

## 2. RELEVANCE TO PUBLIC HEALTH

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO SULFUR MUSTARD IN THE UNITED STATES

Sulfur mustard (bis[2-chloroethyl]sulfide;  $C_4H_8Cl_2S$ ; CASRN: 505-60-2) or as it is commonly called, ‘mustard gas’, is one of a class of vesicant chemical warfare agents with the ability to form vesicles or blisters on exposed skin. Sulfur mustard is a viscous liquid at ambient temperature, but becomes a solid at 58 °F (14 °C). It is heavier than water as a liquid and heavier than air as a vapor. Sulfur mustard is a component of the H-series blister agents including undistilled sulfur mustard (H; sulfur mustard with 20–30% impurities, also known as Levinstein mustard), distilled sulfur mustard (HD or HS; approximately 96% pure), a mustard-lewisite mixture (HL), an HD/agent T mixture (HT; a mixture of HD and nonvolatile agent T), and an HD/agent Q mixture (HQ; a mixture of HD and nonvolatile agent Q; agent Q is also known as sesqui-mustard).

Sulfur mustard was first manufactured in 1822. It was utilized as early as the late 1880s, when it was used as a pesticide and to treat minor tumors. It was first used as a war gas in 1917, during World War I by the Germans on the British at Ypres. For this reason, sulfur mustard is also called yperite. Sulfur mustard was used in the Iran-Iraq War of 1980–1988, and there are reports of sulfur mustard being utilized in other conflicts. The production of sulfur mustard in the United States was discontinued in 1968. Sulfur mustard does not naturally occur, and, therefore, there are no background levels in the soil, air, water, or food. The major possibilities of exposure of the general public are through accidental release from the Army bases where it is stored. Occupational exposures in the United States are expected when handling, disposing and treating hazardous wastes containing sulfur mustard. It is also possible that workers involved in plastics manufacturing may be exposed to mustard agents inadvertently, resulting from process contamination with sulfur or nitrogen impurities, as occurred in a vinyl chloride monomer manufacturing facility in Plaquemine, Louisiana in 1996. If sulfur mustard was released into the air, the primary routes of exposure would be contact with eyes and skin or inhalation. Children are expected to be exposed to sulfur mustard by the same routes as adults.

The U.S. stockpile of sulfur mustard is currently stored at seven sites in the continental United States, and formerly at one site located on Johnston Island in the Pacific Ocean. All of these locations are heavily

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guarded, and storage buildings are sealed. Sulfur mustard may also be found in non-stockpile locations at current and former military base sites and testing sites across the United States. Non-stockpile sites include locations that may contain buried chemical munitions or contaminated sites formerly used in production and storage of sulfur mustard. The Army has taken many precautions to protect the public from exposure to sulfur mustard. People who work at Army bases that store sulfur mustard are more likely to be exposed than the general public. Currently, all of the sulfur mustard at these Army bases will be destroyed by either incineration or neutralization. U.S. law requires that the Department of Defense destroy all sulfur mustard by 2004. However, complete destruction of the entire stockpile of sulfur mustard may continue beyond this date. The United States also ratified the international Chemical Weapons Convention treaty, according to which, the United States must destroy its stockpile of mustard agents by April 2007. Sulfur mustard has been found in at least 3 of the 1,636 current or former NPL sites, the EPA's listing of the most serious hazardous waste sites in the nation. At hazardous waste sites, exposure to sulfur mustard is also possible by dermal contact with contaminated soil or containers.

The National Advisory Committee for the Acute Exposure Guideline Levels for Hazardous Substances has developed acute exposure guideline levels (AEGLs) for sulfur mustard. 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 AEGLs for sulfur mustard are summarized below. For sulfur mustard, the AEGL-1 values are based on human data for conjunctivitis; the AEGL-2 values are based on human data for conjunctivitis, edema, photophobia, and eye irritation, and the AEGL-3 values are for lethality in mice. For a more detailed description of the derivation of the sulfur mustard AEGLs, see Appendix D.

Acute Exposure Guideline Level (AEGL) Values for Sulfur Mustard (mg/m<sup>3</sup>)

<u>AEGL Level</u>	<u>10-minute</u>	<u>30-minute</u>	<u>1-hour</u>	<u>4-hour</u>	<u>8-hour</u>
AEGL-1	0.40 mg/m <sup>3</sup>	0.13 mg/m <sup>3</sup>	0.067 mg/m <sup>3</sup>	0.017 mg/m <sup>3</sup>	0.008 mg/m <sup>3</sup>
AEGL-2	0.60 mg/m <sup>3</sup>	0.20 mg/m <sup>3</sup>	0.10 mg/m <sup>3</sup>	0.025 mg/m <sup>3</sup>	0.013 mg/m <sup>3</sup>
AEGL-3	3.9 mg/m <sup>3</sup>	2.7 mg/m <sup>3</sup>	2.1 mg/m <sup>3</sup>	0.53 mg/m <sup>3</sup>	0.27 mg/m <sup>3</sup>

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Information about mustard agents other than sulfur mustard, such as nitrogen mustard and thickened mustard is not included in this document (see Chapter 4).

**2.2 SUMMARY OF HEALTH EFFECTS**

Sulfur mustard or other chemical warfare agents containing sulfur mustard are no longer produced or used commercially in the United States and general population exposures are expected to be low. People whose work is connected with chemical weapons or who work at military sites where these compounds are stored have the potential of being exposed. The primary adverse health effects of sulfur mustard exposure are ocular, respiratory and dermal direct contact effects, reproductive effects and cancer following inhalation, oral, and dermal exposure. Numerous reports of battlefield exposures provide strong evidence of the toxic potential of sulfur mustard; however, combat sulfur mustard exposure levels have not been quantified, and blast effects may be present concurrently. Additional information on the acute health effects of sulfur mustard is available from studies of sulfur mustard testing of volunteer subjects. Clinical studies of mustard agent filling plant workers provide evidence of health effects following chronic exposure to sulfur mustard; however, these studies are complicated by possible concurrent exposure to other toxic agents because factories generally produced multiple chemical warfare agents. Some evidence has also surfaced regarding delayed toxic effects several years after acute sulfur mustard exposure during battlefield operations or occupational exposure. The following symptoms have appeared from 2 months to several years after exposure to sulfur mustard: cough, chest pain, shortness of breath, fatigue, wheezing, insomnia, fever, relapsing keratitis (inflammation of the cornea), marked sensitivity to pulmonary irritants, and increased susceptibility to respiratory infections. Animal studies have shown that sulfur mustard induces similar toxic effects in animals and humans, with the exception of blistering of animals that have fur.

**Ocular Effects.** The eye is one of the organs that is most sensitive to the acute effects of sulfur mustard vapor. Studies with volunteer soldiers wearing respirators indicated conjunctivitis (inflammation of the conjunctiva), manifested as early as 30 minutes after exposure, as the first sign of exposure to sulfur mustard. The ocular effects are due to direct contact of sulfur mustard with the corneal/conjunctival epithelium. This is supported by experiments in animals that have shown little involvement of the eye when sulfur mustard was administered parenterally at dose levels known to be systemically toxic and lethal. The severity of ocular injury is a function of dose/concentration, duration, and

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temperature. Respiratory tract and skin irritations have occurred at about the same threshold vapor concentration, but the latency periods were generally longer ( $\geq 12$  hours). Other signs and symptoms of acute exposure include ocular irritation, redness, lacrimation, burning pain, swelling of the eyelids, photophobia (sensitivity of the eyes to light), blepharospasm (spasm of eyelid muscle), and corneal damage. When the severity of the injury was such that corneal damage occurred, necrotic ulcers, with or without bacterial infection, have developed. It has been reported that normal corneal epithelial regeneration occurred rapidly if the underlying stroma was intact, but if damaged, regeneration could be incomplete with continued erosion and neovascularization. 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.

Follow-up studies of battlefield exposures and long-term animal studies indicate that delayed or recurrent keratitis and/or ulceration of the cornea may result from severe burns. A sudden increase in the number of veterans with these signs of disease has been observed 8–25 years after the initial sulfur mustard injury. Long-term studies examining delayed ocular effects in rabbits acutely exposed to sulfur mustard showed that, similar to the human condition, migration of fatty and/or cholesterol deposits to the surface of the eye occurred 7–8 months after the initial injury, causing secondary ulceration. Exposure of the eye to liquid droplets of sulfur mustard can result in severe corneal damage, with possible perforation of the cornea and loss of the eye.

There are no rigorous human studies evaluating the occurrence of ocular sensitivity to sulfur mustard. From early chamber tests that indicated conjunctivitis as the initial sign of toxicity, conducted with three groups of men, those having no previous exposure, those who were exposed to “very low”, but unspecified, concentrations of sulfur mustard through their work, but who experienced no symptoms or burns, and those with unspecified occupational exposure who experienced one or more burns at various times, one investigator concluded that the toxicity of sulfur mustard did not appear to increase with previous exposure. However, details upon which this conclusion was based were lacking. Animal data suggest that ocular sensitization occurs following exposures to levels in the air that produce severe effects. While quantitative exposure data are not available, conjunctivitis, altered corneal pigmentation, photophobia, lacrimation, impaired vision, and blepharospasm have been reported in studies of workers at sulfur mustard research laboratories and manufacturing plants with longer-than-acute ( $>14$  days) exposure durations. However, these studies are limited by possible exposures to multiple toxic chemicals, confounding factors of age and smoking history, and comparisons to controls. Chronic keratitis has been observed in dogs and rats exposed to sulfur mustard vapor for  $\geq 7.5$  months.

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The Agency for Toxic Substances and Disease Registry (ATSDR) has derived acute and intermediate-duration inhalation Minimum Risk Levels (MRLs) based on ocular effects (see Appendix A). The National Advisory Committee for Acute Exposure Guideline Levels (AEGs) for Hazardous Substances has established AEGs and the Army has established an air exposure limit for the general population for chronic exposures (GPL) based on ocular effects (see Chapter 8).

**Respiratory Effects.** Early respiratory effects of sulfur mustard exposure include hoarseness, sore throat, a burning sensation of the vocal cords, shortness of breath, and hemorrhagic inflammation of the tracheobronchial mucosa accompanied by severe erosions or membranous lesions. In children, cough was the first respiratory symptom. Erosions of the airway mucosa have also been reported in animals. Respiratory infections are often a secondary complication following sulfur-mustard-induced injury, and pulmonary edema and bronchopneumonia may develop. Acute exposures to sulfur mustard have resulted in long-term damage manifested as asthma-like conditions, emphysematous bronchitis, and increases in incidence of secondary respiratory infections (bronchopneumonia and tuberculosis). Epidemiological studies of World War I victims exposed to sulfur mustard revealed an association between acute respiratory exposure and the risk of developing respiratory tract cancer. Prolonged inhalation exposure, as experienced by workers exposed to factory ambient levels of sulfur mustard for a number of years, can also result in these same conditions and/or cancer. Several studies of workers occupationally exposed to sulfur mustard have revealed elevated risks of respiratory tract tumors after long-term exposure.

**Dermal and Other Direct Contact Effects.** Data from soldiers and civilians exposed during combat, mustard agent factory workers, sulfur mustard testing volunteers, and people who were accidentally exposed to sulfur mustard provide ample evidence of the toxic potential of sulfur mustard to tissues coming into direct contact with sulfur mustard. Sulfur mustard exposure results in burning of the skin, which begins several hours after exposure. The severity of cutaneous injury is a function of dose, duration, temperature, humidity, and/or perspiration and is directly related to the sulfur mustard alkylation levels in skin. It is likely that direct contact with other tissues would have these same dependencies. Stomach irritation and inflammation and bleeding of the gastric mucosa were reported in victims of combat exposure where at least small amounts were likely ingested. Similar effects have been observed in animal studies. Occupational dermal exposure to sulfur mustard has produced abnormal skin pigmentation and Bowen's disease (precancerous dermatitis) in humans. There is also some evidence that former sulfur mustard factory workers may have an increased risk of developing digestive tract and skin tumors.

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ATSDR has derived an intermediate-duration oral MRL based on gastrointestinal effects (see Appendix A). The U.S. Army has derived an oral reference dose (RfD) based on gastrointestinal effects (see Chapter 8).

**Reproductive Effects.** Reduced sperm counts were reported in a follow-up study of men who were exposed to sulfur mustard during the Iran-Iraq War. An increased rate of fetal deaths and an altered sex ratio were reported in progenies of Iranian survivors of chemical attacks that included sulfur mustard. It is also important to note that reproductive success can be adversely affected by impaired sexual function caused by scarring of genital tissues resulting subsequent to blistering from direct contact with sulfur mustard. While the routes of exposure differ, animal reproductive toxicity data support the long-term effects reported in humans. Increases of early fetal resorptions and preimplantation losses and decreases in live embryo implants were observed in male dominant studies in which male rats, orally administered sulfur mustard, were mated with untreated females. An increase in the percentage of abnormal sperm was also detected in these treated rats. The reproductive effects appear to be male dominant as no female dominant lethal effects have been observed. The timing of the dominant lethal effects is consistent with an effect during the post-meiotic stages of spermatogenesis, possibly involving the generally sensitive spermatids. An altered sex ratio and a decrease in growth rate during nursing were observed in the offspring of parental rats that had been orally exposed to sulfur mustard during fetal and neonatal development, as well as pre mating, mating, and gestation. Sulfur mustard has also induced dominant and sex-linked recessive lethal mutations in *Drosophila*.

**Cancer.** There is sufficient evidence that sulfur mustard is carcinogenic to humans. Epidemiological studies of World War I victims exposed to sulfur mustard revealed an association between respiratory exposure and the risk of developing respiratory tract cancer. Factory workers exposed to sulfur mustard for a number of years have been shown to develop respiratory cancer. Although most human studies have found an association between sulfur mustard exposure and respiratory cancer, some studies have not found a significant relationship, possibly due to lower exposure levels. It is also documented that occupational dermal exposure to sulfur mustard produces Bowen's disease (precancerous dermatitis) in humans. There is some evidence that former sulfur mustard factory workers may have an increased risk of developing digestive tract and skin tumors. Two animal studies, of low predictive quality due to species strain tendency to develop lung tumors, insufficient animals, and inadequate doses, have also shown increases in tumors from exposure to sulfur mustard in the air. Subcutaneous, intramuscular, and intravenous injections of sulfur mustard into mice have also produced increased tumors at the site of the

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injection, in the mammary glands, or in the lungs. Sulfur mustard has been shown to induce a wide variety of genetic mutations in many types of mammalian cells *in vitro* in a dose-related fashion. Sulfur mustard has also induced genetic damage *in vivo* in peripheral blood lymphocytes from exposed individuals at low doses. This is not unexpected considering sulfur mustard is a bi-functional alkylating agent that can cross-link DNA strands.

IARC has classified sulfur mustard as “carcinogenic to humans” (Group 1) based on sufficient evidence in humans, limited evidence in experimental animals, supporting evidence that sulfur mustard is a bi-functional alkylating agent, and positive results in a number of assays for genotoxic effects.

The Army’s current health-based environmental screening levels (HBESLs) for sulfur mustard include an oral cancer potency value (slope factor), a cancer inhalation unit risk value, and an inhalation cancer potency value. However, ongoing evaluations of alternative approaches for quantitatively estimating cancer risk may result in changes to these values (see Chapter 8).

### 2.3 MINIMAL RISK LEVELS

#### Inhalation MRLs

- An MRL of 0.0007 mg/m<sup>3</sup> has been derived for acute-duration inhalation exposure (14 days or less) to sulfur mustard.

The acute-duration inhalation MRL was based on a concentration of sulfur mustard vapors of 0.06 mg/m<sup>3</sup> at which minimal ocular effects occurred in men who underwent a 3-day chamber test with sulfur mustard (Guild et al. 1941). The corresponding time-weighted average (TWA) concentration of 0.02 mg/m<sup>3</sup> was considered a minimal lowest-observed-adverse-effect level (LOAEL) for the MRL derivation. An uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability) was applied to derive the MRL. Male soldiers wearing respirators (2–6 men/group) were exposed to sulfur mustard vapor concentrations ranging from 0.06 to 320 mg/m<sup>3</sup>. Continuous exposure durations ranged from 15 seconds to 10 hours, yielding concentration time (Ct) products in the range of 42–144 mg-minute/m<sup>3</sup>. Two repeated-exposure tests were also conducted; a group of four men was exposed to 0.22 mg/m<sup>3</sup>, 2.5 hours/day for 2 days, and another group of four men was exposed to 0.06 mg/m<sup>3</sup>, 8 hours/day, for 3 days (intermittent Cts of 66 and 86 mg-minute/m<sup>3</sup>, respectively). At the lowest continuous Ct of 42 mg-minute/m<sup>3</sup> (1.4 mg/m<sup>3</sup> for 30 minutes), four of four soldiers showed a slight generalized conjunctival

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reaction. Slight to moderate degree of conjunctival congestion was reported for the Ct range of 80–90 mg-minute/m<sup>3</sup>. Photophobia occurred at Cts  $\geq 99$  mg-minute/m<sup>3</sup>. A scarcely discernable generalized conjunctival reaction (incidence unspecified) was reported in subjects undergoing the 3-day repeated exposure. 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  $\geq 80$  mg-minute/m<sup>3</sup>.

Support for ocular effects as a critical detection of effect end point comes from other chamber tests with human subjects (Anderson 1942; Reed 1918) and numerous reports of eye injuries in humans following combat exposure to sulfur mustard (Hughes 1942; Pechura and Rall, 1993; Philips 1940). A range of ocular effects, including conjunctivitis, chronic keratitis, and corneal ulcerations, has 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).

- An MRL of 0.00002 mg/m<sup>3</sup> has been derived for intermediate-duration inhalation exposure (15–364 days) to sulfur mustard.

The intermediate-duration inhalation MRL was based on a no-observed-adverse-effect level (NOAEL) of 0.001 mg/m<sup>3</sup> for ocular effects (conjunctivitis and chronic keratitis) in dogs (McNamara et al. 1975). Male and female beagle dogs were exposed to sulfur mustard vapor at a concentration of 0.001 mg/m<sup>3</sup> for 24 hours/day, or to 0.1 mg/m<sup>3</sup> for 6.5 hours followed by exposure to 0.0025 mg/m<sup>3</sup> for the remaining 17.5 hours of the day, 5 days/week (TWAs of 0.0007 and 0.0206 mg/m<sup>3</sup>, respectively), for durations up to 1 year. No dogs died during the study. No clinical signs of toxicity were observed in the dogs at the low concentration. Ocular effects at the high concentration first appeared after 16 weeks of exposure and included corneal opacity, pannus, chronic keratitis, vascularization, pigmentation, and granulation. The TWA concentration of 0.0007 mg/m<sup>3</sup> was used in the MRL derivation.

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 (Pechura and Rall 1993; Uhde and Dunphy 1946).

A chronic-duration (365 days or more) inhalation MRL for sulfur mustard was not derived because quantitative data were not available to determine NOAELs or LOAELs. However, using a different



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derivation procedure than that used for chronic-duration inhalation MRLs, the Army has established an air exposure limit for the general population for chronic exposures (GPL) of 0.00002 mg/m<sup>3</sup> as a 24-hour time-weighted average, 7 days/week (USACHPPM 2000a). The key critical effect chosen for the GPL was ocular effects, as the data indicate the eyes to yield the most sensitive response to vapor exposures of sulfur mustard. A previously established GPL of 0.0001 mg/m<sup>3</sup> for sulfur mustard was promulgated by the Centers for Disease Control and Prevention (CDC) in 1988 (DHHS 1988). The Army has also derived an inhalation reference dose (RfD; an estimate of a daily ingestion exposure level for the human population, including sensitive subpopulations, that is likely to be without appreciable risk of deleterious noncancer health effects during a lifetime) of 0.00003 mg/kg/day from this GPL by assuming a human inhalation rate of 20 m<sup>3</sup>/day and a body weight of 70 kg (USACHPPM 1999).

**Oral MRLs**

- An MRL of 0.0005 mg/kg/day (0.5 µg/kg/day) has been derived for acute-duration oral exposure (14 days or less) to sulfur mustard.

The acute-duration oral MRL was based on a LOAEL of 0.5 mg/kg/day for inflamed mesenteric lymph nodes in rat dams administered sulfur mustard in sesame oil by gavage (DOA 1987). The dose is also a LOAEL for reduced ossification in the fetuses. An uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) was applied to the LOAEL to derive the MRL. In the teratology study that formed the basis for the acute-duration oral MRL, there were no treatment-related deaths in groups of 25–27 mated Sprague-Dawley female rats (10–11 weeks old) that were dosed acutely on gestation days 6–15 (10 days) with 0, 0.5, 1.0, or 2.0 mg/kg/day sulfur mustard (95.9–96.1% purity) dissolved in sesame oil. Significant incidences of inflamed mesenteric lymph nodes in dams and reduced ossification in fetuses occurred with sulfur mustard doses  $\geq 0.5$  mg/kg/day.

There is some evidence for sulfur mustard-induced lymph system effects in humans. Lymph node discoloration and spleen pathology were found in autopsies of sulfur mustard victims (Alexander 1947). Additional animal studies also indicate sulfur mustard-induced damage to the lymph system (Cameron et al. 1946; Coutelier et al. 1991; Venkateswaran et al. 1994a). In other oral studies in animals in which sulfur mustard dissolved in sesame oil was administered by gavage, increased incidence of inflamed mesenteric lymph nodes occurred in rats at  $\geq 0.4$  mg/kg/day in dose-range experiments (DOA 1987) and another lymphoretic effect, enlarged Peyer's patches, was observed in rabbits at 0.5 mg/kg/day in a range-

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finding study and at 0.4 mg/kg/day in the subsequent full-scale teratology study (incidence data not reported) (DOA 1987).

- An MRL of 0.00007 mg/kg/day (0.07 µg/kg/day) has been derived for intermediate-duration oral exposure (15–364 days) to sulfur mustard.

The intermediate-duration oral MRL was based on a LOAEL of 0.03 mg/kg/day for forestomach epithelium lesions in rats administered sulfur mustard in sesame oil by gavage in a 2-generation reproduction study (Sasser et al. 1996a). In that study, groups of 8-week-old Sprague-Dawley rats (27 females and 20 males/group/generation) were dosed with 0, 0.03, 0.1, or 0.4 mg/kg/day sulfur mustard (97.3% purity) dissolved in sesame oil. Male and female rats were dosed 5 days/week for 13 weeks before mating and during a 2-week 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. The dosing of F1 dams continued until pup weaning, at which time, the study was terminated. Significant dose-related severity and incidences of forestomach squamous epithelium lesions occurred in both sexes with sulfur mustard doses  $\geq 0.03$  mg/kg/day. This LOAEL corresponds to a TWA LOAEL of 0.02 mg/kg/day, which was used for MRL derivation. An uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability) was applied to the TWA LOAEL to derive the MRL.

In support of the forestomach epithelial lesions as the key critical effect for the intermediate-duration MRL, gastrointestinal effects (stomach irritation and inflammation, hyperemia, epithelial loss, necrosis, ulceration, vomiting, nausea, bleeding, anorexia, and abdominal pain) have been reported in humans following combat exposure to sulfur mustard, in sulfur mustard testing volunteers, and in sulfur mustard factory workers (Alexander 1947; Momeni and Aminjavaheri 1994; Pierard et al. 1990; Sinclair 1948; Yamakido et al. 1985). Gastrointestinal effects (edema, hemorrhage or sloughing of the mucosa, and ulceration) were also observed in rabbits following 14-day exposures at  $\geq 0.4$  mg/kg/day (DOA 1987), in rats following 10-day exposures at  $\geq 2.0$  mg/kg/day (DOA 1987), and in rats following 13-week exposures at  $\geq 0.1$  mg/kg/day (Sasser et al. 1996b).

A chronic-duration (365 days or more) oral MRL for sulfur mustard was not derived because a chronic bioassay was not located. However, using a derivation procedure different than that used for chronic-duration oral MRLs, the Army has derived an oral RfD of 0.007 µg/kg/day (Oak Ridge National

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Laboratory 1996; Opresko et al. 1998, 2001; USACHPPM 1999, 2000b) that has also been approved by the National Research Council (NRC 1999b).