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-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Phenol
CAS Numbers: 108-95-2
Date: August 10, 2006
Profile Status: Third Draft
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 1
Species: Rat

Minimal Risk Level: 0.02 [ ] mg/kg/day [x] ppm

Reference: Hoffman GM, Dunn BJ, Morris CR, et al. 2001. Two-week (ten-day) inhalation toxicity and two-week recovery study of phenol vapor in the rat. Int J Toxicol 20:45-52.

Experimental design: Groups of Fisher 344 rats (20/sex/group) were exposed nose-only to phenol vapors in concentrations of 0, 0.5, 5, or 25 ppm 6 hours/day, 5 days/week for 2 weeks. Rats were observed daily for morbidity and mortality and for adverse neurobehavioral signs. At termination, 10 rats/sex/group were used for clinical chemistry and hematology evaluations and for histopathological examinations of nasopharyngeal tissues, larynx, trachea, lungs with mainstem bronchi, kidney, liver, and spleen. The remaining 10 rats per group were kept for a 2-week recovery period, after which time they were sacrificed.

Effect noted in study and corresponding doses: There were no chemical-related deaths. The only clinical signs were observations of a red nasal discharge during the 2 weeks of exposure. However, the investigators stated that there was no clear pattern and that the signs had almost disappeared after the 2-week recovery period. It should be noted that an unpublished version of the study (CMA 1998) showed that the incidence of the red nasal discharge was concentration-related in males during the second week of exposure. Pairwise comparison with controls shows a statistically significant increased incidence at 5 and 25 ppm in males. However, there is evidence that a tear-like nasal discharge in rats can be a generalized response to stress from a variety of causes. Porphyrins in the discharge lead to a red color. A red nasal discharge also was noticed in rats in a two-generation drinking water study in all groups, including controls, although the incidence was higher in phenol-treated rats (Ryan et al. 2001). The fact that the incidences were concentration-related in the Hoffman et al. (2001) study suggests that the effect is likely related to phenol, possibly to the irritating properties of phenol. Yet, in the absence of nasal histopathology, the nasal discharge is not considered an adverse effect. There were no significant alterations in body weight gain during the study. The only significant hematology change was an increase in prothrombin time in 0.5 ppm females at the recovery sacrifice. The only significant clinical chemistry change was an increase in serum albumin in 25 ppm females at the recovery sacrifice. Significant changes in organ weights were limited to a decrease in relative liver and spleen weight in 5 ppm females at terminal sacrifice and a decrease in spleen to brain weight in the same group of females. Gross and microscopic examinations of the tissues were unremarkable. The study NOAEL is 25 ppm; no LOAEL was defined.

Dose and end point used for MRL derivation: 25 ppm is a NOAEL for nasal effects

[x] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans with dosimetric adjustment
[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: The acute-duration inhalation MRL was calculated using EPA's methodology (EPA 1994a) for a category 1 gas.

$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RGDR_r$ where

$NOAEL_{[ADJ]}$ = 25 ppm x 6/24 hours x 5/7 days = 4.5 ppm and

$RGDR_{ET}$ = ratio of the regional gas dose in rats to that of humans for the extrathoracic region

$RGDR_{ET} = (VE/SA_{ET})_A / (VE/SA_{ET})_H$ where

VE = minute volume (0.137 L/minute for rats, 13.8 L/minute for humans [EPA 1994a]) and

SA_{ET} = surface area of the extrathoracic region (15 cm^2 for rats and 200 cm^2 for humans [EPA 1994a])

$NOAEL_{[HEC]}$ = 4.5 ppm x (0.137 L/minute/15 cm^2) / (13.8 L/minute/200 cm^2) = 0.6 ppm

Was a conversion used from intermittent to continuous exposure? Yes, see above.

Other additional studies or pertinent information that lend support to this MRL: An issue that had to be decided was what the critical end point should be because the highest exposure concentration was a NOAEL. The choices were the respiratory tract or a systemic extrarespiratory end point (i.e., hepatic, renal). Given that phenol is a recognized respiratory irritant, the respiratory tract was chosen as critical target, and, within the respiratory tract, the nasal region was selected, as it is likely to be the first region of contact and the most sensitive.

The acute-duration inhalation database for phenol is very limited. It includes a few animal studies of limited scope (Aranyi et al. 1986; De Ceaurriz et al. 1981; Flickinger 1976) and a well-conducted study that used modern methodology to evaluate a number of relevant end points (Hoffman et al. 2001). No relevant human studies were located. In the animal studies, a target for phenol toxicity was not clearly defined; however, for an irritant substance such as phenol, it is reasonable to assume that portals of entry, such as the respiratory tract, could be potential targets. Of the studies mentioned above, only Hoffman et al. (2001) conducted a careful evaluation of the respiratory tract. Hoffman et al. (2001) exposed rats to various exposure levels for 2 weeks and evaluated a number of end points including histopathology, hematology, and clinical chemistry and reported no adverse effects. De Ceaurriz et al. (1981) exposed

mice to various concentrations of phenol in air for 5 minutes and determined an RD_{50} (concentration that reduced the respiratory rate by 50%, a protective reflex response in rodents) of 166 ppm. Aranyi et al. (1986) also exposed mice to 5 ppm phenol 3 hours/day for 5 days and reported no significant changes in susceptibility to airborne bacterial agents relative to mice exposed to filtered air. Flickinger (1976) observed loss of coordination and tremors in rats exposed to 234 ppm phenol for 8 hours; a 1-hour exposure was without effect. No other exposure concentration was tested and no control group was used. Fourteen days later, the rats were sacrificed and subjected to gross necropsy. Flickinger (1976) indicated that no gross lesions were observed, but the scope of the examination was not specified. Of all the studies available, the one conducted by Hoffman et al. (2001) is the most complete, better-reported, and used modern methodology.

Agency Contacts (Chemical Managers): Jewel Crawford; Obaid Faroon; Jewell Wilson

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Phenol
CAS Numbers: 108-95-2
Date: August 10, 2006
Profile Status: Third Draft
Route: [ ] Inhalation [x] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 13
Species: Rat

Minimal Risk Level: 0.6 [x] mg/kg/day [ ] ppm

Reference: York. 1997. Oral (gavage) developmental toxicity study of phenol in rats. Proctor & Gamble Co. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0573686.

Experimental design: Groups of pregnant Sprague-Dawley rats (25/dose group) were dosed 3 times daily with 0, 20, 40, or 120 mg phenol/kg (total daily doses of 0, 60, 120, and 360 mg/kg) by gavage in water on gestation days (GDs) 6–15; the dosing volume was 10 mL/kg. Maternal end points evaluated included clinical signs, body weight, and food consumption. Dams were also observed for abortions and premature deliveries. Dams were sacrificed on GD 20 and a gross necropsy was conducted. The uterus was examined for pregnancy, number and distribution of implantations, live and dead fetuses, and early and late resorptions. Fetuses were weighed and examined for sex and gross external alterations. Half of the fetuses were examined for soft tissue alterations and the remaining fetuses were examined for skeletal alterations.

Effect noted in study and corresponding doses: One dam in the 360 mg/kg/day group died on GD 11 and the death was attributed to phenol treatment. Clinical signs considered treatment-related included excess salivation and tachypnea in rats exposed to 360 mg/kg/day. Gross necropsy of the dams did not reveal any treatment-related alterations. In the 120 mg/kg/day group, maternal body weight gain was significantly reduced for GDs 6–16 (11%) and for GDs 12–16 (19%), whereas in the 360 mg/kg/day group, body weight gain was reduced 38% for gestation days 6–16. Maternal final body weight in the 360 mg/kg/day group was reduced, but <10% relative to controls. Food consumption was reduced in the 360 mg/kg/day group by 16% for GDs 6–20 and by 15% for GDs 0–20; in the 120 mg/kg/day group, food consumption for GDs 6–16 was reduced 11%. Fetal body weight at the 360 mg/kg/day level was reduced 5–7% relative to controls. There was a significant decrease in ossification sites on the hindlimb metatarsals in the 360 mg/kg/day group. At the 120 and 360 mg/kg/day dose levels, there were increases in litters with fetuses with "any alteration" and with "any variation", but neither reached statistical significance and there were no clear dose-response relationships. There were no significant effects on corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, and percent resorbed conceptuses. Based on decreased fetal body weight and delayed ossification, the dose of 360 mg/kg/day is a LOAEL for developmental effects; the NOAEL is 120 mg/kg/day. Based on decreased weight gain during gestation, the dose of 120 mg/kg/day is a LOAEL for decreased maternal body weight gain; the NOAEL is 60 mg/kg/day. The MRL was derived by applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the maternal NOAEL of 60 mg/kg/day.

Data from York (1997) also were analyzed using the BMD approach for MRL derivation. BMD models in the EPA Benchmark Dose Software (BMDS version 1.3.2) (linear, polynomial, power, and Hill models) were fit to the maternal body weight gain data to determine potential points of departure for the MRL. The linear model with homogeneous variance, which is the simplest model and the model that

provided the best fit for the data, was selected. In the absence of a clear criteria as to what level of change in weight gain during pregnancy should be considered adverse, the benchmark response (BMR) was defined as a change in mean body weight gain equal to one standard deviation from the control mean (EPA 2000c). The corresponding BMD was 152 mg/kg/day; the corresponding benchmark dose limit (BMDL) was 125 mg/kg/day. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the BMDL results in an acute-duration oral MRL of 1 mg/kg/day. The MRL of 0.6 mg/kg/day derived using the NOAEL/LOAEL approach is preferred because it is more health protective than the MRL derived using the BMD methodology.

Dose and end point used for MRL derivation: 60 mg/kg/day is a NOAEL for maternal weight gain.

[x] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[x] 10 for extrapolation from animals to humans
[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: In another developmental study, rats were gavaged with phenol in doses of 0, 30, 60, and 120 mg/kg/day in a dosing volume of 5 mL/kg during GDs 6–15 (NTP 1983a). There was no maternal toxicity, but mean fetal body weight at this dose level was approximately 7% lower than controls. However, since historical control data showed that the concurrent control fetal weight for the CD rat was much higher (22%) than the historical control weight and a larger litter size in the high-dose group may have contributed to the smaller fetal weight in the high-dose group, the dose of 120 mg/kg/day can be considered an equivocal LOAEL for developmental effects; the NOAEL was 60 mg/kg/day and supports the NOAEL of 60 mg/kg/day identified in the York (1997) study.

As discussed in Section 2.3, effects of phenol administered to animals by oral gavage are different than those observed in drinking water studies. Phenol administered by gavage is much more toxic than administered in the drinking water and this is related to the pharmacokinetics of phenol. Furthermore, it has been shown that the volume of administration is important; the smaller the volume, the greater the toxicity of a given amount of phenol (NTP 1983a). Studies have shown that the toxicity of phenol is correlated with peak blood concentration rather than with total dose, such as the area under the phenol blood concentration curve (AUC) (Hiser et al. 1994). In general, NOAELs in oral gavage studies were 5–10 times lower than in drinking water studies. The York (1997) study was considered an appropriate study for MRL derivation because it used a divided dosing protocol that resembles more closely a potential environmental exposure scenario to phenol.

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APPENDIX A

BENCHMARK MODELING OF MATERNAL WEIGHT GAIN IN RATS

Benchmark dose models in the EPA Benchmark Dose Sofware (BMDS version 1.3.2) (linear, polynomial, power, and Hill models) were fit to the maternal body weight gain data (see Tables A-1, and A-2, and Figure A-1) to determine potential points of departure for the MRL. The linear model with homogeneous variance, which is the simplest model and provided the best fit, was selected. In the absence of a clear criteria as to what level of change in weight gain during pregnancy should be considered adverse, the BMR was defined as a change in mean body weight gain equal to one standard deviation from the control mean (EPA 2000c).

Table A-1. Data for the Change in Body Weight Gain in Pregnant Rats Exposed to Phenol on Gestation Days 6–15

Dose (mg/kg/day)	Number of animals tested	Body weight gain (g)	Standard deviation
0	23	64	10.7
60	25	58	9.4
120	23	56.8	10.8
360	25	39.8	9.5

Source: York 1997

The corresponding BMD was 152.1 mg/kg/day; the corresponding BMDL was 124.6 mg/kg/day. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the BMDL results in an acute-duration oral MRL of 1 mg/kg/day.

Table A-2. Model Predictions for Changes in Body Weight Gain in Pregnant Rats Exposed to Phenol on Gestation Days 6–15

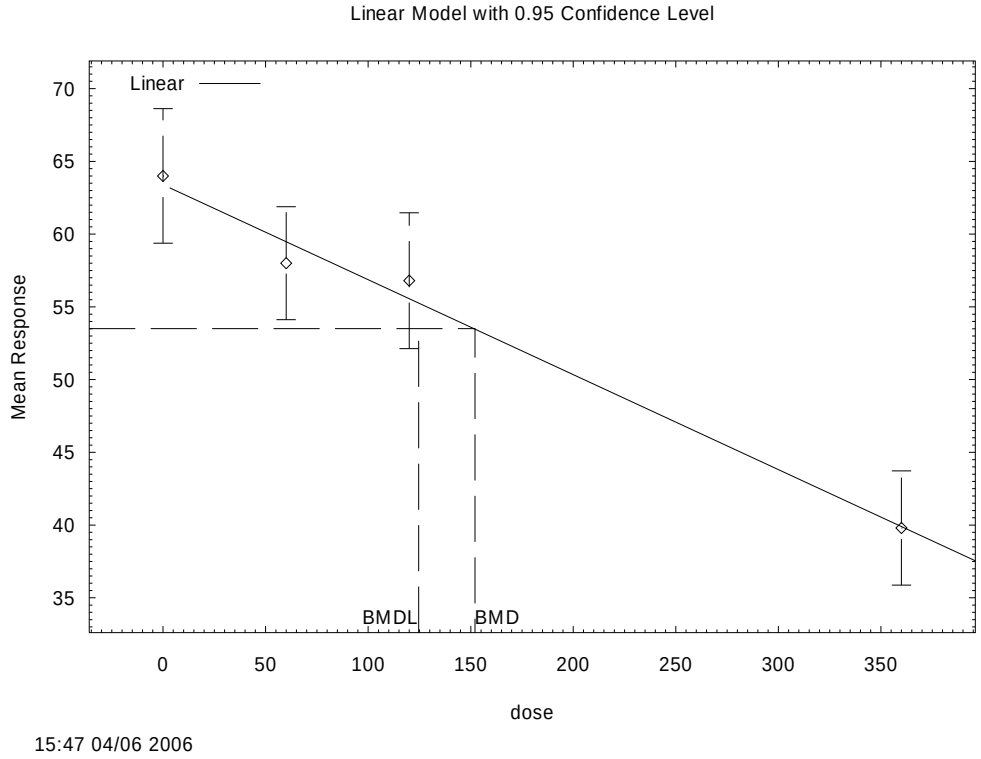
Model	$BMD_{1stddev}$ (mg/kg/day)	$BMDL_{1stddev}$ (mg/kg/day)	p-value[a]	AIC-fitted
Linear[b]	152.1	124.6	0.6055	540.79
2-degree polynomial	157.0	92.9	0.3191	542.78
Power	152.1	124.6	0.3165	544.79
Hill	151.1	129.2	NA	544.79

[a]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[b]Best-fitting model

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; NA = not applicable; p = p value from the Chi-squared test

Source: York 1997

Figure A-1. Changes in Body Weight Gain in Pregnant Rats Exposed to Phenol on Gestation Days 6–15*



*BMDs and BMDLs indicated are for a change of 1 standard deviation and are in units of mg/kg/day.

Source: York 1997

The homogeneous variance linear model form of the response function for the change in maternal body weight gain is:

Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

Linear Model Parameter Estimates for the Change in Maternal Body Weight Gain:

Variable	Estimate	Standard Error
alpha	98.6	14.2
beta_0	63.4	1.4
beta_1	-0.07	0.007

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

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

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

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

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.

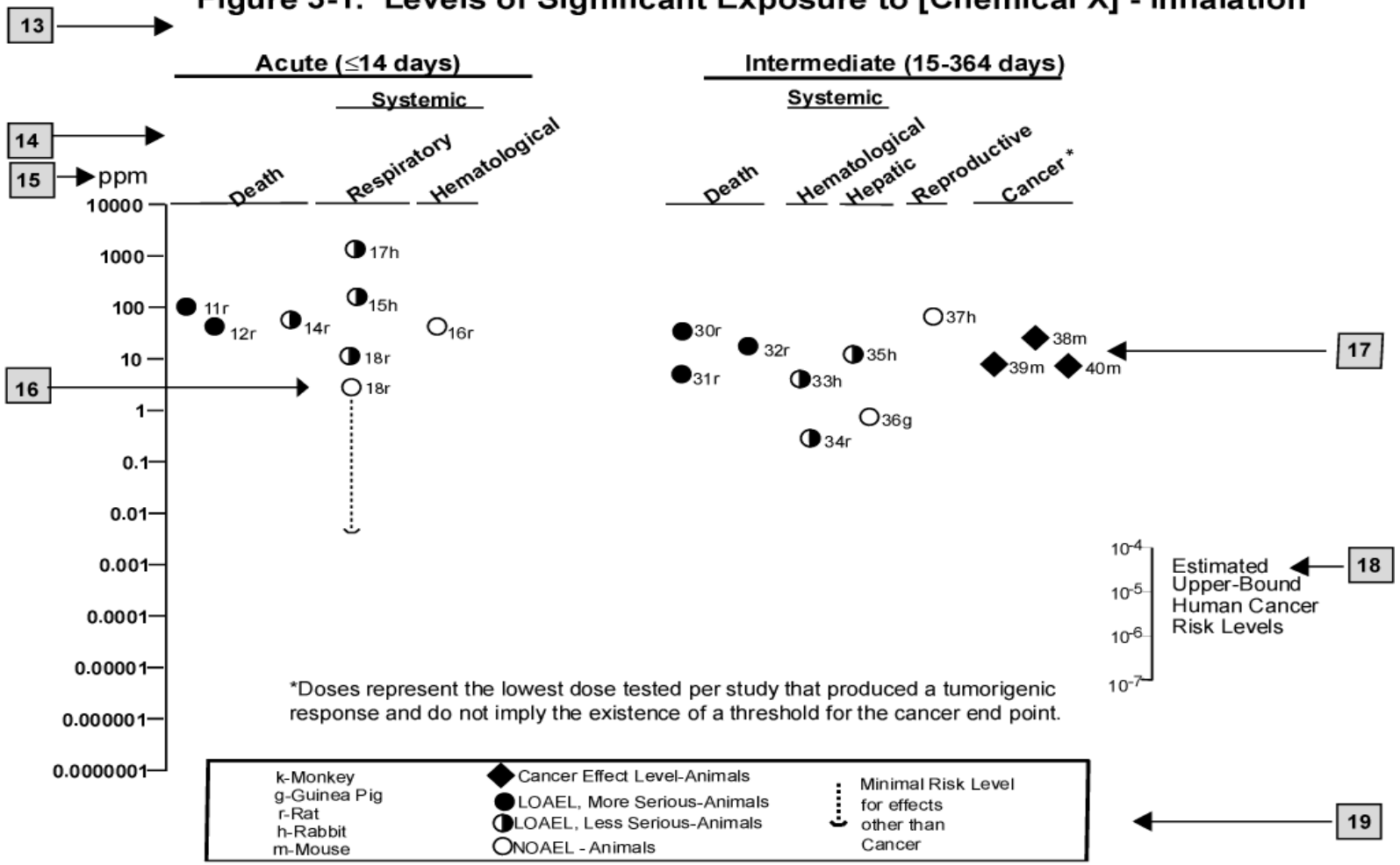
SAMPLE

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).

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	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

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
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