APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlorobenzene
CAS Numbers: 108-90-7
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: Available information regarding adverse effects following acute-duration inhalation exposure to chlorobenzene is limited to evaluations of lethality (Rozenbaum et al. 1947), developmental toxicity studies of rats and rabbits in which no adverse effects were observed at exposure concentrations as high as 590 ppm (John et al. 1984), and a study that evaluated effects of a single 30-minute exposure at 2,990–7,970 ppm (Shell Oil Co. 1991).

Agency Contacts (Chemical Managers): Breanna Alman, MPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlorobenzene
CAS Numbers: 108-90-7
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL.

Rationale for Not Deriving an MRL: Available information regarding the effects of intermediate-duration inhalation exposure to chlorobenzene is limited. Chlorobenzene exposure-related liver effects (increased liver weight and increased incidence of hepatocellular hypertrophy) and kidney effects (renal lesions including chronic interstitial nephritis and foci of regenerative epithelium) were reported for two generations of parental male (but not female) rats repeatedly exposed to chlorobenzene vapor at 150 ppm (NOAEL of 50 ppm) for 18–20 weeks (Nair et al. 1987). NIOSH (1977) reported significantly increased relative liver and kidney weights 31 and 13%, respectively, greater than controls) among rats (but not rabbits) repeatedly exposed to chlorobenzene vapor for up to 24 weeks at 250 ppm; however, there were no increased incidences of exposure-related histopathological liver or kidney lesions. Similar exposure of rabbits resulted in no significant changes in liver or kidney weight and no evidence of exposure-related increased incidence of histopathological liver or kidney lesions. No effects on liver or kidney were noted among dogs repeatedly exposed to chlorobenzene vapor at concentrations as high as 453.2 ppm for up to 6 months (Monsanto Co. 1980). No data were located to support the findings of liver and kidney effects in the 2-generation study of rats (Nair et al. 1987) at exposure levels as low as 150 ppm. No intermediate-duration inhalation MRL was derived for chlorobenzene because intermediate-duration inhalation studies of rats and rabbits (NIOSH 1977) and dogs (Monsanto Co. 1980) did not identify effects on liver or kidney at exposure levels approximately 2–3 times higher than the LOAEL of 150 ppm for parental male rats of the 2-generation study (Nair et al. 1987).

Agency Contacts (Chemical Managers): Breanna Alman, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlorobenzene
CAS Numbers: 108-90-7
Date: October 2020
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: No exposure-response human or animal data are available for the chronic-duration inhalation exposure to chlorobenzene.

Agency Contacts (Chemical Managers): Breanna Alman, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlorobenzene
CAS Numbers: 108-90-7
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: Limited studies that evaluated the effects of acute-duration oral exposure to chlorobenzene found adverse effects only at doses that also caused lethality (Monsanto Co. 1977; NTP 1985).

Agency Contacts (Chemical Managers): Breanna Alman, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlorobenzene
CAS Numbers: 108-90-7
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL 0.07 mg/kg/day
Critical Effect: Hepatic effect; bile duct hyperplasia
Reference: Monsanto Co. 1967a
Point of Departure: $BMDL_{10}$ of 9.59 mg/kg ($BMDL_{ADJ}$ of 6.85 mg/kg/day)
Uncertainty Factor: 100
LSE Graph Key: 9
Species: Dog

MRL Summary: An intermediate-duration oral MRL of 0.07 mg/kg/day was derived for chlorobenzene based on dose-related hepatic changes (bile duct hyperplasia) in dogs treated orally (via capsule) with chlorobenzene 5 days/week for 13 weeks (Monsanto Co. 1967a). The MRL is based on a $BMDL_{10}$ of 9.59 mg/kg, which was adjusted to continuous duration exposure to a $BMDL_{ADJ}$ of 6.85 mg/kg/day and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). 1967a

Selection of the Critical Effect: There are no intermediate-duration oral studies in humans. Several intermediate-duration oral studies are available for rats or mice treated with chlorobenzene by gavage (Monsanto Co. 1967b; NTP 1985) or dogs treated via capsule (Monsanto Co. 1967a). NOAELs and LOAELs identified in these studies are summarized in Table A-1. The effects observed at the lowest LOAEL (55 mg/kg/day for liver and kidney effects in dogs) were considered to represent the critical effects for deriving an intermediate-duration oral MRL for chlorobenzene.

Table A-1. Intermediate-Duration Oral NOAELs and LOAELs for Chlorobenzene

Species (dosing)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Body weight				
Rat (GO, 5 days/week)	125	250	12% lower mean final body weight in males	NTP 1985
Mouse (GO, 5 days/week)	125	250	15–20% lower mean final body weight	NTP 1985
Dog (C, 5 days/week)	55	280	Emaciation, weight loss at lethal dose	Monsanto Co.1967a
Rat (GO, 7 days/week)	250			Monsanto Co. 1967b
Hematological				
Dog (C, 5 days/week)	55	280	Low hemogram, increased numbers of immature WBCs	Monsanto Co. 1967a
Rat (GO, 7 days/week)	250			Monsanto Co. 1967b

Table A-1. Intermediate-Duration Oral NOAELs and LOAELs for Chlorobenzene

Species (dosing)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic				
Dog (C, 5 days/week)	28	55	22% increased liver weight, bile duct hyperplasia (2/4 males)	Monsanto Co. 1967a
Rat (GO, 5 days/week)	60	125	19% increased liver weight in females (LOAEL of 250 mg/kg in males)	NTP 1985
Mouse (GO, 5 days/week)	60	125	14% increased liver weight in males	NTP 1985
		250	Hepatic necrosis/degeneration in males and females	
Rat (GO, 7 days/week)	100	250	27–29% increased mean relative liver weight	Monsanto Co. 1967b
Renal				
Rat (GO)	100	250	13–14% increased kidney weight	Monsanto Co. 1967b
Mouse (GO, 5 days/week)	125	250	Renal necrosis/degeneration	NTP 1985
Dog (C, 5 days/week)	55	280	Increased kidney weight; tubule dilatation, vacuolation, epithelial degeneration	Monsanto Co. 1967a
Rat (GO, 5 days/week)	250	500	13–15% increased kidney weight	NTP 1985
Immunological				
Mouse (GO, 5 days/week)	125	250	Lymphoid depletion/necrosis in thymus and spleen; myeloid depletion in bone marrow in males; lymphoid depletion/necrosis in spleen in females	NTP 1985
Rat (GO, 5 days/week)	500	750	Myeloid depletion in bone marrow, lymphoid depletion in spleen	NTP 1985

C = capsule administration; GO = gavage in oil; LOAEL = lowest-observed-adverse-effect-level; NOAEL = no-observed-adverse-effect level; WBC = white blood cell

Selection of the Principal Study: The study of Monsanto Co. (1967a) was selected as the principal study for deriving an intermediate-duration oral MRL for chlorobenzene because it identified the lowest LOAEL of 55 mg/kg/day for increases in liver and kidney weight and increased incidences of histopathologic liver and kidney lesions in chlorobenzene-treated dogs (see Table A-1).

Summary of the Principal Study:

Monsanto Co. 1967a. 13-Week oral administration- dogs. Monochlorobenzene final report. Monsanto Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0200587. 877800212. 8DHQ10780212.

Groups of beagle dogs (4/sex/group) were treated with chlorobenzene orally (in capsule) at 0, 0.025, 0.05, or 0.25 mL/kg/day (0, 28, 55, and 280 mg/kg/day, respectively, based on a density of 1.1058 g/mL for chlorobenzene), 5 days/week for 13 weeks. Dogs were monitored for survival, clinical signs, food intake,

and body weight. At study initiation and 1 and 3 months, blood was collected for clinical chemistry and hematology and urine was collected for urinalysis. At death or terminal sacrifice, all animals were subjected to gross pathological examination; organ or tissues weighed included heart, liver, spleen, kidneys, testes, thyroid, and adrenals. Selected tissues were processed for histopathologic examination.

All dogs in control, 28, and 55 mg/kg/day groups survived to terminal sacrifice. Four of eight dogs dosed at 280 mg/kg/day died or were sacrificed moribund (between weeks 3 and 5). Decedents exhibited decreased appetite, decreased activity, anorexia, and body weight loss. There were no clear signs of exposure-related body weight effects at 28 and 55 mg/kg/day dose levels. Other effects observed at 280 mg/kg/day included liver and kidney effects (56–77% increased mean relative liver weight, 62–87% increased mean relative kidney weight, increased incidences of pathologic liver and kidney lesions), increased adrenal weight, alterations in selected hematological parameters (low hemogram, increased numbers of immature WBCs), increases in selected serum chemistry parameters (low blood sugar; increased alkaline phosphatase, ALT, total bilirubin, and total cholesterol), increased urinary acetone and bilirubin, and death. The small numbers of animals (4/sex/group) limit the power to determine dose levels resulting in statistically significant changes in liver and kidney lesion incidences. However, as shown in Table A-2, the high-dose level (280 mg/kg/day) is an adverse effect level for liver effects in males (87% increased mean relative liver weight and centrilobular degeneration and bile duct hyperplasia in 4/4 high-dose males; no incidences in controls) and females (62% increased mean relative liver weight and centrilobular degeneration in 3/4 high-dose females; no incidences in controls). Bile duct hyperplasia was noted in 2/4 male dogs and 1/4 female dogs in the 55 mg/kg/day dose group (4/4 males and 3/4 females in the 280 mg/kg/day dose group, compared to no incidences among control or 28 mg/kg/day groups of males or females). The incidences of bile duct hyperplasia in the 55 mg/kg/day group of male dogs is considered to represent a LOAEL for chlorobenzene-induced liver effects. Furthermore, after combining sexes, the bile duct hyperplasia exhibited a dose-response characteristic (incidences of 3/8 and 7/8 at 55 and 280 mg/kg/day, respectively). The 28 mg/kg/day dose level is considered a NOAEL for liver effects and the 280 mg/kg/day dose level is considered a serious LOAEL for multiple degenerative liver effects (e.g., centrilobular degeneration, vacuolation, bile duct hyperplasia). As shown in Table A-3, the 280 mg/kg/day dose level represents a LOAEL for increased incidences of kidney lesions (e.g., significantly increased incidences of tubule dilatation, vacuolation, epithelial degeneration in combined sexes). The smaller number and nature of the reported histopathologic kidney lesions at the low- and mid-dose levels (28 and 55 mg/kg/day) and/or lack of dose-response characteristics suggest that the mid-dose (55 mg/kg/day) represents a NOAEL for kidney effects.

Table A-2. Liver Lesion Incidences in Male and Female Dogs Administered Chlorobenzene in Capsules 5 days/week for 13 Weeks[a]

	Chlorobenzene dose (mg/kg)							
	0		28		55		280	
Effect	Male	Female	Male	Female	Male	Female	Male	Female
Parenchymal irregularity			3/4 (1)		2/4 (1)	3/4 (1)		
Chronic hepatitis		1/4 (1)						
Portal fibrosis			1/4 (1)		1/4 (1)			
Stromal infiltration		1/4 (1)			2/4 (1)	1/4 (1)		

Table A-2. Liver Lesion Incidences in Male and Female Dogs Administered Chlorobenzene in Capsules 5 days/week for 13 Weeks[a]

	Chlorobenzene dose (mg/kg)							
	0		28		55		280	
Effect	Male	Female	Male	Female	Male	Female	Male	Female
Focal leukocyte infiltration			2/4 (1)		1/4 (1)			
Pigment deposition				1/4 (1)			1/4 (1)	2/4 (1–2)
Extramedullary blood production	1/4 (1)	1/4 (1)						
Centrilobular degeneration							4/4[b] (3)	4/4[b] (1–3)
Vacuolation						1/4 (1)	3/4 (2–4)	3/4 (1–3)
Bile duct hyperplasia					2/4 (1)	1/4 (1)	4/4[b] (+/0–4)	3/4 (1)
Cytologic changes					1/4 (1)		2/4 (2–3)	2/4 (1–2)
Cloudy swelling					2/4 (1–3)	1/4 (1)		
Cholangitis							1/4 (2)	1/4 (1)
Bile stasis							2/4 (1–3)	2/4 (3)

[a]Numbers in parentheses denote relative severity of lesion (4 represents highest degree of severity).
[b]Significantly different from control incidence ($p<0.05$).

Source: Monsanto Co. 1967a

Table A-3. Kidney Lesion Incidences in Male and Female Dogs Administered Chlorobenzene in Capsules 5 days/week for 13 Weeks[a]

	Chlorobenzene dose (mg/kg)							
	0		28		55		280	
Effect	Male	Female	Male	Female	Male	Female	Male	Female
Pelvic epithelial irregularity		1/4 (2)	2/4 (1–2)					
Terminal proximal tubule swelling	3/4 (2)		3/4 (1–3)		3/4 (3)		1/4 (3)	1/4 (1)
Terminal proximal tubule vacuolation			1/4 (1)					2/4 (4)

Table A-3. Kidney Lesion Incidences in Male and Female Dogs Administered Chlorobenzene in Capsules 5 days/week for 13 Weeks[a]

	Chlorobenzene dose (mg/kg)							
	0		28		55		280	
Effect	Male	Female	Male	Female	Male	Female	Male	Female
Tubule dilatation					1/4 (1)	1/4 (1)	2/4 (1–2)	2/4 (2)
Tubule epithelial degeneration					1/4 (1)		1/4 (2)	3/4 (1–3)
Proximal convoluted tubule swelling							1/4 (1)	1/4 (1)
Proximal convoluted tubule vacuolation						1/4 (1)	1/4 (1)	3/4 (2–3)
Glomerular swelling							1/4 (2)	
Glomerulosclerosis	1/4 (1)	1/4 (1)		4/4 (1)	1/4 (1)	3/4 (1)	1/4 (1)	
Chronic pyelitis		2/4 (2–3)	1/4 (1)			1/4 (2)		
Intraluminal foreign matter								1/4 (1)
Epithelial pigment deposition							2/4 (2–3)	1/4 (+/0)

[a]Numbers in parentheses denote relative severity of lesion (4 represents highest degree of severity).

Source: Monsanto Co. 1967a

Selection of the Point of Departure: Among available rat, mouse, and dog studies that employed intermediate-duration oral exposure, the lowest LOAEL is 55 mg/kg/day for liver effects in the dogs; the corresponding NOAEL is 28 mg/kg/day. Because the study employed only four dogs/sex/group, results for each sex were combined for each reported liver lesion type. The dataset for bile duct hyperplasia for combined sexes (see Table A-4) was considered adequate for benchmark dose (BMD) analysis. The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 3.12) using the extra risk option. A benchmark response (BMR) of 10% over the control incidence was used. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residual at the data point (except the control) closest to the predefined BMR, BMDL that is not 10 times lower than the lowest non-zero dose, and visual inspection of the dose-response curve.

Table A-4. Dataset for Benchmark Dose Analysis of Bile Duct Hyperplasia Incidences in Male and Female Dogs Administered Chlorobenzene in Capsule for 13 Weeks[a]

	Chlorobenzene dose (mg/kg/day)			
	Control	28	55	280
Males	0/4	0/4	2/4 (1)	4/4[b]
Females	0/4	0/4	1/4 (1)	3/4 (1)

Table A-4. Dataset for Benchmark Dose Analysis of Bile Duct Hyperplasia Incidences in Male and Female Dogs Administered Chlorobenzene in Capsule for 13 Weeks[a]

	Chlorobenzene dose (mg/kg/day)			
	Control	28	55	280
Males and females (combined)	0/8	0/8	3/8 (1)	7/8[b] (+/0–4)

[a]Numbers in parentheses denote relative severity of lesion (4 represents highest degree of severity).
[b]Significantly different from control incidence ($p<0.05$).

Source: Monsanto Co. 1967a

The model predictions are presented in Table A-5. Among all models providing adequate fit to the data, the lowest BMDL (Multistage 1-degree model) was selected as the point of departure because the difference between the BMDLs estimated from these models was >3-fold.

Table A-5. Results from BMD Analysis of Bile Duct Hyperplasia Incidence in Male and Female Dogs Administered Chlorobenzene in Capsule 5 Days/Week for 13 Weeks (Monsanto Co. 1967a)

					Scaled residuals[b]	
Model	BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)	p-Value[a]	AIC	Dose near BMD	Control group
Dichotomous Hill	47.04	20.44	0.959	22.62	3.00×10^{-3}	-3.49×10^{-4}
Gamma[c]	29.15	10.37	0.182	25.05	-9.13×10^{-1}	-3.49×10^{-4}
Log-Logistic[d]	31.35	11.08	0.507	22.57	-8.40×10^{-1}	-3.49×10^{-4}
Multistage Degree 3[e]	23.07	9.96	0.165	25.43	-1.05	-3.49×10^{-4}
Multistage Degree 2[e]	23.07	9.96	0.165	25.43	-1.05	-3.55×10^{-4}
Multistage Degree 1[e,f]	**16.41**	**9.59**	**0.593**	**21.81**	**-1.26**	**-3.49×10^{-4}**
Weibull[c]	26.73	10.20	0.176	25.20	-9.73×10^{-1}	-3.71×10^{-4}
Logistic	54.72	30.85	0.118	25.77	1.61	-7.80×10^{-1}
Log-Probit	32.93	12.70	0.523	22.41	-7.74×10^{-1}	-3.49×10^{-4}
Probit	52.18	31.71	0.123	25.55	1.64	-7.21×10^{-1}

[a]Values <0.1 fail to meet adequate fit
[b]Scaled residuals for dose group near the BMD and for the control dose group
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Recommended model. All models provided adequate fit to the data. BMDLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMDL was selected (1-degree Multistage).

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

BMD modeling was also conducted on selected kidney lesion data (tubule dilatation, tubule epithelial degeneration, and proximal convoluted tubule vacuolation) for combined sexes (see Table A-6) because they exhibited some evidence of dose-response characteristics and statistically significantly increased incidences for these lesions were observed at the highest dose (280 mg/kg/day). Each dataset was fit to all available dichotomous models in EPA's BMDS (version 3.1.2) using the BMD approach described for the liver lesion data above.

Table A-6. Dataset for Benchmark Dose Analysis of Selected Kidney Lesion in Male and Female Dogs Administered Chlorobenzene in Capsule in 13 Weeks

	Chlorobenzene dose (mg/kg)			
	Control	28	55	280
Tubule dilatation				
Males	0/4	0/4	1/4	2/4
Females	0/4	0/4	1/4	2/4
Males and females combined	0/8	0/8	2/8	4/8[a]
Tubule epithelial degeneration				
Males	0/4	0/4	1/4	1/4
Females	0/4	0/4	0/4	3/4
Males and females combined	0/8	0/8	1/8	4/8[a]
Proximal convoluted tubule vacuolation				
Males	0/4	0/4	0/4	1/4
Females	0/4	0/4	1/4	3/4
Males and females combined	0/8	0/8	1/8	4/8[a]

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

All models provided adequate fit to each dataset for kidney lesions. The model results for tubule dilatation are presented in Table A-7. Most models provided adequate fit to the incidence data. The estimated BMDLs varied by greater than 3-fold, thus, the model with the lowest BMDL was selected (Log-Logistic model). The model for tubule dilatation estimated a BMD_{10} of 37.71 mg/kg and $BMDL_{10}$ of 14.07 mg/kg. The incidence data for proximal convoluted tubule vacuolation and tubule epithelial degeneration were the same. The results of the BMD modeling for these two endpoints are presented in Table A-8. All models provided adequate fit and the Log-Probit model was selected because it had the lowest BMDL value. This model estimated a BMD_{10} of 61.67 mg/kg and $BMDL_{10}$ of 13.99 mg/kg.

Table A-7. Results from BMD Analysis of Renal Tubule Dilatation Incidence in Male and Female Dogs Administered Chlorobenzene in Capsule 5 Days/Week for 13 Weeks (Monsanto Co. 1967a)

Model	BMD_{10}[a] (mg/kg)	$BMDL_{10}$[a] (mg/kg)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Control group
Dichotomous Hill	48.55	16.15	0.999	24.09	$3.92x10^{-3}$	$-3.49x10^{-4}$
Gamma[d]	38.94	21.00	0.682	24.03	$-7.93x10^{-1}$	$-3.49x10^{-4}$
Log-Logistic[e,f]	**37.71**	**14.07**	**0.511**	**25.91**	**$-7.94x10^{-1}$**	**$-3.49x10^{-4}$**
Multistage Degree 3[g]	38.94	21.00	0.682	24.03	$-7.93x10^{-1}$	$-3.49x10^{-4}$
Multistage Degree 2[g]	38.94	21.00	0.682	24.03	$-7.93x10^{-1}$	$-3.49x10^{-4}$
Multistage Degree 1[g]	38.94	21.00	0.682	24.03	$-7.93x10^{-1}$	$-3.49x10^{-4}$
Weibull[d]	38.94	21.00	0.682	24.03	$-7.93x10^{-1}$	$-3.49x10^{-4}$
Logistic	104.66	63.17	0.190	27.86	1.48	$-6.94x10^{-1}$
Log-Probit			0.531	25.77	$-7.40x10^{-1}$	$-3.49x10^{-4}$
Probit	95.50	58.90	0.199	27.70	1.47	$-6.54x10^{-1}$

[a]BMD and BMDL values for models that do not provide adequate are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals for dose group near the BMD and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Recommended model. BMDLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMDL was selected (Log-Logistic).
[g]Betas restricted to ≥0.

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

Table A-8. Results from BMD Analysis of Renal Proximal Tubule Vacuolation and Tubule Epithelial Degeneration Incidences in Male and Female Dogs Administered Chlorobenzene in Capsule 5 Days/Week for 13 Weeks (Monsanto Co. 1967a)

Model	BMD_{10}[a] (mg/kg)	$BMDL_{10}$[a] (mg/kg)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Control group
Dichotomous Hill	53.67	20.27	1.000	21.12	$8.67x10^{-4}$	$-3.49x10^{-4}$
Gamma[d]	65.97	25.36	0.480	23.83	$4.88x10^{-1}$	$-3.55x10^{-4}$
Log-Logistic[e]	63.81	19.73	0.497	23.80	$4.51x10^{-1}$	$-3.56x10^{-4}$
Multistage Degree 3[f]	67.37	25.06	0.461	23.94	$4.74x10^{-1}$	$-3.52x10^{-4}$
Multistage Degree 2[f]	67.37	25.06	0.762	21.94	$4.74x10^{-1}$	$-3.49x10^{-4}$
Multistage Degree 1[f]	47.59	24.41	0.904	20.17	$9.19x10^{-2}$	$-3.49x10^{-4}$
Weibull[d]	66.14	25.28	0.476	23.86	$4.80x10^{-1}$	$-3.49x10^{-4}$
Logistic	127.20	75.54	0.497	22.78	$9.37x10^{-1}$	$-4.60x10^{-1}$
Log-Probit[g]	**61.67**	**13.99**	**0.534**	**23.68**	**$4.23x10^{-1}$**	**$-8.93x10^{-3}$**
Probit	114.82	69.29	0.522	22.65	$9.10x10^{-1}$	$-4.21x10^{-1}$

[a]BMD and BMDL values for models that do not provide adequate are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals for dose group near the BMD and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. BMDLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMDL was selected (Log-Probit).

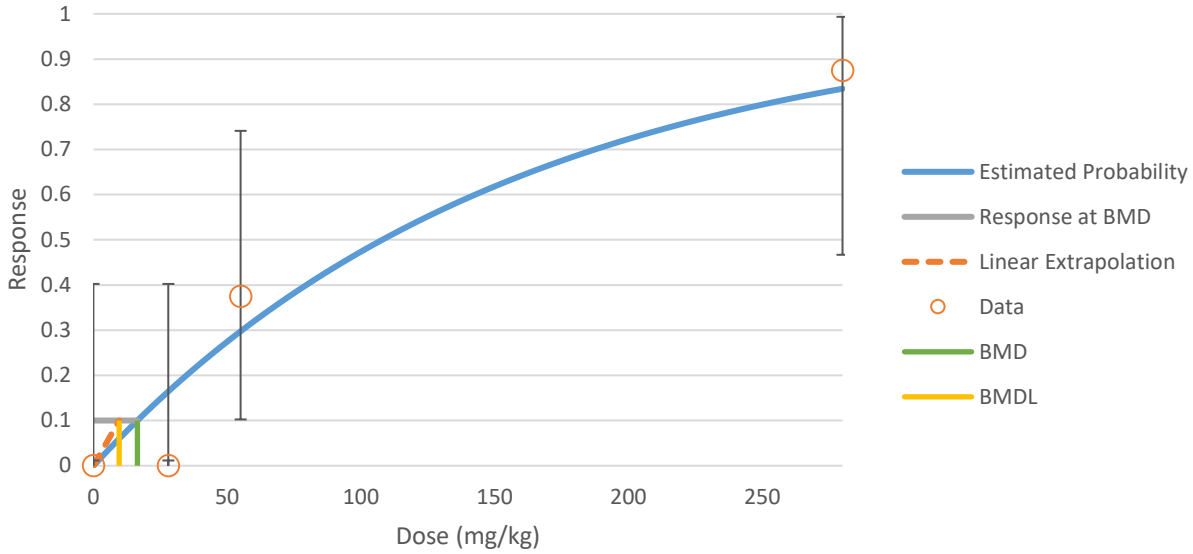
AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure dose associated with a 10% relative deviation from control)

A comparison of the BMD values for the liver and kidney endpoint was made:

- BMD_{10} of 16.41 mg/kg for bile duct hyperplasia ($BMDL_{10}$ of 9.59 mg/kg),
- BMD_{10} of 37.71 mg/kg for renal tubular dilation ($BMDL_{10}$ of 14.07 mg/kg), and
- BMD_{10} of 61.67 mg/kg for proximal convoluted tubule vacuolation and tubule epithelial degeneration ($BMDL_{10}$ of 13.99 mg/kg)

The bile duct hyperplasia had the lowest BMD_{10} and was selected as the critical effect. The $BMDL_{10}$ of 9.59 mg/kg for this endpoint was selected as the POD for the MRL. This $BMDL_{10}$ was estimated using the 1-degree Multistage model, which is presented in Figure A-1.

Figure A-1. Fit of 1-Degree Multistage Model for Bile Duct Hyperplasia in Male and Female Dogs Administered Chlorobenzene 5 Days/Week for 13 Weeks (Monsanto Co. 1967a)



Intermittent Exposure: The $BMDL_{10}$ of 9.59 mg/kg/day was adjusted for intermittent exposure (5 days/7 days) resulting in adjusted value of 6.85 mg/kg/day.

$$BMDL_{ADJ} = 9.59 \text{ mg/kg} \times (5 \text{ days}/7 \text{ days}) = 6.85 \text{ mg/kg/day}$$

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

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

$$MRL = BMDL_{ADJ} \div UFs$$
$$6.85 \text{ mg/kg/day} \div (10 \times 10) = 0.0685 \text{ mg/kg/day} \approx 0.07 \text{ mg/kg/day}$$

Other Additional Studies or Pertinent Information that Lend Support: As shown in Table A-1, liver and kidney effects were observed in rats and mice treated orally with chlorobenzene for intermediate-duration periods (Monsanto Co. 1967b; NTP 1985).

Agency Contacts (Chemical Managers): Breanna Alman, MPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chlorobenzene
CAS Numbers: 108-90-7
Date: October 2020
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: One 2-year oral toxicity and carcinogenicity study of rats gavaged with chlorobenzene at 60 or 120 mg/kg/day reported decreased survival and increased incidences of neoplastic liver lesions at 120 mg/kg/day in the absence of other signs of exposure-related adverse effects (NTP 1985). There were no signs of adverse effects in mice similarly treated at 30 or 60 mg/kg/day (males) or 60 or 120 mg/kg/day (females) (NTP 1985). No nonlethal and nonneoplastic effects were observed in the rats or mice following chronic-duration oral exposures at doses resulting in adverse nonneoplastic effects in animals following intermediate-duration exposures. Therefore, no chronic-duration oral MRL was derived for chlorobenzene.

Agency Contacts (Chemical Managers): Breanna Alman, MPH

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CHLOROBENZENE

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 chlorobenzene.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for chlorobenzene. 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 chlorobenzene 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 chlorobenzene 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 chlorobenzene released for public comment in 2019; thus, the literature search was restricted to studies published between April 2016 and April 2020. The following main databases were searched in April 2020:

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for chlorobenzene. 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 chlorobenzene 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	
04/2020	((108-90-7[rn] OR "chlorobenzene"[nm]) OR (("Benzene chloride"[tw] OR "Benzene, chloro-"[tw] OR "Chlorbenzene"[tw] OR "Chlorbenzol"[tw] OR "Chlorobenzene"[tw] OR "Chlorobenzene, mono-"[tw] OR "Chlorobenzine"[tw] OR "Chlorobenzol"[tw] OR "I P Carrier T 40"[tw] OR "IP Carrier T 40"[tw] OR "Monochlorbenzene"[tw] OR "Monochlorobenzene"[tw] OR "Monochlorobenzenes"[tw] OR "Phenyl chloride"[tw] OR "Tetrosin SP"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR chlorobenzenes/ai OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "pharmacology"[sh:noexp] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh] OR cancer[sb] OR toxicokinetics[mh:noexp] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])))) OR (("Benzene chloride"[tw] OR "Benzene, chloro-"[tw] OR "Chlorbenzene"[tw] OR "Chlorbenzol"[tw] OR "Chlorobenzene"[tw] OR "Chlorobenzene, mono-"[tw] OR "Chlorobenzine"[tw] OR "Chlorobenzol"[tw] OR "I P Carrier T 40"[tw] OR "IP Carrier T 40"[tw] OR "Monochlorbenzene"[tw] OR "Monochlorobenzene"[tw] OR "Monochlorobenzenes"[tw] OR "Phenyl chloride"[tw] OR "Tetrosin SP"[tw]) NOT medline[sb])) AND (2017/04/01:3000[mhda] OR 2017/04/01:3000[crdt] OR 2017/04/01:3000[edat] OR 2016/04/01:3000[dp])
NTRL	
04/2020	"Benzene chloride" OR "Benzene, chloro-" OR "Chlorbenzene" OR "Chlorbenzol" OR "Chlorobenzene" OR "Chlorobenzene, mono-" OR "Chlorobenzine" OR "Chlorobenzol" OR "I P Carrier T 40" OR "IP Carrier T 40" OR "Monochlorbenzene" OR "Monochlorobenzene" OR "Monochlorobenzenes" OR "Phenyl chloride" OR "Tetrosin SP"
Toxcenter	
04/2020	FILE 'TOXCENTER' ENTERED AT 09:15:35 ON 29 APR 2020 L1 9299 SEA FILE=TOXCENTER 108-90-7

Table B-2. Database Query Strings

Database search date	Query string
	L2 7919 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 510 SEA FILE=TOXCENTER L2 AND ED>=20170401 L4 717 SEA FILE=TOXCENTER L2 AND PY>2015 L5 741 SEA FILE=TOXCENTER L3 OR L4 ACT TOXQUERY/Q --------- L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L21 QUE (ENDOCRIN? AND DISRUPT?) L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L28 QUE (NEPHROTOX? OR HEPATOTOX?)

Table B-2. Database Query Strings

Database search date	Query string
	L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L31 QUE L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 L32 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L34 QUE L31 OR L32 OR L33 L35 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L36 QUE L34 OR L35 --------- L37 242 SEA FILE=TOXCENTER L5 AND L36 L38 7 SEA FILE=TOXCENTER L37 AND MEDLINE/FS L39 235 SEA FILE=TOXCENTER L37 NOT MEDLINE/FS L40 236 DUP REM L38 L39 (6 DUPLICATES REMOVED) ANSWERS '1-236' FROM FILE TOXCENTER L*** DEL 7 S L37 AND MEDLINE/FS L*** DEL 7 S L37 AND MEDLINE/FS L41 7 SEA FILE=TOXCENTER L40 L*** DEL 235 S L37 NOT MEDLINE/FS L*** DEL 235 S L37 NOT MEDLINE/FS L42 229 SEA FILE=TOXCENTER L40 L43 229 SEA FILE=TOXCENTER (L41 OR L42) NOT MEDLINE/FS D SCAN L43

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
04/2020	Compounds searched: 108-90-7
NTP	
04/2020	108-90-7 "Benzene chloride" "Chlorobenzene" "Monochlorobenzene" "Phenyl chloride" "Benzene, chloro-" "Chlorbenzene" "Chlorbenzol" "Chlorobenzene, mono-" "Chlorobenzine" "Chlorobenzol" "I P Carrier T 40" "IP Carrier T 40" "Monochlorbenzene" "Monochlorobenzenes" "Tetrosin SP"
NIH RePORTER	
05/2020	Search Criteria: Text Search: "Benzene chloride" OR "Benzene, chloro-" OR "Chlorbenzene" OR "Chlorbenzol" OR "Chlorobenzene" OR "Chlorobenzene, mono-"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	OR "Chlorobenzine" OR "Chlorobenzol" OR "I P Carrier T 40" OR "IP Carrier T 40" OR "Monochlorbenzene" OR "Monochlorobenzene" OR "Monochlorobenzenes" OR "Phenyl chloride" OR "Tetrosin SP" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2020 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 486
- Number of records identified from other strategies: 38
- Total number of records to undergo literature screening: 524

B.1.2 Literature Screening

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

- 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.

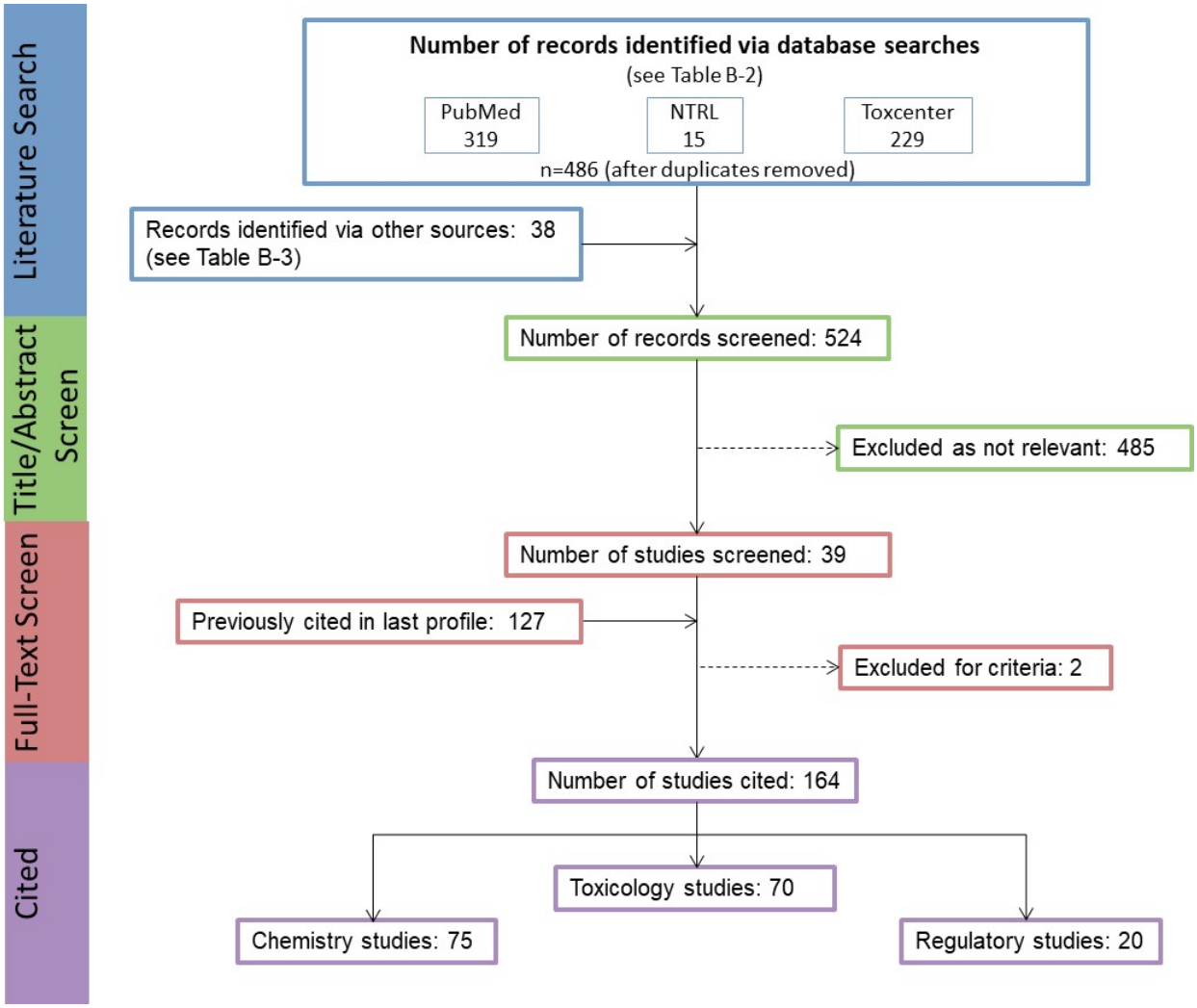
- Number of titles and abstracts screened: 524
- Number of studies considered relevant and moved to the next step: 39

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: 39
- Number of studies cited in the pre-public draft of the toxicological profile: 127
- Total number of studies cited in the profile: 164

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

Figure B-1. April 2020 Literature Search Results and Screen for Chlorobenzene



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)

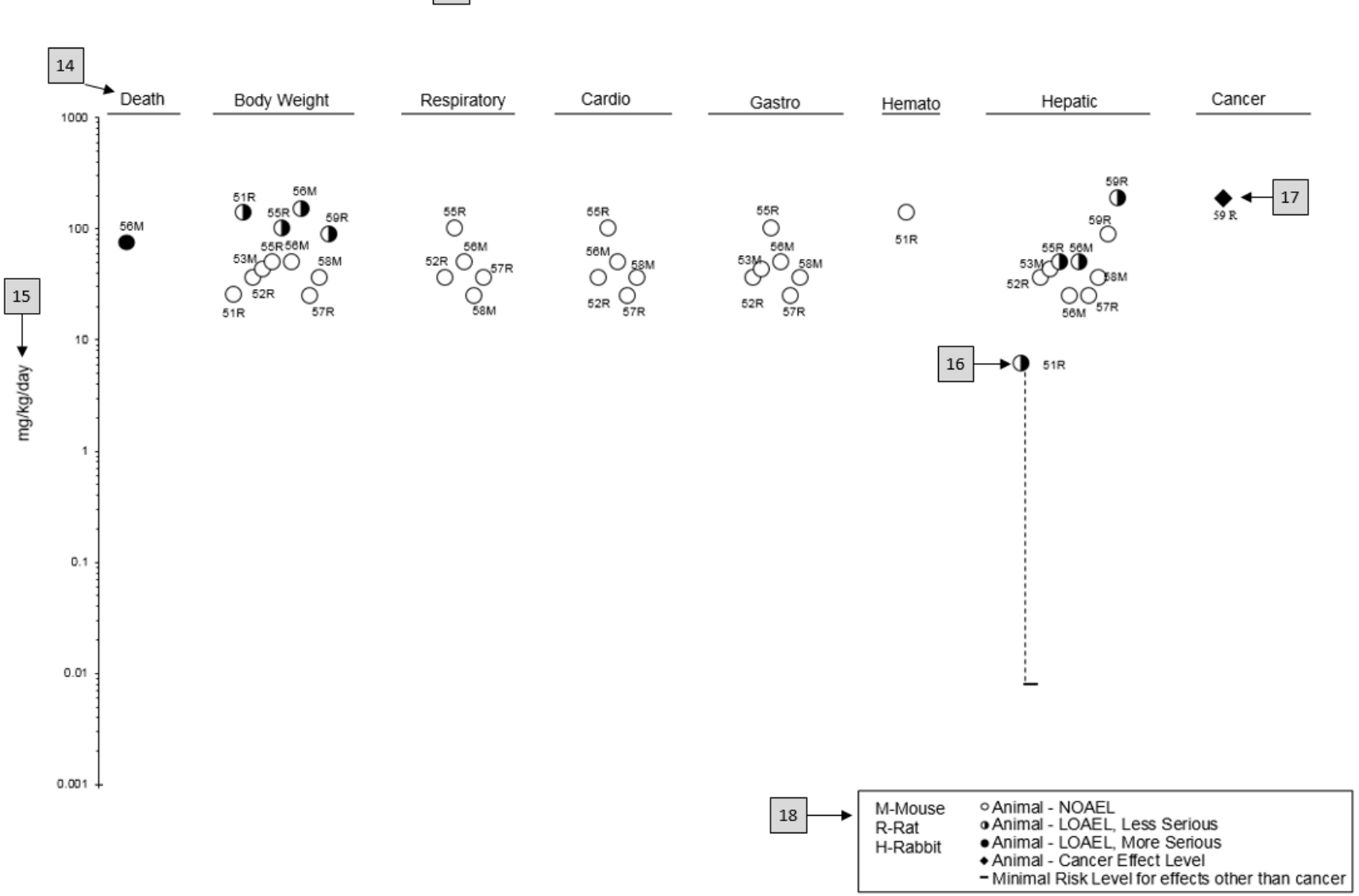
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0,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