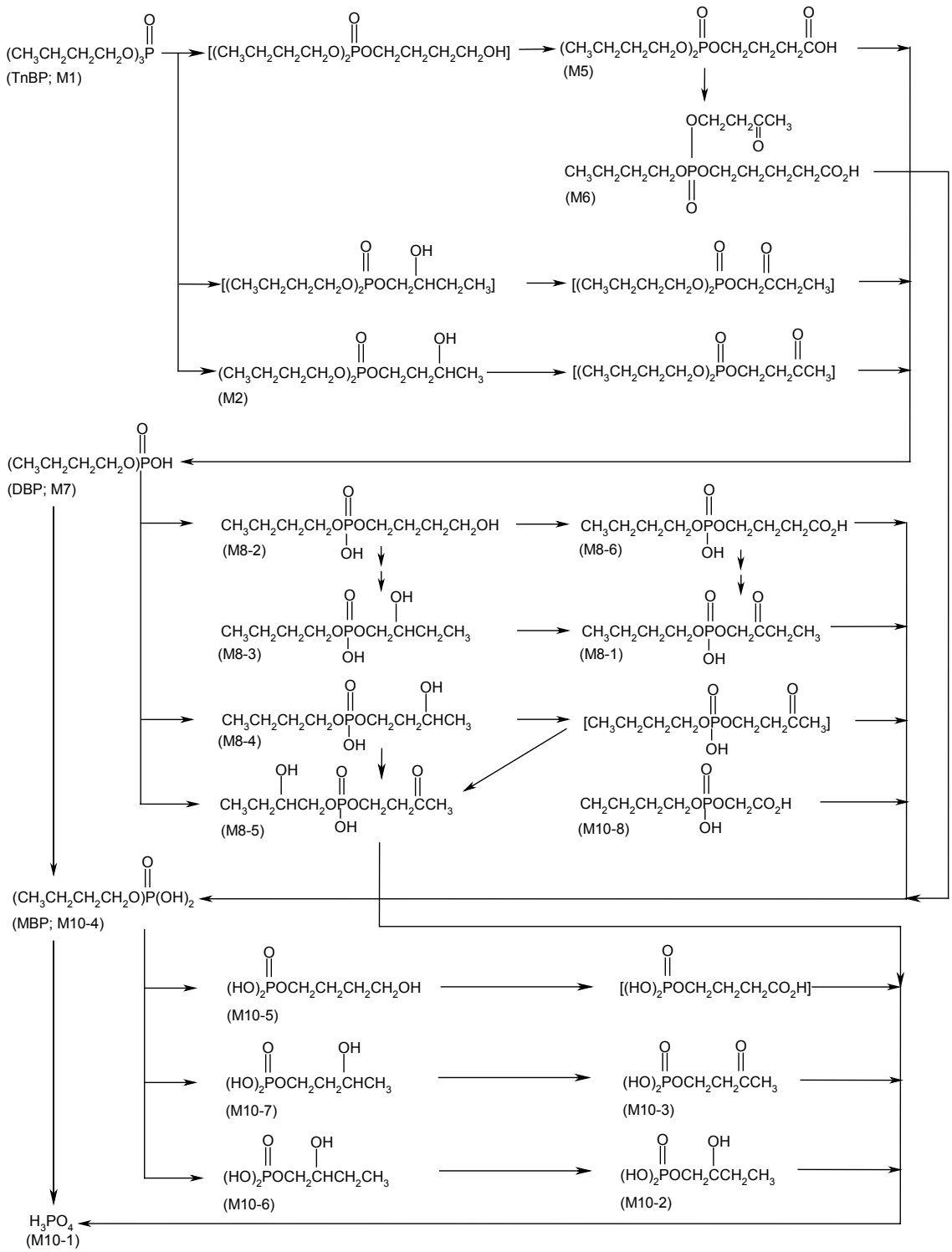
Source: Suzuki et al. 1984b

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.

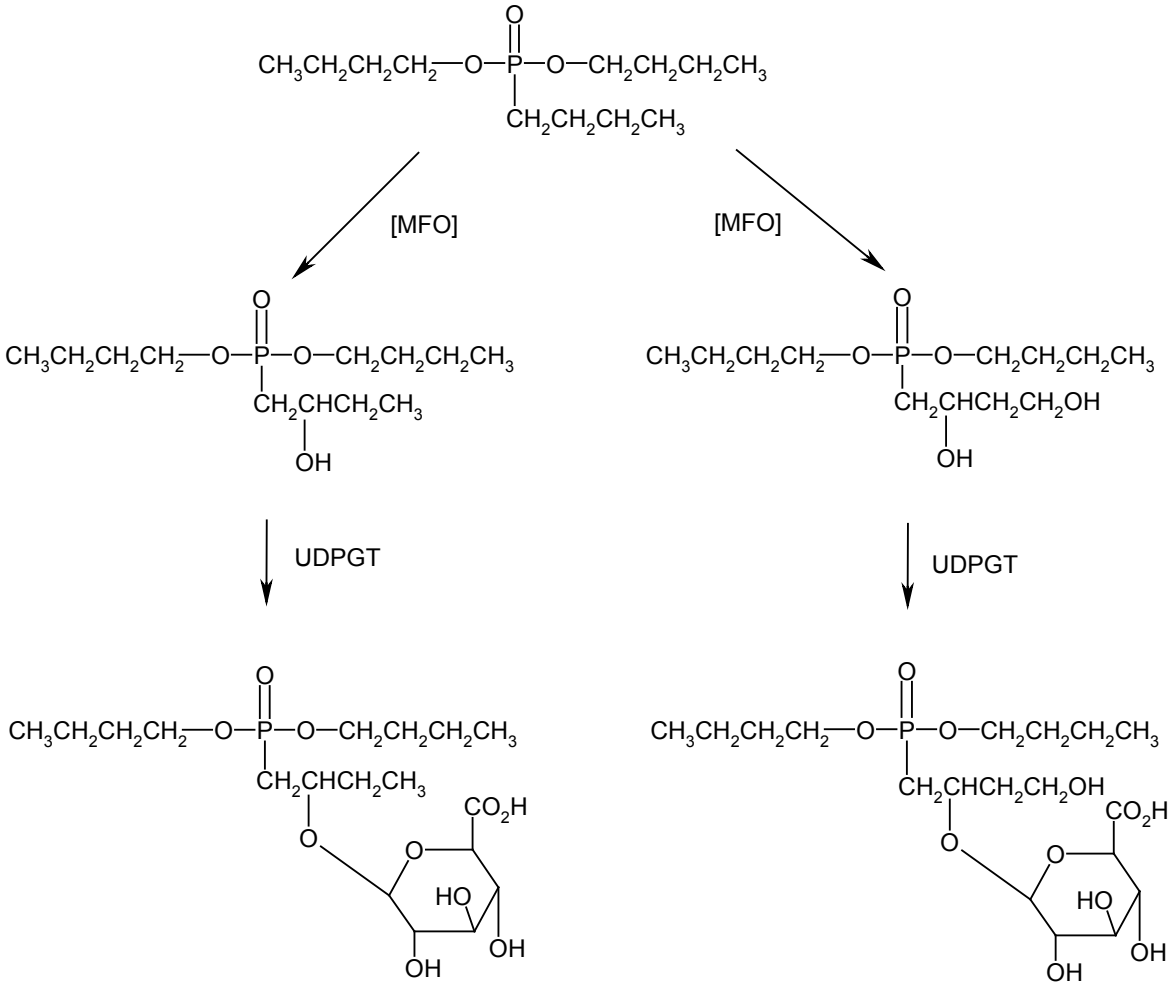
Figure 3-10. Suggested Biotransformation Scheme of TnBP in Rats



[ ] 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.

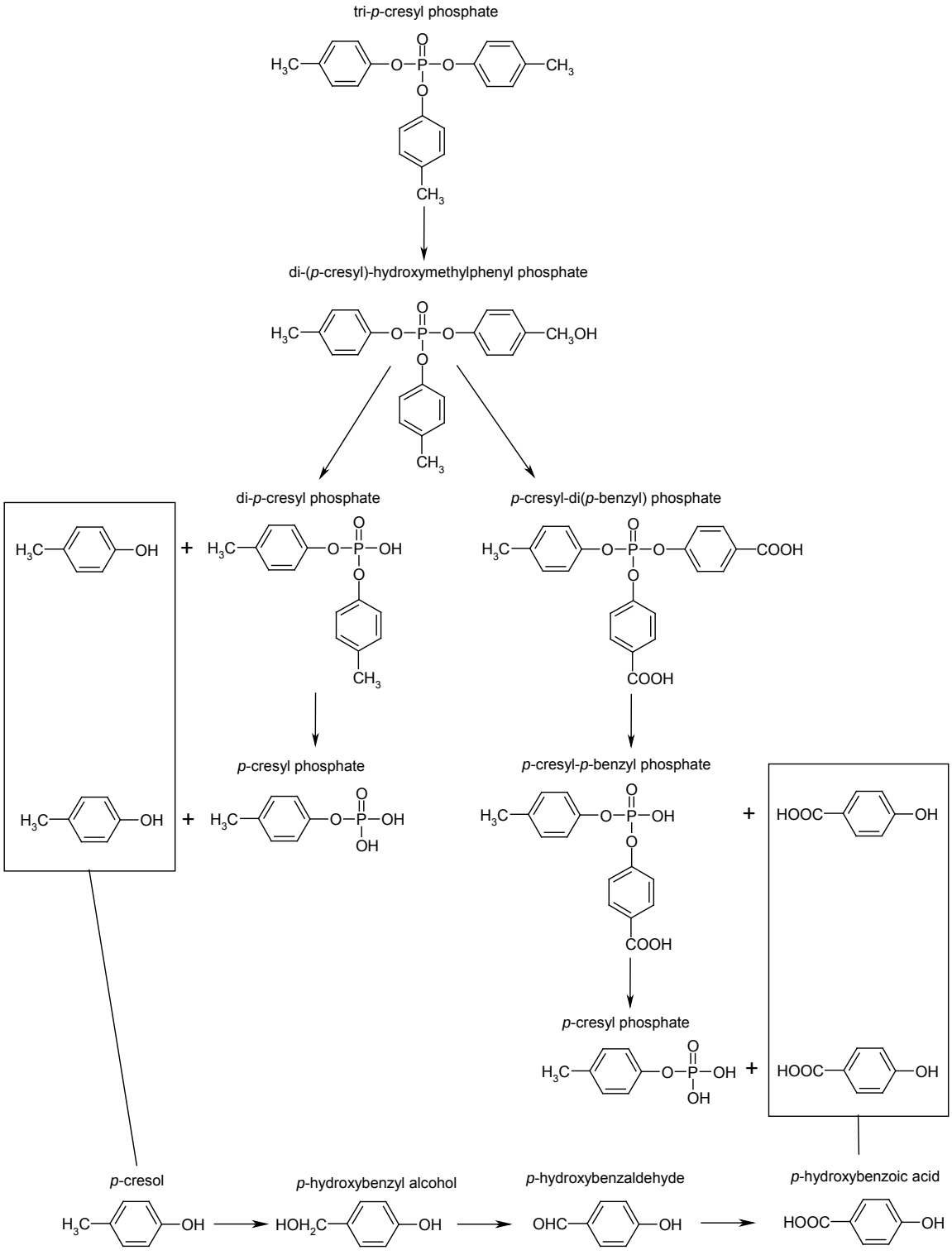
3.4.4.1 Inhalation Exposure

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.

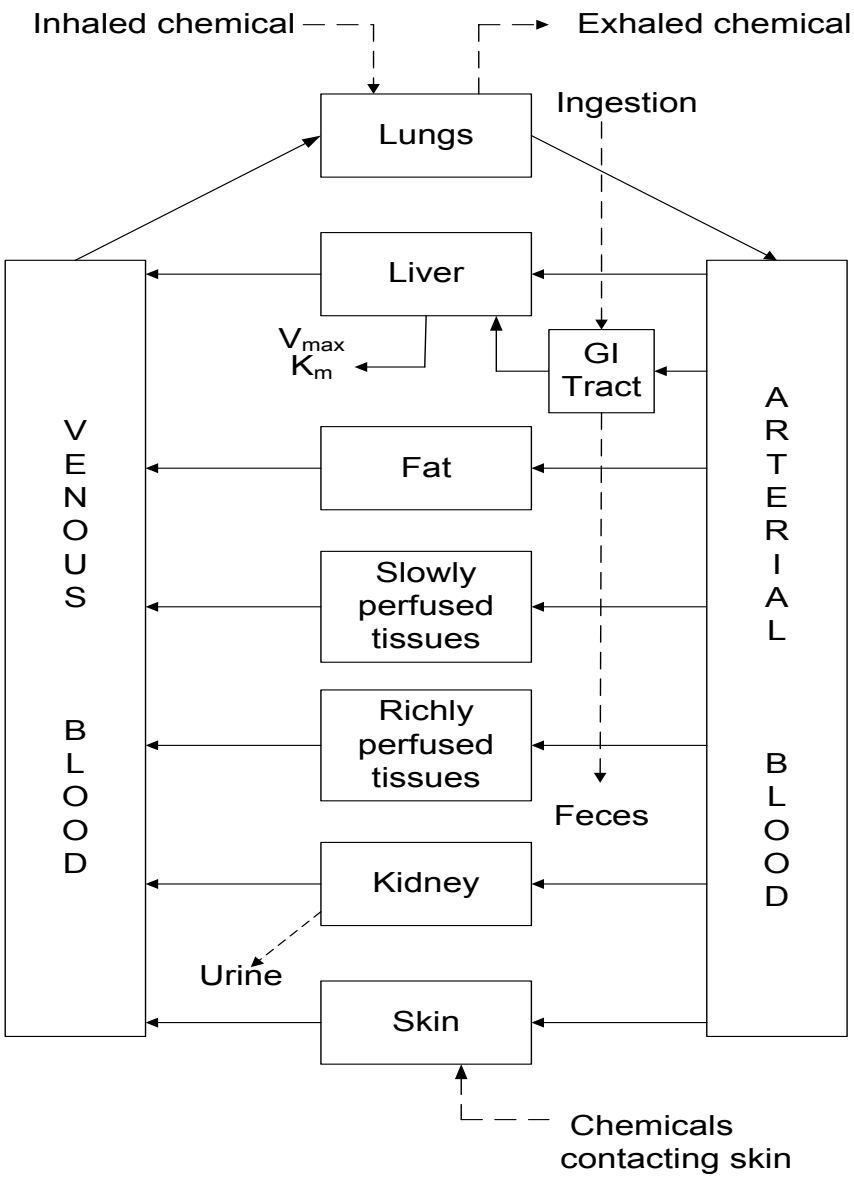
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 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

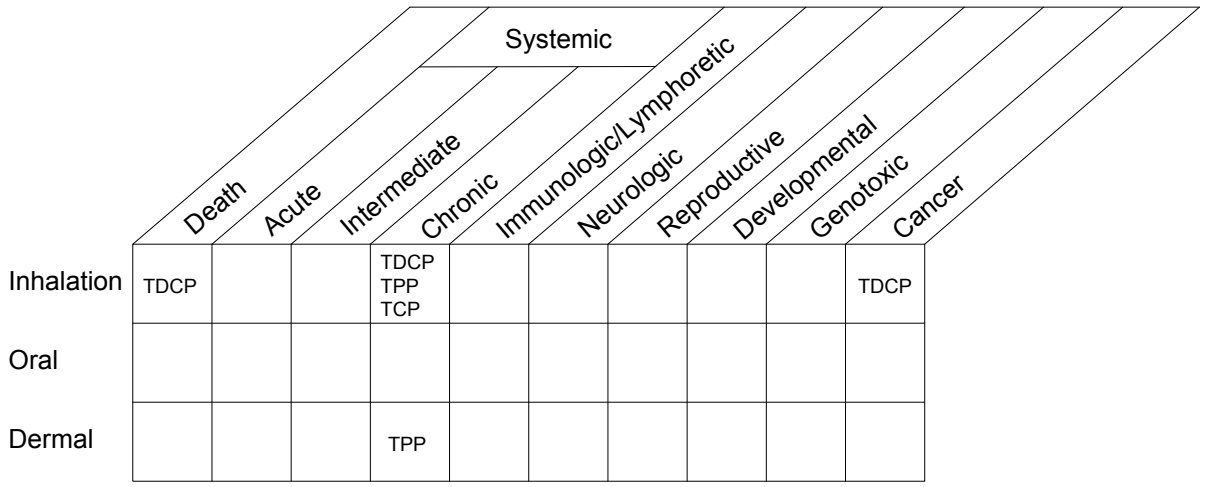
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of phosphate ester flame retardants is available. Where adequate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

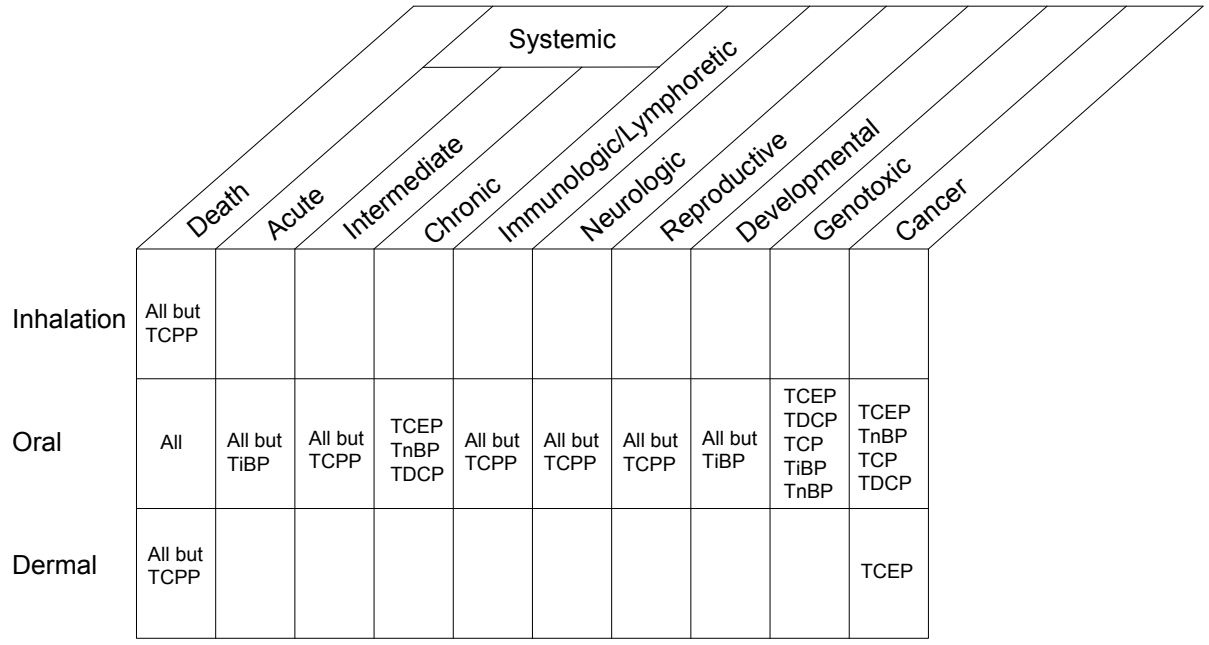
3.12.1 Existing Information on Health Effects of Phosphate Ester Flame Retardants

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.