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 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 MRLs. 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*:** S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 74-48-8
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: Available acute-duration inhalation data were not considered adequate for derivation of an acute-duration inhalation MRL for tribufos.

Rationale for Not Deriving an MRL: No exposure-response human data are available. Available acute-duration inhalation information for tribufos in experimental animals is restricted to a single acute lethality study that reported 4-hour LC_{50} values of 4,650 and 2,460 mg/m^3 for male and female Sprague-Dawley rats, respectively. This study is inadequate for deriving an acute-duration inhalation MRL for tribufos.

Agency Contacts (Chemical Managers): Rae T. Benedict, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 74-48-8
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.04 mg/m^3
Critical Effect: Decreased red blood cell acetylcholinesterase (RBC AChE) activity
Reference: EPA 1992b
Point of Departure: NOAEL of 2.43 mg/m^3 ($NOAEL_{HEC}$ of 1.22 mg/m^3)
Uncertainty Factor: 30
LSE Graph Key: 2
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.04 mg/m^3 has been derived for tribufos based on decreased RBC AChE activity among female Wistar rats exposed to tribufos aerosol for 6 hours/day, 5 days/week for 13 weeks (EPA 1992b). The MRL is based on a $NOAEL_{HEC}$ of 1.22 mg/m^3 and a total uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: No exposure-response human data are available. Available animal data are restricted to a single well-designed of rats intermittently exposed to tribufos aerosol for 13 weeks (EPA 1992b). In the study, decreased RBC AChE activity was the most sensitive effect of tribufos toxicity.

Selection of the Principal Study: The 13-week inhalation study of Wistar rats (EPA 1992b) is the only available intermediate-duration inhalation study. The study monitored multiple parameters and endpoints and thus was considered adequate in design to serve as basis for deriving an intermediate-duration inhalation MRL for tribufos.

Summary of the Principal Study:

EPA. 1992b. Data evaluation report. Study of the subchronic inhalation toxicity to rats in accordance with OECD guideline No. 413; J. Pauluhn; Bayer AG, FRG; Report No: 102697; June 2, 1992; MRID 423998-01.

Groups of Wistar rats (10/sex/group) were exposed (head-only) to tribufos aerosol (MMAD 1.2–1.3 µm) for 6 hours/day, 5 days/week for 13 weeks at nominal concentrations of 0, 1, 2, 12, or 60 mg/m^3 (analytically-determined concentrations of 0, 0.93, 2.43, 12.2, and 59.5 mg/m^3, respectively). Body weights were monitored, and appearance and behavior were evaluated before and after exposure (not during exposure) and on days without exposure. Rectal temperatures were determined for five rats/sex/group monthly immediately following exposure. Blood samples were obtained monthly for hematology and clinical chemistry evaluations. Urine was collected individually during the 12^{th} exposure week for urinalysis. Eye examinations were performed on all rats prior to the first exposure and near the end of the study. Electroretinographic tests were performed on five rats/sex from controls and 59.5 mg/m^3 groups during week 10 and on five rats/sex from controls and each exposure group prior to terminal sacrifice. At necropsy, selected organs and tissues (adrenals, brain, heart, kidneys, liver, lungs, spleen, thymus, thyroid, ovaries, and testes) were removed and weighed. Histopathological examinations were performed on samples from all major organs and tissues.

The most sensitive effect of repeated inhalation exposure to tribufos was that of decreased RBC AChE activity at various time points during the 13-week study. There were no tribufos exposure-related deaths or signs of morbidity. Three rats were sacrificed or died as a result of nontreatment-related causes. Clinical signs were noted in all rats of the 59.5 mg/m^3 exposure group and included altered gait, decreased movement, changes in respiration, narrowed eyelids, constricted pupils, piloerection and unpreened coat, aggressive behavior, sensitivity to touch, convulsions with spastic head movements, salivation, exophthalmos (abnormal protrusion of eyeballs), and hypothermia. No clinical signs were observed at lower tribufos exposure levels. There were no exposure-related adverse effects on body weight, hematology, urinalysis, or clinical chemistry assessments, with the exception of RBC and brain AChE activity in males (Table A-1) and females (Table A-2). In male rats, significantly lower RBC AChE activity was observed in the 1 mg/m^3 exposure group (27% less than controls) at week 0 (but not at other time points) and in the 2.43 mg/m^3 exposure group (26 and 21% less than controls at exposure weeks 0 and 8, respectively, but not at other time points); these results are considered spurious and not related to tribufos exposure. Significantly decreased RBC AChE activity was noted for all time points (weeks 0, 4, 8, 12, and 13) among 12.2 mg/m^3 male and female rats (25–65% less than controls) and 59.5 mg/m^3 (49–91% less than controls). At sacrifice, brain AChE activity among male and female rats was significantly decreased only at the 59.5 mg/m^3 exposure level (40% less than controls). Treatment-related 20–59% RBC AChE inhibition is considered to represent a less serious adverse effect and ≥60% inhibition is considered to represent a serious adverse effect in the absence of more clear indicators of neurotoxicity (Chou and Williams-Johnson 1998). Ophthalmological examinations revealed no signs of tribufos exposure-related effects. However, at the 59.5 mg/m^3 exposure level, male and female rats exhibited significantly depressed amplitude of a- and b-waves in electroretinographic testing, which was considered a tribufos-induced adverse effect. Male rats of the 59.5 mg/m^3 exposure level exhibited significantly increased mean absolute and relative adrenal weight and significantly increased cortical fat deposition in the adrenals (magnitudes not included in the available DER). Minor changes in histology of the nasal and paranasal cavities and lungs were noted across all groups and were considered related to inhalation of vehicle rather than tribufos.

Table A-1. Effect of Tribufos Aerosol on RBC and Brain AChE Activity in Male Wistar Rats Exposed for 6 Hours/Day, 5 Days/Week for 13 Weeks

Exposure parameters			
Testing week	Exposure level (mg/m^3)	Mean RBC AChE activity in kU/L (change from controls)	Mean brain AChE activity in U/g (change from controls)
0	0	1.44	NA
	0.93	1.05 (-27%)[a]	NA
	2.43	1.06 (-26%)[b]	NA
	12.2	0.92 (-36%)[c]	NA
	59.5	0.63 (-56%)[c]	NA
4	0	0.74	NA
	0.93	0.63 (-15%)	NA
	2.43	0.64 (-14%)	NA
	12.2	0.37 (-50%)[c]	NA
	59.5	0.09 (-88%)[c]	NA
8	0	0.78	NA
	0.93	0.69 (-12%)	NA
	2.43	0.62 (-21%)[b]	NA
	12.2	0.35 (-55%)[c]	NA
	59.5	0.08 (-90%)[c]	NA
12	0	1.18	NA
	0.93	1.15 (-3%)	NA
	2.43	1.11 (-6%)	NA
	12.2	0.45 (-62%)[c]	NA
	59.5	0.13 (-89%)[c]	NA
13	0	0.80	12.01
	0.93	0.76 (-5%)	11.78 (-2%)
	2.43	0.64 (-20%)	12.23 (+2%)
	12.2	0.28 (-65%)[c]	11.78 (-2%)
	59.5	0.15 (-81%)[c]	7.15 (-40%)[c]

[a]Not statistically significantly different from control.
[b]Statistically significantly different from control ($p \leq 0.05$), but considered spurious due to lack of significant change at other time points.
[c]Statistically significantly different from control ($p \leq 0.01$).

AChE = acetylcholinesterase; kU = kiloU, where U = a measure of enzymatic activity (1 U = amount of an enzyme that catalyzes the conversion of 1 µmol of substrate per minute); NA = not applicable; RBC = red blood cell

Source: EPA 1992b

Table A-2. Effect of Tribufos Aerosol on RBC and Brain AChE Activity in Female Wistar Rats Exposed for 6 Hours/Day, 5 Days/Week for 13 Weeks

Exposure parameters			
Testing week	Exposure level (mg/m^3)	Mean RBC AChE activity in kU/L (change from controls)	Mean brain AChE activity in U/g (change from controls)
0	0	1.32	NA
	0.93	1.20 (-9%)	NA
	2.43	1.35 (+2%)	NA
	12.2	0.99 (-25%)[a]	NA
	59.5	0.67 (-49%)[b]	NA
4	0	0.90	NA
	0.93	0.91 (+1%)	NA
	2.43	0.96 (+5%)	NA
	12.2	0.36 (-60%)[b]	NA
	59.5	0.17 (-81%)[b]	NA
8	0	0.62	NA
	0.93	0.65 (+5%)	NA
	2.43	0.69 (+11%)	NA
	12.2	0.32 (-48%)[b]	NA
	59.5	0.07 (-89%)[b]	NA
12	0	1.09	NA
	0.93	1.10 (+1%)	NA
	2.43	1.14 (+5%)	NA
	12.2	0.41 (-62%)[a]	NA
	59.5	0.10 (-91%)[b]	NA
13	0	0.92	11.69
	0.93	0.93 (+1%)	11.87 (+2%)
	2.43	0.81 (-12%)	11.64 (-0%)
	12.2	0.33 (-64%)[b]	11.45 (-2%)
	59.5	0.12 (-87%)[b]	6.99 (-40%)[b]

[a]Statistically significantly different from control ($p \leq 0.05$).
[b]Statistically significantly different from control ($p \leq 0.01$).

AChE = acetylcholinesterase; kU = kiloU, where U = a measure of enzymatic activity (1 U = amount of an enzyme that catalyzes the conversion of 1 µmol of substrate per minute); NA = not applicable; RBC = red blood cell

Source: EPA 1992b

Selection of the Point of Departure for the MRL: The most sensitive effect of repeated inhalation exposure to tribufos was that of decreased RBC AChE activity at various time points during the 13-week study. Benchmark dose (BMD) analysis of the critical effect dataset (RBC AChE activity) was performed on the datasets for RBC AChE activity in the male and female rats at the 13-week timepoint. Although the publicly-available DER (EPA 1992b) of the unpublished study included only mean values for RBC AChE activity without a measure of variance, standard deviation values were reported in the unpublished study (MRID42399801). All available continuous variable models in EPA's Benchmark Dose Software

(BMDS, Version 3.1.1) were fit to the data for RBC AChE activity in the male and female rats separately using a benchmark response (BMR) of 20% change from controls.

None of the models provided adequate fit to the modeled variance ($p<0.05$) for males or females using either constant or nonconstant variance. Therefore, a BMD approach to deriving an intermediate-duration inhalation MRL was not used. However, an intermediate-duration inhalation MRL for tribufos can be derived using a NOAEL/LOAEL approach. The principal study identified a NOAEL of 2.43 mg/m^3 and a serious LOAEL of 12.2 mg/m^3 for >60% decreased RBC AChE activity in male and female Wistar rats. The NOAEL (2.43 mg/m^3) serves as the point of departure (POD) for deriving an intermediate-duration inhalation MRL for tribufos.

Adjustment for Intermittent Exposure: The NOAEL of 2.43 mg/m^3 was adjusted from intermittent to continuous exposure as follows:

$NOAEL_{ADJ}$ = 2.43 mg/m^3 x 6 hours/24 hours x 5 days/7days = 0.43 mg/m^3

Human Equivalent Concentration: A regional deposited dose ratio ($RDDR_{ER}$) of 2.839 for extrarespiratory effects (RBC AChE inhibition) in female Wistar rats (slightly lower than the $RDDR_{ER}$ of 2.926 for the males and therefore considered slightly more protective) was used to extrapolate from rats to humans. The $RDDR_{ER}$ was calculated using EPA's software (Version 2.3) (EPA 1994) for calculating RDDRs and the parameters listed in Table A-3.

Table A-3. Parameters[a] Used to Calculate the Regional Deposited Dose Ratio ($RDDR_{ER}$) for Tribufos-induced Extrarespiratory Effects Using EPA's Software (Version 2.3) and $RDDR_{ER}$ Values for Male and Female Wistar Rats

	Wistar rat		
Biological parameters[b]	Male	Female	Human
Surface area			
Extrathoracic	15 cm^2	15 cm^2	200 cm^2
Tracheobronchial	22.5 cm^2	22.5 cm^2	3,200 cm^2
Pulmonary	0.34 m^2	0.34 m^2	54 m^2
Minute ventilation	122.1 mL	160.1	147.24 mL
Body weight	217 g	156 g	70 kg
$RDDR_{ER}$	2.926	2.839	–

[a]Mass median aerodynamic diameter (MMAD) =1.2 µm; geometric standard deviation =1.4 µm (EPA 1992b).
[b]Parameters are default values for rats and humans from the U.S. Environmental Protection Agency (EPA) software, except for default subchronic body weights for male and female Wistar rats (EPA 1988) because quantitative body weight data were not included in the available DER (EPA 1992b).

Source: EPA 1992b

The human equivalent concentration was calculated using Equation 4-5 (EPA 1994) as follows:

$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x $RDDR_{ER}$ = 0.43 mg/m^3 x 2.839 = 1.22 mg/m^3

Uncertainty Factor: The $NOAEL_{HEC}$ of 1.22 mg/m^3 was divided by a total uncertainty factor of 30:

- 3 for extrapolation from animals to humans using dosimetric adjustment
- 10 for human variability

MRL = $NOAEL_{HEC}$ ÷ uncertainty factors
1.22 mg/m^3 ÷ (3 x 10) = 0.04 mg/m^3

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Available animal studies that evaluated the effects of intermediate-duration oral exposure to tribufos identified decreased RBC AChE activity as the most sensitive effect of tribufos toxicity (Astroff et al. 1998; CalEPA 2004; EPA 1991b, 1992c, 2005a, 2013).

Agency Contacts (Chemical Managers): Rae T. Benedict, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 74-48-8
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: No human or animal data were located regarding health effects from chronic-duration inhalation exposure to tribufos.

Rationale for Not Deriving an MRL: No chronic-duration inhalation data are available.

Agency Contacts (Chemical Managers): Rae T. Benedict, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 74-48-8
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: Available acute-duration oral data were not considered adequate for derivation of an acute-duration inhalation MRL for tribufos.

Rationale for Not Deriving an MRL: No human data are available. Acute-duration oral animal studies evaluated body weight, clinical signs, AChE activity, reproductive, and/or developmental endpoints (Astroff and Young 1998; EPA 1990b, 1990c, 2012a, 2012b, 2012c, 2012d, 2012e, 2012f). The lowest LOAEL for tribufos-mediated body weight effects was 9 mg/kg/day in a rabbit study (EPA 1990c). NOAELs for developmental endpoints in rat and rabbit studies ranged from 7 to 28 mg/kg/day (Astroff and Young 1998; EPA 1990b, 1990c, 2012f). Collectively, the acute-duration oral studies identified decreased RBC AChE activity as the most sensitive tribufos-mediated effect from acute-duration oral exposure. Table A-4 summarizes NOAELs and LOAELs for tribufos-mediated effects on RBC AChE activity following intermediate-duration oral exposure. The rabbit study (EPA 1990c) identified the lowest LOAEL (1 mg/kg/day) for tribufos-induced RBC AChE inhibition. The effect occurred at the lowest dose tested and represented a serious effect (>60% RBC AChE inhibition). ATSDR does not derive an MRL based on a serious LOAEL in the absence of an identified NOAEL. Results from available rat studies were not considered appropriate PODs for deriving an acute-duration oral MRL for tribufos because they identified LOAELs at doses ≥5 times higher than the serious LOAEL from the rabbit study in the absence of NOAELs. Therefore, ATSDR elected not to derive an acute-duration oral MRL for tribufos.

Table A-4. NOAELs and LOAELs for RBC AChE Inhibition Following Acute-Duration Oral Exposure to Tribufos

Study design (doses in mg/kg/day)	Dose (RBC AChE % inhibition) NOAEL[a]	LOAEL[b]	Serious LOAEL[c]	Reference
Young adult female Sprague-Dawley rats GO, 1 time (0, 80)	ND	ND	80 (up to 90%)	EPA 2012c
Young adult female Sprague-Dawley rats GO, 1 time (0, 2, 10, 80)	10	ND	80 (74%)	EPA 2012d
11-Day-old Sprague-Dawley rat pups GO, 1 time (0, 50)	M: ND F: ND	M: ND F: ND	M: 50 (90%) F: 50 (92%)	EPA 2012b
11-Day-old Sprague-Dawley rat pups GO, 1 time (0, 20, 40, 50)	M: ND F: ND	M: 20 (59%) F: ND	M: 40 (76%) F: 20 (71%)	EPA 2012a
11-Day-old Sprague-Dawley rat pups GO, 1 time (0, 2, 10, 50)	M: 2 F: ND	M: 10 (47%) F: 2 (27%)	M: 50 (86%) F: 50 (89%)	EPA 2012d
Young adult female Sprague-Dawley rats GO, 1 time/day, 11 days (0, 0.1, 1, 5)	1	ND	5 (64%)	EPA 2012e
11-Day-old Sprague-Dawley rat pups GO, 1 time/day, 11 days (0, 0.1, 1, 5)	M: 1 F: 1	M: ND F: ND	M: 5 (66%) F: 5 (69%)	EPA 2012e
11-Day-old Sprague-Dawley rat pups GO, 1 time/day, 11 days (0, 5, 10, 15, 20)	M: ND F: ND	M: 5 (49%) F: 5 (36%)	M: 15 (83%) M: 15 (66%)	EPA 2012a
Pregnant Sprague-Dawley rats, G, 1 time/day, GDs 6–15 (0, 1, 7, 28)	1	ND	7 (71%)	Astroff and Young 1998; EPA 1990b
Pregnant Sprague-Dawley rats GO, 1 time/day GDs 6–19 (0, 0.3–0.8, 7, 28)	0.3[d]	ND	7 (75%)	EPA 2012f
Pregnant American Dutch rabbits G, 1 time/day, GDs 7–19 (0, 1, 3, 9)	ND	ND	1 (70%)	EPA 1990c

[a]<20% decrease in RBC and/or brain AChE represents a NOAEL.
[b]20–59% decrease in RBC and/or brain AChE activity represents a less serious adverse effect.
[c]≥60% decrease in RBC and/or brain AChE activity represents a serious adverse effect.
[d]Low test substance concentrations measured in the 1 mg/kg/day dose group resulted in estimated time-weighted average dosing in the range of 0.3–0.8 mg/kg/day; using a conservative approach, the lowest dose in the range is considered the NOAEL.

AChE = acetylcholinesterase; F = females; G = gavage; GD = gestation day; GO = gavage in oil; LOAEL = lowest-observed-adverse-effect level; M = males; ND = not determined; NOAEL = no-observed-adverse-effect level; RBC = red blood cell

Agency Contacts (Chemical Managers): Rae T. Benedict, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 74-48-8
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.003 mg/kg/day
Critical Effect: Decreased red blood cell acetylcholinesterase (RBC AChE) activity
Reference: Astroff et al. 1998; EPA 1992c
Point of Departure: NOAEL of 0.28 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 14
Species: Rat

MRL Summary: An intermediate-duration oral MRL of 0.003 mg/kg/day has been derived for tribufos based on decreased RBC AChE activity in Sprague-Dawley rats administered tribufos in the diet in a 2-generation toxicity study (Astroff et al. 1998; EPA 1992c). The MRL is based on a NOAEL of 0.28 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Potential candidate critical effects for deriving an intermediate-duration oral MRL for tribufos are summarized in Table A-5. Quantitative data were not available for the reported hematological effects in the rat study summarized by CalEPA (2004) and EPA (1992d). Therefore, the neurological effect (tribufos-mediated decreased RBC AChE activity) was selected as the critical effect for deriving an intermediate-duration oral MRL for tribufos.

Table A-5. Summary of Potential Candidate Critical Effects for Deriving an Intermediate-Duration Oral MRL for Tribufos from Dietary Studies

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hematological effects					
Fischer 344 rat	3- and 6-month evaluations in 2-year study	0.2 M 0.2 F	1.8 M 2.3 F	Decreases in RBC count, hemoglobin, hematocrit (quantitative data not available)	CalEPA 2004; EPA 1992d
Neurological effects					
Sprague-Dawley rat	2 generations (premating–lactation)	F0 M: 0.28 F0 F: 0.31	F0 M: 2.00 F0 F: 2.25	35 and 37% decreased RBC AChE activity in F0 males and females, respectively, during premating	Astroff et al. 1998; EPA 1992c

Table A-5. Summary of Potential Candidate Critical Effects for Deriving an Intermediate-Duration Oral MRL for Tribufos from Dietary Studies

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Han Wistar rat	4 weeks	0.43	4.32	66% decreased RBC AChE activity (serious LOAEL)	EPA 2013
Wistar rat	42 days (GD 0–LD 21)	0.4	3.4	76% decreased RBC AChE activity (serious LOAEL)	EPA 2005a
CD-1 mouse	8 weeks	3.4 M 5.6 F	9.4 M 14.3 F	37 and 44% decreased RBC AChE activity in males and females, respectively	CalEPA 2004
Beagle dog	364 days	0.4 M 0.4 F	1.7 M 2.0 F	24 and 29% decreased RBC AChE activity in males and females, respectively	EPA 1991b

AChE = acetyl cholinesterase; F = female(s); GD = gestation day; LD = lactation day; LOAEL = lowest observed adverse effect level; M = male(s); NOAEL = no-observed-adverse-effect level; RBC = red blood cells

Selection of the Principal Study: The 364-day dietary study in dogs (CalEPA 2004; EPA 1991b) and the 2-generation dietary study in rats (Astroff et al. 1998; EPA 1992c) identified similar LOAEL values (1.7 mg/kg/day for male dogs versus 2.0 and 2.09 mg/kg/day for the F0 and F1 male rats, respectively). The NOAEL for the F0 and F1 male rats (0.28 mg/kg/day) was slightly lower than the NOAELs for the F0 and F1 female rats (0.31 mg/kg/day) and the male dogs (0.4 mg/kg/day). Furthermore, the rat study employed more animals per dose group than the dog study (10 rats/sex/dose versus 4 dogs/sex/dose). Therefore, the 2-generation rat study was selected as the principal study for deriving an intermediate-duration oral MRL for tribufos.

Summary of the Principal Study:

Astroff AB, Freshwater KJ, Eigenberg DA. 1998. Comparative organophosphate-induced effects observed in adult and neonatal Sprague-Dawley rats during the conduct of multigeneration toxicity studies. Reprod Toxicol 12(6):619-645.

EPA. 1992c. A two-generation dietary reproduction study in rats using tribufos (DEF). D.A. Eigenberg, Mobay, Corporate Toxicology Department, study number 88-971-AK; Sept 10, 1991. MRID 420401-01. Memorandum. Tribufos (DEF) reproduction studies. U.S. Environmental Protection Agency.

Groups of Sprague-Dawley rats (30/sex/group) were administered tribufos in the diet for 10 weeks prior to mating and up to 21 or 28 days of mating, and throughout 3 weeks of gestation (F0 males and females) and 3 weeks of lactation (F0 females) at concentrations of 0, 4, 32, or 260 ppm. Groups of F1 offspring (30/sex/group) were continued on the same treatment schedule as their parents to produce F2 weanlings. Parental rats were monitored for clinical signs, body weight, and food consumption. Estrous cyclicity was evaluated in selected female parental rats. At sacrifice (F0 and F1 parental males following delivery of F1 and F2 litters, respectively; F0 and F1 parental females at F1 and F2 pup weaning, respectively), parental rats were subjected to comprehensive gross pathological examination; histopathological examinations were performed on reproductive organs and tissues, pituitary, and gross lesions. Plasma ChE and RBC AChE activities were determined from 10 parental rats/sex from each generation at 56 days (F0) and 62 days (F1) of premating tribufos treatment and again at terminal sacrifice, at which time brain tissue was removed and processed for brain AChE activity determination. F1 pups surviving to lactation

day 21 and all F2 pups were monitored periodically for body weight during the lactation period. F1 litters were culled to four pups/litter on lactation day 4. Plasma ChE activity and RBC and brain AChE activities were determined for one F1 and one F2 pup of each sex from each of 10 litters at lactation days 4 and 21. Selected reproductive endpoints, fertility, and fetal and pup viability were evaluated.

The study authors calculated tribufos doses (reported in Astroff et al. 1998) based on dietary concentrations, food intake, and body weight data. At dietary concentrations of 4, 32, and 260 ppm, author-calculated tribufos doses to F0 parental rats were 0.28, 2.0, and 17.6 mg/kg/day, respectively, for the males and 0.31, 2.25, and 20.04 mg/kg/day, respectively, for the females during pre-mating treatment. Calculated doses to dams were 0.27, 2.03, and 18.07 mg/kg/day, respectively, during gestation and 0.81, 6.13, and 42.23 mg/kg/day, respectively, during lactation. Author-calculated tribufos doses to F1 parental rats were 0.28, 2.09, and 20.63 mg/kg/day, respectively, for the males, and 0.31, 2.40, and 22.93 mg/kg/day, respectively, for the females during pre-mating treatment. Calculated doses to the F1 dams were 0.28, 2.08, and 19.03 mg/kg/day, respectively, during gestation and 0.84, 6.77, and 49.61 mg/kg/day, respectively, during lactation.

There were no remarkable clinical signs or gross or histopathologic findings among adults or pups of either generation. Body weight was not affected in male or female F0 parental rats during the premating phase. Gestational body weight of high-dose F0 dams was 7% lower than that of controls on GD 20; maternal body weight was decreased by 8–12% throughout the lactation period and was accompanied by decreased maternal food consumption (approximately 20% less than that of controls). Significantly lower mean body weights were observed in high-dose F1 parental rats during the 10-week pre-mating phase (quantitative data for F1 males were not presented in the available DER). The high-dose F1 dams exhibited approximately 25% lower mean body weight than controls at the beginning of the pre-mating phase, which decreased in magnitude to approximately 8% less than controls at the end of the pre-mating period. During gestation, the high-dose mean maternal body weight was significantly lower (approximately 6% less than that of controls) only at the end of gestation. During lactation, the high-dose F1 dam mean body weight was significantly less (approximately 10%) than that of controls at all time periods and was accompanied by significantly decreased maternal food consumption during lactation weeks 2 and 3 (magnitude not specified; however, appears to have been approximately 10%). High-dose F1 pup mean body weight ranged from 11% lower than that of controls on lactation day 0 to 21–30% lower on lactation days 4–21, which may reflect decreased gestational body weight and decreased food consumption of the high-dose parental dams during lactation. High-dose F1 pup mean body weight gain during lactation was 32% less than that of controls. High-dose F2 pup mean body weight was significantly less (approximately 14–22%) than that of controls during lactation days 7–21, which may reflect, in part, decreased gestational body weight, decreased food consumption of the high-dose parental F1 dams during lactation, and/or decreased quality of rat milk produced during lactation. High-dose F2 pup mean body weight gain during lactation was approximately 25% less than that of controls.

The high-dose F0 dams exhibited significantly lower indices for gestation, birth, viability, and lactation. Mean litter size was significantly lower than that of controls. The high-dose F1 dams exhibited significantly lower indices for birth, viability, and lactation. The significant effects on reproduction, fertility, and pup viability and body weight occurred at a dose level resulting in significantly lower mean body weight and food consumption among the F0 dams during gestation and lactation and the F1 dams from pre-mating through lactation.

Decreased plasma ChE activity was observed in low-dose F0 females, mid-dose F0 males and females and F1 parental females, and high-dose F0 and F1 parental males and females. Among pups, effects on plasma ChE were limited to mid- and high-dose F1 male and female pups, mid- and high-dose F2 male pups, and high-dose F2 female pups.

Mid- and high-dose F0 and F1 parental rats exhibited significantly decreased RBC AChE activity (26–53% less than that of controls). At terminal sacrifice, significantly decreased brain AChE activity (29–35% less than that of controls) was noted in mid-dose F0 and F1 parental rats. At the high-dose level, brain AChE activity was decreased by 33–35% in F0 and F1 parental males and by 80% in F0 and F1 parental females. Toxicologically significant decreases in pup AChE activity were restricted to high-dose groups at sacrifice on lactation day 21 and included 24% decreased RBC AChE activity in F2 males and 23 and 38% decreased RBC AChE activity in high-dose F1 and F2 females, respectively.

Selection of the Point of Departure for the MRL: The dataset for the F0 male rats was considered preferable to the dataset for the F1 male rats because it represented the greatest magnitude of RBC AChE inhibition at the lowest LOAEL (35% inhibition at 2.0 mg/kg/day for F0 males versus 26% inhibition at 2.09 mg/kg/day for the F1 males). A BMD modeling approach was considered to identify a potential POD for deriving an intermediate-duration oral MRL for tribufos based on the results from the F0 male rats of the 2-generation study. For BMD analysis, mean RBC AChE activity data (Table A-6) were fit to continuous models in EPA's BMDS (version 3.1.1) using a BMR of 20% decrease from control. The following procedure for fitting continuous data was used. Adequate model fit was judged by three criteria: χ^2 goodness-of-fit p-value ($p \geq 0.1$), visual inspection of the dose-response curve, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. Among models providing adequate fit to the data, the lowest BMDL was selected as the POD when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was chosen.

Table A-6. Day 56 RBC AChE Activity in F0 Male Sprague-Dawley Rats Administered Tribufos in the Diet from 10 Weeks Prior to Mating to Delivery of F1 Pups

Concentration in food (ppm)	0	4	32	260
Dose (mg/kg/day)	0	0.28	2	17.6
Number of rats	10	10	10	10
Mean RBC AChE activity (IU/mL)	2.85	2.83	1.96[a]	1.35[a]
Standard deviation	0.16	0.17	0.09	0.04

[a]Significantly different from control ($p<0.05$).

AChE = acetylcholinesterase; RBC = red blood cell

Source: Astroff et al. 1998; EPA 1992c

BMD analysis of the datasets for the F0 male rats from the 2-generation dietary study (Astroff et al. 1998; EPA 1992c) resulted in inadequate fit using either constant variance or nonconstant variance. Therefore, a NOAEL/LOAEL approach was applied to derive an intermediate-duration oral MRL for tribufos. The NOAEL of 0.28 mg/kg/day for the F0 male rats was selected as the POD.

Adjustment for Intermittent Exposure: Not applicable

Uncertainty Factor: The NOAEL of 0.28 mg/kg/day was divided by a total uncertainty factor of 100:

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

MRL = NOAEL ÷ uncertainty factors
0.28 mg/kg/day ÷ (10 x 10) = 0.003 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The selection of the NOAEL of 0.28 mg/kg/day for F0 male rats of the principal study (Astroff et al. 1998; EPA 1992c) as basis for an intermediate-duration oral MRL for tribufos is supported by results from several studies (Table A-5).

Agency Contacts (Chemical Managers): Rae T. Benedict, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** S,S,S-Tributyl phosphorotrithioate (Tribufos)
CAS Numbers: 74-48-8
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 0.0005 mg/kg/day
Critical Effect: Vacuolar degeneration in small intestines
Reference: CalEPA 2004; EPA 1992d
Point of Departure: $BMDL_{10}$ of 0.05 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 20
Species: Rat

MRL Summary: A chronic-duration oral MRL of 0.0005 mg/kg/day has been derived for tribufos based on vacuolar degeneration in the small intestines of Fischer 344 rats administered tribufos in the diet for 2 years (CalEPA 2004; EPA 1992d). The MRL is based on a $BMDL_{10}$ of 0.05 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Chronic-duration oral studies of mice and rats identified tribufos-mediated effects on red blood cell acetylcholinesterase (RBC AChE) activity and nonneoplastic lesions in the small intestine as the most sensitive effects. Table A-7 summarizes NOAELs and LOAELs for these tribufos-mediated effects. Based on NOAELs and LOAELs, rats appear to be more sensitive than mice to tribufos toxicity following oral exposure. Therefore, the rat data were considered the more appropriate species for consideration of MRL derivation. In the rat study, the lowest LOAEL is 1.8 mg/kg/day for tribufos-induced RBC AChE inhibition and for histopathologic lesions in the small intestines. Therefore, tribufos-mediated histopathologic intestinal lesions and RBC AChE inhibition in the rats were initially selected to represent critical effects for deriving a chronic-duration oral MRL for tribufos. Although selected hematological values in the 1.8 mg/kg/day dose group of rats were significantly different from those of controls at interim evaluation, at least some values had returned to normal at 2 years. Therefore, hematological changes were not considered as a basis for MRL derivation.

Table A-7. NOAELs and LOAELs for RBC AChE Activity and Incidences of Nonneoplastic Lesions in the Small Intestine of Rats and Mice Following Chronic-Duration Oral Exposure to Tribufos

Effect Species (duration)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Decreased RBC AChE activity			
Mouse (90 weeks)			CalEPA 2004; EPA 1990a
Males	1.5	8.4	
Females	2.0	11.3	
Rat (2 years)			CalEPA 2004; EPA 1992d
Males	0.2	1.8	
Females	0.2	2.3	

Table A-7. NOAELs and LOAELs for RBC AChE Activity and Incidences of Nonneoplastic Lesions in the Small Intestine of Rats and Mice Following Chronic-Duration Oral Exposure to Tribufos

Effect Species (duration)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Vacuolar degeneration in small intestine			
Mouse (90 weeks)			CalEPA 2004; EPA 1990a
Males	1.5	8.4	
Females	2.0	11.3	
Rat (1-year interim sacrifice)			CalEPA 2004; EPA 1992d
Males	0.2	1.8	
Females	0.2	2.3	
Rat (2-year terminal sacrifice)			CalEPA 2004; EPA 1992d
Males	0.2	1.8	
Females	0.2	2.3	
Hyperplasia in small intestine			
Rat (2-year terminal sacrifice)			CalEPA 2004; EPA 1992d
Males	0.2	1.8	
Females	0.2	2.3	

AChE = acetylcholinesterase; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; RBC = red blood cell

Selection of the Principal Study: Available animal studies include a 90-week dietary study of CD-1 mice (CalEPA 2004; EPA 1990a) and a 2-year dietary study of Fischer 344 rats (CalEPA 2004; EPA 1992d). The mouse study (CalEPA 2004; EPA 1990a) identified NOAELs of 1.5 and 2.0 mg/kg/day for males and females, respectively, and LOAELs of 8.4 and 11.3 mg/kg/day for males and females, respectively, based on decreased RBC AChE activity (>20% less than respective controls) and significantly increased incidences of vacuolar degeneration in the small intestine (males and females) and extramedullary hematopoiesis in the spleen (males). The NOAELs and LOAELs from the mouse study (CalEPA 2004; EPA 1990a) are higher than those identified in the rat study (CalEPA 2004; EPA 1992d) that identified a NOAEL of 0.2 mg/kg/day (males and females) and LOAELs of 1.8 and 2.3 mg/kg/day (males and females, respectively) for >20% RBC AChE inhibition and increased incidences of histopathologic lesions (vacuolar degeneration and hyperplasia) in the small intestine. Therefore, the rat study (CalEPA 2004; EPA 1992d) was selected as the principal study for deriving a chronic-duration oral MRL for tribufos.

Summary of the Principal Study:

CalEPA. 2004. S,S,S-Tributyl phosphorotrithioate (tribufos) risk characterization document (Revision No. 1). California Environmental Protection Agency, Department of Pesticide Regulation. www.cdpr.ca.gov/docs/risk/rcd/def_r1.pdf.

EPA. 1992d. Memorandum: Tribufos (DEF), rat combined chronic/oncogenicity study. Technical grade tribufos (DEF): A chronic feeding study in the Fischer 344 rat, W.R. Christenson, Miles Inc. Study No. 88-271-AA, Report # 102675, May 1, 1992. MRID 423351-01. U.S. Environmental Protection Agency.

Groups of Fischer 344 rats (50/sex/dose) were administered tribufos in the diet for 2 years at nominal concentrations of 0, 4, 40, or 320 ppm (recovery from food was 96.5%) (CalEPA 2004; EPA 1992d). CalEPA (2004) reported mean tribufos doses as 0, 0.2, 1.8, and 16.8 mg/kg/day, respectively, for the males and 0, 0.2, 2.3, and 21.1 mg/kg/day, respectively, for the females. Other groups of rats (10 or 20/sex/group) were included for interim sacrifice at 12 months. Still other rats (20/sex/group) were included for 12- and 24-month histopathologic evaluation of brain, spinal cord, sciatic nerves and their branches, and eyes and optic nerves. Rats were monitored for survival, clinical signs, body weight, and food intake. Ophthalmologic examinations were performed at the start of dosing and just prior to terminal sacrifice. Electroretinographic examinations were performed on selected 2-year animals and all surviving 2-year neurotoxicity animals just prior to terminal sacrifice. Blood was collected from 20 rats/sex/group at 3, 6, 12, 18, and 24 months on study for hematological and clinical chemistry evaluation (including plasma ChE and RBC AChE activity); where possible, the same rats were used at each time interval. Determination of brain AChE activity was made at terminal sacrifice. Urine was collected for urinalysis (collection time schedule not specified in available study summaries). Gross pathological examinations were performed on all rats at termination. Organs and tissues weighed were adrenals, brain, heart, kidneys, liver, lungs, spleen, testes, ovaries, and thymus. Tissues were collected and processed for histopathological examination.

The high-dose rats exhibited increased incidences of pale eyes, ocular opacity, rough coats, rash, raised zones on the skin, urine stains, clear discharge, soft feces, and diarrhea (CalEPA 2004). A slight (but not statistically significant) decrease in survival was observed in both sexes of high-dose rats. Both sexes of high-dose rats exhibited slightly increased mean food consumption, but approximately 15% depressed mean body weight gain.

There were no signs of treatment-related ocular effects at 12-month interim evaluation. At 24-month examination, the high-dose rats exhibited significantly increased incidences of cataracts, corneal opacity, corneal neovascularization, and iritis and/or uveitis. High-dose females also exhibited significantly increased incidence of lens opacity. High-dose male and female rats exhibited high rates of bilateral unrecordable (flat) responses in the electroretinographic tests; significantly increased incidences of bilateral retinal atrophy were noted in high-dose rats at 1-year sacrifice and 2-year sacrifice. Significantly increased incidences of optic nerve atrophy were noted in high-dose rats at 2-year sacrifice. Histopathologic examination of the eye at 2 years confirmed uveitis, cataract, and neovascularization in the high-dose males and females.

Mid- and high-dose rats exhibited significant decreases in RBC counts, hemoglobin, and hematocrit at 6 and 12 months, but some of these values had returned to normal by 18 and 24 months. At terminal sacrifice, significant increases in RBC count and hematocrit were noted in high-dose males and significant increases in hemoglobin and hematocrit were observed in high-dose females, indicating the possible involvement of some compensatory mechanism. The low-dose treatment level was considered a NOAEL for hematological effects and the mid-dose level a LOAEL.

At 6-month evaluation, mid- and high-dose groups exhibited decreases in plasma glucose, cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total protein, albumin, and globulin; and increases in blood urea nitrogen (BUN), triglycerides, and creatine kinase. By 24-month evaluation, some of these values had returned to control levels (AST, ALT, creatine kinase, and triglycerides) in mid- and high-dose groups. Other values (total protein, albumin, globulin, and BUN) returned to control levels only in the mid-dose rats. The toxicological significance of the changes in clinical chemistry is questionable in the absence of histopathological changes in liver, kidney, or heart. Urinalysis revealed no apparent treatment-related effects.

At study termination, mean plasma ChE activity was significantly decreased at all dose levels (16 and 6% lower in low-dose males and females, respectively; 56 and 60% lower in mid-dose males and females, respectively; 80 and 83% lower in high-dose males and females, respectively). Mean RBC AChE activity was significantly decreased in mid- and high-dose groups (27 and 28% lower in mid-dose males and females, respectively; 48 and 47% lower in high-dose males and females, respectively). Brain AChE activity was significantly decreased only at the high-dose level (60 and 68% lower in males and females, respectively).

Gross pathologic examinations revealed abnormal consistency and discoloration in the small intestine of both sexes at mid- and high-dose levels, enlarged adrenals in high-dose males and females, and ocular opacity in high-dose males. Mid- and high-dose groups of male and female rats exhibited increased incidences of histopathologic lesions in the small intestines (vacuolar degeneration and hyperplasia) at 1-year interim sacrifice and 2-year terminal sacrifice (Table A-7). The lesions in the small intestine accompanied gross findings of abnormal consistency and discoloration. Significantly increased incidences of vacuolar degeneration were noted in adrenal glands from high-dose rats (35/49 males versus 6/50 controls; 41/50 females versus 10/50 controls). This lesion was accompanied by gross pathology (enlarged adrenals) and significantly increased adrenal weight. There was no evidence of dose-related increased incidences of histopathologic lesions in the brain, spinal cord, or sciatic nerve and no indications of treatment-related increased incidences of benign or malignant tumors at any site. The study identified a NOAEL of 0.2 mg/kg/day (males and females) and LOAELs of 1.8 mg/kg/day (males) and 2.3 mg/kg/day (females) for 27–28% decreased RBC AChE activity and increased incidences of nonneoplastic lesions in the small intestine. Changes in selected hematology parameters, observed in mid- and high-dose rats at 3-, 6-, and 12-month interim evaluations, had at least partially returned to normal by terminal sacrifice.

Selection of the Point of Departure for the MRL: As shown in Table A-7, RBC AChE inhibition and histopathologic lesions (vacuolar degeneration and hyperplasia) in the small intestines in the 2-year rat study represent the lowest LOAEL (1.8 mg/kg/day) for adverse effects among available study results. BMD analysis is preferable to a NOAEL/LOAEL approach for identifying an appropriate point of departure for MRL derivation. The datasets for vacuolar degeneration and for hyperplasia in the small intestines of the rats are amenable to BMD analysis. BMD analysis of the dataset for RBC AChE inhibition is precluded by lack of mean RBC AChE activity and variance data in publicly-available summaries (CalEPA 2004; EPA 1992d) of the unpublished study.

Incidence data for vacuolar degeneration at 1- and 2-year sacrifice and for hyperplasia at 2-year sacrifice (Table A-8) were fit to all dichotomous models in EPA's BMDS (version 3.1.1) using a BMR of 10% change from control incidence. Adequate model fit was judged by three criteria: chi-square goodness-of-fit p-value ($p \geq 0.1$), visual inspection of the dose-response curve, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. Among models providing adequate fit to the data, the lowest $BMDL_{10}$ was selected as the POD when the difference between the BMDLs estimated from these models was >3 fold; otherwise, the $BMDL_{10}$ from the model with the lowest Akaike's Information Criterion (AIC) was chosen.

Table A-8. Incidence Data for Selected Nonneoplastic Lesions in the Small Intestine of Male and Female Fischer 344 Rats Administered Tribufos in the Diet for 1 Year (Interim Sacrifice) or 2 Years (Terminal Sacrifice)

		Interim sacrifice (1 year)	Terminal sacrifice (2 years)	
Exposure level (ppm)	Estimated dose (mg/kg/day)	Vacuolar degeneration	Hyperplasia	Vacuolar degeneration
Males				
0	0	0/20 (0%)	0/50 (0%)	0/50 (0%)
4	0.2	0/10 (2%)	3/50 (6%)	1/50 (2%)
40	1.8	7/10[a] (70%)	23/50[a] (46%)	24/50[a] (48%)
320	16.8	18/20[a] (90%)	34/50[a] (68%)	37/50[a] (74%)
Females				
0	0	0/20 (0%)	1/50 (2%)	0/50 (0%)
4	0.2	0/10 (0%)	0/50 (0%)	0/50 (0%)
40	2.3	8/10[a] (80%)	11/50[b] (22%)	19/50[a] (38%)
320	21.1	16/20[a] (80%)	30/50[a] (60%)	35/50[a] (70%)

[a]Significantly different from control according to Fisher's exact test ($p<0.001$).
[b]Significantly different from control according to Fisher's exact test ($p<0.01$).

Source: CalEPA 2004

The Loglogistic, Logprobit, and dichotomous Hill models provided adequate fit to the data for vacuolar degeneration in the male rats at 1-year interim sacrifice (Table A-9); the Logprobit model was selected as the best-fitting model (lowest $BMDL_{10}$). BMD analysis of small intestine vacuolar degeneration in the male rats at 2-year terminal sacrifice resulted in inadequate fit to the data. The Logprobit model provided adequate fit to the data for hyperplasia in the male rats at 2-year terminal sacrifice (Table A-10).

The dichotomous Hill model provided adequate fit to the data for vacuolar degeneration in the female rats at 1-year interim sacrifice (Table A-11). The Loglogistic and Logprobit models provided adequate fit to the data for vacuolar degeneration (Table A-12) in the small intestine of the female rats at 2-year terminal sacrifice; the Logprobit model was selected as the best-fitting model (lowest AIC). The Loglogistic and Logprobit models provided adequate fit to the data for hyperplasia (Table A-13) in the small intestine of the female rats at 2-year terminal sacrifice; the Loglogistic model was selected as the best-fitting model (lowest AIC).

Table A-9. Results from BMD Analysis of Incidences of Male Fischer 344 Rats with Vacuolar Degeneration in the Small Intestine at 1-Year Interim Sacrifice During Dietary Exposure to Tribufos

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma[c]	2	10.39	0.006	-0.63	2.77	2.77	38.42		
Logistic	2	19.73	0.00	3.80	-0.43	3.80	49.88		
Loglogistic[d]	2	2.54	0.28	-0.95	1.03	1.03	32.52	0.24	0.08
Logprobit[e]	**2**	**2.67**	**0.26**	**-0.90**	**1.20**	**1.20**	**32.62**	**0.25**	**0.05**
Multistage (1-degree)[f]	2	10.39	0.006	-0.63	2.77	2.77	38.42		
Multistage (2-degree)[f]	3	10.39	0.02	-0.63	2.77	2.77	36.42		
Multistage (3-degree)[f]	3	10.39	0.02	-0.63	2.77	2.77	36.42		
Probit	2	20.03	0.00	3.88	-0.37	3.88	49.7		
Weibull[c]	2	10.39	0.006	-0.63	2.77	2.77	38.42		
Dichotomous Hill	2	<0.001	1.00	-0.002	<0.001	-0.002	29.22	1.15	0.16

[a]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. The Loglogistic, Logprobit, and dichotomous Hill models provided adequate fit to the data. BMDLs for models providing adequate fit differed by >3-fold; therefore, the model with the lowest $BMDL_{10}$ was selected (Logprobit).
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = dose associated with 10% extra risk); DF = degree of freedom

Table A-10. Results from BMD Analysis of Incidences of Male Fischer 344 Rats with Hyperplasia in the Small Intestine Following Dietary Exposure to Tribufos for 2 Years

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma[c]	2	28.59	0.00	-0.38	4.66	4.66	185.23		
Logistic	2	36.33	0.00	4.90	-0.43	4.90	197.95		
Loglogistic[d]	3	10.67	0.01	0.27	1.98	-2.58			
Logprobit[e]	**2**	**3.41**	**0.18**	**-0.001**	**1.41**	**1.41**	**161.85**	**0.20**	**0.07**
Multistage (1-degree)[f]	2	28.59	0.00	-0.38	4.66	4.66	185.23		
Multistage (2-degree)[f]	2	28.59	0.00	-0.38	4.66	4.66	185.23		
Multistage (3-degree)[f]	2	28.59	0.00	-0.38	4.66	4.66	185.23		
Probit	2	20.03	0.00	3.88	-0.37	3.88	49.7		
Weibull[c]	2	28.59	0.00	-0.38	4.66	4.66	185.23		
Dichotomous Hill	0	3.93	NA	-0.001	-1.12	1.44	166.44		

[a]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. The Logprobit model was the only one to provide adequate fit to the data.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = dose associated with 10% extra risk); DF = degree of freedom; NA = not applicable (degrees of freedom = 0, saturated model, goodness of fit p-value could not be calculated)

Table A-11. Results from BMD Analysis of Incidences of Female Fischer 344 Rats with Vacuolar Degeneration in the Small Intestine at 1-Year Interim Sacrifice During Dietary Exposure to Tribufos

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma[c]	3	21.32	0.00	-0.49	4.20	4.20	49.23		
Logistic	2	25.36	0.00	4.36	-0.36	4.36	60.34		
Loglogistic[d]	3	6.84	0.08	1.85	-1.59	1.85	39.39		
Logprobit	2	5.54	0.06	-1.15	1.86	1.86	40.90		
Multistage (1-degree)[e]	3	21.32	0.00	-0.49	4.20	4.20	49.23		
Multistage (2-degree)[e]	3	21.32	0.00	-0.49	4.20	4.20	49.23		
Multistage (3-degree)[e]	3	21.32	0.00	-0.49	4.20	4.20	49.23		
Probit	2	20.03	0.00	3.88	-0.37	3.88	49.7		
Weibull[c]	3	21.32	0.00	-0.49	4.20	4.20	49.23		
Dichotomous Hill[f]	**2**	**0.002**	**1.00**	**-0.025**	**0.03**	**0.03**	**34.03**	**0.71**	**0.18**

[a]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. The dichotomous Hill model was the only model to provide adequate fit to the data.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = dose associated with 10% extra risk); DF = degree of freedom

Table A-12. Results from BMD Analysis of Incidences of Female Fischer 344 Rats with Vacuolar Degeneration in the Small Intestine Following Dietary Exposure to Tribufos for 2 Years

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma[c]	3	21.42	0.00	-0.89	4.11	4.11	147.70		
Logistic	2	35.44	0.00	4.83	-0.40	4.83	171.52		
Loglogistic[d]	3	6.13	0.11	-1.28	1.70	1.70	136.91	0.68	0.47
Logprobit[e]	**2**	**3.99**	**0.14**	**-1.24**	**1.38**	**1.38**	**136.86**	**0.60**	**0.29**
Multistage (1-degree)[f]	2	21.42	0.00	-0.89	4.11	4.11	147.70		
Multistage (2-degree)[f]	3	21.42	0.00	-0.89	4.11	4.11	147.70		
Multistage (3-degree)[f]	3	21.42	0.00	-0.89	4.11	4.11	147.70		
Probit	2	35.08	0.00	4.86	-0.44	4.86	170.57		
Weibull[c]	2	21.42	0.00	-0.89	4.11	4.11	149.70		
Dichotomous Hill	0	<0.01	NA	-0.02	<0.01	-0.02	135.49		

[a]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. The loglogistic and logprobit models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close; therefore, the model with the lowest AIC was selected (logprobit).
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = dose associated with 10% extra risk); DF = degree of freedom; NA = not applicable (degrees of freedom = 0, saturated model, goodness of fit p-value could not be calculated)

Table A-13. Results from BMD Analysis of Incidences of Female Fischer 344 Rats with Hyperplasia in the Small Intestine Following Dietary Exposure to Tribufos for 2 Years

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma[c]	2	6.54	0.04	-1.14	2.14	2.14	140.82		
Logistic	2	15.49	<0.01	3.16	-0.19	3.16	150.78		
Loglogistic[d,e]	**2**	**3.01**	**0.22**	**-1.18**	**1.02**	**-1.18**	**138.03**	**1.37**	**0.93**
Logprobit	1	2.02	0.16	-1.05	0.66	-1.05	138.81	1.23	0.60
Multistage (1-degree)[f]	2	6.54	0.04	-1.14	2.14	2.14	140.82		
Multistage (2-degree)[f]	2	6.54	0.04	-1.14	2.14	2.14	140.82		
Multistage (3-degree)[f]	2	6.54	0.04	-1.14	2.14	2.14	140.82		
Probit	2	14.97	<0.01	3.14	-0.24	3.14	150.09		
Weibull[c]	2	6.54	0.04	-1.14	2.14	2.14	140.82		
Dichotomous Hill	0	1.01	NA	-0.71	-0.00	0.71	139.19		

[a]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. The Loglogistic and Logprobit models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close; therefore, the model with the lowest AIC was selected (Loglogistic).
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = dose associated with 10% extra risk); DF = degree of freedom; NA = not applicable (degrees of freedom = 0, saturated model, goodness of fit p-value could not be calculated)

The most conservative POD for deriving a chronic-duration oral MRL for tribufos is the $BMDL_{10}$ of 0.05 mg/kg/day for vacuolar degeneration in the small intestine of the male rats at 1-year interim sacrifice generated from the logprobit model (Table A-14). Visual inspection of the dose-response curve for the logprobit model indicated adequate fit to the mean data (Figure A-1).

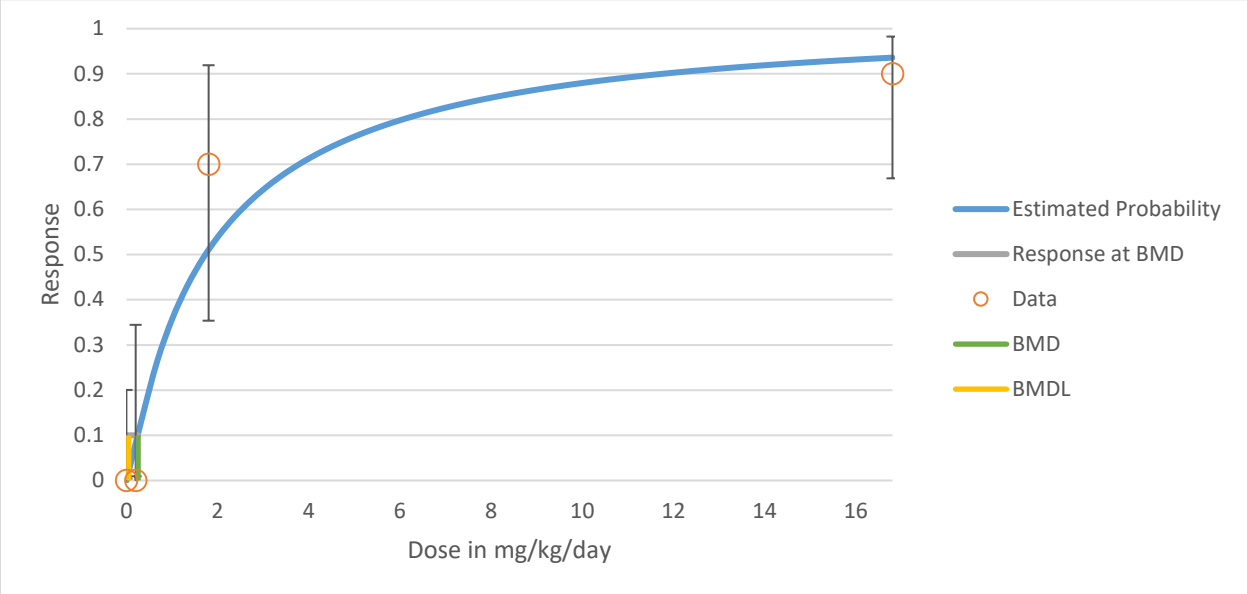
Table A-14. Potential PODs for Deriving a Chronic-Duration Oral MRL for Tribufos Based on BMD Analysis of Nonneoplastic Lesions in the Small Intestine of Rats Administered Tribufos in the Diet for up to 2 Years

Effect Species (duration)	$BMDL_{10}$ (mg/kg/day)	Reference
Vacuolar degeneration in small intestine		
Rat (1-year interim sacrifice)		CalEPA 2004; EPA 1992d
Males	0.05[a]	
Females	0.18	
Rat (2-year terminal sacrifice)		CalEPA 2004; EPA 1992d
Males	Inadequate fit	
Females	0.29	
Hyperplasia in small intestine		
Rat (2-year terminal sacrifice)		CalEPA 2004; EPA 1992d
Males	0.07	
Females	0.93	

[a]Selected as the POD for deriving a chronic-duration oral MRL for tribufos.

BMD =benchmark dose; $BMDL_{10}$ = 95% lower confidence limit on the BMD using 10% change from control incidence as the benchmark response (BMR); MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; POD = point of departure

Figure A-1. Dose-Response Curve for Logprobit Model Data for Vacuolar Degeneration in the Small Intestine from Male Fischer 344 Rats Administered Tribufos in the Diet for 1 Year During a 2-Year Oral Study



Adjustment for Intermittent Exposure: Not applicable

Uncertainty Factor: The $BMDL_{10}$ of 0.05 mg/kg/day was divided by a total uncertainty factor of 100:

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

$MRL = BMDL_{10} \div$ uncertainty factors
$0.05 \text{ mg/kg/day} \div (10 \times 10) = 0.0005 \text{ mg/kg/day}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Histopathologic lesions in the small intestines were observed in CD-1 mice receiving tribufos from the diet for 90 weeks at estimated doses of 8.4 and 11.13 mg/kg/day for males and females, respectively (EPA 1990a).

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APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR TRIBUFOS

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 tribufos.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were 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 tribufos. 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 tribufos 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 tribufos 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
    - Developmental effects

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

	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 tribufos released for public comment in 2018. The following main databases were searched in March 2019:

- PubMed
- National Library of Medicine's TOXLINE
- 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 tribufos. 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 tribufos 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	
03/2019	((78-48-8[rn] OR "butyl phosphorotrithioate"[nm] OR "B 1,776"[tw] OR "B 1776"[tw] OR "Butifos"[tw] OR "Butiphos"[tw] OR "Butyl phosphorotrithioate"[tw] OR "butyphos"[tw] OR "DEF 6"[tw] OR "DEF Defoliant"[tw] OR "De-Green"[tw] OR "E-Z-Off D"[tw] OR "Fosfall"[tw] OR "Fos-Fall A"[tw] OR "Fossfall"[tw] OR "Ortho phosphate defoliant"[tw] OR "Phosphorotrithioic acid, S, S, S-tributyl ester"[tw] OR "S, S, S-Tributyl phosphorotrithioate"[tw] OR "S, S, S-Tributyl trithiophosphate"[tw] OR "S, S, S-Tributylphosphorotrithioate"[tw] OR "S, S, S-Tributyltrithiophosphate"[tw] OR "TBPT"[tw] OR "TBTP"[tw] OR "Tribufos"[tw] OR "Tribuphos"[tw] OR "Tributyl phosphorotrithioate"[tw] OR "tributyl S, S, S-phosphorotrithioate"[tw] OR "Tributyl trithiophosphate"[tw] OR "Tributylphosphorotrithioate"[tw] OR "Tributyltrithiophosphate"[tw] OR ("DEF"[tw] AND (defoliant OR defoliants OR "Defoliants, Chemical"[mh] OR "Defoliants, Chemical"[pa])) OR ("Phosphorotrithioic"[tw] AND ("tributyl"[tw] OR "butyl"[tw]))) AND (2014/12/01 : 3000[dp] OR 2015/12/01 : 3000[mhda] OR 2015/12/01 : 3000[crdat] OR 2015/12/01 : 3000[edat])) OR ("DEF, total"[tw] OR "Merphos oxide"[tw] OR "S,S,S-Tributyl phosphorotrithioic acid"[tw] OR "Tributyl phosphorotrithioic acid"[tw])
Toxline	
03/2019	Year of Publication 2014 through 2019 (78-48-8[rn] OR "B 1,776" OR "B 1776" OR "Butifos" OR "Butiphos" OR "Butyl phosphorotrithioate" OR "butyphos" OR "DEF 6" OR "DEF Defoliant" OR "De-Green" OR "E-Z-Off D" OR "Fosfall" OR "Fos-Fall A" OR "Fossfall" OR "Ortho phosphate defoliant" OR "Phosphorotrithioic acid, S,S,S-tributyl ester" OR "S,S,S-Tributyl phosphorotrithioate" OR "S,S,S-Tributyl trithiophosphate" OR "S,S,S-Tributylphosphorotrithioate" OR "S,S,S-Tributyltrithiophosphate" OR "TBPT" OR "TBTP" OR "Tribufos" OR "Tribuphos" OR "Tributyl phosphorotrithioate" OR "tributyl S,S,S-phosphorotrithioate" OR "Tributyl trithiophosphate" OR "Tributylphosphorotrithioate" OR "Tributyltrithiophosphate") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] ("DEF, total" OR "Merphos oxide" OR "S,S,S-Tributyl phosphorotrithioic acid" OR "Tributyl phosphorotrithioic acid") AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
03/2019	L1 931 SEA FILE=TOXCENTER 78-48-8 L2 849 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 847 SEA FILE=TOXCENTER L2 NOT TSCATS/FS L4 30 SEA FILE=TOXCENTER L3 AND ED>=20151201

Table B-2. Database Query Strings

Database search date	Query string
	L7 47 SEA FILE=TOXCENTER L3 AND PY>2014 L8 47 SEA FILE=TOXCENTER L4 OR L7 L9 47 DUP REM L8 (0 DUPLICATES REMOVED) ANSWERS '1-47' FROM FILE TOXCENTER L*** DEL 47 S L4 OR L7 L*** DEL 47 S L4 OR L7 L10 47 SEA FILE=TOXCENTER L9 L11 41 SEA FILE=TOXCENTER L10 NOT MEDLINE/FS D SCAN L11

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via Chemview	
03/2019	Compound searched: 78-48-8
NTP	
03/2019	"Tributylphosphorotrithioate" 78-48-8 "Butifos" "Butiphos" "Butyl phosphorotrithioate" "butyphos" "DEF 6" "DEF Defoliant" "TBPT" "TBTP" "Tribufos" "Tribuphos" "Tributyl phosphorotrithioate" "tributyl S, S, S-phosphorotrithioate" "Tributyltrithiophosphate"
Regulations.gov	
03/2019	78-48-8
NPIRS	
03/2019	78-48-8
NIH RePORTER	
08/2019	Text Search: "Butifos" OR "Butiphos" OR "Butyl phosphorotrithioate" OR "butyphos" OR "Fosfall" OR "Fos-Fall A" OR "Fossfall" OR "Ortho phosphate defoliant" OR "Phosphorotrithioic acid, S, S, S-tributyl ester" OR "S, S, S-Tributyl phosphorotrithioate" OR "S, S, S-Tributyl trithiophosphate" OR "S, S, S-Tributylphosphorotrithioate" OR "S, S, S-Tributyltrithiophosphate" OR "Tribufos" OR "Tribuphos" OR "Tributyl phosphorotrithioate" OR "tributyl S, S, S-phosphorotrithioate" OR "Tributyl trithiophosphate" OR "Tributylphosphorotrithioate" OR "Tributyltrithiophosphate" OR "TBPT" OR "TBTP" OR "DEF 6" OR "DEF Defoliant" OR "De-Green" OR "E-Z-Off D" OR "Phosphorotrithioic" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2019 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 67
- Number of records identified from other strategies: 38
- Total number of records to undergo literature screening: 105

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on tribufos:

- 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.

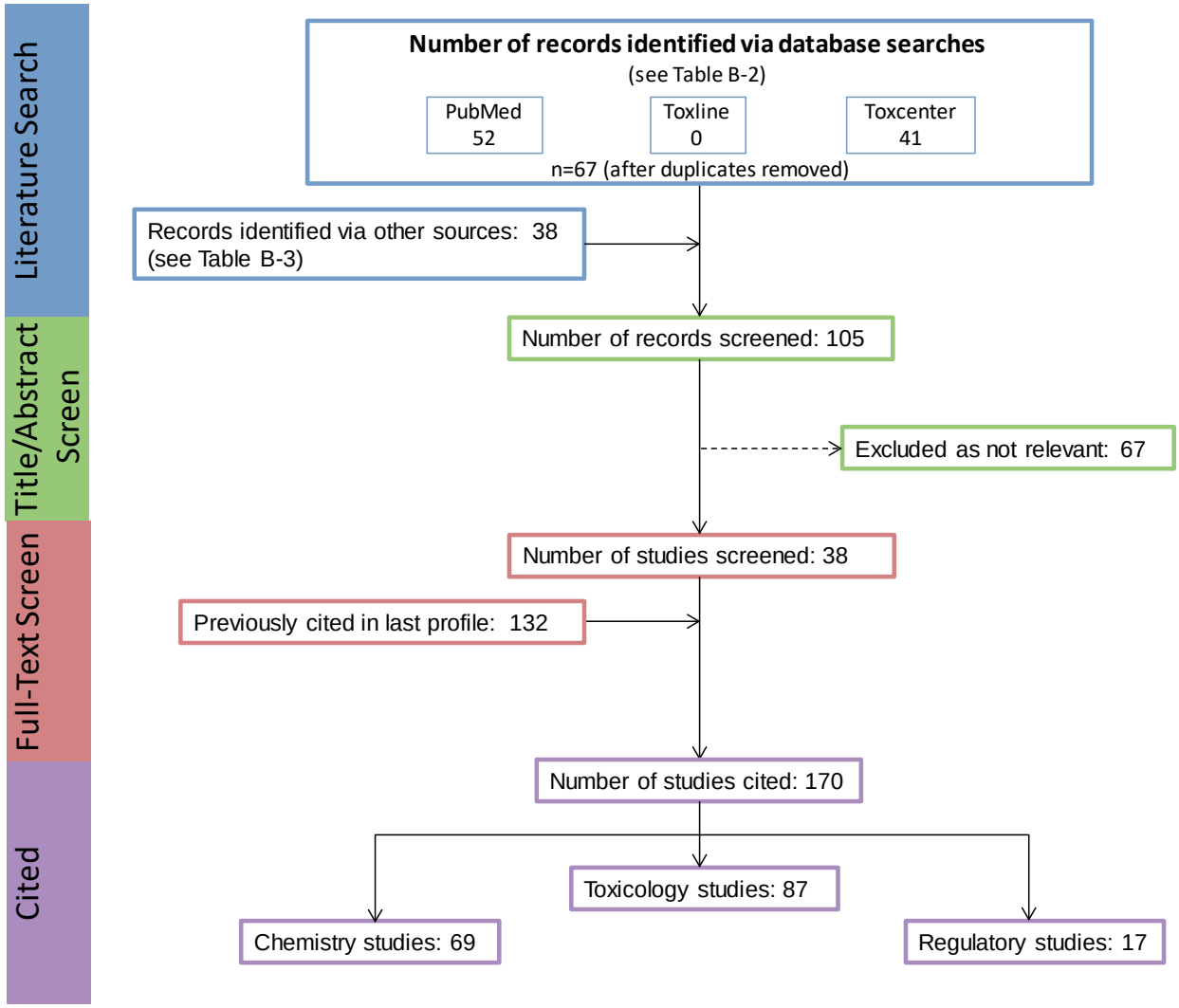
- Number of titles and abstracts screened: 105
- Number of studies considered relevant and moved to the next step: 38

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: 38
- Number of studies cited in the pre-public draft of the toxicological profile: 132
- Total number of studies cited in the profile: 170

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

Figure B-1. March 2019 Literature Search Results and Screen for Tribufos



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.

(13) 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.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints 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) 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).

(17) 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.

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

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

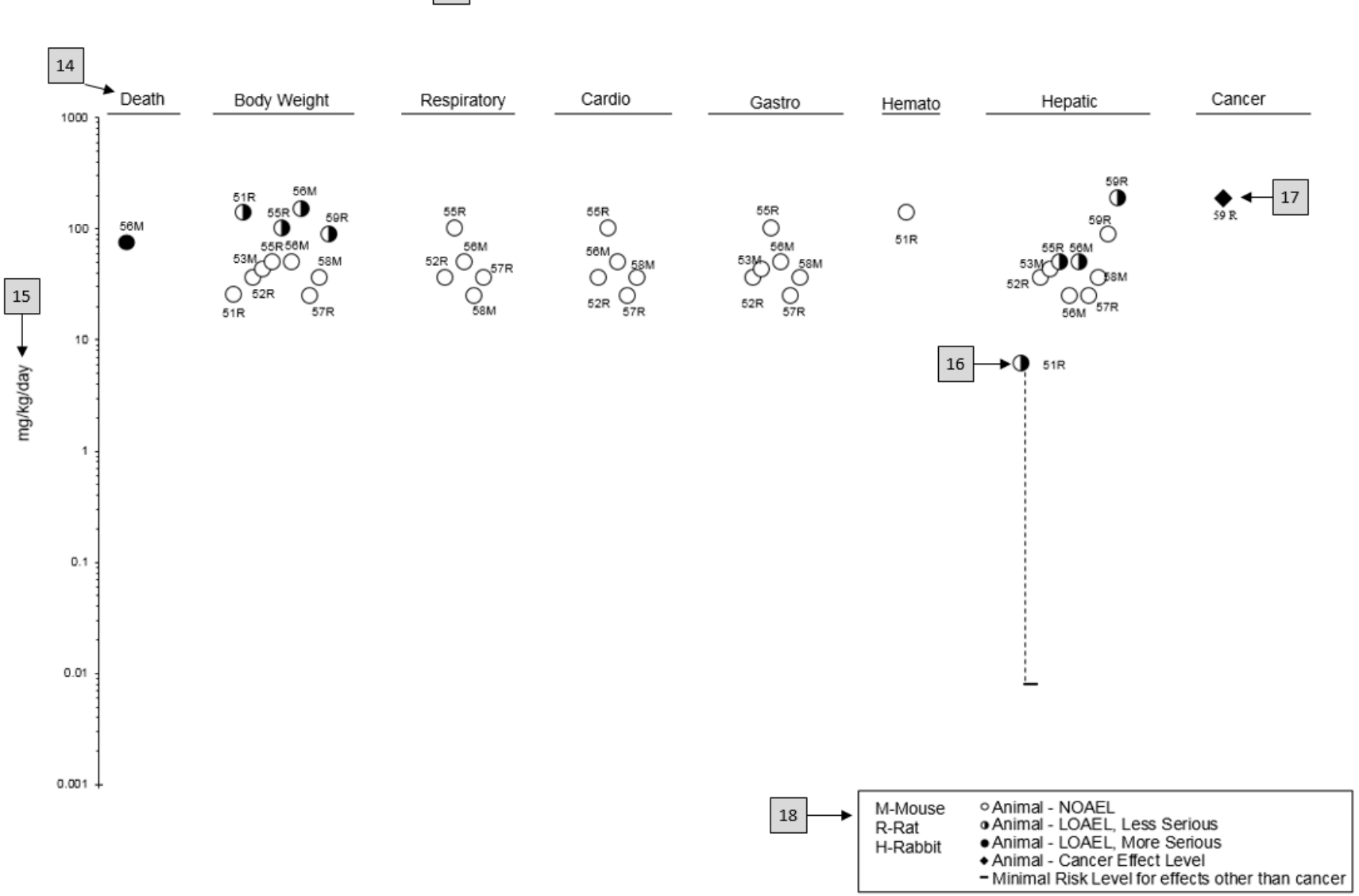
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 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 (10)									
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.

(11) [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).

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 three-volume 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). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

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
NTE	neurotoxic target esterase
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
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