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 route and 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 substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.
MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 2,4-D
CAS Numbers: 94-75-7
Date: February 2017
Profile Status: Final Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 98
Species: Rats

Minimal Risk Level: 0.009 [X] mg/kg/day [ ] ppm


Experimental design: Groups of female Wistar rats (6–8/group) were fed a diet that provided 0, 2.5, 5, 10, 15, 25, 50, or 70 mg/kg/day 2,4-D (98% pure) on postpartum days 1–16. Dams were checked daily for clinical signs, and food consumption and body weight were monitored. Milk ejection was assessed by changes in body weight of the pups after allowing the pups to suckle during 15-minute periods on postpartum days 11–13. Blood was collected from the dams on postpartum day 12 for determination of growth hormone, prolactin, and oxytocin. Dams were sacrificed on postpartum day 16, and the arcuate nucleus and the anterior lobe of the pituitary were isolated for biochemical analyses of monoamines and metabolites in the 15, 25, and 50 mg/kg/day dose groups.

Effect noted in study and corresponding doses: Exposure to 2,4-D did not affect maternal body weight, and no pups died during the test period. Exposure to 2,4-D significantly reduced pup weight beginning on postnatal day (PND) 7 in all exposed groups except the lowest dose group; this group showed a significant reduction in body weight beginning on PND 10. Milk ejection was significantly reduced in all treated groups on postpartum day 13 by >50%, reaching approximately 75% reduction in the highest dose group. However, there were no significant differences between the lowest four treated groups (2.5, 5, 10, and 15 mg/kg/day groups). An injection of oxytocin to the dams partially restored milk production, indicating that 2,4-D, at least in part, inhibited oxytocin release, but not the capacity of the mammary gland to produce or secrete milk. Serum prolactin appeared to be reduced in all treated groups, although Figure 3A in the study does not indicate statistically significant differences between the controls and exposed groups. Serum oxytocin was significantly reduced at ≥25 mg 2,4-D/kg/day. Serotonin was significantly reduced in the arcuate nucleus at ≥15 mg 2,4-D/kg/day and dopamine was significantly increased at ≥25 mg/kg/day. Dopamine was also increased in the anterior pituitary at ≥15 mg 2,4-D/kg/day.

The offspring body weight data on PND 16 (Table A-1) were fit to all available continuous models in EPA’s Benchmark Dose Software (BMDS) version 2.4.0 using a BMR of 5% change from control.
Table A-1. Dataset for Offspring Weight on Postnatal Day 16

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>Litter number</th>
<th>Mean pup weight (g)</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12</td>
<td>30.1</td>
<td>0.3</td>
</tr>
<tr>
<td>2.5</td>
<td>8</td>
<td>27.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.8</td>
</tr>
<tr>
<td>5.0</td>
<td>8</td>
<td>26.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.8</td>
</tr>
<tr>
<td>15.0</td>
<td>8</td>
<td>26.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.8</td>
</tr>
<tr>
<td>25.0</td>
<td>8</td>
<td>26.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.6</td>
</tr>
<tr>
<td>50.0</td>
<td>8</td>
<td>24.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.6</td>
</tr>
<tr>
<td>70.0</td>
<td>8</td>
<td>25.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.8</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data from Table 1 in Stürtz et al. (2010).
<br><sup>b</sup>p<0.001.

Although there are no established guidelines as to what minimal change in a continuous end point such as body weight is biologically significant, a 10% change is generally used for adult body weight. However, because fetal or neonatal organisms may be more susceptible than adults, a 5% change was deemed appropriate. The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance (p≥0.1), then the fit of the linear model to the means was evaluated and the polynomial, power, exponential, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: 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. Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on BMC) was selected as the POD when the difference between the BMCLs estimated from these models were >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMCS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit (p≥0.1) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, exponential, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and POD selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling.

Because no models fit the complete dataset, first the highest dose and subsequently the next highest dose were dropped.

As seen in Table A-2, only two BMD models (Exponential model 4 and Hill model) provided an adequate fit by the various statistical criteria. Because the BMDL<sub>RD05</sub> values are sufficiently close, the model with the lowest AIC (Exponential model 4) was selected. The Exponential model calculated BMD<sub>RD05</sub> and BMDL<sub>RD05</sub> values of 1.27 and 0.93 mg/kg/day, respectively, for decreased pup body weight on PND 16 (see Figure A-1). Dividing the BMDL<sub>RD05</sub> of 0.93 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) yields an intermediate-duration oral MRL of 0.009 mg/kg/day for 2,4-D.
Table A-2. Model predictions for Decreased Pup Body Weight Gain on Postnatal Day 16 (Stürtz et al. 2010)

<table>
<thead>
<tr>
<th>Model</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt; for fit: lack dose response?</th>
<th>p-value&lt;sup&gt;b&lt;/sup&gt; for fit: good variance model?</th>
<th>Scaled residuals&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Dose below BMD</th>
<th>Dose above BMD</th>
<th>Overall largest</th>
<th>AIC</th>
<th>BMD&lt;sub&gt;RD05&lt;/sub&gt; (mg/kg/day)</th>
<th>BMDL&lt;sub&gt;RD05&lt;/sub&gt; (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant variance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.06</td>
<td>&lt;0.0001</td>
<td>-1.91</td>
<td>-0.73</td>
<td>4.83</td>
<td>88.54</td>
<td>23.63</td>
<td>20.27</td>
</tr>
<tr>
<td>Nonconstant variance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.16</td>
<td>&lt;0.0001</td>
<td>-0.75</td>
<td>-2.41</td>
<td>4.66</td>
<td>88.12</td>
<td>25.98</td>
<td>21.72</td>
</tr>
<tr>
<td>High dose dropped</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant variance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.05</td>
<td>&lt;0.0001</td>
<td>-1.71</td>
<td>0.20</td>
<td>4.44</td>
<td>69.97</td>
<td>16.72</td>
<td>14.32</td>
</tr>
<tr>
<td>Nonconstant variance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.097</td>
<td>&lt;0.0001</td>
<td>-1.73</td>
<td>0.14</td>
<td>4.10</td>
<td>61.85</td>
<td>18.57</td>
<td>16.46</td>
</tr>
<tr>
<td>Two highest doses dropped</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant variance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.03</td>
<td>&lt;0.0001</td>
<td>-3.37</td>
<td>-1.07</td>
<td>3.74</td>
<td>62.83</td>
<td>12.64</td>
<td>9.99</td>
</tr>
<tr>
<td>Nonconstant variance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exponential (model 2)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.35</td>
<td>&lt;0.0001</td>
<td>-1.61</td>
<td>1.19</td>
<td>3.65</td>
<td>59.58</td>
<td>15.38</td>
<td>11.69</td>
</tr>
<tr>
<td>Exponential (model 3)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.35</td>
<td>&lt;0.0001</td>
<td>-1.61</td>
<td>1.19</td>
<td>3.65</td>
<td>59.58</td>
<td>15.38</td>
<td>11.69</td>
</tr>
<tr>
<td>Exponential (model 4)&lt;sup&gt;e,f&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.35</td>
<td>0.82</td>
<td>-0.07</td>
<td>0.61</td>
<td>0.61</td>
<td>4.60</td>
<td>1.27</td>
<td>0.93</td>
</tr>
<tr>
<td>Exponential (model 5)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.35</td>
<td>0.0008</td>
<td>-1.02x10^-6</td>
<td>2.83</td>
<td>2.83</td>
<td>17.51</td>
<td>0.73</td>
<td>1.07x10^-3</td>
</tr>
<tr>
<td>Hill&lt;sup&gt;e&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.35</td>
<td>0.95</td>
<td>-0.05</td>
<td>0.32</td>
<td>-0.33</td>
<td>6.21</td>
<td>1.83</td>
<td>0.70</td>
</tr>
<tr>
<td>Linear&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.35</td>
<td>&lt;0.0001</td>
<td>-1.65</td>
<td>1.16</td>
<td>3.69</td>
<td>60.05</td>
<td>15.75</td>
<td>12.23</td>
</tr>
<tr>
<td>Polynomial (2-degree)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.35</td>
<td>&lt;0.0001</td>
<td>-1.65</td>
<td>1.16</td>
<td>3.69</td>
<td>60.05</td>
<td>15.75</td>
<td>12.23</td>
</tr>
<tr>
<td>Polynomial (3-degree)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.35</td>
<td>&lt;0.0001</td>
<td>-1.65</td>
<td>1.16</td>
<td>3.69</td>
<td>60.05</td>
<td>15.75</td>
<td>12.23</td>
</tr>
<tr>
<td>Polynomial (4-degree)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.35</td>
<td>&lt;0.0001</td>
<td>-1.65</td>
<td>1.16</td>
<td>3.69</td>
<td>60.05</td>
<td>15.75</td>
<td>12.23</td>
</tr>
<tr>
<td>Power&lt;sup&gt;e&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.35</td>
<td>&lt;0.0001</td>
<td>-1.65</td>
<td>1.16</td>
<td>3.69</td>
<td>58.05</td>
<td>15.75</td>
<td>12.23</td>
</tr>
</tbody>
</table>

<sup>a</sup>Values >0.05 fail to meet conventional goodness-of-fit criteria.
<sup>b</sup>Values <0.10 fail to meet conventional goodness-of-fit criteria.
<sup>c</sup>Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
<sup>d</sup>Coefficients restricted to be negative.
<sup>e</sup>Power restricted to ≥1.
<sup>f</sup>Selected model. No models fit the full dataset. With the two highest doses dropped, the nonconstant variance models fit the variance data and only two models, Exponential model 4 and the Hill model, were fit to the means. BMDLs for models providing adequate fit were sufficiently close (differed by <2–3-fold), so the model with the lowest AIC was selected (Exponential model 4).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 05 = dose associated with 5% extra risk); RD = relative deviation.

***DRAFT FOR PUBLIC COMMENT***
Figure 1. Selected Model (Exponential Model 4) for Decreased Pup Body Weight on Postnatal Day 16 (Stürtz et al. 2010)

Exponential Model 4, with BMR of 0.05 Rel. Dev. for the BMD and 0.95 Lower Confidence Level for BMI

Dose and end point used for MRL derivation: Decreased offspring body weight on PND 16 at maternal doses of 0–25 mg 2,4-D/kg/day on postpartum days 1–16. Modeling used dose ranges from 0 to 25 mg/kg/day. The POD was 2.5 mg/kg/day.

[X] NOAEL  [ ] LOAEL  [X] BMDL_{RD05}

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[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? No.

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? No.

Other additional studies or pertinent information that lend support to this MRL: Reduced offspring body weight was also reported in other studies in which rat dams were exposed to 2,4-D for longer periods that also included postpartum, although at higher estimated maternal doses of 2,4-D. For example, in a 2-generation reproductive study, pup body weight was reduced significantly on PND 28 at estimated maternal doses ≥35 mg 2,4-D/kg/day during lactation, but not at 10 mg 2,4-D/kg/day (EPA 1986). Marty et al. (2013) reported significantly reduced pup weight (about 10%) on PND 22 at estimated maternal doses of approximately 9 mg 2,4-D/kg/day during lactation, but lower doses were not tested. In a 3-generation study, reduced pup weight was noted at maternal doses of approximately 111 mg 2,4-D/kg/day, but not 37 mg/kg/day (Hansen et al. 1971). The reasons for the apparent discrepancy regarding maternal dose levels at which offspring weight is significantly affected are not clear, but could be related to the different manners of estimating maternal intake of test material. Other studies that reported reduced offspring weight at higher maternal 2,4-D doses include Bortolozzi et al. (1999), Mazhar et al. (2014), and Troudi et al. (2012a, 2012b). While there seems to be some discrepancy between the results of these developmental studies with regard to fetal weight, there does not seem to be a good reason to discount the results of Stürtz et al. (2010).

Agency Contact (Chemical Manager): Obaid Faroon
This page is intentionally blank.
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.

***DRAFT FOR PUBLIC COMMENT***
MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. 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 include 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 adverse 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").
**APPENDIX B**

(9) **LOAEL.** A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) **Reference.** The complete reference citation is given in Chapter 9 of the profile.

(11) **CEL.** A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) **Footnotes.** Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND**

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

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

(13) **Exposure Period.** The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) **Health Effect.** These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) **Levels of Exposure.** Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day.

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

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

***DRAFT FOR PUBLIC COMMENT***
(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.
Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

<table>
<thead>
<tr>
<th>Key to figure&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Exposure frequency/duration</th>
<th>System</th>
<th>NOAEL (ppm)</th>
<th>LOAEL (effect)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Less serious (ppm)</td>
<td>Serious (ppm)</td>
</tr>
</tbody>
</table>

**INTERMEDIATE EXPOSURE**

2

Systemic

<table>
<thead>
<tr>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
</table>

3

18 Rat 13 wk Resp 3<sup>b</sup> 10 (hyperplasia)

Nitschke et al. 1981

**CHRONIC EXPOSURE**

Cancer

4

<table>
<thead>
<tr>
<th>38</th>
<th>39</th>
<th>40</th>
</tr>
</thead>
</table>

38 Rat 18 mo Resp 20 (CEL, multiple organs)

Wong et al. 1982

39 Rat 89–104 wk Resp 10 (CEL, lung tumors, nasal tumors)

NTP 1982

40 Mouse 79–103 wk Resp 10 (CEL, lung tumors, hemangiosarcomas)

NTP 1982

<sup>a</sup> The number corresponds to entries in Figure 3-1.

<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5x10<sup>-3</sup> 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

Chronic (≥ 365 days)

Intermediate (15-364 days)

*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

k-Monkey  g-Guinea Pig  r-Rat  h-Rabbit  m-Mouse

Cancer Effect - Level-Animals

Minimal Risk Level for effects other than Cancer

LOAEL, More Serious-Animals

LOAEL, Less Serious-Animals

NOAEL, Animals

Estimated Upper-Bound Human Cancer Risk Levels
This page is intentionally blank.
APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH  American Conference of Governmental Industrial Hygienists
ACOEM  American College of Occupational and Environmental Medicine
ADI    acceptable daily intake
ADME   absorption, distribution, metabolism, and excretion
AED    atomic emission detection
AFID   alkali flame ionization detector
AFOSH  Air Force Office of Safety and Health
ALT    alanine aminotransferase
AML    acute myeloid leukemia
AOAC   Association of Official Analytical Chemists
AOEC   Association of Occupational and Environmental Clinics
AP     alkaline phosphatase
APHA   American Public Health Association
AST    aspartate aminotransferase
atm    atmosphere
ATSDR  Agency for Toxic Substances and Disease Registry
AWQC   Ambient Water Quality Criteria
BAT    best available technology
BCF    bioconcentration factor
BEI    Biological Exposure Index
BMD/C  benchmark dose or benchmark concentration
BMDX   dose that produces a X% change in response rate of an adverse effect
BMDLX  95% lower confidence limit on the BMDX
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
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

***DRAFT FOR PUBLIC COMMENT***
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
F1 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 kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
Koc organic carbon partition coefficient
Kow octanol-water partition coefficient
L liter
LC liquid chromatography
LC50 lethal concentration, 50% kill
LCLo lethal concentration, low
LD50 lethal dose, 50% kill
LDLo lethal dose, low
LDH lactic dehydrogenase
LH luteinizing hormone
LOAEL lowest-observed-adverse-effect level
LSE Levels of Significant Exposure
LT50 lethal time, 50% kill
m meter
MA trans,trans-muconic acid
MAL maximum allowable level
mCi millicurie
MCL maximum contaminant level

***DRAFT FOR PUBLIC COMMENT***
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
mt  metric ton
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
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
q1*  cancer slope factor
–  negative
+  positive
(+) weakly positive result
(–) weakly negative result