

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR PHOSGENE

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ABSTRACT

AEGL values represent one-time exposures for increasingly severe effects with AEGL-1 being least and AEGL-3 being most severe. Phosgene is a colorless gas at ambient temperature and pressure. Appropriate data were not available for deriving AEGL-1 values for phosgene. Odor cannot be used as a warning for potential exposure. The odor threshold is reported to be between 0.5 to 1.5 ppm, a value above or approaching AEGL-2 and AEGL-3 values, and tolerance to the pleasant odor of phosgene occurs rapidly. Furthermore, following odor detection and minor irritation, serious effects may occur after a clinical latency period of ≤ 24 hours. AEGL-2 values (0.6 ppm, 0.6 ppm, 0.3 ppm, 0.08, and 0.04 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hr, respectively) were based on chemical pneumonia in rats exposed to 2 ppm for 90 min. The 90 minute value was then scaled to the 30-minute, 1-, 4-, and 8-hour AEGL exposure periods, using $c^n \times t = k$, where $n = 1$ (Haber's Law) because Haber's Law has been shown to be valid for phosgene within certain limits. The 30-minute value was also adopted as the 10-minute value because extrapolation would yield a 10-minute AEGL-2 value approaching concentrations producing alveolar edema in rats. The 30-min, 1-, 4-, and 8-hr AEGL-3 values (1.5 ppm, 0.75 ppm, 0.20 ppm, and 0.09 ppm, respectively) were based on the highest concentration causing no mortality in rats after a 30-minute exposure (15 ppm). The value was scaled to the 1-, 4-, and 8-hour AEGL periods, using $c^n \times t = k$, where $n = 1$. The 10-min AEGL-3 value (3.6 ppm) was based on the highest concentration causing no mortality in the rat or mouse (36 ppm) after a 10-minute exposure. For all AEGL-2 and -3 values, an uncertainty factor (UF) of 3 was applied for interspecies extrapolation because little species variability is observed for both lethal and nonlethal effects after exposure to phosgene. A UF of 3 was applied to account for sensitive individuals due to the steep concentration-response curve which implied limited variability.

INTRODUCTION

• AEGLs represent threshold exposure limits for the general public; are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. As data permit, AEGL levels will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. Recommended exposure levels are applicable to the general population including infants, children, and other individuals who may be susceptible. The three AEGLs have been defined as follows:

• AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m³]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory 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/m³) 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/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

PHOSGENE TOXICITY

• Inhalation is the most important route of exposure. Mild upper respiratory, eye and skin irritancy, and a mildly pleasant odor preclude actively seeking escape before lower respiratory damage occurs.

• Clinical presentation after phosgene exposure includes brief (≤ 20 min.) ocular and throat irritation, cough, nausea and vomiting, and dizziness, followed by a period (≤ 24 hr) of apparent well being.

• Following latent phase, more severe effects occur: cough accompanied by expectoration, sensation of pain or tightness of the chest, shortness of breath, and choking sensation.

• Death occurs from pulmonary edema.

• Animal studies suggest little interspecies variability in response to acute phosgene exposure; type and sequence of effects are similar in humans and experimental animals.

TEMPORAL EXTRAPOLATION (Time Scaling)

• Concentration-exposure time relationship for many irritant and systemically-acting vapors and gasses can be described by the relationship $c^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al., 1986).

• The concept of "death product" introduced by Haber to explain relationship between extent of exposure to phosgene and death (Haber, 1924).

• "Haber's Law": biological effect of phosgene is directly proportional to the product of the atmospheric concentration (C) and the time of exposure (T) or $CT = k$, where k can be death, pulmonary edema, or other biological effects of phosgene exposure.

• Haber's Law shown by other investigators to be valid for both nonlethal and lethal effects.

– Similar respiratory response at similar CT (Rinehart, 1962; Rinehart and Hatch, 1964) .

– Linear regression analysis of 10- to 60-minute rat and mouse LC₅₀ data yield values of the exponent, n , of 0.93 and 1.3, respectively (Zwart et al., 1990).

• $c^n \times t = k$, where $n = 1$ was used for AEGL development.

UNCERTAINTY FACTORS

Uncertainty factors applied to derived AEGL values for Phosgene:

Interspecies: 3, minimal species variability.

Comparison of Phosgene LC ₅₀ Values Between Rats and Mice (Zwart et al., 1990)		
Exposure Duration	Mouse LC ₅₀	Rat LC ₅₀
10 minutes	77 ppm	80 ppm
30 minutes	18 ppm	20 ppm
60 minutes	9 ppm	12 ppm

Intraspecies: 3, steep concentration-response curve implies limited individual variability

Total uncertainty factor = 10.

DERIVATION OF AEGL-1

• Appropriate data were not available for derivation of AEGL-1 values for phosgene.

• Odor inappropriate as a warning. Odor threshold reported as 0.5 to 1.5 ppm.

– Above or approaching AEGL-2 and AEGL-3 values.

– Tolerance to the pleasant odor of phosgene occurs rapidly.

• Following odor detection and minor irritation, serious effects may occur after a clinical latency period of ≤ 24 hours.

• AEGL-1 values for phosgene are not recommended.

DERIVATION OF AEGL-2

• AEGL-2 values for phosgene developed using the data from Gross et al. (1965) showing chemical pneumonia in rats exposed to 2 ppm phosgene for 90 minutes.

– At this CT product of 180 ppm·min ~60% of rats exhibited chemical pneumonia.

– At CT products < 180 ppm·min, only 15% of exposed rats showed pneumonia or chemical pneumonitis.

• Total uncertainty factor of 10 (3 for interspecies variability and 3 for intraspecies variability) applied.

• Time scaling accomplished using $c^n \times t = k$, where $n = 1$.

– 30-minute value adopted for 10 minutes.

– Extrapolation would yield a 10-minute AEGL-2 value approaching concentrations producing alveolar edema in rats (Diller et al., 1985).

DERIVATION OF AEGL-3

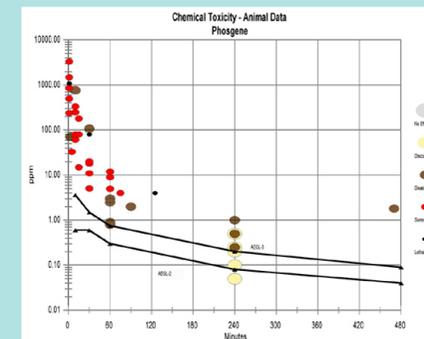
• Highest concentration causing no mortality in the rat and mouse after a 10-minute exposure is 36 ppm (Zwart et al., 1990); basis for the 10-minute AEGL-3.

• Highest concentration causing no mortality in the rat after a 30-minute exposure is 15 ppm (Zwart et al., 1990); basis for the 30-minute, 1-hour, 4-hour, and 8-hour AEGL-3.

• Total uncertainty factor of 10 (3 for interspecies variability and 3 for intraspecies variability) applied.

• Scaling of AEGL-3 values across time for the 1-hour, 4-hour, and 8-hour AEGL-3 values for phosgene was accomplished using $c^n \times t = k$, where $n = 1$.

AEGL Values for Phosgene						
	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1	NR	NR	NR	NR	NR	Not recommended due to lack of appropriate data and clinical latency period
AEGL-2	0.60 ppm	0.60 ppm	0.30 ppm	0.08 ppm	0.04 ppm	Chemical pneumonia rats (Gross et al., 1965)
AEGL-3	3.6 ppm	1.5 ppm	0.75 ppm	0.20 ppm	0.09 ppm	Highest concentration causing no mortality in the rat after a 30-minute or 10-minute exposure (Zwart et al., 1990)



SUMMARY/CONCLUSIONS

• AEGL-1 values for phosgene are not recommended.

• Both the AEGL-2 and AEGL-3 values were based upon effect endpoints consistent with the respective AEGL definitions (i.e., threshold for chemical pneumonia [AEGL-2] and threshold for lethality [AEGL-3]).

• A robust data set allowed for the use of uncertainty factors of 3 each for interspecies and intraspecies variability.

• Haber's Law has been shown to be valid for both nonlethal and lethal effects of phosgene; thus, $c^n \times t = k$, where $n = 1$ was appropriate.

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