

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Carbon Tetrachloride
CAS Number: 56-23-5
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 30
Species: Rat

Minimal Risk Level: 0.03 mg/kg/day ppm

Reference: Adams EM, Spencer HC, Rowe VK, et al. 1952. Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Arch Ind Hyg Occup Med 6:50-66.

Experimental design: Groups of Wistar rats (15–25 males, 15–23 females) were exposed to vapors of carbon tetrachloride (5, 10, 25, 50, 100, 200, and 400 ppm) for 173–205 days (5 days/week, 7 hours/day). Two kinds of control groups were used: ‘unexposed controls’ that were maintained in the animal quarters and ‘air-exposed controls’ that were exposed to room air while in exposure chambers at equivalent frequency and duration as compound-exposed animals. Animals were weighed twice weekly and observed frequently for clinical signs. Food consumption was monitored. Hematological (prothrombin time) and biochemical indices (blood urea nitrogen, phospholipid, esterified cholesterol) were monitored in selected groups. Gross necropsy was performed and organ weights were determined for lung, heart liver, kidneys, spleen, and testes. Histopathological examination was performed on these and 11 other organs.

Effects noted in study and corresponding doses: No effects were observed in the 5 ppm exposure groups for any of the parameters measured. In rats, fatty degeneration of the liver and increased liver weight were evident at concentrations of ≥ 10 ppm and hepatic cirrhosis and pathology of the renal tubular epithelium (moderate cloudy swelling) occurred at ≥ 50 ppm. At ≥ 200 ppm, hepatic necrosis, increased kidney weight, degeneration of the renal tubular epithelium, and some testicular atrophy were observed. The severity of effects increased with exposure level.

Dose and end point used for MRL derivation: The MRL was based on a NOAEL of 5 ppm and a LOAEL of 10 ppm for fatty degeneration and increased liver weights.

NOAEL LOAEL

Uncertainty Factors used in MRL derivation:

- 10 for use of a LOAEL
- 3 for extrapolation from animals to humans using a dosimetric adjustment
- 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? Not applicable.
If so, explain:

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If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

A human equivalent concentration was calculated from the rat NOAEL of 5 ppm in the principal study for an extrarspiratory effect of a type 3 gas, as recommended by EPA (1994) guidance for derivation of inhalation reference concentrations. A human equivalent concentration of the identified rat NOAEL of 5 ppm (NOAEL_{HEC}) was calculated by multiplying the duration-adjusted rat NOAEL (NOAEL_{ADJ}) by the ratio of the rat and human blood:gas partition coefficients. The NOAEL_{ADJ} is 0.9 ppm (5 ppm x 7 hours/24 hours x 5 days/7 days) and the blood:gas partition coefficient ratio is 1.7 (4.52/2.64). Because the ratio was greater than 1, a default value of 1 was applied, resulting in a NOAEL_{HEC} of 0.9 ppm. An uncertainty factor of 30 was applied to the NOAEL_{HEC} of 0.9 ppm (3 for extrapolation from animals to humans using a dosimetric adjustment and 10 for human variability).

Other additional studies or pertinent information which lend support to this MRL: Limited human data are available for intermediate-duration inhalation exposure to carbon tetrachloride. Effects in humans exposed intermittently included gastrointestinal effects (nausea, dyspepsia) at 20–50 ppm, central nervous system depression at 40 ppm, and narcosis at 80 ppm (Elkins 1942; Heiman and Ford 1941; Kazantzis and Bomford 1960). An occupational study of hepatic effects in workers exposed from <1 to >5 years indicated that serum levels of hepatic enzymes were significantly elevated only at exposures >1 ppm, but the actual durations of exposure were not reported (Tomenson et al. 1995). Interpretation of this study is also limited by the finding that the group estimated to have had the highest exposure did not show the highest levels of serum enzymes. The liver appears to be the most sensitive target in animals exposed for intermediate durations. Fatty degeneration, sometimes with increased liver weight, was observed at a LOAEL of 10 ppm in rats, mice, and guinea pigs treated 6–8 hours/day, 5 days/week for 12–36 weeks or continuously for 90 days (Adams et al. 1952; DOE 1999; Japan Bioassay Research Center 1998; Prendergast et al. 1967), and 50–100 ppm in monkeys (Adams et al. 1952; Smyth et al. 1936). Increased serum enzymes and necrosis were observed in mice at 20 ppm and hamsters at 100 ppm (DOE 1999). Exposure to higher concentrations resulted in cirrhosis in guinea pigs (25 ppm) and rats (50–270 ppm) (Adams et al. 1952; Japan Bioassay Research Center 1998; Prendergast et al. 1967; Smyth et al. 1936). In studies examining other organs, renal effects (tubular degeneration) were noted at 50–200 ppm in rats (Adams et al. 1952; Smyth et al. 1936), at 90 ppm in rats and mice (Japan Bioassay Research Center 1998), and at 200 ppm in monkeys (Smyth et al. 1936). Injury to sciatic and optical nerves was noted in rats at 50 ppm (Smyth et al. 1936); hematological effects (decreased erythrocytes, hemoglobin, hematocrit; hemolysis, increased spleen weight) were observed in rats and mice exposed to 90–270 ppm (Japan Bioassay Research Center 1998; Smyth et al. 1936), and reproductive toxicity (decreased litters, testicular atrophy) was noted at 200 ppm (Adams et al. 1952; Smyth et al. 1936). Hepatotoxicity is identified as the critical effect of intermediate-duration inhalation exposure to carbon tetrachloride since it was noted at the lowest LOAELs. The study by Adams et al. (1952) is selected as the principal study because it identified the lowest LOAEL and the highest NOAEL for the critical effect.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Carbon Tetrachloride
CAS Number: 56-23-5
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 50
Species: Rat

Minimal Risk Level: 0.03 mg/kg/day ppm

References: Japan Bioassay Research Center. 1998. Subchronic inhalation toxicity and carcinogenicity studies of carbon tetrachloride in F344 rats and BDF1 mice (Studies Nos. 0020, 0021, 0043, and 0044). Kanagawa, Japan Industrial Safety and Health Association, Japan Bioassay Research Center (Unpublished report to the Ministry of Labor). Hirasawa Hadano Kanagawa, 257 Japan. (In 2001, T. Matsushima provided to SRC organ weight data tables for these studies.)

(Methods published in: Nagano K, Nishizawa T, Yamamoto S, et al. 1998. Inhalation carcinogenesis studies of six halogenated hydrocarbons in rats and mice. In: Chiyotani K, Hosoda Y, Aizawa Y, eds. Advances in the prevention of occupational respiratory diseases. Elsevier Science B.V., 741-746.)

Experimental design: Groups of 50 male and 50 female F344/DuCrj rats were exposed (whole-body) to vapors of carbon tetrachloride (>99% pure) at concentrations of 0, 5, 25, or 125 ppm, 6 hours/day, 5 days/week for 104 weeks. Rats were observed daily for clinical signs, behavioral changes, and mortality. Body weights were measured weekly for the first 13 weeks and every 4 weeks thereafter. Urinalysis was performed at the end of the dosing period. Hematology and serum chemistry were measured in blood samples taken during final euthanization after overnight fasting. All organs and tissues were examined for gross lesions, weighed, and fixed for histopathological analysis.

Effects noted in study and corresponding concentrations: Male rats at ≥ 5 ppm exhibited enhanced hemosiderin deposition in the spleen; this was apparently a residual effect of anemia that was observed in the 13-week study, but not at 104 weeks. No significant hepatic effects were noted at 5 ppm. At ≥ 25 ppm, significant hepatic effects were observed: statistically significant elevations relative liver weights, serum parameters (total bilirubin, ALT, AST), and increased incidences of liver histopathology (fatty change, granulation, foci in the liver, deposition of ceroid, and serious effects such as fibrosis and cirrhosis). Chronic nephropathy was observed in all groups, including controls, but at greater severity at 25 ppm and above; significant proteinuria (dipstick values of 3+ or 4+) was also observed in all groups (in >90% of controls), but at higher severity in males treated at 5 ppm and females at 25 ppm and above. At 25 ppm, females had significant hematological changes (decreased hemoglobin, hematocrit, and lymphocyte counts and increased leukocyte and segmented neutrophil counts). At 125 ppm, body weights were decreased and there was increased mortality from chronic nephrosis and tumors.

The tumors observed at 125 ppm included: hepatocellular adenomas in 21/50 males and 40/50 females and hepatocellular carcinomas in 32/50 males and 15/50 females. At 25 ppm, females had significant hematological changes (decreased hemoglobin, hematocrit, and lymphocyte counts and increased leukocyte and segmented neutrophil counts).

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Dose and end point used for MRL derivation: A NOAEL of 5 ppm LOAEL of 25 ppm for increased liver weight, serum enzymes, and liver histopathology (fatty change, granulation, foci, deposition of ceroid, fibrosis, and cirrhosis).

NOAEL LOAEL

Uncertainty Factors used in MRL derivation:

10 for use of a LOAEL

3 for extrapolation from animals to humans using dosimetric adjustment

10 for human variability

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

If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent concentration: A human equivalent concentration was calculated from the rat NOAEL of 5 ppm in the principal study for an extrapulmonary effect of a type 3 gas, as recommended by EPA (1994) guidance for derivation of inhalation reference concentrations. A human equivalent concentration of the identified rat NOAEL of 5 ppm for hepatic effects (Japan Bioassay Research Center 1998) was calculated by multiplying the duration-adjusted rat NOAEL (NOAEL_{ADJ}) by the ratio of the rat and human blood:gas partition coefficients. The NOAEL_{ADJ} is 0.9 ppm (5 ppm x 6 hours/24 hours x 5 days/7 days) and the blood:gas partition coefficient ratio is 1.7 (4.52/2.64). Because the ratio was greater than 1, a default value of 1 was applied, resulting in a NOAEL_{HEC} of 0.9 ppm. An uncertainty factor of 30 was applied to the NOAEL_{HEC} to derive the chronic-duration inhalation MRL.

Other additional studies or pertinent information which lend support to this MRL: The chronic-duration inhalation database for carbon tetrachloride includes the occupational study by Tomenson et al. (1995) and 2-year bioassays in rats and mice (Japan Bioassay Research Center 1998; Nagano et al. 1998). As discussed under the intermediate-duration MRL, elevated hepatic serum enzymes were observed in workers who had been exposed to concentrations >1 ppm for <1-5> years, but the actual durations of exposure were not reported (Tomenson et al. 1995). Interpretation of this study is also limited by the finding that the group estimated to have had the highest exposure did not show the highest levels of serum enzymes. In the 2-year bioassay in BDF₁ mice, groups of 50/sex were treated at 0, 5, 25, or 125 ppm, 6 hours/day, 5 days/week for 104 weeks (Japan Bioassay Research Center 1998; Nagano et al. 1998). No effects were noted at the lowest concentration of 5 ppm. In mice, 25 ppm was a LOAEL for most observed effects: hematological (increased extramedullary hematopoiesis in spleen associated with recovery from anemia), body weight (reduced body weight gain), renal (protein casts and altered clinical chemistry values), and hepatic (increased liver weights, degeneration, cyst, deposition of ceroid, increased serum enzymes, cholesterol, bilirubin in both sexes, and thrombus and necrosis in females). Mice at ≥25 ppm also exhibited significant increases in the incidences of hepatic adenoma and carcinoma with increased mortality.

One effect in rat was noted at 5 ppm, but was not selected as the critical effect of chronic-duration inhalation exposure. The severity of proteinuria, but not renal histopathology, was elevated in male and female rats treated at 5 ppm compared to controls; however, as the severity in control rats was so high (>90% with scores of 3+ or 4+), this lesion was not used as the basis for MRL derivation. Hepatotoxicity is selected as the critical effect of chronic-duration inhalation exposure because the severity of effects at 25 ppm was greater compared to other end points. Furthermore, selection of hepatotoxicity as the critical effect of chronic exposure is consistent with the database for intermediate-duration inhalation exposure. The 2-year bioassay in rats is selected as the principal study for the chronic-duration inhalation MRL.

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since it provided a NOAEL of 5 ppm and a LOAEL of 25 ppm for hepatic effects without increased mortality.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Carbon Tetrachloride
CAS Number: 56-23-5
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 23
Species: Rat

Minimal Risk Level: 0.02 mg/kg/day ppm

Reference: Smialowicz RJ, Simmons JE, Luebke RW, et al. 1991. Immunotoxicologic assessment of subacute exposure of rats to carbon tetrachloride with comparison to hepatotoxicity and nephrotoxicity. *Fundam Appl Toxicol* 17:186-196.

Experimental design: Groups of 5–6 male Fischer 344 rats were dosed by gavage for 10 consecutive days with 0, 5, 10, 20, or 40 mg/kg/day of carbon tetrachloride in corn oil. Serum chemistry profiles, hepatic cytochrome P-450 content and activity, and kidney and liver organ weight and histopathology were assessed. Various immune function parameters were also examined in these animals, and in another set exposed to 40, 80, or 160 mg/kg/day. Immune function end points included relative spleen and thymus weights; natural killer cell activity; lymphoproliferative response to concanavalin A, phytohemagglutinin, pokeweed mitogen, and *Salmonella typhimurium* mitogen; allogeneic cytotoxic T lymphocyte reaction; and primary antibody response to sheep red blood cells.

Effects noted in study and corresponding doses: No hepatic effects were observed in controls. Minimal centrilobular vacuolar degeneration was detectable in all rats at 5 mg/kg/day; degeneration was mild in all rats treated at 10 and 20 mg/kg/day and 5/6 rats at 40 mg/kg/day and moderate in one high-dose rat. Hepatocellular necrosis was minimal in 3/6 rats at 10 mg/kg/day, 5/6 rats at 20 mg/kg/day, and 5/6 rats at 40 mg/kg/day, and mild in one high-dose rat. Serum ALT and AST levels were significantly elevated 1.5–5.4-fold compared to controls at doses of 20 and 40 mg/kg/day. Mean relative liver weight was significantly ($p < 0.01$) increased by 17.7% compared to controls at 40 mg/kg/day. Treatment with carbon tetrachloride had no significant effect compared to controls on body weight, absolute liver weight, or renal parameters at doses from 5 to 40 mg/kg/day. However, when three separate 40 mg/kg/day groups and their controls were analyzed by two-way ANOVA with carbon tetrachloride and replicates as factors, a significant decrease in weight gain was detected. Body weight gain was significantly reduced at 80 mg/kg/day and higher, as determined by comparison of the slopes of weight gains over the dosing period. There were no adverse effects on immunological parameters at doses up to 160 mg/kg/day.

Dose and end point used for MRL derivation: LOAEL of 5 mg/kg/day for minimal vacuolar degeneration of centrilobular hepatocytes.

NOAEL LOAEL

Uncertainty Factors used in MRL derivation:

- 3 for use of a minimal LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

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

If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Not applicable.

Other additional studies or pertinent information which lend support to this MRL: In humans, hepatic toxicity (fatty accumulation, necrosis) has been noted following ingestion of single doses of carbon tetrachloride in the range of 80–180 mg/kg (Docherty and Burgess 1922; Docherty and Nicholls 1923; Phelps and Hu 1924). Single doses of 70 mg/kg had no overt neurological effect, but various neurological symptoms indicative of depression of the central nervous system have been reported at doses between 114 and 10,800 mg/kg (Cohen 1957; Hall 1921; Leach 1922; Stevens and Forster 1953; Stewart et al. 1963). Gastrointestinal effects in humans following ingestion of single doses include nausea at ≥ 100 mg/kg (Ruprah et al. 1985) and vomiting and abdominal pain at 680–910 mg/kg (Hardin 1954; New et al. 1962; Smetana 1939; Umiker and Pearce 1953; von Oettingen 1964). In laboratory animals, mild hepatic effects (cytoplasmic vacuolization and increased serum enzymes) have been reported to occur following treatment with single doses of 40–80 mg/kg or repeated dosing at 5–20 mg/kg/day (Bruckner et al. 1986; Kim et al. 1990b; Korsrud et al. 1972; Smialowicz et al. 1991). No renal effects or positive results in special tests for immunological function were observed in rats following repeated administration at 5–160 mg/kg/day (Bruckner et al. 1986; Smialowicz et al. 1991). Renal effects (fatty degeneration, swelling of convoluted tubules) were observed in dogs given single doses of 3,200–6,400 mg/kg (Chandler and Chopra 1926; Gardner et al. 1925). Hepatic toxicity is selected as the critical effect of acute-duration oral exposure to carbon tetrachloride because effects were observed at the lowest effect level. The study of Smialowicz et al. (1991) is selected as the principal study because it provides the lowest LOAEL of 5 mg/kg/day for the critical effect.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Carbon Tetrachloride
CAS Number: 56-23-5
Date: June 2005
Profile Status: Final Post-Public Comment Draft
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 46
Species: Rat

Minimal Risk Level: 0.007 mg/kg/day ppm

Reference: Bruckner JV, MacKenzi WF, Muralidhara S, et al. 1986. Oral toxicity of carbon tetrachloride: Acute, subacute and subchronic studies in rats. *Fundam Appl Toxicol* 6:16–34.

Experimental design: Male Sprague-Dawley rats (15–16/dose) were administered carbon tetrachloride (0, 1, 10, or 33 mg/kg) in corn oil by gavage 5 days/week for 12 weeks. Body weight was monitored twice weekly. Blood samples were collected from five rats per group just before dosing at 2, 4, 6, 8, 10, and 12 weeks for measurement of serum levels of sorbitol dehydrogenase (SDH), ornithine carbamyl transferase (OCT), alanine aminotransferase (ALT), and blood urea nitrogen (BUN). Each rat served as a blood donor twice during the study at 6-week intervals. At the end of the 12-week period, 7–9 rats per group were sacrificed and the remaining were maintained for 13 days without dosing before sacrifice. Histopathological examination of the liver and kidneys was performed.

Effects noted in study and corresponding doses: No adverse effects were noted at 1 mg/kg. Body weight gain was reduced in the 33 mg/kg group by 17% compared to controls after 90 days ($p < 0.05$). At 10 mg/kg, there were statistically significant increases in serum SDH activity, 2-fold higher than controls, observed as early as 10 weeks; a statistically significant 35% elevation in serum ALT was observed in this group at 12 weeks. Elevations in these serum parameters returned to control levels during the recovery period. Mild centrilobular vacuolization was observed in the liver of all animals treated at 10 mg/kg/day for 12 weeks. Substantial liver toxicity was observed at 33 mg/kg as early as 2 weeks. At 2 weeks, serum ALT was elevated 5-fold, OCT 6-fold, and SDH 38-fold compared to controls; after 12 weeks, serum ALT was elevated 20-fold, OCT 5-fold, and SDH 45-fold compared to controls. Only the serum ALT elevation (2-fold) was still statistically different from controls after 2 weeks of recovery. The liver:body weight ratio was significantly elevated by 46% in the 33 mg/kg group compared to controls. Extensive hepatic lesions observed in the 33 mg/kg group after 12 weeks included vacuolization, periportal fibrosis, bile duct hyperplasia, hyperplastic nodules, and single-cell necrosis. Treatment with carbon tetrachloride had no significant effect on kidney:body weight ratios, a kidney-related serum parameter (BUN) or on the incidence of kidney lesions.

Dose and end point used for MRL derivation: The NOAEL of 1 mg/kg for mild centrilobular vacuolization and increased serum SDH was used to derive the MRL. The NOAEL was adjusted for intermittent exposure (5 days/7 days), resulting in a duration-adjusted NOAEL of 0.71 mg/kg/day.

NOAEL LOAEL

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Uncertainty Factors used in MRL derivation:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

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

If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Not applicable.

Other additional studies or pertinent information which lend support to this MRL: The intermediate-duration oral toxicity database for carbon tetrachloride is somewhat limited in that no human data are available and many studies in laboratory animals restricted analysis to the liver or to the liver and kidney. The incidence and severity of hepatic effects were dose-related in animal studies. Whereas no hepatic effects were noted at 1 mg/kg, significantly elevated sorbitol dehydrogenase (SDH) and mild centrilobular vacuolization were noted in rats exposed at 10 mg/kg 5 days/week for 12 weeks (Bruckner et al. 1986). In mice ingesting carbon tetrachloride 5 days/week for 12–13 weeks, no hepatic effects were detected at a dose of 1.2 mg/kg (Condie et al. 1986). Significant elevation in some serum enzymes (ALT, aspartate aminotransferase [AST], lactate dehydrogenase [LDH]), and mild necrosis were seen in mice at doses of 12 mg/kg and higher (Condie et al. 1986; Hayes et al. 1986). More extensive hepatic lesions (fatty accumulation, fibrosis, cirrhosis, necrosis) were noted in rats at doses of 20–25 mg/kg and higher (Allis et al. 1990; Bruckner et al. 1986; Koporec et al. 1995). At 100 mg/kg/day, hepatic effects in rats also included cytomegaly and various types of hyperplasia, which were perhaps adaptive responses to necrosis (Koporec et al. 1995). Effects in other organ systems include reduced body weight gain at doses between 33 and 100 mg/kg/day (Bruckner et al. 1986; Koporec et al. 1995) and neurological effects (increased serotonin synthesis) at 290 mg/kg/day (Bengtsson et al. 1987). No renal effects were observed in mice exposed at 1,200 mg/kg/day despite hepatic effects at lower levels (Hayes et al. 1986). Increased mortality was observed in rats exposed at 25 mg/kg/day (Koporec et al. 1995) and cancer (hepatoma) in mice treated with 20 mg/kg/day for 120 days and hamsters treated once weekly with 120 mg/kg/day for 30 weeks (Eschenbrenner and Miller 1946; Della Porta et al. 1961). Hepatic effects were selected as the critical effects of intermediate-duration oral exposure to carbon tetrachloride because they occurred at the lowest effect level. The rat study of Bruckner was selected as the principal study because it provided the lowest LOAEL for the critical effect.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

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

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

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MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

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

- (1) **Route of Exposure.** One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.
- (2) **Exposure Period.** Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) **Health Effect.** The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) **Key to Figure.** Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).
- (5) **Species.** The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) **Exposure Frequency/Duration.** The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to "Chemical x" via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).
- (7) **System.** This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.
- (8) **NOAEL.** A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

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- (9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference. The complete reference citation is given in Chapter 9 of the profile.
- (11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

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

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.
- (14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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

SAMPLE

1 →

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

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

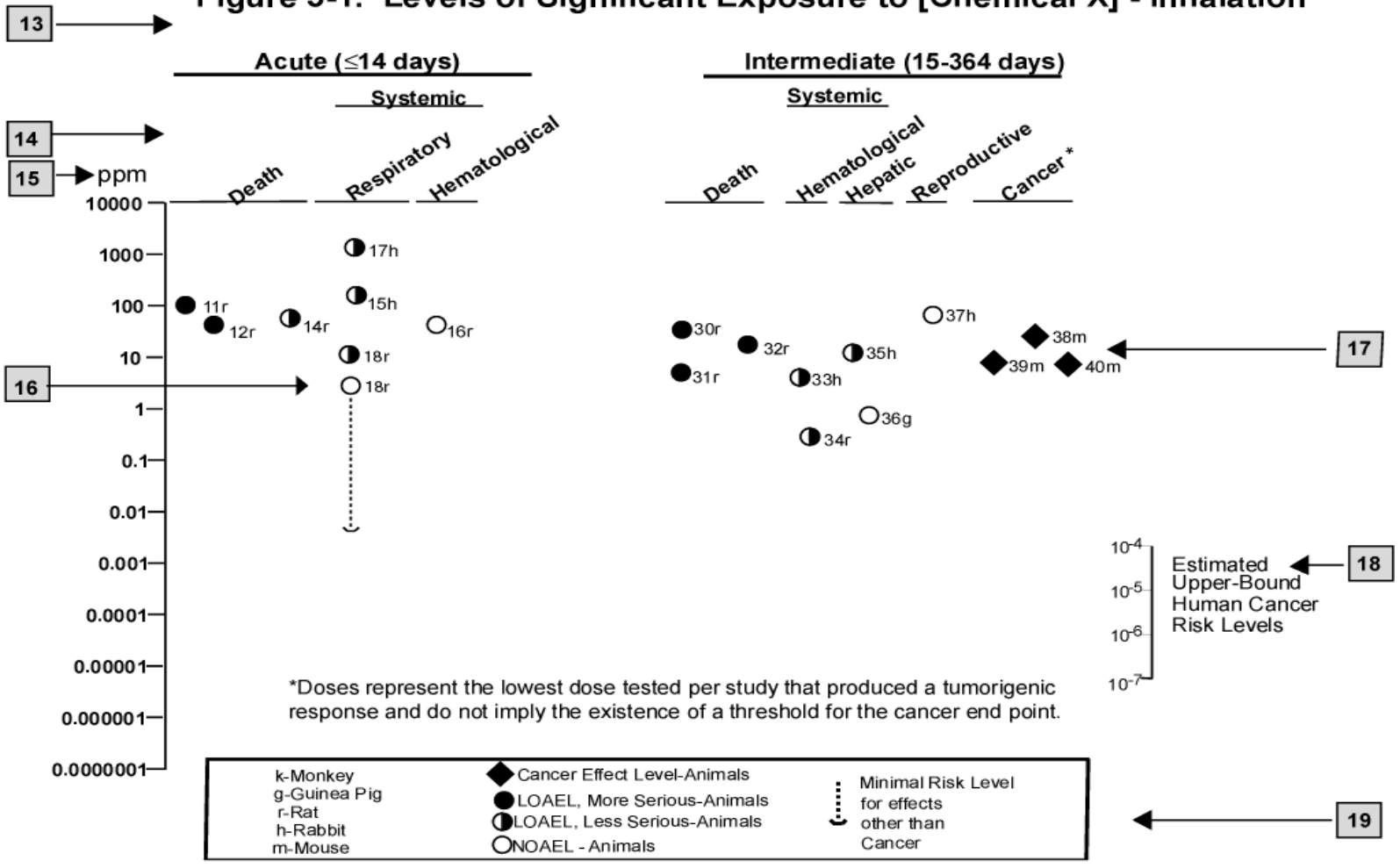
12 →

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

^b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

APPENDIX C

| | |
|--------------------|---|
| DOT/UN/ NA/IMCO | Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code |
| DWEL | drinking water exposure level |
| ECD | electron capture detection |
| ECG/EKG | electrocardiogram |
| EEG | electroencephalogram |
| EEGL | Emergency Exposure Guidance Level |
| EPA | Environmental Protection Agency |
| F | Fahrenheit |
| F ₁ | first-filial generation |
| FAO | Food and Agricultural Organization of the United Nations |
| FDA | Food and Drug Administration |
| FEMA | Federal Emergency Management Agency |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| FPD | flame photometric detection |
| fpm | feet per minute |
| FR | Federal Register |
| FSH | follicle stimulating hormone |
| g | gram |
| GC | gas chromatography |
| gd | gestational day |
| GLC | gas liquid chromatography |
| GPC | gel permeation chromatography |
| HPLC | high-performance liquid chromatography |
| HRGC | high resolution gas chromatography |
| HSDB | Hazardous Substance Data Bank |
| IARC | International Agency for Research on Cancer |
| IDLH | immediately dangerous to life and health |
| ILO | International Labor Organization |
| IRIS | Integrated Risk Information System |
| K _d | adsorption ratio |
| kg | kilogram |
| kgg | metric ton |
| K _{oc} | organic carbon partition coefficient |
| K _{ow} | octanol-water partition coefficient |
| L | liter |
| LC | liquid chromatography |
| LC ₅₀ | lethal concentration, 50% kill |
| LC _{Lo} | lethal concentration, low |
| LD ₅₀ | lethal dose, 50% kill |
| LD _{Lo} | lethal dose, low |
| LDH | lactic dehydrogenase |
| LH | lutinizing hormone |
| LOAEL | lowest-observed-adverse-effect level |
| LSE | Levels of Significant Exposure |
| LT ₅₀ | lethal time, 50% kill |
| m | meter |
| MA | <i>trans,trans</i> -muconic acid |
| MAL | maximum allowable level |
| mCi | millicurie |
| MCL | maximum contaminant level |

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

APPENDIX C

| | |
|------------------|--|
| OWRS | Office of Water Regulations and Standards, EPA |
| PAH | polycyclic aromatic hydrocarbon |
| PBPD | physiologically based pharmacodynamic |
| PBPK | physiologically based pharmacokinetic |
| PCE | polychromatic erythrocytes |
| PEL | permissible exposure limit |
| pg | picogram |
| PHS | Public Health Service |
| PID | photo ionization detector |
| pmol | picomole |
| PMR | proportionate mortality ratio |
| ppb | parts per billion |
| ppm | parts per million |
| ppt | parts per trillion |
| PSNS | pretreatment standards for new sources |
| RBC | red blood cell |
| REL | recommended exposure level/limit |
| RfC | reference concentration |
| RfD | reference dose |
| RNA | ribonucleic acid |
| RQ | reportable quantity |
| RTECS | Registry of Toxic Effects of Chemical Substances |
| SARA | Superfund Amendments and Reauthorization Act |
| SCE | sister chromatid exchange |
| SGOT | serum glutamic oxaloacetic transaminase |
| SGPT | serum glutamic pyruvic transaminase |
| SIC | standard industrial classification |
| SIM | selected ion monitoring |
| SMCL | secondary maximum contaminant level |
| SMR | standardized mortality ratio |
| SNARL | suggested no adverse response level |
| SPEGL | Short-Term Public Emergency Guidance Level |
| STEL | short term exposure limit |
| STORET | Storage and Retrieval |
| TD ₅₀ | toxic dose, 50% specific toxic effect |
| TLV | threshold limit value |
| TOC | total organic carbon |
| TPQ | threshold planning quantity |
| TRI | Toxics Release Inventory |
| TSCA | Toxic Substances Control Act |
| TWA | time-weighted average |
| UF | uncertainty factor |
| U.S. | United States |
| USDA | United States Department of Agriculture |
| USGS | United States Geological Survey |
| VOC | volatile organic compound |
| WBC | white blood cell |
| WHO | World Health Organization |

APPENDIX C

| | |
|------------------|--------------------------|
| > | greater than |
| ≥ | greater than or equal to |
| = | equal to |
| < | less than |
| ≤ | less than or equal to |
| % | percent |
| α | alpha |
| β | beta |
| γ | gamma |
| δ | delta |
| μm | micrometer |
| μg | microgram |
| q ₁ * | cancer slope factor |
| - | negative |
| + | positive |
| (+) | weakly positive result |
| (-) | weakly negative result |

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