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(s): Ethylene glycol
CAS number(s): 107-21-1
Date: August 2007
Profile status: Final Draft Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 2
Species: Human

MRL: 2 [ ] mg/kg/day [ ] ppm [X] mg/m^3

Reference: Wills JH, Coulston F, Harris ES, et al. 1974. Inhalation of aerosolized ethylene glycol by man. Clin Toxicol 7(5):463-476.

Experimental design: Health effects were assessed in 19 male prisoners who voluntarily were exposed to ethylene glycol aerosol for 20–22 hours/day for 30 days. The diameter of the aerosol droplets ranged from 1 to 5 μm. Mean daily and mean weekly concentrations during the first 14 days of the study ranged from 0.8 to 44.8 and from 17 to 29 mg/m^3, respectively. Mean daily and mean weekly concentrations during the entire 30-day exposure period were 0.8–67 and 17–49 mg/m^3, respectively. The average mean weekly exposure was 23 mg/m^3 for days 1–14 and 30 mg/m^3 for days 1–30. The average exposure levels did not include brief periods in which the concentration was intentionally raised to higher levels to assess acute responses. A control group consisted of 14 male prisoners; 10 of these men were never exposed to ethylene glycol, whereas the remaining 4 men had been exposed to a mean concentration of 37 mg/m^3 for 20–22 hours/day for 7 days during the week that preceded the start of the study. Subjective responses (symptoms) were monitored throughout the study. During the last 10 days of the study, the concentration of ethylene glycol was occasionally intentionally increased to various high levels (up to 308 mg/m^3) when the volunteers left the exposure chamber during meals; subjective responses to short exposures to the high concentrations were assessed when they reentered the chamber. Complete physical examinations that included slit-lamp, electrocardiographic, and electroencephalographic studies, and a battery of psychological tests designed to reveal effects on simple reaction time, reaction time with discrimination, visual-motor coordination, depth perception, and mental ability (encoding and subtraction accuracy), were conducted on all subjects pre-exposure and after 14 and 30 days of exposure. Blood samples were collected on days 0, 1, 3, 5, 8, 12, 19, 22, 26, and 29 for evaluation of hematology, clinical chemistry (including blood urea nitrogen, serum creatinine, and liver enzymes), and ethylene glycol concentration. Urine was evaluated daily for oxalate crystals, erythrocytes, and ethylene glycol, and twice weekly for volume, specific gravity, color, clarity, pH, amino acid nitrogen, and creatinine.

Effects noted in study and corresponding doses: Concentrations of ethylene glycol in the blood and urine were similar in the exposed and control groups. The near-continuous exposure levels (average 23 mg/m^3 for days 1–14 and 30 mg/m^3 for days 1–30) were tolerated with effects that were limited to occasional complaints of upper respiratory tract irritation, slight headache, and low backache (incidences and other information not reported). The short-term, high-exposure sessions showed that the irritation became common at approximately 140 mg/m^3, and tolerated for only 15 minutes at 188 mg/m^3, 2 minutes at 244 mg/m^3, and one or two breaths at 308 mg/m^3. Based on these results and those of other trials, the investigators concluded that concentrations of about ≥200 mg/m^3 were intolerable due to strong irritation of the upper respiratory tract that included a burning sensation in the trachea and a burning cough. Because the near-continuous exposures were tolerated with respiratory irritation that was infrequent and not serious, and not accompanied by neurological, hematology, clinical chemistry, or urinalysis findings indicative of renal or other systemic effects, the interim (12–14-day) findings in this study identified a

NOAEL of 23 mg/m^3 for acute-duration exposure in humans. The LOAEL was 140 mg/m^3 because brief exposures to this concentration commonly caused respiratory irritation.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 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 (inhalation study).

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

Exposure concentrations were not converted from mg/m^3 to ppm because ppm is unsuitable for aerosols.

Was a conversion used from intermittent to continuous exposure? The NOAEL of 23 mg/m^3 was not adjusted for discontinuous daily exposure (20 hours/24 hours) because the critical effect is concentration dependent and not duration dependent.

Other additional studies or pertinent information that lend support to this MRL: The only other information on effects of acute-duration inhalation exposure to ethylene glycol is available from three developmental toxicity studies in rats and mice (Tyl 1988a; Tyl et al. 1995a, 1995b).

In a developmental toxicity study in CD-1 mice using whole-body exposure to nominal concentrations of 0, 150, 1,000, or 2,500 mg/m^3 for 6 hours/day on Gd 6–15, maternal body weight gain was decreased, but corrected weight was unaffected, at concentrations ≥1,000 mg/m^3 (Tyl 1988a; Tyl et al. 1995a). Significant effects on implant viability, weight of live fetuses, and on the incidence of external, visceral, and skeletal malformations were observed at concentrations ≥1,000 mg/m^3. Maternal toxicity (e.g., increased liver weight in rats and reduced body weight gain in mice) was evident at 2,500 and 1,000 mg/m^3 in rats and mice, respectively (Tyl et al. 1995a). In CD rats exposed similarly in the same study, there were significant increases in absolute and relative liver weight among maternal animals exposed to 2,500 mg/m^3; kidney weights were unchanged, and liver and kidney histopathology was not evaluated. In addition, reduced ossification at some sites in the axial skeleton was observed with exposure to 1,000 and 2,500 mg/m^3; however, in an Expert Panel Review of this study, NTP-CERHR (2004) concluded that the relationship of this effect to treatment was uncertain due to the lack of a dose-response relationship. Both of the whole-body experiments were confounded by significant ingestion of ethylene glycol deposited on the fur and consumed during grooming; the authors estimated that the ingestion dose comprised the majority of exposure (Tyl 1985, 1988a; Tyl et al. 1995a).

In a follow-up developmental study aimed at reducing the confounding from ingestion exposure, pregnant CD-1 mice were exposed nose-only to target concentrations of 0, 500, 1,000, or 2,500 mg/m^3 aerosolized ethylene glycol for 6 hours/day on Gd 6–15 (Tyl 1988a; Tyl et al. 1995b). In maternal animals, there were no effects other than changes in kidney weights. Absolute kidney weight was significantly increased at 1,000 and 2,500 mg/mg^3, and relative kidney weight was increased at 2,500 mg/m^3; however, microscopic examination of kidneys did not indicate any histopathological changes. At 2,500 mg/m^3, live

fetal body weight was significantly reduced, and there was a significant increase in the one type of skeletal malformation (fused ribs). Increases in some skeletal variations were observed at 2,500 mg/m^3, and one type (extra ossification sites in the sagittal suture) was significantly increased at concentrations ≥500 mg/m^3. The authors designated the 1,000 mg/m^3 concentration a developmental NOAEL and the 500 mg/m^3 concentration a NOAEL for maternal effects. However, the authors noted that the animals in the nose-only experiment were also exposed by ingestion of ethylene glycol during preening of the face after exposure (Tyl 1988a; Tyl et al. 1995b). Furthermore, NTP-CERHR (2004) noted that stress from restraint in the single nose-only exposure study may have contributed to the developmental effects observed with ethylene glycol, which were similar in nature to effects observed in a study of restrained nose-only exposure to water vapor (Tyl et al. 1994).

Because of the confounding oral exposures in both the whole-body and nose-only developmental toxicity studies, NTP-CERHR (2004) concluded that the data from these studies were not suitable for evaluation of effect levels from inhalation exposure to ethylene glycol. The available data do, however, provide a conservative estimate of the inhalation NOAEL, with the caveat that total exposure to ethylene glycol in these studies included intake via ingestion. Collectively, these studies suggest that inhalation exposure to ethylene glycol at a nominal concentration of about 150 mg/m^3 is not associated with developmental toxicity in mice or rats, or renal toxicity in mice (kidney histopathology not assessed in rats). The next highest concentration (500 mg/m^3 in the nose-only study) was associated with developmental effects (increased incidence of skeletal variations), but it is not possible to conclusively relate these effects to inhalation of ethylene glycol.

As indicated above, the developmental studies (Tyl 1988a; Tyl et al. 1995a, 1995b) collectively suggest that 150 mg/m^3 is a conservative NOAEL for developmental toxicity in rats and kidney toxicity in mice. This concentration is similar to the 140 mg/m^3 LOAEL for respiratory tract irritation in humans (Wills et al. 1974). The human NOAEL of 23 mg/m^3 is a suitable basis for MRL derivation because it is based on evaluations for renal and other systemic effects as well as for local irritation, and is well within the NOAEL range for developmental toxicity in animals.

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APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Ethylene glycol
CAS number(s): 107-21-1
Date: August 2007
Profile status: Final Draft Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 51
Species: Mouse

MRL: 0.8 [X] mg/kg/day [ ] ppm [ ] mg/m^3

References: Neeper-Bradley TL, Tyl RW, Fisher LC, et al. 1995. Determination of a no-observed-effect level for developmental toxicity of ethylene glycol administered by gavage to CD rats and CD-1 mice. Fundam Appl Toxicol 27:121-130.

Tyl RW. 1989. Developmental toxicity evaluation of ethylene glycol administrated by gavage to CD-1 mice: Determination of a "no-observed-effect-level" (NOEL). Bushy Run Research Center, CMA Project Report 51-591.

Experimental design: Groups of 30 timed-pregnant CD-1 mice were given doses of 50, 150, 500, or 1,500 mg/kg ethylene glycol daily by gavage on Gd 6–15; vehicle controls were given water on the same schedule (Neeper-Bradley et al. 1995; Tyl 1989). Maternal animals were observed daily for clinical signs and weighed periodically; water intake was measured throughout gestation. At sacrifice on Gd 18, body weight, gravid uterine weight, liver weight, and kidney weight were measured in dams. Kidneys from control and high-dose dams were examined microscopically. Corpora lutea and uterine contents were evaluated, and live fetuses were weighed and sexed. External, visceral, and skeletal malformations and variations in the fetuses were evaluated.

Effects noted in study and corresponding doses: No effects on maternal body weight, water consumption, or liver or kidney weight were observed. There were no significant effects on the number of corpora lutea/dam, on the number of total, nonviable, or viable implants/litter, or on sex ratio. Average fetal body weight per litter was reduced (13% below controls) at 1,500 mg/kg/day. The incidence of individual external or visceral malformations was not significantly increased in any treatment group relative to the vehicle control; however, exencephaly (a malformation observed by Price et al. [1985] at higher doses) was observed in two fetuses in the 500 mg/kg/day group and in three fetuses of the 1,500 mg/kg/day dose group. There was a significant increase in the incidence of two skeletal malformations (fused ribs or thoracic arches) in the 1,500 mg/kg/day group (15/21 litters with fused ribs vs. 1/19 controls; 8/21 litters with fused thoracic arches vs. 0/19 controls). Further, the incidence of total malformations per litter (external, visceral, and skeletal) was significantly increased both at 500 and 1,500 mg/kg/day (3/19, 7/20, 5/24, 12/24, and 17/21 from control to high dose). The incidences of 23 skeletal variations were increased in the 1,500 mg/kg/day group. One of these variations (bilateral extra rib 14) was also significantly increased at ≥500 mg/kg/day (4/19, 4/20, 6/24, 17/24, and 21/21 in control through high dose groups, respectively). This study identified a developmental NOAEL of 150 mg/kg/day and LOAEL of 500 mg/kg/day for increased incidence of total malformations and bilateral extra rib 14. The high dose (1,500 mg/kg/day) was a NOAEL for maternal effects.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

To derive a point of departure for MRL derivation, BMD dose modeling was conducted using the mouse data on the incidence of litters with malformations (of any kind) and on the incidence of one skeletal variation (bilateral extra rib 14). The incidences for both end points are presented in Table A-1. These two end points were observed at lower doses than other observed effects (skeletal malformations, pup body weight reductions).

Table A-1. Incidences of Developmental Effects in Offspring of Mice Exposed to Ethylene Glycol by Gavage on Gestation Days 6–15

	Dose (mg/kg/day)				
Effect[a]	0	50	150	500	1,500
Extra lumbar rib[b]	4/19	4/20	6/24	17/24[c]	21/21[c]
Total malformations	3/19	7/20	5/24	12/24[d]	17/21[c]

[a]Number of litters with effects/number of litters examined.
[b]Extra rib 14, first lumbar arch, bilateral.
[c]$p<0.01$.
[d]$p<0.05$.

Sources: Neeper-Bradley et al. 1995; Tyl 1989

All dichotomous variable models in the EPA Benchmark Dose Software (Version 1.4.1) were fit to the malformation and skeletal variation data. Although one of the end points modeled (total malformations) represents a more serious effect, the group sizes in this study (19–24 litters/dose examined) did not support a BMR lower than 10%; thus, an extra risk incidence of 10% above controls was selected as the BMR. Model results for the data on total malformations are shown in Table A-2. All available dichotomous models provided adequate fit to the data ($p>0.1$). Comparing across models, a better fit is generally indicated by a lower Akaike's Information Criteria (AIC). The multistage and quantal linear models converged on the same model providing the best fit (as assessed by AIC) to the data on total malformations; these models both predicted a BMD_{10} of 113.84 mg/kg/day and a $BMDL_{10}$ of 75.59 mg/kg/day. Figure A-1 shows the fit of the multistage (1-degree polynomial) model to the malformation data.

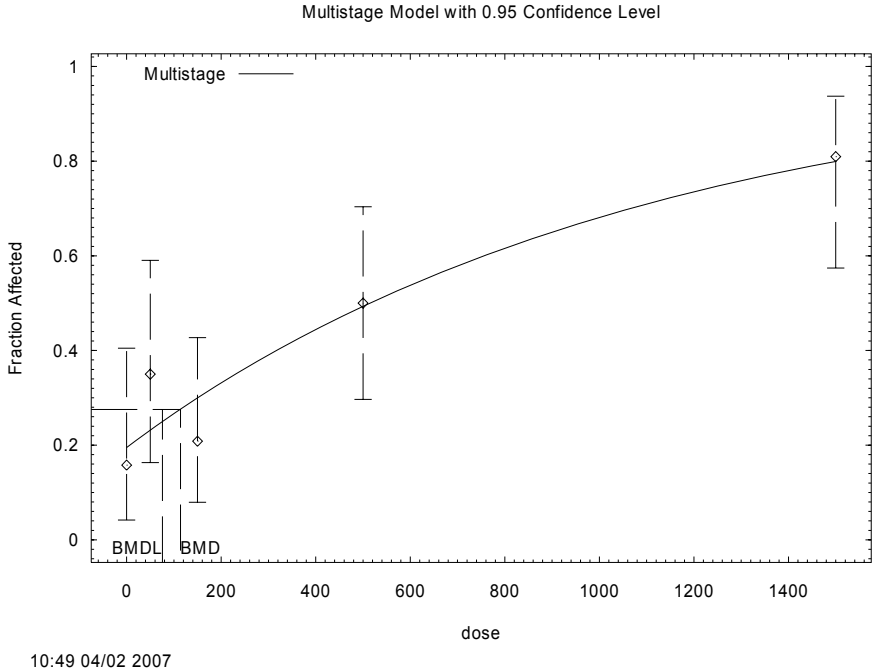
Table A-2. Model Predictions for the Incidence of Total Malformations in Offspring of Mice Exposed to Ethylene Glycol by Gavage on Gestation Days 6–15

Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	χ^2 p-value	AIC
Gamma[a]	162.51	75.95	0.27	129.33
Logistic	211.23	156.53	0.41	127.64
Log-logistic[b]	213.64	48.14	0.28	129.24
Multi-stage[c]	**113.84**	**75.59**	**0.44**	**127.40**
Probit	208.48	159.25	0.41	127.66
Log-probit[b]	242.07	140.87	0.28	129.21
Quantal linear	**113.84**	**75.59**	**0.44**	**127.40**
Quantal quadratic	392.59	307.59	0.26	128.84
Weibull[a]	152.27	75.98	0.27	129.33

[a]Power restricted to ≥1.
[b]Slope restricted to ≥1.
[c]Betas restricted to ≥0; lowest degree polynomial with adequate fit is reported; degree of polynomial = 1.

Sources: Neeper-Bradley et al. 1995; Tyl 1989

Figure A-1. Predicted and Observed Incidence of Total Malformations in Offspring of Mice Exposed to Ethylene Glycol by Gavage on Gestation Days 6–15*



*BMD and BMDL associated with a 10% extra risk increase over control are shown; doses given in units of mg/kg/day.

Sources: Neeper-Bradley et al. 1995; Tyl 1989

Model results for the data on bilateral extra rib 14 are shown in Table A-3. For these data, the probit model provided the best fit (as assessed by AIC); a BMD_{10} of 99.35 mg/kg/day and $BMDL_{10}$ of 75.56 mg/kg/day were predicted. Figure A-2 shows the fit of the probit model to the skeletal variation data.

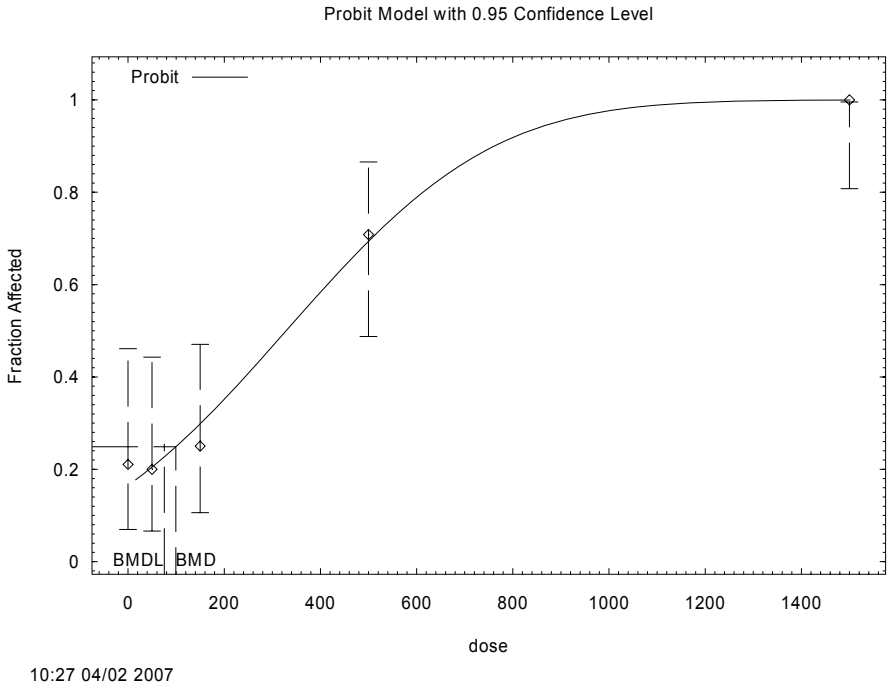
Table A-3. Model Predictions for the Incidence of Bilateral Extra Lumbar Ribs in Offspring of Mice Exposed to Ethylene Glycol by Gavage on Gestation Days 6–15

Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	χ^2 p-value	AIC
Gamma[a]	200.86	64.02	0.98	101.59
Logistic	103.80	77.82	0.90	100.16
Log-logistic[b]	419.85	101.67	0.91	101.72
Multi-stage[c]	49.956	35.31	0.36	103.53
Probit	**99.35**	**75.56**	**0.90**	**100.12**
Log-probit[b]	353.71	97.62	0.91	101.72
Quantal linear	49.96	35.31	0.36	103.53
Weibull[a]	192.89	60.78	0.99	101.55

[a]Power restricted to ≥1.
[b]Slope restricted to ≥1.
[c]Betas restricted to ≥0; lowest degree polynomial with adequate fit is reported; degree of polynomial = 1.

Sources: Neeper-Bradley et al. 1995; Tyl 1989

Figure A-2. Predicted and Observed Incidence of Extra Lumbar Ribs in Offspring of Mice Exposed to Ethylene Glycol by Gavage on Gestation Days 6–15*



*BMD and BMDL associated with a 10% extra risk increase over control are shown; doses given in units of mg/kg/day.

Sources: Neeper-Bradley et al. 1995; Tyl 1989

Modeling of both the malformation and skeletal variation end points resulted in the same $BMDL_{10}$, indicating that an acute oral MRL based on this point of departure should provide protection against both effects.

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

Although some mechanistic information suggests that humans may be less sensitive than rodents to the developmental effects of ethylene glycol, the available data are not adequate to support a lower interspecies uncertainty factor; thus, a full 10-fold uncertainty factor was used for interspecies extrapolation. While *in vitro* data suggest that humans metabolize glycolic acid (the proximate developmental toxicant) more efficiently than rats (Booth et al. 2004; Corley et al. 2005a), NTP-CERHR (2004) observed that the data supporting the glycolic acid metabolic rate in humans are limited. In addition, NTP-CERHR (2004) reviewed preliminary data indicating that the inverted yolk sac placenta, a stage in placental development that does not exist in humans, tends to concentrate weak acids such as glycolic acid in the embryonic fluids. These data suggest enhanced sensitivity to ethylene glycol developmental effects in rodents compared with humans; however, NTP-CERHR (2004) characterized the available data as inconclusive. A 10-fold uncertainty factor for interindividual variability was also used. Ethylene glycol metabolism is known to involve alcohol dehydrogenase and aldehyde

dehydrogenase, and may also involve cytochrome p450 isozymes (NTP-CERHR 2004). Polymorphisms in the genes encoding these enzymes may lead to wide variability in the production and elimination of glycolic acid and other metabolites in humans exposed to ethylene glycol, but data quantifying the range of variability are not currently available (NTP-CERHR 2004). In addition, fetal and/or placental differences in expression of these enzymes over the course of gestation will affect local concentrations of glycolic acid and other metabolites to which the developing conceptus is exposed, yet little is known about these differences (NTP-CERHR 2004).

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

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 acute-duration oral developmental toxicity studies in rodents, fetal effects have consistently been observed at doses that are not maternally toxic. Furthermore, the teratogenic effects observed after ethylene glycol exposure appear to be generally consistent across studies and across species, with the primary end point consisting of skeletal malformations. The incidence of malformations was increased in CD-1 mice at doses of ≥500 mg/kg/day when administered by gavage during gestation (Gd 6–15) (Neeper-Bradley et al. 1995; Tyl 1989). Embyrotoxicity was also manifested as a reduction in fetal body weight in CD-1 mice given doses of ≥750 mg/kg/day on Gd 6–15 (Neeper-Bradley 1990; Price et al. 1985; Tyl 1989). In rats, doses of ≥1,000 mg/kg/day by gavage on Gd 6–15 resulted in an increased incidence of skeletal malformations in offspring (Neeper-Bradley 1990; Neeper-Bradley et al. 1995; Price et al. 1985). Decreases in pup body weight and increases in both the number of litters with malformations and the number of malformed fetuses per litter were observed in rats treated during Gd 6–15 with doses ≥2,500 mg/kg/day (Price et al. 1985; Neeper-Bradley 1990; Neeper-Bradley et al. 1995). In mice given doses of 3,000 mg/kg/day during Gd 6–15, neural tube and craniofacial defects were increased, and the number of live fetuses per litter was decreased (Price et al. 1985). In contrast to the results in rodents, no teratogenic effects were observed in rabbits exposed to maternally lethal doses of 2,000 mg/kg/day during gestation (Tyl et al. 1993).

No effects were observed on hematology parameters, but dose-related effects on bone marrow and erythropoiesis were observed when doses of 0, 50, 100, or 250 mg/kg/day ethylene glycol were given for 4 consecutive days by gavage to B6C3F1 mice. Seven mice per sex were sacrificed on 1 day postexposure for measurement of body, liver, thymus, spleen, kidney, and testis weights, and histopathology of these organs as well as the lung, heart, adrenals, stomach, bone marrow, urinary bladder, intestines, and uterus. Hematology, bone marrow parameters, and erythropoiesis were evaluated in other groups of mice evaluated between 1 and 14 days after exposure. Microscopic examination of the spleen and bone marrow did not reveal any histopathological changes, and there were no significant changes to hematological parameters (hemoglobin, hematocrit, mean corpuscular volume, erythrocyte and leukocyte counts) evaluated 5 days after exposure termination. Exposure to ethylene glycol resulted in statistically significant decreases in bone marrow cellularity (up to about 25% below control values) at doses of ≥100 mg/kg/day; this effect persisted up to 14 days after exposure in males. Granulocyte-macrophage progenitor formation was suppressed (~15% below controls) at 50 mg/kg/day in males evaluated 14 days postexposure and at higher doses in both males and females evaluated at earlier time points. The magnitude of reduction in granulocyte-macrophage progenitor formation ranged up to 40% below controls at 250 mg/kg/day. Iron uptake in the bone marrow was suppressed (38% below controls) in males exposed to 250 mg/kg/day.

While bone marrow effects were observed in male mice exposed to doses of 50–250 mg/kg/day in this study, the biological significance of these effects is uncertain. No effects were observed on any hematological parameters, or on bone marrow or spleen histology (Hong et al. 1988). Histology was evaluated only 1 day after exposure, and hematological parameters were evaluated 5 days postexposure; thus, these evaluations would not have captured delayed effects on these parameters. However, studies using much higher doses and longer durations have failed to indicate effects on bone marrow, spleen, or hematology in mice, and provide inconsistent findings in rats. No histological changes in the bone marrow were observed in mice or rats exposed to higher doses of ethylene glycol for longer durations; these included B6C3F1 mice exposed to ≤16,000 mg/kg/day in diet for 13 weeks or ≤12,000 mg/kg/day in diet for 2 years (Melnick 1984; NTP 1993), F344 rats exposed to ≤10,000 mg/kg/day in diet for 13 weeks (Melnick 1984), and Sprague-Dawley rats exposed to ≤7,327 mg/kg/day in drinking water for 10 or 90 days (Robinson et al. 1990). Results of routine hematology evaluations in these studies were unremarkable except for some alterations in the 10- and 90-day studies in rats. In the 10-day study, statistically significant decreases in hemoglobin, hematocrit, erythrocytes, and total leukocytes (7.3, 8.9, 8.5, and 34.8% less than controls, respectively) occurred in female rats at 7,327 mg/kg/day (Robinson et al. 1990). In the 90-day study, total leukocyte counts were significantly reduced in female rats at 597, 3,087, and 5,744 mg/kg/day (32, 30, and 50% less than controls, respectively) (Robinson et al. 1990). Results of differential counts were not reported, and no clear hematological changes occurred in male rats in either study. Hematology evaluations were also negative in other studies that did not examine bone marrow histology; these included studies of B6C3F1 mice exposed to ≤12,000 mg/kg/day in diet for 2 years (DePass et al. 1986a), Wistar rats exposed to ≤2,000 mg/kg/day by gavage for 4 weeks (Schladt et al. 1998), and Wistar rats exposed to ≤1,128 mg/kg/day in diet for 16 weeks (Gaunt et al. 1974). In male F344 rats exposed to 1,000 mg/kg/day in the diet for 2 years, significant hematological changes were observed, but this dose also caused mortality due to renal toxicity (DePass et al. 1986a).

The hematopoietic system is an established target system for several ethylene glycol ethers (e.g., ethylene glycol monomethyl ether, ethylene glycol monobutyl ether (IRIS 2007). For these compounds, hematological effects are consistently observed across different species, doses, and exposure durations. In contrast, few studies have suggested hematological effects from ethylene glycol exposure, and those with positive findings were at higher doses than Hong et al. (1988) and gave inconsistent results. Given the lack of supporting evidence for hematological, bone marrow, or splenic effects in mice and rats exposed to much higher doses of ethylene glycol and for longer durations, the biological significance of the effects observed by Hong et al. (1988) is considered uncertain, and this study was not used to derive the acute oral MRL.

In a 10-day drinking water study, groups of 10 male and 10 female Sprague-Dawley rats were administered 0, 0.5, 1.0, 2.0, or 4.0% ethylene glycol; reported mean compound consumption was 649, 1,343, 2,615, and 5,279 mg/kg/day in males, and 794, 1,506, 2,953, and 7,327 mg/kg/day in females (Robinson et al. 1990). The incidence and severity of renal lesions were significantly increased and dose-related in males at ≥2,615 mg/kg/day; effects included tubular dilation, degeneration, necrosis, and intratubular calcium oxalate crystals. Effects on body weight, organ weights, and hematological parameters were observed at the high dose only. Changes in serum chemistry parameters were observed at lower doses in both males and females; however, these were not accompanied by histopathological changes in the liver. This study identified a LOAEL of 2,615 mg/kg/day for renal toxicity in male rats. As discussed above, other studies identified bone marrow effects and developmental toxicity at lower doses; thus, this study was not considered for use in acute oral MRL derivation.

Corley et al. (2005a) published a PBPK model for rats, but no model has yet been developed for mice, the species used in the study selected for MRL derivation. As a result, available data do not support the use of PBPK modeling to derive an acute oral MRL for ethylene glycol based on developmental toxicity in mice.

A key uncertainty in the acute-duration oral MRL stems from the use of gavage administration in the critical study. Bolus doses from gavage administration lead to higher peak concentrations of glycolic acid in the blood than occur with equivalent doses at slower dose-rates associated with environmentally-relevant exposures (Carney et al. 2001; NTP-CERHR 2004). Because the key study used gavage administration, the dose at which effects were observed may be lower than would be observed with non-bolus dosing. In support of this, Maronpot et al. (1983) observed neither fetal nor maternal toxicity at dietary doses up to 1,000 mg/kg in F344 rats, while Neeper-Bradley et al. (1995) reported skeletal malformations and effects on fetal body weight in CD rats given 1,000 mg/kg via gavage. While strain differences in susceptibility to ethylene glycol cannot be ruled out as the source of the differing results, the data supporting glycolic acid as the proximate toxicant, and the evidence for much lower serum levels of glycolic acid with continuous dosing than with bolus dosing, suggest that the lack of developmental toxicity observed by Maronpot et al. (1983) likely resulted from the difference in dose-rate.

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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

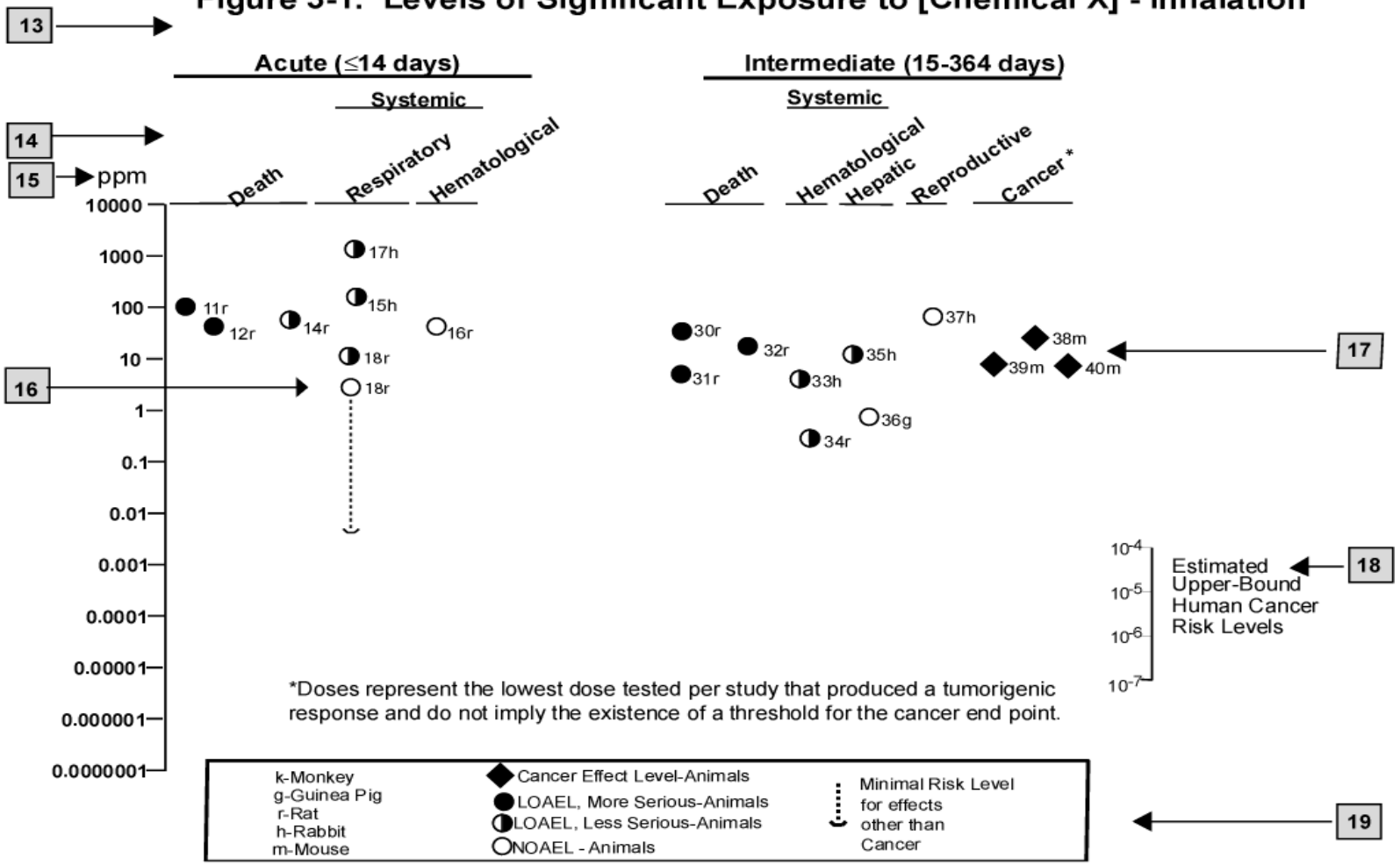
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	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	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