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.

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-62, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: RDX
CAS Numbers: 121-82-4
Date: August 2011
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 22
Species: Rat

Minimal Risk Level: 0.2 [X] mg/kg/day [ ] ppm

Reference: U.S. Army. 2006. Toxicology study no. 85-XC-5131-03. Subchronic oral toxicity of RDX in rats. Aberdeen Proving Ground, MD: U.S. Army Center for Health Promotion and Preventive Medicine.

Experimental design: Groups of six male and six female Sprague-Dawley rats were administered via gavage 0, 2.125, 4.25, 8.5, 17.00, 25.50, 34.00, or 42.5 mg/kg/day as a suspension of RDX/1% methyl-cellulose/0.2% Tween 80 in distilled water 7 days/week for 14 days. Rats were monitored daily for toxic signs and morbidity. Body weights and feed consumption were measured on days 0, 1, 3, 7, and 14. Additional parameters used to assess toxicity included clinical chemistry (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, sodium, potassium, chlorine, cholesterol, creatinine kinase, creatinine, glucose, lactate dehydrogenase, total bilirubin, total protein, triglycerides) and hematology (hemoglobin, hematocrit, erythrocytes, mean cell hemoglobin concentration, mean cell volume, mean cell hemoglobin, red blood cell distribution width, total and differential leukocytes, platelets, and mean platelet volume) values, organ weights (brain, heart, liver, kidneys, spleen, adrenals, thymus, epididymides, uterus, testes, ovaries), and gross necropsies.

Effect noted in study and corresponding doses: A significant increase in early deaths was observed at ≥25.5 mg/kg/day. Tremors and convulsions were observed in rats exposed to ≥17 mg/kg/day. In the males exposed to ≥17 mg/kg/day, blood stains around the mouth and nose and low arousal were also observed. Increased arousal, blood around the mouth and nose, barbering, and lacrimation were observed in females exposed to ≥17 mg/kg/day. No signs of neurological alterations were observed in rats exposed to ≤8.5 mg/kg/day. Significant decreases in body weight were observed in male rats exposed to ≥17 mg/kg/day on days 1 and 7, but there were no significant alterations in male body weight at termination. In female rats, significant decreases in body weight gain were observed at ≥34 mg/kg/day on day 1 and in the 8.5 mg/kg/day group on day 14; however, the magnitude of the decreased body weight was less than 10% and no significant alterations were observed at higher dose levels. Significant decreases in food consumption were also observed during the first 7 days of exposure in males and females exposed to ≥8.5 mg/kg/day. Significant decreases in absolute liver weights and liver-to-brain weights and increases in blood cholesterol levels were observed in females exposed to 8.5 mg/kg/day; these effects were not observed at higher dose levels or in males. Due to the lack of dose-response relationships for the alterations in liver weight and blood cholesterol levels, these changes observed in the 8.5 mg/kg/day female group were not considered biologically relevant. No significant alterations in hematological parameters or other clinical chemistry parameters or organ weights were observed.

Dose and end point used for MRL derivation: The MRL is based on a $NOAEL_{HED}$ of 6.45 mg/kg/day for tremors and convulsions in a 14-day study.

[X] NOAEL [ ] LOAEL

PBPK modeling was used to estimate internal dose metrics for brain RDX levels and for estimating HEDs. Code for an RDX oral PBPK model was provided by LM Sweeney along with documentation of parameter values (Sweeney et al. 2012). The Sweeney et al. (2012) model is based on the rat model reported by Krishnan et al. (2009) with modifications made to the gastrointestinal tract parameters, to include two compartments (stomach and small intestine). Sweeney et al. (2012) scaled the rat model to the human and estimated human gastrointestinal absorption and liver metabolism parameter values based on optimization against serum RDX-time profiles from humans accidentally exposed to RDX. Code for the Sweeney et al. (2012) model was implemented in acsLX v 3.0.1.6, without modification to the human or rat parameter values. Performance of the implementation was verified by comparing output to plots shown in Figure 2-4 of Sweeney et al. (2012).

The model was used for interspecies extrapolation of rat internal dosimetry to humans using the following procedure:

1. The rat model was used to simulate external rat dosages used in relevant bioassays and to predict the corresponding internal dose metric, peak concentration of RDX in brain (CB_{peak}) and mean concentration of RDX in brain (CB_{mean}).

2. Gavage doses (mg/kg/day) were assumed to be delivered as a single bolus each day, at the exposure frequency (days/week) used in the bioassay.

3. Rat model simulations were carried out for 14 days for acute exposures.

4. Rat body weights used in the simulations were the time-weighted average (TWA) body weights for each dose group.

5. The human model was used to predict the daily dosage (mg/kg/day) corresponding to the NOAEL for peak brain concentration in the rat.

6. A body weight of 70 kg was assumed for humans.

7. Daily doses (mg/kg/day) in humans were assumed to be delivered in 12 consecutive hourly doses, separated by 12-hour intervals, 7 days/week.

8. Human model simulations were carried out for 14 days for acute exposures.

The peak and mean brain concentrations for each dose are presented in Table A-1.

Table A-1. Estimated Peak and Mean Brain Concentrations in Rats Administered RDX Via Gavage 7 Days/Week for 14 Days

Dose (mg/kg/day)	TWA body weight (kg)	Peak brain concentration (mg/L)	Mean brain concentration (mg/L)
Males			
0	0.2039	0	0
2.13	0.2044	1.602	0.6645
4.25	0.2017	3.198	1.3232
8.5	0.1915	6.351	2.6018
17	0.1826	12.619	5.1232
25.5	0.1886	19.012	7.7666
34	0.1693[a]	24.979	9.9956
42.5	0.1683[a]	31.198	12.4702
Females			
0	0.1403	0	0
2.13	0.1375	1.518	0.5835
4.25	0.1397	3.042	1.1732
8.5	0.131	6.033	2.2974
17	0.1347	12.1211	4.6369
25.5	0.1374	18.214	7.0007
34	0.1250[a]	23.982	9.0492
42.5	0.1262[a]	30.016	11.3470

[a]Day 1 body weight used due to high mortality (100% mortality on day 1 in 42.5 mg/kg/day males and females and 34 mg/kg/day females and 83% mortality on day 1 in 34 mg/kg/day males)

TWA = time-weighted average

Source: U.S. Army 2006

The acute-duration oral MRL was derived using the NOAEL/LOAEL approach; the lack of incidence data for the neurological effects precluded using a benchmark dose approach. The U.S. Army (2006) study identified a NOAEL of 8.5 mg/kg/day and LOAEL of 17 mg/kg/day for neurological effects. The PBPK model was used to predict peak brain RDX concentrations and mean brain RDX concentrations associated with these dose levels. In animals dosed with 8.5 mg/kg/day, the model predicted peak brain concentrations of 6.351 mg/L in males and 6.033 mg/L in females and mean brain concentrations of 2.602 and 2.297 mg/L in males and females, respectively. Mechanistic data provide strong support that the mode of action for seizures involves binding to GABA receptors and there is a direct relationship between RDX levels in the brain and the onset of seizures (Gust et al. 2009; Williams et al. 2011). However, there are insufficient data to determine whether peak brain RDX concentration or mean brain RDX concentration is the most appropriate internal dose metric. As presented in Table A-2, a comparison of the NOAEL and LOAEL values for seizures in rats exposed for intermediate or chronic durations suggests that peak brain concentration may be the most appropriate internal dose metric. The mean brain concentrations are similar for rats exposed to 8 mg/kg/day for 90 days or 2 years; however, seizures/convulsions were observed at this dose level in the 90-day study, but not in the 2-year study. In contrast to the mean concentrations, the peak brain concentration in the 90-day study was 34% higher

than in the 2-year study; this difference in peak concentrations may explain the apparent difference in seizure threshold. Thus, peak brain concentration was selected as the internal dose metric for derivation of the acute-duration oral MRL. Since the U.S. Army (2006) study did not identify gender-specific differences in RDX sensitivity, the peak brain concentrations were averaged for the male and females rats. In the rats administered 8.5 mg/kg/day RDX, the average peak brain RDX concentration was predicted to be 6.192 mg/L. This peak brain concentration was used to predict a HED of 6.455 mg/kg/day using the PBPK model.

Table A-2. Comparison of NOAEL and LOAEL Values Using Different Dose Metrics Following Intermediate- and Chronic-Duration Exposure to RDX

	Intermediate exposure[a] (U.S. Army 2006)	Chronic exposure[b] (U.S. Army 1983a)
NOAEL[c]		
Administered dose	4 mg/kg/day	8 mg/kg/day
Peak brain concentration	2.923 mg/L	4.051 mg/L
Mean brain concentration	1.308 mg/L	2.959 mg/L
LOAEL[c]		
Administered dose	8 mg/kg/day	40 mg/kg/day
Peak brain concentration	6.013 mg/L	18.694 mg/L
Mean brain concentration	2.615 mg/L	14.403 mg/L

[a]RDX administered via gavage, 7 days/week for 90 days
[b]RDX administered via the diet for 2 years
[c]Average of male and female values

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

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

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

Other additional studies or pertinent information that lend support to this MRL: Human case reports have noted convulsions and seizures in individuals ingesting RDX (Hollander and Colbach 1969; Ketel and Hughes 1972; Küçükardalĭ et al. 2003; Merrill 1968; Stone et al. 1969; Woody et al. 1986). Several acute toxicity studies have reported convulsions, seizures, or tremors in rats at doses slightly higher than the LOAEL of 17 mg/kg/day identified in the U.S. Army (2006) study. These LOAEL values are 20 mg/kg/day in two gestational exposure studies (U.S. Army 1980b, 1986d) and 25 mg/kg in rats administered a single gavage dose (Burdette et al. 1988). In addition, decreases in motor activity and learning were observed in rats receiving a single gavage dose of 12.5 mg/kg/day (U.S. Army 1985b).

Although the potential for systemic effects has not been well investigated following acute exposure, intermediate-duration studies (U.S. Army 1980b, 1983a, 2006; U.S. Navy 1974b) provide support that neurotoxicity is the most sensitive effect of RDX.

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: RDX
CAS Numbers: 121-82-4
Date: August 2011
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 50
Species: Rat

Minimal Risk Level: 0.1 [X] mg/kg/day [ ] ppm

Reference: U.S. Army. 2006. Toxicology study no. 85-XC-5131-03. Subchronic oral toxicity of RDX in rats. Aberdeen Proving Ground, MD: U.S. Army Center for Health Promotion and Preventive Medicine.

Experimental design: Groups of 10 male and 10 female F344 rats were administered via gavage 0, 4, 8, 10, 12, or 15 mg/kg/day as a suspension of RDX/1% methylcellulose/0.2% Tween 80 in distilled water 7 days/week for 90 days. Rats were monitored weekly for toxic signs and FOB observations (home-cage, hand held, and open arena observations); body weights and feed consumption were also measured weekly. Additional parameters used to assess toxicity included neurobehavioral tests after week 11 (motor activity, grip strength, and sensory reactivity to different types of stimuli), ophthalmic examination, urinalysis (volume, color, appearance, pH, specific gravity, glucose, bilirubin, urobilinogen, ketone, blood, protein, nitrite, leukocytes), clinical chemistry (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, sodium, potassium, chlorine, cholesterol, creatinine kinase, creatinine, glucose, lactate dehydrogenase, total bilirubin, total protein, triglycerides), hematology (hemoglobin, hematocrit, erythrocytes, mean cell hemoglobin concentration, mean cell volume, mean cell hemoglobin, red blood cell distribution width, total and differential leukocytes, platelets, and mean platelet volume) values, coagulation (average and activated prothrombin time), organ weights (brain, heart, liver, kidneys, spleen, adrenals, thymus, epididymides, uterus, testes, ovaries), gross necropsies, and histopathological examination of major tissues and organs from rats exposed to 0 or 15 mg/kg/day. In addition, potential immunotoxicity was assessed using the following tests: red and white blood cell populations and spleen and thymus relative organ weights, cellularity as a proportion of organ weight, and proportion of cell surface markers.

Effect noted in study and corresponding doses: Increased mortality was observed at ≥8 mg/kg/day; the number of preterm deaths were 2/20, 5/20, 8/20, and 7/20 in the 8, 10, 12, and 15 mg/kg/day groups, respectively. Convulsions were observed in most animals dying early. Transient clinical signs included changes in arousal, blepharosis, increased salivation, blood stains around mouth and nose, rough haircoat, tremors, and convulsions; the incidence and severity of these effects increased with dose. Neuromuscular effects were observed within the first week of exposure in the higher dose groups and persisted throughout the study. Increased arousal was observed in 25, 40, and 100% of rats in the 10, 12, and 15 mg/kg/day groups; convulsions were observed in 15, 30, 65, and 60% of rats in the 8, 10, 12, and 15 mg/kg/day groups, respectively; and tremors were observed in 10 and 20% of rats in the 12 and 15 mg/kg/day groups. Increased urine volume was observed in females exposed to 12 or 15 mg/kg/day; the investigators noted that the increased urine volume may be related to the palatability of the suspension since higher dose animals were frequently observed drinking immediately after dosing. Significant decreases in body weight gain were observed in the male rats; however, body weights were typically within 10% of controls. In the females, significant increases in body weight were observed; at termination, the females in the 10, 12, and 15 mg/kg/day groups weighed at least 14% more than controls.

Significant alterations in organ weights were observed in male rats; these included increased brain weight at 12 and 15 mg/kg/day, decreased relative (to body weight and brain weight) testes weight at ≥10 mg/kg/day, and decreased relative (to brain weight) epididymis weight at ≥8 mg/kg/day. In the females, significant alterations in organ weights included increased spleen, liver, and kidney weights at 10, 12 (spleen only), or 15 mg/kg/day; relative brain weight at ≥10 mg/kg/day; and increased relative (to brain) kidney, liver, and spleen weights at 10 and 15 mg/kg/day. Significant increases in mean cell volume were observed at 8 (males only), 10, and 12 mg/kg/day and significant decreases in cholesterol levels were observed in males exposed to ≥8 mg/kg/day. No significant increases in the incidence of histopathological alterations were observed. A significant increase in abnormal skin appearance (stained haircoat) was observed in females exposed to 15 mg/kg/day during week 12. The presence of barbering was significantly increased in females exposed to 15 mg/kg/day during weeks 9 and 12. No RDX related alterations in immunological parameters were observed. Although the incidence of convulsions was not statistically significant at 8 mg/kg/day, this dose level, which likely falls just below the NOAEL/LOAEL boundary, was considered a LOAEL due the seriousness of the effect.

Dose and end point used for MRL derivation: The $BMDL_{HED}$ of 4.1308 mg/kg/day for convulsions was used as the point of departure for the MRL.

[ ] NOAEL [ ] LOAEL [X] $BMDL_{10}$

PBPK modeling was used to estimate internal dose metrics for brain RDX levels and for estimating HEDs. Code for an RDX oral PBPK model was provided by LM Sweeney along with documentation of parameter values (Sweeney et al. 2012). The Sweeney et al. (2012) model is based on the rat model reported by Krishnan et al. (2009) with modifications made to the gastrointestinal tract parameters, to include two compartments (stomach and small intestine). Sweeney et al. (2012) scaled the rat model to the human and estimated human gastrointestinal absorption and liver metabolism parameter values based on optimization against serum RDX-time profiles from humans accidentally exposed to RDX. Code for the Sweeney et al. (2012) model was implemented in acsLX v 3.0.1.6, without modification to the human or rat parameter values. Performance of the implementation was verified by comparing output to plots shown in Figure 2-4 of Sweeney et al. (2012).

The model was used for interspecies extrapolation of rat internal dosimetry to humans using the following procedure:

1. The rat model was used to simulate external rat dosages used in relevant bioassays and to predict the corresponding internal dose metrics, peak concentration of RDX in brain (CB_{peak}) and mean concentration of RDX in brain (CB_{mean}).

2. Gavage doses (mg/kg/day) were assumed to be delivered as a single bolus each day, at the exposure frequency (days/week) used in the bioassay.

3. Rat model simulations were carried out until steady state had been achieved for intermediate-duration exposures.

4. Rat body weights used in the simulations were the TWA body weights for each dose group.

5. The human model was used to predict the daily dosage (mg/kg/day) corresponding to the BMDL for peak brain concentration in the rat.

6. A body weight of 70 kg was assumed for humans.

7. Daily doses (mg/kg/day) in humans were assumed to be delivered in 12 consecutive hourly doses, separated by 12-hour intervals, 7 days/week.

8. Human model simulations were carried out until steady state had been achieved for intermediate-duration exposures.

The peak and mean brain concentrations for each dose are presented in Table A-3.

Table A-3. Estimated Peak and Mean Brain Concentrations in Rats Administered RDX Via Gavage 7 Days/Week for 90 Days

Dose (mg/kg/day)	TWA body weight (kg)	Peak brain concentration (mg/L)	Mean brain concentration (mg/L)
Males			
0	0.2558	0	0
4	0.2435	3.090	1.3947
8	0.2362	6.154	2.7616
10	0.2418	7.718	3.4787
12	0.2446	9.277	4.1903
15	0.2579	11.683	5.3301
Females			
0	0.1642	0	0
4	0.1626	2.923	1.2209
8	0.1682	5.873	2.4692
10	0.1714	7.359	3.1057
12	0.1722	8.837	3.7325
15	0.1849	11.154	4.7764

TWA = time-weighted average

Source: U.S. Army 2006

The intermediate-duration oral MRL was derived using a benchmark dose modeling approach. Peak brain concentration and mean brain concentration were considered potential internal dose metrics for the benchmark dose modeling. Mechanistic data provide strong support that the mode of action for seizures involves binding to GABA receptors and there is a direct relationship between RDX levels in the brain and the onset of seizures (Gust et al. 2009; Williams et al. 2011). However, there are insufficient data to determine whether peak brain RDX concentration or mean brain RDX concentration is the most appropriate internal dose metric. As presented in Table A-4, the empirical data for seizures/convulsions appears to support using peak brain concentration as the internal dose metric. The mean brain concentrations are similar for rats exposed to 8 mg/kg/day for 90 days or 2 years; however, seizures/convulsions were observed at this dose level in the 90-day study, but not in the 2-year study. In contrast to the mean concentrations, the peak brain concentration in the 90-day study was 34% higher than in the 2-year study; this difference in peak concentrations may explain the apparent difference in seizure threshold.

Table A-4. Comparison of NOAEL and LOAEL Values Using Different Dose Metrics Following Intermediate- and Chronic-Duration Exposure to RDX

	Intermediate exposure[a] (U.S. Army 2006)	Chronic exposure[b] (U.S. Army 1983a)
NOAEL[c]		
Administered dose	4 mg/kg/day	8 mg/kg/day
Peak brain concentration	2.923 mg/L	4.051 mg/L
Mean brain concentration	1.308 mg/L	2.959 mg/L
LOAEL[c]		
Administered dose	8 mg/kg/day	40 mg/kg/day
Peak brain concentration	6.013 mg/L	18.694 mg/L
Mean brain concentration	2.615 mg/L	14.403 mg/L

[a]RDX administered via gavage, 7 days/week for 90 days.
[b]RDX administered via the diet for 2 years.
[c]Average of male and female values.

Data for the incidence of convulsions (summarized in Table A-5) were fit to all available dichotomous models in the EPA Benchmark Dose Software (BMDS) (version 2.1.2) using the extra risk option and using peak brain RDX concentration as the dose metric. Since the study did not identify gender-specific differences in RDX sensitivity, the peak brain concentrations were averaged for the male and female rats and these combined values were used for benchmark dose modeling. Adequate model fit was judged by three criteria: χ^2 goodness-of-fit p-value ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. BMDs and lower bounds on the BMD (BMDL) associated with a BMR of 10% extra risk were calculated for all models and are presented in Table A-6. As assessed by the χ^2 goodness-of-fit statistic, all of the models with the exception of the quantal linear and 1-degree polynomial models provided adequate fit to the data. Among all of the models providing adequate fit to the data, the BMDL from the model with the lowest Akaike's Information Criteria (AIC) was chosen. The log-probit model provided the best fit to the convulsion incidence data and is presented in Figure A-1. The BMDL of 3.9627 mg/L was used to predict a HED of 4.131 mg/kg/day using the PBPK model.

Table A-5. Incidence of Convulsions in Male and Female Fischer 344 Rats Administered RDX 7 Days/Week for 90 Days

Dose (mg/kg/day)	Peak brain concentration (mg/L)	Incidence
0	0	0/20
4	3.005	0/20
8	6.013	3/20
10	7.539	6/20
12	9.057	13/20
15	11.419	12/20

Source: U.S. Army 2006

Table A-6. Model Predictions for the Incidence of Convulsions in Rats Administered RDX via Gavage for 90 Days Using Peak Brain Concentration as the Internal Dose Metric

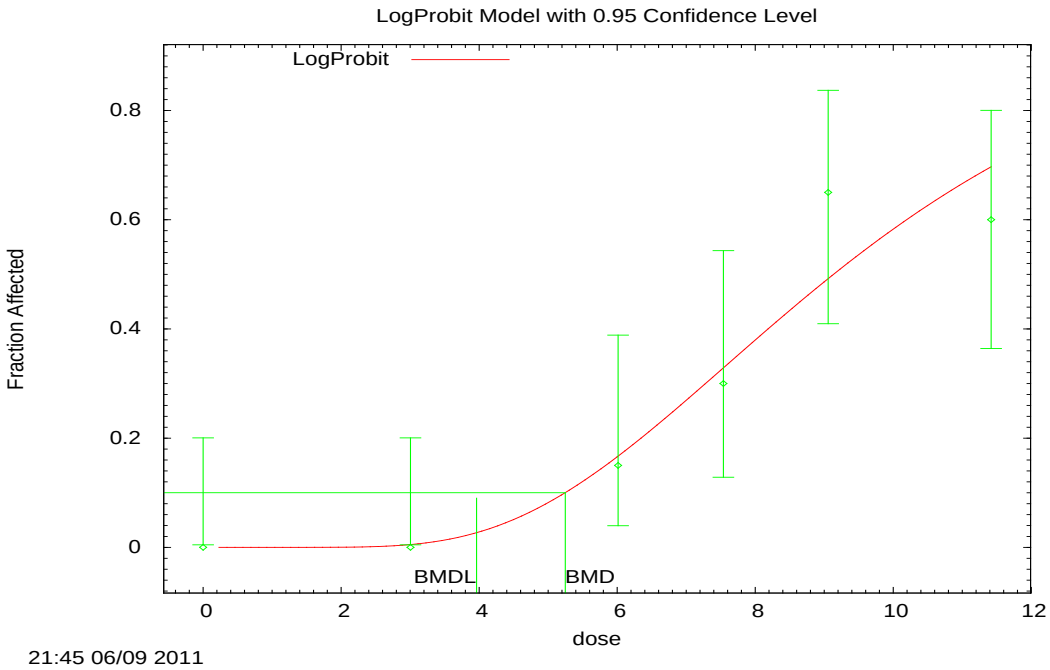
Model	χ^2 Goodness of fit p-value[a]	AIC	BMD_{10} (mg/L)	$BMDL_{10}$ (mg/L)
Gamma[b]	0.4648	101.924	5.17803	3.79207
Logistic	0.2121	104.808	5.14052	3.99687
LogLogistic	0.4945	101.781	5.18956	3.8386
LogProbit	**0.5406**	**101.353**	**5.24819**	**3.9627**
Multistage (1-degree polynomial)[c]	0.3663	111.445	3.75703	2.82257
Multistage (2-degree polynomial[c]	0.0383	102.99	NA	NA
Probit	0.2696	103.851	5.11305	3.88122
Weibull[b]	0.352	103.06	4.87416	3.43247
Quantal-Linear	0.0383	111.445	NA	NA

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Betas restricted to ≥0.

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD; NA = not applicable, model does not provide adequate fit to the data

Source: U.S. Army 2006

Figure A-1. Fit of Log Probit Model to Data on the Incidence of Convulsions in Rats Administered RDX via Gavage for 90 Days Using Peak Brain RDX Concentration as the Dose Metric



Source: U.S. Army 2006

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

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

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

Other additional studies or pertinent information that lend support to this MRL: No human studies have examined the toxicity of RDX following intermediate-duration exposure. Several animal studies have reported neurological effects, primarily convulsions, seizures, and/or tremors in rats at doses of ≥8 mg/kg/day (U.S. Army 1983a, 2006; von Oettingen et al. 1949), monkeys at 10 mg/kg/day (U.S. Navy 1974b), and dogs at 50 mg/kg/day (von Oettingen et al. 1949). Hyperactivity was noted in rats exposed to 100 mg/kg/day (Levine et al. 1981, 1990). The results of the U.S. Army (2006) study suggest that there is a steep dose-response curve for seizure induction. The occurrences of seizures were 0% at 4 mg/kg/day, 20–30% at 8 mg/kg/day, 45–50% at 10 mg/kg/day, and 80–90% at 12 or 15 mg/kg/day.

In addition to these neurological effects, less serious adverse health effects have been observed at similar or higher dose levels. Several studies have found changes in serum chemistry parameters suggestive of

impaired liver function, although histological alterations were not generally found in the liver. Decreases in serum cholesterol and/or triglycerides were observed at ≥8 mg/kg/day (U.S. Army 1983a, 2006; Levine et al. 1981) and decreases in serum alanine aminotransferase levels were observed at 28 mg/kg/day (U.S. Army 1980b). The magnitude of these alterations was small and not likely to be biologically significant. Minor hematological effects (small decreases in erythrocyte and hemoglobin levels) were observed in rats exposed to 40 mg/kg/day (U.S. Army 1983a) and mice exposed to 160 mg/kg/day (U.S. Army 1980b); however, other studies have not found significant alterations in hematological parameters (U.S. Army 1980b, 2006; von Oettingen et al. 1949). Emesis was observed in monkeys administered via gavage 10 mg/kg/day for 90 days (U.S. Navy 1974b); the incidence in monkeys administered 1 mg/kg/day was not considered to be different from the controls. There is limited evidence that RDX is a reproductive toxicant. Spermatic granuloma in the prostrate was observed in rats exposed to 40 mg/kg/day for 6 months (U.S. Army 1983a). Decreases in F_2 pup body weight and increases in the incidence of renal cysts were observed at 16 mg/kg/day and an increase in the number of stillbirths and decreased pup survival were observed in the F_1 generation at 50 mg/kg/day was observed in a two-generation study in rats (U.S. Army 1980b).

Agency Contacts (Chemical Managers): Henry Abadin

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: RDX
CAS Numbers: 121-82-4
Date: August 2011
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 65
Species: Rat

Minimal Risk Level: 0.1 [X] mg/kg/day [ ] ppm

Reference: U.S. Army. 1983a. Determination of the chronic mammalian toxicological effects of RDX: Twenty-four month chronic toxicity/carcinogenicity study of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) in the Fischer 344 rat: Phase V. Vol. 1. Frederick, MD: U.S. Army Medical Research and Development Command. ADA160774. (author: Levine BS et al.)

Experimental design: Groups of male and female Fischer 344 rats (75/sex/group) were exposed to 0, 0.3, 1.5, 8.0, or 40.0 mg/kg/day RDX in the diet for 2 years. Ten animals/sex/dose were sacrificed during weeks 27 and 53. The following parameters were used to assess toxicity: daily observations; ophthalmic examinations during weeks 2, 25, 51, 76, and 103; hematology (hematocrit, hemoglogin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, erythrocyte count, total and differential leukocyte count, and platelet count) and clinical chemistry (glucose, blood urea nitrogen, alanine aminotransferase, bilirubin, creatinine phosphokinase, lactic dehydrogenase, alkaline phosphatase, triglycerides, total cholesterol, total protein, albumin, globulin, sodium, potassium, chloride, and calcium levels) of blood samples collected during weeks 13, 26, 52, 78, and 104; organ weights (adrenal, brain, heart, kidneys, liver, ovaries, spleen, and testes), and complete histopathology of major tissues and organs of rats in the 0 or 40.0 mg/kg/day groups, and histopathological examination of the brain, gonads, heart, liver, kidneys, spleen, and spinal cord of rats in the 0.3, 1.5, and 8.0 mg/kg/day groups. Actual RDX doses were within 3% of the intended dose.

Effect noted in study and corresponding doses: Deaths were observed at 40 mg/kg/day; 88% of males and 41% of females died by week 88. The mean survival time for the 40 mg/kg/day males was 14.6 months compared with 22.3 months for the control males. A 20.6 month survival time was seen for the 40 mg/kg/day females vs. 22.0 months for the control females at 40 mg/kg/day. A significant decrease in survival time was also observed in the males exposed to 1.5 mg/kg/day (21.0 months); however, no alterations in survival time was observed in the females exposed to 1.5 mg/kg/day (22.2 months) or in the males (22.2 months) or females (22.4 months) exposed to 8 mg/kg/day. Additionally, there were no significant differences in mortality incidence in the 1.5 or 8 mg/kg/day groups, as compared to controls. Decreased body weight gain was observed in males (20–30%) and females (10–15%) exposed to 40.0 mg/kg/day; significant decreases in body weight gain were also observed at 8.0 mg/kg/day, but the body weight was within 5% of controls. Slight, but significant, reductions in food intake were observed in males at 40.0 mg/kg/day. Tremors and convulsions were observed prior to death at 40 mg/kg/day beginning after 26 weeks of exposure. Animals were hyperreactive to approach and had increased fighting; hyperreactivity was first observed after 9 weeks of exposure to 40 mg/kg/day. No adverse clinical signs were noted for the lower dose groups. Significant decreases in hemoglobin and erythrocyte counts were observed in the 40 mg/kg/day group beginning at week 26; the study investigators noted that the anemic state was considered slight and there was no evidence of physiologic compensatory responses. Thrombocytosis was observed in rats exposed to 40 mg/kg/day and elevated platelet counts were

observed in 8 mg/kg/day males during weeks 13 and 26. Significant decreases in blood glucose, total cholesterol, and triglyceride levels were observed in the 40 mg/kg/day group starting at week 13. Significant decreases in serum alanine aminotransferase levels were observed in males exposed to 8 or 40 mg/kg/day at weeks 26 and 52 and in females at 40 mg/kg/day at week 26. Other clinical chemistry alterations included decreases in globulin and albumin levels at weeks 52 and 78 and increases in serum potassium levels at weeks 26, 52, and 78. A significant increase in the incidence of cataracts was observed in females in the 40 mg/kg/day group during weeks 78 and 104. Splenic extramedullary hematopoiesis and spermatic granuloma of the prostate were observed in rats exposed to 40 mg/kg/day for 6 months. At 1 year, histological alterations in the urinary bladder (luminal distention and cystitis), kidneys (medullary papillary necrosis), and testes (germinal cell degeneration, enlarged seminal vesicles) were observed in males exposed to 40 mg/kg/day and in the spleen (enlarged dark-red spleens with histological evidence of sinusoidal congestion) of males and females exposed to 40 mg/kg/day. The following effects were observed at 2 years: suppurative inflammation of the prostate in the 1.5, 8, and 40 mg/kg/day groups; renal medullary papillar necrosis, renal pyelitis, and urinary bladder luminal distension and cystitis in males exposed to 40 mg/kg/day; splenic extramedullary hematopoiesis in female rats exposed to 40 mg/kg/day; and hemosiderin-like pigment in males exposed to 1.5, 8, or 40 mg/kg/day. In the absence of altered hematological parameters or other effects on the spleen, the increased pigment levels observed at 1.5 or 8 mg/kg/day were not considered adverse.

Dose and end point used for MRL derivation: The MRL is based on a $NOAEL_{HED}$ of 4.223 mg/kg/day for tremors and convulsions in a 2-year study.

[X] NOAEL [ ] LOAEL

PBPK modeling was used to estimate internal dose metrics for brain RDX levels and for estimating HEDs. Code for an RDX oral PBPK model was provided by LM Sweeney along with documentation of parameter values (Sweeney et al. 2012). The Sweeney et al. (2012) model is based on the rat model reported by Krishnan et al. (2009) with modifications made to the gastrointestinal tract parameters, to include two compartments (stomach and small intestine). Sweeney et al. (2012) scaled the rat model to the human and estimated human gastrointestinal absorption and liver metabolism parameter values based on optimization against serum RDX-time profiles from humans accidentally exposed to RDX. Code for the Sweeney et al. (2012) model was implemented in acsLX v 3.0.1.6, without modification to the human or rat parameter values. Performance of the implementation was verified by comparing output to plots shown in Figure 2-4 of Sweeney et al. (2012).

The model was used for interspecies extrapolation of rat internal dosimetry to humans using the following procedure:

1. The rat model was used to simulate external rat dosages used in relevant bioassays and to predict the corresponding internal dose metric, peak concentration of RDX in brain (CB_{peak}) and mean concentration of RDX in brain (CB_{mean}).

2. Dietary doses (mg/kg/day) were assumed to be delivered in 12 consecutive hourly doses, separated by 12-hour intervals, at the exposure frequency (days/week) used in the bioassay.

3. Rat model simulations were carried out until steady state had been achieved for chronic-duration exposures.

4. Rat body weights used in the simulations were the TWA body weights for each dose group.

5. The human model was used to predict the daily dosage (mg/kg/day) corresponding to the NOAEL for peak brain concentration in the rat.

6. A body weight of 70 kg was assumed for humans.

7. Daily doses (mg/kg/day) in humans were assumed to be delivered in 12 consecutive hourly doses, separated by 12-hour intervals, 7 days/week.

8. Human model simulations were carried out until steady state had been achieved for chronic-duration exposures.

The peak brain concentrations for each dose are presented in Table A-7.

Table A-7. Estimated Peak and Mean Brain Concentrations in Rats Administered RDX Via the Diet for 2 Years

Dose (mg/kg/day)	TWA body weight (kg)	Peak brain concentration (mg/L)	Mean brain concentration (mg/L)
Males			
0	0.3889	0	0
0.3	0.3904	0.165	0.122
1.5	0.3848	0.823	0.607
8	0.373	4.344	3.205
40	0.3244	20.885	15.304
Females			
0	0.2302	0	0
0.3	0.2297	0.142	0.102
1.5	0.2278	0.707	0.511
8	0.2248	3.763	2.712
40	0.2218	18.694	13.502

TWA = time-weighted average

Source: U.S. Army 1983a

The U.S. Army (1983a) study identified a NOAEL of 8 mg/kg/day and LOAEL of 40 mg/kg/day for tremors and convulsions in rats exposed to RDX in the diet for 2 years. A chronic-duration oral MRL was derived using the NOAEL/LOAEL approach; benchmark dose modeling could not be utilized because the investigators did not report incidence data for neurological signs. The NOAEL from the U.S. Army (1983a) study corresponds to peak brain concentrations of 4.344 and 3.763 mg/L in males and females, respectively, and mean brain RDX concentrations of 3.205 and 2.712 mg/L in males and females, respectively. Mechanistic data provide strong support that the mode of action for seizures involves binding to GABA receptors and there is a direct relationship between RDX levels in the brain and the onset of seizures (Gust et al. 2009; Williams et al. 2011). However, there are insufficient data to determine whether peak brain RDX concentration or mean brain RDX concentration is the most appropriate internal dose metric. As presented in Table A-8, a comparison of the NOAEL and LOAEL values for seizures in rats exposed for intermediate or chronic durations suggests that peak brain

concentration may be the most appropriate internal dose metric. The mean brain concentrations are similar for rats exposed to 8 mg/kg/day for 90 days or 2 years; however, seizures/convulsions were observed at this dose level in the 90-day study, but not in the 2-year study. In contrast to the mean concentrations, the peak brain concentration in the 90-day study was 34% higher than in the 2-year study; this difference in peak concentrations may explain the apparent difference in seizure threshold. Thus, peak brain concentration was selected as the internal dose metric for derivation of the acute-duration oral MRL. Since the U.S. Army (1983a) study did not identify gender-specific differences in RDX sensitivity, the peak brain concentrations were averaged for the male and females rats. The average peak brain concentration of 4.051 mg/L was used to predict a HED of 4.223 mg/kg/day using the PBPK model.

Table A-8. Comparison of NOAEL and LOAEL Values Using Different Dose Metrics Following Intermediate- and Chronic-Duration Exposure to RDX

	Intermediate exposure[a] (U.S. Army 2006)	Chronic exposure[b] (U.S. Army 1983a)
NOAEL[c]		
Administered dose	4 mg/kg/day	8 mg/kg/day
Peak brain concentration	2.923 mg/L	4.051 mg/L
Mean brain concentration	1.308 mg/L	2.959 mg/L
LOAEL[c]		
Administered dose	8 mg/kg/day	40 mg/kg/day
Peak brain concentration	6.013 mg/L	18.694 mg/L
Mean brain concentration	2.615 mg/L	14.403 mg/L

[a]RDX administered via gavage, 7 days/week for 90 days.
[b]RDX administered via the diet for 2 years.
[c]Average of male and female values.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

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

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

Other additional studies or pertinent information that lend support to this MRL: No human studies have examined the chronic toxicity of RDX following oral exposure. A number of human case reports have noted convulsions and seizures in individuals ingesting RDX (Hollander and Colbach 1969; Ketel and Hughes 1972; Küçükardalĩ et al. 2003; Merrill 1968; Stone et al. 1969; Woody et al. 1986). The chronic oral toxicity of RDX has been evaluated in two rat studies (U.S. Army 1983a; U.S. Navy 1976) and a mouse study (U.S. Army 1984c). A number of adverse health effects have been observed in rats exposed to 40 mg/kg/day including tremors, convulsions, and hyperresponsiveness; decreased hematocrit,

hemoglobin, and erythrocyte levels; hepatomegaly and decreased serum cholesterol and triglycerides; renal papillary necrosis and increased blood urea nitrogen levels; testicular degeneration; and cataracts (females only) (U.S. Army 1983a). This dose was also associated with an 88% mortality rate. In addition to these effects, significant increases in the incidence of suppurative inflammation were observed in the prostate of rats exposed to ≥1.5 mg/kg/day (U.S. Army 1983a). U.S. Army (2006) noted that inflammation of the prostate gland is a common condition in older rodents and is generally not due to toxicity; additionally, the prostate effects in the U.S. Army (1983a) study were predominantly found in rats dying early.

In the second rat study, no adverse effects were observed at doses as high as 10 mg/kg/day (U.S. Navy 1976). This study did not include a histological examination of the prostate, and the animals were monitored weekly for overt signs of toxicity. In mice, increases in serum cholesterol levels were observed in females exposed to 35 mg/kg/day and increased relative kidney weights and cytoplasmic vacuolization in the kidney were observed at 100 mg/kg/day. The NOAEL for the hepatic effects was 7 mg/kg/day.

Agency Contacts (Chemical Managers): Henry Abadin

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

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

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a 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.

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 (<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,

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/m^3 or ppm and oral exposure is reported in mg/kg/day.

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

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

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

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

SAMPLE

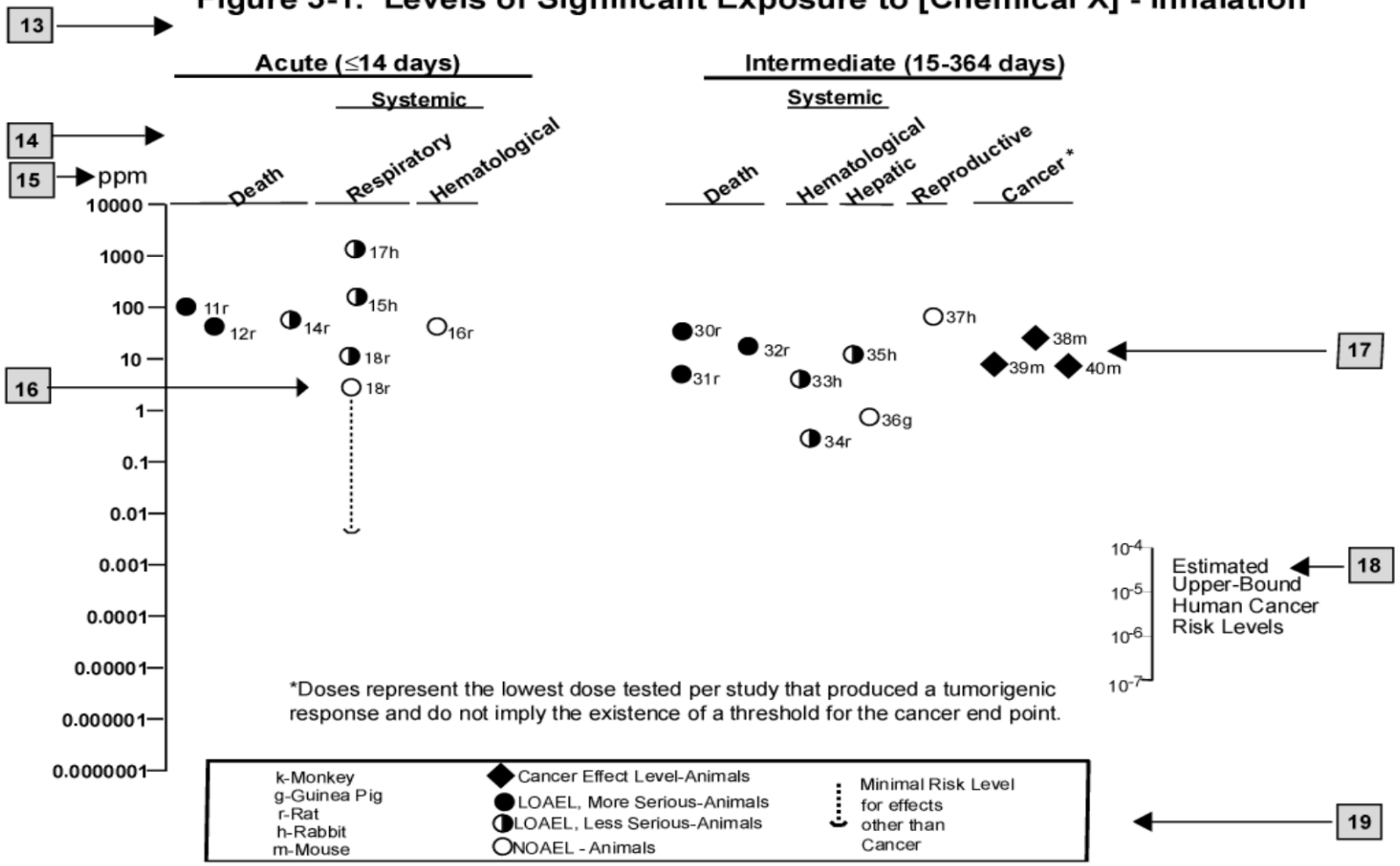
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

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

SAMPLE

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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
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
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid

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

OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
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

>	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

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APPENDIX D. INDEX