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 a hundredfold 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, 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, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop E-29, Atlanta, GA 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Sulfur mustard [bis(2-chlorethyl) sulfide]
CAS number(s): 505-60-2
Date: August 29, 2003
Profile status: Third Draft
Route: [X] Inhalation [Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 2
Species: Human

Minimal Risk Level: 0.0007 [ ] mg/kg/day [ ] ppm [X] mg/m^3

Reference: Guild WJF, Harrison KP, Fairley A, et al.. 1941. The effect of mustard gas vapor on the eyes. Chemical Board, Physiological Sub-Committee and Panel of Opthalmic Specialists. Porton Report 2297. Chemical Defense Experimental Station, Porton, UK.

Experimental design: Male soldiers wearing respirators (2–6 men/group) were exposed to sulfur mustard vapor concentrations, checked by continuous chemical sampling, ranging from 0.06 to 320 mg/m^3. Continuous exposure durations ranged from 15 seconds to 10 hours, yielding concentration time (Ct) products in the range of 42–144 mg-minute/m^3. Two repeated-exposure tests were also conducted; a group of four men was exposed to 0.22 mg/m^3, 2.5 hours/day, for 2 days, and another group of four men was exposed to 0.06 mg/m^3, 8 hours/day, for 3 days (intermittent Cts of 66 and 86 mg-minute/m^3, respectively). Chamber temperatures for each experiment were not provided, but chamber temperatures were stated to range from 55 to 80 ºF during the testing. Soldiers were in good health and had no previous exposures to sulfur mustard. The subject's eyes were examined for evidence of toxicity subsequent to exposure.

Effects noted in study and corresponding doses: No deaths occurred. For continuous exposures, ocular effects and severity depended on the concentration and duration, or Ct. At the lowest continuous Ct of 42 mg-minute/m^3 (1.4 mg/m^3 for 30 minutes), four of four soldiers showed a slight generalized conjunctival reaction. A slight or just discernable or slight conjunctival reaction was also reported at the lowest concentration of 0.1 mg/m^3 for 8 and 10 hours exposures (Cts of 48 and 60 mg-minute/m^3, respectively). Just discernable angular congestion of the bulbar conjunctiva was reported for Cts ranging from 48 to 75 mg-minute/m^3. Slight to moderate degree of conjunctival congestion was reported for the Ct range of 80-90 mg-minute/m^3. The first casualties (two of two men) [casualty meaning any interference with vision or any lesion of the eyes sufficiently severe to render a soldier, for a time, incapable of carrying out his normal duties] were reported at a Ct of 99 mg-minute/m^3 (16.5 mg/m^3 for 6 minutes). Both subjects showed generalized established conjunctivitis with photophobia. At a Ct of 144 mg-minute/m^3, six of six subjects showed marked generalized conjunctival congestion, with photophobia in one of six subjects. While specific results were not reported for the 2-day repeated exposure (0.22 mg/m^3, 2.5 hours/day, for 2 days), the authors stated that there was no discernable difference in the degree of conjunctival reaction between subjects in this group and subjects exposed to the same concentration for 5 hours (Ct of 66 mg-minute/m^3). A scarcely discernable generalized conjunctival reaction (incidence unspecified) was reported in subjects undergoing the 3-day repeated exposure (0.06 mg/m^3, 8 hours/day, for 3 days; intermittent Cts of 86 mg-minute/m^3). The severity of conjunctivitis for the 3-day intermittent exposure was described as far slighter than the moderate degree of conjunctivitis observed from continuous exposures with Cts ≥80 mg-minute/m^3.

Dose and end point used for MRL derivation: The 3-day repeated exposure experiment is considered to best represent a potential acute exposure, and the time-weighted average concentration of 0.02 mg/m^3 (0.06 mg/m^3 x 8 hours/24 hours) is considered a minimal LOAEL for ocular effects.

[ ] NOAEL [X] LOAEL

Uncertainty factors (UF) and Modifying Factor (MF) used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA

Was a conversion used from intermittent to continuous exposure? Yes
$LOAEL_{[ADJ]}$=0.06 mg/m^3 · (8 hours/24 hours) =0.02 mg/m^3

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information that lend support to this MRL: Ocular effects were reported in other chamber tests reported by Reed (1919) and Anderson (1942); however, these studies did not include repeated exposures. Conjunctivitis with photophobia and blepharospasm were reported as the initial signs of exposure in two subjects who underwent chamber tests wearing no respirators and clad only in khaki uniform pants without shirts (Reed 1918). The two subjects were exposed to 1.2 mg/m^3 of sulfur mustard vapor for 20 and 45 minutes (Cts of 24 and 54 mg-minute/m^3), respectively. The variation in sensitivity to sulfur mustard was demonstrated by a latency of 3 hours for the subject exposed to the Ct of 24 mg-minute/m^3, as compared to 6 hours for the subject exposed to the higher Ct. In subsequent chamber tests conducted by Reed (1918), no signs were reported in six subjects exposed to the lowest Ct of 1.0 mg-minute/m^3 (0.1 mg/m^3 for 10 minutes), whereas one of two subjects showed slight, but distinct, conjunctival injection at the next higher Ct of 1.5 mg-minute/m^3 (0.1 mg/m^3 for 15 minutes). In continuous flow tests with human subjects, with only the face and one eye exposed, conjunctivitis was observed at Cts as low as 7 mg-minute/m^3 (0.7 mg/m^3 for 10 minutes); Cts as low as 1.5 mg-minute/m^3 (0.1 mg/m^3 for 15 minutes) were tested (Reed 1918). However, it should be noted that methods for measuring low vapor concentrations of sulfur mustard were not yet validated at the time of these studies. In chamber tests conducted by Anderson (1942), using male soldier wearing respirators, a trace of angular conjunctivitis and "band of fine injection" across the exposed part bulbar conjunctiva were reported at the lowest Ct of 12.5 mg-minute/m^3 (6.25 mg/m^3 for 2 minutes). A "fine injection band" over the exposed sclera was reported at the lowest concentration of 1.7 mg/m^3 (33 min; Ct=56.1 mg-minute/m^3) (Anderson 1942). In addition to chamber testing, numerous reports exist of ocular lesions that occurred in soldiers exposed to sulfur mustard during World War I (Hughes 1942; Philips 1940). In a more recent study of Iranian fighters with a history of sulfur mustard poisoning, delayed ocular lesions from undetermined, presumably acute, exposures included chronic conjunctivitis in 75/85 (32%), keratoconjunctivitis in 7/85 (3%) and blindness in 2/85 (1%) (Balali-Mood 1986). A range of ocular effects, including conjunctivitis, chronic keratitis, and corneal ulcerations, have been reported in dogs and rabbits following acute exposure to sulfur mustard depending on the concentration and duration of exposures (Balali-Mood 1986; Gates and Moore 1946; Laughlin 1944a; Maumenee and Scholts 1948; Reed 1918; Warthin and Weller 1919).

Agency Contact (Chemical Manager): Zemoria A. Rosemond

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Sulfur mustard [bis(2-chlorethyl) sulfide]
CAS number(s): 505-60-2
Date: August 29, 2003
Profile status: Third Draft
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 11
Species: Dog

Minimal Risk Level: 0.00002 [ ] mg/kg/day [ ] ppm [X] mg/m^3

Reference: McNamara BP, Owens EJ, Christensen MK, et al. 1975. Toxicological basis for controlling levels of mustard in the environment. Edgewood Arsenal Special Publication. Aberdeen Proving Ground, Maryland: Department of the Army. EB-SP-74030.

Experimental design: Male and female beagle dogs (6 initially and 4 added), rats (140), A/J mice (140), rabbits (12 initially and 6 added), and guinea pigs (30 initially and 12 added) were exposed to sulfur mustard vapor at a concentration of 0.001 mg/m^3 for 24 hours/day, 5 days/week (time-weighted average concentration of 0.0007 mg/m^3), for varying durations up to 1 year. The same number of animals of each species were exposed to 0.1 mg/m^3 for 6.5 hours followed by exposure to 0.0025 mg/m^3 for the remaining 17.5 hours of the day, 5 days/week, for durations up to a year. The latter exposure is equivalent to a time-weighted average concentration of 0.0206 mg/m^3 [{0.1 mg/m^3 x (6.5 hours/24 hours) + 0.0025 mg/m^3 x (17.5 hours/24 hours)} x (5 days/7 days) = 0.0206 mg/m^3]. Unexposed controls consisted of 10 dogs (6 initially and 4 added), 100 rats, 140 A/J mice (120 initially and 20 added), 22 rabbits (7 initially and 15 added), and 32 guinea pigs (20 initially and 12 added). The treatment protocol was unusual in that new animals were added to replace exposed animals that were sacrificed periodically. At about 7 months after the study was initiated, 100 ICR Swiss albino mice were added to the test chambers, and 50 A/J mice were added about 3 months later. At these same times, the same numbers of each strain were added to the study as additional controls. The animals were observed periodically for clinical signs of toxicity. Body weights were recorded. Red and white blood cell counts, hematocrit, and hemoglobin were measured in dogs and rabbits, but not other species. Clinical chemistry analyses including blood urea nitrogen (BUN), lactic dehydrogenase (LDH), alkaline phosphatase (ALP), and serum alanine aminotransferase (ALT) were conducted in dogs. Gross and microscopic examinations were performed.

Effects noted in study and corresponding doses: No dogs died during the study. Mortality was unrelated to concentration in rabbits and guinea pigs, and comparable to controls in exposed ICR Swiss mice. While no control rats died, death occurred in 3/140 and 16/140 at the low- and high-concentrations, respectively. In the first group of A/J mice, mortality incidence was concentration-related; 4/140, 14/140, and 24/140 in the control, low- and high-concentration groups, respectively. However, in the second group of A/J mice, 3/50 animals in the low-concentration group died, while there were no deaths in the control and high-concentration groups. Because of the lack of correlation between deaths and exposure in the ICR Swiss mice and the second group of A/J mice the authors concluded that deaths were more likely due to conditions of animal storage than treatment. Of 79 rats exposed to the lower concentration and necropsied, 5 developed chronic keratitis. This lesion was not observed in control or high-dose rats. No clinical signs of toxicity were observed in any of the other species exposed to the low concentration. At the high concentration, the only overt signs of toxicity were ocular effects, observed only in dogs. Ocular effects first appearing after 16 weeks of exposure, including corneal opacity, pannus, chronic keratitis, vascularization, pigmentation, and granulation were reported in 3 of 10 high-concentration dogs exposed

for 7.5 or 12 months. The time-weighted average concentration of 0.0206 mg/m^3 is considered a LOAEL for ocular effects in beagle dogs.

Dose and end point used for MRL derivation: The lowest concentration tested in dogs, 0.001 mg/m^3, is a NOAEL for ocular effects (conjunctivitis and chronic keratitis).

[X] NOAEL [ ] LOAEL

Uncertainty factors (UF) and Modifying Factor (MF) used in MRL derivation:

[X] 10 for human variability
[X] 3 for animal-to-human extrapolation

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA

Was a conversion used from intermittent to continuous exposure? Yes
$NOAEL_{[ADJ]}$=0.001 mg/m^3 · (24 hours/24 hours) · (5 days/7 days)=0.0007 mg/m^3

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Gates and Moore (1946) reported that the human eye is about four times more sensitive to sulfur mustard than the rabbit eye based on the observation of corneal ulceration produced in rabbits and dogs at Cts of 4 and 2 times the value, respectively, at which this effect occurred in humans. This is consistent with the observation by McNamara et al. (1975) of ocular effects in dogs, but not in rabbits, at the high concentration. Thus, an uncertainty factor of 3 for extrapolation of data from dogs to humans is considered appropriate for derivation of the MRL.

Other additional studies or pertinent information that lend support to this MRL: The intermediate-duration inhalation MRL was based on the same critical endpoint as the acute-duration inhalation MRL. In addition to the supporting information for ocular lesions as provided for the acute-duration MRL, there are numerous reports of eye burns in workers accidentally exposed to large quantities of sulfur mustard vapor, as well as to slow leaks that were not detected by smell (Hughes 1945a; Pechura and Rall 1993; Uhde 1946).

Agency Contact (Chemical Manager): Zemoria A. Rosemond

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Sulfur mustard [bis(2-chlorethyl) sulfide]
CAS number(s): 505-60-2
Date: August 29, 2003
Profile status: Third Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 5, 6
Species: Rat

Minimal Risk Level: 0.5 [X] µg/kg/day [ ] ppm [ ] mg/m^3

Reference: DOA. 1987. Teratology studies on lewisite and sulfur mustard agents: Effects of sulfur mustard in rats and rabbits. Fort Detrick, MD: U.S. Army Medical Research and Development Command, U.S. Department of Army. ADA187495.

Experimental design: Sulfur mustard (95.9–96.1% purity) dissolved in sesame oil was administered by intragastric intubation to mated Sprague-Dawley female rats (10–11 weeks old) on gestation days 6 through 15 (10 days). The administered doses were 0, 0.5, 1.0, or 2.0 mg/kg/day and there were 25–27 animals/dose group, of which 20–26/dose group were pregnant. All animals were observed for clinical signs of toxicity prior to and following administration of sulfur mustard. Treated rats were weighed on gestation days 0, 6–15 (exposure days), and on day 20. Necropsy was performed on all rats found dead or in moribund condition. Scheduled necropsy was performed on gestation day 20. Blood samples were collected from maternal animals for hematocrit measurement prior to sacrifice. The animals were examined for gross lesions of major organ systems. The numbers of corpora lutea, implantation sites, resorptions, and live and dead fetuses were determined. Uterine weights were recorded. Live fetuses were removed, weighed, sexed, and examined for gross, soft tissue, and skeletal anomalies.

Effects noted in study and corresponding doses: There were no treatment-related deaths. In rats, a significant dose-related decrease in maternal body weight was observed by gestation day 12 at 0.5 mg/kg/day (4.1–6.6%) and by gestation day 9 in the 1.0 (4.7–9.1%) and 2.0 (6.5–16.0%) mg/kg/day groups. Extragestation weight gain was significantly reduced at ≥0.5 mg/kg/day with dose-related reductions of 25, 38, and 57% at 0.5, 1.0, and 2.0 mg/kg/day, compared to controls. A significantly decreased (16%) gravid uteri weight was measured at the highest dose. Maternal hematocrit values were statistically significantly reduced by 5.4% at 1.0 and 2.0 mg/kg/day. Gastric mucosa inflammation was observed in 2/30 (6.7%) rats at 2.0 mg/kg/day, but not in any of the lower dose or control groups. A significantly increased incidence of inflamed mesenteric lymph nodes was found at ≥0.5 mg/kg/day; the incidences were 0/27 controls, and 11/25 (44%), 16/25 (64%), and 15/27 (56%) rats at 0.5, 1.0, and 2.0 mg/kg/day, respectively.

Fetal body weight was significantly decreased (6–7%) from controls in litters exposed to doses of ≥1.0 mg/kg/day; no clear dose-relation was evident. The sex ratio (percent males) was significantly lower than control at the highest dose (46.2 vs. 51.0%). Placental weight was also significantly reduced (8.4%) at the highest dose. Supernumerary ribs were found in 9/299 (3%) fetuses of one litter in the highest dose group, while this anomaly was not found in any of the fetuses in the lower dose or control groups. The incidence of reduced ossification of the vertebrae and/or sternebrae in all treated groups was significantly higher than controls when individual pup data were compared, but not with litter comparisons, 42/272 (15%) in controls, 51/229 (22%) at 0.5 mg/kg/day, 76/315 (24%) at 1.0 mg/kg/day, and 72/299 (24%) at 2.0 mg/kg/day. All fetal effects in rats occurred at doses that also produced maternal toxicity.

Dose and end point used for MRL derivation: The lowest dose tested in rats, 0.5 mg/kg/day is a LOAEL for inflamed mesenteric lymph nodes in the dams and reduced ossification in the fetuses.

[ ] NOAEL [X] LOAEL

Uncertainty factors (UF) and Modifying Factor (MF) used in MRL derivation:

[X] 10 for LOAEL-to-NOAEL extrapolation
[X] 10 for human variability
[X] 10 for animal-to-human extrapolation

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA

Was a conversion used from intermittent to continuous exposure? NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information that lend support to this MRL: In support of the critical effect, there is some evidence in humans to indicate that sulfur mustard affects the lymph system. Discoloration of the lymph nodes in the axillary, inguinal, and mesenteric glands were noted in autopsies of victims of the World War II Bari Harbor incident, during which sulfur mustard was released in to the air and water (Alexander 1947). The spleen also demonstrated evidences of gross pathology in 33 of 53 (62%) autopsies (Alexander 1947). In the majority of cases, the spleen was described as shrunken in size with pale color. Microscopically, only 2 of 32 spleens examined showed degeneration or necrosis; pyknosis and karyorrhexis of lymphocytes in some corpuscles were observed in one and slight necrosis of the malpighian follicle, was observed in the other. Additional studies in animals also revealed sulfur mustard-induced damage to the lymph system. Cameron et al. (1946), after observing damage to the cervical lymph nodes and lymphoid tissue throughout the body in rabbits and monkeys that had undergone tracheal cannulation and had been exposed to chamber concentrations of sulfur mustard ranging from 30 to 350 mg/m^3 (5–54 ppm), administered sulfur mustard to animal skin topically or by subcutaneous injection and observed identical changes to the lymph tissue, suggesting that lymphoid tissue damage may be due to systemic absorption. Sulfur mustard produced a significant dose-related decrease in the weight of peripheral lymph nodes (12–44%) when topically applied at single doses of 3.88, 7.75, or 15.5 mg/kg to the shaved backs of Balb/c mice (Venkateswaran et al. 1994a). A significant decrease in the weight of mesenteric lymph nodes (18%) was noted at the highest dose. Incidence and severity of histological changes in the thymus and spleen were also dose-related. Spleen histopathology included hypocellularity, atrophy of the lymphoid follicles, degeneration of germinal centers, and red pulp infiltrated with macrophages. The cortex and medulla regions of the thymus showed atrophy and hypocellularity. A significant dose-related decrease in the cellularity of the spleen (24–45%) was measured. A dose-related decrease in the cellularity of the thymus was also found, and was significant at the mid- and high doses (36–42%). A significant dose-related reduction in spleen cell number was measured in female mice 7 days after intraperitoneal injection with sulfur mustard (23% at 5 mg/kg and 49% at 10 mg/kg) (Coutelier et al. 1991).

The principal study (DOA 1987) identified the lowest LOAEL of 0.5 mg/kg/day for inflamed mesenteric lymph nodes in rats following acute administration of sulfur mustard. In range-finding experiments, conducted prior to the principal teratology study, in which rats were dosed with 0, 0.2, 0.4, 0.8, 1.6, 2.0, or 2.5 mg/kg/day (3–9 animals/dose group of which 2–7/dose group were pregnant) on gestation days 6–15, significant incidences of inflamed mesenteric lymph nodes occurred at ≥0.4 mg/kg/day (DOA 1987). Also in support of the critical dose, another lymphoretic effect, enlarged Peyer's patches, was observed in

rabbits at 0.5 g/kg/day in a range-finding study and at 0.4 g/kg/day in a teratology study (incidence data were not reported) (DOA 1987).

Agency Contact (Chemical Manager): Zemoria A. Rosemond

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Sulfur mustard [bis(2-chlorethyl) sulfide]
CAS number(s): 505-60-2
Date: August 29, 2003
Profile status: Third Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 9
Species: Rat

Minimal Risk Level: 0.07 [X] µg/kg/day [ ] ppm [ ] mg/m^3

Reference: Sasser LB, Cushing JA, Dacre JC. 1996a. Two-generation reproduction study of sulfur mustard in rats. Repro Toxicol 10(4):311-319.

Experimental design: Sulfur mustard (97.3% purity) dissolved in sesame oil was administered intragastrically by intubation to groups of 8-week-old Sprague-Dawley rats (27 females and 20 males/group/generation) at doses of 0, 0.03, 0.1, or 0.4 mg/kg/day. Male and female rats were dosed 5 days/week for 15 weeks that included 13 weeks before and 2 weeks during the mating period. Females were dosed daily (7 days/week) throughout the 21-day gestation period and 4–5 days/week during the 21-day lactation period. Males were dosed 5 days/week during the 21-day gestation period and sacrificed at the birth of their pups. Dams were sacrificed when their pups were weaned. Male and female F1 pups were treated with sulfur mustard until they were mated and the females became pregnant and gave birth. F1 males were sacrificed at the birth of their pups. The dosing of F1 dams continued until pup weaning, at which time, the study was terminated. Animals were weighed weekly. A complete gross necropsy was performed on all rats found dead or in moribund condition. Weights of the testis, prostate, epididymis, ovary, and uterus were recorded. Histopathological evaluations were performed on reproductive organs of the high dose group and control group of the F0 and F1 adults and on the forestomach of animals in all dose groups.

Effects noted in study and corresponding doses: There were no treatment-related deaths. The body weights of the F0 sulfur mustard-exposed rats were not significantly different from controls; however, the growth rate of the high-dose males tended to decline after about 7 weeks of exposure. Body weight gain was significantly lower ($p<0.05$) than control values in F1 rats of both sexes born to high-dose parents beginning 1 or 2 weeks after dosing was started (approximately 20% for males and 15–24% for females). No significant dose-response in body weight occurred at the lower doses. Breeding and reproductive performance in F0 and F1 animals was not affected by treatment. The only statistically significant birth parameter difference was an altered sex ratio (an increase in the fraction of males) of the high-dose F0 offspring. Although not significantly different, litter weights and number of pups per litter tended to decrease in both F1 and F2 animals at the highest exposure level. Except for a slight reduction in absolute ovary weight in high-dose F0 females, absolute and/or relative male and female reproductive organ weights were unaffected by treatment. Microscopic examination of the reproductive organs revealed no evidence of treatment-related effects. Dose-related incidence and severity of lesions of the squamous epithelium of the forestomach characterized by cellular disorganization of the basilar layer, an apparent increase in mitotic activity of the basilar epithelial cells and thickening of the epithelial layer, occurred in both sexes of each treatment group. The incidence of squamous acanthosis (combined F0 and F1 males and females; minimal to marked severity) was 0/94 controls, 69/94 (73%; 27 males/42 females) in the low-dose groups, 90/94 (96%; 39 males/51 females) in the mid-dose groups, and 94/94 in the high-dose groups. Benign neoplasms of the forestomach (squamous papilloma) occurred in 0/94 controls, 0/94 in the low-dose groups, 8/94 (9%) in the mid-dose groups, and 10/94 (11%) in the high-dose groups.

Dose and end point used for MRL derivation: The lowest dose tested, 0.03 mg/kg/day, is a LOAEL for gastric lesions (mild epithelial acanthosis of the forestomach). Although humans do not have forestomachs, the primary mechanism of toxicity of sulfur mustard is epithelial tissue damage from direct contact and, therefore, epithelial acanthosis is considered a suitable critical noncancer end point for deriving an oral MRL. Tissue damage would be expected to occur at the point of contact, even if it were another part of the gastrointestinal tract.

[ ] NOAEL [X] LOAEL

Uncertainty factors (UF) and Modifying Factor (MF) used in MRL derivation:

[X] 10 for LOAEL-to-NOAEL extrapolation
[X] 10 for human variability
[X] 3 for animal-to-human extrapolation*

*Because sulfur mustard is a highly corrosive agent, epithelial lesions at the point of entry into the stomach are likely to occur across species. For this reason, the typical default value of 10 for the uncertainty factor for extrapolation of data from animals to humans is considered to be too high and a lower value of 3 is applied.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA

Was a conversion used from intermittent to continuous exposure? A time-weighted average (TWA) daily dose was calculated as follows. Females were dosed during the lactation period while males were not. Female rats were treated 5 days/week for 15 weeks (75 days), total dose=2.25 mg/kg (75 days x 0.03 mg/kg/day); daily for 3 gestation weeks (21 days), total dose=0.63 mg/kg; and 4 days/week for 3 lactation weeks (12 days), total dose=0.36 mg/kg. The cumulative dose for females over the 21-week period is 3.24 mg/kg (2.25+0.63+0.36 mg/kg). Dividing the cumulative dose of 3.24 by 147 days (21 weeks) yields a TWA dose of 0.02 mg/kg/day. For males, the same TWA daily dose results; however, different time weighting applies [0.03 mg/kg/day x (5 days/7 days)=0.02 mg/kg/day].

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information that lend support to this MRL: Injury to the gastric mucosa (mild epithelial acanthosis of the forestomach) is a portal-of-entry direct contact toxic effect that is consistent with the vesicant properties of sulfur mustard following oral exposure. In support of the critical effect, gastrointestinal effects have been reported in humans following combat exposure to sulfur mustard, in sulfur mustard testing volunteers, and in sulfur mustard factory workers. In all of these cases, exposure was likely by multiple routes including inhalation, oral, and dermal. In 19 of 53 (36%) victims of the World War II Bari Harbor incident autopsied, stomach irritation and inflammation were documented. The lesions varied from simple hyperemia to focal loss of epithelium, necrosis, and ulceration (Alexander 1947). In a review of the clinical manifestations of sulfur mustard exposure in the Iran-Iraq war victims, Pierard et al. (1990) reported that endoscopy frequently revealed acute gastritis. Incidences of gastrointestinal effects of nausea (64%), vomiting (43%), and bleeding (14%) were reported in a group of 14 children and teenagers following exposure to sulfur mustard from air bombs during the Iran-Iraq war (Momeni and Aminjavaheri 1994). Gastrointestinal neoplasms were reported in Japanese sulfur mustard factory workers who were involved with the production of chemical agents during World War II (Yamakido et al. 1985). Sulfur mustard testing volunteers who were wearing respirators and who were exposed to unspecified levels of sulfur mustard vapors and liquids had skin burns, but also complained of nausea, vomiting, anorexia, abdominal pain, diarrhea, headache, and lassitude (Sinclair

1948). These signs could have been primary effects of the sulfur mustard on the rapidly dividing cells of the gastrointestinal epithelium, secondary effects from the skin burns, or psychological effects not related to the sulfur mustard exposure at all.

In addition to the principal study, Sasser et al. (1996a), similar gastric effects, edema, hemorrhage or sloughing of the mucosa, and ulceration) have been identified in rabbits following 14-day exposures at ≥0.4 mg/kg/day (DOA 1987), in rats following 10-day exposures at ≥2.0 mg/kg/day (DOA 1987), and in rats following 13-week exposures at ≥0.1 mg/kg/day (Sasser et al. 1996b). Regarding the relevance of the toxic effects to humans lacking a forestomach, tissue damage at the point of contact would be expected by a vesicant and direct alkylating agent such as sulfur mustard, regardless of the location in the gastrointestinal tract.

Agency Contact (Chemical Manager): Zemoria A. Rosemond

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 they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, 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. If data are located in the scientific literature, a table of genotoxicity information is included.

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, we have derived minimal risk levels (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.

They 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 the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

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 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 LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) 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, minimal risk levels (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 No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (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.

APPENDIX B

LEGEND

See LSE Table 3-1

(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. When sufficient data exists, 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 Table 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 2 "18r" data points in 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 regimen 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 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 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, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (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 Lowest-Observed-Adverse-Effect Level (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 Cancer Effect Level (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 the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

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 intermediate and chronic 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 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level 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)		Reference
					Less serious (ppm)	Serious (ppm)	
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

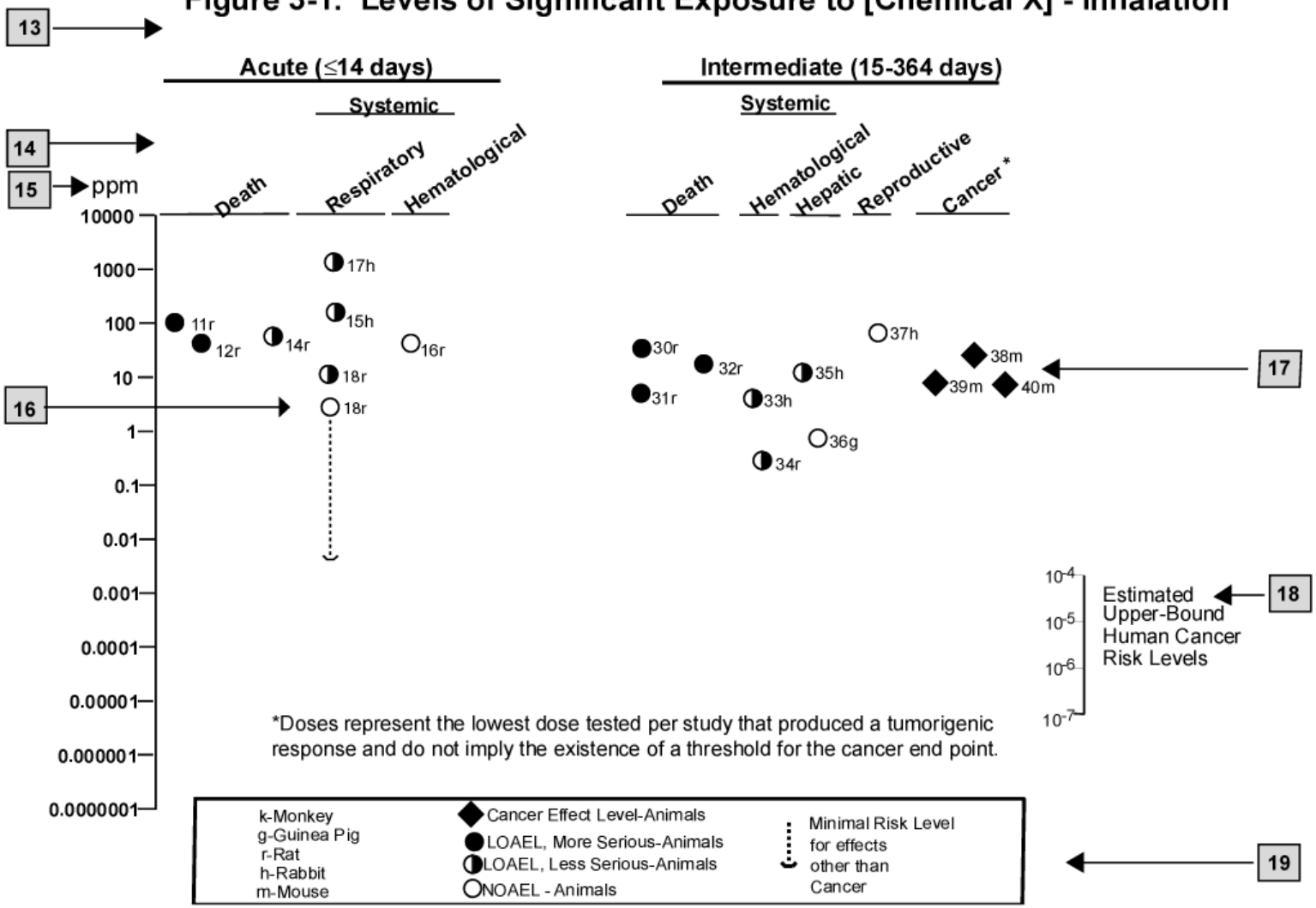
12 →

[a] The number corresponds to entries in Figure 3-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-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



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
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
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotranferase
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
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
Ct	concentration time product
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/International 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
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LCt_{50}	lethal Ct, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
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
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
NHANES	National Health and Nutrition Examination Survey
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
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
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
PID	photo ionization detector

pg	picogram
pmol	picomole
PHS	Public Health Service
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
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
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

APPENDIX D. ACUTE EXPOSURE GUIDELINE LEVELS (AEGLS) FOR SULFUR MUSTARD

The National Advisory Committee for the Acute Exposure Guideline Levels for Hazardous Substances has developed acute exposure guideline levels (AEGLs) for sulfur mustard (NAC/AEGL 2001). The AEGLs are threshold exposure limit values for the general public applicable to emergency exposure periods ranging from 10 minutes to 8 hours. For each chemical, three levels of AEGLs, distinguished by varying degrees of severity of toxic effects, are developed: at exposure levels above the AEGL-1, the general population could experience notable discomfort, irritation, or asymptomatic, nonsensory effects; above AEGL-2, the general population could experience irreversible or other serious, long lasting health effects or impaired ability to escape; and above AEGL-3, the general population could experience life-threatening health effects or death. At each AEGL level, values are developed for five exposure periods: 10 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours.

The derivation of the AEGLs for sulfur mustard presented below was excerpted from NRC (2003).

5. DATA ANALYSIS FOR AEGL-l

5.1. Summary of Human Data Relevant to AEGL-l

Walker et al. (1928) reported that four of seven men exposed to sulfur mustard at 0.001 mg/L (1 mg/m^3) for 5-45 min exhibited conjunctivitis, and two exhibited skin burns. It was also reported that, of 17 men exposed at 0.0005 mg/L (0.5 mg/m^3) for 10-45 min (5-22.5 mg·min/m^3), six exhibited conjunctivitis, and one had a skin burn. Three of 13 men exposed for 10-30 min at 0.0001 mg/L (0.1 mg/m^3; Ct of 1-3 mg·min/m^3) showed slight but distinct conjunctivitis. Although not of a severity consistent with an AEGL-2 level, those effects are of greater severity than would be acceptable for AEGL-l development. Guild et al. (1941) also conducted experiments using humans and reported that (1) exposure to Ct values <70 mg·min/m^3 would result in mild conjunctival responses that would not be indicative of a casualty (temporary loss of vision); (2) Ct values of 70-100 mg·min/m^3 would produce some casualties and; (3) Ct values >l00 mg·min/m^3 would be expected to produce disabling ocular effects of several days' duration. Because the subjects wore respiratory protection, effects on the respiratory tract could not be determined.

In experiments with human volunteers exposed to varying concentration-time regimens, Anderson (1942) found that an exposure concentration-time product of 12 mg·min/m^3 was without effects and 30 mg·min/m^3 represented the upper range for mild effects (conjunctival injection and minor discomfort with no functional decrement). Ct products slightly higher than that (e.g., 34-38.1 mg·min/m^3) were,

however, also without appreciable effects, thereby indicating that the response to 30 mg·min/m^3 is consistent with AEGL-l effects.

Odor thresholds of 1 mg·min/m^3 (Bloom 1944), 0.15 mg/m^3 (Ruth 1986) and 0.6 mg/m^3 (Dudley and Wells 1938; Bowden 1943; Fuhr and Krakow 1945) have been reported.

Analysis of the exposure-effect values from the human studies indicated that the 12-mg·min/m^3 value represented a defensible estimate of the threshold for effects consistent with the AEGL-l definition. The 12-mg·min/m^3 exposure was without a symptomatic effect and, therefore, provides the basis for protective AEGL-l values consistent with the AEGL- 1 definition.

5.2. Summary of Animal Data Relevant to AEGL-l

The effects described in the animal studies tend to be of a greater severity than those associated with AEGL-l (i.e., signs of severe ocular irritation, body weight loss, respiratory depression, evidence, evidence of respiratory tract histopathology, etc.). There were no definitive exposure-response data in animals that were considered appropriate for the development of AEGL-l values.

5.3. Derivation of AEGL-l

The most tenable AEGL-l values were developed using data reported by Anderson (1942) in which three to four human volunteers were exposed to agent HD at varying concentration-time regimens. In an analysis of those data, Anderson found that an exposure concentration-time product of 30 mg·min/m^3 represented the upper range for mild effects (conjunctival injection and minor discomfort with no functional decrement) and that 12 mg·min/m^3 represented a threshold for such effects. The 12 mg·min/m^3 represents a defensible estimate of the threshold for AEGL-1 effects. The 12-mg·min/m^3 exposure resulted in only minor conjunctival injection and no sensation of irritation. Ocular effects appear to be the most sensitive indicator of sulfur mustard exposure and toxicity, thereby justifying ocular irritation as an appropriate end point for development of AEGL values. All of the data considered were from human subjects, and, therefore, the uncertainty factor (UF) application to the 12-mg·min/m^3 value was limited to 3 for protection of sensitive individuals. The adjustment is considered appropriate for acute exposures to chemicals whose mechanism of action primarily involves surface contact irritation of ocular and/or respiratory tract rather than systemic activity that involves absorption and distribution of the parent chemical or a biotransformation product to a target tissue. In addition, Anderson (1942) noted that there was little variability in the ocular responses among the individuals participating in the study. That the AEGL-1 values are based on a sensitive end point is also reflected in that they are below reported odor thresholds (0.6 mg/m^3 and 1 mg·min/m^3).

Because exposure-response data were unavailable for all of the AEGL- specific exposure durations, temporal extrapolation was used in the development of AEGL-1 values for the AEGL-specific time periods. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the exponent *n* ranges from 0.8 to 3.5 (ten Berge et al. 1986). Analyses of available data regarding AEGL-1 type effects reported by Reed (1918), Reed et al. (1918), Guild et al. (1941), and Anderson (1942) indicate that for the exposure periods up to several hours, the concentration-exposure time relationship is a near-linear function (i.e., Haber's law where $n = 1$ for $C^n \times t = k$) as shown by *n* values of 1.11 and 0.96 for various data sets consistent with AEGL-l effects (Appendix B). Therefore, an empirically derived, chemical-specific estimate of $n = 1$ was used, rather than a default value, based on the ten Berge (1986) analyses. The derivation of the exponent (*n*) utilized human response data where 75-100% of the responders showed a mild response that would be consistent with the definition of AEGL-l effects. In addition, the data provided by Anderson (1942) were indicative of a linear concentration-time relationship. The AEGL-l values developed using the 12-$mg \cdot min/m^3$ exposure value reported by Anderson (1942) are shown in Table 2-9. The AEGL-l values are below the odor threshold for sulfur mustard (0.6 mg/m^3 and 1 $mg \cdot min/m^3$).

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Quantitative data regarding the human experience and AEGL-2 level effects are limited to responses ranging from signs of mild ocular irritation to ocular irritation that impairs normal visual function. Reed (1918) reported that 20-45 min exposure of himself and a volunteer at 1.2 mg/m^3 resulted in severe ocular irritation and dermal lesions. In a report of a subsequent experiment, Reed et al. (1918) noted that exposure of human volunteers at 0.1- 4.3 mg/m^3 for 5 -45 min produced ocular irritation and skin burns (0.5 mg/m^3 for 30 min) and very severe conjunctivitis, photophobia, skin bums, and nasopharyngeal exfoliation (1.0 mg/m^3 for 45 min). The analytical techniques used in these experiments were suspect; actual exposures were likely 30-40% higher. The report by Guild et al. (1941) of human exposure experiments did not provide findings of effects consistent with the AEGL-2 definition. Anderson (1942) reported on a series of human exposures resulting in varying degrees of ocular responses ranging from nonsymptomatic ocular injection to ocular irritation that required medical treatments and was considered severe enough to impair normal function.

6.2. Summary of Animal Data Relevant to AEGL-2

With the exception of a study reported by Warthin and Weller (1919) regarding the effects in rabbits following acute exposure, there is little exposure-response data for animals consistent with AEGL-2-severity effects. Weller and Warthin reported severe ocular effects and dermal burns in rabbits exposed for 12 h to

sulfur mustard at 130 mg/m^3. That study, however, was compromised by the use of single animals and lacks detail. Kumar and Vijayaraghavan (1998) reported alterations in purine catabolism exposed for 1 h to sulfur mustard at 21.2- 84.6 mg/m^3 but those exposures also represented 0.5, 1.0, and 2.0 LC^{50} responses. Statistically significant reductions in body weights were also observed for the mice at 14 d following a 1-h exposure to concentrations at 16.9- 42.3 mg/m^3; however at least some of the exposures were also associated with lethality. Dogs, rats, mice, and guinea pigs exposed continuously to sulfur mustard at 0.001 mg/m^3 or discontinuously (6.5 h/d, 5 d/wk) at 0.1 mg/m^3 for up to 52 wk did not exhibit effects consistent with the AEGL-2 definition (McNamara et al. 1975).

Table **2-9 AEGL-l Values for Sulfur Mustard (ppm [mg/m^3]) [a]**

10-min	30-min	1-h	4-h	8-h
0.06 (0.40)	0.02 (0.13)	0.01 (0.067)	0.003 (0.017)	0.001 (0.008)

[a]The AEGL-1 values are at or below the odor threshold for sulfur mustard.

6.3. Derivation of AEGL-2

The AEGL-2 values for sulfur mustard were developed using data from Anderson (1942). The study utilized three or four human volunteers' exposed to varying concentrations of sulfur mustard (1. 7-15.6mg/m^3) for time periods varying from 2 to 33 min. Anderson considered a Ct value of 60 mg·min/m^3 as the lowest concentration-time product for which ocular effects could be characterized as military casualties and that personnel exposed might be ineffective for up to (but no more than) 7 d. Effects included irritation, soreness, and widespread conjunctivitis, frequently accompanied by chemosis and photophobia. The 60-mg·min/m^3 exposure was used as the basis for developing the AEGL-2 values because it is representative of an acute exposure causing an effect severe enough to impair normal visual function and, although not irreversible, would certainly result in potential for additional injury. The ocular irritation and damage were also considered appropriate as a threshold estimate for AEGL-2 effects, because the eyes are generally considered the most sensitive indicator of sulfur mustard exposure, and irritation would likely occur in the absence of vesication effects and severe pulmonary effects. The fact that the AEGL-2 is based on human data precludes the use of an interspecies UF. A factor of 3 was applied for intraspecies variability (protection of sensitive populations). The factor was limited to 3 under the assumption that the primary mechanism of action of sulfur mustard involves a direct effect on the ocular surface and that the response will not vary greatly among individuals (as noted by Anderson [1942]). A modifying factor of 3 was applied to accommodate potential onset of long-term ocular or respiratory effects. It was justified by the absence of long-term follow-up in the subjects of the Anderson (1942) study to confirm or deny development of permanent ocular or respiratory tract damage. Because the factors of 3 each represent a logarithmic mean (3.16) of 10, their product is 3.16 x 3.16 = 10. Further reduction by the

application of additional modifying factors was not warranted because of the use of a sensitive indicator representing an AEGL-2 effect of marginal severity. As is the case for AEGL-1 values, time scaling was conducted using an *n* of 1 for all time points (Appendix B). The resulting AEGL-2 values are shown in Table 2-10, and their derivation is presented in Appendix A. Similar to the AEGL-l values, all of the AEGL-2 values are at or below the reported odor thresholds (0.6 mg/m^3 and 1 $mg \cdot min/m^3$).

TABLE 2-10 AEGL-2 Values for Sulfur Mustard (ppm [mg/m^3])[a]

10-min	30-min	1-h	4-h	8-h
0.09 (0.60)	0.03 (0.20)	0.02 (0.10)	0.004 (0.025)	0.002 (0.013)

[a]The AEGL-2 values are at or below odor threshold for sulfur mustard.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Human lethality data are limited to an inhalation LCt_{50} estimate of 1,500 $mg \cdot min/m^3$ and percutaneous LCt^{50} estimate of 10,000 $mg \cdot min/m^3$ estimated from animal data (DA 1974). The NRC (1997) concluded that an estimated LCt^{50} for humans of 900 $mg \cdot min/m^3$ developed by the U. S. Army based on an average of animal LCt^{50} data was scientifically valid but was developed in reference to healthy male military personnel and does *not* apply to civilians.

7.2. Summary of Animal Data Relevant to AEGL-3

Various lethality values have been reported for laboratory species exposed to sulfur mustard. Vijayaraghavan (1997) reported a 1-h LC^{50} of 42.5 mg/m^3 for mice (head-only exposure). In a follow-up study reported by Kumar and Vijayaraghavan (1998), 1-h exposure of mice at 21.2 mg/m^3 did not result in lethality. Lethality estimates were based on deaths occurring up to 14 d after exposure. Langenberg et al. (1998) reported a 5-min LCt_{50} of 800 $mg \cdot min/m3$ for rabbits (deaths determined up to 96 h after exposure). These studies utilized up-to-date exposure and analytical systems and provided lethality estimates based on adequate numbers of animals evaluated at post exposure time frames appropriate for the known latency in sulfur-mustard-induced lethality.

7.3. Derivation of AEGL-3

As noted in Section 3.1.4, the lethality data from earlier reports were not verifiable but are not inconsistent with those from later studies. The 1-h LC_{50} values for rats and mice derived from the 840 and 860 $mg \cdot min/m^3$ 60-min LCt5o values reported by Fuhr and Krakow (1945) are similar to the lower confidence limit of the mouse 1-h LC_{50} reported by Vijayaraghavan (1997) (i.e., 14.0, 14.3,

and 13.5 mg/m^3, respectively; the corresponding Ct values are 840,858, and 810 mg·min/m^3). The values are also similar to a 1-h LC_{50} of 13.3 mg/m^3 for guinea pigs extrapolated (assuming $C^1 \times t = k$) from the 5-min LCt_{50} of 800 mg·min/m^3 reported by Langenberg et al. (1998). However, the values from the earlier studies are not verifiable. In the inhalation toxicity study by Vijayaraghavan (1997), mice were exposed head only) for 60 min to sulfur mustard at concentrations of 0.0, 8.5, 16.9, 21.3, 26.8, 42.3 or 84.7 mg/m^3. The study investigator derived a 60-min LC_{50} of 42.5 mg/m^3 based on lethality at 14 d post exposure (95% confidence interval: 13.5-133.4 mg/m^3). In a follow-up study (Kumar and Vijayaraghavan 1998), there was no mortality in mice exposed at 0.5 LC_{50} mg/m^3). Therefore, the 1-h exposure at 21.2 mg/m^3 was selected as an estimate of the lethality threshold in mice.

When compared with the human exposure-effect data, the 21.2-mg/m^3 concentration (Ct of 1,272 mg·min/m^3 for a 60-min exposure) is not an exposure that has been associated with lethality in humans (see Section 2.1). An intraspecies UF of 3 was applied for protection of sensitive individuals. This adjustment was considered appropriate for acute exposures to chemicals whose mechanism of action primarily involves surface contact irritation of ocular and/or respiratory tract tissue rather than systemic activity that involves absorption and distribution of the parent chemical or a biotransformation product to a target tissue. An interspecies UP was limited to 3 because available data do not suggest that humans are notably more sensitive than animals regarding lethality from inhalation exposure to sulfur mustard. The mechanism of pulmonary injury leading to lethality appears to be a function of the direct contact of an alkylating agent with epithelial tissue. This mechanism is likely to be more similar than different across mammalian species. Furthermore, the AEGL-3 values resulting from the aforementioned complement of UFs (total UF adjustment was 10; see Section 6.3) are equivalent to exposures known to cause only mild ocular effects in humans. The modifying factor of 3 utilized in the development of AEGL-2 values to account for uncertainties regarding the latency and persistence of the irritant effects of low-level exposure to sulfur mustard was not applied for AEGL-3 because lethality of the mice was assessed at 14 d post exposure in the key studies by Vijayaraghavan (1997) and Kumar and Vijayaraghavan (1998).

For derivation of the AEGL-3 values, there was uncertainty regarding the validity of applying linear extrapolation based on ocular effects to concentration-time extrapolations for lethality. As reported by ten Berge et al. (1986), the concentration-time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. Therefore, in the absence of chemical-specific lethality data, time scaling was performed using exponential extrapolation ($n = 3$) for shorter time periods and linear extrapolation ($n = 1$) for longer time periods, thereby providing a somewhat more conservative (i.e., protective) estimate of the AEGL-3 values than would be obtained using an n value based on ocular irritation. The AEGL-3 values were derived by scaling from the 1-h LC_{50} of 21.2 mg/m^3 reported by

Kumar and Vijayaraghavan (1998) using C^n x t = k where n = l or 3 (Appendix A). The concentration-time constant, k, was 1,272 mg·min/m^3 where n = 1 and 571,687.68 mg·min/m^3 where n = 3. The AEGL-3 values are shown In Table 2-11, and their derivation is presented in Appendix A. The 4-h and 8-h AEGL-3 values are at or below reported odor thresholds.

TABLE 2-11 AEGL-3 Values for Sulfur Mustard (ppm [mg/m^3])

10 min	30 min	1 h	4 h	8 h
0.59 (3.9)	0.41 (2.7)	0.32 (2.1)	0.08 (0.53)	0.04 (0.27)

Note: The 4 –h and 8 – h AEGL-3 values are below the odor threshold for sulfur mustard.

When comparing the Ct values generated by the draft AEGL-3 numbers the human exposure data, any further reduction appears indefensible. The Ct values resulting from theAEGL-3 numbers (i.e., 39-130 mg·min/m^3) are similar to cumulative exposures shown to cause only ocular irritation in humans (Guild et al. 1941; Anderson 1942) and are similar to the ECt_{50} of 100 mg·min/m^3 for severe ocular effects (for soldiers) determined by Reutter and Wade (1994) and the NRC (1997). Furthermore, the AEGL-3 values are nearly similar to those developed using the human lethality estimate of 900 mg·min/m^3 (Reutter and Wade 1994) that was derived from multiple-species animal data and reviewed by the NRC (1997). Assuming a 3-fold reduction for estimation of a lethality threshold ([900 mg·min/m^3]/3 = 300 mg·min/m^3) and another 3-fold reduction for consideration of sensitive populations ([300 mg·min/m^3]/3 = 100 mg·min/m^3), the resulting AEGL-3 values from the Reutter and Wade (1994) and NRC (1997) reports would be 4.8, 3.3, 1.7, 0.42, and 0.21 mg/m^3 for 10 min, 30 min, and 1, 4, 8 h, respectively. These highly derivative estimates are comparable to, and supportive of, AEGL-3 estimates derived from the experimental data of Kumar and Vijayaraghavan (1998) (see Table 2-11).

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

Human data are available from several independent sources that define exposure-response for AEGL-l and AEGL-2 effects. Although a definitive demarcation of the exposure-response for sensitive populations was not provided by those data, the human data eliminated the uncertainties inherent in the use of data from animal studies. Both the AEGL-l and AEGL-2 values were based on effect end points consistent with the respective AEGL definitions (i.e., threshold for barely discernible ocular irritation [AEGL-l] and threshold for ocular irritation indicative of functional impairment [AEGL-2]). Areas of uncertainty were associated with the sensitive responders and the relationship between ocular effects and the onset of respiratory effects. Human data from which to develop AEGL-3 values were

unavailable. The AEGL-3 was based on an estimated lethality threshold from studies in mice (Vijayaraghavan 1997; Kumar and Vijayaraghavan 1998). When compared with human exposure-response data and lethality estimates, the mouse lethality data were considered a defensible approach to AEGL-3 derivation. AEGL-3 values based on a human lethality estimate of 900 $mg \cdot min/m^3$ (Reutter and Wade 1994; NRC 1997) were very similar to those developed using the animal data of Vijayaraghavan (1997) and Kumar and Vijayaraghavan (1998). An estimate of theoretical excess cancer risk based upon a geometric mean of inhalation slope factors developed using various data sets and procedures revealed that exposure concentrations representing a theoretical 10^{-4} lifetime risk were similar to the AEGL-3 exposure concentration values. The exposures for theoretical excess lifetime cancer risk at 10^{-5} and 10^{-6} levels would be correspondingly reduced. The use of excess cancer risk estimates in setting AEGL values is precluded by the uncertainties involved in assessing excess cancer risk following a single acute exposure of 8-h or less duration, by the relatively small population exposed in an emergency release situation, and by the potential risks associated with evacuations.

The AEGL values for sulfur mustard are summarized in Table 2-12. Extrapolation to exposure durations of less than 10 min is not recommended in the absence of careful evaluation of existing data and comparison of any derivative values with those data.

8.2. Comparison with Other Standards and Guidelines

Comparison of the draft AEGL values with other existing standards and guidelines is shown in Table 2-13. No other standards or guidelines from other agencies or programs (e.g., NIOSH, ERPG, ACGIH, MAK, MAC, and OSHA) were available.

8.3. Data Adequacy and Research Needs

The AEGL-1 values are based on human data and are considered estimates for exposures that would cause no significant health effects or sensations of irritation beyond minimal conjunctivitis.

TABLE 2-12 Summary of AEGL Values for Sulfur Mustard[a]

AEGL Level	10 min	30 min	1 h	4 h	8 h
AEGL-1[a] (Nondisabling)	0.06 ppm (0.40 mg/m^3)	0.02 ppm (0.13 mg/m^3)	0.01 ppm (0.067 mg/m^3)	0.003 ppm (0.017 mg/m^3)	0.001 ppm (0.008 mg/m^3)
AEGL-2[a] (Disabling)	0.09 ppm (0.60 mg/m^3)	0.03 ppm (0.20 mg/m^3)	0.02 ppm (0.10 mg/m^3)	0.004 ppm (0.025 mg/m^3)	0.002 ppm (0.013 mg/m^3)
AEGL-3[a]	0.59 ppm (3.9 mg/m^3)	0.41 ppm (2.7 mg/m^3)	0.32 ppm (2.1 mg/m^3)	0.08 ppm (0.53 mg/m^3)	0.04 ppm (0.27 mg/m^3)

A AEGL-1 and AEGL-2 values, and the 4- and 8-h AEGL-3 values are at or below the odor threshold for sulfur mustard.

The ocular irritation on which the AEGL-l and AEGL-2 values are based is the most sensitive response to sulfur mustard vapor. The AEGL-2 values provide Ct exposures that are well below those known to induce severe ocular effects in normal humans (i.e., 70-90 mg·min/m^3). AEGL-3 values provide Ct values (39-130 mg·min/m^3) that are at levels known to cause moderate to severe ocular irritation and possible respiratory tract irritation in human subjects Anderson 1942; Guild et al. 1941) but no life-threatening effects or death. Although the overall database for acute inhalation exposure to sulfur mustard is not extensive, the AEGL values are supported by the available data.

The absence of multiple-species lethality data for acute exposures limits a thorough understanding of variability. Data providing definitive demarcation of the threshold for serious and/or irreversible effects would provide a more complete picture of responses resulting from acute inhalation exposure to sulfur mustard. That is especially relevant to assessing the potential for serious respiratory tract damage or permanent ocular pathology following acute exposure. Although sulfur mustard is a genotoxic chemical capable of inducing tumors in animals and humans, the carcinogenic potential of acute inhalation exposures has not been defined.

TABLE 2-13 Comparison of AEGL Values for Sulfur Mustard with Other Extant Standards and Guidelines

Guideline	10 min	30 min	1 h	4 h	8 h	Other
AEGL-1	0.40 mg/m^3 (0.06 ppm)	0.13 mg/m^3 (0.02 ppm)	0.067 mg/m^3 0.01 ppm)	0.017 mg/m^3 (0.003 ppm)	0.008 mg/m^3 0.001 ppm)	
AEGL-2	0.60 mg/m^3 (0.09 ppm)	0.20 mg/m^3 (0.03 ppm)	0.10 mg/m^3 (0.02 ppm)	0.025 mg/m^3 (0.004 ppm)	0.013 mg/m^3 (0.002 ppm)	
AEGL-3	3.9 mg/m^3 (0.59 ppm)	2.7 mg/m^3 (0.41 ppm)	2.1 mg/m^3 (0.32 ppm)	0.53 mg/m^3 (0.08 ppm)	0.27 mg/m^3 (0.04 ppm)	
Department of the Army/Civilian Occupational WPL[a]					0.003mg/m^3 (0.0005 ppm)	
Department of the Army/Civilian GPL[b]						0.0001 mg/m^3 (1.5×10^{-5} ppm)
CDC-CSEPP (Thacker, 1994)[c]						2.0 $mg \cdot min/m^3$ (0.3 ppm)

[a]Worker Population Exposure Limit (DA 1991, 1997; DHHS 1988), 8-h TWA, 5 d/wk
[b]General Population Limit (no observable effects), 24-h TWA, 7 d/wk
[c]Recommended acute effects levels for determining emergency evacuation distances in the Chemical Stockpile Emergency Preparedness Program (CSEPP); no set exposure time.

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APPENDIX A

Derivations of AEGL Values

Derivation of AEGL-l

Key Study: Anderson (1942)

Toxicity End point: Exposure concentration-time product of 12 mg·min/m^3 represented the threshold for ocular effects (conjunctival injection and minor discomfort with no functional decrement) for human volunteers exposed to agent HD at varying exposure regimens. The eye is generally considered to be the most sensitive organ/tissue relative to agent HD exposure.

Scaling: The concentration-time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Analysis of available data indicated n to be near unity (Appendix B), hence, $C^1 \times t = k$.

Uncertainty factors: Total adjustment of 3. A factor of 3 was applied for intraspecies variability (protection of sensitive populations). This factor was limited to 3 under the assumption that the primary mechanism of action of agent HD involves a direct effect on the ocular surface and that the response will not vary greatly among individuals. In

addition, subjects in the Anderson (1942) study exhibited little variability in ocular response.

Because the AEGL-l is based on human data, the interspecies UF is 1.

10-min AEGL-l: C^1 x 10 min = 12 mg·min/m^3
C = 1.2 mg/m^3
10-min AEGL-1 = (1.2 mg/m^3)/3 = 0.40 mg/m^3
(0.06 ppm)

30-min AEGL-l: C^1 x 30 min= 12mg·min/m^3
C = 0.4 mg/m^3
30-min AEGL-1 = (0.4 mg/m^3)/3 = 0.13 mg/m^3
(0.02 ppm)

l-h AEGL-l: C^1 x 60 min = 12 mg·min/m^3
C= 0.2 mg/m^3
1-h AEGL-1 = (0.2 mg/m^3)/3 = 0.067 mg/m^3
(0.01 ppm)

4-h AEGL-l: C^1 x 240 min = 12 mg·min/m^3
C= 0.05 mg/m^3
4-h AEGL-1 = (0.05 mg/m^3)/3 = 0.017 mg/m^3
(0.003 ppm)

8-h AEGL-l: C^1 x 480 min = 12 mg·min/m^3
C = 0.025 mg/m^3
8-h AEGL-1 = (0.025 mg/m^3)/3 = 0.008 mg/m^3
(0.001ppm)

Derivation of AEGL-2

Key study: Anderson (1942)

Toxicity end point: A concentration-time product of 60 mg·min/m^3 was considered the lowest exposure causing ocular effects (we1l-marked, generalized conjunctivitis, edema, photophobia, and irritation) resulting in effective performance decrement and characterized as a military casualty requiring treatment for up to 1 wk.

Scaling: The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n x\ t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al.

1986). Analysis of available data indicated *n* to be near unity (Appendix B), hence, $C^1 \times t = k$.

Uncertainty Factors: Total adjustment of 10. A factor of 3 was applied for intraspecies variability (protection of sensitive populations). This factor was limited to 3 under the assumption that the primary mechanism of action of agent HD involves a direct effect on the ocular surface and that this response will not vary greatly among individuals. Because the AEGL-l is based on human data, the interspecies UF is 1. A modifying factor of 3 was applied to accommodate potential onset of long-term ocular or respiratory effects.

Because the factors of 3 each represent a logarithmic mean (3.16) of 10, their product is 3.16 x 3.16 = 10.

10-min AEGL-2: $C^1 \times 10 \text{ min} = 60 \text{ mg}^{\cdot}\text{min/m}^3$
$C = 6\text{mg}$
10-min AEGL-2 = $(6 \text{ mg/m}^3)/10 = 0.60 \text{ mg/m}^3$
(0.09 ppm)

30-min AEGL-2: $C^1 \times 30 \text{ min} = 60 \text{ mg}^{\cdot}\text{min/m}^3$
$C = 2.00$ mg
30-min AEGL-2 = $(2.00 \text{ mg/m}^3)/10 = 0.20 \text{ mg/m}^3$
(0.03 ppm)

1.-h AEGL-2: $C^1 \times 60 \text{ min} = 60 \text{ mg}^{\cdot}\text{min/m}^3$
$C = 1.00 \text{ mg/m}^3$
1-h AEGL-2 = $(1.00 \text{ mg/m}^3)/10 = 0.10$
(0.02 ppm)

4 –h AEGL-2: $C^1 \times 240 \text{ min} = 60 \text{ mg}^{\cdot}\text{min/m}^3$
$C = 0.25 \text{ mg/m}^3$
4-h AEGL-2 = $(0.25 \text{ mg/m}^3)/10 = 0.025 \text{ mg/m}^3$
(0.004 ppm)

8-h AEGL-2: $C^1 \times 480 \text{ min} = 60 \text{ mg}^{\cdot}\text{min/m}^3$
$C = 0.125 \text{ mg/m}^3$
8-h AEGL-2 = $(0.125 \text{ mg/m}^3)/10 = 0.013 \text{ mg/m}^3$
(0.002 ppm)

Derivation of AEGL-3

Key study: Kumar and Vijayaraghavan (1998)

Toxicity end point: Estimated lethality threshold of 21.2 mg/m^3 for 1 h based on no deaths in mice exposed to that concentration, which is 0.5 of the 1-h LC_{50} in mice reported by Vijayaraghavan (1997).

Scaling: The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Analysis of available data pertaining to ocular effects indicated n to be near unity (Appendix B). However, there was uncertainty regarding the validity of applying linear extrapolation based on ocular effects to concentration-time extrapolations for lethality. Therefore, in the absence of chemical-specific lethality data, time scaling was performed using exponential extrapolation (n = 3) for shorter time periods (<1 h) and linear extrapolation (n = 1) for longer time periods (> 1 h), thereby providing a somewhat more conservative (i.e., protective) estimate of the AEGL-3 values than would be obtained using an n value based on ocular irritation. The concentration-time constant, k, was 1272 mg^n·min/m^3 where n = 1 and 571,687.68 mg^n·min/m^3 where n = 3.

Uncertainty factors: Total UF was 10. A UF for interspecies was limited to 3 because human data are available showing that exposures to the AEGL-3 values are more likely to produce only severe ocular irritation and possible minor or moderate irritation of the upper respiratory tract. Intraspecies variability was limited to 3 because lethality appears to be a function of extreme pulmonary damage resulting from direct contact of the agent with epithelial surfaces. No modifying factor was applied because the basis of lethality estimate was from studies utilizing a 14-d observation period to assess the lethal response from a 1-h exposure.

Because the factors of 3 each represent a logarithmic mean (3.16) of 10, their product is 3.16 x 3.16 = 10.

10-min AEGL-3:
$C^3 \times 10$ min = 571,687.68 mg^n·min/m^3
C^3 = 57,168.76 mg^n·min/m^3
C = 38.52 mg/m^3
10-min AEGL-3 = (38.52 mg/m^3)/10 = 3.9 mg/m^3
(0.59 ppm)

30-min AEGL-3:
$C^3 \times 30$ min = 571,687.68 mg^n·min/m^3
C^3 = 19,056.26 mg^n·min/m^3
C= 26.7 mg/m^3

30-min AEGL-3 = (26.7 mg/m^3)/10 = 2.7 mg/m^3
(0.41 ppm)

1 –h AEGL-3: C^1 x 60 min = 1,272 mg·min/m^3
C= 21.2 mg/m^3
1-h AEGL-3 = (21.2 mg/m^3)/10 = 2.1 mg/m^3
(0.32 ppm)

4 –h AEGL-3: C^1 x 240 min = 1,272 mg·min/m^3
C = 5.3 mg/m^3
4-h AEGL-3 = (5.3 mg/m^3)/10= 0.53 mg/m^3
(0.08 ppm)

8-h AEGL-3: C^1 x 480 min = 1,272 mg·min/m^3
C = 2.65 mg/m^3
8-h AEGL-3 = (2.65 mg/m3)/10 = 0.27 mg/m^3
(0.04 ppm)

APPENDIX B

Determination of Temporal Scaling Factor *(n)* for AEGL Derivations

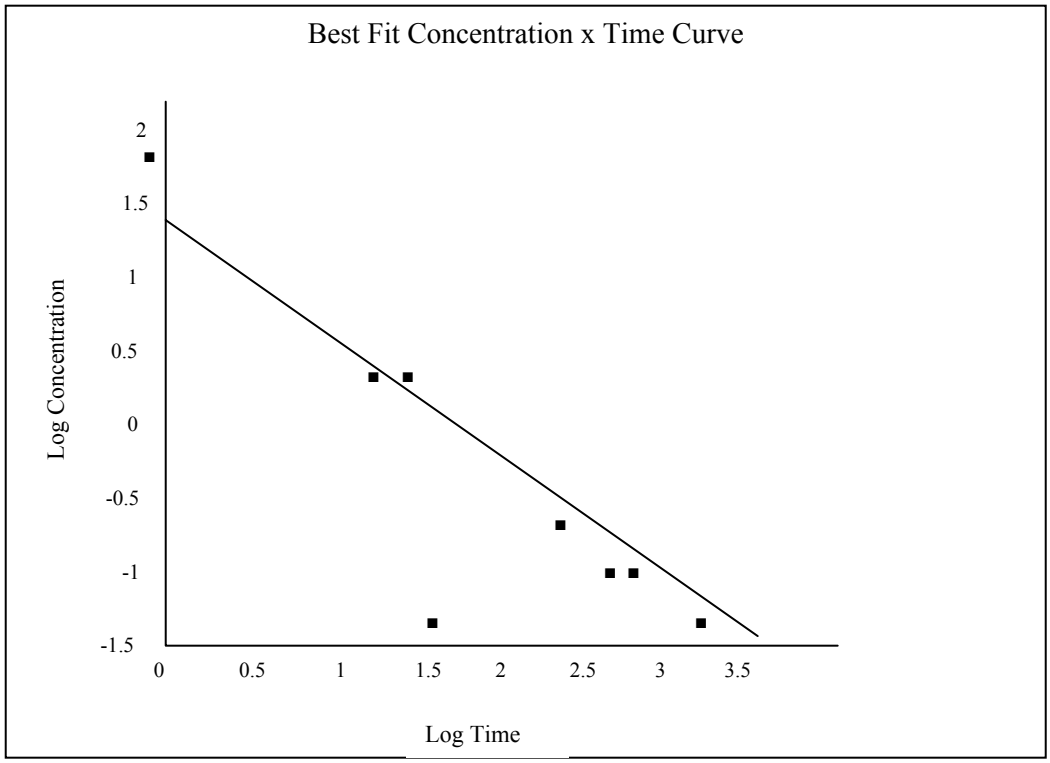
Derivation of *n* for C^n x *t* = *k;* data points indicative of a 100% response for mild ocular irritation following exposure to sulfur mustard agent HD) at various concentrations and times (Reed 1918; Reed et al., 1918; Guild et a1. 1941; Anderson 1942)

Time	Concentration	Log Time	Log Concentration
1	72	0.0000	1.8573
30	1.4	1.4771	0.1461
30	0.06	1.4771	-1.2218
45	1.4	1.6532	0.6198
210	0.24	2.3222	-0.6198
480	0.1	2.6812	-1.0000
600	0.1	2.7782	-1.0000
1,440	0.06	3.1584	-1.2218

Regression output:

Intercept	1.3852
Slope	-0.9002
R squared	0.7434
Correlation	-0.8622
Degrees of Freedom	6
Observations	8

$n = 1.11$
$k = 34.58$



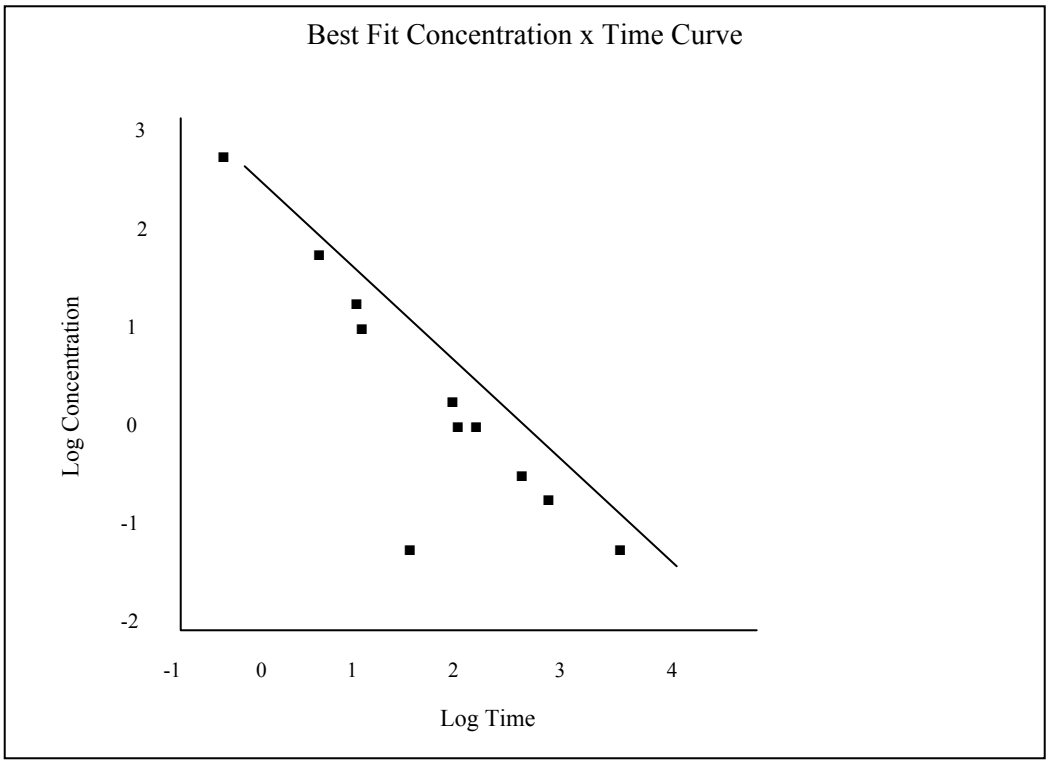
Derivation of n for $C^n \times t = k$; data points indicative of a 75-100% *response* for mild ocular irritation following exposure to sulfur mustard (agent HD) at various concentrations and times (Reed 1918; Reed et al. 1918; Guild et al. 1941; Anderson 1942)

Time	Concentration	Log Time	Log Concentration
1	72	0.0000	1.8573
30	1.4	1.4771	0.1461
30	0.06	1.477	-1.2218
45	1.4	1.6532	0.1461
210	0.24	2.3222	-0.6198
480	0.1	2.6812	-1.0000
600	0.1	2.7782	-1.0000
1,440	0.06	3.1584	-1.2218
33	1.7	1.5185	0.2304
3	12.7	0.4771	1.1038
3	30	0.4771	1.4771
2.5	30	0.3979	1.4771
2	30	0.3010	1.4771
0.25	320	-0.6021	2.5051

Regression Output:

Intercept	1.7240
Slope	-1.0356
R squared	0.8891
Correlation	-0.9429
Degrees of freedom	12
Observations	14

n = 0.96
k = 46.05



APPENDIX C

Carcinogenicity Assessment for Acute Exposure to Sulfur Mustard (Agent HD)

The cancer assessment for acute inhalation exposure to sulfur mustard was conducted following the NRC methodology for EEGLs, SPEGLs, and CEGLs (NRC 1986). The virtually safe dose (VSD) was determined from an inhalation slope factor of 14 $(mg/kg/d)^{-1}$ for the general population (USACHPPM 2000). The slope factor was a geometric mean of slope factors developed using various data sets and procedures and was considered the most tenable quantitative assessment for potential cancer risk from inhalation exposure to sulfur mustard. The corresponding Inhalation Unit Risk was 0.0041 $(\mu g/m^3)^{-1}$ or 4.1 $(mg/m^3)^{-1}$ (USACHPPM2000). The VSD was calculated as follows:

VSD = Risk Level/Unit Risk

$$\frac{\text{VSD} = 1 \times 10^{-4} \text{ risk} = 2.5 \times 10^{-5} \text{ mg/m}^3}{(4.1 \text{ mg/m}^3)^{-1}}$$

Assuming the carcinogenic effect to be a linear function of cumulative dose (d), a single-day exposure is equivalent to d x 25,600 d (average lifetime).

$$\begin{aligned}\text{24-h exposure} &= \text{VSD} \times 25{,}600 \\ &= (2.5 \times 10^{-5} \text{ mg/m}^3) \times 25{,}600 \\ &= 0.64 \text{ mg/m}^3\end{aligned}$$

Adjustment to allow for uncertainties in assessing potential cancer risks under short term exposures under the multistage model (Crump and Howe 1984).

$$\frac{\text{24- hr exposure}}{6} \quad \frac{0.64 \text{ mg/m}^3}{6} = 0.1 \text{ mg/m}^3$$

If the exposure is limited to a fraction (*f*) of a 24-h period, the fractional exposure becomes l/*f* x 24 h (NRC 1985). For a 1 x 10^{-4}, 1 x 10^{-5}, and 1 x 10^{-6} risk, the fractional exposures are shown below.

Exposure Duration	10^{-4}	10^{-5}	10^{-6}
24-h	0.1 mg/m^3 (0.02 ppm)	0.01 mg/m^3 (0.002 ppm)	0.001 mg/m^3 (0.002 ppm)
8-h	0.3 mg/m^3 (0.05 ppm)	0.03 mg/m^3 (0.005 ppm)	0.003 mg/m^3 (0.0005 ppm)
4-h	0.6 mg/m^3 (0.09 ppm)	0.06 mg/m^3 (0.009 ppm)	0.006 mg/m^3 (0.0009 ppm)
1-h	2.4 mg/m^3 (0.36 ppm)	0.24 mg/m^3 (0.036 ppm)	0.024 mg/m^3 (0.0036 ppm)
30-min	4.8 mg/m^3 (0.72 ppm)	0.48 mg/m^3 (0.072 ppm)	0.048 mg/m^3 (0.0072 ppm)
10-min	14.1 mg/m^3 (2.16 ppm)	1.41 mg/m^3 (0.22 ppm)	0.141 mg/m^3 (0.022 ppm)

Because the derivation of the cancer slope factor requires conversion of animal doses to human equivalent doses, no reduction of exposure levels is applied to account for interspecies variability. With the exception of the 10-min, 30-min, and 1-h values for 10^{-4} risk and the 10- min 10^{-5} risk, these exposures are at or below the odor threshold for sulfur mustard. A cancer risk assessment based on a geometric mean of inhalation slope factors developed using various data sets and procedures indicated an excess cancer risk of 1 in 10,000 (10^{-4}) may be associated with exposures similar to the AEGL-3 values. The use of excess cancer risk

estimates in setting AEGL values is precluded by the uncertainties involved in assessing excess cancer risk following a single acute exposure of 8-h or less duration, by the relatively small population exposed in an emergency release situation, and by the potential risks associated with evacuations.

APPENDIX D

DERIVATION SUMMARY FOR ACUTE EXPOSURE GUIDELINES LEVELS

Sulfur Mustard (CAS NO.505-60-2)

AEGL-1				
10 min	30 min	1 h	4 h	8 h
0.40 mg/m^3 (0.06 ppm)	0.13 mg/m^3 (0.02 ppm)	0.067 mg/m^3 (0.01 ppm)	0.017 mg/m^3 (0.003 ppm)	0.008 mg/m^3 (0.001 ppm)
Key Reference: Anderson, J.S. 1942. The effect of mustard gas vapour on eyes under Indian hot weather conditions. CDRE Report No. 241. Chemical Defense Research Establishment (India)				
Test species/strain/gender/number: 3-4 human volunteers				
Exposure route/concentrations/durations: Vapor exposure to varying concentrations (1.7 – 15.6 mg/m^3) for varying durations (2-33 min)				
Effects: Mild ocular effects (mild injection to notable conjunctivitis)				
End point/concentration/rationale: Concentration-time threshold of 12 mg·min/m^3 for ocular effects (conjunctival injection with minor discomfort and no functional decrement.				
Uncertainty factors/rationale: Interspecies: 1 (human subjects) Intraspecies: A factor of 3 was applies for intraspecies variability (protection of sensitive populations). This factor was limited to 3 under the assumption that the primary mechanism of action of agent HD involves a direct effect on the ocular surface and that the response will not vary greatly among individuals. Furthermore, little variability was observed in the tested subjects regarding ocular responses.				
Modifying factor: None applied				
Animal to human dosimetric adjustment: Not applicable				
Time scaling: $C^n \times t = k$, where $n = 1$ based on analysis of available human exposure data for ocular effects.				
Data adequacy: The key study was conducted using human volunteers thus avoiding uncertainties associated with animal studies. Ocular irritation is considered the most sensitive end point for assessing the effects of acute exposure to sulfur mustard and the available data were sufficient for developing AEGL-1 values.				

AEGL-2				
10 min	30 min	1 h	4 h	8 h
0.60 mg/m^3 (0.09 ppm)	0.20 mg/m^3 (0.03 ppm)	0.10 mg/m^3 (0.02 ppm)	0.025 mg/m^3 (0.004 ppm)	0.013 mg/m^3 (0.002 ppm)
Key Reference: Anderson, J.S. 1942. The effect of mustard gas vapour on eyes under Indian hot weather conditions. CDRE Report No. 241. Chemical Defense Research Establishment (India)				
Test species/strain/gender/number: 3-4 human volunteers				
Exposure route/concentrations/durations: Vapor exposure to varying concentrations (1.7 – 15.6 mg/m^3) for varying durations (2-33 min)				
Effects: Ocular effects ranging from mild injection to notable conjunctivitis, photophobia, lacrimation, blepharospasm				
End point/concentration/rationale: Exposure-concentration time product of 60 mg·min/m^3 representing exposure at which ocular irritation (Well marked, generalized conjunctivitis, edema, photophobia, and irritation) will occur resulting in performance decrement and necessitating medical treatment.				
Uncertainty factors/rationale: Interspecies: 1 (human subjects) Intraspecies: A factor of 3 was applies for intraspecies variability (protection of sensitive populations). This factor was limited to 3 under the assumption that the primary mechanism of action of agent HD involves a direct effect on the ocular surface and that the response will not vary greatly among individuals. Furthermore, little variability was observed in the tested subjects regarding ocular responses.				
Modifying factor: A modifying factor of 3 was applied to accommodate uncertainties regarding the onset of potential long-term ocular effects of respiratory effects.				
Animal to human dosimetric adjustment: Not applicable				
Time scaling: $C^n \times t = k$, where $n = 1$ based on analysis of available human exposure data for ocular effects.				
Data adequacy: The key study was conducted using human volunteers thus avoiding uncertainties associated with animal studies. The AEGL-2 values are based on ocular effects that may be considered severe enough to impair vision. The data were considered sufficient for developing AEGL-2 values.				

AEGL-3				
10 min	30 min	1 h	4 h	8 h
3.9 mg/m^3 (0.59 ppm)	2.7 mg/m^3 (0.41 ppm)	2.1 mg/m^3 (0.32 ppm)	0.053 mg/m^3 (0.08 ppm)	0.27 mg/m^3 (0.04 ppm)
Key Reference: Kumar, O., and R. Vijayaraghavan. 1998. Effect of sulfur mustard inhalation exposure on some urinary variables in mice. J. Appl. Toxicol. 18:257-259.				
Test species/strain/gender/number: Swiss mice/femal/4 per exposure group.				
Exposure route/concentrations/durations: Head-only inhalation exposure for 1 h to sulfur mustard (>99% purity) at 21.2, 42.3, or 84.6 mg/m^3 (equivalent to 0.5, 1.0, and 2.0LC_{50}). Subjects were sacrificed at 6, 24, or 48 h or 7 d after exposure. Three groups of 10 mice were exposed at each concentration and observed for up to 14 d.				
Effects: Lethality assessed up to 14 d post exposure				
End point/concentration/rationale: No mortality in mice at 14 d following 10h exposure at 21.2 mg/m^3. The exposure was considered an estimate of the lethality threshold in mice.				
Uncertainty factors/rationale: Total uncertainty factor: 10 Interspecies: A factor of 3 was applied to account for possible interspecies variability in the lethal response to sulfur mustard. Application of any additional uncertainty factors or modifying factors was not warranted because the AEGL-3 values are equivalent to exposures in humans that are known to produce only ocular and respiratory tract irritation. Intraspecies: Intraspecies variability was limited to 3 because lethality appears to be a function of extreme pulmonary damage resulting from direct contact of the agent with epithelial surfaces.				
Modifying factor: No modifying factor was applied because the basis of lethality estimate was from a study utilizing a 14-d observation period to assess the lethal response from a 1-h exposure.				
Animal to human dosimetric adjustment: Insufficient data				
Time scaling: $C^n \times t = k$, where $n = 1$ or 3. The concentration-time relationship for many irritant and systemically acting vapors and gases can be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of chemical-specific lethality data, time scaling was performed using exponential extrapolation ($n = 3$) for shorter time periods and linear extrapolation ($n = 1$) for longer time periods, thereby providing a somewhat more conservative (i.e., protective) estimate of the AEGL-3 values than would be obtained using an n value of 1 based on ocular irritation.				
Data adequacy: Uncertainties exist regarding a definitive lethality threshold for single acute exposures to sulfur mustard. However, the key study appeared to be well-designed and properly conducted and is considered sufficient for developing AEGL-3 values.				