APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

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

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chlorine gas
CAS Numbers: 7782-50-5
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 7, 9, 10, 11
Species: Human

Minimal Risk Level: 0.06 [ ] mg/kg/day [X] ppm

References: Anglen DA. 1981. Sensory response of human subjects to chlorine in air. Ann Arbor, MI: University of Michigan.

D'Alessandro A, Kuschner W, Wong H, et al. 1996. Exaggerated responses to chlorine inhalation among persons with nonspecific airway hyperreactivity. Chest 109:331-337.

Rotman HH, Fliegelman MJ, Moore T, et al. 1983. Effects of low concentrations of chlorine on pulmonary function in humans. J Appl Physiol 54:1120-1124.

Schins RPF, Emmen H, Hoogendijk L, et al. 2000. Nasal inflammatory and respiratory parameters in human volunteers during and after repeated exposure to chlorine. Eur Respir J 16:626-632.

Shusterman D, Murphy, MA, Balmes J. 1998. Subjects with seasonal allergic rhinitis and nonrhinitic subjects react differentially to nasal provocation with chlorine gas. J Allergy Clin Immunol 101:732-740.

Shusterman D, Murphy, MA, Balmes J. 2003b. Influence of age, gender, and allergy status on nasal reactivity to inhaled chlorine. Inhal Toxicol 15:1179-1189.

Experimental design and effects noted in each study: Anglen (1981) exposed up to 29 male and female volunteers to 0, 0.5, 1, or 2 ppm chlorine for either 4 or 8 hours. Sensations were recorded before and during exposure, and pulmonary function was monitored by measuring FVC and FEV_1 before and at various times during exposure. Itching and burning of the throat were the highest responses and were most prevalent by the end of an 8-hour exposure to 1 ppm chlorine. Responses for sensations of itching or burning of the nose and eyes were also prevalent at 1 ppm chlorine. In general, males provided stronger irritation responses than females. Exposure to 1 or 2 ppm chlorine for 8 hours produced significant changes in pulmonary function, but similar exposures to 0.5 ppm did not. Exposure to 2 ppm for up to 30 minutes produced no increase in subjective irritation and exposure to 2 ppm for 2 hours did not alter pulmonary function.

Rotman et al. (1983) studied eight healthy male volunteers exposed to target concentrations of 0, 0.5, or 1 ppm chlorine (Rotman et al. 1983). Pulmonary tests were conducted before exposure, after a 4- and 8-hour exposure period and again 2 and 24 hours after exposure ceased. During exposure, the subjects exercised on a treadmill for 15 minutes of each hour to simulate light-to-moderate work that raised the heart rate to 100 beats per minute. Specific respiratory parameters measured included FVC, FEV_1, FEV_1% forced expired volume in 1 second as %FVC (FEV1%), peak expiratory flow rate (PEFR), FEF_{50} and FEF_{25}, TLC, expiratory reserve volume (ERV), functional residual capacity (FRC), residual volume, airway resistance (Raw), single-breath DL_{CO}, closing volume, and difference in nitrogen concentrations between 750 and 1,250 mL of inhaled vital capacity (ΔN_2). Exposure to 1 ppm chlorine caused runny

nose and mild burning in the throat, but no such effects were reported at 0.5 ppm. Significant changes in pulmonary function tests were mostly restricted to the 1 ppm exposure level and were evident after 4 hours of exposure. Changes were observed in FEV_1, PEFR, FEF_{50}, FEF_{25}, TLC, Raw, and ΔN_2. Greater changes in some of these parameters were seen after 8 hours of exposure. Few changes were still evident 24 hours after exposure, but most parameters had returned to pre-exposure values by that time. It should be noted that one volunteer who was atopic experienced severe distress during exposure to 1 ppm and was forced to exit the chamber before the full 8-hour period due to shortness of breath and wheezing.

D'Alessandro et al. (1996) evaluated pulmonary function in subjects with (n=10) and without (n=5) airway hyperreactivity (HR, defined by baseline methacholine hyperresponsiveness). The HR subjects were exposed to 0.4 or 1.0 ppm chlorine, whereas the healthy subjects were exposed to 1.0 ppm chlorine. All exposures lasted 60 minutes. Airflow and airway resistance were measured immediately before and immediately after exposure. Also, lung volumes, airflow, diffusing capacity, airway resistance, and responsiveness to methacholine were measured 24 hours before and 24 hours after exposure. Exposure of the HR group to 0.4 ppm chlorine resulted in no significant change in airflow or resistance either immediately or 24 hours after exposure. Exposure to 1.0 ppm chlorine resulted in an immediate decrease in FEV_1 and $FEF_{25–75\%}$ and increase in airway resistance among normal and HR subjects, but the magnitude of the effects among HR subjects was significantly greater than in healthy subjects. Twenty-four hours after exposure, there were no significant changes for healthy or HR subjects in airflow, lung volumes, diffusing capacity, resistance, or methacholine responsiveness. Comparing relative changes from baseline immediately after exposure between normal and HR subjects showed that HR subjects had much greater changes in pulmonary function tests.

Schins et al. (2000) studied eight volunteers exposed to chlorine 6 hours/day on 3 consecutive days to each of the four exposure conditions, 0, 0.1, 0.3, and 0.5 ppm chlorine (Schins et al. 2000). Pulmonary function including effort-dependent parameters and effort-independent parameters were evaluated before and after exposures. In addition, nasal lavage measurements were performed before and after each exposure and 1 and 4 days after each exposure. The nasal lavage fluid was examined for total cells, epithelial cells, neutrophils, lymphocytes, eosinophils, monocytes, albumin (an indicator of epithelial permeability), and interleukin-8 (indicator of inflammatory response). Subjective complaints by the subjects were judged to be not treatment-related. Examination of the nasal lavages gave no indication of an inflammatory response or irritant effects on the nasal epithelium. The results of the pulmonary function tests showed that the only significant effect related to chlorine exposure was a difference in maximal mid expiratory flow (MMEF) between 0 and 0.5 ppm exposure; however, this was attributed to an unexplained shift in baseline values during control exposure (0 ppm).

Shusterman et al. (2003b) measured nasal airway resistance in 52 healthy adults (24 males and 28 females) before and after exposure to 0 or 1 ppm chlorine for 15 minutes. Subjects were stratified on age (18–34, 35–51, 52–69 years), gender, and allergic rhinitis status (27 were positive). Nasal airway resistance was measured by active posterior rhinomanometry. Exposures to air and chlorine were a week apart. Subjects with allergic rhinitis showed a significantly greater increase in nasal airway resistance (49% increase from baseline) than healthy subjects (10% increase from baseline) 15 minutes after exposure. The increase in nasal airway resistance was most pronounced in older subjects and least pronounced in the youngest group. No significant differences were seen between males and females. In an earlier study, the same group of investigators had reported that subjects with SAR (n=8) exposed to 0.5 ppm chlorine for 15 minutes experienced a much greater increase in nasal airway resistance than subjects without SAR (n=8), as measured by active posterior rhinomanometry (Shusterman et al. 1998). However, when subjective responses to odor, nasal irritation, and nasal congestion were analyzed separately by rhinitis status, no significant exposure-related changes were observed for rhinorrhea, postnasal drip, or headache either on a pool or stratified basis. In addition, within either the SAR or non-SAR group, there was no relationship between subjective and objective congestion after chlorine

exposure. Pulmonary peak flow tests showed that none of the subjects exhibited clinically significant changes in peak flow, nor did they complain of cough, wheezing, or chest tightness on chlorine exposure days. The increased nasal airway resistance instrumentally detected in subjects with SAR is not considered an adverse effect since the subjects did not perceive it as such.

Collectively, this group of studies provides evidence of sensory irritation and transient pulmonary changes occurring in humans exposed to 1 ppm chlorine for up to 8 hours/day. The pulmonary changes indicated increased airway resistance and reduced air flow. No such changes were reported in volunteers exposed to 0.5 ppm chlorine

Dose and end point used for MRL derivation: 0.5 ppm is a NOAEL for sensory irritation and pulmonary function.

The MRL is derived by adjusting for continuous exposure based on the fact that Rotman et al. (1983) reported that exposure to 1 ppm for 8 hours induced greater changes in pulmonary function tests than exposure to the same concentration for 4 hours, suggesting that the response was related to some function of concentration and duration rather than to concentration alone.

MRL = 0.5 ppm (8 hours/24 hours) = 0.167 ppm

8 hours was the longest period of exposure for which there is information.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Although sensitive individuals were tested in some of these studies, the number of individuals tested at the region of the NOAEL (0.4–0.5 ppm) was small. Therefore, an uncertainty factor of 3 is used to account for sensitive populations.

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

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

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

Other additional studies or pertinent information that lend support to this MRL: Results from the five studies summarized above are supportive of each other.

Agency Contacts (Chemical Managers): G. Daniel Todd

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chlorine gas
CAS Numbers: 7782-50-5
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 30
Species: Rat

Minimal Risk Level: 0.002 [ ] mg/kg/day [X] ppm

Reference: Kutzman RS. 1983. A study of Fisher-344 rats subchronically exposed to 0, 0.5, 1.5, or 5.0 ppm chlorine. Upton, NY: Brookhaven National Laboratory. BNL 32710.

Experimental design: Groups of F344 rats (24 males, 10 females) were exposed to 0, 0.5, 1.5, or 5 ppm chlorine 6 hours/day, 5 days/week for 62 days (Kutzman 1983). Pulmonary function tests (plethysmograph-based assessment of multiple end points, including lung and tidal volumes, breathing frequency, transpulmonary pressure, lung compliance, N_2 washout, diffusing capacity for CO_2, maximum expiratory flow volume, peak expiratory flow, and airway resistance) were conducted in 21–24 anesthetized males 6 hours after the last exposure. Respiratory tissues from these rats were prepared for histopathology. The lung from some of these rats was also examined for collagen, elastin, total protein, and DNA. Histopathology of selected organs (nasal turbinates, lungs, peribronchial lymph node, brain, kidney, liver, spleen, testes, and heart) was evaluated in eight males per group. Also, 8 males were mated with untreated females and 10 exposed females were mated with untreated males for reproductive studies on females sacrificed on GD 19. In addition, 1 day after the last exposure, samples of blood and bone marrow from 10 males per group were prepared for analysis of chromosomal aberrations and sister chromatid exchanges.

Effects noted in study and corresponding doses: Exposure to 5 ppm cause severe eye and upper respiratory irritation, whereas rats exposed to 1.5 ppm showed occasionally less severe signs of irritation, and exposure to 0.5 ppm caused no obvious signs of irritation or discomfort. Female rats exposed to 5 ppm lost weight. Final weight was approximately 32% lower than controls; at 1.5 and 0.5 ppm, final weight was approximately 15 and 11% lower than in control rats, respectively. In males exposed to 5 ppm, final weight was approximately 15% lower than controls. No information was provided regarding food and water intake. Changes in organ weights were unremarkable. The tests of pulmonary function did not reveal marked abnormalities. The most significant effect was a reduction in airflow at 25% vital capacity in all exposed groups, indicating some degree of small airway involvement. An electro-cardiogram did not reveal any significant cardiac alterations due to chlorine exposure. The lung biochemistry only showed an increased collagen concentration at 1.5 and 5 ppm. The cytogenetic studies showed no increased incidence of sister chromatid exchange or cellular proliferation in bone marrow and no increase in sister chromatid exchanges or chromosomal aberrations in peripheral lymphocytes. Analysis of sperm morphology was unremarkable. Results of the reproductive studies showed no effects on fertility, number of corpora lutea, viable embryos, early or late deaths, or preimplantation loses. There were no significant exposure-related increases in the incidences of animals with histological lesions in any of the examined tissues with the exception of a loss of cilia in the trachea. The incidences of slight to moderate loss of tracheal cilia were 1/23, 12/23, 4/23, and 13/23 in the 0, 0.5, 1.5, and 5 ppm exposure groups, respectively. Although the incidence for this lesion in the mid-exposure group was not significantly different from the control incidence, a statistically significant ($p=0.0055$) Cochran-Armitage trend test for these data can be demonstrated. However, when attempts were made to apply dose-response

models to the data, no adequate fits of EPA Benchmark Dose Software models to the data were obtained (p-values for chi-square goodness of fit statistics were <0.1).

Dose and end point used for MRL derivation: 0.5 ppm is a minimal LOAEL for tracheal lesions.

Uncertainty Factors used in MRL derivation:

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

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

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The intermediate-duration inhalation MRL was calculated using EPA's methodology (EPA 1994a) for a category 1 gas.

$LOAEL_{[HEC]} = LOAEL_{[ADJ]} \times RGDR_{TB}$

where:

$LOAEL_{[ADJ]}$ = 0.5 ppm x 6/24 hours x 5/7 days = 0.09 ppm and
$RGDR_{TB}$ = ratio of the regional gas dose in rats to that of humans for the tracheobronchial region

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

where:

VE = minute volume (0.137 L/minute for rats, 13.8 L/minute for humans [EPA 1994a]) and
SA_{TB} = surface area of the tracheobronchial region (22.5 cm^2 for rats and 3,200 cm^2 for humans [EPA 1994a])

$LOAEL_{[HEC]}$ = 0.09 ppm x (0.137 L/minute/22.5 cm^2) / (13.8 L/minute/3,200 cm^2) = 0.14 ppm

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

Other additional studies or pertinent information that lend support to this MRL: In a similar study, Barrow et al. (1979) evaluated the respiratory response in F344 rats exposed to 0, 1, 3, or 9 ppm chlorine 6 hours/day, 5 days/week for 6 weeks. Nasal discharge was seen occasionally in rats exposed to 1 ppm, but was common in rats exposed to 3 and 9 ppm. Respiratory difficulty was also apparent in some rats exposed to 9 ppm. At termination, gross necropsy revealed accumulation of inflammatory reactions in the upper nasal passages in rats exposed to 3 and 9 ppm chlorine. Microscopic evaluations showed indications of inflammatory reactions in the upper and lower respiratory tract of high-dose males and females. The nasal turbinates showed mucopurulent inflammation with secretory material and erosions of the mucosal epithelium. Changes in the trachea and bronchi consisted mostly of hyperplasia of the epithelial lining and inflammatory reactions. The alveolar sacs contained macrophages and secretory material and epithelial cells showed necrosis, hypertrophy, and hyperplasia. Alterations in rats exposed to 1 and 3 ppm were less extensive and were limited to focal mucopurulent inflammation of the nasal turbinates in females. Males exposed to 1 or 3 ppm showed deeper pulmonary changes consisting of slight to moderate inflammatory reaction around the respiratory bronchioles and alveolar ducts, increased alveolar macrophages, and isolated areas of atelectasis (incomplete expansion). A LOAEL of 1 ppm for respiratory effects can be defined in this study based on the presence of inflammatory changes in the nasal

turbinates of females and in the lungs of males; no NOAEL was established. Incidences of animals with respiratory lesions were not presented in this study.

Agency Contacts (Chemical Managers): G. Daniel Todd

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chlorine gas
CAS Numbers: 7782-50-5
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 34
Species: Monkey

Minimal Risk Level: 0.00005 [ ] mg/kg/day [X] ppm

Reference: Klonne DR, Ulrich CE, Riley MG, et al. 1987. One-year inhalation toxicity study of chlorine in Rhesus monkeys (*Macaca mulatta*). Fundam Appl Toxicol 9:557-572.

Experimental design: Male and female Rhesus monkeys (4/sex/exposure level) were exposed to 0, 0.1, 0.5, or 2.3 ppm chlorine 6 hours/day, 5 days/week for 1 year (Klonne et al. 1987). Pulmonary diffusing capacity of CO and distribution of ventilation, body weights, urinalysis, EKG, hematology, and clinical chemistry were evaluated monthly during the study. At termination, the heart, lungs plus trachea, liver, gonads, kidneys, spleen, and brain were weighed. Histological evaluations were done on all major tissues and organs. The nasal tissues (at the first palatine ridge and just posterior to the third, fifth, and seventh palatine ridges), trachea, and lungs were also examined.

Effects noted in study and corresponding doses: Exposure to chlorine did not significantly affect body weight, hematology and clinical chemistry parameters, urinalysis, or the EKG. At approximately week 6 of exposure, monkeys in the 2.3 ppm group showed overt signs of ocular irritation (tearing, reddened eyes, rubbing the eyes) during the daily exposures; no signs of irritation were seen in the other exposure groups. Examination of the eyes at termination showed irritation of the conjunctiva at 2.3 ppm, but no evidence of gross changes; the corneas were not affected. During the study, there was a statistically significant trend in each group, including controls, for increasing pulmonary diffusing capacity and distribution of ventilation. However, there was no evidence of treatment-related effects at any interval during the study. The only treatment-related histopathological effects consisted of focal epithelial hyperplasia characterized by increased cell numbers and loss of cilia and goblet cells in the respiratory epithelium of the nose and trachea. The affected areas of the nasal passages showed hypercellularity with loss of goblet cells and cilia. In some of these areas, the nuclei showed altered polarity. Lesions were more frequent on the angular margins of the turbinates and less frequent on the lateral wall or septum adjacent to these margins. In some cases, the respiratory epithelial hyperplasia was associated with mild suppurative inflammatory response. Lesions in the trachea resembled those in the nose, but were less severe and involved only a small circumferential section of the ventral and ventrolateral trachea. The combined incidences of hyperplasia in the nasal epithelium with loss of goblet cells and cilia, characterized as trace and mild in males and females, were 1/8, 3/8, 6/8, and 8/8 in the control, 0.1, 0.5, and 2.3 ppm exposure groups, respectively. The exposure concentration of 0.1 ppm is considered a LOAEL for nasal lesions in monkeys.

Incidence data for nasal lesions in male and female monkeys exposed to chlorine gas (Klonne et al. 1987) were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 1.4.1) (i.e., Gamma, Logistic, Log-logistic, Multi-stage, Probit, Log-probit, Quantal linear, Weibull) were fit to the nasal lesion data to determine potential points of departure for the MRL. A Quantal linear model provided the best fit to the data. The predicted exposure concentration associated with a 10% extra risk

(BMC_{10}) for nasal lesions in monkeys was 0.04 ppm; the lower 95% confidence limit on this concentration ($BMCL_{10}$) was 0.02 ppm.

Dose and end point used for MRL derivation: $BMCL_{10}$ of 0.02 ppm for nasal lesions in monkeys.

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

Uncertainty Factors used in MRL derivation:

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

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

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The intermediate-duration inhalation MRL was calculated using EPA's methodology (EPA 1994a) for a category 1 gas.

$$BMCL_{10[HEC]} = BMCL_{10[ADJ]} \times RGDR_{ET}$$

where:

$BMCL_{10[ADJ]}$ = 0.02 ppm x 6/24 hours x 5/7 days = 0.004 ppm and
$RGDR_{ET}$ = ratio of the regional gas dose in rats to that of humans for the extrathoracic region

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

where:

VE = minute volume 2.1 m^3/day for monkeys, calculated using the allometric equation for monkeys in EPA (1988) assuming a body weight of 7 kg for Rhesus monkeys with nasal cavity surface area of 62 cm^2 (Gross and Morgan 1991); 20 m^3/day for humans (EPA 1994a) and
SA_{ET} = 62 cm^2 surface area of the nasal cavity in Rhesus monkeys weighing 7 kg (Gross and Morgan 1991); 200 cm^2 for humans (EPA 1994a)

$$RGDR_{ET} = (2.1\ m^3/day / 62\ cm^2) / (20\ m^3/day / 200\ cm^2) = 0.34$$

$$BMCL_{10[HEC]} = 0.004\ ppm \times 0.34 = 0.00136\ ppm$$

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

Other additional studies or pertinent information that lend support to this MRL: Wolf et al. (1995) exposed groups of F344 rats and $B6C3F_1$ mice (approximately 70/sex/exposure level) to 0, 0.4, 1, or 2.5 ppm chlorine gas for 2 years. Males from both species and female mice were exposed 6 hours/day, 5 days/week, whereas female rats were exposed 6 hours/day, 3 days/week. The reduced exposure of female rats was based on unpublished data from the investigators that showed female rats to have a greater sensitivity to repeated long-term exposure to chlorine. End points evaluated included gross and microscopic examination of the respiratory tract; the nasal passages were examined microscopically at

five different levels. Both in rats and mice, there were no gross lesions attributable to exposure to chlorine, and microscopic evaluation of the respiratory tract showed that chlorine-related effects were restricted to the nasal passages. In the study, the incidences were presented as percentages of all animals for which the nasal passages were adequate for microscopic examination, but the number of animals examined was not provided. No lesions were seen in the larynx, trachea, bronchi, or bronchioles. In general, rats and mice exhibited similar types of lesions. For the most part, the nasal lesions were site-specific, but the severity and/or incidence were not always concentration-dependent. The majority of the nasal responses exhibited a rostral-to-caudal severity gradient. The lesions rarely extended to the nasopharyngeal meatus. Lesions observed included respiratory and olfactory epithelial degeneration, septal fenestration, mucosal inflammation, respiratory epithelial hyperplasia, squamous metaplasia, and goblet cell (only rats) hypertrophy and hyperplasia, and secretory metaplasia of the transitional epithelium of the lateral meatus. Also observed was intracellular accumulation of eosinophilic proteinaceous material involving the respiratory, transitional, and olfactory epithelia. Lesions were also observed in controls, but the incidences were significantly lower than in the treated groups. One of the lesions with the lowest incidence in controls was Goblet cell hyperplasia in female rats (4%); the respective incidences in the 0.4, 1, and 2.5 ppm group were 71, 90, and 91%. In mice, olfactory epithelium atrophy exhibited one of the lowest incidences in controls (3%); the respective incidences in the 0.4, 1, and 2.5 ppm group were 20, 21, and 39%. In both cases, severity also was concentration-related. Based on the increased incidence of various types of lesions in the nasal passages, the exposure level of 0.4 ppm constitutes a LOAEL for respiratory effects in rats and mice; a NOAEL was not defined.

Agency Contacts (Chemical Managers): G. Daniel Todd

BENCHMARK MODELING OF NASAL LESIONS IN MONKEYS

Incidence data for nasal lesions in male and female monkeys exposed to chlorine gas (Klonne et al. 1987) were analyzed using the BMD approach for MRL derivation (Table A-1). Models in the EPA BMDS (version 1.4.1) (i.e., Gamma, Logistic, Log-logistic, Multi-stage, Probit, Log-probit, Quantal linear, Weibull) were fit to the nasal lesion data to determine potential points of departure for the MRL. A Quantal linear model provided the best fit to the data (Table A-2).

Table A-1. Incidence of Nasal Lesions Observed in Monkeys Exposed to Chlorine for 1 Year

Dose (ppm)	Total number of monkeys	Number of monkeys with lesions
0	8	1
0.1	8	3
0.5	8	6
2.3	8	8

Source: Klonne et al. 1987

Table A-2. Modeling Predictions for the Incidence of Nasal Lesions Observed in Monkeys Exposed to Chlorine for 1 Year

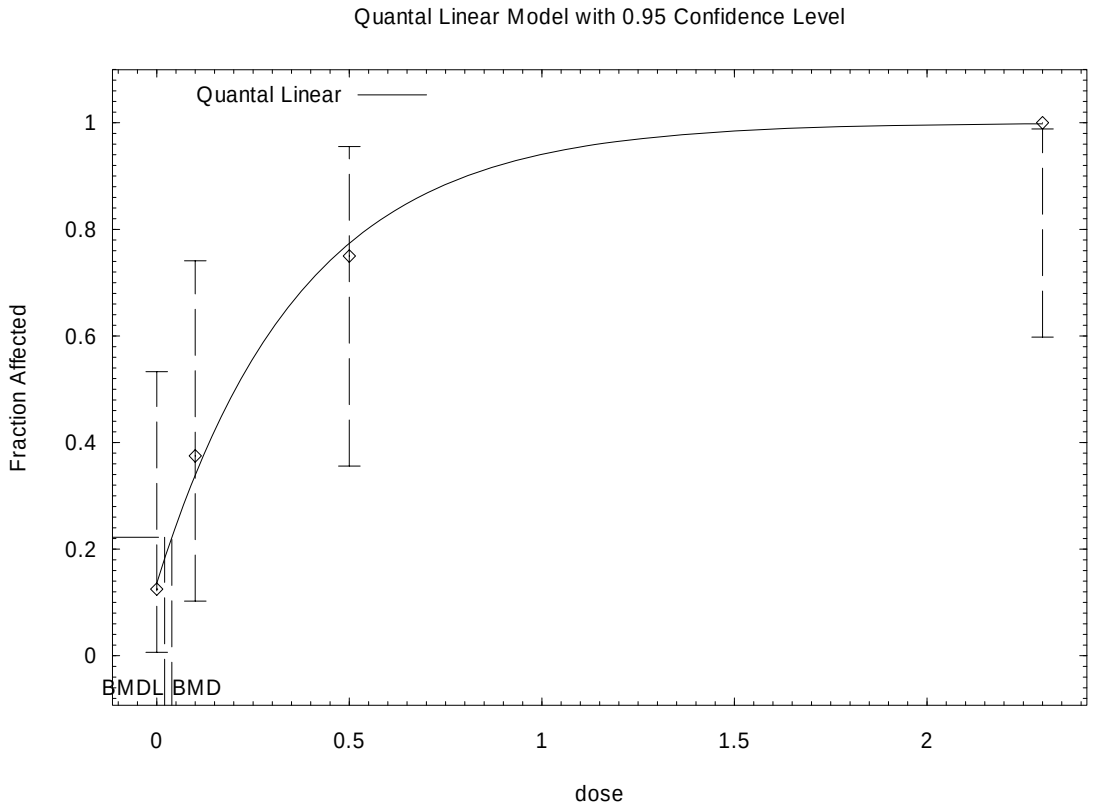
Model	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)	x^2 p-value	AIC
Gamma[a]	0.04	0.02	0.95	29.72
Logistic	0.09	0.05	0.76	30.17
Log-logistic[b]	0.05	0.009	0.53	32.21
Multi-stage[c]	0.04	0.02	0.95	29.72
Probit	0.08	0.05	0.77	30.14
Log-probit[b]	0.06	0.03	0.81	30.09
Quantal linear	0.04	0.02	0.95	29.72
Weibull[a]	0.04	0.02	0.95	29.72

[a]Restrict power $\geq$1.
[b]Slope restricted to >1.
[c]Restrict betas $\geq$0; lowest degree polynomial with an adequate fit is reported; degree of polynomial = 1.

Source: Klonne et al. 1987

From this model, the predicted exposure concentration associated with a 10% extra risk (BMC_{10}) for nasal lesions in monkeys was 0.04 ppm; the lower 95% confidence limit on this concentration ($BMCL_{10}$) was 0.02 ppm (Figure A-1).

Figure A-1. Predicted and Observed incidence of Nasal Mucosal Lesions in Monkeys Exposed to Chlorine for 1 Year



The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Background = 0.135767

Slope = 2.67521

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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

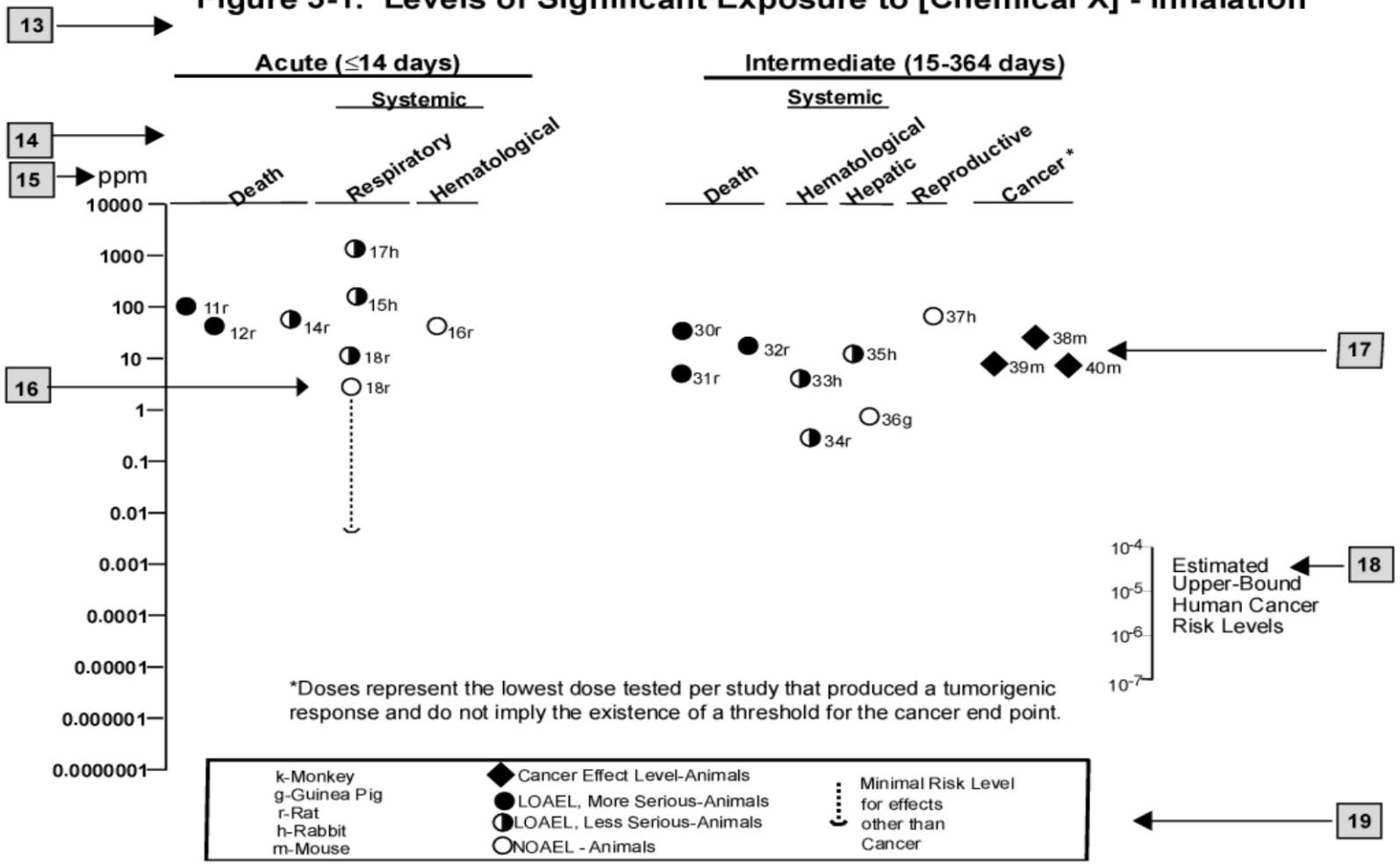
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	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/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

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

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

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX