2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TRICHLOROBENZENES IN THE UNITED STATES

The manufacture and use of trichlorobenzenes as solvents, chemical intermediates, and dye carriers has led to their release into the environment. Trichlorobenzenes may also be released into the environment indirectly from the degradation of higher chlorinated benzenes (tetrachlorobenzene, pentachlorobenzene, and hexachlorobenzene) and the pesticide lindane (γ-hexachlorocyclohexane). They may also be present as a minor impurity in other chlorinated substances and are formed unintentionally during the combustion of organic materials when chlorine is present (for example during the incineration of wastes containing polyvinyl chloride).

Trichlorobenzenes are volatile substances that are relatively persistent in the environment. They are expected to possess low mobility in soil and generally do not leach into groundwater except in the case of a large spill or their subsurface disposal at hazardous waste sites. Volatilization is considered an important environmental fate process in soils and water; however, their tendency to adsorb to soil and sediment may attenuate the rate of volatilization. In the atmosphere, trichlorobenzenes degrade through their reaction with photochemically-generated hydroxyl radicals. The half-life for this reaction in air is approximately 16–38 days. In soil and water, trichlorobenzenes degrade slowly under aerobic conditions but undergo reductive dechlorination resulting in the formation of mono- and dichlorobenzenes as degradation products under methanogenic conditions.

1,2,4-Trichlorobenzene is one of 188 chemicals that is designated as a hazardous air pollutant (HAP) under the Clean Air Act. Monitoring data from 2008 indicate that average atmospheric levels in the United States are typically less than 1 part per billion by volume (<1 ppbv); however, maximum levels above 3 ppbv have been observed. In atmospheric samples, 1,2,3- and 1,3,5-trichlorobenzene are detected less frequently than 1,2,4-trichlorobenzene since they have fewer uses and subsequently fewer direct emissions. Trichlorobenzenes are detected infrequently in groundwater unless a large spill occurs to a soil surface. Both 1,2,3- and 1,2,4-trichlorobenzene were monitored for, but not detected in, aquifer samples in a comprehensive survey conducted by the U.S. Geological Survey (USGS) of volatile organic compounds in private and public groundwater wells used for drinking water. Neither isomer was detected in samples obtained from nearly 2,000 public and private wells across the United States. Municipal drinking water samples have occasionally been shown to contain low levels of trichlorobenzenes at the

parts per trillion levels. Trichlorobenzenes have been detected in fish and wildlife, particularly in the vicinity of chemical manufacturing plants that produce chlorinated substances. They have also been detected in various food items. Leafy vegetables, fruits, milk, and eggs/meat purchased at grocery stores in Canada contained trichlorobenzene levels of 0.11–0.40, 0.12–0.14, 0.14–1.2, and 0.70–0.74 μg/kg, respectively.

The general population is exposed to trichlorobenzene from inhalation of ambient air and ingestion of food and drinking water. In a European Union Risk Assessment Report for 1,2,4-trichlorobenzene, the total daily intake was calculated as 0.0715 mg/kg/day for the exposure scenario which yielded the highest estimated total daily intake for humans. The estimates suggest that the most important human intake routes are ingestion of root crops, fish, and drinking water. Occupational exposure may occur through inhalation and dermal exposure where trichlorobenzenes are produced or used. Chapter 7 provides details of analytical methods used to determine whether exposure to trichlorobenzenes has occurred; however, not enough data are available to determine what baseline levels are in human tissues.

2.2 SUMMARY OF HEALTH EFFECTS

There is very limited information regarding health effects in humans following exposure to trichlorobenzenes. A review of the literature indicates that an adult male who inhaled trichlorobenzene for several hours during the repair of a pump suffered massive hemoptysis (blood-stained sputum), and that some trichlorobenzene production workers developed chloroacne. There is also a case report of aplastic anemia in a woman with prolonged exposure through the soaking of her husband's work clothes in trichlorobenzene. None of these reports provided exposure details or specified the isomer involved. Citing an unpublished source, the American Conference of Governmental Industrial Hygienists (ACGIH) stated that minimal eye and throat irritation could occur in some people exposed to 3–5 ppm 1,2,4-trichlorobenzene. This information is insufficient to determine a clear target for trichlorobenzenes in humans. However, based on information from effects of other chlorinated benzenes in humans, and from limited information on the metabolism of 1,2,4-trichlorobenzene by microsomal preparations from human livers that indicated that cytochrome P-450 enzymes might be involved in the metabolism of trichlorobenzenes, it is reasonable to suggest that excessive exposure to trichlorobenzenes might induce liver effects such as porphyria in humans.

Studies have been conducted in animals exposed to trichlorobenzenes by the inhalation, oral, and dermal routes. 1,2,4-Trichlorobenzene has been the most extensively studied of the three trichlorobenzene

isomers. Repeated inhalation studies in multiple species exposed to up to 100 ppm 1,2,4-trichlorobenzene showed the liver to be a target, and rats appeared to be more sensitive than other species. Liver effects consisted mostly of increases in liver weight not accompanied by histological alterations. Exposure to 30 or 100 ppm 1,2,4-trichlorobenzene also increased the urinary excretion of porphyrins in rats. No target could be identified for 1,3,5-trichlorobenzene in rats in the only 13-week inhalation study located for this isomer. No inhalation data were located for 1,2,3-trichlorobenzene.

Trichlorobenzenes produced transitory irritation of the skin of animals when applied for short periods of time. As the duration of exposure increases, the severity of the effects also increases. Trichlorobenzenes also produced transitory eye irritation when instilled into the eyes of rabbits for short periods of time.

Considerable more data are available in animals exposed orally to trichlorobenzenes. Significantly more information is available for 1,2,4-trichlorobenzene than for the other two isomers. Acute-, intermediate-, and chronic-duration studies showed that the liver and kidneys are targets for 1,2,4-trichlorobenzene in rats. The liver was also the target for 1,2,4-trichlorobenzene in mice in an intermediate-duration study. Liver changes included increases in the weight of the organ and histological alterations consisting of periportal cytoplasmic eosinophilia and anisokaryosis (variation in size) of hepatocellular nuclei in acute-duration studies in rats dosed with ≥150 mg/kg/day 1,2,4-trichlorobenzene or ≥300 mg/kg/day 1,2,3- or 1,3,5-trichlorobenzene. Liver necrosis was reported in a 10-day study in rats dosed with 500 mg/kg/day 1,2,4-trichlorobenzene. Moderate liver histopathology was reported in rats dosed with ≥49 mg/kg/day of the trichlorobenzene isomers for 90 days. Extending the duration of exposure to 1,2,4-trichlorobenzene to 2 years resulted in increased incidences of various lesions including hepatocellular hypertrophy, focal cystic degeneration, and diffuse fatty change in rats. No chronic-duration studies were located with the other two trichlorobenzene isomers.

In addition to inducing morphological alterations in the liver, 1,2,4-trichlorobenzene has been shown to be a potent inducer of phase I and phase II metabolic enzymes. In addition, in rats, 1,2,4-trichlorobenzene induces δ-aminolevulinic acid (ALA) synthetase, the rate-limiting enzyme in the biosynthesis of heme, which is consistent with the development of porphyria in rats administered 1,2,4-trichlorobenzene. Studies by Kato and coworkers have shown that both the induction of drug-metabolizing enzymes and ALA synthetase are not due to 1,2,4-trichlorobenzene itself but to its metabolite, 2,3,5-trichlorophenyl methyl sulfone.

Kidney lesions were observed in male rats dosed with 144 mg/kg/day 1,2,4-trichlorobenzene for 13 weeks. The lesions consisted of dilated tubules, granular casts, hyaline droplets, and papillary mineral deposition. Also increased was the incidence or severity of interstitial nephritis and regenerative tubular epithelium. These lesions, particularly the hyaline droplets, are consistent with a $\alpha_{2\mu}$-globulin nephropathy induced by a variety of organic chemicals in male rats. The $\alpha_{2\mu}$-globulin is not present in human kidneys; hence, this particular nephropathy has no significance for humans. Increased incidences of transitional renal cell hyperplasia and renal papilla mineralization were reported in male rats dosed with 66.5 mg/kg/day 1,2,4-trichlorobenzene for 104 weeks. This is also consistent with the occurrence of male-specific nephropathy. None of these lesions were seen in female rats or in mice. 1,3,5-Trichlorobenzene was also reported to induce renal lesions in rats in a 13-week study. The alterations were also consistent with the male-specific nephropathy and were characterized by eosinophilic inclusions, enlargement and anisokaryosis of the epithelial lining cells, and hyperplasia of renal tubular epithelial cells.

Less clear than the effects on the liver and on the kidneys of male rats are reported alterations on the thyroid of rats induced by trichlorobenzenes. The three trichlorobenzene isomers reportedly induced mild histological changes in the thyroid from pregnant female rats administered the chemicals on gestation days (Gd) 6–15 and sacrificed on Gd 22. The alterations occurred with doses ≥300 mg/kg/day and were characterized as reductions in follicle size and increased epithelial height accompanied by cytoplasmic vacuolization. Similar findings were reported in rats dosed with 78–82 mg/kg/day trichlorobenzenes for 13 weeks. However, neither study showed the data or provided quantitative analyses of the lesions that would have helped determine whether differences between dose groups were statistically significant. A 13-week study in rats that used comparable doses and a 104-week study in rats that provided quantitative data did not report treatment-related histological alterations in the thyroid. Intermediate- and chronic-duration studies in mice also did not report histological changes in the thyroid. None of these studies measured levels of thyroid hormones or thyrotrophin (TSH) in blood.

1,2,4-Trichlorobenzene did not affect fertility in rats in a multi-generation reproductive study. None of the intermediate-duration oral, inhalation, or dermal studies conducted with trichlorobenzenes reported treatment-related histological alterations in the reproductive organs of male and female animals. Most studies that examined whether 1,2,4-trichlorobenzene is a developmental toxicant reported negative results. The only effects reported were the presence of microscopic alterations in the lenses of the eye of fetuses from rats treated with 150 mg/kg/day 1,2,4-trichlorobenzene on Gd 6–15 and sacrificed on Gd 22. However, no lesions were observed in fetuses from dams dosed with 75 or 300 mg/kg/day 1,2,4-trichloro-

benzene. This lesion was also observed in fetuses from dams dosed with 150, 300, or 600 mg/kg/day 1,3,5-trichlorobenzene. Since no quantitative data were presented, it is not known whether the incidences were dose-related. The lesion was characterized as central areas of cellular disorientation and disaggregation with ballooning and granular degeneration. Another gestational exposure study reported retarded development of the fetuses from rats dosed with 360 mg/kg/day 1,2,4-trichlorobenzene on Gd 9–13 and sacrificed on Gd 14. This dose level was lethal to two out of nine dams and induced significant weight loss in dams that survived. In studies of pregnant mice dosed with 0 or 130 mg/kg/day 1,2,4-trichlorobenzene on Gd 8–12, the chemical did not affect pup's viability or growth or offspring's locomotor activity or fertility to produce a second generation.

1,2,4-Trichlorobenzene did not significantly increase the incidence of malignancies in rats fed a diet that provided up to 66.5 mg/kg/day to males or 81.4 mg/kg/day to females. However, it did increase the incidence of hepatocellular carcinoma in mice fed a diet that provided ≥100.6 mg/kg/day to males and ≥127 mg/kg/day to females for 104 weeks. A dermal bioassay was also conducted with 1,2,4-trichlorobenzene in mice. Tumors developed in the lungs, kidneys, stomach, urinary bladder, mammary gland, and skin in both treated and control groups. Several limitations of this study rendered it inadequate for assessing the potential carcinogenicity of 1,2,4-trichlorobenzene following dermal exposure. EPA classified 1,2,4-trichlorobenzene in Group D: not classifiable as to human carcinogenicity, or as a chemical for which there is "Inadequate Information to Assess Carcinogenic Potential" according to the Guidelines for Carcinogen Risk Assessment. EPA's classification was done in 1988 and was last revised in 1991. No cancer studies were available for 1,2,3-trichlorobenzene or 1,3,5-trichlorobenzene.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for trichlorobenzenes. 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

1,2,4-Trichlorobenzene

Acute-Duration MRL. No relevant human data were located for 1,2,4-trichlorobenzene. The only data in animals is that exposure of rats (2–4/sex) to ≥70 ppm for 6 hours caused lethargy and initial lacrimation (Gage 1970), and that exposure of two rats to an average concentration of 293 ppm of 1,2,4-trichlorobenzene vapors 6 hours/day for 12 days did not cause gross or microscopic alterations in unspecified organs (E.I. Dupont 1971). This information is insufficient for MRL derivation.

Intermediate-Duration MRL. No relevant human data were located. Several intermediate-duration studies in various species are available. Continuous exposure of cynomolgous monkeys (9 males/group), Sprague-Dawley rats (30 males/group) rats, or New Zealand rabbits (16 males/group) to 0, 25, 50, or 100 ppm 1,2,4-trichlorobenzene vapors did not result in significant gross or microscopic appearance of the major organs at termination or in significant deviations in hematology or clinical chemistry tests conducted at various times during the study (Coate et al. 1977). Exposure-related histopathological changes characterized as mild (only qualitative descriptions were provided) were observed in the liver and kidneys from rats usually after 4 or 13 weeks of exposure, but not at week 26. Pulmonary function tests and operant behavior tests conducted in monkeys during the study were unremarkable. In another intermediate-duration study, exposure of Sprague-Dawley rats (20 males/group), beagle dogs (2 males/group), and New Zealand rabbits (4 males/group) to 0, 30, or 100 ppm 1,2,4-trichlorobenzene vapors 5 days/week for a total of 30 exposures did not result in gross or histological changes in any major tissues and organs, including the liver and kidneys (Kociba et al. 1981). Hematology and clinical chemistry tests also were unremarkable. The only significant changes in organ weights were an 11% increase in relative liver weight in rats and a 27–30% increase in absolute and relative liver weight in dogs. Increased urinary excretion of porphyrins was reported in exposed rats, which the investigators attributed to hepatic enzyme induction by 1,2,4-trichlorobenzene. In yet an additional intermediate-

duration earlier study, Alderley Park rats (2–4/sex/group) were exposed 6 hours/day to 20 ppm 1,2,4-trichlorobenzene vapors for 20 exposures or to 70 or 200 ppm for 15 exposures (Gage 1970). Exposure to 70 or 200 ppm 1,2,4-trichlorobenzene produced lacrimation and lethargy, presumably during exposures, although it was not explicitly stated, but did not induce histological alterations in the lung, liver, heart, intestines, adrenals, spleen, or thymus. Although there is suggestive evidence from some studies that the liver might be a target for 1,2,4-trichlorobenzene, inadequacies in the studies (no quantitative data, only a few animals tested) preclude derivation of an intermediate-duration inhalation MRL for this isomer.

Chronic-Duration MRL. No chronic-duration inhalation studies were available in humans or animals for 1,2,4-trichlorobenzene; therefore, a chronic-duration inhalation MRL was not derived for this isomer.

1,2,3-Trichlorobenzene

No inhalation studies in humans or in animals were located for 1,2,3-trichlorobenzene; therefore, no inhalation MRLs were derived for this compound.

1,3,5-Trichlorobenzene

Acute-Duration MRL. No pertinent information in humans was located for 1,3,5-trichlorobenzene. The only acute data in animals is that head-only exposure of Sprague-Dawley rats (8/sex) for 60 minutes to 1,209 ppm 1,3,5-trichlorobenzene vapors appeared to cause some irritation around the eyes (Jorgenson et al. 1976). No clinical signs or mortality occurred during 14 days after the exposure, but exposed males and females weighed 44 and 60%, respectively, less than unexposed control rats. Gross necropsy did not reveal compound-related alterations. This information is inadequate for MRL derivation.

Intermediate-Duration MRL. Only one intermediate-duration inhalation study was located for 1,3,5-trichlorobenzene. In this study, male and female CD rats (20/sex/group) were exposed to 0, 1.3, 13, or 130 ppm 1,3,5-trichlorobenzene vapors 6 hours/day, 5 days/week for 13 weeks (Sasmore et al. 1983). A dried red material was often seen on the faces of rats during exposures, including controls, although the incidence was noticeably higher in the 13 and 130 ppm groups. Exposure to 1,3,5-trichlorobenzene had no significant effect on body weight or on hematology or clinical chemistry tests conducted at termination. Methemoglobin was slightly higher at week 13 than at week 4, but according to the investigators, the values did not reach significant levels (data not shown). Urinalyses performed on

samples collected on weeks 4 and 13 showed an apparent increase in porphyrins in male rats on week 13, but the large standard deviations rendered the differences with controls nonsignificant. Relative liver weight was significantly increased (11%) in male rats on week 4 but not at termination. At termination, a total of 34 organs and tissues (not all specified) from the control and high-exposure group were examined microscopically, including the nasal passages. The only treatment-related histopathology was the presence of squamous metaplasia and hyperplasia in the respiratory epithelium of the nasal passages of three high-exposure rats (3/20); this incidence is not significantly different from controls (0/20) as determined by the Fisher Exact Test. The lack of clear effects precludes the use of this study for MRL derivation. The study NOAEL was the highest exposure concentration tested, 130 ppm, but the true NOAEL may have been higher.

Chronic-Duration MRL. No chronic-duration inhalation studies were available for 1,3,5-trichlorobenzene; therefore, a chronic-duration inhalation MRL was not derived for this isomer.

Oral MRLs

1,2,4-Trichlorobenzene

Acute-Duration MRL. An acute-duration oral MRL was not derived for 1,2,4-trichlorobenzene due to inadequacies of the data base. No relevant human data were located. Other than acute lethality studies, the animal database consists of developmental studies in rats (Black et al. 1988; Kitchin and Ebron 1983) and mice (Chernoff and Kavlock 1983; Gray and Kavlock 1984; Gray et al. 1986) and two studies aimed mainly at evaluating the effects of 1,2,4-trichlorobenzene on porphyrin metabolism (Rimington and Ziegler 1963), liver weight, and liver microsomal enzymes (Carlson and Tardiff 1976). These studies identified the liver as a target for 1,2,4-trichlorobenzene. In the study by Black et al. (1988), microscopic examination of the major tissues and organs from the dams exposed on Gds 6–15 and sacrificed on Gd 22 showed mild histological alterations in the liver and thyroid at doses of 300 mg/kg/day but not 150 mg/kg/day. However, the investigators provided only qualitative descriptions of the histological changes; incidences of lesions were not provided. Hemoglobin and hematocrit were decreased 6–7% in rats dosed with ≥150 mg/kg/day 1,2,4-trichlorobenzene relative to controls. This difference is not considered biologically significant since the values in treated rats were within the normal range. Rats dosed with 300 mg/kg/day 1,2,4-trichlorobenzene showed an 11% increase in relative liver weight; the investigators stated that absolute weight of rats dosed with 300 mg/kg/day was significantly increased but did not provide the values for the control group, and therefore the magnitude of the increase cannot be assessed. There were no significant effects on number of pregnancies, fetal weight, litter size, number of

resorptions and dead fetuses, or incidences of skeletal or visceral anomalies. The only developmental effect reported was the presence of microscopic lesions in the lenses of the eyes of fetuses from dams treated with 150 mg/kg/day 1,2,4-trichlorobenzene; no such lesions were reported in groups dosed with 75 or 300 mg/kg/day. This study is inadequate for MRL derivation due to the lack of quantitative histology data, which precludes constructing dose-response relationships to determine points of departure for the MRL.

In the other developmental study in rats, pregnant animals were administered 0, 36, 120, or 360 mg/kg/day 1,2,4-trichlorobenzene on Gd 9–13 and were sacrificed on Gd 14 (Kitchin and Ebron 1983). Rats that received the highest dose, 360 mg/kg/day, lost weight and had moderate hepatocellular hypertrophy (only the liver was examined microscopically); the no-observed-adverse-effect level (NOAEL) for these effects was 120 mg/kg/day. While doses of 360 mg/kg/day did not increase resorptions or cause significant embryolethality or teratogenicity, they significantly retarded fetal development as measured by reduced head length, crown-rump length, somite number, and protein content. These end points were evaluated only in dams administered 360 mg/kg/day 1,2,4-trichlorobenzene and controls, but not in groups dosed with 36 or 120 mg/kg/day 1,2,4-trichlorobenzene, which makes this study inadequate for MRL derivation because the NOAEL for weight loss and liver effects (120 mg/kg/day) may not be the NOAEL for retarded fetal development.

In the developmental studies in mice, pregnant mice were administered 0 or 130 mg/kg 1,2,4-trichlorobenzene on Gd 8–12 (Chernoff and Kavlock 1983; Gray and Kavlock 1984; Gray et al. 1986). This treatment did not significantly affect offspring viability, reactive locomotor activity of the pups evaluated at various times up to 200 days of age, or reproductive performance of the offspring to produce a second generation. The use of only one dose level in these studies precludes constructing dose-response relationships for the end points measured. The lack of reported effects also precludes using this study for MRL derivation.

Rimington and Ziegler (1963) reported increased liver microsomal enzyme activities, increased urinary excretion of porphyrins, and also elevated levels of porphyrins in the liver of rats following daily gavage doses of 500 mg/kg/day for 10 days. The limited scope and single dose level precludes considering this study for MRL derivation. Carlson and Tardiff (1976) administered 1,2,4-trichlorobenzene in doses of 0, 10, 20, or 40 mg/kg/day to male rats by gavage in corn oil for 14 days. Sacrifices were conducted on day 15, and liver microsomal enzymes were analyzed. Blood was also collected for hemoglobin and hematocrit determinations. Sections of the liver were also prepared for histological examination.

Administration of 1,2,4-trichlorobenzene resulted in dose-related increases in cytochrome c reductase, cytochrome P-450, glucuronyltransferase, EPN detoxification, and azoreductase. 1,2,4-Trichlorobenzene induced a dose-related increase in relative liver weight (all doses, 15% at the lowest dose, 28% at the highest dose). There were no significant effects on hemoglobin concentration or hematocrit. No specific information regarding liver histopathology was provided. Because the Carlson and Tardiff (1976) study is of limited scope and provided no information regarding histology of the liver, it is considered inadequate for MRL derivation.

- An MRL of 0.1 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to 1,2,4-trichlorobenzene.

No relevant intermediate-duration studies in humans were located. The intermediate-duration oral database for 1,2,4-trichlorobenzene consists of two 3-month dietary studies in rats (CMA 1989; Côté et al. 1988), a 13-week dietary study in mice (Hiles 1989), two studies in rats aimed mainly at evaluating porphyrin metabolism and enzyme induction in the liver by 1,2,4-trichlorobenzene (Carlson and Tardiff 1976; Rimington and Ziegler 1963), and a multi-generation reproductive study in rats (Robinson et al. 1981). As a whole, these studies suggested that the liver and kidneys are targets for 1,2,4-trichlorobenzene and that male rats may be more sensitive than females. Administration of 730 mg/kg/day 1,2,4-trichlorobenzene (only dose level tested) by gavage to male albino rats caused intense necrosis and fatty change in the liver (only organ examined) and increased urinary porphyrins (Rimington and Ziegler 1963). Treatment of male albino rats via the diet with a much smaller dose, 40 mg/kg/day, increased relative liver weight (9–14%) and induced microsomal enzymes, but did not induce histological alterations in the liver (Carlson and Tardiff 1976).

In the multi-generation study, doses of up to 33 mg/kg/day in males and 54 mg/kg/day in females (mean doses estimated by the investigators consumed by 83 days of age F0 generation of rats) did not affect fertility in the F0 or F1 generation or affect the time of vaginal opening in F2 females (Robinson et al. 1981). Treatment with 1,2,4-trichlorobenzene did not affect neonates' weight, litter size, or viability during the pre-weaning period in any generation. Post-weaning growth of F1 rats was not affected by 1,2,4-trichlorobenzene. Tests for locomotor activity in the F1 or F2 generation rats were unremarkable. Of the organs weighed in the study (which included the liver and kidneys), only the adrenals were affected by 1,2,4-trichlorobenzene. Absolute weight of the adrenals of F0 and F1 males and females were significantly increased relative to controls (11–12% in F0 and 4–6% in F1); no histological evaluation of the glands was conducted. No histological damage was found in the livers and kidneys. Results from blood chemistry tests in F0 and F1 rats did not reveal any treatment-related alterations. The significance

of the increase in adrenals weight is unknown. EPA (IRIS 2010) states that a 1-month study was performed by the Agency in which five rats/group were dosed by gavage with 53 mg/kg/day 1,2,4-trichlorobenzene in corn oil. Microscopic examination of the adrenals from treated rats showed moderate vacuolization of the zona fasciculata; the control group showed only slight vacuolization. A 14% increase in absolute adrenal gland weight and a 13% increase in relative adrenal weight were found. According to EPA (IRIS 2010, last revised 11/01/96), this study indicated that the increase in adrenal gland weight observed by Robinson et al. (1981) could be associated with vacuolization of the zona fasciculata. Since these observations are not supported by results from an acute-duration study (Black et al. 1988), two 3-month studies (CMA 1989; Côté et al. 1988), or a 104-week dietary study in rats, all of which conducted gross and microscopic evaluation of the adrenals from rats, the biological significance of the effects reported by Robinson et al. (1981) remains unclear. Since aside from the changes in adrenals weight, no adverse effect was identified in this multi-generation study, the study is considered inadequate for MRL derivation.

In the 13-week study in mice, groups of $B6C3F_1$ mice (10/sex/group) were administered a diet with 0, 220, 3,850, or 7,700 ppm 1,2,4-trichlorobenzene (Hiles 1989). The diet provided doses of 0, 67, 850, or 1,222 mg/kg/day to males and 0, 86, 1,183, or 1,345 mg/kg/day to females. End points monitored included clinical signs twice daily, and body weight and food consumption weekly. Hematology and clinical chemistry tests were conducted at initiation and during week 14. At termination, gross necropsy was conducted, selected organs were weighed, and selected tissues were examined microscopically. The lungs, liver, and kidneys from all groups were examined; other organs from only the control and high-dose groups were examined. Ophthalmologic examinations were conducted at initiation and termination. One control female and one high-dose female were accidentally killed during the study. Final body weight was significantly reduced in high-dose males (9%) and females (8.3%). Cumulative body weight gain was significantly reduced in low-dose males (27%), high-dose males (40%), and high-dose females (33%); these changes were associated with significant reductions in food consumption throughout the study. Significant, treatment-related alterations occurred only in the liver from males dosed with ≥850 mg/kg/day and females dosed with ≥1,183 mg/kg/day; the respective NOAELs were 67 and 86 mg/kg/day. The lesions consisted of hepatocellular cytomegaly with karyomegaly and hepatocellular atrophy and degeneration. The incidences in males and females were 0/10, 0/10, 10/10, and 10/10 and 0/9, 0/10, 10/10, and 9/9, respectively.

One of the 3-month studies in Sprague-Dawley rats that evaluated hematology, clinical chemistry, and histopathology of the major organ and tissues reported histological alterations in the liver, kidneys, and

thyroid in the various dose groups (doses ranged from 0.07 to 82 mg/kg/day in males and from 0.11 to 101 mg/kg/day in females) (Côté et al. 1988). However, the investigators provided only a qualitative description of the results, such that dose-response relationships for the histological changes could not be constructed. In that study, high-dose males showed increases of 13 and 20% in absolute and relative liver weight, respectively, and of 31 and 36% in absolute and relative kidneys weight, respectively. Hematology and clinical chemistry tests were unremarkable. Because quantitative data regarding the histological effects were not presented, potential points of departure for the MRL could not be identified and the study is considered inadequate for MRL derivation.

In the 3-month study conducted by CMA (1989), groups of Fisher-344 rats (10/sex/group) were fed a diet containing 0, 200, 600, or 1,800 ppm 1,2,4-trichlorobenzene for 14 weeks; this diet provided doses of 0, 14.6, 45.6, or 133.7 mg/kg/day for males and 0, 17.0, 52.5, or 150.6 mg/kg/day for females. End points monitored included clinical signs (daily), physical examination (weekly), ophthalmology (initiation and termination), body weight and food consumption (weekly), hematology and clinical chemistry (termination), gross necropsy (all rats at termination), selected organ weights, and histopathology of all major organs and tissues of the control and high-dose group and liver and kidney of the low- and mid-dose groups. Treatment with 1,2,4-trichlorobenzene did not affect survival rate. Clinical signs were limited to chromodacryorrhea and lacrimation, which occurred more frequently in treated groups, but without dose-response. The test for ocular abnormalities did not reveal compound-related effects. Administration of 1,2,4-trichlorobenzene did not significantly affect body weight or weight gain. Food consumption was significantly higher in the mid- and high-dose groups than in controls. Significant hematological alterations consisted of decreased mean erythrocyte count (5%), hemoglobin (7%), and hematocrit (5%) in males dosed with 133.7 mg/kg/day and decreased hemoglobin (4%) and hematocrit (4%) in females dosed with 150.6 mg/kg/day. These changes are within the normal range and are not considered biologically significant. Platelets were significantly increased (16%) in males dosed with 133.7 mg/kg/day; the clinical significance of this finding is unclear; however, thrombocytosis is usually caused by a reaction to injury or inflammation. Significant clinical chemistry changes included elevated blood urea nitrogen (BUN) in high-dose males (12%) and females (20%), elevated total protein, albumin, and calcium in high-dose males, and lower serum aspartate aminotransferase (AST) activity in males dosed with 45.6 mg/kg/day (22%) and 133.7 mg/kg/day (28%). The elevated BUN was consistent with microscopic alterations in kidneys from male rats. The clinical significance of the alterations in protein and calcium were unclear and the lower transaminase activity was not considered of biological significance. Significant changes in organ weight included dose-related increases in absolute and relative liver weight in all treated male groups and in females dosed with 52.5 and 150.6 mg/kg/day, and

increased absolute and relative kidney weight and absolute testes weight in males dosed with 133.7 mg/kg/day. No compound-related gross lesions were observed. Histological alterations were limited to the kidneys and liver. Kidney lesions were evident in males dosed with 45.6 and 133.7 mg/kg/day and consisted of dilated tubules, granular casts, hyaline droplets, interstitial nephritis, and papillary mineral deposition. In the liver, centrilobular hepatocyte hypertrophy occurred in males dosed with 45.6 and 133.7 mg/kg/day (0/10, 0/10, 5/10, and 10/10) and in females dosed with 150.6 mg/kg/day (0/10, 0/10, 0/10, and 10/10). Liver changes were more prominent in males than in females.

Both the 14-week study in rats by CMA (1989) and the 13-week study in mice by Hiles (1989) evaluated a comprehensive number of end points and presented the results in a manner useful for establishing dose-response relationships, and can potentially be used for MRL derivation.

Data sets of centrilobular hepatocyte hypertrophy in male rats and relative liver weights in male and female rats (CMA 1989), as well as hepatocyte atrophy and degeneration in male mice (Hiles 1989) were analyzed using the benchmark dose (BMD) approach for MRL derivation. Data for renal effects in male rats were not considered for modeling due to the strong suggestive evidence that this may be a unique response of the male rat and not relevant for human risk assessment (EPA 1991). Specific indications that this may be the case include the increased incidences of hyaline droplets, granular casts, and tubule dilation, and the fact that none of these lesions occurred in female rats. In addition, since there is not enough evidence to dissociate the interstitial nephritis from the male-specific nephropathy, interstitial nephritis was also not considered for modeling. In support of this position is the fact that interstitial nephritis did not occur in female rats.

Models in the EPA Benchmark Software (BMDS version 2.1) were fit to the data sets for centrilobular hepatocyte hypertrophy in male rats and relative liver weights in male and female rats from the CMA (1989) study, as well as hepatocyte atrophy and degeneration in male mice from the Hiles (1989) study. A benchmark response (BMR) of 10% was selected in the absence of data that would support a lower BMR. In accordance with EPA (2000a) guidance, BMDs and the lower-bound confidence limits on the BMDs (BMDLs) associated with an extra risk of 10% are calculated for all models. For continuous data, in the absence of a clear criteria as to what level of change in organ weight should be considered adverse, the BMR was defined as a change in mean body weight gain equal to 1 standard deviation from the control mean (EPA 2000a). Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control)

closest to the predefined BMR. Among all of the models providing adequate fit to the data, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) is chosen. None of the models could provide an adequate fit for relative liver weight in female rats, but the lowest dose, 17.0 mg/kg/day, was a NOAEL. A summary of the modeling results is presented in Table 2-1.

Table 2-1. Summary of End Points Modeled in 13-Week Studies

End point	BMD_{1SD}/BMD_{10} (mg/kg/day)	$BMDL_{1SD}/BMDL_{10}$ (mg/kg/day)	Best fitting model
Relative liver weight (male rats)[a]	11.27	9.41	Linear
Hepatocyte hypertrophy (male rats)[a]	**33.09**	**14.35**	**Gamma**
Hepatocyte atrophy and degeneration (male mice)[b]	220.61	58.94	Gamma

[a]CMA 1989
[b]Hiles 1989

Although Table 2-1 shows that the $BMDL_{1SD}$ of 9.41 mg/kg/day for relative liver weight would be a slightly more protective point of departure for MRL derivation than the $BMDL_{10}$ of 14.35 mg/kg/day for hepatocyte hypertrophy in male rats, the latter is preferred as the point of departure on the basis of being a more biologically meaningful end point. The MRL is derived by dividing the $BMDL_{10}$ of 14.35 mg/kg/day for centrilobular hepatocyte hypertrophy by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability). This yields an intermediate-duration oral MRL of 0.1 mg/kg/day for 1,2,4-trichlorobenzene. Detailed information regarding the modeling of hepatocyte hypertrophy in male rats is presented in Appendix A. Note that rounding to one decimal place would give the same MRL if based on relative liver weight.

- An MRL of 0.1 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to 1,2,4-trichlorobenzene.

No relevant chronic data in humans exposed orally to 1,2,4-trichlorobenzene were located, but there are 104-week dietary bioassays in rats (Moore 1994a) and in mice (Moore 1994b). In the study in rats, groups of Fisher-344 rats (50/sex/group) were fed a diet containing 0, 100, 350, or 1,200 ppm 1,2,4-trichlorobenzene for 104 weeks. The diet provided doses of 0, 5.6, 19.4, or 66.5 mg/kg/day 1,2,4-trichlorobenzene to males and 0, 6.9, 23.5, or 81.4 mg/kg/day 1,2,4-trichlorobenzene to females. Parameters evaluated included mortality (twice daily), clinical signs, body weight and food consumption (weekly for 16 weeks and every 4 weeks thereafter), hematology (week 52 and 78 for cellular morphology and leukocyte differential, from control and high-dose groups), organ weight (at termination,

brain, brainstem, liver, kidneys, testes, and epididymis), and gross necropsy and histological examination of all major organs and tissues at termination. Treatment with 1,2,4-trichlorobenzene resulted in a significant reduction in survival rate in males dosed with 66.5 mg/kg/day. Survival rate in the control, 5.6, 19.4, and 66.5 mg/kg/day males at week 104 were 84, 80, 84, and 60% respectively. There were no distinct or pronounced compound-related differences in clinical signs between treated and control groups. Differences in body weight between treated and control rats were <10% throughout the study. Food consumption was decreased 4–7% in treated groups relative to controls during the study. The only statistically significant hematology findings were a decrease in basophiles at week 52 and monocytes at week 105 in males dosed with 66.5 mg/kg/day, which the investigators considered minor. No evidence of leukemia was noted. Gross necropsy at termination showed increased incidence of liver and kidney abnormalities in males dosed with 19.4 and 66.5 mg/kg/day and a slight increase in incidence of uterine masses in treated females relative to controls; these changes were not discussed any further. Significant changes in organ weight were limited to an increase in absolute and relative liver weight in both male and female rats receiving the highest doses of 1,2,4-trichlorobenzene and a decrease in absolute and relative testes weight in males dosed with 5.6 and 19.4 mg/kg/day. Treatment-related histological alterations were restricted to the liver of males and females and to the kidneys of males and consisted of the following: hepatocellular hypertrophy, focal cystic degeneration, diffuse fatty change, transitional renal cell hyperplasia, and increased severity of chronic rat nephropathy in males. Incidences of liver lesions are presented in Table 2-2 (note that a smaller number of animals from the low-dose groups were examined for histopathology).

The incidences of transitional cell hyperplasia in the kidneys of male rats were as follows: 2/50, 0/19, 2/50, and 34/50 in males dosed with 0, 5.6, 19.4, and 66.5 mg/kg/day 1,2,4-trichlorobenzene, respectively. Since there is strong evidence from the 14-week study (CMA 1989) suggesting that the renal lesions in male rats may represent a male-specific response not relevant for MRL derivation and that renal cell hyperplasia reported in the 104-week study is a typical response seen in the male rat nephropathy, renal cell hyperplasia is not considered any further as a potential end point for MRL derivation.

In the study in mice, groups of $B6C3F_1$ mice (50/sex/group) were fed a diet containing 0, 150, 700, or 3,200 ppm 1,2,4-trichlorobenzene for 104 weeks (Moore 1994b). The diet provided doses of 0, 21, 100.6, or 519.9 mg/kg/day 1,2,4-trichlorobenzene to males and 0, 26.3, 127, or 572.6 mg/kg/day 1,2,4-trichlorobenzene to females. End points monitored were the same as in the study in rats described above (Moore 1994a). The liver was the target for 1,2,4-trichlorobenzene in mice. The most significant effect was an

increase incidence of hepatocellular carcinoma in mid- and high-dose mice (8/50, 5/50, 27/50, and 50/50 in males and 1/50, 1/50, 28/50, and 46/50 in females). Centrilobular hepatocytomegaly was also significantly increased in mid- and high-dose males (0/50, 0/50, 27/50, and 20/50). Since non-neoplastic effects were observed only at higher doses than in rats and carcinoma occurred at that same dose level, this study will not be considered any further for MRL derivation.

Table 2-2 shows that: (1) diffuse fatty change was significantly increased in males and females only at the highest dose; (2) focal cystic degeneration occurred at lower incidence in the low- and mid-dose males compared to controls, and was significantly increased only at the highest dose; (3) hepatocellular hypertrophy in female rats occurred at increased frequency only at the highest dose; and (4) only hepatocellular hypertrophy in male rats exhibited dose-response characteristics. Based on these facts, only the hepatocellular hypertrophy in male rats was considered for MRL derivation.

Table 2-2. Incidence of Liver Lesions in Rats in a 104-Week Dietary Study

Males				
Dose (mg/kg/day)	0	5.6	19.4	66.5
Hepatocellular hypertrophy	2/50 (4%)	1/26 (3.8%)	5/50 (10%)	30/50 (60%)
Focal cystic degeneration	9/50 (18%)	3/26 (11.5%)	4/50 (8%)	19/50 (38%)
Diffuse fatty change	5/50 (10%)	3/26 (11.5%)	5/50 (10%)	14/50 (28%)
Females				
Dose (mg/kg/day)	0	6.9	23.5	81.4
Hepatocellular hypertrophy	6/50 (12%)	5/25 (20%)	5/50 (10%)	37/50 (74%)
Diffuse fatty change	15/50 (30%)	6/25 (24%)	21/50 (42%)	30/50 (60%)

Source: Moore 1994a

Models in the EPA Benchmark Software (BMDS version 2.1) were fit to the data set for hepatocellular hypertrophy in the liver of male rats. A BMR of 10% was selected in the absence of data that would support a lower BMR. In accordance with EPA (2000a) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the BMDL from the model with the lowest AIC is chosen. The Multistage (2-degree) model provided the best fit for the data yielding a BMD_{10} of 23.25 mg/kg/day and a corresponding $BMDL_{10}$ of 13.33 mg/kg/day.

The MRL is derived by dividing the $BMDL_{10}$ of 13.33 mg/kg/day for hepatocellular hypertrophy in male rats by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability). This yields a chronic-duration oral MRL of 0.1 mg/kg/day for 1,2,4-trichlorobenzene. Detailed information regarding the modeling of hepatocellular hypertrophy in male rats is presented in Appendix A.

1,2,3-Trichlorobenzene

Acute-Duration MRL. An acute-oral MRL for 1,2,3-trichlorobenzene was not derived due to inadequacy of the available data. No human data were located for 1,2,3-trichlorobenzene. Only one acute-duration oral animal study was located for 1,2,3-trichlorobenzene. In that study, pregnant Sprague-Dawley rats (14/group) were administered 0, 150, 300, or 600 mg/kg/day 1,2,3-trichlorobenzene by gavage in corn oil on Gd 6–15 (Black et al. 1988). The dams were sacrificed on Gd 22 and the uterus and ovaries were removed. Dams were reweighed and the internal organs were weighed. In addition, blood was collected for hematology and clinical chemistry tests. Fetuses were examined grossly for birth defects and skeletal and visceral anomalies. Fetuses were also preserved for histological examinations. The major organs and tissues from the dams were examined microscopically. There were no treatment-related deaths and no clinical signs, but mean body weight of the high-dose group tended to be lower (data not shown). Organ weights were not significantly affected. Hemoglobin was reduced in the 300 and 600 mg/kg/day groups (6–7%) and hematocrit was reduced (~6%) in the 600 mg/kg/day groups. Given the magnitude of these hematological changes, the effects are not considered biologically significant since the values are within the normal range. No significant clinical chemistry effects were reported. Reported histological changes were limited to the kidneys, liver, and thyroid. However, the investigators provided only a qualitative description of the results; incidences of lesions were not provided. There were no significant effects on number of pregnancies, fetal weight, litter size, number of resorptions and dead fetuses, or incidences of skeletal or visceral anomalies. Histological examination of the fetuses did not reveal treatment-related alterations. The lack of a quantitative presentation of the results of the histological examination of the maternal tissues renders this study inadequate for MRL derivation because of the inability to inspect dose-response relationships.

Intermediate-Duration MRL. No intermediate-duration oral MRL was derived for 1,2,3-trichloro-benzene. No relevant human data were located. Only one intermediate-duration study was available for this compound (Côté et al. 1988). In that study, groups of Sprague-Dawley rats (10/sex/group) were fed a diet containing 0, 1, 10, 100, or 1,000 ppm 1,2,3-trichlorobenzene for 13 weeks. This diet provided doses

of 0, 0.08, 0.78, 7.6, 78 mg/kg/day 12,3-trichlorobenzene to males and 0, 0.13, 1.3, 12, or 113 mg/kg/day to females. End points evaluated included body weight (weekly), food consumption (weeks 1, 4, 8, 12), urinalysis (weeks 4, 8, 12), and clinical signs (daily). At termination, the rats were necropsied and blood was collected for hematological and clinical chemistry testing. Hepatic microsomal aniline hydroxylase (AH), aminopyrine demethylase (APDM) activities, and liver protein content were also determined. Bone marrow from the femur was aspirated for cytological evaluation. All major tissues and organs were prepared for microscopic examination. There were no treatment-related deaths. Food consumption was not affected; body weight gain from high-dose males was reduced 10.2% relative to controls (only data for males shown). There were no significant alterations in hematology or clinical chemistry parameters, and urinalyses were unremarkable. No significant gross changes in tissues were reported. Statistically significant changes in organs weight were limited to increases in relative liver weight (14%) in males dosed with 78 mg/kg/day and in relative kidney weight in males dosed with 0.08 mg/kg/day (14%), 0.78 mg/kg/day (14%), and 78 mg/kg/day (21%). 1,2,3-Trichlorobenzene had no significant effect on the hepatic mixed function oxidase activities measured. For the most part, compound-related histopathology was reported as mild and was limited to the liver and thyroid of generally high-dose rats and appeared to be more severe in males. However, the investigators provided only a qualitative description of the histological examinations; incidences of lesions were not presented. In the liver, most treated groups showed mild-to-moderate increases in cytoplasmic volume and anisokaryosis of hepatocytes, mostly in perivenous and midzone areas. High-dose rats showed mild aggregated basophilia as well as mild widespread midzonal vacuolization due to fatty infiltration. Changes in the thyroid consisted of reduction in follicular size, increased epithelial height from flattened cuboidal cells to columnar shape, and reduced colloid density. Changes in the high-dose group varied from mild to moderate. The urinalyses were unremarkable. Since no dose-responses can be constructed with the histological data and since the increases in relative kidney weight in males were not accompanied by any histological changes, this study is considered inadequate for use as basis for MRL derivation.

Chronic-Duration MRL. No chronic-duration oral data in humans or in animals were located for 1,2,3-trichlorobenzene. Therefore, a chronic-duration oral MRL was not derived for this compound.

1,3,5-Trichlorobenzene

Acute-Duration MRL. No acute-duration oral MRL was derived for 1,3,5-trichlorobenzen due to inadequacies of the database. No relevant human data were located. The acute-duration oral database for 1,3,5-trichlorobenzene in animals is limited to information regarding acute lethal doses (Côté et al. 1988;

Jorgenson et al. 1976) and a developmental study in rats (Black et al. 1988). In the developmental study, pregnant Sprague-Dawley rats (14/group) were administered 0, 150, 300, or 600 mg/kg/day 1,3,5-trichlorobenzene by gavage in corn oil on Gd 6–15. The dams were sacrificed on Gd 22 and the uterus and ovaries were removed. Dams were reweighed and the internal organs were also weighed. Blood was collected for hematology and clinical chemistry tests. Fetuses were examined grossly for birth defects and skeletal and visceral anomalies. Fetuses were also preserved for histological evaluations. The major organs and tissues from the dams were examined microscopically. There were no treatment-related deaths. There were no clinical signs, but mean maternal body weight gain in the high-dose group was 34% lower than controls. Food consumption data were not provided. Significant increases in relative liver weight were observed at 300 and 600 mg/kg/day (9 and 25%, respectively); the investigators also stated that absolute liver weights from rats in the 300 and 600 mg/kg/day groups were significantly increased but did not provide the values for the control group, and therefore, the magnitude of the changes cannot be assessed. Hemoglobin and hematocrit were reduced in the 600 mg/kg/day group (10–11%). This is not considered a biologically significant change since it is still within the normal range. Maternal histological changes were restricted to the kidneys, liver, and thyroid. However, only a qualitative description of the histological changes was provided; incidences of lesions were not presented. There were no significant effects on the number of pregnancies, fetal weight, litter size, number of resorptions and dead fetuses, or incidences of skeletal and visceral abnormalities. However, histological examination of the fetuses showed lesions in the lenses of the eyes of pups from all treated groups (150, 300, and 600 mg/kg/day). These changes consisted of central areas of cellular disorientation and disaggregation with ballooning and granular degeneration. The lack of quantitative histology data precludes the use of this study for MRL derivation.

Intermediate-Duration MRL. An intermediate-duration oral MRL for 1,3,5-trichlorobenzene was not derived due to inadequacy of the database. No relevant human studies were located. Only one intermediate-duration oral study in animals was available for 1,3,5-trichlorobenzene. In that study, groups of Sprague-Dawley rats (10/sex/group) were fed a diet containing 0, 1, 10, 100, or 1,000 ppm 1,3,5-trichlorobenzene for 13 weeks (Côté et al. 1988). This diet provided doses of 0, 0.08, 0.81, 7.7, and 82 mg/kg/day for males and 0, 0.13, 1.5, 17, and 146 mg/kg/day for females. End points evaluated included body weight (weekly), food consumption (weeks 1, 4, 8, 12), urinalysis (weeks 4, 8, 12), and clinical signs (daily). At termination, the rats were necropsied and blood was collected for hematological and clinical chemistry testing. Hepatic microsomal AH, APDM activities, and liver protein content were also determined. Bone marrow from the femur was aspirated for cytological evaluation. All major tissues and organs were prepared for microscopic examination. Gross observations did not reveal any

significant treatment-related alterations. Significant changes in organs weight were limited to an increase in relative liver weight in males dosed with 82 mg/kg/day (11%), an increase in absolute kidney weight in males dosed with 0.81 and 7.7 mg/kg/day (~20%), and increases in relative kidney weight in males dosed with 0.81 (14%), 7.7 (25%), and 82 mg/kg/day (14%). There were no significant alterations in hematology or clinical chemistry parameters. 1,3,5-Trichlorobenzene had no significant effect on AH and APDM activities. For the most part, compound-related histopathology was mild and was limited to the liver, thyroid, and kidneys, generally high-dose rats, and appeared to be more severe in males. However, the investigators only provided a qualitative description of the histological changes; incidences of lesions were not presented. In the liver, most treated groups showed mild-to-moderate increase in cytoplasmic volume and anisokaryosis of hepatocytes mostly in perivenous and midzone areas. High-dose rats showed aggregated basophilia as well as widespread midzonal vacuolization due to fatty infiltration. Changes in the thyroid consisted of reduction in follicular size, increased epithelial height from flattened cuboidal cells to columnar shape, and reduced colloid density. Changes in the high-dose group varied from mild to moderate. Changes in the kidneys were characterized by eosinophilic inclusion, enlargement and anisokariosis of the epithelial lining cells, and hyperplasia of renal tubular epithelial cells. Only the changes associated with the high-dose diet were considered to be biologically significant by the investigators. Since no dose-responses can be constructed with the histological data and increases in relative kidneys weights in males did not coincide with biologically significant histological changes, this study is inadequate for use as the basis for MRL derivation.

Chronic-Duration MRL. No chronic-duration oral data in humans or animals were located for 1,3,5-trichlorobenzene; therefore, a chronic-duration oral MRL was not derived for this compound.