APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

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

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, 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: Trichloroethylene
CAS Numbers: 79-01-6
Date: June 2019
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 61, 86
Species: Mouse, Rat

Minimal Risk Level: 0.0004 [ ] mg/kg/day [X] ppm

The ATSDR chronic-duration inhalation MRL of 0.0004 ppm for trichloroethylene was adopted as the ATSDR intermediate-duration inhalation MRL (see chronic-duration inhalation MRL worksheet for more information). The ATSDR chronic-duration inhalation MRL is based, in part, on results of PBPK modeling exercises that simulated 100 weeks of exposure for humans (EPA 2011e). Sample simulations for a 52-week exposure (within the range of an ATSDR-defined intermediate-duration exposure [15–364 days]) resulted in the same internal dose point of departure (idPOD) as the idPOD resulting from simulations for the 100-week exposure.

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Trichloroethylene
CAS Numbers: 79-01-6
Date: June 2019
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 61, 86
Species: Mouse, Rat

Minimal Risk Level: 0.0004 [ ] mg/kg/day [X] ppm

The chronic-duration inhalation MRL is based on the results of two critical oral exposure studies that reported decreased thymus weight in female mice (Keil et al. 2009) and fetal heart malformations in rats (Johnson et al. 2003). In the EPA assessment for trichloroethylene (EPA 2011e), EPA developed a PBPK model, which was used to calculate the idPOD and perform route-to-route extrapolation to human equivalency concentrations (HECs) for these studies. The resulting HEC_{99} values were 0.033 ppm based on thymus weight and 0.0037 ppm based on fetal heart malformations. The HEC_{99} of 0.033 ppm for thymus weight was divided by a total uncertainty factor of 100 (to account for use of a LOAEL and to account for species extrapolation and human variability using a PBPK model); the resulting candidate chronic RfC was 0.00033 ppm. The HEC_{99} of 0.0037 ppm for fetal heart malformations was divided by a total uncertainty factor of 10 (to account for species extrapolation and human variability using a PBPK model); the resulting candidate chronic RfC was 0.00037 ppm. EPA (2011e) selected the midpoint value of the studies (0.0004 ppm, rounded up from 0.00035 ppm) as the chronic RfC for trichloroethylene. ATSDR agreed that this was a reasonable approach. The resulting chronic-duration inhalation MRL is 0.0004 ppm.

Keil et al. (2009)

Reference: Keil DE, Peden-Adams MM, Wallace S, et al. 2009. Assessment of trichloroethylene (TCE) exposure in murine strains genetically-prone and non-prone to develop autoimmune disease. J Environ Sci Health A Tox Hazard Subst Environ Eng 44(5):443-453.

Experimental design: Groups of 9-week-old female B6C3F1 mice (9–10/group) were administered trichloroethylene in the drinking water at 0, 1,400, or 14,000 ppb (1.4 or 14 ppm) in 1% emulphor vehicle for 30 weeks. During the exposure period, serum levels of total IgG and autoantibodies (anti-ssDNA, -dsDNA, and -glomerular antigen [GA]) were monitored. Body weights were recorded 1 day prior to the initiation of trichloroethylene exposure and again at exposure termination. At sacrifice, the spleen, thymus, liver, and kidneys were weighed. Spleen and thymus were processed for assessment of cell counts and activity. Kidneys were processed for histopathologic evaluation; renal pathology was scored by grading glomerular inflammation, crescent formation, and necrosis in histopathology slides.

Effect noted in study and corresponding doses: Decreased thymus weight (30% lower than controls) and increased serum levels of IgG and selected autoantibodies at 1.4 ppm trichloroethylene in the drinking water (EPA-estimated dose of 0.35 mg/kg/day).

Dose and end point used for MRL derivation: A PBPK model was used to calculate the idPOD (idPOD=0.139 mg trichloroethylene metabolized/$kg^{3/4}$/day) from the applied dose LOAEL of 0.35 mg/kg/day. The mouse idPOD was converted to a HEC_{99} (HEC_{99}=0.033 ppm) for lifetime

continuous exposure derived from combined interspecies, intraspecies, and route-to-route extrapolation using the PBPK model for trichloroethylene.

[ ] NOAEL [ ] LOAEL [X] HEC_{99}

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3.16 for extrapolation from animals to humans because a PBPK model was used
[X] 3.16 for human variability because a PBPK model was used to characterize human toxicokinetic variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? EPA estimated doses using the average of subchronic and chronic reference values for generic body weight and water consumption rates for female B6C3F1 mice.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Johnson et al. (2003)

Reference: Johnson PD, Goldberg SY, Mays MZ, et al. 2003. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect 111(3):289-292.

Experimental design: Groups of pregnant Sprague-Dawley rats (9–13/exposure level) were administered trichloroethylene in the drinking water throughout gestation (GDs 1–22) at concentrations of 0, 0.0025, 0.25, 1.5, or 1,000 ppm. At termination on GD 22, dams and fetuses were examined for gross abnormalities and fetuses were weighed, measured for crown-rump length, and sexed. Fetal hearts and great vessels were examined for gross malformations and prepared for histopathologic evaluations.

Effect noted in study and corresponding doses: Increased incidences of fetuses with cardiac malformations at maternal exposure levels ≥0.25 ppm (estimated maternal doses ≥0.048 mg/kg/day).

Dose and end point used for MRL derivation: Using a benchmark response (BMR) of 1% extra risk that was preferred due to accounting for intralitter effects using a nested model, and pups being the unit of measure, EPA (2011e) calculated a rat lower 95% confidence limit on the benchmark dose ($BMDL_{01}$) of 0.0207 mg/kg/day from the fetal heart malformation incidence data. The highest dose group (1,000-fold higher than next highest) was dropped to improve model fit. The rat $BMDL_{01}$ was 0.0207 mg/kg/day. A PBPK model was used to calculate the idPOD of 0.0142 mg trichloroethylene metabolized by oxidation/kg body $weight^{3/4}$/day. The rat idPOD was converted to a HEC_{99} of 0.0037 ppm for continuous lifetime exposure derived from route-to-route extrapolation and combined interspecies and intraspecies extrapolation using the PBPK model.

[ ] NOAEL [ ] LOAEL [X] HEC_{99}

Uncertainty Factors used in MRL derivation:

[X] 3.16 for extrapolation from animals to humans because a PBPK model was used

[X] 3.16 for human variability because a PBPK model was used to characterize human toxicokinetic variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Studies in humans and animals have identified a number of potential targets of trichloroethylene toxicity, including the central nervous system, liver, kidney, immune system, male reproductive system, and the developing fetus. The toxicity of trichloroethylene does not appear to be route-specific; similar effects have been observed following inhalation and oral exposure. The most sensitive toxicity targets appear to be the immune system, the developing fetus, and the kidneys. Immunological effects include alterations in thymus weight and immune function. Decreases in thymus weights were observed in mice exposed to 0.35 mg/kg/day trichloroethylene in drinking water for 30 weeks (Keil et al. 2009) and an impaired response to SRBCs and delayed hypersensitivity were observed in the pups of mice exposed to 0.37 mg/kg/day trichloroethylene in drinking water on GDs 0–21 and for 3 or 8 weeks postpartum (Peden-Adams et al. 2006). At higher doses, other studies have reported increases in splenic lymphocytes (Blossom and Doss 2007) and impaired immune function (Blossom et al. 2008; Sanders et al. 1982). Developmental toxicity studies have demonstrated a number of effects including increases in the occurrence of cardiac malformations in the offspring of rats exposed to 0.048 mg/kg/day trichloroethylene on GDs 0–21 (Johnson et al. 2003) or 0.218 mg/kg/day trichloroethylene in drinking water prior to mating and during gestation (Dawson et al. 1993; Johnson et al. 1998); at higher doses, neurobehavioral effects, decreases in pup body weight, and perinatal mortality have been observed (Manson et al. 1984; NTP 1986; Taylor et al. 1985). Observed renal effects include toxic nephropathy in rats administered via gavage 500 mg/kg trichloroethylene 5 days/week for 2 years (NTP 1988).

EPA employed a PBPK model to calculate an idPOD for plausible internal dose-metrics based on present understanding of the role different trichloroethylene metabolites play in trichloroethylene toxicity and the mode of action for toxicity. The PBPK model was used to estimate interspecies and intraspecies pharmacokinetic variability and resulted in HEC_{99} values for candidate critical effects.

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Trichloroethylene
CAS Numbers: 79-01-6
Date: June 2019
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 54, 56, 69
Species: Mouse, Rat

Minimal Risk Level: 0.0005 [X] mg/kg/day [ ] ppm

The ATSDR chronic-duration oral MRL of 0.0005 mg/kg/day for trichloroethylene was adopted as the ATSDR intermediate-duration oral MRL (see chronic-duration oral MRL worksheet for more information). The ATSDR chronic-duration oral MRL is based, in part, on results of PBPK modeling exercises that simulated 100 weeks of exposure for humans (EPA 2011e). Sample simulations for a 52-week exposure (within the range of an ATSDR-defined intermediate-duration exposure [15–364 days]) resulted in the same idPOD as the idPOD resulting from simulations for the 100-week exposure.

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Trichloroethylene
CAS Numbers: 79-01-6
Date: June 2019
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 54, 56, 69
Species: Mouse, Rat

Minimal Risk Level: 0.0005 [X] mg/kg/day [ ] ppm

The chronic-duration oral MRL is based on the results of three critical oral exposure studies that reported immunotoxicity (decreased plaque-forming cell response and increased delayed-type hypersensitivity) in mice (Peden-Adams et al. 2006), decreased thymus weight in female mice (Keil et al. 2009), and fetal heart malformations in rats (Johnson et al. 2003). In the EPA assessment for trichloroethylene (EPA 2011e), independent candidate chronic RfD values were calculated for each of these effects. The Peden-Adams et al. (2006) immunotoxicity LOAEL of 0.37 mg/kg/day was divided by a total uncertainty factor of 1,000 (to account for use of a LOAEL, interspecies extrapolation, and human variability), resulting in a candidate chronic RfD of 0.00037 mg/kg/day. The Keil et al. (2009) thymus weight LOAEL of 0.35 mg/kg/day was used to derive a PBPK model-based human equivalent dose (HED_{99}) of 0.048 mg/kg/day, which was divided by a total uncertainty factor of 100 (to account for use of a LOAEL, interspecies extrapolation, and human variability using a PBPK model), resulting in a candidate chronic RfD of 0.00048 mg/kg/day. The Johnson et al. (2003) fetal heart malformation data were subjected to benchmark dose analysis. The resulting $BMDL_{01}$ (1% extra risk) of 0.0207 mg/kg/day was used to calculate a PBPK model-based HED_{99} of 0.0051 mg/kg/day, which was divided by a total uncertainty factor of 10 (to account for interspecies extrapolation and human variability using a PBPK model). The resulting candidate chronic RfD was 0.00051 mg/kg/day. EPA (2011e) elected to use a chronic RfD value of 0.0005 mg/kg/day and noted that this value was supported by results for multiple effects. ATSDR agreed that this was a reasonable approach. Therefore, the chronic-duration oral MRL is 0.0005 mg/kg/day.

Peden-Adams et al. (2006)

Reference: Peden-Adams MM, Eudaly JG, Heesemann LM, et al. 2006. Developmental immunotoxicity of trichloroethylene (TCE): studies in B6C3F1 mice. J Environ Sci Health A Tox Hazard Subst Environ Eng 41(3):249-271.

Experimental design: Groups of C3H/HeJ male and C57BL/6N female mice (5/sex/group) were administered trichloroethylene in the drinking water at 0, 1.4, or 14 ppm, beginning at pairing (1:1) and continuing for 7 days of mating and throughout gestation (at least for the dams) and lactation. Pups (strain B6C3F1 is produced from the paired parental strains) were evaluated for body length (crown-rump), and timing of eye opening and ear unfolding. At weaning of the pups at 3 weeks of age, 5–7 pups/treatment group, were weighed and sacrificed to assess kidney, liver, thymus, and spleen weights. Trichloroethylene-related effects on the immune system were assessed by measuring splenic lymphocyte proliferation, NK cell activity, SRBC-specific IgM production (PFC response), splenic B220+ cells, and thymic and splenic T-cell immunophenotypes. The remaining pups (4–5 pups/treatment group) were assessed at 8 weeks of age in a manner similar to those assessed at 3 weeks of age, with additional assessments of autoantibodies to dsDNA and delayed type hypersensitivity response (indicated by foot pad swelling following subcutaneous injection of SRBC).

Effect noted in study and corresponding doses: Decreased PFC response was observed in 3- and 8-week-old pups and increased delayed-type sensitivity was noted in 8-week-old pups at 1.4 and 14 ppm trichloroethylene in the drinking water (author-estimated maternal doses of 0.37 and 3.7 mg/kg/day, respectively).

Dose and end point used for MRL derivation: 0.37 mg/kg/day for decreased PFC response and increased delayed-type sensitivity.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 to account for extrapolation from animals to humans
[X] 10 to account for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses were estimated by the study authors.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Keil et al. (2009)

Reference: Keil DE, Peden-Adams MM, Wallace S, et al. 2009. Assessment of trichloroethylene (TCE) exposure in murine strains genetically-prone and non-prone to develop autoimmune disease. J Environ Sci Health A Tox Hazard Subst Environ Eng 44(5):443-453.

Experimental design: Groups of 9-week-old female B6C3F1 mice (9–10/group) were administered trichloroethylene in the drinking water at 0, 1,400, or 14,000 ppb (1.4 or 14 ppm) in 1% emulphor vehicle for 30 weeks. During the exposure period, serum levels of total IgG and autoantibodies (anti-ssDNA, -dsDNA, and -GA) were monitored. Body weights were recorded 1 day prior to the initiation of trichloroethylene exposure and again at exposure termination. At sacrifice, the spleen, thymus, liver, and kidneys were weighed. Spleen and thymus were processed for assessment of cell counts and activity. Kidneys were processed for histopathologic evaluation; renal pathology was scored by grading glomerular inflammation, crescent formation, and necrosis in histopathology slides.

Effect noted in study and corresponding doses: Decreased thymus weight (30% lower than controls) and increased serum levels of IgG and selected autoantibodies at 1.4 ppm trichloroethylene in the drinking water (EPA-estimated dose of 0.35 mg/kg/day).

Dose and end point used for MRL derivation: A PBPK model was used to calculate the idPOD (idPOD=0.139 mg trichloroethylene metabolized/$kg^{3/4}$/day) from the applied dose LOAEL of 0.35 mg/kg/day. The mouse idPOD was converted to a HED_{99} of 0.048 mg/kg/day for lifetime continuous exposure derived from combined interspecies and intraspecies extrapolation using the PBPK model for trichloroethylene.

[ ] NOAEL [ ] LOAEL [X] HED_{99}

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3.16 for extrapolation from animals to humans because a PBPK model was used
[X] 3.16 for human variability because a PBPK model was used to characterize human toxicokinetic variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? EPA estimated doses using the average of subchronic and chronic reference values for generic body weight and water consumption rates for female B6C3F1 mice.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Johnson et al. (2003)

Reference: Johnson PD, Goldberg SY, Mays MZ, et al. 2003. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect 111(3):289-292.

Experimental design: Groups of pregnant Sprague-Dawley rats (9–13/exposure level) were administered trichloroethylene in the drinking water throughout gestation (GDs 1–22) at concentrations of 0, 0.0025, 0.25, 1.5, or 1,000 ppm. At termination on GD 22, dams and fetuses were examined for gross abnormalities and fetuses were weighed, measured for crown-rump length, and sexed. Fetal hearts and great vessels were examined for gross malformations and prepared for histopathologic evaluations.

Effect noted in study and corresponding doses: Increased incidences of fetuses with cardiac malformations at maternal exposure levels ≥0.25 ppm (estimated maternal doses ≥0.048 mg/kg/day).

Dose and end point used for MRL derivation: Using a BMR of 1% extra risk that was preferred due to accounting for intralitter effects using a nested model, and pups being the unit of measure, EPA (2011e) calculated a rat $BMDL_{01}$ of 0.0207 mg/kg/day from the fetal heart malformation incidence data. The highest dose group (1,000-fold higher than next highest) was dropped to improve model fit. The rat $BMDL_{01}$ was 0.0207 mg/kg/day. A PBPK model was used to calculate the idPOD of 0.0142 mg trichloroethylene metabolized by oxidation/kg body weight$^{3/4}$/day. The rat idPOD was converted to a HED_{99} of 0.0051 mg/kg/day for continuous lifetime exposure derived from combined interspecies and intraspecies extrapolation using the PBPK model for trichloroethylene.

[ ] NOAEL [ ] LOAEL [X] HED_{99}

Uncertainty Factors used in MRL derivation:

[X] 3.16 for extrapolation from animals to humans because a PBPK model was used
[X] 3.16 for human variability because a PBPK model was used to characterize human toxicokinetic variation

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Studies in humans and animals have identified a number of potential targets of trichloroethylene toxicity including the central nervous system, liver, kidney, immune system, male reproductive system, and the developing fetus. The toxicity of trichloroethylene does not appear to be route-specific; similar effects have been observed following inhalation and oral exposure. The most sensitive toxicity targets appear to be the immune system, the developing fetus, and the kidneys. Immunological effects include alterations in thymus weight and immune function. Decreases in thymus weights were observed in mice exposed to 0.35 mg/kg/day trichloroethylene in drinking water for 30 weeks (Keil et al. 2009) and an impaired response to SRBCs and delayed hypersensitivity were observed in the pups of mice exposed to 0.37 mg/kg/day trichloroethylene in drinking water on GDs 0–21 and for 3 or 8 weeks postpartum (Peden-Adams et al. 2006). At higher doses, other studies have reported increases in splenic lymphocytes (Blossom and Doss 2007) and impaired immune function (Blossom et al. 2008; Sanders et al. 1982). Developmental toxicity studies have demonstrated a number of effects including increases in the occurrence of cardiac malformations in the offspring of rats exposed to 0.048 mg/kg/day trichloroethylene on GDs 0–21 (Johnson et al. 2003) or 0.218 mg/kg/day trichloroethylene in drinking water prior to mating and during gestation (Dawson et al. 1993; Johnson et al. 1998); at higher doses, neurobehavioral effects, decreases in pup body weight, and perinatal mortality have been observed (Manson et al. 1984; NTP 1986; Taylor et al. 1985). Observed renal effects include toxic nephropathy in rats administered via gavage 500 mg/kg trichloroethylene 5 days/week for 2 years (NTP 1988).

EPA employed a PBPK model to calculate an idPOD for plausible internal dose-metrics based on present understanding of the role different trichloroethylene metabolites play in trichloroethylene toxicity and the mode of action for toxicity. The PBPK model was used to estimate interspecies and intraspecies pharmacokinetic variability and resulted in HED_{99} values for candidate critical effects.

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

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

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

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

Interpretation of Minimal Risk Levels

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

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. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

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

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

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

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

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures include death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(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 end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

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

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

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

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

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

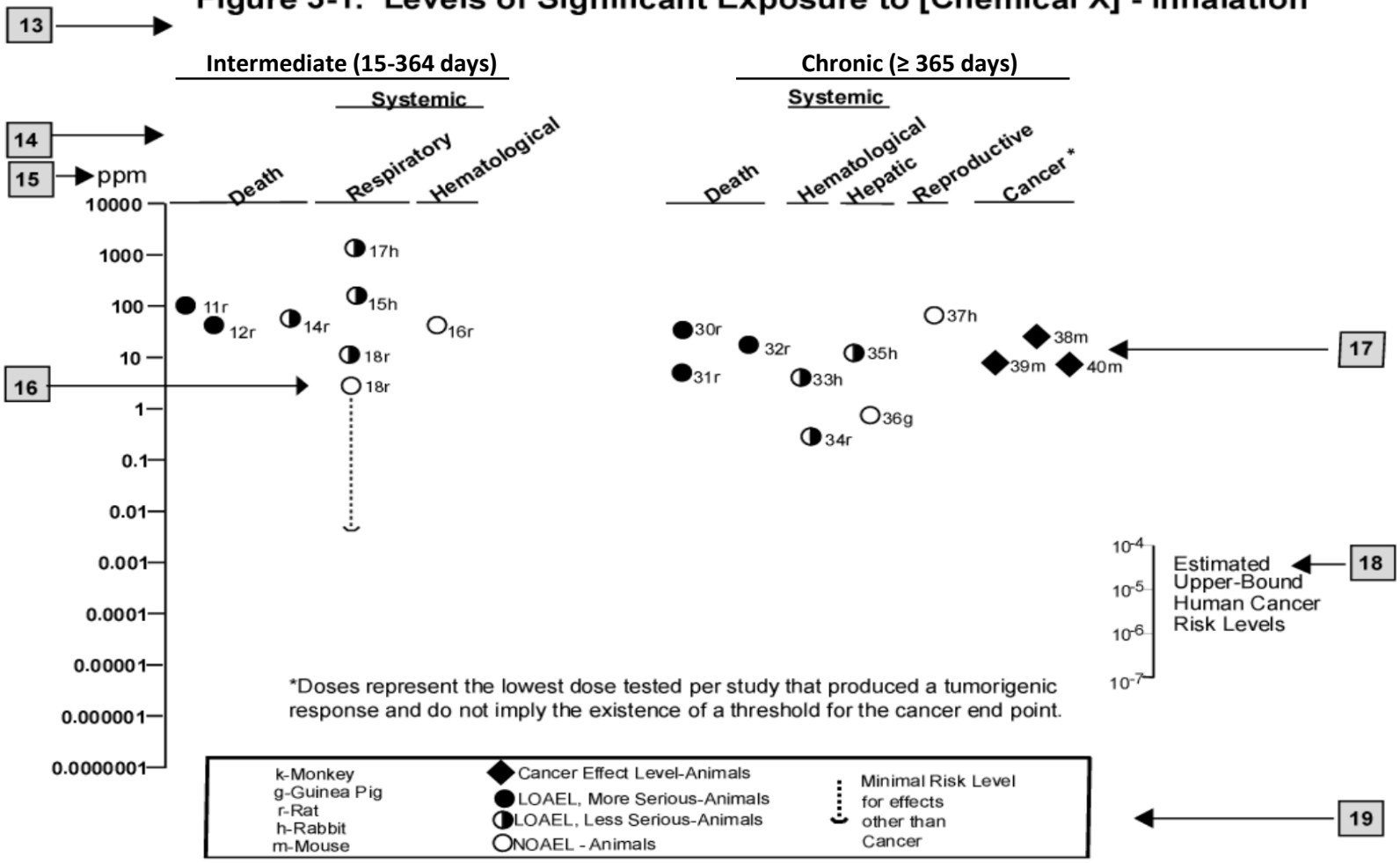
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
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	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

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

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

WHO	World Health Organization

>	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