

# ACUTE EXPOSURE GUIDELINE LEVELS (AEGLS) FOR SULFUR MUSTARD (AGENT HD)

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## ABSTRACT

Sulfur mustard (Agent HD) is an alkylating chemical vesicant that affects any epithelial surface with which it comes in contact; it has been historically developed and used as a warfare agent. For AEGL estimation, both human and animal exposure data were analyzed. AEGL-1 values (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>, and 0.008 mg/m<sup>3</sup> for 10 min, 30 min, 1 hr, 4 hrs, and 8 hrs, respectively) were based upon data from informed human volunteers. An exposure concentration-time product (Ct) of 12 mg-min/m<sup>3</sup> represented a threshold for conjunctival injection and minor discomfort but no functional decrement. An intraspecies uncertainty factor of 3, applied to protect potentially sensitive individuals, was considered appropriate. AEGL-2 values (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>, and 0.013 mg/m<sup>3</sup> for 10 min, 30 min, 1 hr, 4 hrs, and 8 hrs, respectively) were based upon human exposure data showing a Ct of ~60 mg-min/m<sup>3</sup> to be the lower margin of the concentration-effect zone to the eye that resulted in ineffective military performance. Due to the latency in development of effects, the AEGL-1 and AEGL-2 values are considered protective. Variability in the ocular responses was minimal among the volunteers, thereby justifying an intraspecies adjustment of only 3. A modifying factor of 3 accommodated potential onset of long-term ocular or respiratory effects for which available data were silent. AEGL-3 values (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>, and 0.27 mg/m<sup>3</sup> for 10 min, 30 min, 1 hr, 4 hrs, and 8 hrs, respectively) were based upon an estimated lethality threshold of 21.2 mg/m<sup>3</sup> in mice exposed for 1 hr. A 3-fold downward adjustment accounted for intraspecies variability and an uncertainty factor of 3 was applied to account for possible interspecies variability in the lethal response to sulfur mustard. For AEGL-1 and AEGL-2, scaling of exposures to AEGL-specific durations was linear (C<sup>n</sup> x t = k, where n = 1). For AEGL-3, time scaling was exponential (n = 3) for shorter time periods and linear (n = 1) for longer time periods.

## HUMAN DATA STATEMENT

These findings are based on the results of mustard agent vapor exposures to informed volunteers who were under clinical supervision during the periods of exposure, as well as for post-exposure periods of several months. The level of clinical supervision was appropriate for the time.

## INTRODUCTION

• AEGLs represent threshold exposure limits for general public; are applicable to emergency exposure periods ranging from 10 minutes to 8 hrs. As data permit, AEGL levels will be developed for each of five exposure periods (10 min, 30 min, 1 hr, 4 hrs, 8 hrs), and will be distinguished by varying degrees of severity of toxic effects with AEGL-3 as most severe. Recommended exposure levels applicable to the general population including infants, children, and other individuals who may be sensitive and susceptible. Definitions follow:

• AEGL-1 is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

• AEGL-2 is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

• AEGL-3 is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

AEGL Values for Sulfur Mustard [ppm (mg/m <sup>3</sup> )]						
Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 <sup>a</sup>	0.06 ppm (0.40)	0.02 ppm (0.13)	0.01 ppm (0.067)	0.003 ppm (0.017)	0.001 ppm (0.008)	Conjunctival injection, minor discomfort; no functional decrement in human volunteers (Anderson, 1942)
AEGL-2 <sup>a</sup>	0.09 ppm (0.60)	0.03 ppm (0.20)	0.02 ppm (0.10)	0.004 ppm (0.025)	0.002 ppm (0.013)	Well marked, generalized conjunctivitis, edema, photophobia, and eye irritation in human volunteers (Anderson, 1942)
AEGL-3 <sup>a</sup>	0.59 ppm (3.9)	0.41 ppm (2.7)	0.32 ppm (2.1)	0.08 ppm (0.53)	0.04 ppm (0.27)	Lethality estimate in mice (Kumar and Vijayaraghavan, 1998)

<sup>a</sup>AEGL-1 and AEGL-2 values, and the 4- and 8-hour AEGL-3 values are at or below the 0.6 mg/m<sup>3</sup> odor threshold for sulfur mustard.

## AGENT HD (SULFUR MUSTARD)

• Sulfur mustard (Agent HD): alkylating chemical vesicant and cell poison, affects any epithelial surface contacted; historically developed and used as early warfare agent. Active component is bis(2-chloroethyl)sulfide (CAS No. 505-60-2).

• Clinical presentation in humans following acute exposure to vapor may involve dermal, ocular, and respiratory tract effects.

• Liquid at ordinary ambient temperature; volatility results in vapor generation.

• Ambient and body temperature, humidity govern degree of “casualty effect.” Under hot, humid conditions, lower mustard concentrations generate adverse effects.

• Sulfur mustard has garlic-like odor

• Persistent in the environment due to low aqueous solubility

## SUMMARY OF HUMAN DATA

• Either inhalation or percutaneous exposure to sulfur mustard vapor may result in lethality, inhalation exposure is more sensitive route. Human lethality data available as extrapolation estimates from animal data. Estimated human LC<sub>50</sub> values are 1,000 mg-min/m<sup>3</sup> and 10,000 mg-min/m<sup>3</sup>, respectively, for inhalation and percutaneous vapor exposure (Grotte and Yang, 2001).

• Ocular surfaces are sensitive, rapidly responding tissues.

• Ct values of 60-75 mg-min/m<sup>3</sup> are exposures associated with conjunctivitis, photophobia, ocular irritation (Anderson 1942)

• Ct values of 75-90 mg-min/m<sup>3</sup> would cause a high proportion of casualties (more severe ocular damage requiring several weeks of exposure). At higher concentrations, pulmonary regions are also affected.

• For all tissues, there is a latency period between initial exposure and development of effects.

## SUMMARY OF ANIMAL DATA

• Data available for 8 species (monkey, dog, rat, mouse, guinea pig, rabbit, cat, goat)

• Acute and long-term exposure assessments (exposure durations of 2 min - 52 wks)

• Carcinogenicity and developmental toxicity studies (dermal and pulmonary tumor assessments)

• LC<sub>50</sub> values for 2-60 min (42.5 mg-min/m<sup>3</sup> - 4140 mg-min/m<sup>3</sup>)

## DERIVATION OF AEGL-1

• AEGL-1 values developed using data reported by Anderson (1942) in which 3-4 informed human volunteers exposed to agent HD at varying concentration-time (Ct) regimens and different ambient temperatures.

• A Ct of 30 mg-min/m<sup>3</sup> represented upper range for mild effects (conjunctival injection and minor discomfort with no functional decrement); 12 mg-min/m<sup>3</sup> represented effects threshold. A Ct of 12 mg-min/m<sup>3</sup> represents defensible estimate of threshold for AEGL-1 effects (resulted in only minor conjunctival injection and no sensation of irritation).

• Ocular effects are the most sensitive indicator of sulfur mustard exposure and toxicity; ocular irritation justified as appropriate endpoint for AEGL derivation.

• Uncertainty factor application to 12 mg-min/m<sup>3</sup> Ct limited to 3 for protection of sensitive individuals. Adjustment appropriate for acute exposures to chemicals with mechanism of action involving surface contact irritation of ocular and/or respiratory tract tissue (not systemic activity involving absorption/distribution of parent chemical or biotransformation product to target tissue).

## DERIVATION OF AEGL-2

• AEGL-2 values developed using data from Anderson (1942) in which 3-4 informed human volunteers were exposed to concentrations of sulfur mustard (1.7-15.6 mg/m<sup>3</sup>) for time periods varying from 2-33 minutes.

• Ct value of 60 mg-min/m<sup>3</sup> considered lowest Ct for which ocular effects (irritation, soreness, widespread conjunctivitis frequently accompanied by chemosis and photophobia) could be characterized as military casualties; such personnel might be ineffective for up to (but no more than) 7 days.

• The 60 mg-min/m<sup>3</sup> Ct used as basis for derivation; representative of acute exposure causing effect severe enough to impair normal visual function; not irreversible; would certainly result in additional injury potential [meets AEGL-2 criteria].

• Protective AEGL-2 endpoint because eyes are most sensitive indicator of sulfur mustard exposure; ocular effects expected to occur prior to, and in absence of, vesicant and severe pulmonary effects.

• Intraspecies UF = 3 (protection of sensitive populations).

• Modifying factor = 3 (accommodate potential onset of long-term ocular or respiratory effects).

– No long-term follow-up for Anderson (1942) subjects to confirm or deny development of permanent ocular or respiratory tract damage

– AEGL-2 values at or below reported odor threshold (0.6 mg/m<sup>3</sup>).

## DERIVATION OF AEGL-3

• Vijayaraghavan (1997) reported 60-min LC<sub>50</sub> of 42.5 mg/m<sup>3</sup> for lethality of mice at 14 days post exposure (95% confidence interval: 13.5-133.4 mg/m<sup>3</sup>); (Kumar and Vijayaraghavan, 1998) reported no mortality in mice exposed to 0.5 LC<sub>50</sub> (21.2 mg/m<sup>3</sup>).

• 1-hour exposure to 21.2 mg/m<sup>3</sup> was selected as an estimate of lethality threshold.

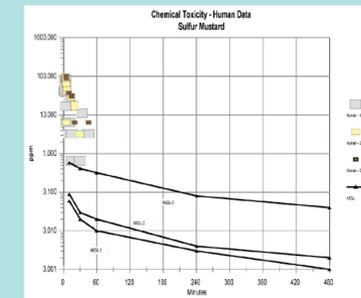
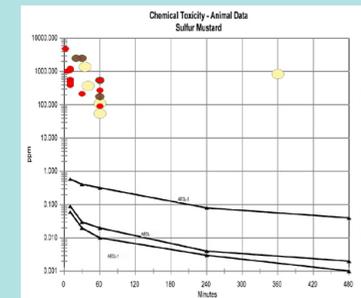
• AEGL-3 values derived by scaling from the 1-hour lethality threshold of 21.2 mg/m<sup>3</sup> reported by Kumar and Vijayaraghavan (1998) using C<sup>n</sup> x t = k where n = 1 or 3

• Intraspecies UF = 3 (appropriate for acute exposures to chemicals with mechanism of action involving surface contact corrosion of ocular and/or respiratory tract tissue, and not systemic activity).

• Interspecies UF +3 (mechanism of pulmonary injury leading to lethality is function of direct alkylating agent contact with epithelial tissue).

– Mechanism likely to be more similar than it is different across mammalian species.

• Derived AEGL-3 values equivalent to exposures known to cause mild ocular effects in humans as depicted in category plot.



## TEMPORAL EXTRAPOLATION (TIME SCALING)

• When exposure-response data unavailable for all of AEGL-specific exposure durations, temporal extrapolation applied to attain exposure values for AEGL-specific time periods.

• The concentration-exposure time relationship for many irritant and systemically acting vapors and gases described by C<sup>n</sup> x t = k, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al., 1986).

• Analysis of exposure response data reported by Reed (1918), Reed et al. (1918), Guild et al. (1941), and Anderson (1942) indicates the concentration-exposure time relationship to be a near-linear function (where n = 1 for C<sup>n</sup> x t = k) as shown by n values of 1.11 and 0.96.

## SUMMARY/CONCLUSIONS

• Both AEGL-1 and AEGL-2 values based upon effect endpoints consistent with respective AEGL definitions.

• Use of the mouse lethality data represents a defensible approach to AEGL-3 derivation.

• Excess cancer risk estimate based upon geometric mean of inhalation slope factors revealed that exposure concentrations representing a 10<sup>-4</sup> lifetime risk were similar to the AEGL-3 exposure concentration values.

• Extrapolation to exposure durations <10 min not recommended.

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