# APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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 route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. 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 NOAEL/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) 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 substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, 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 MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3-Trichloropropane
***CAS Numbers:*** 96-18-4
***Date:*** August 2021
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Acute
***MRL:*** 0.001 ppm
***Critical Effect:*** Decreased thickness of nasal olfactory epithelium
***Reference:*** Miller et al. 1986b
***Point of Departure:*** NOAEL of 1 ppm ($NOAEL_{HEC}$ of 0.03 ppm)
***Uncertainty Factor:*** 30
***LSE Graph Key:*** 5
***Species:*** Rat

***MRL Summary:*** An acute-duration inhalation MRL of 0.001 ppm was derived for 1,2,3-trichloropropane based on decreased thickness of the nasal olfactory epithelium of rats exposed 6 hours/day for 9 days over an 11-day period (Miller et al. 1986b). The MRL is based on a NOAEL of 1 ppm, which was adjusted to continuous duration exposure and converted to a human equivalent concentration ($NOAEL_{HEC}$) of 0.03 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

***Selection of the Critical Effect:*** A small number of studies have evaluated the toxicity of 1,2,3-trichloropropane following acute-duration inhalation exposure. In humans, a 15-minute exposure to 100 ppm 1,2,3-trichloropropane resulted in eye and throat irritation (Silverman et al. 1946). Acute inhalation studies in experimental animals (rats and mice) identify the respiratory tract and liver as the most sensitive targets of 1,2,3-trichloropropane toxicity; a summary of relevant NOAEL and LOAEL values for respiratory and hepatic effects is presented in Table A-1. The respiratory effects consisted of decreases in the thickness of nasal olfactory epithelium at the lowest adverse effect levels (3 ppm in rats and 10 ppm in mice) (Miller et al. 1986b), degeneration and inflammation of olfactory epithelium at 13 ppm in rats (Miller et al. 1986a), subacute inflammation of olfactory epithelium at 40 ppm in mice (Miller et al. 1986b), and multifocal fibrosis of nasal submucosa at 132 ppm in rats (Miller et al. 1986a). The Miller et al. (1986a) rat study demonstrated that the severity of the nasal lesions increased with concentration; the degeneration of olfactory epithelium was graded as slight at 13 ppm, moderate at 40 ppm, and severe at 132 ppm. The liver effects consisted of increases in absolute and relative liver weights in rats and mice exposed to 132 ppm (Miller et al. 1986a), very slight individual cell hepatocellular necrosis in male rats exposed to 132 ppm (Miller et al. 1986a), and very slight hepatocellular vacuolization at 132 ppm in mice (Miller et al. 1986a). Other acute-duration studies have primarily focused on lethality (Gushow and Quast 1984; Johannsen et al. 1988; Smyth et al. 1962; Union Carbide 1958). Based on the available data, the nasal olfactory epithelium appears to be the most sensitive target of toxicity following acute-duration inhalation exposure.

**Table A-1. Summary of Relevant LOAEL Values Following Acute Inhalation Exposure to 1,2,3-Trichloropropane[a]**

| Species | NOAEL (ppm) | LOAEL (ppm) | Effect | Reference |
|---|---|---|---|---|
| Nasal effects | | | | |
| F344 rat | | 13 | Degeneration and inflammation of nasal olfactory epithelium | Miller et al. 1986a |
| F344 rat | 1 | 3 | Decreased thickness of olfactory epithelium | Miller et al. 1986b |
| B6C3F1 mouse | | 13 | Decreased thickness of olfactory epithelium | Miller et al. 1986a |
| B6C3F1 mouse | 3 | 10 | Nasal olfactory inflammation | Miller et al. 1986b |
| Hepatic effects | | | | |
| F344 rat | 40 | 132 | Very slight hepatocellular necrosis | Miller et al. 1986a |
| B6C3F1 mouse | 40 | 132 | Hepatocellular vacuolization | Miller et al. 1986a |

[a]Rats and mice were exposed 6 hours/day for 9 exposures in an 11-day period.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

***Selection of the Principal Study:*** Based on a comparison of NOAEL and LOAEL values and the observed effects, rats appear to be more sensitive than mice to 1,2,3-trichloropropane-induced nasal toxicity. The Miller et al. (1986b) rat study, which identified a NOAEL of 1 ppm and a LOAEL of 3 ppm, was selected as the principal study.

***Summary of the Principal Study:***

Miller RR, Quast JF, Momany-Pfruender JJ. 1986b. 1,2,3-Trichloropropane: 2-Week vapor inhalation study to determine the no-adverse-effect level in rats and mice. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0517055. 86870002265. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0517055.xhtml. May 19, 2020.

Groups of five male and five female Fischer 344 rats were exposed to 0, 1, 3, or 10 ppm 1,2,3-trichloropropane 6 hours/day, 5 days/week for 9 exposures in an 11-day period. The following parameters were used to assess toxicity: observations after each exposure period, body weight measurements prior to 1$^{st}$, 3$^{rd}$, 5$^{th}$, and 7$^{th}$ exposure, urinalysis (bilirubin, glucose, ketones, occult blood, pH, protein, urobilinogen, and specific gravity), organ weights (brain, heart, liver, kidneys, thymus, and testes), gross necropsy of major tissues and organs, and histopathological examination of nasal tissue.

There were no deaths or alterations in body weight gain, or urinalysis, or organ weights. A very slight decrease in olfactory epithelial thickness was observed in 10/10 rats exposed to 3 ppm, but was not observed in controls or other groups of exposed rats. The investigators did not suggest a reason why these lesions were only observed at 3 ppm, but did not consider this an adverse effect level. Very slight olfactory epithelial degeneration was observed in 10/10 rats at 10 ppm and in 0/10 control rats. Very slight multifocal, bilateral subacute inflammation of olfactory epithelium was observed in 6/10, 4/10, 2/10, and 10/10 rats in the 0, 1, 3, and 10 ppm groups, respectively. No alterations were observed on gross necropsy.

***Selection of the Point of Departure for the MRL:*** The NOAEL/LOAEL approach was used to select the point of departure (POD) for the MRL. The incidence data for olfactory epithelial alterations were not

considered suitable for benchmark dose (BMD) modeling due to the lack of concentration-response data, 0% incidence in controls and 1 ppm groups and 100% in the 3 ppm group. Thus, the NOAEL of 1 ppm was selected as the POD for the MRL.

***Intermittent Exposure:*** The NOAEL of 1 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$NOAEL_{ADJ}$ = 1 ppm x (6 hours/24 hours) x (9 exposures/11 days) = 0.20 ppm.

***Human Equivalent Concentration:*** A human equivalent concentration (HEC) was calculated by multiplying the duration-adjusted NOAEL by the regional gas dose ratio (RDGR). The RGDR for extrathoracic respiratory tract effects was calculated using the following equation:

$RDGR_{ET} = ([V_E/SA_{ET}]_A) /([V_E/SA_{ET}]_H)$

Where:

$V_e$ is the minute volume and $SA_{ET}$ is the surface area of the extrathoracic (ET) region of the respiratory tract.

Minute volume ($V_e$)

Human: 13.8 L/minute (EPA 1994)

Rat: 0.138 L/minute; calculated using the following EPA equation:

$$\ln(V_e) = b_0 + b_1\ln(BW)$$

For rats, $b_0$ equals -0.578 and $b_1$ equals 0.821.

An average body weight for male and female rats of 0.181 kg was used.

EPA (1994) rat and human respiratory surface area reference values for the extrathoracic region:

Human: 200 $cm^2$

Rat: 15.0 $cm^2$

$RGDR_{ET}$ = (0.138 L/min/15.0 $cm^2$) ÷ (13.8 L/min/200 $cm^2$) = 0.133

$NOAEL_{HEC} = NOAEL_{ADJ}$ x $RGDR_{ET}$

$NOAEL_{HEC}$ = 0.20 ppm x 0.133= 0.03 ppm

***Uncertainty Factor:*** The $NOAEL_{HEC}$ of 0.03 ppm was divided by a total uncertainty factor (UF) of 30:

- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability

MRL = $NOAEL_{HEC}$ ÷ UFs

0.03 ppm ÷ (3 x 10) = 0.001 ppm

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** Although the principal study only included histological examination of the nasal cavity, a companion study (Miller et al. 1986a) examined a wide range of endpoints and demonstrated that the olfactory epithelium was the most sensitive target of toxicity.

***Agency Contact (Chemical Manager):*** Malcolm Williams

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3-Trichloropropane
***CAS Numbers:*** 96-18-4
***Date:*** August 2021
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate

***MRL Summary:*** The available intermediate inhalation data were not considered adequate for derivation of an intermediate-duration inhalation MRL for 1,2,3-trichloropropane.

***Rationale for Not Deriving an MRL:*** An intermediate-duration inhalation MRL was not derived for 1,2,3-trichloropropane because derivation of an MRL based on the available intermediate studies resulted in an MRL that was higher than the acute-duration inhalation MRL and the only available study did not examine nasal tissue (the most sensitive target following acute exposure).

Reliable information on the intermediate-duration toxicity of 1,2,3-trichlorochloropropane is limited to a series of studies in rats conducted by Johannsen et al. (1988). These studies identified several sensitive targets of toxicity including the respiratory tract, liver, and the hematological system. In a 4-week preliminary study (6 hours/day, 5 days/week), increases in liver weight were observed at ≥95 ppm; the study did not include histological examinations. In a more extensive 13-week study (6 hours/day, 5 days/week), exposure to 4.5 ppm resulted in peribronchial lymphoid hyperplasia, midzonal hepatocellular hypertrophy, and extramedullary hematopoiesis in the spleen. At 15 ppm, decreases in body weight gain and excessive lacrimation were observed. No adverse effects were observed at the two lowest test concentrations (0.05 and 1.54 ppm). It is noted that the Johannsen et al. (1988) study did not include examination of nasal tissue, which was the most sensitive target of toxicity following acute inhalation exposure. In a reproductive/developmental toxicity study, no alterations in mating, fertility, histopathology of reproductive tissues, gestation length, number of live births, litter size at birth or postnatal days 4–21, birth weight, pup body weight, or pup survival through postnatal day 21 were observed in male and female rats exposed to concentrations as high as 15 ppm for a 10-week pre-mating period, 30–40-day mating period, and gestation days 0–14.

Based on the available data, an MRL could be derived based on the lung, liver, and spleen effects observed in rats exposed to ≥4.5 ppm; the NOAEL for these effects is 1.54 ppm. Adjusting the NOAEL concentration for intermittent exposure results in a $NOAEL_{ADJ}$ of 0.275 ppm. A $NOAEL_{HEC}$ of 0.275 ppm is calculated by multiplying the $NOAEL_{ADJ}$ by an extra-respiratory RGDR of 1. Because blood:gas partition coefficients are not available for rats or humans, the default ratio of 1 was used for the $RGDR_{ER}$. It is noted that the peribronchial lymphoid hyperplasia observed in the lungs was not considered a portal-of-entry effect since the effect occurred in lymphoid tissue rather than lung tissue. Dividing the $NOAEL_{HEC}$ POD of 0.275 ppm by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) results in a candidate MRL of 0.009 ppm. This value is higher than the acute-duration inhalation MRL of 0.001 ppm based on nasal lesions observed in rats exposed to 1,2,3-trichloropropane for 11 exposures (Miller et al. 1986b). Thus, an intermediate-duration inhalation MRL was not derived for 1,2,3-trichloropropane.

***Agency Contact (Chemical Manager):*** Malcolm Williams

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3-Trichloropropane
***CAS Numbers:*** 96-18-4
***Date:*** August 2021
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** The available chronic inhalation data were not considered adequate for derivation of chronic-duration inhalation MRL for 1,2,3-trichloropropane.

***Rationale for Not Deriving an MRL:*** No chronic-duration inhalation studies were identified for 1,2,3-trichloropropane.

***Agency Contact (Chemical Manager):*** Malcolm Williams

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3-Trichloropropane
***CAS Numbers:*** 96-18-4
***Date:*** August 2021
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** The available acute oral data were not considered adequate for derivation of an acute-duration oral MRL for 1,2,3-trichloropropane.

***Rationale for Not Deriving an MRL:*** A small number of studies have examined the toxicity of 1,2,3-trichloropropane following acute oral exposure. Increases in mortality were observed at ≥150 mg/kg (Albert 1982; NTP 1993; Smyth et al. 1962). The most sensitive effect identified in the available database was an increase in relative liver weights observed in rats administered via gavage ≥29.5 mg/kg/day for 10 days (Merrick et al. 1991). At 118 mg/kg/day, decreases in body weight gain; myocardial inflammation, degeneration, and necrosis; and thymic atrophy were observed in rats administered 1,2,3-trichloropropane via gavage for 10 days (Merrick et al. 1991). Two studies examining reproductive effects in male rats did not find increases in the incidence of histological alterations at 60 mg/kg/day for 10 days (Dix 1979) or 80 mg/kg/day for 5 days (Saito-Suzuki et al. 1982) or dominant lethality at 80 mg/kg/day (Saito-Suzuki et al. 1982).

Although the available acute-duration studies identified several effects, the database was not considered suitable for MRL derivation. The increase in liver weight was considered a LOAEL based on intermediate and chronic studies that reported histological alterations in the liver. However, no significant increases in liver lesions were observed in the Merrick et al. (1991) study, although centrilobular hepatic necrosis was observed in 3/20 animals at 118 mg/kg/day. Heart lesions were observed in acute- and intermediate-duration studies conducted by Merrick et al. (1991), but no cardiovascular effects have been observed in other acute, intermediate, or chronic oral studies; this endpoint was not considered suitable for MRL derivation due to the lack of corroborative data. Interpretation of the thymic atrophy observed at 118 mg/kg/day is difficult given that a 22–25% decrease in body weight gain was also observed at this dose level.

***Agency Contact (Chemical Manager):*** Malcolm Williams

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3-Trichloropropane
***CAS Numbers:*** 96-18-4
***Date:*** August 2021
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Intermediate
***MRL:*** 0.03 mg/kg/day
***Critical Effect:*** Decreased hematocrit
***Reference:*** NTP 1993
***Point of Departure:*** $BMDL_{1SD}$ of 4.03 mg/kg ($BMDL_{ADJ}$ of 2.9 mg/kg/day)
***Uncertainty Factor:*** 100
***LSE Graph Key:*** 9
***Species:*** Rat

***MRL Summary:*** An intermediate-duration oral MRL of 0.03 mg/kg/day was derived for 1,2,3-trichloropropane based on decreased hematocrit levels observed in female rats administered via gavage 1,2,3-trichloropropane 5 days/week for 8 weeks (NTP 1993). The MRL is based on a $BMDL_{1SD}$ of 4.03 mg/kg, which was adjusted to a continuous duration exposure to a $BMDL_{ADJ}$ of 2.9 mg/kg/day and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

***Selection of the Critical Effect:*** Four studies have evaluated the intermediate-duration oral toxicity of 1,2,3-trichloropropane. These studies identified a number of targets of toxicity: body weight, respiratory tract, heart, forestomach, hematological system, liver, kidney, and reproductive/developmental systems. The NOAEL and LOAEL values for these effects are summarized in Table A-2.

**Table A-2. Summary of NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to 1,2,3-Trichloropropane**

| Species | Exposure | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| Body weight effects | | | | | |
| Sprague-Dawley rat | 30 days (GO) | 14.7 | 58.9 | 14–20% decrease in body weight gain | Merrick et al. 1991 |
| F344 rat | 17 weeks, 5 days/week (GO) | 23[a] | 45[a] | 11% decreases in body weight gain in males (females at 89 mg/kg/day) | NTP 1993 |
| Sprague-Dawley rat | 13 weeks (W) | 17 | 113 | Reduced body weight gain | Villeneuve et al. 1985 |
| B6C3F1 mouse | 17 weeks, 5 days/week (GO) | 179[a] | | No effect on body weight gain | NTP 1993 |
| Respiratory effects | | | | | |
| F344 rat | 17 weeks, 5 days/week (GO) | 45[a] | 89[a] | Necrosis in nasal turbinates | NTP 1993 |

**Table A-2. Summary of NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to 1,2,3-Trichloropropane**

| Species | Exposure | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| B6C3F1 mouse | 17 weeks, 5 days/week (GO) | 23[a] | 45[a] | Regeneration of bronchiolar epithelium in the lungs in females (males at ≥89 mg/kg/day) | NTP 1993 |
| Cardiovascular effects | | | | | |
| Sprague-Dawley rat | 30 days (GO) | 14.7 | 58.9 | Myocardial inflammation, degeneration, and necrosis | Merrick et al. 1991 |
| F344 rat | 17 weeks, 5 days/week (GO) | 89[a] | | No histological alterations | NTP 1993 |
| Sprague-Dawley rat | 13 weeks (W) | 113 | | No histological alterations | Villeneuve et al. 1985 |
| B6C3F1 mouse | 17 weeks, 5 days/week (GO) | 179[a] | | No histological alterations | NTP 1993 |
| Gastrointestinal effects | | | | | |
| F344 rat | 17 weeks, 5 days/week (GO) | 89[a] | | No histological alterations | NTP 1993 |
| B6C3F1 mouse | 17 weeks, 5 days/week (GO) | 23[a] | 45[a] | Hyperkeratosis and acanthosis of forestomach | NTP 1993 |
| Hematological effects | | | | | |
| F344 rat | 17 weeks, 5 days/week (GO) | 5.7[a] | 11[a] | Decreases in hematocrit, hemoglobin, and erythrocyte levels after 8 and 17 weeks | NTP 1993 |
| Sprague-Dawley rat | 13 weeks (W) | 113 | | No hematological alterations | Villeneuve et al. 1985 |
| B6C3F1 mouse | 17 weeks, 5 days/week (GO) | 179[a] | | No hematological alterations | NTP 1993 |
| Hepatic effects | | | | | |
| Sprague-Dawley rat | 30 days (GO) | 7.4 | 14.7 | Increased relative liver weight | Merrick et al. 1991 |
| | | 14.7 | 58.9 | Bile duct hyperplasia | |
| F344 rat | 17 weeks, 5 days/week (GO) | 5.7[a] | 11[a] | Increased absolute liver weight | NTP 1993 |
| | | | 89[a] | Hepatocellular necrosis and hemorrhage, bile duct hyperplasia | |
| Sprague-Dawley rat | 13 weeks (W) | 17 | 113 | Anisokaryosis, accentuated zonation and fatty vacuolation | Villeneuve et al. 1985 |
| | | | 149 | Biliary hyperplasia (females only) | |

**Table A-2. Summary of NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to 1,2,3-Trichloropropane**

| Species | Exposure | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| B6C3F1 mouse | 17 weeks, 5 days/week (GO) | 45[a] | 89[a] | Increased liver weights | NTP 1993 |
| | | | 179[a] | Focal hepatocellular necrosis | |
| Renal effects | | | | | |
| F344 rat | 17 weeks, 5 days/week (GO) | 11[a] | 23[a] | Increased absolute and relative liver weight in males | NTP 1993 |
| | | | 45[a] | Regenerative hyperplasia after 8 weeks of exposure; not observed after 17 weeks of exposure | |
| Sprague-Dawley rat | 13 weeks (W) | 17 | 113 | Eosinophilic inclusions, pyknosis, nuclear displacement, fine glomerular adhesions, interstitial reactions, and histologic proteinuria | Villeneuve et al. 1985 |
| B6C3F1 mouse | 17 weeks, 5 days/week (GO) | | 179[a] | Multifocal tubular necrosis in animals dying early | NTP 1993 |
| Reproductive/developmental effects | | | | | |
| Swiss mice | 98 days (GO) | 30 | 60 | Decreased number of live pups per litter | NTP 1990 |
| | | 120 | | No alterations in epididymal sperm motility, count, or morphology or estrous cycle length | |
| | | | 120 | Ovarian amyloidosis | |
| Swiss mice | Prenatal exposure, post weaning, mating, and gestation exposure | 60 | 120 | Decreases in mating, fertility, and pregnancy indices | NTP 1990 |

[a]Administered doses of 8, 16, 32, 63, 125, or 250 mg/kg were adjusted for intermittent exposure (5 days/week) resulting in continuous doses of 5.7, 11, 23, 45, 89, and 179 mg/kg/day.

GO = gavage in oil; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; W = drinking water administration

Based on a comparison of the lowest LOAEL values for each endpoint, the liver appears to be one of the most sensitive targets of toxicity. At gavage doses ≥11 mg/kg/day, >10% increases in absolute liver weight were observed in rats (NTP 1993); a similar LOAEL of 14.7 mg/kg/day was identified in another rat gavage study (Merrick et al. 1991). An increase in liver weight was also observed in mice administered ≥89 mg/kg/day (NTP 1993). Serum clinical chemistry alterations have also been observed at lower doses; decreases in pseudocholinesterase levels, likely due to decreased synthesis in the liver, were observed at ≥5.7 mg/kg/day (NTP 1993) and increases in serum total bilirubin and alanine

aminotransferase were observed at ≥58.9 mg/kg/day (NTP 1993). At higher doses, hepatocellular necrosis was observed in rats and mice administered 89 and 179 mg/kg/day, respectively (NTP 1993), and anisokaryosis and fatty vacuolation were observed in rats at 113 mg/kg/day (Villeneuve et al. 1985). Additionally, bile duct hyperplasia was observed in rats at 58.9 mg/kg/day (Merrick et al. 1991), 89 mg/kg/day (NTP 1993), and 149 mg/kg/day (Villeneuve et al. 1985).

The lowest LOAEL for hematological effects is also 11 mg/kg/day identified in the NTP (1993) rat study. The hematological effects consisted of decreases in hematocrit, hemoglobin, and erythrocyte levels in female rats. NTP noted that the observed anemia was nonregenerative and possibly associated with depressed erythropoiesis. No hematological effects were observed in a 13-week rat drinking water study (Villeneuve et al. 1985) or in a 17-week gavage mouse study (NTP 1993).

At the next highest LOAEL of 23 mg/kg/day, increases in kidney weights were observed in male rats (NTP 1993); the adversity of this finding is supported by histological alterations in the kidney observed at ≥45 mg/kg/day (NTP 1993; Villeneuve et al. 1985). Other effects that have been observed in rats and mice at higher LOAELs included decreases in body weight gain (lowest LOAEL of 45 mg/kg/day) (Merrick et al. 1991; NTP 1993; Villeneuve et al. 1985), regeneration of bronchiolar epithelium (45 mg/kg/day) (NTP 1993), hyperkeratosis and acanthosis of the forestomach, myocardial inflammation, degeneration, and necrosis (58.9 mg/kg/day) (Merrick et al. 1991), decreases in reproductive function (60 mg/kg/day) (NTP 1990), and necrosis in nasal turbinates (89 mg/kg/day) (NTP 1993).

***Selection of the Principal Study:*** NTP (1993) was selected as the principal study because it identified the lowest LOAEL (11 mg/kg/day) for liver and hematological effects.

***Summary of the Principal Study:***

NTP. 1993. Toxicology and carcinogenesis of 1,2,3-trichloropropane (CAS No. 96-18-4) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program. TR384. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr384.pdf. May 19, 2020.

Groups of 20 male and 20 female F344/N rats were administered 8, 16, 32, 63, 125, or 250 mg/kg 1,2,3-trichloropropane in corn oil 5 days/week for 17 weeks; a vehicle control group consisted of 30 males and 30 females. After 8 weeks of exposure, 10 rats/sex/group were sacrificed. The following parameters were used to assess toxicity: weekly clinical observations, weekly body weights, organ weights (brain, epididymis, heart, kidney, liver, lung, testis, thymus), urinalysis, hematology, serum clinical chemistry, and histopathology of major tissues and organs (control and 125 mg/kg groups and other groups as needed).

A number of adverse effects have been observed in animals exposed for 8 or 17 weeks; these effects are described below and summarized in Table A-3.

- ***Death.*** Deaths were observed in all male and female rats in the 250 mg/kg group by week 5 and 2, respectively, and in 1/10 males and 4/10 females at 125 mg/kg. The cause of death in the 250 mg/kg group was kidney or hepatic toxicity. There was no mortality at lower doses.
- ***Body weight.*** Body weight gain was reduced in males at 63 mg/kg (11% lower than controls) and in males (21%) and females (24%) at 125 mg/kg. Food consumption was markedly reduced at 250 mg/kg prior to death.
- ***Respiratory.*** There was a significant increase in relative lung weight after 17 weeks in males at 125 mg/kg. Epithelial necrosis and attenuation of epithelial lining of the dorsal portion of nasal turbinates was observed at 125 mg/kg; in females, the lesions were observed after 8 and 17 weeks of exposure.

- ***Hematological.*** Significant decreases in hematocrit, hemoglobin, and erythrocyte levels were observed at 63 and 125 mg/kg after 17 weeks of exposure; decreases in hemoglobin levels were also observed in females at 16 and 32 mg/kg. After 8 weeks of exposure, decreases in hematocrit, hemoglobin, and erythrocyte levels were observed at ≥16 mg/kg and hematocrit and erythrocyte levels were also decreased in females at ≥8 mg/kg.
- ***Hepatic.*** After 8 weeks of exposure, significant increases were observed in total bilirubin at ≥63 mg/kg, ALT in females at ≥63 mg/kg, aspartate aminotransferase (AST) in females at ≥125 mg/kg, lactic acid dehydrogenase (LDH) at ≥63 mg/kg in females and 125 mg/kg in males, and sorbitol dehydrogenase (SDH) at 125 mg/kg. Pseudocholinesterase levels were significantly decreased in males 32 and 125 mg/kg after 8 weeks and ≥32 mg/kg in males at 17 weeks, and ≥8 mg/kg in females at 8 and 17 weeks. The investigators suggested that the decrease in pseudocholinesterase levels suggest a decrease in synthesis due to hepatocellular damage. Significant increases in absolute liver weight were observed in males after 17 weeks of exposure at ≥8 mg/kg and in females at ≥16 mg/kg; the increases in absolute liver weight in the males did not appear to be dose-related. Significantly increased relative liver weights were observed at ≥32 mg/kg in males and ≥16 mg/kg in females. In the liver, necrosis, hemorrhage, and bile duct hyperplasia were observed in females at 125 mg/kg after 8 or 17 weeks of exposure; degeneration and hemorrhage were observed in males at 250 mg/kg after 8 weeks of exposure. There were no treatment-related effects in lower dose groups after 17 weeks.
- ***Renal.*** Blood urea nitrogen (BUN) levels were decreased in females at 16, 63, and 125 mg/kg after 8 weeks of exposure and in males at 125 mg/kg and females at ≥32 mg/kg after 17 weeks. Absolute and relative kidney weights were increased ($p<0.05$) after 17 weeks at ≥32 mg/kg in males and at ≥63 mg/kg in females. Renal regenerative hyperplasia was observed at ≥63 mg/kg after 8 weeks of exposure and at 125 mg/kg after 17 weeks of exposure in males; necrosis and karyomegaly (males only) were also observed at 250 mg/kg after 8 weeks of exposure.
- ***Other Effects.*** The investigators noted that thymic lymphoid depletion, hypocellularity of sternal bone marrow, splenic atrophy, uterine hypoplasia, adrenal cortical cell vacuolation, and myocardial chronic inflammation occurred less frequently in animals dying during the study; however, incidence data were not provided and NOAEL and LOAEL values could not be identified for these effects.

**Table A-3. NOAEL and LOAEL Values for Adverse Health Effects Observed in Rats Administered 1,2,3-Trichloropropane 5 Days/Week for 17 Weeks**

| Endpoint | NOAEL (mg/kg) | LOAEL (mg/kg) | Effect | AEL (mg/kg) |
|---|---|---|---|---|
| Death | | 250 | | |
| Body weight | 32 M | 63 M | Decreased body weight gain (11%) | 63 M |
| Respiratory | 63 M | 125 M | Increased relative lung weight (13%) | 125 M |
| | | | Epithelial necrosis in nasal turbinates | 125 M |
| Hematological | | 8 F | Decreases in hemoglobin (5%) and erythrocytes (19%) at 8 weeks | 8 F |
| Hepatic | 8F | 16 F | Increased absolute liver weight (11% in males at 8 mg/kg and 18% in females at 16 mg/kg) | 8 M<br>16 F |
| | | | Increased relative liver weight (24% in males at 32 mg/kg and 12% in females at 16 mg/kg) | 32 M<br>16 F |
| | | | Necrosis, hemorrhage, and bile duct hyperplasia (females only) | 250 M<br>125 F |

**Table A-3. NOAEL and LOAEL Values for Adverse Health Effects Observed in Rats Administered 1,2,3-Trichloropropane 5 Days/Week for 17 Weeks**

| Endpoint | NOAEL (mg/kg) | LOAEL (mg/kg) | Effect | AEL (mg/kg) |
|---|---|---|---|---|
| Renal effects | 16 M | 32 M | Increased absolute (15%) and relative (12%) kidney weight | 32 M |
| | | | Regenerative hyperplasia | 63 M |

AEL = adverse-effect level; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Source: NTP 1993

***Selection of the Point of Departure for the MRL:*** The $BMDL_{1SD}$ of 6.91 mg/kg for decreases in hemoglobin levels in female rats estimated from the frequentist restricted Hill model was selected as the point of departure for the intermediate-duration oral MRL for 1,2,3-trichloropropane.

The lowest LOAEL identified in the NTP (1993) rat study was 8 mg/kg. At this dose level, decreases in hematocrit and erythrocyte levels were observed in female rats administered 1,2,3-trichloropropane for 8 weeks. The lowest LOAEL identified in rats administered 1,2,3-trichloropropane for 17 weeks was 16 mg/kg for increases in absolute and relative liver weight in females and decreases in hemoglobin and erythrocyte levels in females. The absolute and relative liver weights in females exposed for 17 weeks (Table A-4) and hematocrit and erythrocyte levels in females exposed for 8 weeks (Table A-5) were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 3.1.2) using the extra risk option. The 8-week hematological data were selected over the 17 week data since a lower LOAEL was identified at 8 weeks and the magnitude of change was greater at 8 weeks compared to 17 weeks. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR), BMDL that is not 10 times lower than the lowest non-zero dose, and visual inspection of the dose-response curve. A BMR of 10% change from the control was used for liver weights and 1 standard deviation change relative to controls was used for hemoglobin and erythrocyte levels.

**Table A-4. Summary of Absolute and Relative Liver Weights in Female Rats Administered via Gavage 1,2,3-Trichloropropane for 17 Weeks**

| | | Mean±standard deviation[a] | |
|---|---|---|---|
| Dose (mg/kg)[b] | Number of rats | Absolute liver weight (g) | Relative liver weight (mg/g BW) |
| 0 | 10 | 5.14±0.32 | 25.7±1.26 |
| 8 | 10 | 5.49±0.28 | 27.5±1.90 |
| 16 | 10 | 6.07±0.51[c] | 28.9±1.26[c] |
| 32 | 10 | 6.00±0.28[d] | 30.2±1.90[c] |

**Table A-4. Summary of Absolute and Relative Liver Weights in Female Rats Administered via Gavage 1,2,3-Trichloropropane for 17 Weeks**

| | | Mean±standard deviation[a] | |
|---|---|---|---|
| Dose (mg/kg)[b] | Number of rats | Absolute liver weight (g) | Relative liver weight (mg/g BW) |
| 63 | 10 | 6.79±0.54[c] | 35.2±2.53[c] |
| 125 | 6 | 8.25±0.49[c] | 52.6±5.63[c] |

[a]Mean±standard deviation; standard deviations estimated from reported SEM.
[b]Animals administered 1,2,3-trichloropropane via gavage 5 days/week.
[c]Significantly different from controls, p≤0.01.
[d]Significantly different from controls, p≤0.05.

BW = body weight; SEM = standard error of the mean

Source: NTP 1993

**Table A-5. Summary of Hematocrit and Erythrocyte Levels in Female Rats Administered via Gavage 1,2,3-Trichloropropane for 8 Weeks**

| | | Mean±standard deviation[a] | |
|---|---|---|---|
| Dose (mg/kg)[b] | Number of rats | Hematocrit (%) | Erythrocyte ($10^6$/μL) |
| 0 | 10 | 46.7±1.26 | 8.59±0.25 |
| 8 | 10 | 45.0±1.26[c] | 8.31±0.22[c] |
| 16 | 10 | 42.1±1.58[d] | 7.77±0.32[d] |
| 32 | 10 | 41.3±2.21[c] | 7.60±10.41[d] |
| 63 | 10 | 39.9±1.58[d] | 7.39±0.25[d] |
| 125 | 9 | 38.7±2.40[d] | 7.60±0.48[d] |

[a]Mean±standard deviation; standard deviations estimated from reported standard error of the mean (SEM).
[b]Animals administered 1,2,3-trichloropropane via gavage 5 days/week.
[c]Significantly different from controls, p≤0.05.
[d]Significantly different from controls, p≤0.01.

Source: NTP 1993

None of the models provided adequate fit to the absolute liver weight data with constant or nonconstant variance and after dropping the highest dose. BMD modeling provided adequate fit for the relative liver weight, hematocrit, and erythrocyte data. The model predictions for relative liver weight, are presented in Table A-6. All of the models except Exponential 4 and Exponential 5 models provided adequate fit to the data with the assumption of nonconstant variance; the 4-degree Polynomial had the lowest Akaike Information Criterion (AIC) and is the recommended model. This model estimated a $BMD_{1SD}$ of 19.11 mg/kg and a $BMDL_{1SD}$ of 15.99 mg/kg. For the hematocrit data after 8 weeks of exposure, only the Exponential 5 and Hill models (constant variance) provided adequate fit; model predictions are presented in Table A-7. The Exponential 5 model had the lowest AIC and is the recommended model; this model estimated $BMD_{1SD}$ and $BMDL_{1SD}$ values of 5.97 and 4.03 mg/kg, respectively. The model predictions (constant variance) for erythrocyte levels are presented in Table A-8. Three models provided adequate fit; the Hill model was recommended because it had the lowest AIC. The Hill model estimated a $BMD_{1SD}$ of 8.44 mg/kg and a $BMDL_{1SD}$ of 5.57 mg/kg.

**Table A-6. Results from BMD Analysis (Nonconstant Variance) of Relative Liver Weight in Female Rats Administered 1,2,3-Trichloropropane 5 Days/Week for 17 Weeks (NTP 1993)**

| Model | $BMD_{RD10}$[a] (mg/kg) | $BMDL_{RD10}$[a] (mg/kg) | Test 4 p-value[b] | AIC | Scaled residuals[c] | |
|---|---|---|---|---|---|---|
| | | | | | Dose near BMD | Control group |
| Exponential 2[d] | 18.14 | 16.58 | 0.157 | 243.99 | 1.20 | -0.71 |
| Exponential 3[d] | 20.80 | 16.89 | 0.103 | 245.55 | 1.42 | -1.16 |
| Exponential 4[d] | | | 0.014 | 249.85 | 0.78 | -0.30 |
| Exponential 5[d] | | | 0.009 | 250.76 | 1.69 | -1.60 |
| Hill[d] | 23.70 | 16.28 | 0.008 | 251.14 | 1.69 | -1.62 |
| Polynomial Degree 5[d] | 18.56 | 15.73 | 0.227 | 244.33 | 1.08 | -0.92 |
| **Polynomial Degree 4[d,e]** | **19.11** | **15.99** | **0.375** | **242.48** | **1.14** | **-0.99** |
| Polynomial Degree 3[d] | 20.21 | 16.43 | 0.292 | 243.10 | 1.26 | -1.12 |
| Polynomial Degree 2[d] | 21.69 | 16.68 | 0.117 | 245.25 | 1.46 | -1.29 |
| Power[d] | | | 0.026 | 248.60 | 1.65 | -1.55 |
| Linear | | | 0.015 | 249.77 | 0.79 | -0.31 |

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals for dose group near the BMD and for the control dose group.
[d]Restricted model.
[e]Recommended model. There was an adequate fit to the variance when assuming nonconstant variance. Of the models providing adequate fit, the BMDLs were sufficiently close (differed by <3-fold); therefore, the model with the lowest AIC was selected (Polynomial 4 degree).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{RD10}$ = exposure dose associated with a 10% relative deviation from control)

**Table A-7. Results from BMD Analysis (Constant Variance) of Hematocrit Levels in Female Rats Administered 1,2,3-Trichloropropane 5 Days/Week for 8 Weeks (NTP 1993)**

| Model | $BMD_{1SD}$[a] (mg/kg) | $BMDL_{1SD}$[a] (mg/kg) | Test 4 p-value[b] | AIC | Scaled residuals[c] | |
|---|---|---|---|---|---|---|
| | | | | | Dose near BMD | Control group |
| Exponential 2[d] | | | <0.0001 | 265.21 | -2.04 | 2.94 |
| Exponential 3[d] | | | <0.0001 | 265.21 | -2.04 | 2.94 |
| Exponential 4[d] | | | <0.0001 | 267.19 | -2.04 | 2.94 |
| **Exponential 5[d,e]** | **5.97** | **4.03** | **0.225** | **239.95** | **0.90** | **-0.06** |
| Hill[d] | 6.16 | 3.21 | 0.200 | 240.81 | 0.82 | -0.16 |
| Polynomial Degree 5[d] | | | <0.0001 | 266.92 | -2.08 | 3.07 |
| Polynomial Degree 4[d] | | | <0.0001 | 266.92 | -2.08 | 3.07 |
| Polynomial Degree 3[d] | | | <0.0001 | 266.92 | -2.08 | 3.07 |
| Polynomial Degree 2[d] | | | <0.0001 | 266.92 | -2.08 | 3.07 |
| Power[d] | | | <0.0001 | 266.92 | -2.08 | 3.07 |
| Linear | | | <0.0001 | 266.92 | -2.08 | 3.07 |

[a]BMD and BMDL values for models that do not provide adequate are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals for dose group near the BMD and for the control dose group.
[d]Restricted model.
[e]Recommended model. There was an adequate fit to the variance when assuming constant variance. Of the two models providing adequate fit, the Exponential 5 model had the lowest AIC.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control)

**Table A-8. Results from BMD Analysis (Constant Variance) of Erythrocyte Levels in Female Rats Administered 1,2,3-Trichloropropane 5 Days/Week for 8 Weeks (NTP 1993)**

| Model | $BMD_{1SD}$[a] (mg/kg) | $BMDL_{1SD}$[a] (mg/kg) | Test 4 p-value[b] | AIC | Scaled residuals[c] | |
|---|---|---|---|---|---|---|
| | | | | | Dose near BMD | Control group |
| Exponential 2[d] | | | <0.0001 | 78.61 | -2.24 | 3.02 |
| Exponential 3[d] | | | <0.0001 | 78.61 | -2.24 | 3.02 |
| Exponential 4[d] | 5.00 | 3.33 | 0.117 | 44.86 | 1.45 | -0.48 |
| Exponential 5[d] | 8.57 | 4.69 | 0.242 | 43.80 | 0.02 | -0.01 |
| **Hill[d,e]** | **8.44** | **5.57** | **0.285** | **43.47** | **0.04** | **-0.02** |
| Polynomial Degree 5[d] | | | <0.0001 | 79.39 | -2.31 | 3.10 |
| Polynomial Degree 4[d] | | | <0.0001 | 79.39 | -2.31 | 3.10 |
| Polynomial Degree 3[d] | | | <0.0001 | 79.39 | -2.31 | 3.10 |
| Polynomial Degree 2[d] | | | <0.0001 | 79.39 | -2.31 | 3.10 |
| Power[d] | | | <0.0001 | 79.39 | -2.31 | 3.10 |
| Linear | | | <0.0001 | 79.39 | -2.31 | 3.10 |

[a]BMD and BMDL values for models that do not provide adequate are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals for dose group near the BMD and for the control dose group.
[d]Restricted model.
[e]Recommended model. There was an adequate fit to the variance when assuming constant variance. Of the two models providing adequate fit, the Hill model had the lowest AIC.

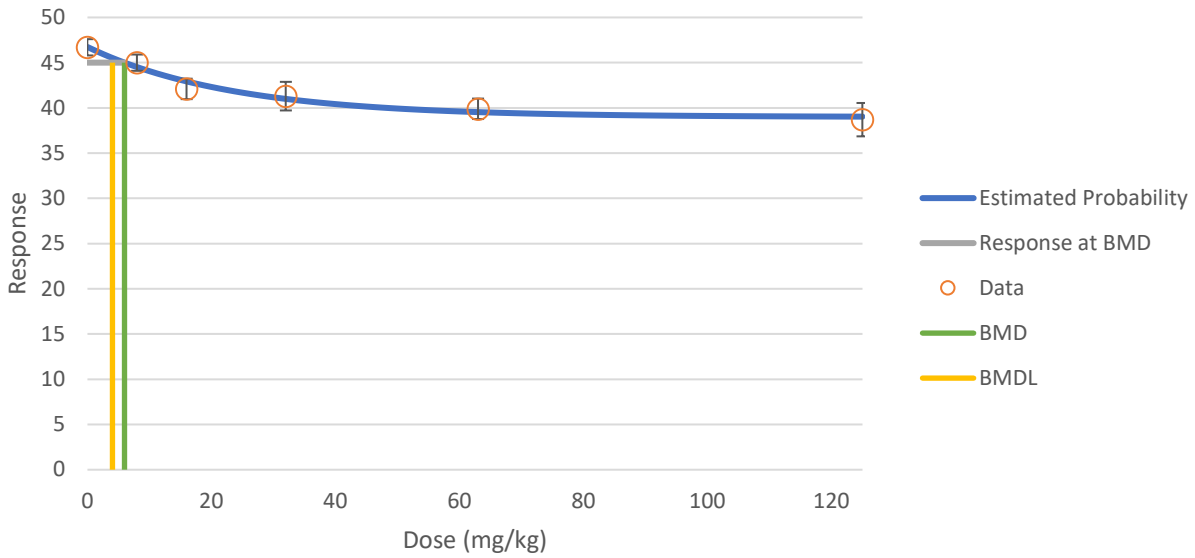
AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control)

To identify the POD for MRL derivation, a comparison was made of the BMD values (relative liver weight, hematocrit, and erythrocyte levels) and the NOAEL value (absolute liver weight):

- NOAEL of 8 mg/kg for absolute liver weight increases in female rats
- $BMD_{RD10}$ of 19.11 mg/kg for relative liver weight increases in female rats
- $BMD_{1SD}$ of 5.97 mg/kg for decreases in hematocrit levels in female rats
- $BMD_{1SD}$ of 8.44 mg/kg for decreases in erythrocyte levels in female rats

The $BMD_{1SD}$ for hematocrit alterations was selected as the critical endpoint because it was the lowest point estimate. The $BMDL_{1SD}$ value of 4.03 mg/kg for decreased hematocrit levels in female rats administered 1,2,3-trichloropropane for 8 weeks was selected as the basis of the POD for the MRL. The $BMDL_{1SD}$ was estimated by the Exponential 5 model (with constant variance) which is presented in Figure A-1.

**Figure A-1. Fit of Exponential 5 Model (with Constant Variance) for Hematocrit Levels in Female Rats Administered 1,2,3-Trichloropropane 5 Days/Week for 8 Weeks (NTP 1993)**




***Intermittent Exposure:*** The $BMDL_{1SD}$ of 4.03 mg/kg was adjusted from intermittent exposure to account for a continuous exposure scenario:

$BMDL_{ADJ}$ = 4.03 mg/kg x (5 days/7 days) = 2.9 mg/kg/day.

***Uncertainty Factor:*** The $BMDL_{ADJ}$ was divided by a total uncertainty factor (UF) of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = $BMDL_{ADJ}$ ÷ UFs
2.9 mg/kg/day ÷ (10 x 10) = 0.029 mg/kg/day ≈ 0.03 mg/kg/day

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** Similar liver and erythrocyte effects have been observed in rats administered 1,2,3-trichloropropane for 15 months (NTP 1993).

***Agency Contact (Chemical Manager):*** Malcolm Williams

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3-Trichloropropane
***CAS Numbers:*** 96-18-4
***Date:*** August 2021
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic
***MRL:*** 0.01 mg/kg/day
***Critical Effect:*** Bile duct hyperplasia
***Reference:*** NTP 1993
***Point of Departure:*** $BMDL_{10}$ of 1.94 mg/kg ($BMDL_{ADJ}$ of 1.38 mg/kg/day)
***Uncertainty Factor:*** 100
***LSE Graph Key:*** 14
***Species:*** Rat

***MRL Summary:*** A chronic-duration oral MRL of 0.01 mg/kg/day was derived for 1,2,3-trichloropropane based on an increased incidence of bile duct hyperplasia in male rats administered gavage doses 5 days/week for 15 months (NTP 1993). The MRL is based on a $BMDL_{10}$ of 1.94 mg/kg, which was adjusted to continuous duration exposure to a $BMDL_{ADJ}$ of 1.38 mg/kg/day and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

***Selection of the Critical Effect:*** The oral toxicity of 1,2,3-trichloropropane following chronic-duration exposure has been investigated in rats and mice (NTP 1993). The rats and mice were administered via gavage 1,2,3-trichloropropane in corn oil 5 days/week for up to 2 years. Decreased survival was observed in rats administered 10 or 30 mg/kg and a decrease in body weight gain (15%) was observed in females at 30 mg/kg. A number of non-neoplastic and neoplastic alterations were observed. Neoplastic lesions were observed at ≥3 mg/kg and included squamous cell papillomas or carcinomas in the forestomach and adenomas of the pancreas at ≥3 mg/kg; squamous cell papillomas or carcinomas in oral mucosa, adenoma in renal tubules, adenoma or carcinoma of the clitoral gland, and adenocarcinoma of the mammary gland (females only) at ≥10 mg/kg; and adenoma or carcinoma in preputial gland and carcinoma in Zymbal's gland (females only) at 30 mg/kg. Non-neoplastic target tissues included esophagus, tongue, hematopoietic tissues, liver and bile duct, kidney, pancreas, and testis; however, some of observed lesions were considered precancerous or were secondary to cancerous lesions. A summary of the effects and NOAEL and LOAEL values for the non-neoplastic lesions is presented in Table A-9. NTP (1993) considered the hematological effects to likely be due to depressed hematopoiesis or by blood loss from neoplasms in the forestomach or oral mucosa. NTP (1993) noted that hyperplasia observed in the pancreas was part of the morphological continuum to adenoma to adenocarcinoma, and focal hyperplasia in the kidney and renal adenomas constituted a morphological continuum. The bile duct hyperplasia and nephropathy effects do not appear to be associated with carcinogenicity and were considered as possible critical effects for the MRL.

**Table A-9. Summary of the Results of the NTP (1993) Chronic-Duration Rat Study[a]**

| | NOAEL (mg/kg) | LOAEL (mg/kg) | Effect |
|---|---|---|---|
| Body weight | 3 | 10 | 15% decrease in body weight gain in females |
| Gastrointestinal | 3 | 10 | Hyperkeratosis of esophagus<br>Acute inflammation of tongue in females (males at 30 mg/kg) |
| Hematological | 3 | 10 | Hematopoietic cell proliferation in spleen at ≥10 mg/kg<br>Decreased hemoglobin, increased leukocytes, increased segmented neutrophils (measured after 15 months) at 30 mg/kg |
| Hepatic | 3 | 10 | Increased liver weight at ≥10 mg/kg<br>Bile duct hyperplasia in males at 10 mg/kg at 15 months, 30 mg/kg at 2 years |
| Renal | 3 | 10 | Renal tubular hyperplasia and increased severity of nephropathy (males only) |
| Endocrine | | 3 | Focal hyperplasia of pancreatic acini |
| Reproductive | 10 | 30 | Interstitial cell hyperplasia in testes |

[a]Rats were administered 1,2,3-trichloropropane 5 days/week for up to 2 years.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

A summary of the hepatic and renal effects observed in rats in the NTP (1993) study are presented in Table A-10. These data clearly demonstrate a LOAEL of 10 mg/kg for increases in the incidences of bile duct hyperplasia in male rats and an increased severity of nephropathy in male rats. The increases in absolute liver and kidney weights in male rats administered 3 mg/kg were considered minimally adverse because the liver and kidney are target tissues and the increases in organ weight may be representative of early-stage adverse effects.

**Table A-10. Summary of Hepatic and Renal Effects Observed in Rats Administered 1,2,3-Trichloropropane for 2 Years**

| | Dose (mg/kg, 5 days/week) | | | |
|---|---|---|---|---|
| | 0 | 3 | 10 | 30 |
| Hepatic effects | | | | |
| Serum alanine aminotransferase (IU/L) | | | | |
| Males | 99 | 91 (-8.1%)[a] | 90 (-9.1%) | 68 (-31%)[b] |
| Females | 58 | 57 (-1.7%) | 65 (12%) | 66 (14%) |
| Absolute liver weight at 15 months (g) | | | | |
| Males | 14.27 | 15.63[b] (9.5%) | 16.8[b] (17.7%) | 18.23[b] (27.7%) |
| Females | 7.79 | 8.87[b] (13.9%) | 9.00[b] (15.5%) | 10.4[b] (33.5%) |

**Table A-10. Summary of Hepatic and Renal Effects Observed in Rats Administered 1,2,3-Trichloropropane for 2 Years**

| | Dose (mg/kg, 5 days/week) | | | |
|---|---|---|---|---|
| | 0 | 3 | 10 | 30 |
| Relative liver weight at 15 months (mg organ weight/g body weight) | | | | |
| Males | 31.2 | 33.1 (6.1%) | 36[b] (15.4%) | 39.8[b] (27.6%) |
| Females | 30.8 | 30.9 (0.32%) | 34.6[b] (12.3%) | 43.2[b] (40.3%) |
| Bile duct hyperplasia at 15 months | | | | |
| Males | 1/10 | 2/10 | 5/10[c] | 8/10[c] |
| Females | 0/10 | 0/10 | 1/8 | 3/8 |
| Bile duct hyperplasia at 2 years | | | | |
| Males | 0/50 | 0/50 | 1/49 | 12/52[c] |
| Females | 0/50 | 0/49 | 0/52 | 2/52 |
| Renal effects | | | | |
| Absolute kidney weight at 15 months (g) | | | | |
| Males | 1.35 | 1.46[b] (8.1%) | 1.51[b] (11.8%) | 1.75[b] (29.6%) |
| Females | 0.786 | 0.839 (6.7%) | 0.869[b] (10.6%) | 0.971[b] (23.5%) |
| Relative kidney weight at 15 months (mg organ weight/g body weight) | | | | |
| Males | 2.96 | 3.09 (4.4%) | 3.25[b] (9.8%) | 3.82[b] (29.0%) |
| Females | 3.08 | 2.93 (-4.9%) | 3.34[b] (8.4%) | 4.04[b] (31.2%) |
| Nephropathy at 2 years | | | | |
| Males | 48/50 (2.0)[d] | 50/50 (2.0) | 48/49 (2.6) | 52/52 (2.4) |
| Females | 18/50 | 21/47 | 17/52 | 5/51 |

[a]Percent differences from controls.
[b]Significantly different (p≤0.05) from controls.
[c]Significantly different (p≤0.05) from controls; Fisher Exact Test performed by ATSDR.
[d]Mean severity score; 1=minimal (<25% renal tubules involved), 2=mild (25–50% involvement), 3=moderate (50–75% involvement) and 4=marked (>75% involvement).

Source: NTP 1993

The toxicity of 1,2,3-trichloropropane appears to differ in mice, as compared to rats. A decrease in survival was observed in mice administered ≥6 mg/kg 5 days/week for 2 years (NTP 1993); a 12–18% decrease in body weight gain was observed at 60 mg/kg. Non-neoplastic effects observed in mice included bronchiole hyperplasia at 60 mg/kg and hepatocellular necrosis at 60 mg/kg. Squamous cell hyperplasia was also observed in the forestomach, but this was part of the continuum to forestomach adenocarcinomas. Likewise, the hematopoietic cell proliferation observed in the spleen at ≥6 mg/kg may have been due to bleeding from the forestomach tumors. Increases in the incidence of neoplastic lesions were observed at all dose levels: squamous cell papilloma or carcinoma in the forestomach and hepatocellular adenoma or carcinoma in males at ≥6 mg/kg; harderian gland adenoma in males at ≥20 mg/kg; squamous cell papilloma or carcinoma in oral mucosa in females, harderian gland adenoma in females, and uterine stromal polyps and endometrial adenoma or adenocarcinoma at 60 mg/kg. The lowest LOAEL in mice for an effect unrelated to carcinogenicity is 60 mg/kg for increases in bronchiole hyperplasia and hepatocellular necrosis.

***Selection of the Principal Study:*** The NTP (1993) rat gavage study was selected as the principal study because it identified the lowest LOAELs for non-carcinogenic effects.

***Summary of the Principal Study:***

NTP. 1993. Toxicology and carcinogenesis of 1,2,3-trichloropropane (CAS No. 96-18-4) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program. TR384. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr384.pdf. May 19, 2020.

Groups of 60 male and 60 female F344/N rats were administered 0, 3, 10, or 30 mg/kg 1,2,3-trichloropropane in corn oil by gavage 5 days/week for 2 years. Due to high mortality, rats in the 30 mg/kg groups were terminated after 77 (males) or 67 (females) weeks of exposure. After 15 months of exposure, 10 animals/sex/group were sacrificed. Parameters used to assess toxicity included twice daily clinical observations, body weights (weekly for 13 weeks and monthly thereafter), organ weights (brain, liver, kidney; evaluated at 15 months), hematological and serum clinical chemistry indices (evaluated at 15 months), and histopathology of major tissues and organs.

Significant decreases in survival were observed in rats at 10 and 30 mg/kg; mean survival days were 596 and 465 days in the 10 mg/kg males and females, respectively, and 580 and 366 days in the 30 mg/kg males and females, respectively, compared to 647 and 649 days in control males and females, respectively. In rats dying early, emaciation, lethargy, diarrhea, dyspnea, and tissue masses were observed; most of these signs were attributed to neoplasms of the oral mucosa or forestomach. No compound-related clinical signs were observed. Small decreases in body weight gain (<5%) were observed at 30 mg/kg in males; in females, body weight in the last year of the study was 15% lower than controls. Increases in absolute liver weights were observed at ≥3 mg/kg; relative liver weights were observed at ≥10 mg/kg. Increases in absolute kidney weights were observed at ≥3 mg/kg in males and ≥10 mg/kg in females; increases in relative kidney weights were observed at ≥10 mg/kg. Decreased hemoglobin levels were observed at 30 mg/kg; increases in leukocytes and segmented neutrophils were also observed at this dose level. Hematopoietic cell proliferation was observed at 10 and 30 mg/kg. Histological alterations were observed in the oral mucosa (pharynx and tongue), forestomach, pancreas, liver, kidney, preputial gland, clitoral gland, mammary gland, Zymbal's gland, and intestines. Acute inflammation was observed in the tongue of male rats treated with 30 mg/kg and female rats at 10 mg/kg. Oral mucosal lesions consisted of squamous cell papillomas or carcinomas at 10 mg/kg (37 and 54% in males and females, respectively) and 30 mg/kg (77 and 62% in males and females, respectively), but not at 3 mg/kg (8 and 12% in males and females, respectively) or controls (2 and 2% in males and females, respectively). Hyperkeratosis of the esophagus was observed in males at 30 mg/kg and females at ≥10 mg/kg. Squamous cell papillomas or carcinomas were also observed in the forestomach at 3 (20 and 33% in males and females, respectively), 10 mg/kg (40 and 63% in males and females, respectively), and 30 mg/kg (83 and 37% in males and females, respectively); no tumors were observed in controls. Increases in the incidence of forestomach tumors were also observed in the 10 and 30 mg/kg groups after 15 months of exposure. In the pancreas, focal hyperplasia of pancreatic acini was observed at ≥3 mg/kg/day (56, 92, 94, and 92% in males at 0, 3, 10, or 30 mg/kg and 10, 29, 46, and 17% in females) and adenomas were observed in males at ≥3 mg/kg (10, 42, 73, and 56% in males and 0, 0, 4, and 0% in females); the investigators noted that there was a morphologic continuum from the acinar hyperplasia to adenomas. Bile duct hyperplasia was observed in males at 10 and 30 mg/kg after 15 months and at 30 mg/kg after 2 years. Renal tubular hyperplasia in males at ≥10 mg/kg and females at 30 mg/kg; an increase in nephropathy was observed in males at 10 or 30 mg/kg, although the incidence was similar to controls (98–100% compared to 96% in controls). The mean severity scores were 2.0, 2.0, 2.6, and 2.4 in the 0, 3, 10, and 30 mg/kg groups, respectively. An increase in the incidence of adenomas in the kidneys was observed in males at 10 and 30 mg/kg; an increased incidence was also observed in the 30 mg/kg group after 15 months of exposure. Significant increases in the incidence of adenoma or carcinoma were

observed in the preputial gland at 30 mg/kg and in the clitoral gland at ≥10 mg/kg. In females, increases in the incidence of adenocarcinomas of the mammary gland were observed at 10 and 30 mg/kg. An increased incidence on Zymbal's gland carcinoma was observed in females at 30 mg/kg. Adenomatous polyps or adenocarcinomas were observed in the 30 mg/kg group; although the incidence was not statistically higher than controls, the investigators considered them to be treatment-related given the rarity of the lesion in historical controls and the decreased survival in rats in this group. In the testes, interstitial cell hyperplasia was observed at 30 mg/kg.

***Selection of the Point of Departure for the MRL:*** Exposure data for several endpoints were considered as the POD for the MRL: increases in absolute liver weight at 15 months, bile duct hyperplasia at 15 months, increases in absolute kidney weight at 15 months, and increases in the severity of nephropathy in male rats at 2 years. The 15-month data were used for liver and kidney weights because organ weights were not assessed at 2 years; 15-month incidence data for bile duct hyperplasia were used because the LOAEL was lower than after 2 years of exposure.

BMD modeling was attempted for the increases in absolute liver and kidney weights and for bile duct hyperplasia; because only mean severity scores were reported for nephropathy, the data were not suitable for BMD modeling. The absolute liver and kidney weight data (Table A-11) were fit to all available continuous models in EPA's BMDS (version 3.1.2) and bile duct hyperplasia incidence data (Table A-11) were fit to all dichotomous models in EPA's BMDS (version 3.1.2) using the extra risk option. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residual at the data point (except the control) closest to the predefined BMR, a BMDL that was not 10 times lower than the lowest non-zero dose, and visual inspection of the dose-response curve. A BMR of 10% change from the control was used for liver and kidney weights; a BMR of 10% was used for the bile duct hyperplasia incidence data.

**Table A-11. Summary of Absolute Liver Weight, Absolute Kidney Weight, and Bile Duct Hyperplasia in Male Rats Following 15-Month Oral Exposure to 1,2,3-Trichloropropane**

| Dose (mg/kg)[b] | Number of rats | Mean±standard deviation[a] | | Incidence of bile duct hyperplasia |
|---|---|---|---|---|
| | | Absolute liver weight (g) | Absolute kidney weight (g) | |
| 0 | 10 | 14.27±1.17 | 1.35±0.095 | 1/10 |
| 3 | 10 | 15.63±1.17 | 1.46±0.126 | 2/10 |
| 10 | 10 | 16.80±1.52 | 1.51±0.095 | 5/10 |
| 30 | 8 | 18.23±1.47 | 1.75±0.141 | 8/8 |

[a]Mean±standard deviation; standard deviations estimated from reported standard error of the mean (SEM).
[b]Animals administered 1,2,3-trichloropropane via gavage 5 days/week.

Source: NTP 1993

The model predictions for increases in absolute liver weight are presented in Table A-12. Only three models provided adequate fit to the data (Exponential 4-degree, Exponential 5-degree, and Hill models); the other models had goodness-of-fit p-values that were <0.1. Of the models providing adequate fit, the Hill model was recommended because it had the lowest AIC.

**Table A-12. Results from BMD Analysis (Constant Variance) of Absolute Liver Weight in Male Rats Administered 1,2,3-Trichloropropane 5 Days/Week for 15 Months (NTP 1993)**

| Model | $BMD_{RD10}$[a] (mg/kg) | $BMDL_{RD10}$[a] (mg/kg) | Test 4 p-value[b] | AIC | Scaled residuals[c] | |
|---|---|---|---|---|---|---|
| | | | | | Dose near BMD | Control group |
| Exponential 2[d] | | | 0.0325 | 138.38 | 1.58 | -1.73 |
| Exponential 3[d] | | | 0.0325 | 138.38 | 1.58 | -1.73 |
| Exponential 4[d] | 4.33 | 2.18 | 0.5079 | 133.96 | 0.50 | -0.25 |
| Exponential 5[d] | 4.36 | 2.17 | 0.5078 | 133.96 | 0.50 | -0.25 |
| **Hill[d,e]** | **3.77** | **1.60** | **0.6766** | **133.70** | **0.28** | **-0.10** |
| Polynomial Degree 3[d] | | | 0.0456 | 137.70 | 1.48 | -1.62 |
| Polynomial Degree 2[d] | | | 0.0456 | 137.70 | 1.48 | -1.62 |
| Power[d] | | | 0.0456 | 137.70 | 1.48 | -1.62 |
| Linear | | | 0.0456 | 137.70 | 1.48 | -1.62 |

[a]BMD and BMDL values for models that do not provide adequate are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals for dose group near the BMD and for the control dose group.
[d]Restricted model.
[e]Recommended model. Constant variance model provided adequate fit to variance data. With constant variance model applied, the only models that provided adequate fit to the means were the Exponential 4 and 5 models (the Exponential 5 converged on to the Exponential 4) and the Hill model. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with lowest AIC was selected (Hill).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{RD10}$ = exposure dose associated with a 10% relative deviation from control)

All BMD models provided adequate fit to the absolute kidney weight data (with constant variance); the model outputs are presented in Table A-13. The BMDLs were sufficiently close (<3-fold difference) and the model with the lowest AIC (Linear model) was selected.

**Table A-13. Results from BMD Analysis (Constant Variance) of Absolute Kidney Weight in Male Rats Administered 1,2,3-Trichloropropane 5 Days/Week for 15 Months (NTP 1993)**

| Model | $BMD_{RD10}$ (mg/kg) | $BMDL_{RD10}$ (mg/kg) | Test 4 p-value[a] | AIC | Scaled residuals[b] | |
|---|---|---|---|---|---|---|
| | | | | | Dose near BMD | Control group |
| Exponential 2[c] | 12.21 | 10.07 | 0.283 | -52.55 | 0.21 | -1.12 |
| Exponential 3[c] | 12.21 | 10.06 | 0.283 | -52.55 | 0.21 | -1.12 |
| Exponential 4[c] | 8.77 | 4.59 | 0.176 | -51.24 | -0.48 | -0.64 |
| Exponential 5[c] | 8.77 | 4.59 | 0.176 | -51.24 | -0.48 | -0.64 |
| Hill[c] | 8.61 | 4.08 | 0.180 | -51.27 | -0.51 | -0.61 |
| Polynomial Degree 3[c] | 11.22 | 9.00 | 0.328 | -52.84 | 0.04 | -0.99 |
| Polynomial Degree 2[c] | 11.22 | 9.00 | 0.328 | -52.84 | 0.04 | -0.99 |
| Power[c] | 11.22 | 9.00 | 0.328 | -52.84 | 0.04 | -0.99 |
| **Linear[d]** | **11.22** | **9.00** | **0.328** | **-52.84** | **0.04** | **-0.99** |

[a]Values <0.1 fail to meet adequate fit.
[b]Scaled residuals for dose group near the BMD and for the control dose group.
[c]Restricted model.
[d]Recommended model. Constant variance model provided adequate fit to variance data. With constant variance model applied, all models provided adequate fit to the means. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with lowest AIC was selected (Linear).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{RD10}$ = exposure dose associated with a 10% relative deviation from control)

All of the dichotomous models in BMD software provided adequate fit to the bile duct hyperplasia incidence data; model outputs are summarized in Table A-14. The BMDL values were within 3-fold of each; thus, the model with the lowest AIC (Probit) was selected.

**Table A-14. Results from BMD Analysis of Bile Duct Hyperplasia Incidence in Male Rats Administered 1,2,3-Trichloropropane 5 Days/Week for 15 Months (NTP 1993)**

| Model | $BMD_{10}$ (mg/kg) | $BMDL_{10}$ (mg/kg) | p-Value[a] | AIC | Scaled residuals[b] | |
|---|---|---|---|---|---|---|
| | | | | | Dose near BMD | Control group |
| Dichotomous Hill | 8.96 | 1.53 | 0.531 | 36.77 | 0.00 | -0.44 |
| Gamma[c] | 6.05 | 0.96 | 0.541 | 36.76 | 0.44 | -0.41 |
| Log-Logistic[d] | 8.96 | 1.53 | 0.822 | 34.77 | 0.00 | -0.44 |
| Multistage Degree 3[e] | 2.90 | 0.98 | 0.940 | 36.38 | 0.04 | -0.02 |
| Multistage Degree 2[e] | 3.56 | 0.99 | 0.730 | 36.54 | 0.19 | -0.09 |
| Multistage Degree 1[e] | 1.32 | 0.79 | 0.503 | 36.43 | 0.30 | 0.30 |
| Weibull[c] | 4.31 | 0.99 | 0.679 | 36.56 | 0.30 | -0.21 |
| Logistic | 3.25 | 2.03 | 0.940 | 34.57 | 0.16 | 0.01 |
| Log-Probit | 8.19 | 1.56 | 0.531 | 36.77 | 0.00 | -0.44 |
| **Probit[f]** | **3.04** | **1.94** | **0.975** | **34.45** | **0.10** | **0.01** |

[a]Values <0.1 fail to meet adequate fit.
[b]Scaled residuals for dose group near the BMD and for the control dose group.
[c]Restricted model.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Recommended model. All models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with lowest AIC was selected (Probit).

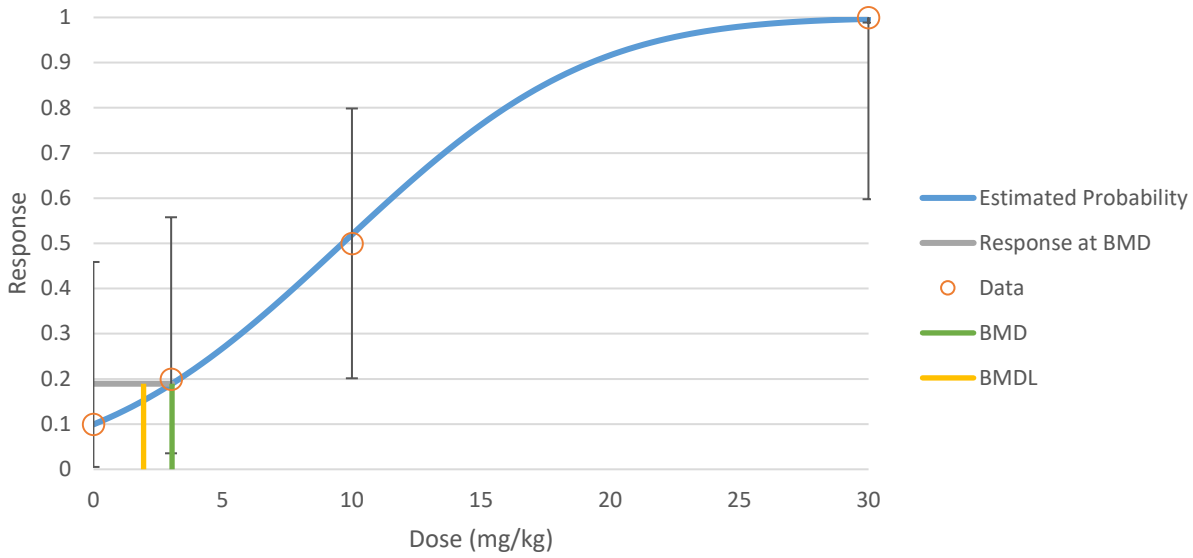
AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure dose associated with a 10% relative deviation from control)

To identify the POD for MRL derivation, a comparison was made of the BMD values (absolute liver weight, absolute kidney weight, and bile duct hyperplasia) and the NOAEL for nephropathy severity:

- $BMD_{RD10}$ of 3.77 mg/kg for absolute liver weight increases in male rats
- $BMD_{RD10}$ of 11.22 mg/kg for absolute kidney weight increases in male rats
- $BMD_{10}$ of 3.04 mg/kg for increases in incidence of bile duct hyperplasia in male rats at 15 months
- NOAEL of 3 mg/kg for increases in severity of nephropathy in male rats

The lowest BMD was 3.04 mg/kg for bile duct hyperplasia; this value is essentially the same as the NOAEL for increases in the severity of nephropathy. The bile duct hyperplasia was selected as the critical effect because its POD takes into consideration responses over a range of doses as compared to the NOAEL for nephropathy which only considers the response at a single dose level. The $BMDL_{10}$ for bile duct hyperplasia estimated from the Probit model is 1.94 mg/kg; this value was selected as the POD for the MRL. The fit of the Probit model is presented in Figure A-2.

**Figure A-2. Fit of Probit Model for Bile Duct Hyperplasia in Male Rats Administered 1,2,3-Trichloropropane 5 Days/Week for 15 Months (NTP 1993)**




***Intermittent Exposure:*** The $BMDL_{10}$ of 1.94 mg/kg was adjusted for intermittent exposure (5 days/7 days) resulting in adjusted value of 1.38 mg/kg/day.

$BMDL_{ADJ}$ = 1.94 mg/kg x (5 days/7 days) = 1.38 mg/kg/day

***Uncertainty Factor:*** The $BMDL_{ADJ}$ was divided by a total uncertainty factor (UF) of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = $BMDL_{ADJ}$ ÷ UFs
1.38 mg/kg/day ÷ (10 x 10) = 0.01 mg/kg/day

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** Identification of the liver and kidney as sensitive targets of toxicity is supported by intermediate-duration oral studies, which also found increases in liver and kidney weights, bile duct hyperplasia, and regenerative tubular hyperplasia in rats exposed for up to 17 weeks (NTP 1993).

***Agency Contact (Chemical Manager):*** Malcolm Williams

# APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR 1,2,3-TRICHLOROPROPANE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to 1,2,3-trichloropropane.

## B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 1,2,3-trichloropropane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of 1,2,3-trichloropropane have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of 1,2,3-trichloropropane are presented in Table B-1.

**Table B-1. Inclusion Criteria for the Literature Search and Screen**

| |
|---|
| Health Effects |
| Species |
| Human |
| Laboratory mammals |
| Route of exposure |
| Inhalation |
| Oral |
| Dermal (or ocular) |
| Parenteral (these studies will be considered supporting data) |
| Health outcome |
| Death |
| Systemic effects |
| Body weight effects |
| Respiratory effects |
| Cardiovascular effects |
| Gastrointestinal effects |
| Hematological effects |
| Musculoskeletal effects |
| Hepatic effects |
| Renal effects |
| Dermal effects |
| Ocular effects |
| Endocrine effects |
| Immunological effects |
| Neurological effects |
| Reproductive effects |

**Table B-1. Inclusion Criteria for the Literature Search and Screen**

| |
|---|
| Developmental effects |
| Other noncancer effects |
| Cancer |
| Toxicokinetics |
| Absorption |
| Distribution |
| Metabolism |
| Excretion |
| PBPK models |
| Biomarkers |
| Biomarkers of exposure |
| Biomarkers of effect |
| Interactions with other chemicals |
| Potential for human exposure |
| Releases to the environment |
| Air |
| Water |
| Soil |
| Environmental fate |
| Transport and partitioning |
| Transformation and degradation |
| Environmental monitoring |
| Air |
| Water |
| Sediment and soil |
| Other media |
| Biomonitoring |
| General populations |
| Occupation populations |

### B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for 1,2,3-trichloropropane released for public comment in 2019; thus, the literature search was restricted to studies published between January 2016 and March 2020. The following main databases were searched in March 2020:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for 1,2,3-trichloropropane. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to 1,2,3-trichloropropane were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

**Table B-2. Database Query Strings**

| Database search date | Query string |
|---|---|
| **PubMed** | |
| 03/2020 | (96-18-4[rn] OR "1,2,3-trichloropropane"[nm] OR "1,2,3-Trichloropropane"[tw] OR "Allyl trichloride"[tw] OR "Glycerol trichlorohydrin"[tw] OR "Glyceryl trichlorohydrin"[tw] OR "Propane, 1,2,3-trichloro-"[tw] OR "Trichlorohydrin"[tw] OR "Trichloropropane"[tw] OR "Trichloropropane, 1,2,3-"[tw]) AND (2017/03/01 : 3000[mhda] OR 2017/03/01 : 3000[crdt] OR 2017/03/01 : 3000[edat] OR 2016/03/01 : 3000[dp]) |
| **NTRL** | |
| 03/2020 | "96-18-4" OR "1,2,3-Trichloropropane" OR "Allyl trichloride" OR "Glycerol trichlorohydrin" OR "Glyceryl trichlorohydrin" OR "Propane, 1,2,3-trichloro-" OR "Trichlorohydrin" OR "Trichloropropane" OR "Trichloropropane, 1,2,3-" |
| **Toxcenter** | |
| 03/2020 | FILE 'TOXCENTER' ENTERED AT 21:11:53 ON 30 MAR 2020<br>CHARGED TO COST=EH038.06.01.LB.02<br>L1 861 SEA FILE=TOXCENTER 96-18-4<br>L2 77 SEA FILE=TOXCENTER L1 AND ED>=20160301<br>L3 72 SEA FILE=TOXCENTER L1 AND PY>2015<br>L4 82 SEA FILE=TOXCENTER L2 OR L3<br>L5 65 SEA FILE=TOXCENTER L4 NOT PATENT/DT<br>ACT TOXQUERY/Q<br>---------<br>L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)<br>L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,<br>IT)<br>L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)<br>L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT<br>L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)<br>L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)<br>L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR<br>DIETARY OR DRINKING(W)WATER?)<br>L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) |

## Table B-2. Database Query Strings

| Database search date | Query string |
|---|---|
| | L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)<br>L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)<br>L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)<br>L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)<br>L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)<br>L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)<br>L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)<br>L21 QUE (ENDOCRIN? AND DISRUPT?)<br>L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)<br>L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)<br>L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)<br>L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)<br>L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)<br>L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)<br>L28 QUE (NEPHROTOX? OR HEPATOTOX?)<br>L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)<br>L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)<br>L31 QUE L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30<br>L32 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)<br>L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)<br>L34 QUE L31 OR L32 OR L33<br>L35 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)<br>L36 QUE L34 OR L35<br>---------<br>L37 36 SEA FILE=TOXCENTER L5 AND L36<br>L38 29 SEA FILE=TOXCENTER L5 NOT L37<br>L39 8 SEA FILE=TOXCENTER L5 AND MEDLINE/FS |

**Table B-2. Database Query Strings**

| Database search date | Query string |
|---|---|
| | L40 57 SEA FILE=TOXCENTER L5 NOT MEDLINE/FS<br>L41 60 DUP REM L39 L40 (5 DUPLICATES REMOVED)<br>ANSWERS '1-60' FROM FILE TOXCENTER<br>L*** DEL 8 S L5 AND MEDLINE/FS<br>L*** DEL 8 S L5 AND MEDLINE/FS<br>L42 8 SEA FILE=TOXCENTER L41<br>L*** DEL 57 S L5 NOT MEDLINE/FS<br>L*** DEL 57 S L5 NOT MEDLINE/FS<br>L43 52 SEA FILE=TOXCENTER L41<br>L44 52 SEA FILE=TOXCENTER (L42 OR L43) NOT MEDLINE/FS<br>D SCAN L44 |

**Table B-3. Strategies to Augment the Literature Search**

| Source | Query and number screened when available |
|---|---|
| **TSCATS via ChemView** | |
| 03/2020 | Compounds searched: 96-18-4 |
| **NTP** | |
| 03/2020 | 96-18-4<br>"Trichloropropane" "Trichlorohydrin" "Allyl trichloride" "Propane, 1,2,3-trichloro-" |
| **NIH RePORTER** | |
| 04/2020 | Text Search: "1,2,3-Trichloropropane" OR "Allyl trichloride" OR "Glycerol trichlorohydrin" OR "Glyceryl trichlorohydrin" OR "Propane, 1,2,3-trichloro-" OR "Trichlorohydrin" OR "Trichloropropane" OR "Trichloropropane, 1,2,3-" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects |
| **Other** | Identified throughout the assessment process |

The 2020 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 72
- Number of records identified from other strategies: 58
- Total number of records to undergo literature screening: 130

### B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on 1,2,3-trichloropropane:

- Title and abstract screen
- Full text screen

***Title and Abstract Screen.*** Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the

second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

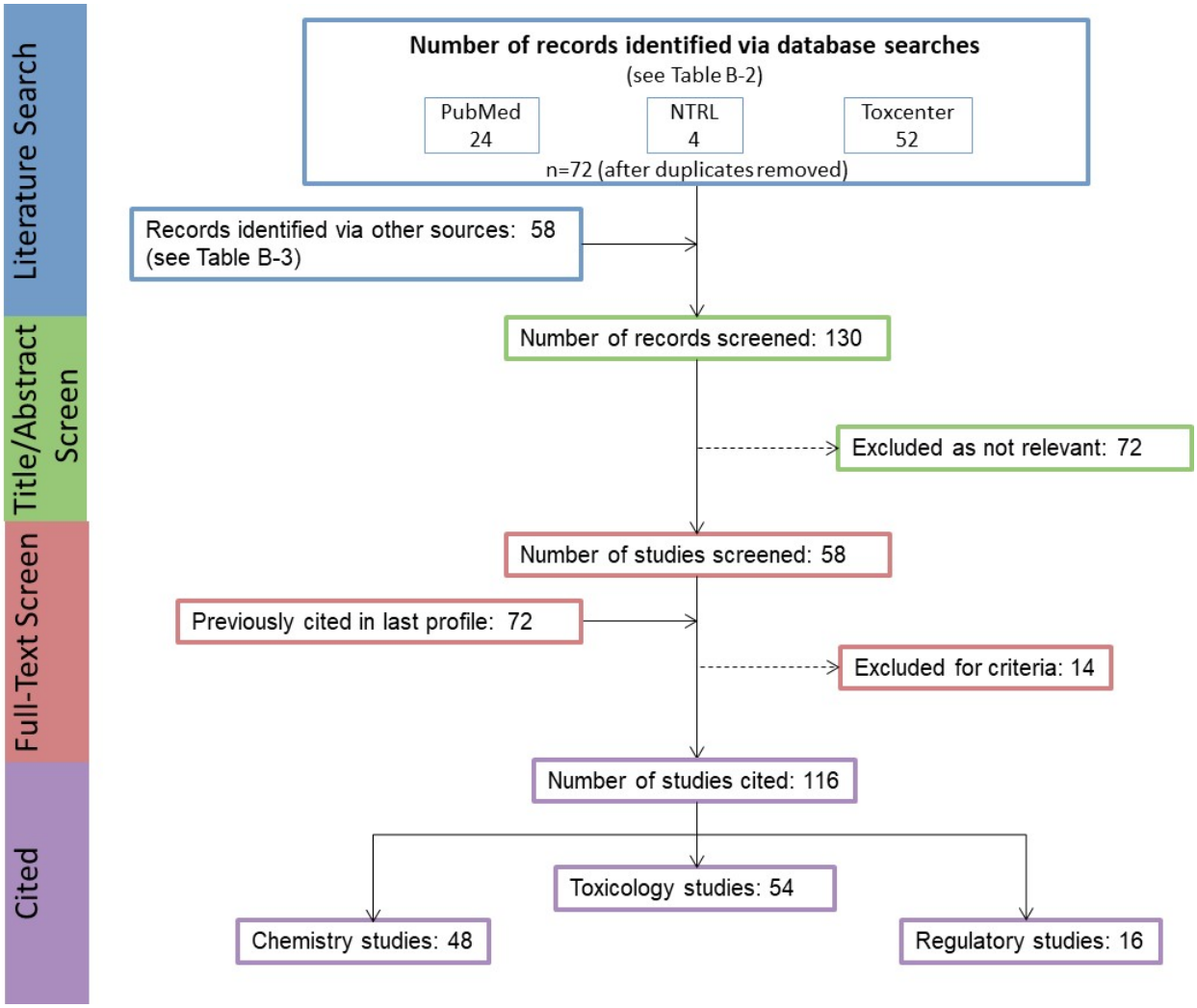
- Number of titles and abstracts screened: 130
- Number of studies considered relevant and moved to the next step: 58

***Full Text Screen.*** The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 58
- Number of studies cited in the pre-public draft of the toxicological profile: 72
- Total number of studies cited in the profile: 116

A summary of the results of the literature search and screening is presented in Figure B-1.

**Figure B-1. March 2020 Literature Search Results and Screen for 1,2,3-Trichloropropane**



# APPENDIX C. USER'S GUIDE

## Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints 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?

### Minimal Risk Levels (MRLs)

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

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance 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. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, 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 endpoint 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 endpoint 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 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 that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

**Chapter 2. 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 and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used 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 tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

**TABLE LEGEND**

**See Sample LSE Table (page C-5)**

(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 figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are 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) Figure key. 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 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, 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.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse 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 endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (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. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

**FIGURE LEGEND**

**See Sample LSE Figure (page C-6)**

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.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in $mg/m^3$ or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX C

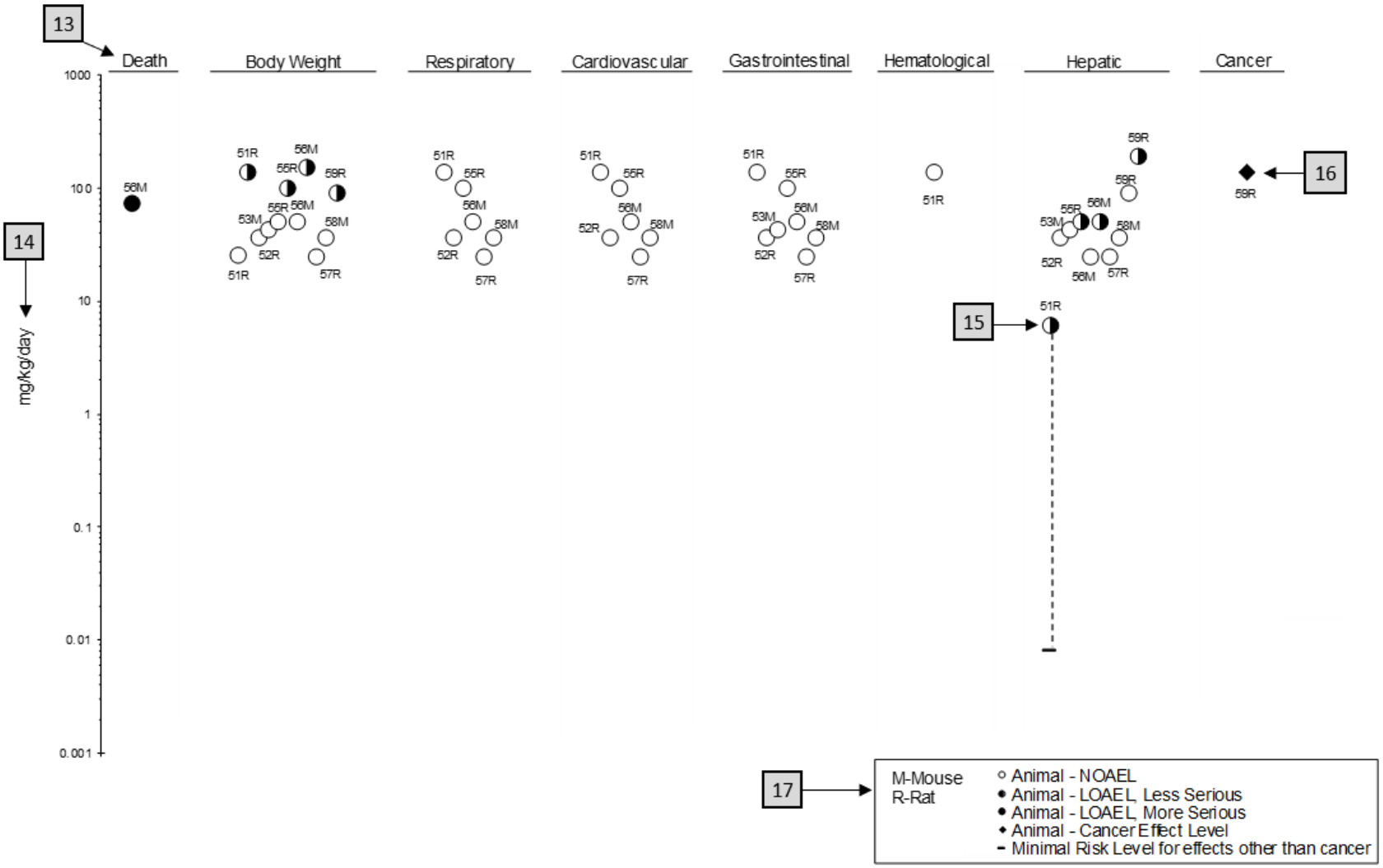
**Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral**

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses (mg/kg/day) | Parameters monitored | Endpoint | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Effect |
|---|---|---|---|---|---|---|---|---|---|
| **CHRONIC EXPOSURE** | | | | | | | | | |
| 51 | Rat (Wistar) 40 M, 40 F | 2 years (F) | M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4 | CS, WI, BW, OW, HE, BC, HP | Bd wt | 25.5 | 138.0 | | Decreased body weight gain in males (23–25%) and females (31–39%) |
| | | | | | Hemato | 138.0 | | | |
| | | | | | Hepatic | | 6.1[c] | | Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure |
| **Aida et al. 1992** | | | | | | | | | |
| 52 | Rat (F344) 78 M | 104 weeks (W) | 0, 3.9, 20.6, 36.3 | CS, BW, FI, BC, OW, HP | Hepatic | 36.3 | | | |
| | | | | | Renal | 20.6 | 36.3 | | Increased incidence of renal tubular cell hyperplasia |
| | | | | | Endocr | 36.3 | | | |
| **George et al. 2002** | | | | | | | | | |
| 59 | Rat (Wistar) 58M, 58F | Lifetime (W) | M: 0, 90 F: 0, 190 | BW, HP | Cancer | | 190 F | | Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided |
| **Tumasonis et al. 1985** | | | | | | | | | |

[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX C

**Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral**



# APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

---

***Primary Chapters/Sections of Interest***

**Chapter 1: Relevance to Public Health**: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

**Chapter 2: Health Effects**: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
***NOTE***: Not all health effects reported in this section are necessarily observed in the clinical setting.

**Pediatrics**:

**Section 3.2 Children and Other Populations that are Unusually Susceptible**
**Section 3.3 Biomarkers of Exposure and Effect**

---

***ATSDR Information Center***

***Phone:*** 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
***Internet***: http://www.atsdr.cdc.gov

The following additional materials are available online:

*Case Studies in Environmental Medicine* are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

*Managing Hazardous Materials Incidents* is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp).

*Fact Sheets (ToxFAQs™)* provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

---

***Other Agencies and Organizations***

*The National Center for Environmental Health* (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

*The National Institute for Occupational Safety and Health* (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

*The National Institute of Environmental Health Sciences* (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

---

***Clinical Resources (Publicly Available Information)***

*The Association of Occupational and Environmental Clinics* (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

*The American College of Occupational and Environmental Medicine* (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

*The American College of Medical Toxicology* (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

*The Pediatric Environmental Health Specialty Units* (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

*The American Association of Poison Control Centers* (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

# APPENDIX E. GLOSSARY

**Absorption—**The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

**Acute Exposure—**Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

**Adsorption—**The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

**Adsorption Coefficient ($K_{oc}$)—**The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

**Adsorption Ratio (Kd)—**The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

**Benchmark Dose (BMD) or Benchmark Concentration (BMC)—**is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a $BMD_{10}$ would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

**Bioconcentration Factor (BCF)—**The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

**Biomarkers—**Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

**Cancer Effect Level (CEL)—**The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

**Carcinogen—**A chemical capable of inducing cancer.

**Case-Control Study—**A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

**Case Report—**A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

**Case Series—**Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

**Ceiling Value—**A concentration that must not be exceeded.

**Chronic Exposure—**Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

**Clastogen—**A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

**Cohort Study—**A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

**Cross-sectional Study—**A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

**Data Needs—**Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

**Developmental Toxicity—**The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

**Dose-Response Relationship—**The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

**Embryotoxicity and Fetotoxicity—**Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

**Epidemiology—**The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

**Excretion—**The process by which metabolic waste products are removed from the body.

**Genotoxicity—**A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

**Half-life—**A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

**Health Advisory—**An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

**Immediately Dangerous to Life or Health (IDLH)—**A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

**Immunotoxicity—**Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

**Incidence—**The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

**Intermediate Exposure—**Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

**Lethal Concentration$_{(LO)}$ ($LC_{LO}$)—**The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

**Lethal Concentration$_{(50)}$ ($LC_{50}$)—**A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose$_{(LO)}$ ($LD_{Lo}$)—**The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

**Lethal Dose$_{(50)}$ ($LD_{50}$)—**The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time$_{(50)}$ ($LT_{50}$)—**A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

**Lowest-Observed-Adverse-Effect Level (LOAEL)—**The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

**Lymphoreticular Effects—**Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

**Malformations—**Permanent structural changes that may adversely affect survival, development, or function.

**Metabolism—**Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

**Minimal Risk Level (MRL)—**An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

**Modifying Factor (MF)—**A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

**Morbidity—**The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

**Mortality—**Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

**Mutagen—**A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

**Necropsy—**The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

**Neurotoxicity—**The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

**No-Observed-Adverse-Effect Level (NOAEL)—**The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

**Octanol-Water Partition Coefficient ($K_{ow}$)—**The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

**Odds Ratio (OR)—**A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

**Permissible Exposure Limit (PEL)—**An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

**Pesticide—**General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

**Pharmacokinetics—**The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

**Pharmacokinetic Model—**A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

**Physiologically Based Pharmacodynamic (PBPD) Model—**A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

**Physiologically Based Pharmacokinetic (PBPK) Model—**A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

**Prevalence—**The number of cases of a disease or condition in a population at one point in time.

**Prospective Study—**A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

**Recommended Exposure Limit (REL)—**A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

**Reference Concentration (RfC)—**An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of $mg/m^3$ or ppm.

**Reference Dose (RfD)—**An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

**Reportable Quantity (RQ)—**The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

**Reproductive Toxicity—**The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

**Retrospective Study—**A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

**Risk—**The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

**Risk Factor—**An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

**Risk Ratio/Relative Risk—**The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

**Short-Term Exposure Limit (STEL)—**A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

**Standardized Mortality Ratio (SMR)—**A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

**Target Organ Toxicity—**This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

**Teratogen—**A chemical that causes structural defects that affect the development of an organism.

**Threshold Limit Value (TLV)—**An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

**Time-Weighted Average (TWA)—**An average exposure within a given time period.

**Toxicokinetic—**The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

**Toxics Release Inventory (TRI)—**The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

**Uncertainty Factor (UF)—**A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

**Xenobiotic—**Any substance that is foreign to the biological system.

# APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

| | |
|---|---|
| AAPCC | American Association of Poison Control Centers |
| ACGIH | American Conference of Governmental Industrial Hygienists |
| ACOEM | American College of Occupational and Environmental Medicine |
| ACMT | American College of Medical Toxicology |
| ADI | acceptable daily intake |
| ADME | absorption, distribution, metabolism, and excretion |
| AEGL | Acute Exposure Guideline Level |
| AIC | Akaike's information criterion |
| AIHA | American Industrial Hygiene Association |
| ALT | alanine aminotransferase |
| AOEC | Association of Occupational and Environmental Clinics |
| AP | alkaline phosphatase |
| AST | aspartate aminotransferase |
| atm | atmosphere |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| AWQC | Ambient Water Quality Criteria |
| BCF | bioconcentration factor |
| BMD/C | benchmark dose or benchmark concentration |
| $BMD_X$ | dose that produces a X% change in response rate of an adverse effect |
| $BMDL_X$ | 95% lower confidence limit on the $BMD_X$ |
| BMDS | Benchmark Dose Software |
| BMR | benchmark response |
| BUN | blood urea nitrogen |
| C | centigrade |
| CAA | Clean Air Act |
| CAS | Chemical Abstract Services |
| CDC | Centers for Disease Control and Prevention |
| CEL | cancer effect level |
| CERCLA | Comprehensive Environmental Response, Compensation, and Liability Act |
| CFR | Code of Federal Regulations |
| Ci | curie |
| CI | confidence interval |
| cm | centimeter |
| CPSC | Consumer Products Safety Commission |
| CWA | Clean Water Act |
| DNA | deoxyribonucleic acid |
| DOD | Department of Defense |
| DOE | Department of Energy |
| DWEL | drinking water exposure level |
| EAFUS | Everything Added to Food in the United States |
| ECG/EKG | electrocardiogram |
| EEG | electroencephalogram |
| EPA | Environmental Protection Agency |
| ERPG | emergency response planning guidelines |
| F | Fahrenheit |
| F1 | first-filial generation |
| FDA | Food and Drug Administration |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| FR | Federal Register |

| | |
|---|---|
| FSH | follicle stimulating hormone |
| g | gram |
| GC | gas chromatography |
| gd | gestational day |
| GGT | γ-glutamyl transferase |
| GRAS | generally recognized as safe |
| HEC | human equivalent concentration |
| HED | human equivalent dose |
| HHS | Department of Health and Human Services |
| HPLC | high-performance liquid chromatography |
| HSDB | Hazardous Substance Data Bank |
| IARC | International Agency for Research on Cancer |
| IDLH | immediately dangerous to life and health |
| IRIS | Integrated Risk Information System |
| Kd | adsorption ratio |
| kg | kilogram |
| kkg | kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton |
| $K_{oc}$ | organic carbon partition coefficient |
| $K_{ow}$ | octanol-water partition coefficient |
| L | liter |
| LC | liquid chromatography |
| $LC_{50}$ | lethal concentration, 50% kill |
| $LC_{Lo}$ | lethal concentration, low |
| $LD_{50}$ | lethal dose, 50% kill |
| $LD_{Lo}$ | lethal dose, low |
| LDH | lactic dehydrogenase |
| LH | luteinizing hormone |
| LOAEL | lowest-observed-adverse-effect level |
| LSE | Level of Significant Exposure |
| $LT_{50}$ | lethal time, 50% kill |
| m | meter |
| mCi | millicurie |
| MCL | maximum contaminant level |
| MCLG | maximum contaminant level goal |
| MF | modifying factor |
| mg | milligram |
| mL | milliliter |
| mm | millimeter |
| mmHg | millimeters of mercury |
| mmol | millimole |
| MRL | Minimal Risk Level |
| MS | mass spectrometry |
| MSHA | Mine Safety and Health Administration |
| Mt | metric ton |
| NAAQS | National Ambient Air Quality Standard |
| NAS | National Academy of Science |
| NCEH | National Center for Environmental Health |
| ND | not detected |
| ng | nanogram |
| NHANES | National Health and Nutrition Examination Survey |
| NIEHS | National Institute of Environmental Health Sciences |

| | |
|---|---|
| NIOSH | National Institute for Occupational Safety and Health |
| NLM | National Library of Medicine |
| nm | nanometer |
| nmol | nanomole |
| NOAEL | no-observed-adverse-effect level |
| NPL | National Priorities List |
| NR | not reported |
| NRC | National Research Council |
| NS | not specified |
| NTP | National Toxicology Program |
| OR | odds ratio |
| OSHA | Occupational Safety and Health Administration |
| PAC | Protective Action Criteria |
| PAH | polycyclic aromatic hydrocarbon |
| PBPD | physiologically based pharmacodynamic |
| PBPK | physiologically based pharmacokinetic |
| PEHSU | Pediatric Environmental Health Specialty Unit |
| PEL | permissible exposure limit |
| PEL-C | permissible exposure limit-ceiling value |
| pg | picogram |
| PND | postnatal day |
| POD | point of departure |
| ppb | parts per billion |
| ppbv | parts per billion by volume |
| ppm | parts per million |
| ppt | parts per trillion |
| REL | recommended exposure level/limit |
| REL-C | recommended exposure level-ceiling value |
| RfC | reference concentration |
| RfD | reference dose |
| RNA | ribonucleic acid |
| SARA | Superfund Amendments and Reauthorization Act |
| SCE | sister chromatid exchange |
| SD | standard deviation |
| SE | standard error |
| SGOT | serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST) |
| SGPT | serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT) |
| SIC | standard industrial classification |
| SLOAEL | serious lowest-observed-adverse-effect level |
| SMR | standardized mortality ratio |
| sRBC | sheep red blood cell |
| STEL | short term exposure limit |
| TLV | threshold limit value |
| TLV-C | threshold limit value-ceiling value |
| 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 |

| | |
|---|---|
| USNRC | U.S. Nuclear Regulatory Commission |
| VOC | volatile organic compound |
| WBC | white blood cell |
| WHO | World Health Organization |

| | |
|---|---|
| > | greater than |
| ≥ | greater than or equal to |
| = | equal to |
| < | less than |
| ≤ | less than or equal to |
| % | percent |
| α | alpha |
| β | beta |
| γ | gamma |
| δ | delta |
| μm | micrometer |
| μg | microgram |
| $q_1^*$ | cancer slope factor |
| – | negative |
| + | positive |
| (+) | weakly positive result |
| (–) | weakly negative result |