2. RELEVANCE TO PUBLIC HEALTH

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

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

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

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

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

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

2.2   SUMMARY OF HEALTH EFFECTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

TCEP, TnBP, TDCP, and TCP have been tested for carcinogenicity in long-term oral bioassays. Doses of 88 mg TCEP/kg/day significantly increased the incidence of renal tubule adenoma or carcinoma in male Fischer-344 rats and renal tubule adenomas in female Fischer-344 rats. Based on these findings, NTP concluded that there was clear evidence of carcinogenic activity for male and female Fischer-344/N rats. TCEP (350 mg/kg/day) also induced a nonsignificant increase in the incidence of a rare renal tubule neoplasm in male B6C3F$_1$ mice, which led NTP to conclude that there was equivocal evidence of carcinogenic activity for male mice. TCEP increased, although not significantly, the incidence of tumors of the Harderian gland in female B6C3F$_1$ mice; based on this, NTP concluded that there was equivocal evidence of carcinogenic activity for female mice. In a dietary study in ddY mice, TCEP increased the incidences of renal (1,333 mg/kg/day) and liver (267 mg/kg/day) tumors in male mice and forestomach tumors (1,333 mg/kg/day) and leukemia (267 mg/kg/day) in female mice. In dermal assays, TCEP showed no significant carcinogenic, initiating, or promoting activity on the skin of female Swiss mice. IARC evaluated TCEP and concluded that the chemical is not classifiable as to its carcinogenicity to humans. Bioassays conducted for TCP in F344/N rats and B6C3F$_1$ mice showed no chemical-related increased incidences of neoplasms in either species. Rats and mice received doses of up to 15 and 37 mg TCP/kg/day, respectively, via the food.

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

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

2.3   MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for phosphate ester
flame retardants. An MRL is defined as an estimate of daily human exposure to a substance that is likely
to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of
exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of
effect or the most sensitive health effect(s) for a specific duration within a given route of exposure.
MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can
be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes.
Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990),
uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional
uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an
example, acute inhalation MRLs may not be protective for health effects that are delayed in development
or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic
bronchitis. As these kinds of health effects data become available and methods to assess levels of
significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

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

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

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

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

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

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

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

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

Oral MRLs

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

TnBP

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

TBEP

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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