

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

APPENDIX A

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

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,1,2,2-Tetrachloroethane
CAS Numbers: 79-34-5
Date: August 2006
Profile Status: Pre-Public Third Draft
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 39
Species: Rat

Minimal Risk Level: [0.3] mg/kg/day ppm

Reference: NTP. 2004. NTP technical report on the toxicity studies of 1,1,2,2-tetrachloroethane (CAS No. 79-34-5) administered in microcapsules in feed to F433/N and B6C3F₁ mice. Research Triangle Park, NC: National Toxicology Program. TR-49. NIH Publication No. 04-4414.

Experimental design: Groups of 10 male and 10 female F344 rats diets containing 0, 268, 589, 1,180, 2,300, or 4,600 ppm of microencapsulated 1,1,2,2-tetrachloroethane for 14 weeks. The reported average daily doses were 0, 20, 40, 80, 170, or 320 mg/kg/day; vehicle control (feed with empty microcapsules) and untreated control groups were used for both sexes. End points evaluated throughout the study included clinical signs, body weight, and feed consumption. Hematology (12 indices) and clinical chemistry (10 indices) were assessed on days 5 and 21 and at the end of the study; urinalyses were not performed. Necropsies were performed on all animals and selected organs (liver, heart, right kidney, lung, right testis, and thymus) were weighed. Comprehensive histological examinations were performed on untreated control, vehicle control, and high dose groups. Tissues examined in the lower dose groups were limited to bone with marrow, clitoral gland, liver, ovary, prostate gland, spleen, testis with epididymis and seminal vesicle, and uterus. Functional observational batteries (FOBs) (21 parameters) were performed on rats in both control groups and the 20, 40, and 80 mg/kg/day groups during weeks 4 and 13. Sperm evaluations and vaginal cytology evaluations were performed at 0, 40, 80, and 170 mg/kg/day. The sperm evaluations consisted of spermatid heads per testis and per gram testis, spermatid counts, and epididymal spermatozoal motility and concentration. The vaginal cytology evaluations consisted of percentage of time spent in the various estrus stages and estrous cycle length.

Effects noted in study and corresponding doses: All rats survived to the end of the study, but clinical signs of thinness and pallor were observed in all animals in the 170 and 320 mg/kg/day groups. Final body weights were statistically significantly lower than vehicle controls in males at 80, 170, and 320 mg/kg/day (7, 29, and 65% lower, respectively) and females at 40, 80, 170, and 320 mg/kg/day (3, 9, 29, and 56% lower, respectively); at 320 mg/kg/day, rats of both sexes lost weight. Feed consumption decreased with increasing dose level at 170 and 320 mg/kg/day and may have contributed to the reduced body weight gain and weight loss. Results of the FOBs showed no exposure-related findings of neurotoxicity. The hematology evaluations indicated that 1,1,2,2-tetrachloroethane affected the circulating erythroid mass in both sexes (Table A-1). There was evidence of a transient erythrocytosis, as shown by increases in hematocrit values, hemoglobin concentration, and erythrocyte counts on days 5 and 21 at ≥ 170 mg/kg/day. The erythrocytosis was not considered clinically significant and disappeared by week 14, at which time it was replaced by minimal to mild, dose-related anemia, as shown by decreases in hematocrit and hemoglobin at ≥ 40 mg/kg/day. For example, although males exposed to 40 mg/kg/day showed a statistically significant decrease in hemoglobin at week 14, the magnitude of the change was small (3.8%). The anemia was characterized as microcytic based on evidence suggesting that the circulating erythrocytes were smaller than expected; this included decreases in mean cell volumes, mean cell hemoglobin values, and mean cell hemoglobin concentration in both sexes at ≥ 80 mg/kg/day at

APPENDIX A

various time points. At week 14, there were no changes in reticulocyte counts, suggesting that there was no erythropoietic response to the anemia; this was supported by bone marrow atrophy observed microscopically. As discussed by NTP (2004), the erythrocytosis suggested a physiological response consistent with the hemoconcentration of dehydration, and compromised nutritional status due to the reduced weight gain and food consumption may have contributed to the development of the anemia.

Table A-1. Body Weight, Liver Weight, and Selected Serum Chemistry and Hematology Changes in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks^a

End point	Vehicle control	Dose (mg/kg/day)				
		20	40	80	170	320
Males (10/group)						
Body weight (g)	366±5	354±9	353±6	341±6 ^b	259±9 ^b	127±5 ^b
Liver weight						
absolute (g)	12.74±0.26	12.99±0.35	14.47±0.44	15.54±0.39	11.60±0.44 ^b	6.57±0.18 ^b
relative (%)	34.79±0.42	36.72±0.44	41.03±0.85 ^b	45.61±0.52 ^b	44.68±0.45 ^b	52.23±1.42 ^b
Serum total protein (g/dL)	7.2±0.1	7.3±0.1	7.3±0.1	7.3±0.1	6.7±0.1 ^b	6.0±0.1 ^b
Serum cholesterol (mg/dL)	73±2	74±3	76±2	67±2	68±2	65±2 ^b
ALT (IU/L)	48±2	49±2	53±2	69±3 ^b	115±8 ^b	292±18 ^b
ALP (IU/L)	256±7	260±5	248±5	245±6	353±12 ^b	432±24 ^b
SDH (IU/L)	23±1	27±1 ^b	26±2	31±1 ^b	47±2 ^b	74±4 ^b
Bile acids (µmol/L)	29.2±2.9	27.5±2.7	27.2±2.7	35.9±3.9	92.0±16.6 ^b	332.4±47.4 ^b
Hematocrit (%) (automated)	45.2±0.5	44.9±0.4	44.0±0.9	43.3±0.7	43.1±0.6 ^b	39.0±1.1 ^b
Hemoglobin (Hb) (g/dL)	15.8±0.1	15.6±0.1	15.2±0.3 ^b	14.9±0.1 ^b	14.6±0.1 ^b	13.6±0.3 ^b
Mean cell volume (fL)	50.7±0.1	51.8±0.3	52.3±0.2	51.3±0.2	49.4±0.2	44.4±0.4 ^b
Mean cell Hb (pg)	17.7±0.1	18.1±0.1	18.0±0.1	17.7±0.2	16.8±0.1 ^b	15.5±0.2 ^b
Platelets (10 ³ /µL)	728.4±12.3	707.0±5.8	727.0±25.2	716.3±9.7	692.8±12.6 ^b	773.4±23.2 ^b

APPENDIX A

Table A-1. Body Weight, Liver Weight, and Selected Serum Chemistry and Hematology Changes in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks^a

End point	Vehicle control	Dose (mg/kg/day)				
		20	40	80	170	320
Females (10/group)						
Body weight (g)	195±4	192±4	189±2	177±2 ^b	139±4 ^b	85±3 ^b
Liver weight						
absolute (g)	6.84±0.17	7.03±0.12	7.14±0.16	7.80±0.08 ^b	6.66±0.21	4.94±0.12 ^b
relative (%)	35.07±0.56	36.69±0.36	37.84±0.51 ^b	44.20±0.27 ^b	48.03±0.89 ^b	58.40±1.42 ^b
Serum total protein (g/dL)	7.2±0.1	7.3±0.0	7.3±0.1	6.9±0.1	6.4±0.1 ^b	5.6±0.1 ^b
Serum cholesterol (mg/dL)	104±4	105±3	98±1	81±2 ^b	64±3 ^b	55±3 ^b
ALT (IU/L)	46±2	42±1	41±2	49±2	112±7 ^b	339±18 ^b
ALP (IU/L)	227±5	216±4	220±3	225±11	341±7 ^b	468±22 ^b
SDH (IU/L)	27±1	27±1	28±2	25±1	45±3 ^b	82±3 ^b
Bile acids (µmol/L)	37.0±7.1	46.6±6.5	39.1±5.6	36.3±3.9	39.3±7.9	321.5±50.6 ^b
Hematocrit (%) (automated)	42.8±0.4	43.2±0.4	42.1±0.4	40.1±0.5 ^b	42.8±0.7	34.7±0.7 ^b
Hb (g/dL)	15.2±0.1	15.3±0.1	14.9±0.1	14.2±0.2 ^b	14.5±0.2 ^b	12.5±0.2 ^b
Mean cell volume (fL)	55.4±0.1	56.1±0.1	55.8±0.1	53.3±0.2 ^b	49.0±0.2 ^b	44.4±0.4 ^b
Mean cell Hb (pg)	19.7±0.1	19.8±0.1	19.7±0.1	18.9±0.1 ^b	16.6±0.2 ^b	16.0±0.2 ^b
Platelets (10 ³ /µL)	742.1±20.4	725.9±12.7	733.9±8.8	727.4±14.2	639.4±9.9 ^b	662.5±19.4 ^b

^aMean±standard error.

^bSignificantly different (p≤0.05) from control value by William's test (body and liver weight data) or Dunn's or Shirley's test (clinical chemistry and hematology data).

ALP = alkaline phosphatase; ALT = alanine aminotransferase; SDH = sorbitol dehydrogenase

Source: NTP 2004

Statistically significant increases in absolute and relative liver weights were observed in males and females exposed to ≥40 mg/kg/day (Table A-1). Significant alterations in absolute and/or relative weights were also observed in several other organs, but these changes likely reflected the decreased body weight gain associated with reduced food intake. Changes in serum clinical chemistry parameters indicative of liver damage were observed in both sexes, generally occurring at all time points (day 5, day 21, and week 14) and generally increasing in magnitude with increasing dose and time. At week 14 (Table A-1), these effects included statistically significant increases in ALT and SDH in males at ≥80 mg/kg/day and females at ≥170 mg/kg/day, increases in ALP in both sexes at ≥170 mg/kg/day, increases in bile acids in males at ≥170 mg/kg/day and females at 320 mg/kg/day, and decreases in serum cholesterol in females at ≥80 mg/kg/day and males at 320 mg/kg/day. There were no exposure-related changes in serum 5'-nucleotidase at week 14, although increases occurred on day 5 in females at ≥20 mg/kg/day and on day 21 in males and females at 80, 170, and/or 320 mg/kg/day. As discussed by NTP (2004), increases in ALT and SDH are specific markers of hepatocellular necrosis or increased cell membrane permeability (leakage) in rodents; increases in bile acids are markers of cholestasis, impaired

APPENDIX A

hepatocellular function, or hepatocellular injury; increases in ALP and 5'-nucleotidase are other markers of cholestasis; and decreases in serum cholesterol could be indicative of liver dysfunction (impaired cholesterol biosynthesis). The LOAEL for serum chemistry effects is 170 mg/kg/day because the magnitude of the changes in serum ALT, SDH, and cholesterol at 80 mg/kg/day were less than 2-fold different from controls and not considered to be biologically significant.

Histological evaluation presented further evidence of the liver as the primary target of 1,1,2,2-tetrachloroethane toxicity; a summary of histological changes is presented in Table A-2. Hepatic cytoplasmic vacuolization was noted in males exposed to 20 mg/kg/day or more and females exposed to 40 mg/kg/day or more. Although the incidence of this alteration was high in affected groups, severity was only minimal-to-mild and did not increase with dose. Females exposed to 80 mg/kg/day showed an increase in the incidence of hepatocyte hypertrophy, which increased in severity and incidence with increasing exposure level; similar results were seen in males, but were not statistically significant below 170 mg/kg/day. At ≥ 170 mg/kg/day, additional effects in the liver in both sexes were hepatocyte necrosis, pigmentation, mitotic alteration and mixed cell foci, and bile duct hyperplasia. Pigmentation of the spleen was increased in male rats exposed to ≥ 80 mg/kg/day and in female rats exposed to ≥ 170 mg/kg/day. Other histological effects included high incidences (70–100%) of atrophy in the spleen (red pulp and lymphoid follicle) of both sexes at 320 mg/kg/day, bone (metaphysis) and bone marrow in females at ≥ 170 mg/kg/day and males at 320 mg/kg/day, and male and female reproductive tissues at 320 mg/kg/day. The reductions in body weight gain at 170 mg/kg/day and body weight losses at 320 mg/kg/day may have contributed to the atrophy of the bone, bone marrow, and reproductive tissues.

Table A-2. Incidences of Selected Histopathological Lesions in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

End point	Vehicle control	Dose (mg/kg/day)				
		20	40	80	170	320
Males (10/group) ^a						
Hepatocyte cytoplasmic vacuolization	0	7 ^b (1.3)	9 ^b (2.0)	10 ^b (1.9)	8 ^b (1.4)	0
Hepatocyte hypertrophy	0	0	0	1 (1.0)	9 ^b (1.3)	10 ^b (3.2)
Hepatocyte necrosis	0	0	0	0	8 ^b (1.0)	10 ^b (1.6)
Hepatocyte pigmentation	0	0	0	0	7 ^b (1.0)	10 ^b (1.9)
Hepatocyte mitotic alteration	0	0	0	0	0	6 ^b (2.0)
Mixed cell foci	0	0	0	0	3	5 ^b
Bile duct hyperplasia	0	0	0	0	0	10 ^b (1.7)
Spleen pigmentation	0	0	1 (1.0)	9 ^b (1.0)	9 ^b (1.0)	9 ^b (1.6)
Spleen red pulp atrophy	0	0	0	0	5 ^b (1.0)	9 ^b (1.4)
Spleen lymphoid follicle atrophy	0	0	0	0	0	5 ^b (1.0)

APPENDIX A

Table A-2. Incidences of Selected Histopathological Lesions in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

End point	Vehicle control	Dose (mg/kg/day)				
		20	40	80	170	320
Females (10/group) ^a						
Hepatocyte cytoplasmic vacuolization	0	0	10 ^b (1.7)	10 ^b (2.2)	4 ^b (1.3)	0
Hepatocyte hypertrophy	0	0	0	4 ^b (1.0)	10 ^b (1.7)	10 ^b (2.8)
Hepatocyte necrosis	0	0	0	1 (1.0)	7 ^b (1.0)	10 ^b (1.1)
Hepatocyte pigmentation	0	0	0	0	10 ^b (1.3)	10 ^b (2.0)
Hepatocyte mitotic alteration	0	0	0	0	3 (2.0)	10 ^b (1.9)
Mixed cell foci	0	0	0	0	8 ^b	1
Bile duct hyperplasia	0	0	0	0	5 ^b (1.0)	10 ^b (1.9)
Spleen pigmentation	1 (1.0)	0	0	4 (1.0)	8 ^b (1.1)	8 ^b (1.3)
Spleen, red pulp atrophy	0	0	0	0	0	9 ^b (1.6)
Spleen lymphoid follicle atrophy	0	0	0	0	0	3 (1.0)

^aValues represent number of animals with the lesion, with the severity score in parenthesis; severity grades are as follows: 1=minimal, 2=mild, 3=moderate, 4=severe.

^bSignificantly different ($p \leq 0.01$) from vehicle control group by the Fisher Exact Test.

Source: NTP 2004

Reproductive effects in the males included statistically significant reductions in sperm motility at ≥ 40 mg/kg/day (18–22% less than vehicle controls), reductions in absolute epididymis weight at ≥ 80 mg/kg/day and absolute left cauda epididymis weight at 170 mg/kg/day (relative organ weights not reported), and increases in incidences (90–100%) of minimal to moderate atrophy of the prostate gland, seminal vesicle, and testicular germinal epithelium at 320 mg/kg/day. Reproductive effects in the females included statistically significant increases in incidences (70–100%) of minimal to mild uterine atrophy at ≥ 170 mg/kg/day, clitoral gland atrophy at 320 mg/kg/day, and ovarian interstitial cell cytoplasmic alterations at 320 mg/kg/day. The vaginal cytology evaluations indicated that the females in the 170 mg/kg/day group (320 mg/kg/day not evaluated) spent more time in diestrus and less time in proestrus, estrus, and metestrus than did the vehicle controls. The body weight loss at 320 mg/kg/day and reduced body weight gain at the lower dose levels could have contributed to the atrophy and other effects in both sexes. The LOAEL for male rat reproductive effects is 320 mg/kg/day based on atrophy in the prostate gland, seminal vesicle, and testicular germinal epithelium. The effects in males at lower doses are not judged to be adverse, indicating that the male reproductive NOAEL is 170 mg/kg/day. In particular, the male reproductive organ weight decreases at 80 and 170 mg/kg/day are not considered adverse due to a lack of accompanying histopathology. The reductions in sperm motility at ≥ 40 mg/kg/day are not considered adverse because the decreases are small, not dose-related, not accompanied by decreased sperm counts, and of unclear reproductive significance. The LOAEL for female rat reproductive effects is 170 mg/kg/day based on uterine atrophy and estrus cycle alterations; the corresponding NOAEL is 80 mg/kg/day.

In summary, this study provides evidence that the liver was the primary target of 1,1,2,2-tetrachloroethane toxicity in rats. At the lowest dose tested, 20 mg/kg/day, there was a significant increase in the incidence of hepatic cytoplasmic vacuolization in males; this minimal effect, which did not increase in severity with

APPENDIX A

dose, was not considered adverse by NTP (2004). At 40 mg/kg/day, significant increases in relative liver weights were observed. Hepatocellular hypertrophy, spleen pigmentation, and decreases in body weight gain (<10%) were observed at 80 mg/kg/day, although these changes were generally of minimal severity or adaptive in nature. Increases in serum ALT and SDH and decreases in serum cholesterol also occurred at ≥ 80 mg/kg/day, but the magnitudes of these changes were biologically significant only at ≥ 170 mg/kg/day. Other effects that occurred at 170 and 320 mg/kg/day included increases in serum ALP and bile acids, hepatocyte necrosis, bile duct hyperplasia, hepatocellular mitotic alterations, foci of cellular alterations, and liver pigmentation. This study identified a NOAEL of 80 mg/kg/day and a LOAEL of 170 mg/kg/day for systemic toxicity based on adverse liver-related serum chemistry changes and histological manifestations of hepatocellular damage. This LOAEL is lower than or equal to the LOAELs for reproductive effects in males (320 mg/kg/day) and females (170 mg/kg/day). A LOAEL for neurotoxicity was not identified because there were no clinical signs of neurotoxicity or exposure-related findings in the FOB at doses as high as 80 mg/kg/day (highest tested dose in the FOB). These findings suggest that the nervous system is less sensitive than the liver for intermediate-duration dietary exposure.

Dose and end point used for MRL derivation:

NOAEL LOAEL BMDL

Based on benchmark dose analysis of dose-response data for various liver effects, a BMDL₁₀ of 53.88 mg/kg/day for hepatocyte necrosis was selected as the point of departure for the MRL. The BMD analysis and basis for selection of the point of departure are presented in the last section of this worksheet.

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Average daily doses were reported by the investigators.

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

Was a conversion used from intermittent to continuous exposure? Not applicable (*ad libitum* dietary exposure).

Other additional studies or pertinent information that lend support to this MRL: The NTP (2004) study also tested mice that were exposed to 1,1,2,2-tetrachloroethane in the diet for 14 weeks. As detailed below, this study found that the mice were less sensitive than the rats, as reflected by the liver toxicity findings, which identified LOAELs and NOAELs that were higher in the mice (300 and 200 mg/kg/day) than in the rats (170 and 80 mg/kg/day). Groups of 10 male and 10 female B6C3F1 mice were exposed to diets containing 0, 589, 1,120, 2,300, 4,550, or 9,100 ppm of microencapsulated 1,1,2,2-tetrachloroethane for 14 weeks. The reported average daily doses were 0, 100, 200, 370, 700, or 1,360 mg/kg/day for males and 80, 160, 300, 600, or 1,400 mg/kg/day for females; vehicle and untreated control groups were used for each sex. End points evaluated throughout the study included clinical signs, body weight, and feed consumption. Clinical chemistry (10 indices) was assessed at the end of the study; hematology evaluations and urinalyses were not performed. Necropsies were conducted on all animals and selected organs (liver, heart, right kidney, lung, right testis, and thymus) were weighed. Comprehensive histological examinations were performed on untreated control, vehicle control, and high dose groups. Tissues examined in the lower dose groups were limited to the liver, spleen, and thymus in both sexes,

APPENDIX A

preputial gland in males, and lungs in females. FOBs (21 parameters) were performed on mice in both control and 160/200, 300/370, and 600/700 mg/kg/day groups during weeks 4 and 13. Sperm motility, vaginal cytology, estrous cycle length, and percentage of time spent in the various estrus stages were evaluated in both control and 160/200, 600/700, and 1,360/1,400 mg/kg/day groups.

All mice survived to the end of the study. A clinical sign of thinness was observed at 300/370 mg/kg/day (3/10 males, 1/10 females), 600/700 mg/kg/day (9/10 males, 2/10 females), and 1,360/1,400 mg/kg/day (10/10 males, 10/10 females). Final body weights were significantly lower than vehicle controls in male mice at 370, 700, and 1,360 mg/kg/day (12, 16, and 33% reduced, respectively) and female mice at 300, 600, and 1,400 mg/kg/day (4, 10, and 11% reduced, respectively) (Table A-3). Feed consumption was slightly less than controls in males at ≥ 700 mg/kg/day, but similar to controls in females. Significant increases in absolute and relative liver weights were observed in the male mice exposed to 200 mg/kg/day or higher and in female mice exposed to 80 mg/kg/day or higher (Table A-3). Other organ weight changes (increased kidney weights in males at ≥ 370 mg/kg/day and increased thymus weights in both sexes at 1,360/1,400 mg/kg/day) were considered to be secondary to the body weight changes. Results of the FOBs showed no exposure-related neurotoxicity.

Table A-3. Body Weight, Liver Weight, and Selected Clinical Chemistry Changes in Mice Exposed to Microencapsulated 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks^a

End point	Vehicle control	Dose (mg/kg/day)				
		100	200	370	700	1,360
Males (10/group)						
Body weight (g)	30.1±0.6	30.6±0.6	30.0±0.3	26.5±0.4 ^b	25.2±0.2 ^b	23.1±0.5 ^b
Liver weight						
absolute (g)	1.47±0.02	1.56±0.04	1.70±0.02 ^b	1.61±0.04 ^b	1.53±0.05	1.56±0.04
relative (%)	48.84±1.17	50.94±0.93	56.82±0.63 ^b	60.63±1.20 ^b	60.71±1.76 ^b	67.43±1.83 ^b
Serum total protein (g/dL)	5.4±0.1	5.2±0.1	5.1±0.1 ^b	5.1±0.1 ^b	5.1±0.1 ^b	5.1±0.1 ^b
Serum cholesterol (mg/dL)	131±7	125±4	94±3 ^b	110±5	112±4	126±5
ALT (IU/L)	66±8	62±19	74±8	207±18 ^b	172±18 ^b	296±24 ^b
ALP (IU/L)	85±2	78±2	89±2	130±3 ^b	143±7 ^b	184±11 ^b
SDH (IU/L)	55±3	53±2	76±3 ^b	288±20 ^b	288±29 ^b	448±25 ^b
5'-Nucleotidase (IU/L)	18±1	16±1	18±0	30±2 ^b	37±3 ^b	62±7 ^b
Bile acids (µmol/L)	25.3±1.2	22.8±1.5	24.8±0.6	56.5±5.1 ^b	63.3±7.5 ^b	108.7±8.1 ^b

APPENDIX A

Table A-3. Body Weight, Liver Weight, and Selected Clinical Chemistry Changes in Mice Exposed to Microencapsulated 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks^a

End point	Vehicle control	Dose (mg/kg/day)				
		80	160	300	600	1,400
Females (10/group)						
Body weight (g)	24.3±0.5	24.2±0.2	24.3±0.6	23.3±0.4	21.7±0.2 ^b	21.5±0.6 ^b
Liver weight						
absolute (g)	1.05±0.03	1.16±0.02 ^b	1.36±0.06 ^b	1.34±0.04 ^b	1.28±0.03 ^b	1.39±0.05 ^b
relative (%)	43.26±1.05	47.90±0.85 ^b	55.54±1.17 ^b	57.39±0.84 ^b	58.73±1.23 ^b	64.42±1.14 ^b
Serum total protein (g/dL)	5.6±0.1	5.6±0.1	5.5±0.0	5.4±0.1 ^b	5.4±0.0 ^b	5.1±0.1 ^b
Serum cholesterol (mg/dL)	109±2	109±3	85±3 ^b	68±2 ^b	64±3 ^b	92±4 ^b
ALT (IU/L)	34±5	50±15	65±5 ^b	189±33 ^b	197±21 ^b	351±35 ^b
ALP (IU/L)	131±5	126±2	139±5	150±3 ^b	161±7 ^b	195±6 ^b
SDH (IU/L)	36±1	44±3 ^b	76±4 ^b	197±15 ^b	243±23 ^b	461±59 ^b
5'-Nucleotidase (IU/L)	59±3	71±2	84±5 ^b	62±2	62±3	83±4 ^b
Bile acids (µmol/L)	27.2±1.2	26.1±1.9	30.9±1.1 ^b	44.2±3.9 ^b	51.5±3.6 ^b	101.7±12.0 ^b

^aMean±standard error.^bStatistically significantly different from control value.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; SDH = sorbitol dehydrogenase

Source: NTP 2004

Clinical chemistry findings in the mice are summarized in Table A-3 and included statistically significant decreases in serum total protein in males at ≥ 200 mg/kg/day, serum total protein in females at ≥ 300 mg/kg/day, and serum albumin in females at 1,400 mg/kg/day. Decreased serum albumin could not fully account for the decreased total protein concentrations, suggesting that other factors (e.g., changes in other protein fractions, hydration status, and/or hepatic function) contributed to the hypoproteinemia (NTP 2004). Other serum chemistry changes were indicative of dose-related liver effects beginning at 160 mg/kg/day; these included statistically significant increased SDH in both sexes at $\geq 160/200$ mg/kg/day, decreased serum cholesterol in females at ≥ 160 mg/kg/day, increased ALT and total bile acids in females at ≥ 160 and males at ≥ 370 mg/kg/day, increased ALP in both sexes at 300/370 mg/kg/day, and increased 5'-nucleotidase in males at ≥ 370 mg/kg/day. As previously discussed for the rat study, these serum indices are markers of hepatocellular damage, cholestasis, and/or impaired hepatic function (NTP 2004). The magnitudes of the serum chemistry changes were biologically significant (e.g., greater than 2-fold increases in serum ALT and SDH) at ≥ 300 mg/kg/day in females and ≥ 370 mg/kg/day in males.

Histopathological findings are consistent with the serum chemistry data in indicating that the liver is the most sensitive target of 1,1,2,2-tetrachloroethane toxicity in the mice. As summarized in Table A-4,

APPENDIX A

minimal hepatocyte hypertrophy was observed at ≥ 160 mg/kg/day in females and ≥ 200 mg/kg/day in males. This effect is likely to be an adaptive non-adverse hepatic response. Degenerative and other adverse liver lesions, including necrosis, pigmentation, and bile duct hyperplasia, occurred at ≥ 300 mg/kg/day in females and ≥ 370 mg/kg/day in males. Other histological findings included increased incidences of preputial gland atrophy in the 100, 700, and 1,360 mg/kg/day male groups (Table A-4), but this effect was not clearly dose-related and is possibly associated with decreased body weight gain. Based on the adverse serum chemistry and histopathological changes at 300 mg/kg/day and higher doses, this study identifies a LOAEL of 300 mg/kg/day for liver toxicity in mice; the corresponding NOAEL is 200 mg/kg/day.

Table A-4. Incidences of Selected Histopathological Lesions in Mice Exposed to Microencapsulated 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

End point	Vehicle control	Dose (mg/kg/day)				
		100	200	370	700	1,360
Males (10/group)^a						
Hepatocyte hypertrophy	0	0	7 ^b (1.0)	10 ^b (2.2)	10 ^b (2.8)	10 ^b (3.1)
Hepatocyte necrosis	0	0	1 (2.0)	8 ^b (1.1)	8 ^b (1.0)	9 ^b (1.0)
Liver focal pigmentation	0	0	0	10 ^b (1.2)	10 ^b (1.4)	8 ^b (1.3)
Bile duct hyperplasia	0	0	0	7 ^b (1.4)	9 ^b (1.3)	10 ^b (2.0)
Preputial gland atrophy	0	4 ^b (2.0)	2 (1.0)	0	4 ^b (2.5)	5 ^b (2.2)
End point	Vehicle control	Dose (mg/kg/day)				
		80	160	300	600	1,400
Females (10/group)^a						
Hepatocyte hypertrophy	0	2 (1.5)	9 ^b (1.0)	10 ^b (1.9)	10 ^b (2.5)	10 ^b (3.0)
Hepatocyte necrosis	0	0	0	3 (1.0)	7 ^b (1.0)	4 ^b (1.0)
Liver focal pigmentation	0	0	2 (1.0)	9 ^b (1.0)	8 ^b (1.0)	7 ^b (1.1)
Bile duct hyperplasia	0	0	0	8 ^b (1.0)	10 ^b (1.4)	10 ^b (2.0)

^aValues represent number of animals with the lesion, with the severity score in parenthesis; severity grades are as follows: 1=minimal, 2=mild, 3=moderate, 4=severe.

^bSignificantly different from vehicle control group.

Source: NTP 2004

Additional information on the intermediate-duration oral toxicity of 1,1,2,2-tetrachloroethane is available from a 21-day gavage study in rats (NTP 1996), a 16-day gavage study in mice (NTP 1993d), 6-week gavage studies in rats and mice (NCI 1978), and 15-day diet studies in rats and mice (NTP 2004). These studies are mainly dose range-finding studies that used small numbers of animals and had limited or no evaluations of clinical chemistry and histology. Key findings include reduced body weight gain in rats exposed to 100 mg/kg/day by gavage for 6 weeks (NCI 1978) or 300 mg/kg/day in the diet for 15 days (NTP 2004), cytoplasmic vacuolation in the liver at 104 mg/kg/day and clinical signs of neurotoxicity and mortality at 208 mg/kg/day in rats exposed by gavage for 21 days (NTP 1996), and hepatocellular degeneration in mice exposed to 337.5 mg/kg/day by gavage for 16 days (NTP 1993d) or 599 mg/kg/day in the diet for 15 days (NTP 2004). The lowest LOAELs in these studies were 100–104 mg/kg/day for reduced body weight gain and hepatocyte cytoplasmic vacuolation in rats exposed by gavage (NCI 1978; NTP 1996) and 337.5 mg/kg/day for hepatocellular degeneration in mice exposed by gavage (NTP

APPENDIX A

1993d). The NTP (2004) 14-week dietary study is the best basis for MRL derivation because it tested wider ranges of doses and varieties of end points, and identified lower LOAELs, than the other intermediate-duration studies.

Potential points of departure for the intermediate-duration oral MRL were derived by BMD analysis of the NTP (2004) rat liver data in Table A-5. All available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for hepatocyte necrosis. The continuous-variable models in the software were applied to the data for changes in relative liver weight and serum ALT, SDH, bile acids, and cholesterol.

Table A-5. Selected Liver Effects in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 weeks

End point	Dose (mg/kg/day)					
	0	20	40	80	170	320
Males (10/group)						
Liver weight						
relative (%)	34.79±0.42	36.72±0.44	41.03±0.85 ^b	45.61±0.52 ^b	44.68±0.45 ^b	52.23±1.42 ^b
Hepatocyte necrosis	0	0	0	0	8 ^b	10 ^b
Serum ALT (IU/L)	48±2	49±2	53±2	69±3 ^b	115±8 ^b	292±18 ^b
Serum SDH (IU/L)	23±1	27±1 ^b	26±2	31±1 ^b	47±2 ^b	74±4 ^b
Bile acids (µmol/L)	29.2±2.9	27.5±2.7	27.2±2.7	35.9±3.9	92.0±16.6 ^b	332.4±47.4 ^b
Females (10/group)						
Liver weight						
relative (%)	35.07±0.56	36.69±0.36	37.84±0.51 ^b	44.20±0.27 ^b	48.03±0.89 ^b	58.40±1.42 ^b
Hepatocyte necrosis	0	0	0	1	7 ^b	10 ^b
Serum ALT (IU/L)	46±2	42±1	41±2	49±2	112±7 ^b	339±18 ^b
Serum SDH (IU/L)	27±1	27±1	28±2	25±1	45±3 ^b	82±3 ^b
Bile acids (µmol/L)	37.0±7.1	46.6±6.5	39.1±5.6	36.3±3.9	39.3±7.9	321.5±50.6 ^b
Serum cholesterol (mg/dL)	104±4	105±3	98±1	81±2 ^b	64±3 ^b	55±3 ^b

^aMean±standard error.

^bStatistically significantly different from control value.

ALT = alanine aminotransferase; SDH = sorbitol dehydrogenase

Source: NTP 2004

For the incidence data, predicted doses associated with 30, 20, 10, 5, and 1% extra risks were calculated as possible alternative BMRs for the best fitting model. Conventionally, a 10% extra risk has served as a point of departure for MRL determination. However, for a study that examined only 10 animals per group, the limit of detection is above the 10% level, likely in the 20–30% range. For the continuous data, the BMDs and the 95% lower confidence limits (BMDLs) calculated are estimates of the doses associated with a change of 1 standard deviation from the control. Predicted doses associated with an increase of 100% (i.e., 2-fold) were also calculated for the best fitting model for the changes in liver enzymes (ALT, SDH) in the serum, as an increase of this magnitude is sometimes considered to be an indicator of clinical significance for these effects. A summary of the predicted BMDs and BMDLs for all of the end points is shown in Table A-6.

APPENDIX A

Table A-6. Summary of BMD Model Predictions for Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks (Best Fitting Models)

End point	BMR	BMD (mg/kg/day)	BMDL (mg/kg/day)
Males			
Hepatocyte necrosis	10% extra risk	139.31	77.95
	1% extra risk	121.94	46.26
	5% extra risk	133.65	66.47
	20% extra risk	145.73	92.04
	30% extra risk	150.16	102.14
Relative liver weight	1 control standard deviation	No adequate fit to the data	
Serum ALT	1 control standard deviation	38.23	26.56
	100% relative deviation	134.06	121.35
Serum SDH	1 control standard deviation	36.71	25.13
	100% relative deviation	179.61	152.27
Bile acids	1 control standard deviation	72.45	57.17
Females			
Hepatocyte necrosis	10% extra risk	82.89	53.88
	1% extra risk	51.02	22.51
	5% extra risk	70.55	40.85
	20% extra risk	99.76	72.51
	30% extra risk	113.30	87.38
Relative liver weight	1 control standard deviation	No adequate fit to the data	
Serum ALT	1 control standard deviation	No adequate fit to the data	
Serum SDH	1 control standard deviation	No adequate fit to the data	
Bile acids	1 control standard deviation	216.74	177.00
Serum cholesterol	1 control standard deviation	No adequate fit to the data	

ALT = alanine aminotransferase; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; BMR = benchmark response; SDH = sorbitol dehydrogenase

Source: NTP 2004

The lowest BMDLs were calculated for the male rat serum ALT and SDH data using 1 standard deviation below the control mean as the BMR. The BMDLs for serum ALT (26.56 mg/kg/day) and serum SDH (25.13 mg/kg/day) are approximately half of the BMDL of 53.88 mg/kg/day calculated using the female rat hepatocyte necrosis incidence data and a BMR of 10%. The BMDLs for the serum enzyme changes appear to be overly conservative predictions that have questionable biological plausibility because they are substantially below the study NOAEL of 80 mg/kg/day. Effects occurring at the NOAEL included increases in serum ALT and SDH that were not biologically significant and hepatocyte necrosis in 1/10 females. The BMDL of 53.88 mg/kg/day for hepatocyte necrosis was selected as the point of departure for the MRL because it is reasonably consistent with the observed findings. The intermediate-duration oral MRL of 0.5 mg/kg/day was derived by dividing the BMDL by a composite uncertainty factor of 100 (10 for extrapolation from humans and 10 for human variability).

APPENDIX A

Details of Benchmark Dose Analysis for the Intermediate-duration Inhalation MRL***Hepatocyte necrosis***

All available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for hepatocyte necrosis in male and female rats (Table A-5). Predicted doses associated with 30, 20, 10, 5, and 1% extra risks were calculated for the best fitting models.

As assessed by the chi-square goodness-of-fit test, several models in the software provided adequate fits to the data for the incidence of hepatocyte necrosis in male rats (χ^2 p-value ≥ 0.1) (Table A-2). Comparing across models, a better fit is indicated by a lower Akaike's Information Criteria value (AIC) (EPA 2000). The log-logistic model was determined to be the best-fitting model, as indicated by the AIC for the male rat data (Table A-7, Figure A-1), and the gamma model was determined to be the best fit to the female data (Table A-8, Figure A-2). Benchmark doses (BMDs and BMDLs) associated with an extra risk of 10% were calculated for all models. Alternative BMRs of 1, 5, 20, and 30% were calculated from the best fitting model for each data set. These are shown in Table A-6.

Table A-7. Goodness of Fit Statistics and BMD10s and BMDL10s from Models Fit to Incidence Data for Hepatocyte Necrosis in Male Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

Model	Degrees of freedom	X ² test statistic	X ² p-value ^a	AIC	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
Gamma ^d	5	12.30	0.9995	12.30	102.95	74.23
Logistic	4	0.00	1.0000	14.01	154.00	81.87
Log-Logistic ^{b,e}	5	0.00	1.0000	12.01	139.31	77.95
Multistage ^{c,f}	4	0.86	0.9304	13.59	88.60	65.67
Probit	4	0.00	1.0000	14.01	140.74	78.18
Log-probit ^e	4	0.00	1.0000	14.01	133.48	76.77
Quantal-linear	5	12.79	0.0255	32.82	20.50	13.77
Quantal-quadratic	5	4.56	0.4718	19.68	53.11	41.50
Weibull ^d	4	0.00	1.0000	14.01	144.11	76.51

^aValues <0.1 fail to meet conventional goodness-of-fit criteria

^bBest-fitting model

^c2-degree polynomial; lowest degree polynomial with adequate fit

^dPower restricted to ≥ 1

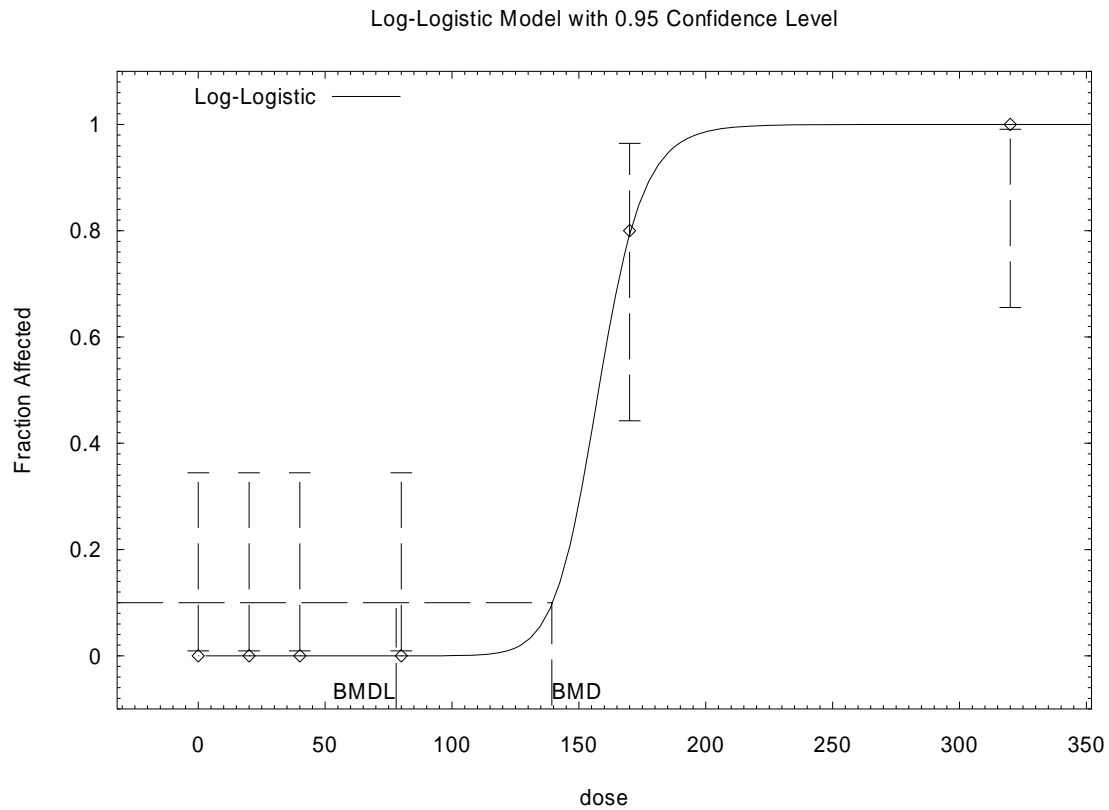
^eSlope restricted to ≥ 1

^fBetas restricted to ≥ 0

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2004

APPENDIX A

Figure A-1. Observed and Predicted Incidences of Hepatocyte Necrosis in Male Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks*

09:46 04/11 2006

*BMDs and BMDLs indicated are for a 10% extra risk and are in units of mg/kg/day.

Source: NTP 2004

APPENDIX A

Table A-8. Goodness of Fit Statistics and BMD10s and BMDL10s from Models Fit to Incidence Data for Hepatocyte Necrosis in Female Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

Model	Degrees of freedom	X ² test statistic	X ² p-value ^a	AIC	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
Gamma ^{b,d}	4	0.11	0.9986	22.89	82.89	53.88
Logistic	4	0.47	0.9765	23.39	92.95	62.34
Log-Logistic ^e	4	0.36	0.9853	23.30	84.90	56.41
Multistage ^{c,f}	4	0.14	0.9978	22.95	84.75	49.88
Probit	4	0.24	0.9933	23.08	87.79	58.48
Log-probit ^e	4	0.20	0.9953	23.03	82.69	56.27
Quantal-linear	5	8.84	0.1156	34.83	20.87	14.04
Quantal-quadratic	5	1.80	0.8755	23.60	54.34	42.71
Weibull ^d	4	0.12	0.9983	22.92	84.37	51.46

^aValues <0.1 fail to meet conventional goodness-of-fit criteria

^bBest-fitting model

^c2-degree polynomial; lowest degree polynomial with adequate fit

^dPower restricted to >=1

^eSlope restricted to >=1

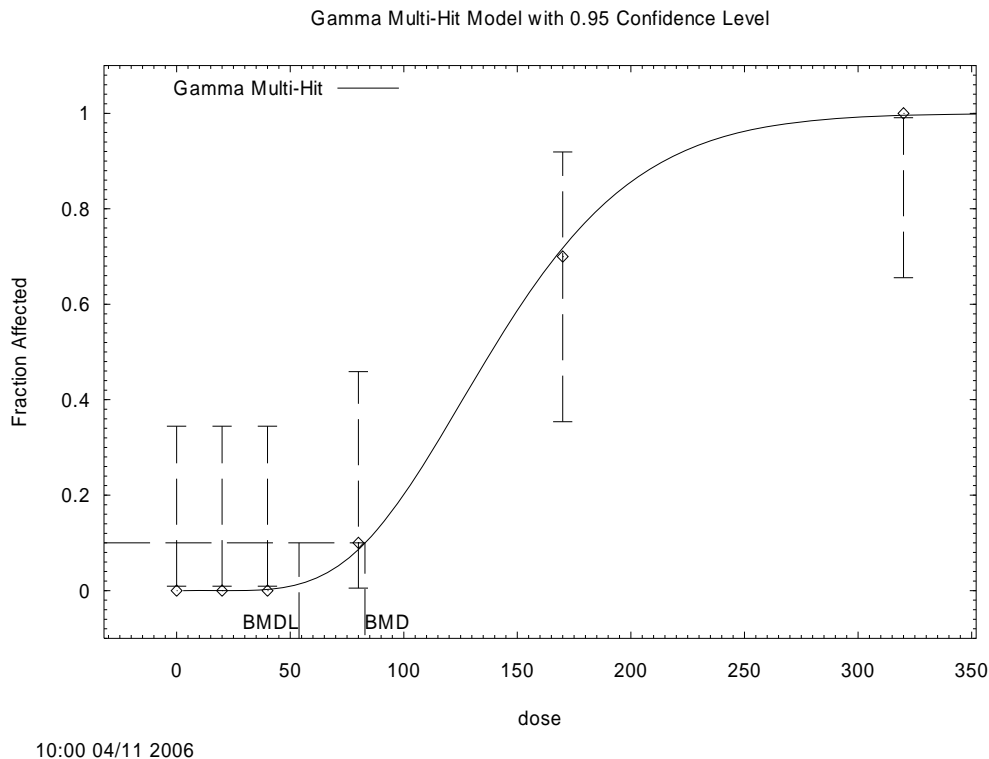
^fBetas restricted to >=0

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2004

APPENDIX A

Figure A-2. Observed and Predicted Incidences of Hepatocyte Necrosis in Female Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks*



*BMDs and BMDLs indicated are for a 10% extra risk and are in units of mg/kg/day.

Source: NTP 2004

Continuous Data

Available continuous-variable models in the EPA Benchmark Dose Software (linear, polynomial, power, and Hill models; BMDS version 1.3.2) were fit to the data shown in Table A-5, for changes in relative liver weight and serum ALT, SDH, bile acids and cholesterol in male and female rats. The BMDs and the 95% lower confidence limits (BMDLs) calculated are estimates of the doses associated with a change of 1 standard deviation from the control. Predicted doses associated with an increase of 100% were also calculated for the changes in serum liver enzymes. For the continuous data, the simplest model (linear) was applied to the data first while assuming constant variance. If the data were consistent with the assumption of constant variance (p -value ≥ 0.1), then the fit of the linear model to the means was evaluated. If the linear model adequately fit the means (p -value ≥ 0.1), then it was selected as the model for BMD derivation. If the linear model did not adequately fit the means, then the more complex models were fit to the data while assuming constant variance. Among those providing adequate fit to the means (p -value ≥ 0.1), the one with the lowest AIC for the fitted model was selected for BMD derivation. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for non-homogenous variance. If the non-homogenous variance model provided an adequate fit (p -value ≥ 0.1) to the variance data, then the fit of the linear model to the

APPENDIX A

means was evaluated. If the linear model did not provide adequate fit to the means while the variance model was applied, then the polynomial, power, and Hill models were fit to the data and evaluated while the variance model was applied. Among those providing adequate fit to the means (p -value ≥ 0.1), the one with the lowest AIC for the fitted model was selected for BMD derivation. If the test for constant variance was negative and the non-homogenous variance model did not provide an adequate fit to the variance data, then the data set was considered not to be suitable for BMD modeling.

Relative liver weight

Statistical tests indicated that variances were not constant across exposure groups (this is reflected in the standard errors listed in Table A-5). The non-homogeneous variance model did not adequately fit the variance data for either males or females; therefore, there was no good fit to the data for change in relative liver weight in either male or female rats (Table A-9).

Table A-9. Model Predictions for Changes in Relative Liver Weight in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

Model	Variance p-value ^a	Means p-value ^b	BMD _{1sd} (mg/kg/day)	BMDL _{1sd} (mg/kg/day)
Male				
Linear (constant variance)	<0.0001	<0.0001	68.02	56.64
Linear (modeled variance)	0.0255	<0.0001	55.05	37.77
Female				
Linear (constant variance)	<0.0001	0.0063	36.16	30.95
Linear (modeled variance)	0.0076	0.0004	22.21	14.61

^aValues <0.05 fail to meet conventional goodness-of-fit criteria

^bValues <0.10 fail to meet conventional goodness-of-fit criteria

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2004

Serum ALT

For the serum ALT data, the assumption of constant variance did not hold for either the male or female data. The non-homogeneous variance model was applied and provided adequate fit to the variance for both the male and female data. With the variance model applied, the linear model did not provide adequate fit to the means for either the male or female data. For the males, both the polynomial and power models provided adequate fit to the means while the variance model was applied. The AIC was slightly lower for the polynomial model, which was selected as the best fitting model. Doses associated with a 100% change from the control (2-fold) from the polynomial model were also calculated (Table A-10, Figure A-3). For the females, none of the models were able to provide adequate fit to the means while the variance model was applied.

APPENDIX A

Table A-10. Model Predictions for Changes in Serum ALT in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

Model	BMR	Variance p-value ^a	Means p-value ^b	AIC	BMD (mg/kg/day)	BMDL (mg/kg/day)
Male						
Linear (constant variance)	1 sd	<0.0001	<0.0001	484.88	43.91	37.37
Linear (modeled variance)	1 sd	0.7223	<0.0001	412.89	12.72	10.07
Polynomial ^{c,d} (modeled variance)	1 sd	0.7223	0.7302	367.955	38.23	26.56
	100%	0.7223	0.7302	367.955	134.06	121.35
Power ^e (modeled variance)	1 sd	0.6731	0.7945	367.956	41.97	32.24
Hill ^f (modeled variance)	NA					
Female						
Linear (constant variance)	1 sd	<0.0001	<0.0001	511.01	44.94	38.22
Linear (modeled variance)	1 sd	0.1849	<0.0001	447.29	17.59	13.50
Polynomial ^g (modeled variance)	1 sd	0.1849	<0.0001	370.32	49.47	45.00
Power ^e (modeled variance)	1 sd	0.1782	0.0074	358.41	64.68	56.13
Hill ^f (modeled variance)	NA					

^aValues <0.05 fail to meet conventional goodness-of-fit criteria

^bValues <0.10 fail to meet conventional goodness-of-fit criteria

^cBest-fitting model

^d2-degree polynomial; lowest degree polynomial with adequate fit

^ePower restricted to ≥ 1

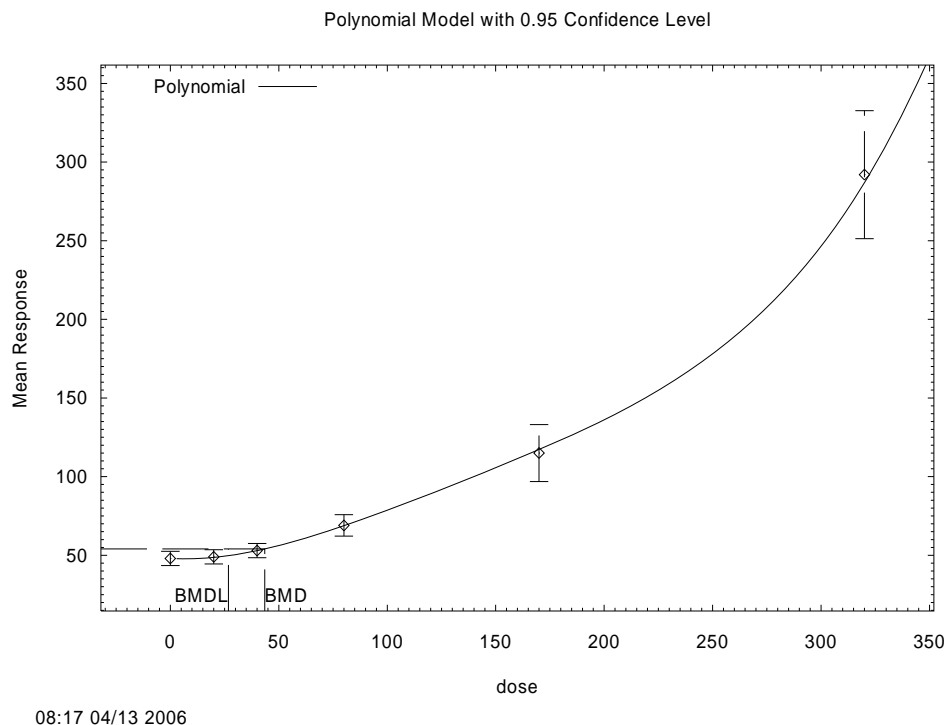
^fN restricted to > 1

^g2-degree polynomial; no adequate fit with any polydegree

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; NA = not available (BMD software could not generate a model output); sd = standard deviation

Source: NTP 2004

APPENDIX A

Figure A-3. Changes in Serum ALT in Male Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks*

*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of mg/kg/day.

Source: NTP 2004

Serum SDH

For the serum SDH data, the assumption of constant variance did not hold for either the male or female data. The non-homogeneous variance model was applied and provided marginally adequate fit to the variance for both the male and female data. With the variance model applied, the linear model did not provide adequate fit to the means for either the male or female data. For the males, both the polynomial and power models provided adequate fit to the means while the variance model was applied. The AIC was slightly lower for the polynomial model, which was selected as the best fitting model. Doses associated with a 100% change from the control (2-fold) from the polynomial model were also calculated (Table A-11, Figure A-4). For the females, none of the models were able to provide adequate fit to the means while the variance model was applied.

APPENDIX A

Table A-11. Model Predictions for Changes in Serum SDH in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

Model	BMR	Variance p-value ^a	Means p-value ^b	AIC	BMD (mg/kg/day)	BMDL (mg/kg/day)
Male						
Linear (constant variance)	1 sd	<0.0001	0.1889	291.96	41.70	35.55
Linear (modeled variance)	1 sd	0.0499	0.0471	274.89	23.86	19.11
Polynomial ^{c,d} (modeled variance)	1 sd	0.0499	0.3259	270.72	36.70	25.13
	100%	0.0499	0.3259	270.72	179.61	152.27
Power ^e (modeled variance)	1 sd	0.0499	0.3044	270.89	44.40	28.51
Hill ^f (modeled variance)	NA					
Female						
Linear (constant variance)	1 sd	<0.0001	<0.0001	319.64	47.70	40.47
Linear (modeled variance)	1 sd	0.0429	<0.0001	310.32	34.45	26.54
Polynomial ^g (modeled variance)	1 sd	0.0429	0.0018	283.22	92.47	69.39
Power ^e (modeled variance)	1 sd	0.0429	0.0018	285.20	90.68	70.92
Hill ^f (modeled variance)	NA					

^aValues <0.05 fail to meet conventional goodness-of-fit criteria

^bValues <0.10 fail to meet conventional goodness-of-fit criteria

^cBest-fitting model

^d2-degree polynomial; lowest degree polynomial with adequate fit

^ePower restricted to ≥ 1

^fN restricted to > 1

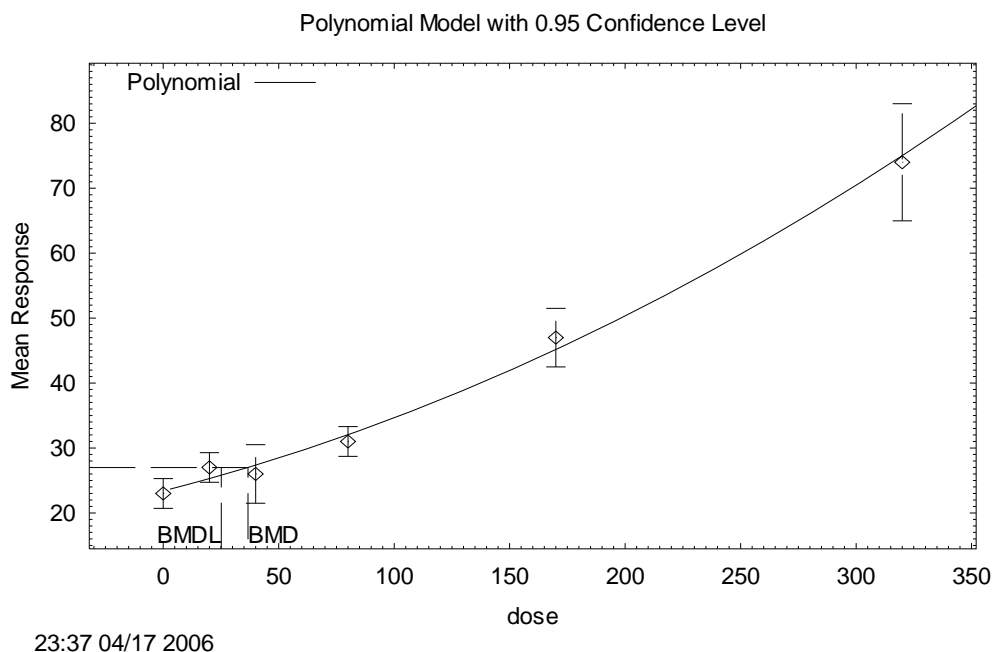
^g2-degree polynomial; no adequate fit with any polydegree

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; NA = not available (BMD software could not generate a model output); sd = standard deviation

Source: NTP 2004

APPENDIX A

Figure A-4. Changes in Serum SDH in Male Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks*



*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of mg/kg/day.

Source: NTP 2004

Bile acids

For the serum bile acids data, the assumption of constant variance did not hold for either the male or female data. The non-homogeneous variance model was applied and provided adequate fit to the variance for both the male and female data. With the variance model applied, the Linear and Hill models did not provide adequate fit to the means for either the male or female data, and the Polynomial model did not provide adequate fit to the mean for the female data. For the males, both the Polynomial and Power models provided adequate fit to the means while the variance model was applied. The Power model was selected as the best fitting model for the male data because it had a slightly lower AIC than the Polynomial model (Table A-12, Figure A-5). For the females, the Power model was the only model that provided adequate fit to the means while the variance model was applied (Table A-12, Figure A-6).

APPENDIX A

Table A-12. Model Predictions for Changes in Bile Acids in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

Model	BMR	Variance p-value ^a	Means p-value ^b	AIC	BMD (mg/kg/day)	BMDL (mg/kg/day)
Male						
Linear (constant variance)	1sd	<0.0001	0.0013	577.11	79.44	61.93
Linear (modeled variance)	1sd	0.7661	<0.0001	464.43	24.81	20.06
Polynomial ^c (modeled variance)	1sd	0.7661	0.1194	428.95	58.37	49.57
Power ^{d,e} (modeled variance)	1sd	0.7661	0.4582	427.70	72.45	57.17
Hill ^f (modeled variance)	NA					
Female						
Linear (constant variance)	1sd	<0.0001	<0.0001	594.57	101.36	81.28
Linear (modeled variance)	1sd	0.4663	<0.0001	576.14	NA	54.83
Polynomial ^g (modeled variance)	1sd	0.4663	<0.0001	487.96	149.50	106.40
Power ^{d,e} (modeled variance)	1sd	0.4663	0.3751	466.68	216.74	177.00
Hill ^f (modeled variance)	NA					

^aValues <0.05 fail to meet conventional goodness-of-fit criteria

^bValues <0.10 fail to meet conventional goodness-of-fit criteria

^c2-degree polynomial; lowest degree polynomial with adequate fit

^dBest-fitting model

^ePower restricted to ≥ 1

^fN restricted to > 1

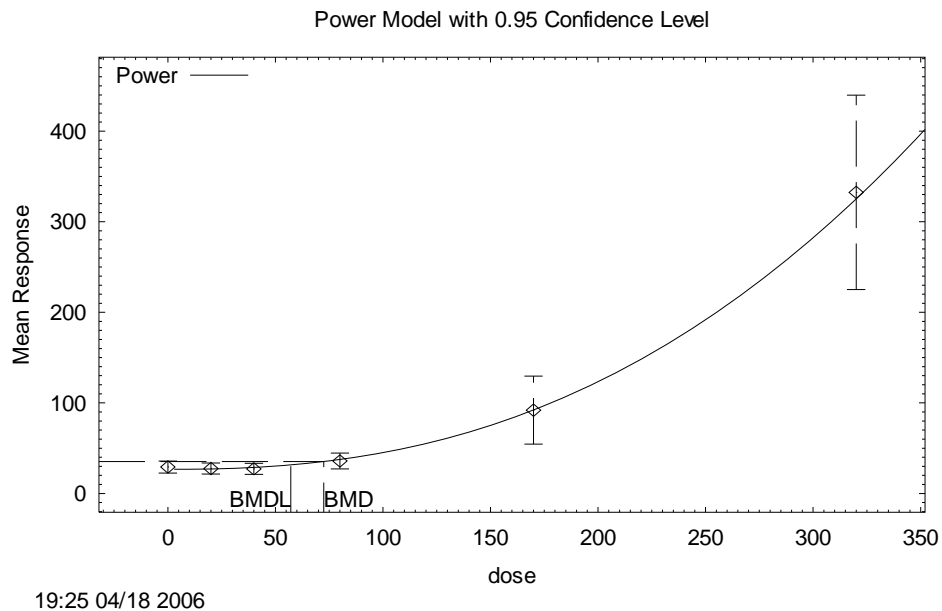
^g2-degree polynomial; no adequate fit with any polydegree

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; NA = not available (BMD software could not generate a model output)

Source: NTP 2004

APPENDIX A

Figure A-5. Changes in Bile Acids in Male Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks*

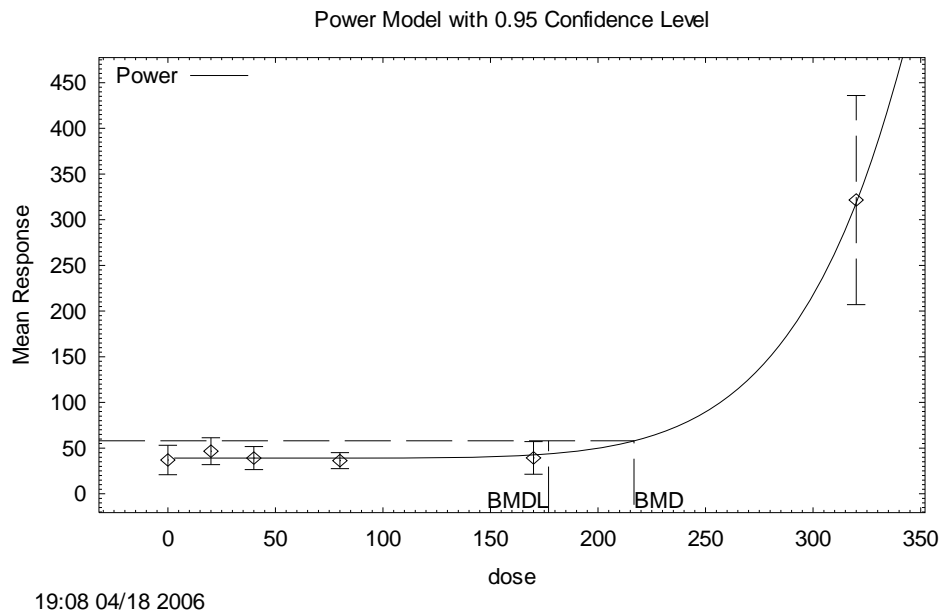


*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of mg/kg/day.

Source: NTP 2004

APPENDIX A

Figure A-6. Changes in Bile Acids in Female Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks*



*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of mg/kg/day.

Source: NTP 2004

Serum cholesterol (females only)

Statistical tests indicated that variances were not constant across exposure groups (this is reflected in the standard deviations listed in Table A-5). The non-homogeneous variance model did not adequately fit the variance data; therefore, there was no good fit to the data for change in serum cholesterol in female rats (Table A-13).

APPENDIX A

Table A-13. Model Predictions for Changes in Serum Cholesterol in Female Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

Model	Variance p-value ^a	Means p-value ^b	BMD _{1sd} (mg/kg/day)	BMDL _{1sd} (mg/kg/day)
Female				
Linear (constant variance)	0.0044	<0.0001	63.66	53.24
Linear (modeled variance)	0.0019	<0.0001	56.37	39.96

^aValues <0.05 fail to meet conventional goodness-of-fit criteria

^bValues <0.10 fail to meet conventional goodness-of-fit criteria

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2004

Agency Contacts (Chemical Managers): Jessilynn Taylor, Henry Abadin, and Eugene Demchuk

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

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

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

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

APPENDIX B

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 chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

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

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

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

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

APPENDIX B

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

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

APPENDIX B

which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

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

LEGEND

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

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

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

APPENDIX B

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

SAMPLE

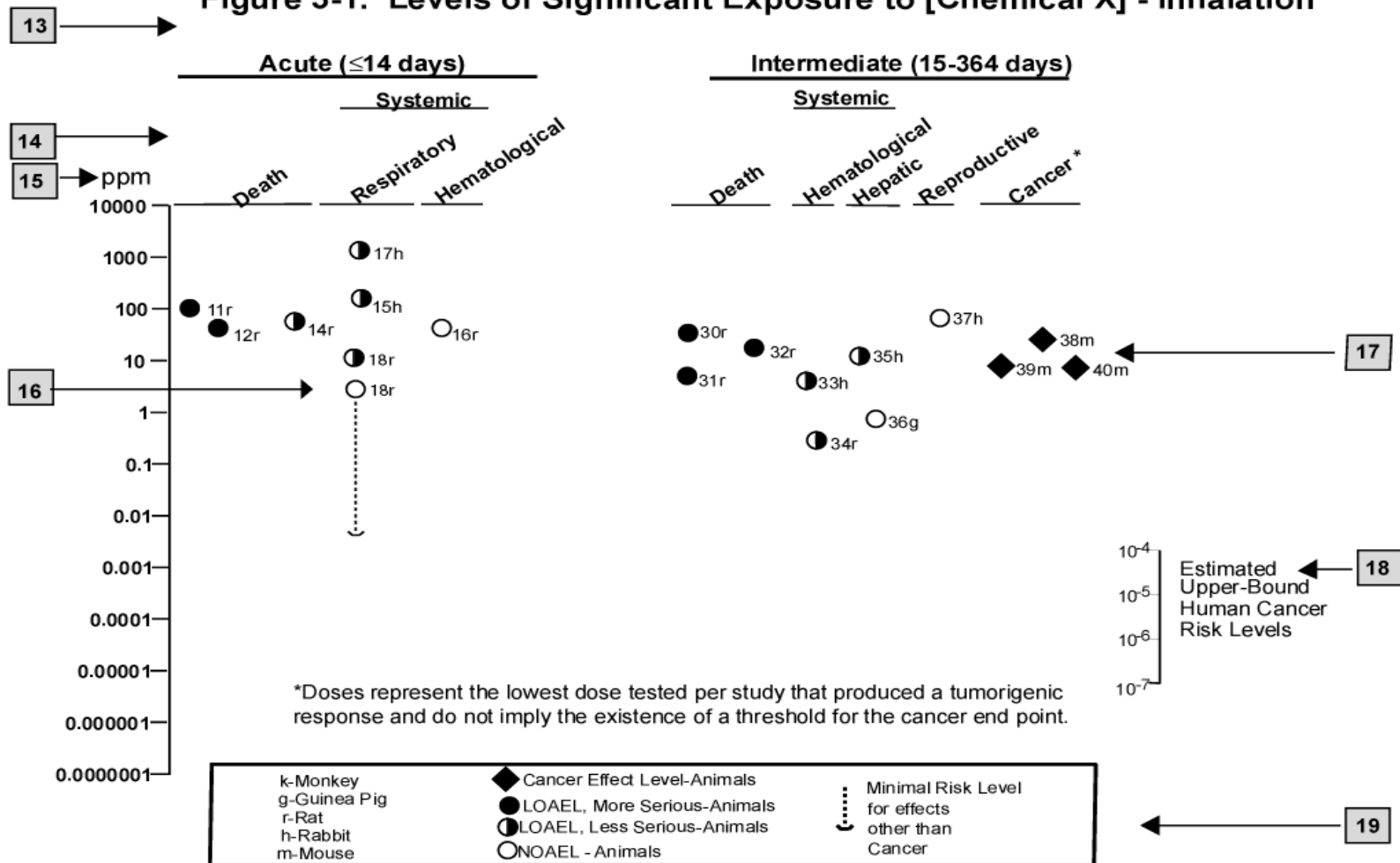
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

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

SAMPLE

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



DRAFT FOR PUBLIC COMMENT

APPENDIX B

This page is intentionally blank.

APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

APPENDIX C

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

APPENDIX C

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

APPENDIX C

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

APPENDIX C

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

APPENDIX C

This page is intentionally blank.

APPENDIX D. INDEX

absorbed dose	77, 78, 82, 89, 106
acetylcholinesterase	15
adrenals	34, 60, 91
adsorbed	142
adsorption	116, 144, 145, 149
aerobic	128, 137
alanine aminotransferase (see ALT)	13, 32
ALT (see alanine aminotransferase)	13, 17, 18, 19, 58, 59
ambient air	9, 121, 139
anaerobic	119, 127, 128, 137, 154
anemia	32
aspartate aminotransferase (see AST)	13
AST (see aspartate aminotransferase)	13, 58
bioaccumulation	138
bioavailability	138, 139
bioconcentration factor	126, 133, 138
biodegradation	9, 119, 126, 127, 128, 137
biomarker	89, 90, 141, 153
blood cell count	32
body weight effects	34, 60, 61, 63, 102
breast milk	5, 88, 135, 139
cancer	4, 11, 14, 22, 38, 63, 64, 87, 96, 97, 101, 104, 157
carcinogen	4, 14, 64, 157, 160
carcinogenic	14, 21, 22, 63, 84, 85, 100
carcinogenicity	14, 19, 38, 64, 84, 157, 160
carcinoma	11, 13, 59, 64, 97
cardiac arrhythmia	93
cardiovascular	31, 63, 64, 65
Cardiovascular Effects	31, 57
chromosomal aberrations	69, 70
clearance	93
death	12, 16, 21, 23, 39, 57, 59, 63, 64, 93, 96, 98, 102, 103
deoxyribonucleic acid (see DNA)	11
dermal effects	23, 60, 65
DNA (see deoxyribonucleic acid)	11, 13, 58, 67, 68, 69, 76, 77, 82, 84, 85, 89, 90
endocrine	34, 60, 85, 86
endocrine effects	34, 60
fetus	5, 31, 87
gastrointestinal effects	31
general population	10, 89, 121, 134, 137
genotoxic	14, 21, 66, 84, 90, 101
genotoxicity	14, 66, 84
germinal epithelium	62, 101
groundwater	2, 3, 9, 119, 121, 124, 126, 127, 132, 136, 137, 138, 139, 150, 154
half-life	9, 89, 121, 125, 126, 127
hematological effects	32, 57, 96
hepatic effects	11, 12, 13, 15, 17, 32, 58, 71, 96, 98
hydrolysis	9, 119, 127, 128, 137, 154
hydroxyl radical	9, 121, 125, 126
immune system	102
immunological	11, 15, 21, 34, 61, 65, 96, 103
LD ₅₀	39, 64, 97, 98

APPENDIX D

leukemia	38, 96, 104
lymphatic	38, 63
lymphoreticular.....	34, 61, 65, 96
milk.....	88, 90
musculoskeletal effects.....	39
neonatal	37, 102
neoplastic.....	84
neurobehavioral	12, 86
nuclear	73, 75, 82, 85, 105
ocular effects	34, 60, 65
partition coefficients.....	72, 76
pharmacodynamic.....	79
pharmacokinetic.....	79, 80, 81, 85, 87, 106
placenta.....	5
rate constant.....	121, 125, 126
renal effects	33, 59, 65
retention	70, 77, 146, 151
solubility	72
thyroid	34, 60, 91, 97
toxicokinetic	21, 106, 153
tremors.....	35, 66, 96
tumors	4, 19, 84, 100
vapor pressure.....	126
volatility.....	67
volatilization	66, 119, 121, 125