

TABLE 1-38 AEGL-3 Values^a for Agent VX (mg/m³ [ppm])

10 min	30 min	1 h	4 h	8 h
0.029 mg/m ³ (0.0027 ppm)	0.015 mg/m ³ (0.0014 ppm)	0.010 mg/m ³ (0.00091 ppm)	0.0052 mg/m ³ (0.00048 ppm)	0.0038 mg/m ³ (0.00035 ppm)

^aThe AEGL values are for vapor exposures only.

GF were considered equipotent for AEGL-1 and AEGL-2 effects, and twice as potent as agent GB. The use of these relative potency measures for the derivation of AEGL-2 values for GA, GD, and GF was a conservative approach compared with an estimate based on a fraction (one-third) of the AEGL-3 concentration level (NRC 2001), which would have resulted in higher AEGL-2 values for GA, GD, and GF.

Lethality data for SD rats were available for the derivation of an AEGL-3 for agent GB. The AEGL-3 values for agents GA, GD, and GF were derived from the AEGL-3 values for GB using a relative potency approach. Agents GB, GD, and GF were considered to have an equivalent lethal potency. The lethal potency of agent GA was considered to be only one-half that of agents GB, GD, and GF.

A secondary derivation of 10-min and 30-min AEGL-3 values for agent GD relied on data from an inhalation study of male Wistar rats exposed to GD for periods up to 30 min (Aas et. al. 1985). The values derived from this secondary study (0.27 mg/m³ for 10 min and 0.15 mg/m³ for 30 min) are in good agreement with those derived by means of relative potency comparison with agent GB (0.38 mg/m³ for 10 min and 0.19 mg/m³ for 30 min) for the same time periods.

Cross-comparison of the AEGL estimates for agent GB with the available human toxicity data (Figure 1-1; see also Tables 1-7, 1-8, and 1-9) reveals that the AEGL-1 values for agent GB are substantially below any reported effect levels, and the AEGL-2 values are below any of the exposure levels that might be considered disabling. Although available human data are clustered in time periods <60 min, it is clear that AEGL-3 estimates are below exposures considered capable of inducing reversible AEGL-2 effects (miosis, dyspnea, changes in SFEMG, etc.) (Baker and Sedgewick 1996) and overlap those where reversible discomfort is observed. Comparisons with animal toxicity data (Figure 1-2) also indicate that the estimated AEGL values for GB are below most reported effect

TABLE 1-39 Relational Comparison of AEGs for Nerve Agents^a GA, GB, GD, GF, and VX

Agent	Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
GA	AEGL-1 (Nondisabling)	0.0010 ppm (0.0069 mg/m ³)	0.00060 ppm (0.0040 mg/m ³)	0.00042 ppm (0.0028 mg/m ³)	0.00021 ppm (0.0014 mg/m ³)	0.00015 ppm (0.0010 mg/m ³)	Based on relative potency from GB ^b
	AEGL-2 (Disabling)	0.013 ppm (0.087 mg/m ³)	0.0075 ppm (0.050 mg/m ³)	0.0053 ppm (0.035 mg/m ³)	0.0026 ppm (0.017 mg/m ³)	0.0020 ppm (0.013 mg/m ³)	Based on relative potency from GB ^b
	AEGL-3 (Lethal)	0.11 ppm (0.76 mg/m ³)	0.057 ppm (0.38 mg/m ³)	0.039 ppm (0.26 mg/m ³)	0.021 ppm (0.14 mg/m ³)	0.015 ppm (0.10 mg/m ³)	Based on relative potency from GB ^c
GB	AEGL-1 (Nondisabling)	0.0012 ppm (0.0069 mg/m ³)	0.00068 ppm (0.0040 mg/m ³)	0.00048 ppm (0.0028 mg/m ³)	0.00024 ppm (0.0014 mg/m ³)	0.00017 ppm (0.0010 mg/m ³)	EC ₅₀ for miosis observed in adult female SD rats exposed to a range of GB vapor concentrations (0.01 to 0.48 mg/m ³) for 10, 60 and 240 min (Mioduszewski et al. 2002b) AND miosis data from secondary and supportive studies with

AEGL-2 (Disabling)	0.015 ppm	0.0085 ppm	0.0060 ppm	0.0029 ppm	0.0022 ppm	marmosets (van Helden et al. 2001, 2002), and humans (Harvey 1952; and Johns 1952). Miosis, dyspnea, RBC-ChE inhibition, single fibre electromyography (SFEMG) changes in human volunteers exposed to 0.5 mg/m ³ for 30 min (Baker and Sedgwick 1996)
AEGL-3 (Lethal)	(0.087 mg/m ³) 0.064 ppm (0.38 mg/m ³)	(0.050 mg/m ³) 0.032 ppm (0.19 mg/m ³)	(0.035 mg/m ³) 0.022 ppm (0.13 mg/m ³)	(0.017 mg/m ³) 0.012 ppm (0.070 mg/m ³)	(0.013 mg/m ³) 0.0087 ppm (0.051 mg/m ³)	Based on experimental SD rat lethality data (LC ₀₁ and LC ₅₀); whole-body dynamic exposure to concentrations between 2-54 mg/m ³ for 3, 10, 30, 60, 90, 240, and 360 min

(Continued)

TABLE 1-39 *Continued*

Agent	Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
							(Mioduszewski et al. 2000; 2001, 2002a)
GD	AEGL-1 (Nondisabling)	0.00046 ppm (0.0035 mg/m ³)	0.00026 ppm (0.0020 mg/m ³)	0.00018 ppm (0.0014 mg/m ³)	0.000091 ppm (0.00070 mg/m ³)	0.000065 ppm (0.00050 mg/m ³)	Based on relative potency from GB ^d
	AEGL-2 (Disabling)	0.0057 ppm (0.044 mg/m ³)	0.0033 ppm (0.025 mg/m ³)	0.0022 ppm (0.018 mg/m ³)	0.0012 ppm (0.0085 mg/m ³)	0.00085 ppm (0.0065 mg/m ³)	Based on relative potency from GB ^d
	AEGL-3 (Lethal)	0.049 ppm (0.38 mg/m ³)	0.025 ppm (0.19 mg/m ³)	0.017 ppm (0.13 mg/m ³)	0.0091 ppm (0.070 mg/m ³)	0.0066 ppm (0.051 mg/m ³)	Based on relative potency from GB. Supported by Wistar rat LC ₅₀ ; dynamic chamber exposures at 21 mg/m ³ for 3 time periods of ≤30min duration (Aas et al. 1985) ^e
GF	AEGL-1 (Nondisabling)	0.00049 ppm (0.0035 mg/m ³)	0.00028 ppm (0.0020 mg/m ³)	0.00020 ppm (0.0014 mg/m ³)	0.00010 ppm (0.00070 mg/m ³)	0.000070 ppm (0.00050	Based on relative potency from GB ^d

	AEGL-2 (Disabling)	0.0062 ppm (0.044 mg/m ³)	0.0035 ppm (0.025 mg/m ³)	0.0024 ppm (0.018 mg/m ³)	0.0013 ppm (0.0085 mg/m ³)	0.00091 ppm (0.0065 mg/m ³)	Based on relative potency from GB ^d
	AEGL-3 (Lethal)	0.053 ppm (0.38 mg/m ³)	0.027 ppm (0.19 mg/m ³)	0.018 ppm (0.13 mg/m ³)	0.0098 ppm (0.070 mg/m ³)	0.0071 ppm (0.051 mg/m ³)	Based on relative potency from GB ^e
VX ^f	AEGL-1 (Non-disabling)	0.000052 ppm (0.00057 mg/m ³)	0.000030 ppm (0.00033 mg/m ³)	0.000016 ppm (0.00017 mg/m ³)	0.0000091 ppm (0.00010 mg/m ³)	0.0000065 ppm (0.000071 mg/m ³)	Derived by relative potency from EC ₅₀ for miosis observed in adult female SD rats exposed to a range of GB vapor concentrations (0.01 to 0.48 mg/m ³) for 10, 60 and 240 min (Mioduszewski et al. 2002b) AND miosis data from secondary and supportive studies of van Helden et al (2001, (Continued)

TABLE 1-39 *Continued*

Agent	Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
							2002), Harvey (1952) and Johns (1952) in marmosets and humans, respectively ^g
	AEGL-2 (Disabling)	0.00065 ppm (0.0072 mg/m ³)	0.00038 ppm (0.0042 mg/m ³)	0.00027 ppm (0.0029 mg/m ³)	0.00014 ppm (0.0015 mg/m ³)	0.000095 ppm (0.0010 mg/m ³)	Derived by relative potency from study of GB vapor exposure to exercising human volunteers exposed to 0.5 mg/m ³ for 30 min; miosis, dyspnea, inhibition of RBC-ChE changes in single fibre electro-myography (SFEMG) (Baker and Sedgwick 1996) ^h
	AEGL-3 (Lethal)	0.0027 ppm (0.029	0.0014 ppm (0.015	0.00091 ppm (0.010	0.00048 ppm (0.0052	0.00035 ppm (0.0038	Derived by relative potency from

mg/m ³)	mg/m ³)	mg/m ³)	mg/m ³)	mg/m ³)	mg/m ³)	experimental SD rat lethality data (LC ₀₁) ⁱ and LC ₅₀); whole-body dynamic exposure to GB vapor concentrations between 2-54 mg/m ³ for 3, 10, 30, 60, 90, 240, and 360 min (Mioduszewski et al. 2000; 2001; 2002a
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^aThe derived AEGL values are for vapor exposures only. Percutaneous absorption of nerve agent vapors is known to be an effective route of exposure; nevertheless, percutaneous vapor concentrations needed to produce similar adverse effects are greater than inhalation vapor concentrations by several orders of magnitude (for agent VX, the percutaneous vapor concentrations needed to produce similar adverse effects are greater than inhalation vapor concentrations by an approximate factor of 10). Thus, the AEGL values presented are considered protective for both inhalation and percutaneous routes of exposure.

^bBased on relative potency equal to that of agent GB (see Section 4.3 and Mioduszewski et al. [1998]).

^cAgent GA is considered approximately one-half as potent as GB in causing lethality; thus, AEGL-3 values for GA are estimated by multiplying each time-specific AEGL-3 value for agent GB by a factor of 2 (see Section 4.3 and Mioduszewski et al. [1998]).

^dAgents GD and GF are considered approximately twice as potent as agents GA and GB for causing miosis, and equipotent to each other. Thus, AEGL-1 and AEGL-2 values are estimated by multiplying each time-specific AEGL-1 or AEGL-2 value for agent GB by a factor of 0.5 (see Section 4.3 and Mioduszewski et al. [1998]).

^eBased on a relative potency for lethality of GD = GF = GB and lethality data of Aas et al. (1985) (which provides a 10-min

AEGL-3 estimate of 0.27 mg/m³ and a 30-min AEGL-3 value of 0.15 mg/m³ and is thus supportive of the GD AEGL-3 estimates derived from relative potency) (see Section 4.3 and Appendix A).

^fBased on relative potency. Agent VX is considered approximately 4 times more potent than agent GB. (See Section 4.3.4, Grob and Harvey [1958], and Sidell and Groff [1974].)

^gDerived from miosis effects noted in young adult female SD rats exposed to agent GB vapor at concentrations (0.010 to 0.48 mg/m³) for 10, 60 and 240 min (Mioduszewski et al. 2002b). VX concentration to achieve same end point estimated by relative potency adjustment presented in footnote *f* above.

^hDerived from transient effects noted in exercising human volunteers exposed to agent GB vapor at 0.5 mg·min/m³ for 30 min (Baker and Sedgwick 1996). VX concentration to achieve same end point estimated by relative potency adjustment presented in footnote *f* above.

ⁱDerived from LC₀₁ values for female Sprague-Dawley rats exposed to GB vapor in dynamic exposure chamber (Mioduszewski et al. 2000, 2001, 2002a). VX concentrations to achieve same end point estimated by relative potency adjustment presented in footnote *f* above.

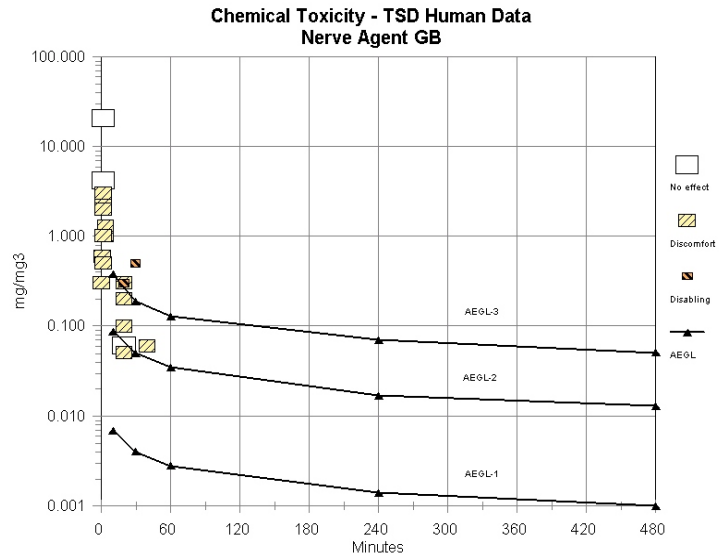


FIGURE 1-1 Comparison of AEGL values for agent GB with human toxicity data.

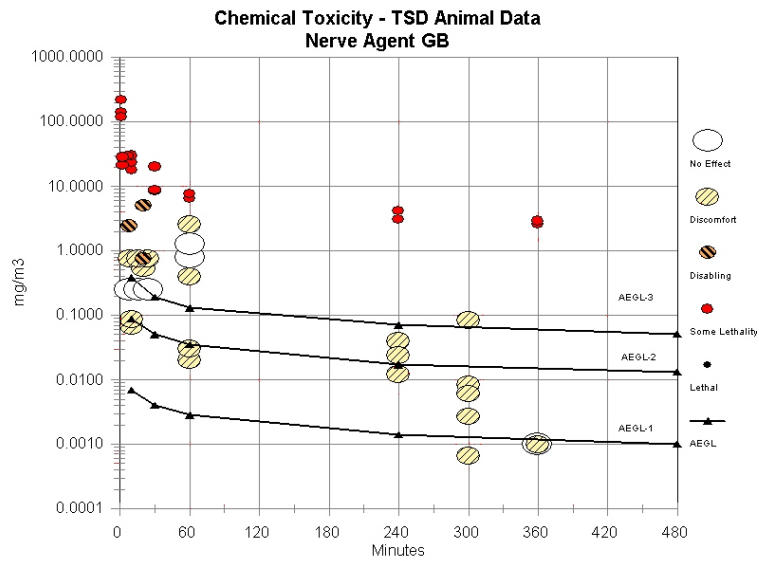


FIGURE 1-2 Comparison of AEGL values for agent GB with animal toxicity data.

levels. Estimates of AEGL-3 for GB for time periods <60 min overlap those considered to cause no effect or discomfort. Therefore, the AEGL estimates for agent GB are considered protective. Although comparative data for the other G agents are quite limited, the animal toxicity data that are available for agent GD and GF (Figures 1-3 and 1-4) further support the conclusion that the current AEGL estimates are protective for all levels of effect.

Agent VX

For the development of AEGL values for Agent VX, toxicity end points specific for each of the three AEGL levels were not available. Therefore, each of the AEGL values was derived from the corresponding critical AEGL study for agent GB, using the relative potency approach and the assumption that the potency of VX was 4 times greater than that of GB. After relative potency adjustment, the 8-h AEGL-3 for VX was scaled from the 6-h experimental data point for GB (see Appendix A).

Cross-comparison of the AEGL estimates for agent VX with available human toxicity data (Figure 1-5) reveals that the AEGL-3 estimates for agent VX are well below reported human exposure levels (median of 3.6 mg/m³) that result in mild, reversible discomfort (headache, chest tightness, and dryness of the mouth) (Koon et al. 1959). Lethal exposures in animals (Figure 1-6) occur 1 to 2 orders of magnitude above AEGL-3 estimates.

These comparisons with available experimental data indicate that the final AEGL estimates for agent VX are protective.

8.2. Comparison with other Standards and Criteria

G Agents

Exposure guidelines for the nerve agents GA, GB, and GD have been established by several organizations. All currently available guidelines are shown in Tables 1-40, 1-41, and 1-42. No comparable values have been established for exposure to agent GF. Values were not found for the following standards and guidelines: ERPGs, PELs, RELs, TLVs, and MAKs.

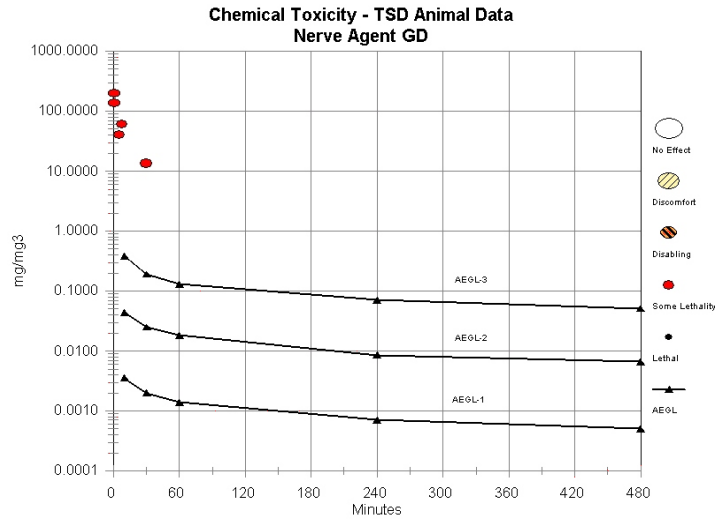


FIGURE 1-3 Comparison of AEGL values for agent GD with animal toxicity data.

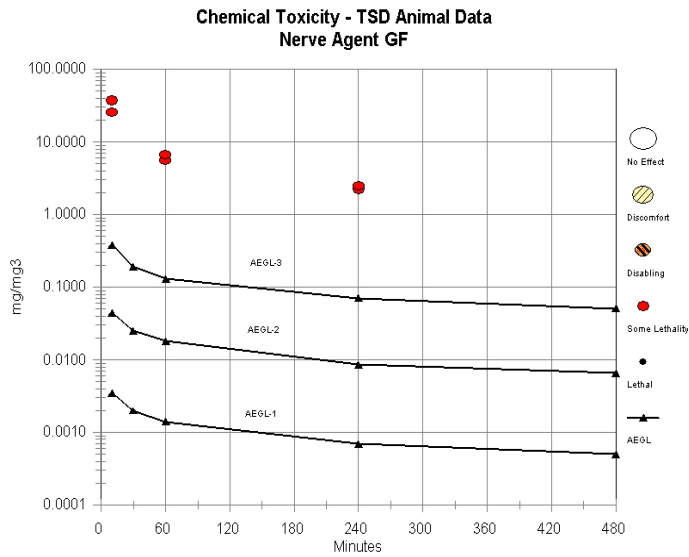


FIGURE 1-4 Comparison of AEGL values for agent GF with animal toxicity data.

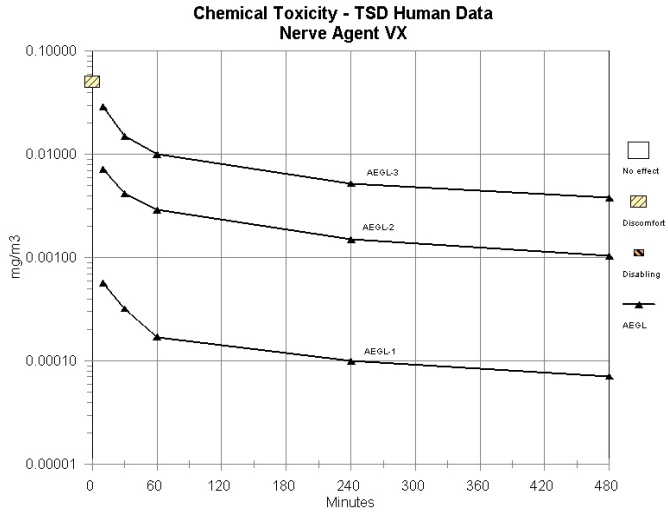


FIGURE 1-5 Comparison of AEGL values for agent VX (RP = 4) with human toxicity data.

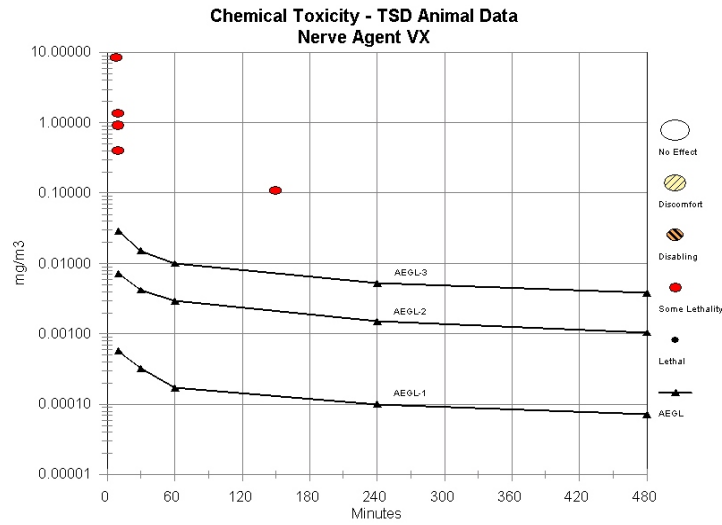


FIGURE 1-6 Comparison of AEGL values for agent VX (RP = 4) with animal toxicity data.

TABLE 1-40 Extant Standards and Guidelines for Nerve Agent GA (mg/m³)^a

Guideline	10 min	30 min	1 h	4 h	8 h	24 h
AEGL-1 ^b	0.0069	0.0040	0.0028	0.0014	0.0010	
AEGL-2 ^b	0.087	0.050	0.035	0.017	0.013	
AEGL-3 ^b	0.76	0.38	0.26	0.14	0.10	
Army IDLH ^c		0.2				
DHHS TWA ^d					0.0001	0.000003

^aExisting exposure guidelines for nerve agents are published in mg/m³; the guidelines are presented here as they exist in the literature and have not been converted to parts per million.

^bPercutaneous absorption of G agent vapor is known to be an effective route of exposure; nevertheless, percutaneous vapor concentrations needed to produce similar adverse effects are greater than inhalation vapor concentrations by several orders of magnitude. Thus, the AEGL values presented are considered protective for both routes of exposure.

^cDA 1997.

^dDHHS 1988; 8-h value is TWA for occupational exposure; 24-h value is TWA for the general population.

At present, the only chemical warfare exposure limits published in the United States for use in civilian community emergency preparedness planning are those developed by the Department of Health and Human Services (DHHS 1988; Thacker 1994). For the agents GA and GB, the current time-weighted average (TWA) to be applied as a no-adverse-health-effect level for 24-h continuous exposure to the general population is 3×10^{-6} mg/m³. For these same agents, the 8-h TWA to be applied as a no-adverse-health-effect level for 8-h continuous workplace exposure for worker populations is 1×10^{-4} mg/m³ (DHHS 1988). Agents GD and GF, which are not part of the unitary stockpile, were not evaluated by DHHS in 1988. As part of a regularly scheduled review process, the Centers for Disease Control and Prevention (CDC) is currently reevaluating the 1988 agent control limits with application of recent risk assessment models and updated scientific data (67 Fed. Reg. 895 [2002]; DHHS 2002). This review is currently (September 2002) in progress, and the CDC has not yet released a final position.

TABLE 1-42 Extant Standards and Guidelines for Nerve Agent GD (mg/m³)^a

Guideline	10 min	30 min	1 h	4 h	8 h	24 h
AEGL-1 ^b	0.0035	0.0020	0.0014	0.00070	0.00050	
AEGL-2 ^b	0.044	0.025	0.018	0.0085	0.0065	
AEGL-3 ^b	0.38	0.19	0.13	0.070	0.051	
Army IDLH ^c		0.06				
Army TWA ^c					0.00003	0.000003

^aExisting exposure guidelines for nerve agents are published in mg/m³; the guidelines are presented here as they exist in the literature and have not been converted to parts per million.

^bPercutaneous absorption of G agent vapor is known to be an effective route of exposure; nevertheless, percutaneous vapor concentrations needed to produce similar adverse effects are greater than inhalation vapor concentrations by several orders of magnitude. Thus, the AEGL values presented are considered protective for both routes of exposure.

^cDA 1997.

The CDC has also established an acute threshold effects level (ATEL) for agent GB (Thacker 1994). An ATEL is a cumulative exposure (Ct) (concentration in mg/m³ multiplied by time in minutes [mg·min/m³]; Ct does not express the amount retained within the organism [Sidell 1997]). These ATELS are considered by CDC to represent “lowest-observed-effect-levels” that “could be exceeded without danger” to the public and form the basis for planning protective actions, such as emergency evacuations, in the Chemical Stockpile Emergency Preparedness Program (CSEPP) of the Federal Emergency Management Agency and the Department of the Army. The Acute Threshold Effect Levels are described by CDC as protective of the general population (including consideration of vulnerable subgroups such as infants, the elderly, and debilitated or ill persons) (Thacker 1994). The ATEL for agent GB is 0.5 mg·min/m³, a protective cumulative exposure at which miosis is not expected to occur in humans (McNamara and Leitnaker 1971). If projected GB concentrations resulting from a release event were to result in Cts > 0.5 mg·min/m³, then the CDC would consider

protective measures (such as evacuation or shelter-in-place) warranted as a means of providing maximal protection to safeguard the general public. The CDC did not designate the exposure time periods applicable to the ATEL.

For comparison to the AEGLs for the G agents, the CDC ATEL for GB can be converted (by direct linear extrapolation) to the following time-specific agent concentrations: 10-min, 0.05 mg/m³; 30-min, 0.017 mg/m³; 1-h, 0.0083 mg/m³; 4-h, 0.0021 mg/m³; or 8-h, 0.0010 mg/m³. These estimated concentrations are all greater than the agent-GB AEGL-1 values (with the exception of the 8-h interval, for which the ATEL and the AEGL-1 values are nominally equal) and less than the agent-GB AEGL-2 values. The estimated AEGL-1 and AEGL-2 values are thus in keeping with the CDC ATEL for agent GB (Thacker 1994).

Acute threshold effects levels have not been established for agents GA, GD, and GF.

Agent VX

Exposure guidelines for the nerve agent VX have been established by several organizations. All currently available guidelines are shown in Table 1-43.

At present, the only chemical warfare agent exposure limits published in the United States for use in civilian community emergency preparedness planning are those developed by the Department of Health and Human Services (DHHS 1988; Thacker 1994). For agent VX, the current time-weighted average (TWA) to be applied as a no-adverse-health-effect level for 24-h continuous exposure to the general population is 3×10^{-6} mg/m³. The 8-h TWA to be applied as a no-adverse-health-effect level for 8-h continuous workplace exposure for worker populations is 1×10^{-5} mg/m³ (DHHS 1988). As stated earlier, this review is currently (September 2002) in progress, and the CDC has not yet released a final position.

ATELs have also been developed by the CDC for agent VX (Thacker 1994). The ATEL value for agent VX is 0.4 mg·min/m³; the CDC did not designate specific exposure time periods applicable to the ATEL. If projected VX concentrations resulting from a release event resulted in VX Cts > 0.4 mg·min/m³, the CDC would consider protective measures (such as evacuation or shelter-in-place) warranted as a means of providing maximal protection to safeguard the general public.

For comparison to AEGLs for VX, the CDC ATEL for VX can be converted by extrapolation to the following time-specific agent concentrations: 10-min, 0.04 mg/m³; 30-min, 0.013 mg/m³; 1-h, 0.0067 mg/m³; 4-h, 0.0017 mg/m³; or 8-h, 0.00083 mg/m³. These values are in excess of AEGL-2 estimates for VX exposure durations ≤ 1 h. They are approximately equivalent to AEGL-2 estimates for VX exposure durations ≥ 4 h.

Because the VX AEGLs are derived in this report by comparison to the AEGL for agent GB, it should be noted that the Acute Threshold Effects Level for agent GB is 0.5 mg-min/m³.

8.3. Data Adequacy and Research Needs

G Agents

Confidence in the AEGL-2 values is limited by the sparse human experimental data for all AEGL-specific time frames and G-series agents. The human data from which the AEGL-2 values were derived were limited by short exposure times (30 min). The AEGL-1 values for agent GB derived from rat data (Mioduszewski et al. 2002b) are supported by 5-h exposure studies conducted on marmosets (van Helden et al. 2001, 2002) and 20-min exposure studies conducted with human volunteers (Harvey 1952; Johns 1952).

Observed differences among studies in identifying the toxicity threshold for low-dose exposures may be due to differences in individual sensitivities and breathing rates among the test populations, the steepness of the dose-response curve, and/or differences in experimental protocols or analytical methods. These variables need further characterization.

Further data analysis and experimentation are needed to more fully understand the degree of susceptibility to lethal exposure exhibited by female populations of test animals. Interspecies susceptibility could be more fully characterized by determining if similar results can be obtained under the same protocol with different test species (particularly nonhuman primates).

The scarcity of dose-response data for agents GA, GD, and GF forces the AEGL analysis to rely on assumptions of relative potency. Thus, AEGL values for these three compounds are largely derivative (with the exception of 10-min and 30-min AEGL-3 values for agent GD, which are confirmed by short-term experimental lethality data for Wistar rats provided by Aas et. al. [1985]).

The relative potency assumptions for estimating AEGL-1, AEGL-2, and AEGL-3 values for agents GA, GD, and GF from the available database for agent GB need experimental confirmation.

Additional research is needed to compare and contrast effects of all nerve agents on noncholinergic neurotransmitters and neurotransmitter receptor sites for correlating reported effects observed in rat hippocampal cells *in vitro* (see Section 4.2) with whole-organism responses to acutely toxic dose levels. Extrapolation of findings from such neurophysiological research to whole organisms may allow a more refined quantitative analysis of the nerve agent relative potency.

Agent VX

The available experimental human acute toxicity data for agent VX are limited by the short exposure times (7 min or less), uncontrolled atmospheres for inhalation studies, inadequate exposure protocols, or inappropriate exposure routes. Longer-term inhalation exposure data would be useful for deriving more reliable AEGL-1 values. The Bramwell et al. (1963) study is a flawed and suspect source and could not be applied in deriving exposure estimates.

Only a single nonlethal animal inhalation toxicity study has been conducted on agent VX (Crook et al. 1983). The results of this animal study are considered nonverifiable and are thus not adequate for deriving an AEGL-1 or an AEGL-2 for VX.

Credible acute animal lethality data for inhalation vapor exposures to agent VX are available only in the form of LC_{t,50} values for exposure times of 10 min or less for two species, mice and goats (Koon et al. 1960, as cited in NRC 1997). Available animal lethality data for VX do not cover the time periods relevant for deriving AEGL-3 values. A comprehensive animal lethality data set is needed for directly deriving AEGL-3 estimates.

Confidence in the AEGL values derived for agent VX is limited by sparse human inhalation data for the AEGL-specific time frames and a definitive assessment of the exposure-response relationship for humans exposed to VX vapor. Derivation of AEGL-1, AEGL-2, and AEGL-3 values using the relative potency method and comparison with agent GB is limited by uncertainties associated with the derivation of the values for agent GB as well as uncertainties associated with estimating the potency of VX relative to that of GB.

Further experimentation is needed to more fully understand the degree of sensitivity to lethal exposure exhibited by female populations of test animals. Interspecies sensitivity could be more fully characterized by determining if similar results can be obtained with different test species (particularly nonhuman primates).

It is noted that specific experimental focus should be put on obtaining data that would reduce uncertainties regarding the relative potency of agents GB and VX, or the potency of agent VX, for critical effects such as miosis, rhinorrhea, and lethality; such studies could be adequately performed on a limited test population and scale. Tests should be performed with a single species (preferably laboratory rat), both genders, and should involve vapor exposures over the range of 10 min to 8 h (minimally, for 10 min, 1 h, and 6 h). It is further recommended that dosages selected begin slightly below the recommended AEGL-1 estimate and increase in 10-fold increments to include the anticipated LCt_{50} . Clinical effects should be observed, and histopathology and necropsy performed on a sample from each Ct group.

In addition, research characterizing the emission profile of vapor and aerosols expected during VX release events is needed for estimation of potential differential exposure and toxicity. Agent VX parameters needing quantification by modern methods and protocols include: generation and yield of vapors versus aerosols; particle size ranges; atmospheric half-times; deposition rates; and rates of degradation in air under various states of humidity, temperature, UV, et cetera. Until these parameters can be more fully characterized to inform the discussion of differential toxicity between VX vapors and aerosols, AEGL determinations will be necessarily based on the assumption of exposure to VX vapor.

9. REFERENCES

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Appendix

APPENDIX A

DERIVATION OF AEGL VALUES

Derivation of AEGL-1

Key study:	Mioduszewski et al. (2002b). Miosis measured in adult female SD rats exposed to a range of GB vapor concentrations for 10, 60, and 240 min. At 10 min, $N = 52$ females; at 60 min, $N = 35$ females; at 240 min, $N = 55$ females.
Toxicity end point:	EC ₅₀ for miosis (defined as “a postexposure pupil diameter 50% or less of the preexposure pupil diameter”) observed in adult female SD rats
EC ₅₀ for GB:	10-min EC ₅₀ = 0.068 mg GB/m ³ 60 min EC ₅₀ = 0.020 mg GB/m ³ 240 min EC ₅₀ = 0.012 mg GB/m ³
Scaling:	$C^n \times t = k$ (ten Berge et al. 1986). Current analyses based on a linear regression of the lethality and miosis data for female SD rats. The LC ₀₁ of GB to female Sprague-Dawley rats (Mioduszewski et al. 2000, 2001, 2002a) yields an n value of 1.93 with an r^2 of 0.9948, while miosis (female Sprague-Dawley rats; Mioduszewski et al. 2002b) yields an n value of 2.00 with an r^2 of 0.4335 (see Appendix B). The anticholinesterase mechanism of mammalian toxicity for nerve agents is known, and all endpoints observed in human and animal studies represent a response continuum to anticholinesterase exposure. Accordingly, it is valid to apply an n value derived from compound-specific lethality data to time scaling for non-lethal effects, and an n value derived for miosis, to consideration of other toxic effects resulting from anticholinesterase exposure. This position is consistent with that of the recently published Science Policy

of the EPA Office of Pesticide Programs (EPA 2000). Therefore, $n = 2$ is used as the scaling function for all AEGL time point derivations.

Uncertainty

factors:

Interspecies: 1 (miosis response to GB vapor is similar across mammal species)

Intraspecies: 10 (adjustment for possible susceptible individuals)

Calculations:

$$(C/\text{uncertainty factors})^2 \times t = k$$

10-min to 30-min extrapolation

$$([0.068 \text{ mg/m}^3]/10)^2 \times (10/60) \text{ h} = k$$

$$7.7 \times 10^{-6} \text{ mg/m}^3 \text{ h} = k$$

4-h to 8-h extrapolation

$$([0.012 \text{ mg/m}^3]/10)^2 \times 4 \text{ h} = k$$

$$5.8 \times 10^{-6} \text{ mg/m}^3 \text{ h} = k$$

10-min AEGL-1:

$$C = 0.068 \text{ mg/m}^3$$

$$10\text{-min AEGL-1} = (0.068 \text{ mg/m}^3)/10 = 0.0068 \text{ mg/m}^3$$

30-min AEGL-1:

$$C^2 \times (0.5 \text{ h}) = (7.7 \times 10^{-6} \text{ mg/m}^3) \times \text{h}$$

$$30\text{-min AEGL-1} = 0.0039 \text{ mg/m}^3$$

1-h AEGL-1:

$$C = 0.020 \text{ mg/m}^3$$

$$1\text{-h AEGL-1} = (0.020 \text{ mg/m}^3)/10 = 0.0020 \text{ mg/m}^3$$

4-h AEGL-1:

$$C = 0.012 \text{ mg/m}^3$$

$$4\text{-h AEGL-1} = (0.012 \text{ mg/m}^3)/10 = 0.0012 \text{ mg/m}^3$$

8-h AEGL-1:

$$C^2 \times (8 \text{ h}) = (5.8 \times 10^{-6} \text{ mg/m}^3) \times \text{h}$$

$$8\text{-h AEGL-1} = 0.00085 \text{ mg/m}^3 = 0.001 \text{ mg/m}^3$$

Derivation of AEGL-1 for Agent GB (Sarin) from Human Data Set

Key study:

Harvey (1952) (see also Johns [1952])

Toxicity end point:	Rhinorrhea, headache, tightness in chest, cramps, nausea, and miosis (mean maximal decrease in pupil diameter) observed in human volunteers exposed to GB at 0.05 mg/m ³ for 20 min. Multiple observations at GB vapor Cts ranging from 0.0 to 6.0 mg·min/m ³ .
LOAEL for GB:	0.05 mg/m ³ for 20 min
Scaling:	$C^n \times t = k$ (ten Berge et al. 1986). Current analyses based on same logic as for AEGL-1 derivation from female SD rat miosis data of Mioduszewski et al (2002b).
Uncertainty factors:	Interspecies: 1 (human data were used) Intraspecies: 10 (adjustment for possible susceptible individuals)
Calculations:	$(C/\text{uncertainty factors})^2 \times t = k$ $([0.05 \text{ mg/m}^3]/10)^2 \times (20/60) \text{ h} = k$ $8.25 \times 10^{-6} \text{ mg/m}^3 \times \text{h} = k$
10-min AEGL-1:	$C^2 \times (0.167 \text{ h}) = (8.25 \times 10^{-6} \text{ mg/m}^3) \times \text{h}$ $C = 0.0069 \text{ mg/m}^3$
30-min AEGL-1:	$C^2 \times (0.5 \text{ h}) = (8.25 \times 10^{-6} \text{ mg/m}^3) \times \text{h}$ $C = 0.0040 \text{ mg/m}^3$
1-h AEGL-1:	$C^2 \times (1 \text{ h}) = (8.25 \times 10^{-6} \text{ mg/m}^3) \times \text{h}$ $C = 0.0028 \text{ mg/m}^3$
4-h AEGL-1:	$C^2 \times (4 \text{ h}) = (8.25 \times 10^{-6} \text{ mg/m}^3) \times \text{h}$ $C = 0.0014 \text{ mg/m}^3$
8-h AEGL-1:	$C^2 \times (8 \text{ h}) = (8.25 \times 10^{-6} \text{ mg/m}^3) \times \text{h}$ $C = 0.0010 \text{ mg/m}^3$

Derivation of AEGL-2 for Agent GB (Sarin)

Key study: Baker and Sedgwick (1996). Eight healthy male servicemen exposed to GB at 0.5 mg/m³ for 30 min in an exposure chamber. During the exposure, test subjects walked at a rate of 96 paces per minute and breathed normally.

Toxicity end point: Observed effects include miosis in eight of eight subjects, dyspnea and photophobia in some individuals (number not given), inhibition of RBC-ChE to approximately 60% (range of 54-66%) of individual baseline at 3 h and 3 d postexposure in eight of eight subjects, and small but measurable changes in single fibre electromyography (SFEMG) of the forearm that were detectable in the lab between 4 and 15 mo postexposure (five of eight subjects). Respiratory effects resolved within minutes; ocular effects resolved within 48 h. Electromyographic changes considered sub-clinical by study authors. No clinical effects.

GB concentration: 0.5 mg/m³ for 30 min

Scaling: $C^n \times t = k$ (ten Berge et al. 1986); $n=2$, see earlier discussion of AEGL-1 scaling

Uncertainty factors: Interspecies: 1 (human data were used)
Intraspecies: 10 (for possible susceptible individuals)

Calculations: $(C/\text{uncertainty factors})^2 \times t = k$

$$([0.5 \text{ mg/m}^3]/10)^2 \times 0.5 \text{ h} = k$$

$$0.0013 \text{ mg/m}^3 \times \text{h} = k$$

10-min AEGL-2: $C^2 \times (0.167 \text{ h}) = (0.0013 \text{ mg/m}^3) \times \text{h}$
 $C = 0.087 \text{ mg/m}^3$

30-min AEGL-2: $C^2 \times (0.5 \text{ h}) = (0.0013 \text{ mg/m}^3) \times \text{h}$

$$C = 0.050 \text{ mg/m}^3$$

$$\begin{aligned} 1\text{-h AEGL-2: } & C^2 \times (1 \text{ h}) = (0.0013 \text{ mg/m}^3) \times \text{h} \\ & C = 0.035 \text{ mg/m}^3 \end{aligned}$$

$$\begin{aligned} 4\text{-h AEGL-2: } & C^2 \times (4 \text{ h}) = (0.0013 \text{ mg/m}^3) \times \text{h} \\ & C = 0.017 \text{ mg/m}^3 \end{aligned}$$

$$\begin{aligned} 8\text{-h AEGL-2: } & C^2 \times (8 \text{ h}) = (0.0013 \text{ mg/m}^3) \times \text{h} \\ & C = 0.0125 \text{ mg/m}^3 \end{aligned}$$

Derivation of AEGL-3 for Agent GB (Sarin)

Key study: Mioduszewski et al. (2000, 2001, 2002a). Fourteen-day acute lethal toxicity of GB to female Sprague-Dawley rats was evaluated for time periods of 10, 30, 60, 90, 240, and 360 min in a whole-body dynamic chamber. Ten females were used for each concentration-time (Ct) combination, and 50 females were used for each time point. GB concentrations ranged from about 2 to 54 mg/m³.

Toxicity end point: Fourteen-day acute lethal toxicity of GB to female Sprague-Dawley rats. Female rats were reported to be more sensitive to GB vapor toxicity than males over the range of exposure concentrations and durations studied. Gender differences for lethality are reported by Mioduszewski et al. (2000, 2001, 2002a) to be statistically significant at $p < 0.01$. Probit analysis (MINITAB, version 13) presented in Mioduszewski et al. (2000) gave the following 14-d LC₅₀ and LC₀₁ values for female rats:

LC₅₀
 18.1 mg/m³ for 10 min in female rats
 8.51 mg/m³ for 30 min in female rats
 6.39 mg/m³ for 60 min in female rats

3.03 mg/m³ for 4 h in female rats
 2.63 mg/m³ for 6 h in female rats

LC₀₁

11.54 mg/m³ for 10 min in female rats
 5.84 mg/m³ for 30 min in female rats
 4.01 mg/m³ for 60 min in female rats
 2.09 mg/m³ for 4 h in female rats
 1.76 mg/m³ for 6 h in female rats

Scaling: $C^n \times t = k$ (ten Berge et al. 1986); $n=2$, see earlier discussion of AEGL-1 scaling; to extrapolate from 6-h value to an 8-h estimate. Scaling to derive 8-h LC₀₁.

Uncertainty factors:

Interspecies: 3 (female rat data); full default value of 10 not considered appropriate since the mechanism of toxicity in rats and humans is the same, cholinesterase inhibition.
 Intraspecies: 10 (for possible susceptible individuals)

Calculations: $(C/\text{uncertainty factors})^2 \times t = k$

$$([1.76 \text{ mg/m}^3]/30)^2 \times 6.0 \text{ h} = k$$

$$0.021 \text{ mg/m}^3 \times \text{h} = k$$

10-min AEGL-3: $C = 11.54 \text{ mg/m}^3$
 10-min AEGL-3 = $(11.54 \text{ mg/m}^3)/30 = 0.38 \text{ mg/m}^3$

30-min AEGL-3: $C = 5.84 \text{ mg/m}^3$
 30-min AEGL-3 = $(5.84 \text{ mg/m}^3)/30 = 0.194 \text{ mg/m}^3$

1-h AEGL-3: $C = 4.01 \text{ mg/m}^3$
 1-h AEGL-3 = $(4.01 \text{ mg/m}^3)/30 = 0.133 \text{ mg/m}^3$

4-h AEGL-3: $C = 2.09 \text{ mg/m}^3$
 4-h AEGL-3 = $(2.09 \text{ mg/m}^3)/30 = 0.069 = 0.070 \text{ mg/m}^3$

$$8\text{-h AEGL-3: } C^2 \times (8 \text{ h}) = (0.021 \text{ mg/m}^3) \times \text{h}$$

$$8\text{-h AEGL-3} = 0.051 \text{ mg/m}^3$$

Derivation of AEGL-3 for Agent GD (Alternate Estimate)

Key study: Aas et al. (1985)

Toxicity end point: Threshold for mortality in rats estimated to be 335 mg·min/m³ for an exposure period of 16 min. The lethal threshold is equivalent to an exposure to a GD concentration of 21 mg/m³ for 16 min.

Scaling: Data insufficient to derive an *n* value from the Aas et al. (1985) study. The anticholinesterase mechanism of mammalian toxicity for nerve agents is known, and all end points observed in human and animal studies represent a response continuum to anticholinesterase exposure. Accordingly, it is valid to apply an *n* value derived from the compound-specific lethality and miosis data for nerve agent GB (Mioduszewski et al. 2000, 2002, 2002a,b) to time scaling for all AEGL effects. This position is consistent with that of the recently published science policy of the EPA Office of Pesticide Programs (EPA 2000). Therefore, *n* = 2 is used as the scaling function for all AEGL time point derivations for the G-series nerve agents.

Uncertainty factors: Interspecies: 10 (sparse data set for agent GD)
Intraspecies: 10 (for possible susceptible individuals; sparse data set for agent GD)

Calculations: $(C/\text{uncertainty factors})^2 \times t = k$
 $([21 \text{ mg/m}^3]/100)^2 \times (16/60) \text{ h} = 0.012 \text{ mg/m}^3 \times \text{h}$

$$10\text{-min AEGL-3: } C^2 \times (0.167) = (0.012 \text{ mg/m}^3) \times \text{h}$$

$$10\text{-min AEGL-3} = 0.27 \text{ mg/m}^3$$

$$30\text{-min AEGL-3: } C^2 \times (0.5 \text{ h}) = (0.012 \text{ mg/m}^3) \times \text{h}$$

$$30\text{-min AEGL-3} = 0.15 \text{ mg/m}^3$$

Derivation of AEGL-1 for Agent VX Vapor from Agent GB Toxicity Data

Key study: Mioduszewski et al. (2002b). Miosis measured in adult female SD rats exposed to a range of GB vapor concentrations for 10, 60, and 240 min. At 10 min, $N = 52$ females; at 60 min, $N = 35$ females; at 240 min, $N = 55$ females.

Toxicity end point: EC_{50} for miosis (defined as “a postexposure pupil diameter 50% or less of the preexposure pupil diameter”) observed in adult female SD rats

EC_{50} for GB: 10-min $EC_{50} = 0.068 \text{ mg/m}^3$
60-min $EC_{50} = 0.020 \text{ mg/m}^3$
240-min $EC_{50} = 0.012 \text{ mg/m}^3$

Estimated EC_{50} for VX: 10-min $EC_{50} = 0.017 \text{ mg/m}^3$ (based on relative potency of 4 as described in Section 4.3)
60-min $EC_{50} = 0.005 \text{ mg/m}^3$ (based on relative potency of 4 as described in Section 4.3)
240-min $EC_{50} = 0.003 \text{ mg/m}^3$ (based on relative potency of 4 as described in Section 4.3)

Scaling: $C^n \times t = k$ (ten Berge et al. 1986). Current analyses based on a linear regression of the lethality and miosis data for female SD rats. The LC_{01} of GB to female Sprague-Dawley rats (Mioduszewski et al. 2000, 2001, 2002a) yields an n value of 1.93 with an r^2 of 0.9948, while miosis (female Sprague-Dawley rats) (Mioduszewski et al. 2002b) yields an n value of 2.00 with an r^2 of 0.4335. The anticholinesterase mechanism of mammalian toxicity for nerve agents is

known, and all end points observed in human and animal studies represent a response continuum to anticholinesterase exposure. Accordingly, it is valid to apply an n value derived from compound-specific lethality data to time scaling for nonlethal effects, and an n value derived for miosis to consideration of other toxic effects resulting from anticholinesterase exposure. This position is consistent with that of the recently published science policy of the EPA Office of Pesticide Programs (EPA 2000). Therefore, $n = 2$ is used as the scaling function for all AEGL time point derivations.

Uncertainty factors:

Interspecies: 1 (miosis response to GB vapor similar across mammal species)
Intraspecies: 10 (adjustment for possible susceptible individuals)

Modifying factor:

3 (for sparse VX data base)

Calculations:

$$(C/\text{uncertainty factors})^2 \times t = k$$

10-min to 30-min extrapolation

$$([0.017 \text{ mg/m}^3]/30)^2 \times (10/60) \text{ h} = k$$

$$5.0 \times 10^{-8} \text{ mg/m}^3 \times \text{h} = k$$

4-h to 8-h extrapolation

$$([0.003 \text{ mg/m}^3]/30)^2 \times 4 \text{ h} = k$$

$$4.0 \times 10^{-8} \text{ mg/m}^3 \times \text{h} = k$$

10-min AEGL-1:

$$C = 0.017 \text{ mg/m}^3$$

$$10\text{-min AEGL-1} = (0.017 \text{ mg/m}^3)/30 = 0.00057 \text{ mg/m}^3$$

30-min AEGL-1:

$$C^2 \times (0.5 \text{ h}) = (5.0 \times 10^{-8} \text{ mg/m}^3) \times \text{h}$$

$$30\text{-min AEGL-1} = 0.00033 \text{ mg/m}^3$$

1-h AEGL-1:

$$C = 0.0050 \text{ mg/m}^3$$

$$1\text{-h AEGL-1} = (0.0050 \text{ mg/m}^3)/30 = 0.00017 \text{ mg/m}^3$$

4-h AEGL-1: $C = 0.003 \text{ mg/m}^3$
 4-h AEGL-1 = $(0.003 \text{ mg/m}^3)/30 = 0.00010 \text{ mg/m}^3$

8-h AEGL-1: $C^2 \times (8 \text{ h}) = (4.0 \times 10^{-8} \text{ mg/m}^3) \times \text{h}$
 8-h AEGL-1 = 0.000071 mg/m^3

Derivation of AEGL-2 for Agent VX Vapor from Agent GB Toxicity Data

Key Study: Baker and Sedgwick (1996)

Toxicity end point: Miosis in all subjects, dyspnea and photophobia in some individuals, inhibition of RBC-ChE to approximately 60% of individual baseline at 3 h and 3 d post-exposure, and small but measurable changes in single fibre electromyography (SFEMG) of the forearm that were detectable in the lab between 4 and 15 mo post-exposure. Baker and Sedgwick (1996) considered these SFEMG changes to be subclinical and reversible. Current analysis considered SFEMG changes to be a protective interpretation of the AEGL-2 definition.

GB concentration: 0.5 mg/m^3 for 30 min

Estimated VX concentration: 0.125 mg/m^3 for 30 min (based on relative potency of 4 for miosis and mild effects as described in Section 4.3)

Scaling: $C^n \times t = k$ (ten Berge et al. 1986). The n value of 2 used for agent GB is also used for agent VX (see text)

Uncertainty factors: Interspecies: 1 (human data were used)
 Intraspecies: 10 (adjustment for possible susceptible individuals)

Modifying

factor (MF): 3 (for sparse VX data base)

Calculations: $(C/[\text{uncertainty factors} \times \text{MF}])^2 \times t = k$

$$([0.125 \text{ mg/m}^3]/[10 \times 3])^2 \times 0.5 \text{ h} = 8.7 \times 10^{-6} \text{ mg/m}^3 \times \text{h}$$

10-min AEGL-2: $([8.7 \times 10^{-6} \text{ mg/m}^3]/0.1667 \text{ h})^{1/2} = 0.0072 \text{ mg/m}^3$

30-min AEGL-2: $([8.7 \times 10^{-6} \text{ mg/m}^3]/0.5 \text{ h})^{1/2} = 0.0042 \text{ mg/m}^3$

1-h AEGL-2: $([8.7 \times 10^{-6} \text{ mg/m}^3]/1 \text{ h})^{1/2} = 0.0029 \text{ mg/m}^3$

4-h AEGL-2: $([8.7 \times 10^{-6} \text{ mg/m}^3]/4 \text{ h})^{1/2} = 0.0015 \text{ mg/m}^3$

8-h AEGL-2: $([8.7 \times 10^{-6} \text{ mg/m}^3]/8 \text{ h})^{1/2} = 0.00104 \text{ mg/m}^3$

Derivation of AEGL-3 for Agent VX Vapor from Agent GB Toxicity Data

Key study: Mioduszewski et al. (2000, 2001, 2002a)

Toxicity

end point: GB-induced lethality in female Sprague-Dawley rats

GB LC₅₀: 18.1 mg/m³ for 10 min
8.51 mg/m³ for 30 min
6.39 mg/m³ for 60 min
3.03 mg/m³ for 4 h
2.63 mg/m³ for 6 h

GB LC₀₁: 11.54 mg/m³ for 10 min
5.84 mg/m³ for 30 min
4.01 mg/m³ for 60 min
2.09 mg/m³ for 4 h
1.76 mg/m³ for 6 h

VX estimated

LC ₀₁ :	2.89 mg/m ³ for 10 min 1.46 mg/m ³ for 30 min 1.00 mg/m ³ for 1 h 0.52 mg/m ³ for 4 h 0.44 mg/m ³ for 6 h (relative potency of 4 when compared with GB; see Section 4.3)
Scaling:	$C^n \times t = k$ (ten Berge et al. 1986). The n value of 2 used for agent GB is also used for agent VX (see text) to derive the 8-h AEGL-3 from the 6-h LC ₀₁ .
Uncertainty factors:	Interspecies: 3 (rat data) Intraspecies: 10 (adjustment for possible susceptible individuals)
Modifying factor (MF):	3 (for sparse VX data base)
Calculations:	$(C/[\text{uncertainty factors} \times \text{MF}])^2 \times t = k$ $([0.44 \text{ mg/m}^3]/[10 \times 3 \times 3])^2 \times 6 \text{ h} =$ $1.16 \times 10^{-4} \text{ mg/m}^3 \times \text{h}$
10-min AEGL-3:	$(2.89 \text{ mg/m}^3)/100 = 0.029 \text{ mg/m}^3$
30-min AEGL-3:	$(1.46 \text{ mg/m}^3)/100 = 0.015 \text{ mg/m}^3$
1-h AEGL-3:	$(1.00 \text{ mg/m}^3)/100 = 0.010 \text{ mg/m}^3$
4-h AEGL-3:	$(0.52 \text{ mg/m}^3)/100 = 0.0052 \text{ mg/m}^3$
8-h AEGL-3:	$([1.16 \times 10^{-4} \text{ mg/m}^3]/8 \text{ h})^{1/2} = 0.0038 \text{ mg/m}^3$

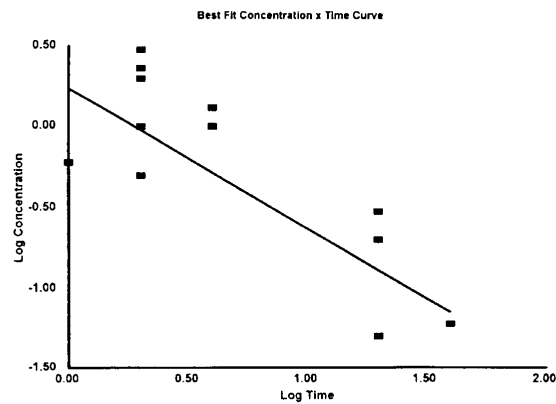
APPENDIX B

Concentration-Time Curve for Sarin-Induced Miosis in Humans and Lethality in SD Rats

Data from Johns (1952), McKee and Woolcott (1949), and Baker and Sedgwick (1996) were used to assess the concentration-time relationship for agent GB-induced miosis

Time	Conc.	Log Time	Log Conc.	Regression Output:	
20	0.05	1.3010	-1.3010	Intercept	0.2371
2	0.5	0.3010	-0.3010	Slope	-0.8629
2	1	0.3010	0.0000	R Squared	0.6704
20	0.2	1.3010	-0.6990	Correlation	-0.8188
2	2	0.3010	0.3010	Observations	16
4	1	0.6021	0.0000		
2	2.3	0.3010	0.3617		
4	1.3	0.6021	0.1139		
20	0.3	1.3010	-0.5229		
2	3	0.3010	0.4771		
1	0.6	0.0000	-0.2218		
40	0.06	1.6021	-1.2218		
20	0.05	1.3010	-1.3010		
2	0.5	0.3010	-0.3010		
1	0.6	0.0000	-0.2218		
40	0.06	1.6021	-1.2218		

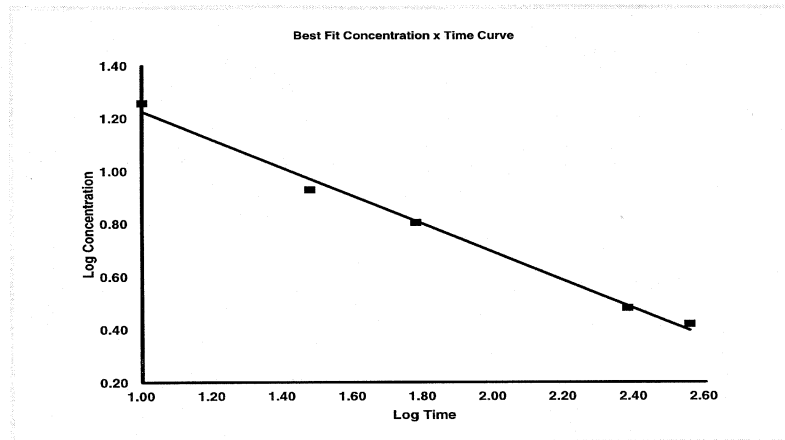
n = 1.16
k = 1.88



Data from Mioduszewski et al. (2000) were used to assess the concentration-time relationship for lethality (LC50) in female Sprague-Dawley rats exposed to GB vapor

Time	Conc.	Log Time	Log Conc.	Regression Output:	
10	18.1	1.0000	1.2577	Intercept	1.7577
30	8.51	1.4771	0.9299	Slope	-0.5325
60	6.39	1.7782	0.8055	R Squared	0.9927
240	3.03	2.3802	0.4814	Correlation	-0.9964
360	2.63	2.5563	0.4200	Observations	5

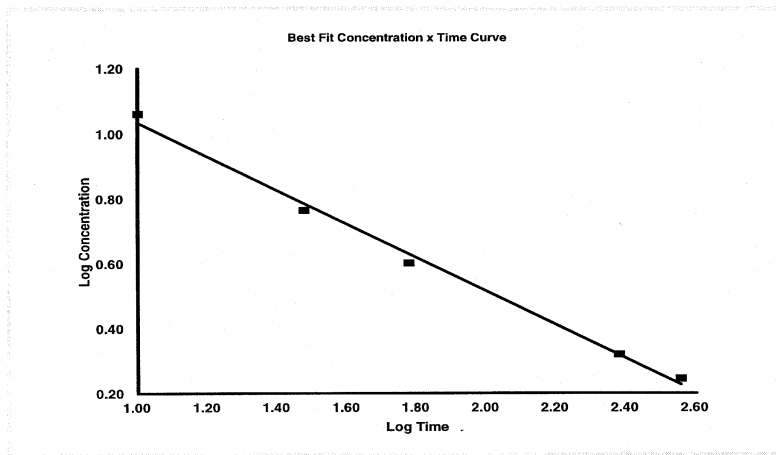
n = 1.88
k = 2000.81



Data from Mioduszewski et al. (2000) were used to assess the concentration-time relationship for lethality (LC01) in female Sprague-Dawley rats exposed to GB vapor

Time	Conc.	Log Time	Log Conc.	Regression Output:	
10	11.54	1.0000	1.0622	Intercept	1.5532
30	5.84	1.4771	0.7664	Slope	-0.5188
60	4.01	1.7782	0.6031	R Squared	0.9948
240	2.09	2.3802	0.3201	Correlation	-0.9974
360	1.76	2.5563	0.2455	Observations	5

n = 1.93
k = 986.04

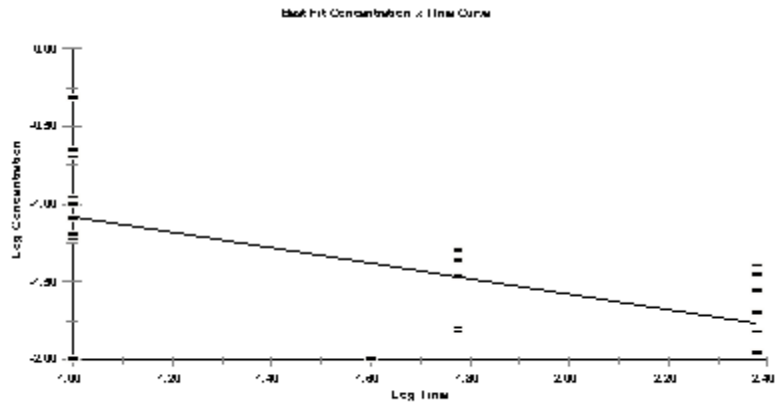


Chemical: GB Vapor
 Study: Mioduszewski et al., 2002b
 Species: SD Rat
 Gender: Female

Time	Concentration	Log Time	Log Concentration	Regression Output	
10	0.010	1.0000	-2.0000	Intercept	-0.5756
10	0.060	1.0000	-1.2218	Slope	-0.5010
10	0.063	1.0000	-1.2007	R2	0.4335
10	0.080	1.0000	-1.0969	Correlation	-0.6584
10	0.100	1.0000	-1.0000	Observations	24
10	0.110	1.0000	-0.9586		
10	0.200	1.0000	-0.6990		
10	0.220	1.0000	-0.6576		
10	0.480	1.0000	-0.3188		
40	0.010	1.6021	-2.0000		
60	0.015	1.7782	-1.8239		
60	0.016	1.7782	-1.7959		
60	0.034	1.7782	-1.4685		
60	0.043	1.7782	-1.3665		
60	0.050	1.7782	-1.3010		
240	0.011	2.3802	-1.9586		
240	0.011	2.3802	-1.9586		
240	0.015	2.3802	-1.8239		
240	0.015	2.3802	-1.8239		
240	0.019	2.3802	-1.7212		
240	0.020	2.3802	-1.6990		
240	0.027	2.3802	-1.5622		
240	0.035	2.3802	-1.4559		
240	0.040	2.3802	-1.3979		

$n = 2.00$

$k = 0.07$



APPENDIX C

Benchmark Exposure Analysis of GB Vapor Lethality Data for Female SD Rats

In August 2001, Mioduszewski et al. (2001) published their final report describing the experimental results of lethality studies in male and female adult SD rats exposed to varying Cts of GB vapor in a whole-body dynamic exposure chamber. Preliminary results of the experiments performed by Mioduszewski and his colleagues (documented in Mioduszewski et al. [2000]) were the basis for the AEGL-3 estimates submitted to the National Advisory Committee in 2000 that attained interim status.

A benchmark exposure calculation has been performed on the female rat 14-d vapor lethality data presented in the Mioduszewski et al. (2001) report, in accordance with guidance provided in the standing operating procedures (NRC 2001; Section 2.2.2.3.3). For comparison, a Number-Cruncher Statistical System analysis has also been completed.

There appears to be some degree of controversy around using the benchmark dose approach for acute lethality data. The SOP workgroup will address this issue in the future.

There are eight models that accept dichotomous data in the benchmark dose (BMD) software package available on the EPA Web site (<http://cfpub.epa.gov/ncea/cfm/bmds.cfm>); gamma, logistic, log-log multistage, probit, log-probit, quantal-linear, quantal-quadratic, and Weibull. Evaluations were performed with all eight (multiplied by five time points, times the 5% response for the 95% lower confidence limit (LCL) and the 1% maximum likelihood estimate (MLE), as per the SOP). The Weibull and gamma programs would not run with the input data; contact with the EPA site Webmaster eventually revealed, through systems testing, that these two models require entry of a zero-concentration effect value in order to converge. The Mioduszewski et al. (2001) data set does not contain any zero-concentration effects data, and its addition would be an artificial alteration of the data set. It was concluded that the content of the Mioduszewski et al. (2001) data set is not compatible with requirements of the Weibull and gamma models; thus no analyses of the vapor lethality data were performed with these two models.

Tables C-1a,b and C-2 summarize the statistical results of this benchmark exposure analysis. Table C-1a,b is a summary of LC₀₁ values obtained from all the BMD software routines; the ones on the low-er tier of the table (logistic, multistage, quantal-linear, quantal quadratic) are poor

TABLE C-2 Comparison of AEGL-3 Values Calculated From Estimates of LC₀₁ for Female Rat GB Vapor Inhalation Lethality (14-d Lethality, Values in mg/m³)^a

Exposure Time	NAC			BMD	
	Interim AEGL ^b	MINITAB Log Probit ^c	NumberCruncher Probit ^d	BMD Probit	Log Probit ^e
10 min	0.38	0.39	0.31	0.36	0.39
30 min	0.19	0.19	0.18	0.16	0.19
60 min	0.13	0.14	0.13	0.13	0.21
240 min (4 h)	0.07	0.059	0.053	0.044	0.059
480 min (8 h)	0.051	0.053	0.053	0.049	0.070

^aInterim values compared with those derived from Mioduszewski et al. (2001), MINITAB, NumberCruncher Probit, BMD Probit, and BMD Log Probit.

^bPublished in 66 Fed. Reg. 21947 (2001) and approved as interim values at NAC-21 on June 10-13, 2001. Derived from estimates of LC₀₁ provided by Mioduszewski et al. from ongoing analysis of female rat lethality data documented in Mioduszewski et al. (2000).

^cDerived from LC₀₁ values provided in "Appendix A: Probit Analysis" of ECBC-TR-183, *ECBC Low-level Operational Toxicology Program; Phase 1—Inhalation Toxicity of Sarin Vapor in Rats as a Function of Exposure Concentration and Duration*, by Mioduszewski et al. (2001). These estimates of LC₀₁ were generated by the probit analysis routine provided in Version 13 of MINITAB, a commercial statistical package offered by Minitab, Inc., of State College, Pennsylvania. The probit analysis in the reliability/survival section of the MINITAB package provides a log-probit analysis of the entered data. This log-probit analysis was duplicated during September 2001 in the Life Sciences Division of ORNL by entry of the female rat lethality data (14-d) from Table 3 (page 38) from ECBC-TR-183 into Release 13 (February 2000) of MINITAB. Performance of the BMD Log Probit analysis, with (forced) entry of a zero-concentration control, generated LC₀₁ values equal to those generated by the log-probit MINITAB analysis (e. g., 10 min of 11.56 mg/m³; 30 min of 5.62 mg/m³; 60 min of 4.24 mg/m³; 4 h of 1.77 mg/m³; 6 h of 1.83 mg/m³).

^dNumberCruncher Statistical System Survival Analysis, Version 5.5 (copyright 1991, Dr. Jerry L Hintz, Kaysville, UT).

^eNo zero-concentration control.

Abbreviations: BMD, benchmark dose.

fits and are rejected from any further consideration. The first column following the exposure times is the set of MLE LC_{01} values used to develop the AEGL-3 estimates published in the *Federal Register* (66 Fed. Reg. 21940 [2001]) notice of May 2, 2001. The LC_{01} values in the second column following the exposure times are those published by Mioduszewski et al. (2001). All the remaining values presented in Table C-1a,b were based on the raw experimental data presented in Mioduszewski et al. (2001). The MINITAB log probit seems to be a reasonable fit with the lethality data. The experimental results on which this analysis is based are published in Mioduszewski et al. (2001, 2002a).

Because the statistical routines used to evaluate the data in Mioduszewski et al. (2000) differ slightly from those used in Mioduszewski et al. (2001), the LC_{01} values employed in developing interim AEGL-3 determinations also differ slightly. The resulting LC_{01} and AEGL-3 estimates developed with the same calculational approach, UFs, and n values as were applied in the AEGL-3 determinations presented earlier (see Appendix A), are summarized in tables C-1a,b and C-2. The *Federal Register* interim values for AEGL-3 (see Table C-2) are consistently lower or equal to the Mioduszewski et al. (2001) log-probit-derived estimates, with the single exception of the 4-h value. In the case of the 4-h value, the NAC interim AEGL-3 (0.070 mg/m^3) is somewhat greater than the 4-h AEGL-3 estimate derived from the Mioduszewski et al. (2001) log-probit derivation (0.059 mg/m^3 ; see Table C-2), a difference of 0.011 mg/m^3 . The variation is slight.

The LC_{01} values presented in Mioduszewski et al. (2001), although slightly different from the preliminary results considered (Mioduszewski et al. 2000), represent a better documented and more widely accessible data set. These differences are acknowledged.

APPENDIX D

DERIVATION SUMMARY FOR ACUTE EXPOSURE GUIDELINE LEVELS FOR NERVE AGENTS

Derivation Summary For Agent GA
(CAS No. 77-81-6) (Tabun; Dimethylamidocyanophosphate)

A EGL-1				
10 min	30 min	1 h	4 h	8 h
0.0010 ppm (0.0069 mg/m ³)	0.00060 ppm (0.0040 mg/m ³)	0.00042 ppm (0.0028 mg/m ³)	0.00021 ppm (0.0014 mg/m ³)	0.00015 ppm (0.0010 mg/m ³)
<p>Key reference: Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D., Crosier, R., Scotto, J., McCaskey, D., Crouse, C., and Matson, K. 2002b. Low-level sarin vapor exposure in rats: Effect of exposure concentration and duration on pupil size. ECBC-TR-235. Edgewood Chemical Biological Center, U.S. Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD. (May 2002).</p> <p>Secondary reference:</p> <p>(1) Van Helden, H.P.M. Trap, H.C, Kuijpers, W.C., Groen, B., Oostdijk, J.P., Vanwersch, R.A.P., Philippens, I.H.C., Langenberg, J.P. and Benschop, H.P. 2002. Low Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Level, and Performance-Incapacitation. Research and Technology Organisation (RTO) Meeting Proceedings 75, Operational Medical Issues in Chemical and Biological Defense [RTO-MP-075, AC/323 (HFM-060) TP/37] held in Estoril, Portugal, 14-17 May 2001. North Atlantic Treaty Organisation, Research and Technology Organisation, BP 25, 7 Rue Ancelle, F-92201 Neuilly-sur-Seine CEDEX, France.</p> <p>(2) Harvey, J. C. 1952. Clinical observations on volunteers exposed to concentrations of GB. Medical Laboratories Research Report No. 114, Publication Control No. 5030-114, MLCR 114 (CMLRE-ML-52). Army Chemical Center, MD.</p> <p>(3) Johns, R.J. 1952. The effect of low concentrations of GB on the human eye. Chemical Corps Medical Laboratories Research Report No. 100, Publication Control</p>				

AEGL-1 Continued
No. 5030-100 (CMLRE-ML-52), Army Chemical Center, MD.
Test species/strain/gender/number: Based on analysis from Section 4.3 of this document and Mioduszewski et al. (1998) that potency of GA is equal to that of agent GB for AEGL-1 effects (please see derivation for GB AEGL-1 derived from female Sprague-Dawley rat data).
Exposure route/concentrations/durations: Based on analysis from Section 4.3 and Mioduszewski et al. (1998) that potency of GA is equal to that of agent GB (please see derivation for GB AEGL-1) for AEGL-1 effects, and derived from GB vapor inhalation exposures for 10, 60, and 240 min in female SD rats.
Effects: Derivation of AEGL-1 values based on relative potency from Section 4.3 and Mioduszewski et al. (1998) study showing that the relative potency of GA is equal to that of agent GB (please see derivation for GB AEGL-1) and from GB vapor exposure study of EC ₅₀ for miosis observed in adult female SD rats exposed to a range of GB vapor concentrations (0.01-0.48 mg/m ³) for 10 min (52 females), 60 min (35 females) and 240 min (55 females) (Mioduszewski et al. 2002b).
End point/concentration/rationale: Derivation of AEGL-1 values based on relative potency from Section 4.3 and Mioduszewski et al. (1998) study showing that the relative potency of GA is equal to that of agent GB (please see derivation for GB AEGL-1) for AEGL-1 effects and EC ₅₀ for miosis determination (a reversible, local, nondisabling, and transient effect) in the Mioduszewski et al. (2002b) study of young female SD rats exposed to agent GB. EC ₅₀ concentrations for miosis in female SD rats (the susceptible gender) are used as points of departure for AEGL-1 estimation. The miosis effects data of van Helden et al. (2001, 2002) (nonhuman primates), Harvey (1952) (human volunteers), and Johns (1952) (human volunteers) are supportive. The EC ₅₀ for miosis (postexposure pupil diameter 50% or less of the preexposure pupil diameter in 50% of exposed population) (Mioduszewski et al. 2002b) is not considered an adverse effect for humans.
Uncertainty factors/rationale: Based on relative potency from Section 4.3 and Mioduszewski et al. (1998) study showing that the relative potency GA is equal to that of agent GB (please see derivation for GB AEGL-1). Total uncertainty factor: 10 Interspecies: 1—miosis response to GB vapor exposure is similar across multiple mammalian species. Intraspecies: 10—for susceptible human subpopulations. Some individuals possess abnormally low levels of blood cholinesterase and carboxylesterase activity that may make them especially susceptible to the

AEGL-1 Continued
effects of cholinesterase inhibitors such as nerve agents (see Section 4.5.3.). Therefore, a factor of 10 was retained.
Modifying factor: None (see derivation for agent GB).
Animal to human dosimetric adjustment: None applied.
Time scaling: Based on relative potency from Section 4.3 and Mioduszewski et al. (1998) study showing that potency of GA is equal to that of agent GB (please see derivation for GB AEGL-1) and $C^n \times t = k$ where $n = 2$ and $k = 7.7 \times 10^{-6} \text{ mg/m}^3 \times \text{h}$ for 10- to 30-min extrapolation, and $k = 5.8 \times 10^{-6} \text{ mg/m}^3 \times \text{h}$ for 4-h to 8-h extrapolation for agent GB.
Data adequacy: Based on relative potency equal to that of agent GB (please see derivation for GB AEGL-1). The scarcity of dose-response data for agent GA forces the AEGL analysis to rely on assumptions of relative potency. Thus, AEGL values for agent GA are derivative. The relative potency assumptions for estimating AEGL-1 values for agent GA from the available database for agent GB need experimental confirmation.

AEGL-2				
10 min	30 min	1 h	4 h	8 h
0.013 ppm (0.087 mg/m ³)	0.0075 ppm (0.050 mg/m ³)	0.0053 ppm (0.035 mg/m ³)	0.0026 ppm (0.017 mg/m ³)	0.0020 ppm (0.013 mg/m ³)
Key Reference: Baker, D.J., Sedgwick, E.M. 1996. Single fibre electromyographic changes in man after organophosphate exposure. <i>Hum. Exp. Toxicol.</i> 15:369-375.				
Test species/strain/gender/number: Based on relative potency estimate from Section 4.3 of this document and Mioduszewski et al. (1998)—potency of GA is equal to that of agent GB for AEGL-2 effects (please see derivation for GB AEGL-2 derived from human volunteer data).				
Exposure route/concentrations/durations: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998)—potency of GA is equal to that of agent GB for AEGL-2 effects (please see derivation for GB AEGL-2) and derived from GB vapor inhalation to humans in exposure chamber (GB at 0.5 mg/m ³ for 30 min while walking at a rate of 96 paces per min and breathing normally [Baker and Sedgwick 1996]).				
Effects: Derivation of AEGL-2 values based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that potency of GA is equal to that of agent GB for AEGL-2 effects (please see derivation for GB AEGL-2) and from GB vapor exposure study (Baker and Sedgwick 1996) in which observed effects included miosis in eight of e subjects, dyspnea and photophobia in some individuals, inhibition of RBC-ChE to approximately 60% (range of 54-66.1%) of individual baseline at 3 h and 3 d postexposure in eight of eight subjects, and small but measurable changes in single fibre electromyography (SFEMG) of the forearm that were detectable in the lab between 4 and 15 mo postexposure (but not detectable at 15-30 mo postexposure) in five of eight human volunteers exposed to GB at 0.5 mg/m ³ for 30 min. SFEMG changes considered subclinical. No permanent effects.				
End point/concentration/rationale: Derivation of AEGL-2 values based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that potency of GA is equal to that of agent GB for AEGL-2 effects (please see derivation for GB AEGL-2). Presence of miosis in all subjects exposed to GB vapor (Baker and Sedgwick 1996), in addition to the other observed signs in portions of the exposed population, indicates a greater level of effect than the EC ₅₀ considered for AEGL-1 determination; thus, there exists a heightened potential for reduced visual acuity following a 30-min exposure to GB at 0.5 mg/m ³ . SFEMG effects are documented as long-lasting, but are subclinical and fully reversible. Such effects are not usually included as a basis for AEGL-2 estimation. However, due to the known steep				

AEGL-2 Continued
dose response for nerve agent vapor exposure, incorporation of the long-lasting SFEMG endpoint is here considered a protective interpretation of the AEGL-2 definition. The point of departure for AEGL-2 estimation is 0.5 mg GB/m ³ for 30 min.
<p>Uncertainty factors/rationale: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that potency of GA is equal to that of agent GB for AEGL-2 effects (please see derivation for GB AEGL-2).</p> <p style="padding-left: 2em;">Total uncertainty factor: 10</p> <p style="padding-left: 4em;">Interspecies: 1—human data</p> <p style="padding-left: 4em;">Intraspecies: 10—for possible susceptible human individuals. Some individuals possess abnormally low levels of blood cholinesterase and carboxylesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (see Section 4.5.3.). Therefore, a factor of 10 was retained.</p>
Modifying factor: None (see derivation for agent GB).
Animal to human dosimetric adjustment: None applied (human data)
Time scaling: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998)—potency of GA is equal to that of agent GB for AEGL-2 effects (please see derivation for GB AEGL-2) and $C^n \times t = k$ where $n = 2$ and $k = 0.0013 \text{ mg/m}^3 \times \text{h}$
Data adequacy: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998)—potency of GA is equal to that of agent GB for AEGL-2 effects (please see derivation for GB AEGL-2). The scarcity of dose-response data for agent GA forces the AEGL analysis to rely on assumptions of relative potency. Thus, AEGL values for agent GA are derivative. The relative potency assumptions for estimating AEGL-2 values for agent GA from the available database for agent GB need experimental confirmation.

AEGL-3				
10 min	30 min	1 h	4 h	8 h
0.11 ppm (0.76 mg/m ³)	0.057 ppm (0.38 mg/m ³)	0.039 ppm (0.26 mg/m ³)	0.021 ppm (0.14 mg/m ³)	0.015 ppm (0.10 mg/m ³)
<p>Key reference: (1) Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D. and Crosier, R. 2000. Estimating the probability of sarin vapor toxicity in rats as a function of exposure concentration and duration. Proceedings of the International Chemical Weapons Demilitarization Conference (CWD-2000), The Hague, NL. May 21-24, 2000.</p> <p>(2) Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B., Muse, W., Anthony, J., Durst, D., Sommerville, D., Crosier, R., Thomson, S., and Crouse, C. 2001. ECBC Low Level Operational Toxicology Program: Phase I—Inhalation toxicity of sarin vapor in rats as a function of exposure concentration and duration. ECBC-TR-183, Edgewood Research Development and Engineering Center, Aberdeen Proving Ground, MD. (August 2001).</p> <p>(3) Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D., and Crosier, R. 2002a. Interaction of exposure concentration and duration in determining acute toxic effects of sarin vapor in rats. Toxicol. Sci. 66: 176-184.</p>				
<p>Test species/strain/gender/number: Based on relative potency estimate from Section 4.3 of this document and Mioduszewski et al. (1998)—potency of GA is approximately one-half that of agent GB for lethality (please see derivation for GB AEGL-3 derived from female Sprague-Dawley rat data).</p>				
<p>Exposure route/concentrations/durations: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998)—potency of GA is approximately one-half that of agent GB for lethality (please see derivation for GB AEGL-3) and study of rat inhalation toxicity in dynamic mode exposure chamber (Mioduszewski et al. 2000, 2001, 2002a).</p>				
<p>Effects: Derivation of AEGL-3 values based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that potency of GA is approximately one-half that of agent GB for lethality (please see derivation for GB AEGL-3) and from GB vapor exposure study (Mioduszewski et al. 2000, 2001, 2002a) in which lethality and sublethal clinical signs monitored during and after exposure. Only lethality data reported at this time.</p>				

AEGL-3 Continued
<p>End point/concentration/rationale: Derivation of AEGL-3 values based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that potency of GA is approximately one-half that of agent GB for lethality (please see derivation for GB AEGL-3) and from GB vapor exposure study (Mioduszewski et al. 2000, 2001, 2002a) which derived 14-d lethality estimates for female Sprague-Dawley rats (female rats were reported to be overall more sensitive to GB vapor toxicity than male rats over the range of exposure concentrations and durations studied). Gender differences in sensitivity are reported to be statistically significant at $p < 0.01$ (Mioduszewski et al. 2000, 2001, 2002a). Probit analysis (MINITAB, version 13) presented in Mioduszewski et al. (2000) study provided 14-d LC_{50} and LC_{01} values for female rats. End point concentrations for LC_{01} reported for female SD rats (the susceptible gender) are used as points of departure from which to derive AEGL-3 estimates.</p>
<p>Uncertainty factors/rationale: Based on relative potency estimate from Mioduszewski et al. (1998) study showing that potency of GA is approximately one-half that of agent GB for lethality (please see derivation for GB AEGL-3)</p> <p style="padding-left: 2em;">Total uncertainty factor: 30</p> <p style="padding-left: 2em;">Interspecies: 3—The full default value of 10 was not considered necessary because the mechanism of toxicity in both rats and humans is the same, cholinesterase inhibition.</p> <p style="padding-left: 2em;">Intraspecies: 10—for possible susceptible human individuals. Some individuals possess abnormally low levels of blood cholinesterase and carboxylesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (see Section 4.5.3). Therefore, a factor of 10 was retained.</p>
<p>Modifying factor: None (see derivation for agent GB).</p>
<p>Animal to Human Dosimetric Adjustment: None applied, insufficient data</p>
<p>Time scaling: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998)—potency of GA is approximately one-half that of agent GB for lethality (please see derivation for GB AEGL-3) and $C^n \times t = k$ where $n = 2$ and $k = 0.021 \text{ mg/m}^3 \times \text{h}$ to extrapolate from 6-h value to 8-h estimate of LC_{01}.</p>
<p>Data adequacy: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) that potency of GA is approximately one-half that of agent GB for lethality (please see derivation for GB AEGL-3). The scarcity of dose-response data for agent GA forces the AEGL analysis to rely on assumptions of relative potency. Thus, AEGL values for agent GA are derivative. The relative potency assumptions for estimating AEGL-3 values</p>

AEGL-3 *Continued*

for agent GA from the available database for agent GB need experimental confirmation.

**Derivation Summary for Agent GB
(CAS No. 107-44-8) (Sarin; Isopropylmethylphosphonofluoridate)**

AEGL-1				
10 min	30 min	1 h	4 h	8 h
0.0012 ppm (0.0069 mg/m ³)	0.00068 ppm (0.0040 mg/m ³)	0.00048 ppm (0.0028 mg/m ³)	0.00024 ppm (0.0014 mg/m ³)	0.00017 ppm (0.0010 mg/m ³)
<p>Key reference: Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D., Crosier, R., Scotto, J., McCaskey, D., Crouse, C., and Matson, K. 2002b. Low-level sarin vapor exposure in rats: Effect of exposure concentration and duration on pupil size. ECBC-TR-235. Edgewood Chemical Biological Center, U.S. Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD. (May 2002).</p> <p>Secondary reference:</p> <p>(1) van Helden, H.P.M. Trap, H.C, Kuijpers, W.C., Groen, B., Oostdijk, J.P., Vanwersch, R.A.P., Philippens, I.H.C., Langenberg, J.P. and Benschop, H.P. 2002. Low Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Level, and Performance-Incapacitation. Research and Technology Organisation (RTO) Meeting Proceedings 75, Operational Medical Issues in Chemical and Biological Defense [RTO-MP-075, AC/323 (HFM-060) TP/37] held in Estoril, Portugal, 14-17 May 2001. North Atlantic Treaty Organisation, Research and Technology Organisation, BP 25, 7 Rue Ancelle, F-92201 Neuilly-sur-Seine CEDEX, France.</p> <p>(2) Harvey, J. C. 1952. Clinical observations on volunteers exposed to concentrations of GB. Medical Laboratories Research Report No. 114, Publication Control No. 5030-114, MLCR 114 (CMLRE-ML-52). Army Chemical Center, MD.</p> <p>(3) Johns, R.J. 1952. The effect of low concentrations of GB on the human eye. Chemical Corps Medical Laboratories Research Report No. 100, Publication Control No. 5030-100 (CMLRE-ML-52), Army Chemical Center, MD.</p>				
Test Species/Strain/Sex/Number: Rat, young adult (8-10 wk) female Sprague Dawley. Numbers of exposed individuals per time duration as follows: 10				

AEGL-1 Continued
min (52 females), 60 min (35 females) and 240 min (55 females) (Mioduszewski et al 2002b).
Exposure route/concentrations/durations: Whole body vapor exposure in 750-L dynamic airflow inhalation chamber to a range of GB vapor concentrations (0.01-0.48 mg/m ³) for 10 min, 60 min, and 240 min (Mioduszewski et al. 2002b).
Effects: Mioduszewski et al. (2002b) document EC ₅₀ for miosis observed in adult female SD rats exposed to a range of GB vapor concentrations (0.01-0.48 mg/m ³) for durations of 10 min (52 females), 60 min (35 females), and 240 min (55 females). EC ₅₀ for miosis defined as a postexposure pupil diameter 50% or less of the preexposure pupil diameter in 50% of the exposed rat population (Mioduszewski et al. 2002b). EC ₅₀ for miosis is a reversible, local, and transient effect. No significant changes from baseline noted in blood RBC-ChE, BuChE, or carboxylesterase. No other clinical signs observed in the exposed rats.
End point/concentration/rationale: Mioduszewski et al. (2002b) document EC ₅₀ for miosis from their study of young female SD rats as a well-defined animal endpoint that is reversible, local, transient, and nondisabling. The EC ₅₀ concentrations for miosis in female SD rats (the susceptible gender) are used as points of departure for AEGL-1 estimation; the resulting AEGL-1 estimates are thus protective. The miosis effects data of van Helden et al. (2001, 2002) (nonhuman primates), Harvey (1952) (human volunteers), and Johns (1952) (human volunteers) are supportive. The EC ₅₀ for miosis effect (postexposure pupil diameter 50% or less of the preexposure pupil diameter in 50% of exposed population) (Mioduszewski et al. 2002b) is not considered an adverse effect for humans.
Uncertainty factors/rationale: Total uncertainty factor: 10 Interspecies: 1—miosis response to GB vapor exposure is similar across multiple mammalian species. Intraspecies: 10—for susceptible human subpopulations. Some individuals possess abnormally low levels of blood cholinesterase and carboxylesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (see Section 4.5.3). Therefore, a factor of 10 was retained.
Modifying factor: None. Strong arguments for not incorporating an additional modifying factor include the following:

AEGL-1 Continued
<ol style="list-style-type: none"> 1. Data are available for multiple species. 2. Data characterizing both lethal and nonlethal endpoints have been used in the analysis; these end points possess exposure-response data. 3. the mechanism of toxicity is known 4. the n value is derived from experimental data and is not the default 5. there are no uncertainties regarding reproductive and developmental effects or issues of carcinogenicity. <p>In consequence, no modifying factor was used in the estimation of AEGL-1 values.</p>
<p>Animal to human dosimetric adjustment: None applied.</p>
<p>Time scaling: $C^n \times t = k$ where $n = 2$ and $k = 7.7 \times 10^{-6} \text{ mg/m}^3 \times \text{h}$ for 10- to 30-min extrapolation, and $k = 5.8 \times 10^{-6} \text{ mg/m}^3 \times \text{h}$ for 4-h to 8-h extrapolation. Current analyses based on a linear regression of the lethality and miosis data for female SD rats. The LC_{01} of GB to female Sprague-Dawley rats (Mioduszewski et al. 2000a,b, 2001, 2002a) yields an n value of 1.93 with an r^2 of 0.9948, while miosis (EC_{50} of GB to female Sprague-Dawley rats) (Mioduszewski et al 2002b) yields an n value of 2.00 with an r^2 of 0.4335 (see Appendix B). The anticholinesterase mechanism of mammalian toxicity for nerve agents is known, and all end points observed in human and animal studies represent a response continuum to anticholinesterase exposure. Accordingly, it is valid to apply an n value derived from compound-specific lethality data to time scaling for nonlethal effects, and an n value derived for miosis, to consideration of other toxic effects resulting from anticholinesterase exposure. This position is consistent with that of the recently published science policy of the EPA Office of Pesticide Programs (EPA 2000). Furthermore, this approach is preferable to use of default values. Therefore, $n = 2$ is used as the scaling function for all AEGL time point derivations for agent GB.</p>
<p>Data adequacy: Confidence in the AEGL-1 values is high due to the robust data set. A total of 423 rats were used in this well-conducted study, of which 130 were controls. Three vapor exposure durations, each of which is an AEGL exposure interval (10, 60, and 240 min) were incorporated into the study design, and a sufficient number of individuals were exposed at each interval: 10 min (52 females), 60 min (35 females), and 240 min (55 females) (Mioduszewski et al. 2002b).</p>

AEGL-2				
10 min	30 min	1 h	4 h	8 h
0.015 ppm (0.087 mg/m ³)	0.0085 ppm (0.050 mg/m ³)	0.0060 ppm (0.035 mg/m ³)	0.0029 ppm (0.017 mg/m ³)	0.0022 ppm (0.013 mg/m ³)
Key reference: Baker, D.J., Sedgwick, E.M. 1996. Single fibre electromyographic changes in man after organophosphate exposure. <i>Hum. Exp. Toxicol.</i> 15:369-375.				
Test species/strain/gender/number: human volunteers (healthy male servicemen), <i>N</i> = 8 adults				
Exposure route/concentrations/durations: Inhalation in exposure chamber; 0.5 mg/m ³ for 30 min while walking at a rate of 96 paces per minute and breathing normally.				
Effects: Baker and Sedgwick (1996) document effects observed in human volunteers (0.5 mg/m ³ for 30 min while subjects in an exposure chamber walked at a rate of 96 paces per minute and breathed normally), including miosis in eight of eight subjects, dyspnea and photophobia in some individuals, inhibition of RBC-ChE to approximately 60% (range of 54-66.1%) of individual baseline at 3 h and 3 d postexposure in eight of eight subjects, and small but measurable changes in single fibre electromyography (SFEMG) of the forearm that were detectable in the lab between 4 and 15 mo postexposure (in five of eight human volunteers), but not detectable at 15-30 mo postexposure. Respiratory effects resolved within minutes; ocular effects resolved within 48 h. SFEMG changes considered subclinical. No permanent effects.				
End point/concentration/rationale: Presence of miosis in all subjects, in addition to other observed signs in portions of exposed population in the key study, indicates a greater level of effect than the EC ₅₀ considered for AEGL-1 determination; thus, there exists a heightened potential for reduced visual acuity following a 30 min exposure at 0.5 mg/m ³ . SFEMG abnormalities detectable in the lab between 4 and 15 mo after a single experimental exposure documents these effects as long-lasting. Such subclinical and fully reversible effects are not usually included as a basis for AEGL-2 estimation. However, due to the known steep dose response for nerve agent vapor exposure, incorporation of the long-lasting SFEMG effect end point is here considered a protective interpretation of the AEGL-2 definition. The point of departure for AEGL-2 estimation is 0.5 mg/m ³ for 30 min.				
Uncertainty factors/rationale: Total uncertainty factor: 10 Interspecies: 1—human data				

AEGL-2 Continued
Intraspecies: 10—for possible susceptible human individuals. Some individuals possess abnormally low levels of blood cholinesterase and carboxylesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (see Section 4.5.3). Therefore, a factor of 10 was retained.
Modifying factor: None (see derivation for AEGL-1).
Animal to human dosimetric adjustment: None applied (human data)
Time scaling: $C^n \times t = k$ where $n = 2$ and $k = 0.0013 \text{ mg/m}^3 \times \text{h}$. The recent data of Mioduszewski et al. (2000, 2001, 2002a,b) are determined to be the best source of an estimate for the n value for GB response (see also Appendix B and derivation for AEGL-1). The Mioduszewski et al. (2000, 2001, 2002a,b) data set is robust and compound-specific for the most completely characterized G-series nerve agent, agent GB. As outlined earlier, the mechanism of mammalian toxicity for nerve agents is known, and all end points observed in human and animal studies represent a response continuum to anticholinesterase exposure. Accordingly, it is valid to apply an n value derived from compound-specific miosis and lethality data to time scaling for all AEGL effects. This position is consistent with that of the recently published science policy of the EPA Office of Pesticide Programs (EPA 2000). Furthermore, this approach is preferable to use of default values. The current analysis is based on a linear regression of the lethality of GB to female Sprague-Dawley rats (Mioduszewski et al. 2000b), which yields an n value of 2.00 (see Appendix B). Therefore, $n = 2$ is used as the scaling function for the AEGL-2 derivations.
Data adequacy: Confidence in the AEGL-2 values is limited by the lack of human experimental data for all AEGL-specific time frames and the lack of a clearly defined exposure-response relationship. The human data from which the AEGL-2 values were derived were limited by the short exposure time (30 min). Observed differences among human studies in identifying the toxicity threshold for low-dose exposures may be due to differences in individual sensitivities and breathing rates among the test populations, the steepness of the dose-response curve, and/or differences in experimental protocols or analytical methods.

AEGL-3				
10 min	30 min	1 h	4 h	8 h
0.064 ppm (0.38 mg/m ³)	0.032 ppm (0.19 mg/m ³)	0.022 ppm (0.13 mg/m ³)	0.012 ppm (0.070 mg/m ³)	0.0087 ppm (0.051 mg/m ³)
<p>Key reference: (1) Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D. and Crosier, R. 2000. Estimating the probability of sarin vapor toxicity in rats as a function of exposure concentration and duration. Proceedings of the International Chemical Weapons Demilitarization Conference (CWD-2000), The Hague, NL. May 21-24, 2000.</p> <p>(2) Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B., Muse, W., Anthony, J., Durst, D., Sommerville, D., Crosier, R., Thomson, S, and Crouse, C. 2001. ECBC Low Level Operational Toxicology Program: Phase I—Inhalation toxicity of sarin vapor in rats as a function of exposure concentration and duration. ECBC-TR-183, Edgewood Research Development and Engineering Center, Aberdeen Proving Ground, MD. (August 2001).</p> <p>(3) Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D., and Crosier, R. 2002a. Interaction of exposure concentration and duration in determining acute toxic effects of sarin vapor in rats. Toxicol. Sci. 66: 176-184.</p>				
Test species/strain/gender/number: Sprague-Dawley rats (8 to 10 wk old, from Charles River Laboratories), 10 females per concentration-time (Ct) combination, 50 females per time point,				
Exposure route/concentrations/durations: Inhalation in dynamic mode exposure chamber; individuals exposed whole-body to one of five concentrations (2-56 mg/m ³) for one of seven exposure times (3, 10, 30, 60, 90, 240, or 360 min).				
Effects: Mioduszewski et al. (2000, 2001, 2002a) document lethality and sublethal clinical signs monitored during and after experimental exposure. Only lethality data reported at this time.				
End point/concentration/rationale: Mioduszewski et al. (2000, 2001, 2002a) document 14-d acute lethal toxicity of GB to female Sprague-Dawley rats. Female rats were reported to be more sensitive to GB vapor toxicity than males over the range of exposure concentrations and durations studied. Gender differences for lethality are reported by Mioduszewski et al. (2000, 2001, 2002a) to be statistically significant at $p < 0.01$; thus, selection of				

AEGL-3 Continued
<p>end point concentrations for LC₀₁ reported for female SD rats (the susceptible gender) as points of departure from which to derive AEGL-3 estimates is protective. Probit analysis (MINITAB, version 13) presented in Mioduszewski et al. (2000) study gave the following 14-d LC₅₀ and LC₀₁ values for female rats:</p> <p style="margin-left: 40px;">LC₅₀</p> <ul style="list-style-type: none"> 18.1 mg/m³ for 10 min in female rats 8.51 mg/m³ for 30 min in female rats. 6.39 mg/m³ for 60 min in female rats 3.03 mg/m³ for 4 h in female rats 2.63 mg/m³ for 6 h in female rats <p style="margin-left: 40px;">LC₀₁</p> <ul style="list-style-type: none"> 11.54 mg/m³ for 10 min in female rats 5.84 mg/m³ for 30 min in female rats. 4.01 mg/m³ for 60 min in female rats 2.09 mg/m³ for 4 h in female rats 1.76 mg/m³ for 6 h in female rats
<p>Uncertainty factors/rationale:</p> <p style="margin-left: 40px;">Total uncertainty factor: 30</p> <ul style="list-style-type: none"> Interspecies: 3 (female rat data). The full default value of 10 was not considered necessary because the mechanism of toxicity in both rats and humans is the same, cholinesterase inhibition. Intraspecies: 10—for possible susceptible human individuals. Some individuals possess abnormally low levels of blood cholinesterase and carboxylesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (see Section 4.5.3). Therefore, a factor of 10 was retained.
<p>Modifying factor: None (see derivation for AEGL-1).</p>
<p>Animal to human dosimetric adjustment: None applied (insufficient data)</p>
<p>Time scaling: $C^n \times t = k$ where $n = 2$ and $k = 0.021 \text{ mg/m}^3 \times \text{h}$. The recent data of Mioduszewski et al. (2000, 2001, 2002a,b) are determined to be the best source of an estimate for the n value for GB response (see also Appendix B and derivation for AEGL-1). The Mioduszewski et al. (2000, 2001, 2002a,b) data set is robust and compound-specific for the most completely characterized G-series nerve agent, agent GB. As outlined earlier, the mechanism of mammalian toxicity for nerve agents is known, and all endpoints observed in human and animal studies represent a response continuum to anticholinesterase exposure. Accordingly, it is valid to apply an</p>

AEGL-3 Continued

n value derived from compound-specific miosis and lethality data to time scaling for all AEGL effects. This position is consistent with that of the recently published science policy of the EPA Office of Pesticide Programs (EPA 2000). Furthermore, this approach is preferable to use of default values. The current analysis is based on a linear regression of the lethality of GB to female Sprague-Dawley rats (Mioduszewski et al. 2000), which yields an *n* value of 2.00 (see Appendix B). Therefore, *n* = 2 is used as the scaling function for the AEGL-3 derivations. Time scaling was used to extrapolate from 6-h value provided by Mioduszewski et al. (2000) data to an 8-h estimate; scaling to derive 8-h LC₀₁. All other time-specific AEGL-3 values were derived directly from the LC₀₁ values for female SD rats in the Mioduszewski et al. (2000) study.

Data adequacy: Further data analysis and experimentation is needed to more fully understand the degree of sensitivity to lethal exposure concentrations exhibited by female populations of test animals. Interspecies sensitivity could be more fully characterized by determining if similar results can be obtained under the same protocol with different test species (particularly nonhuman primates).

**Derivation Summary for Agent GD
(CAS No. 96-64-0) (Soman; Pinacolyl Methylphosphonofluoridate)**

AEGL-1				
10 min	30 min	1 h	4 h	8 h
0.00046 ppm (0.0035 mg/m ³)	0.00026 ppm (0.0020 mg/m ³)	0.00018 ppm (0.0014 mg/m ³)	0.000091 ppm (0.00070 mg/m ³)	0.000065 ppm (0.00050 mg/m ³)
<p>Key reference: Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D., Crosier, R., Scotto, J., McCaskey, D., Crouse, C., and Matson, K. 2002b. Low-level sarin vapor exposure in rats: Effect of exposure concentration and duration on pupil size. ECBC-TR-235. Edgewood Chemical Biological Center, U.S. Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD. (May 2002).</p> <p>Secondary reference:</p> <p>(1) van Helden, H.P.M. Trap, H.C, Kuijpers, W.C., Groen, B., Oostdijk, J.P., Vanwersch, R.A.P., Philippens, I.H.C., Langenberg, J.P. and Benschop, H.P. 2002. Low Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Level, and Performance-Incapacitation. Research and Technology Organisation (RTO) Meeting Proceedings 75, Operational Medical Issues in Chemical and Biological Defense [RTO-MP-075, AC/323 (HFM-060) TP/37] held in Estoril, Portugal, 14-17 May 2001. North Atlantic Treaty Organisation, Research and Technology Organisation, BP 25, 7 Rue Ancelle, F-92201 Neuilly-sur-Seine CEDEX, France.</p> <p>(2) Harvey, J. C. 1952. Clinical observations on volunteers exposed to concentrations of GB. Medical Laboratories Research Report No. 114, Publication Control No. 5030-114, MLCR 114 (CMLRE-ML-52). Army Chemical Center, MD.</p> <p>(3) Johns, R.J. 1952. The effect of low concentrations of GB on the human eye. Chemical Corps Medical Laboratories Research Report No. 100, Publication Control No. 5030-100 (CMLRE-ML-52), Army Chemical Center, MD.</p>				
Test species/strain/gender/number: Based on relative potency from Section 4.3 of technical support document and Mioduszewski et al. (1998)—agent				

AEGL-1 Continued
GD is approximately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1 derived from rat data).
Exposure route/concentrations/durations: Based on relative potency from Section 4.3 and Mioduszewski et al. (1998)—agent GD is approximately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1) and derived from GB vapor inhalation exposures for 10, 60, and 240 min in female SD rats.
Effects: Derivation of AEGL-1 values based on relative potency from Section 4.3 and Mioduszewski et al. (1998) study showing that potency of GD is approximately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1) and from GB vapor exposure study of EC ₅₀ for miosis observed in adult female SD rats exposed to a range of GB vapor concentrations (0.01-0.48 mg/m ³) for 10 min (52 females), 60 min (35 females), and 240 min (55 females) (Mioduszewski et al. 2002b).
End point/concentration/rationale: Derivation of AEGL-1 values based on relative potency from Section 4.3 and Mioduszewski et al. (1998) study showing that potency of GD is approximately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1) and EC ₅₀ for miosis determination (a reversible, local, nondisabling and transient effect) in the Mioduszewski et al. (2002b) study of young female SD rats exposed to agent GB. The EC ₅₀ concentrations for miosis in female SD rats (the susceptible gender) are used as points of departure for AEGL-1 estimation. The miosis effects data of van Helden et al. (2001, 2002) (nonhuman primates), Harvey (1952) (human volunteers), and Johns (1952) (human volunteers) are supportive. The EC ₅₀ for miosis (postexposure pupil diameter 50% or less of the preexposure pupil diameter in 50% of exposed population) (Mioduszewski et al. 2002b) is not considered an adverse effect for humans.
Uncertainty factors/rationale: Based on relative potency from Section 4.3 and Mioduszewski et al. (1998) study showing that agent GD is approximately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1). Total uncertainty factor: 10 Interspecies: 1—miosis response to GB vapor exposure is similar across multiple mammalian species. Intraspecies: 10—for possible susceptible human individuals. Some individuals possess abnormally low levels of blood cholinesterase and carboxylesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (see Section 4.5.3). Therefore, a factor of 10 was retained.
Modifying factor: None (see derivation for agent GB).

AEGL-1 Continued
Animal to human dosimetric adjustment: None applied
Time scaling: Based on relative potency from Section 4.3 and Mioduszewski et al. (1998)—agent GD is approximately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1) and $C^n \times t = k$ where $n = 2$ and $k = 7.7 \times 10^{-6} \text{ mg/m}^3 \times \text{h}$ for 10-min to 30-min extrapolation and $k = 5.8 \times 10^{-6} \text{ mg/m}^3 \times \text{h}$ for 4-h to 8-h extrapolation for agent GB.
Data adequacy: Based on relative potency determination from Section 4.3 and Mioduszewski et al. (1998)—agent GD is approximately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1). The scarcity of dose-response data for agent GD forces the AEGL-1 analysis to rely on assumptions of relative potency. Thus, AEGL-1 values for agent GD are derivative. The relative potency assumptions for estimating AEGL-1 values for agent GD from the available database for agent GB need experimental confirmation.

AEGL-2				
10 min	30 min	1 h	4 h	8 h
0.0057 ppm (0.044 mg/m ³)	0.0033 ppm (0.025 mg/m ³)	0.0022 ppm (0.018 mg/m ³)	0.0012 ppm (0.0085 mg/m ³)	0.00085 ppm (0.0065 mg/m ³)
Key reference: Baker, D.J., Sedgwick, E.M. 1996. Single fibre electromyographic changes in man after organophosphate exposure. <i>Hum. Exp. Toxicol.</i> 15:369-375.				
Test species/strain/gender/number: Based on relative potency estimate from Section 4.3 of this document and Mioduszewski et al. (1998)—agent GD is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2 derived from human volunteer data).				
Exposure route/concentrations/durations: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998)—agent GD is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2) and derived from GB vapor inhalation to humans in exposure chamber; 0.5 mg/m ³ for 30 min while walking at a rate of 96 paces per minute and breathing normally (Baker and Sedgwick 1996).				
Effects: Derivation of AEGL-2 values based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that agent GD is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2) and from GB vapor exposure study (Baker and Sedgwick 1996) in which observed effects included miosis in eight of eight subjects, dyspnea and photophobia in some individuals, inhibition of RBC-ChE to approximately 60% (range of 54-66.1%) of individual baseline at 3 h and 3 d postexposure in eight of eight subjects, and small but measurable changes in single fibre electromyography (SFEMG) of the forearm that were detectable in the lab between 4 and 15 mo postexposure (but not detectable at 15-30 mo postexposure) in five of eight human volunteers exposed to GB at 0.5 mg/m ³ for 30 min. SFEMG changes considered subclinical. No permanent effects.				
End point/concentration/rationale: Derivation of AEGL-2 values based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that agent GD is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2). Presence of miosis in all subjects exposed to GB vapor (Baker and Sedgwick 1996), in addition to other observed signs in portions of exposed population, indicates a greater level of effect than the EC ₅₀ considered for AEGL-1 determination; thus, there exists a heightened potential for reduced visual acuity following a 30-min exposure to 0.5 mg GB/m ³ . SFEMG effects are documented as long-lasting, but are subclinical and fully reversible. Such				

AEGL-2 Continued
<p>effects are not usually included as a basis for AEGL- 2 estimation. However, due to the known steep dose response for nerve agent vapor exposure, incorporation of the long-lasting SFEMG end point is here considered a protective interpretation of the AEGL-2 definition. The point of departure for AEGL- 2 estimation is 0.5 mg/m³ for 30 min.</p>
<p>Uncertainty factors/rationale: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that agent GD is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2).</p> <p style="padding-left: 2em;">Total uncertainty factor: 10</p> <p style="padding-left: 4em;">Interspecies: 1 (human data)</p> <p style="padding-left: 4em;">Intraspecies: 10—for susceptible human subpopulations. Some individuals possess abnormally low levels of blood cholinesterase and carboxylesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (see Section 4.5.3). Therefore, a factor of 10 was retained.</p>
<p>Modifying factor: None (see derivation for agent GB).</p>
<p>Animal to human dosimetric adjustment: None applied (human data)</p>
<p>Time scaling: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998)—agent GD is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2) and $C^n \times t = k$ where $n = 2$ and $k = 0.0013 \text{ mg/m}^3 \times \text{h}$ for agent GB.</p>
<p>Data adequacy: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998)—agent GD is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2). The scarcity of dose-response data for agent GD forces the AEGL analysis to rely on assumptions of relative potency. Thus, AEGL values for agent GD are derivative. The relative potency assumptions for estimating AEGL-2 values for agent GD from the available database for agent GB need experimental confirmation.</p>

AEGL-3				
10 min	30 min	1 h	4 h	8 h
0.049 ppm (0.38 mg/m ³)	0.025 ppm (0.19 mg/m ³)	0.017 ppm (0.13 mg/m ³)	0.0091 ppm (0.070 mg/m ³)	0.0066 ppm (0.051 mg/m ³)
<p>Key reference: (1) Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D. and Crosier, R. 2000. Estimating the probability of sarin vapor toxicity in rats as a function of exposure concentration and duration. Proceedings of the International Chemical Weapons Demilitarization Conference (CWD-2000), The Hague, NL. May 21-24, 2000.</p> <p>(2) Mioduszewski, R.J., Manthei, J., Way R., et al. 2001. ECBC Low Level Operational Toxicology Program: Phase I—Inhalation toxicity of sarin vapor in rats as a function of exposure concentration and duration. ECBC-TR-183, Edgewood Research Development and Engineering Center, Aberdeen Proving Ground, MD. (August 2001).</p> <p>(3) Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D., and Crosier, R. 2002a. Interaction of exposure concentration and duration in determining acute toxic effects of sarin vapor in rats. Toxicol. Sci. 66: 176-184.</p> <p>(4) Aas, P., Sterri, S.H., Hjermsstad, H.P., Fonnum, F. 1985. A method for generating toxic vapors of soman: toxicity of soman by inhalation in rats. Toxicol. Appl. Pharmacol. 80:437-445. (Secondary study.)</p>				
<p>Test species/strain/gender/number: Based on relative potency estimate from Section 4.3 of this document and Mioduszewski et al. (1998)—agent GD is equipotent to agent GB for lethality (please see derivation for GB AEGL-3 derived from female Sprague-Dawley rat data).</p>				
<p>Exposure route/concentrations/durations: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998)—agent GD is equipotent to agent GB for lethality (please see derivation for GB AEGL-3) and study of rat inhalation toxicity in dynamic mode exposure chamber (Mioduszewski et al. 2000, 2001, 2002a).</p>				
<p>Effects: Derivation of AEGL-3 values based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that agent GD is equipotent to agent GB for lethality (please see derivation for GB AEGL-3) and from GB vapor exposure study (Mioduszewski et al. 2000, 2001, 2002a) in which lethality and sublethal clinical signs monitored during and after exposure. Only lethality data reported at this time.</p>				

AEGL-3 Continued
<p>End point/concentration/rationale: Derivation of AEGL-3 values based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that agent GD is equipotent to agent GB for lethality (please see derivation for GB AEGL-3) and from GB vapor exposure study (Mioduszewski et al. 2000, 2001, 2002a) which derived 14-d lethality estimates for female Sprague-Dawley rats (female rats were reported to be overall more sensitive to GB vapor toxicity than male rats over the range of exposure concentrations and durations studied). Gender differences in sensitivity are reported to be statistically significant at $p < 0.01$ (Mioduszewski et al. 2000, 2001, 2002a). Probit analysis (MINITAB, version 13) presented in Mioduszewski et al. (2000) study provided 14-d LC_{50} and LC_{01} values for female rats. End point concentrations for LC_{01} reported for female SD rats (the susceptible gender) are used as points of departure from which to derive AEGL-3 estimates.</p>
<p>Uncertainty factors/rationale: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that agent GD is equipotent to agent GB for lethality (please see derivation for GB AEGL-3).</p> <p style="padding-left: 40px;">Total uncertainty factor: 30</p> <p style="padding-left: 80px;">Interspecies: 3 (female rat data). The full default value of 10 was not considered necessary because the mechanism of toxicity in both rats and humans is the same, cholinesterase inhibition.</p> <p style="padding-left: 80px;">Intraspecies: 10—for possible susceptible human individuals. Some individuals possess abnormally low levels of blood cholinesterase and carboxylesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (see Section 4.5.3). Therefore, a factor of 10 was retained.</p> <p style="padding-left: 40px;">From the secondary study of Aas et al. (1985)</p> <p style="padding-left: 80px;">Interspecies: 10 (rat data). Sparse data set for agent GD.</p> <p style="padding-left: 80px;">Intraspecies: 10—for susceptible human subpopulations, and sparse data set for agent GD. Some individuals possess abnormally low levels of blood cholinesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (see Section 4.5.3. of technical support document). Therefore, a factor of 10 was retained.</p>
<p>Modifying factor: None (see derivation for agent GB).</p>
<p>Animal to human dosimetric adjustment: None applied (insufficient data).</p>
<p>Time scaling: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) that agent GF is equipotent to agent GB for lethality (please see derivation for GB AEGL-3) and $C^n \times t = k$ where $n = 2$ and $k = 0.021 \text{ mg/m}^3 \times \text{h}$ to extrapolate from 6-h value to 8-h estimate of LC_{01}.</p>

AEGL-3 Continued

Data adequacy: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998)—agent GD is equipotent to agent GB for lethality (please see derivation for GB AEGL-3). The relative potency assumptions for estimating AEGL-3 values for agent GD from the available database for agent GB need experimental confirmation. The scarcity of dose-response data for agent GD forces the AEGL analysis to rely on assumptions of relative potency. Thus, AEGL-3 values for agent GD are derivative, with the exception of 10-min and 30-min values, which are confirmed by short-term experimental lethality data for Wistar rats as provided in a secondary study by Aas et al. (1985).

In the secondary study (Aas et al., 1985) of male Wistar rats (200-250 g), six animals tested at each of three exposure levels for periods of time <30 min by means of a dynamic inhalation chamber system; constant air concentration of GD at 21 mg/m³ for undefined exposure periods (each less than 30 min). Aas et al. (1985) reported lethality and enzyme activity changes. Time scaling includes an $n = 2$ and $k = 0.012 \text{ mg/m}^3 \times \text{h}$ to derive 10-min and 30-min AEGL-3 estimates for agent GD. The Aas et al. (1985) data allow an estimate of the threshold for mortality in rats under this study protocol as equal to 335 mg·min/m³ for an exposure period of 16 min. This lethal threshold is equivalent to an exposure to a GD concentration of 21 mg/m³ for 16 min. Resulting AEGL-3 estimates (a 10-min AEGL-3 estimate of 0.27 mg/m³ and a 30-min AEGL-3 estimate of 0.15 mg/m³) are in good agreement with those derived by means of relative potency comparison with agent GB for the same time periods (see Appendix A for details of derivation).

**Derivation Summary for Agent GF
(CAS No. 329-99-7) (O-cyclohexyl-methylfluorophosphate)**

A EGL-1				
10 min	30 min	1 h	4 h	8 h
0.00049 ppm (0.0035 mg/m ³)	0.00028 ppm (0.0020 mg/m ³)	0.00020 ppm (0.0014 mg/m ³)	0.00010 ppm (0.00070 mg/m ³)	0.000070 ppm (0.00050 mg/m ³)
Key reference:	Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D., Crosier, R., Scotto, J., McCaskey, D., Crouse, C., and Matson, K. 2002b. Low-level sarin vapor exposure in rats: Effect of exposure concentration and duration on pupil size. ECBC-TR-235. Edgewood Chemical Biological Center, U.S. Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD. (May 2002).			
Secondary reference:	<p>(1) van Helden, H.P.M. Trap, H.C, Kuijpers, W.C., Groen, B., Oostdijk, J.P., Vanwersch, R.A.P., Philippens, I.H.C., Langenberg, J.P. and Benschop, H.P. 2002. Low Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Level, and Performance-Incapacitation. Research and Technology Organisation (RTO) Meeting Proceedings 75, Operational Medical Issues in Chemical and Biological Defense [RTO-MP-075, AC/323 (HFM-060) TP/37] held in Estoril, Portugal, 14-17 May 2001. North Atlantic Treaty Organisation, Research and Technology Organisation, BP 25, 7 Rue Ancelle, F-92201 Neuilly-sur-Seine CEDEX, France.</p> <p>(2) Harvey, J. C. 1952. Clinical observations on volunteers exposed to concentrations of GB. Medical Laboratories Research Report No. 114, Publication Control No. 5030-114, MLCR 114 (CMLRE-ML-52). Army Chemical Center, MD.</p> <p>(3) Johns, R.J. 1952. The effect of low concentrations of GB on the human eye. Chemical Corps Medical Laboratories Research Report No. 100, Publication Control No. 5030-100 (CMLRE-ML-52), Army Chemical Center, MD.</p>			
Test species/strain/gender/number: Based on relative potency from Section 4.3 of this document and Mioduszewski et al. (1998)—agent GF is approxi-				

AEGL-1 Continued
mately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1 derived from rat data).
Exposure route/concentrations/durations: Based on relative potency from Section 4.3 and Mioduszewski et al. (1998)—agent GF is approximately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1) and derived from GB vapor inhalation exposures for 10, 60, and 240 min in female SD rats.
Effects: Derivation of AEGL-1 values based on relative potency from Section 4.3 and Mioduszewski et al. (1998) study showing that agent GF is approximately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1) and from GB vapor exposure study of EC ₅₀ for miosis observed in adult female SD rats exposed to a range of GB vapor concentrations (0.01-0.48 mg/m ³) for 10 min (52 females), 60 min (35 females), and 240 min (55 females) (Mioduszewski et al. 2002b).
End point/concentration/rationale: Derivation of AEGL-1 values based on relative potency from Section 4.3 and Mioduszewski et al. (1998) study showing that agent GF is approximately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1) and EC ₅₀ for miosis determination (a reversible, local, nondisabling and transient effect) in the Mioduszewski et al. (2002b) study of young female SD rats exposed to agent GB. EC ₅₀ concentrations for miosis in female SD rats (the susceptible gender) are used as points of departure for AEGL-1 estimation. The miosis effects data of van Helden et al. (2001, 2002) (nonhuman primates), Harvey (1952) (human volunteers), and Johns (1952) (human volunteers) are supportive. The EC ₅₀ for miosis (postexposure pupil diameter 50% or less of the preexposure pupil diameter in 50% of exposed population) (Mioduszewski et al. 2002b) is not considered an adverse effect for humans.
<p>Uncertainty factors/rationale: Based on relative potency from Section 4.3 and Mioduszewski et al. (1998) study showing that agent GF is approximately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1).</p> <p style="padding-left: 2em;">Total uncertainty factor: 10</p> <p style="padding-left: 4em;">Interspecies: 1—miosis response to GB vapor exposure is similar across multiple mammalian species.</p> <p style="padding-left: 4em;">Intraspecies: 10—for possible susceptible human individuals. Some individuals possess abnormally low levels of blood cholinesterase and carboxylesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (see Section 4.5.3). Therefore, a factor of 10 was retained.</p>
Modifying factor: None (see derivation for agent GB).

AEGL-1 <i>Continued</i>
Animal to human dosimetric adjustment: None applied (human data).
Time scaling: Based on relative potency from Section 4.3 and Mioduszewski et al. (1998)—agent GF is approximately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1) and $C^n \times t = k$ where $n = 2$ and $k = 7.7 \times 10^{-6} \text{ mg/m}^3 \times \text{h}$ for 10- to 30-min extrapolation, and $k = 5.8 \times 10^{-6} \text{ mg/m}^3 \times \text{h}$ for 4-h to 8-h extrapolation for agent GB.
Data adequacy: Based on relative potency determination from Section 4.3 and Mioduszewski et al. (1998)—agent GF is approximately twice as potent as agents GB and GA for AEGL-1 effects (please see derivation for GB AEGL-1). The scarcity of dose-response data for agent GF forces the AEGL-1 analysis to rely on assumptions of relative potency. Thus, AEGL-1 values for agent GF are derivative. The relative potency assumptions for estimating AEGL-1 values for agent GF from the available database for agent GB need experimental confirmation.

AEGL-2				
10 min	30 min	1 h	4 h	8 h
0.0062 ppm (0.044 mg/m ³)	0.0035 ppm (0.025 mg/m ³)	0.0024 ppm (0.018 mg/m ³)	0.0013 ppm (0.0085 mg/m ³)	0.00091 ppm (0.0065 mg/m ³)
Key reference: Baker, D.J., Sedgwick, E.M. 1996. Single fibre electromyographic changes in man after organophosphate exposure. <i>Hum. Exp. Toxicol.</i> 15:369-375.				
Test species/strain/gender/number: Based on relative potency estimate from Section 4.3 of this document and Mioduszewski et al. (1998)—agent GF is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2 derived from human volunteer data).				
Exposure route/concentrations/durations: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998)—agent GF is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2) and derived from GB vapor inhalation to humans in exposure chamber; GB at 0.5 mg/m ³ for 30 min while walking at a rate of 96 paces per minute and breathing normally (Baker and Sedgwick 1996).				
Effects: Derivation of AEGL-2 values based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that agent GF is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2) and from GB vapor exposure study (Baker and Sedgwick 1996) in which observed effects included miosis in eight of eight subjects, dyspnea and photophobia in some individuals, inhibition of RBC-ChE to approximately 60% (range of 54-66.1%) of individual baseline at 3 h and 3 d postexposure in eight of eight subjects, and small but measurable changes in single fibre electromyography (SFEMG) of the forearm that were detectable in the lab between 4 and 15 mo postexposure (but not detectable at 15-30 mo postexposure) in five of eight human volunteers exposed to GB at 0.5 mg/m ³ for 30 min. SFEMG changes considered subclinical. No permanent effects.				
End point/concentration/rationale: Derivation of AEGL-2 values based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that agent GF is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2). Presence of miosis in all subjects exposed to GB vapor (Baker and Sedgwick 1996), in addition to other observed signs in portions of exposed population, indicates a greater level of effect than the EC ₅₀ considered for AEGL-1 determination; thus there exists a heightened potential for reduced visual acuity following a 30-min exposure to GB at 0.5 mg/m ³ . SFEMG effects are documented as long-lasting, but are subclinical and fully reversible. Such effects are not				

AEGL-2 Continued
usually included as a basis for AEGL-2 estimation. However, due to the known steep dose response for nerve agent vapor exposure, incorporation of the long-lasting SFEMG end point is here considered a protective interpretation of the AEGL-2 definition. The point of departure for AEGL-2 estimation is 0.5 mg/m ³ for 30 min.
<p>Uncertainty Factors/Rationale: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998) study showing that agent GF is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2).</p> <p style="padding-left: 2em;">Total uncertainty factor: 10</p> <p style="padding-left: 4em;">Interspecies: 1 (human data).</p> <p style="padding-left: 4em;">Intraspecies: 10—for susceptible human subpopulations. Some individuals possess abnormally low levels of blood cholinesterase and carboxylesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (see Section 4.5.3). Therefore, a factor of 10 was retained.</p>
Modifying factor: None (see derivation for agent GB).
Animal to human dosimetric adjustment: None applied (human data).
Time scaling: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998)—agent GF is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2) and $C^n \times t = k$ where $n = 2$ and $k = 0.0013 \text{ mg/m}^3 \times \text{h}$ for agent GB.
Data adequacy: Based on relative potency estimate from Section 4.3 and Mioduszewski et al. (1998)—agent GF is approximately twice as potent as agents GB and GA for AEGL-2 effects (please see derivation for GB AEGL-2). The scarcity of dose-response data for agent GF forces the AEGL analysis to rely on assumptions of relative potency. Thus, AEGL values for agent GF are derivative. The relative potency assumptions for estimating AEGL-2 values for agent GF from the available database for agent GB need experimental confirmation.

AEGL-3				
10 min	30 min	1 h	4 h	8 h
0.053 ppm (0.38 mg/m ³)	0.027 ppm (0.19 mg/m ³)	0.018 ppm (0.13 mg/m ³)	0.0098 ppm (0.070 mg/m ³)	0.0071 ppm (0.051 mg/m ³)
<p>Key Reference: (1) Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D. and Crosier, R. 2000. Estimating the probability of sarin vapor toxicity in rats as a function of exposure concentration and duration. Proceedings of the International Chemical Weapons Demilitarization Conference (CWD-2000), The Hague, NL. May 21-24, 2000.</p> <p>(2) Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B., Muse, W., Anthony, J., Durst, D., Sommerville, D., Crosier, R., Thomson, S, and Crouse, C. 2001. ECBC Low Level Operational Toxicology Program: Phase I—Inhalation toxicity of sarin vapor in rats as a function of exposure concentration and duration. ECBC-TR-183, Edgewood Research Development and Engineering Center, Aberdeen Proving Ground, MD. (August 2001).</p> <p>(3) Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D., and Crosier, R. 2002a. Interaction of exposure concentration and duration in determining acute toxic effects of sarin vapor in rats. Toxicol. Sci. 66: 176-184.</p> <p>Secondary reference: Anthony, J.S., Haley, M.V., Manthei, J.H., Way, R.A., Burnett, D.C., Gaviola, B.P., Sommerville, D.R., Crosier, R.B., Mioduszewski, R.J., Jakubowski, E.M., Montgomery, J.L., Thomson, S.A. 2002. Inhalation toxicity of GF vapor in rats as a function of exposure concentration and duration and its potency comparison to GB. Late-breaking Poster presented at 41st Annual meeting of the Society of Toxicology, Nashville, TN (21 Mar 2002).</p>				
<p>Test species/strain/gender/number: Based on relative potency estimate from Section 4.3 of this document and Mioduszewski et al. (1998)—agent GF is equipotent to agent GB for lethality (please see derivation for GB AEGL-3 derived from female Sprague-Dawley rat data). This assumption is supported by the recent study of Anthony et al. (2002).</p>				
<p>Exposure route/concentrations/durations: Based on relative potency estimate from Section 4.3, Mioduszewski et al. (1998), and Anthony et al. (2002)—</p>				

AEGL-3 Continued
agent GF is equipotent to agent GB for lethality (please see derivation for GB AEGL-3) and study of rat inhalation toxicity in dynamic mode exposure chamber (Mioduszewski et al. 2000, 2001, 2002a).
Effects: Derivation of AEGL-3 values based on relative potency estimate from Section 4.3 and the Mioduszewski et al. (1998) and Anthony et al (2002) studies showing that agent GF is equipotent to agent GB for lethality (please see derivation for GB AEGL-3) and from GB vapor exposure study (Mioduszewski, et al. 2000, 2001, 2002a) in which lethality and sublethal clinical signs monitored during and after exposure. Only lethality data reported at this time.
End point/concentration/rationale: Derivation of AEGL-3 values based on relative potency estimate from Section 4.3 and the Mioduszewski et al. (1998) and Anthony et al. (2002) studies showing that agent GF is equipotent to agent GB for lethality (please see derivation for GB AEGL-3) and from GB vapor exposure study (Mioduszewski et al. 2000, 2001, 2002a) which derived 14-d lethality estimates for female Sprague-Dawley rats (female rats were reported to be overall more sensitive to GB vapor toxicity than male rats over the range of exposure concentrations and durations studied). Gender differences in sensitivity are reported to be statistically significant at $p < 0.01$ (Mioduszewski et al. 2000, 2001, 2002a). End point concentrations for LC ₀₁ reported for female SD rats (the susceptible gender) are used as points of departure from which to derive AEGL-3 estimates. Probit analysis (MINITAB, version 13) presented in the Mioduszewski et al. (2000) study provided 14-d LC ₅₀ and LC ₀₁ values for female rats.
Uncertainty factors/rationale: Based on relative potency estimate from Section 4.3 and the Mioduszewski et al. (1998), and Anthony et al. (2002) studies showing that agent GF is equipotent to agent GB for lethality (please see derivation for GB AEGL-3). Total uncertainty factor: 30 Interspecies: 3 (female rat data). The full default value of 10 was not considered necessary because the mechanism of toxicity in both rats and humans is the same, cholinesterase inhibition. Intraspecies: 10—for possible susceptible human individuals. Some individuals possess abnormally low levels of blood cholinesterase and carboxylesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (see Section 4.5.3.). Therefore, a factor of 10 was retained.
Modifying factor: None (see derivation for agent GB).
Time scaling: Based on relative potency estimate from Section 4.3 of this document, Mioduszewski et al. (1998), and Anthony et al. (2002)—agent GF

AEGL-3 *Continued*

is equipotent to agent GB for lethality (please see derivation for GB AEGL-3) and $C^n \times t = k$ where $n = 2$ and $k = 0.021 \text{ mg/m}^3 \times \text{h}$ to extrapolate from 6-h value to 8-h estimate of LC_{01} .

Data adequacy: Based on relative potency estimate from Section 4.3, Mioduszewski et al. (1998), and Anthony et al. (2002)—agent GF is equipotent to agent GB for lethality (please see derivation for GB AEGL-3). The scarcity of dose-response data for agent GF forces the AEGL analysis to rely on assumptions of relative potency. Thus, AEGL-3 values for agent GF are derivative. The relative potency assumptions for estimating AEGL-3 values for agent GF from the available database for agent GB need experimental confirmation.

Derivation Summary for Agent VX Vapor
(CAS No. 50782-69-9)
(O-Ethyl-S-(Isopropyl-Aminoethyl)Methyl Phosphonothiolate)

AEGL-1				
10 min	30 min	1 h	4 h	8 h
0.000052 ppm (0.00057 mg/m ³)	0.000030 ppm (0.00033 mg/m ³)	0.000016 ppm (0.00017 mg/m ³)	0.0000091 ppm (0.00010 mg/m ³)	0.0000065 ppm (0.000071 mg/m ³)
<p>Key reference: Mioduszewski et al. (2002b). Low-level sarin vapor exposure in rats: Effect of exposure concentration and duration on pupil size (ECBC-TR-235). Edgewood Chemical Biological Center, U.S. Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD.</p> <p>Secondary references: (1) Grob, D., and Harvey, J.C. 1958. Effects in man of the anticholinesterase compound Sarin (isopropyl methyl phosphonofluoridate). <i>J. Clin. Invest.</i> 37:350-368 (2) Sidell, F.R., and Groff, W.A. 1974. The reactivitability of cholinesterase inhibited by VX and sarin in man. <i>Toxicol. Appl. Pharmacol.</i> 27:241-252.</p>				
<p>Test species/strain/gender/number: Based on relative potency from Grob and Harvey (1958) and Sidell and Groff (1974)—potency of agent VX is approximately 4 times that of agent GB for AEGL-1 effects (please see derivation for GB AEGL-1, derived from female Sprague-Dawley rat data for EC₅₀ miosis).</p>				
<p>Exposure route/concentrations/durations: Based on relative potency from Grob and Harvey (1958) and Sidell and Groff (1974)—potency of agent VX is approximately 4 times that of agent GB for AEGL-1 effects (please see derivation for GB AEGL-1) and derived from GB vapor exposures to female Sprague-Dawley rats for EC₅₀ miosis at 10, 60, and 240 min</p>				
<p>Effects: Derivation of AEGL-1 values based on relative potency from Grob and Harvey (1958) and Sidell and Groff (1974) studies showing that potency of agent VX is approximately 4 times that of agent GB for AEGL-1 effects (please see derivation for GB AEGL-1) and VX estimates derived from data in GB vapor exposure study (Mioduszewski et al. 2002b) in which EC₅₀ for miosis (a postexposure pupil diameter 50% or less of the preexposure pupil diameter in 50% of the exposed rat population) in female SD rats was determined for 10, 60, and 240 min. Estimated concentrations of VX</p>				

AEGL-1 Continued
<p>expected to produce similar effects are 0.017 mg/m³ for 10 min, 0.005 mg/m³ for 60 min, and 0.003 mg/m³ for 240 min.</p>
<p>End point/concentration/rationale: Derivation of AEGL-1 values based on relative potency from Grob and Harvey (1958) and Sidell and Groff (1974) studies showing that potency of agent VX is approximately 4 times that of agent GB (please see derivation for GB AEGL-1) and determination that the EC₅₀ for miosis is based on a well-defined animal end point in a susceptible gender and is reversible, local, nondisabling, and transient (Mioduszewski et al. [2002b] study of young female SD rats exposed to GB). Estimated concentrations of VX expected to produce similar effects are 0.017 mg/m³ for 10 min, 0.005 mg/m³ for 60 min, and 0.003 mg/m³ for 240 min; selection of these estimated EC₅₀ concentrations for female SD rats (the susceptible gender) as the points of departure for agent VX AEGL-1 estimation is thus protective. The miosis effects data of van Helden et al. (2001, 2002) (nonhuman primates), Harvey (1952) (human volunteers), and Johns (1952) (human volunteers) are supportive. The EC₅₀ for miosis (a postexposure pupil diameter 50% or less of the preexposure pupil diameter in 50% of the exposed rat population) (Mioduszewski et al. 2002b) is not considered an adverse effect for humans. The AEGL values are estimates for VX vapor exposures only.</p>
<p>Uncertainty factors/rationale: Based on relative potency from Grob and Harvey (1958) and Sidell and Groff (1974) studies showing that potency of agent VX is approximately 4 times that of agent GB (please see derivation for GB AEGL-1).</p> <p style="padding-left: 2em;">Total uncertainty factor: 30</p> <p style="padding-left: 4em;">Interspecies: 1—miosis response to nerve agent vapor exposure is similar across mammalian species (as for agent GB AEGL-1 estimation).</p> <p style="padding-left: 4em;">Intraspecies: 10—for possible susceptible human individuals. Some individuals possess abnormally low levels of blood cholinesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (Morgan 1989; Wills 1972; Opresko et al. 1998). Therefore, a factor of 10 was retained.</p>
<p>Modifying factor: 3 (for sparse VX database).</p>
<p>Animal to human dosimetric adjustment: None applied (human data).</p>
<p>Time scaling: Based on relative potency from Grob and Harvey (1958) and Sidell and Groff (1974)—potency of agent VX is approximately 4 times that of agent GB (please see derivation for GB AEGL-1) and $C^n \times t = k$ where $n = 2$, and $k = 5.0 \times 10^{-8} \text{ mg/m}^3 \times \text{h}$ for 10 to 30 min extrapolation, and $k = 4.0 \times 10^{-8} \text{ mg/m}^3 \times \text{h}$ for 4-h to 8-h extrapolation.</p>

AEGL-1 *Continued*

Data adequacy: Based on relative potency—potency of agent VX is approximately 4 times that of agent GB (please see derivation for GB AEGL-1). The scarcity of dose-response data for agent VX forces the AEGL analysis to rely on assumptions of relative potency. Thus, AEGL values for agent VX are derivative. The relative potency assumptions for estimating AEGL-1 values for agent VX from the available database for agent GB need experimental confirmation.

AEGL-2				
10 min	30 min	1 h	4 h	8 h
0.00065 ppm (0.0072 mg/m ³)	0.00038 ppm (0.0042 mg/m ³)	0.00027 ppm (0.0029 mg/m ³)	0.00014 ppm (0.0015 mg/m ³)	0.000095 ppm (0.0010 mg/m ³)
<p>Key reference: Baker, D.J. and Sedgwick, E.M., 1996. Single-fibre electromyographic changes in man after organophosphate exposure. <i>Hum. Exp. Toxicol.</i> 15: 369-375.</p> <p>Secondary references: Grob, D., and Harvey, J.C. 1958. Effects in man of the anticholinesterase compound Sarin (isopropyl methyl phosphonofluoridate). <i>J. Clin. Invest.</i> 37:350-368; Sidell, F.R., and Groff, W.A. 1974. The reactivability of cholinesterase inhibited by VX and sarin in man. <i>Toxicol. Appl. Pharmacol.</i> 27:241-252.</p>				
<p>Test species/strain/gender/number: Based on relative potency from Grob and Harvey (1958) and Sidell and Groff (1974)—potency of agent VX is approximately 4 times that of agent GB for AEGL-2 effects (please see derivation for GB AEGL-2 derived from human volunteer data).</p>				
<p>Exposure route/concentrations/durations: Based on relative potency from Grob and Harvey (1958) and Sidell and Groff (1974)—potency of agent VX is approximately 4 times that of agent GB (please see derivation for GB AEGL-2) and derived from GB vapor inhalation to humans in exposure chamber; 0.5 mg/m³ for 30 min while walking at a rate of 96 paces per minute and breathing normally (Baker and Sedgwick 1996).</p>				
<p>Effects: Derivation of AEGL-2 values based on relative potency from Grob and Harvey (1958) and Sidell and Groff (1974) studies showing that potency of agent VX is approximately 4 times that of agent GB for AEGL-2 effects (please see derivation for GB AEGL-2). VX estimates derived from GB vapor exposure study (Baker and Sedgwick 1996) in which observed effects included miosis in eight of eight subjects, dyspnea and photophobia in some individuals, inhibition of RBC-ChE to approximately 60% of individual baseline at 3 h and 3 d postexposure in eight of eight subjects, and small but measurable changes in single fibre electromyography (SFEMG) of the forearm that were detectable in the lab between 4 and 15 mo postexposure (but not detectable at 15-30 mo postexposure) in five of eight human volunteers exposed to GB at 0.5 mg/m³ for 30 min. SFEMG changes considered subclinical. No permanent effects.</p>				
<p>End point/concentration/rationale: Derivation of AEGL-2 values based on relative potency from Grob and Harvey (1958) and Sidell and Groff (1974)</p>				

AEGL-2 Continued
<p>studies showing that potency of agent VX is approximately 4 times that of agent GB for AEGL-2 effects (please see derivation for GB AEGL-2) and determination that a 30-min exposure to GB at 0.5 mg/m³ results in a greater level of effect than the EC₅₀ considered for AEGL-1 determination (see Baker and Sedgwick [1996]); thus, there exists a heightened potential for reduced visual acuity following experimental exposures. Estimated concentration of VX expected to produce similar effects is 0.125 mg/m³ for 30 min; this concentration is the point of departure for agent VX AEGL-2 estimations. Inclusion of the long-lasting but subclinical and fully reversible SFEMG effect is here considered a protective interpretation of the AEGL-2 definition, given the known steep dose response for nerve agent vapor exposure. The AEGL values are estimates for VX vapor exposures only.</p>
<p>Uncertainty Factors/Rationale: Based on relative potency from Grob and Harvey (1958) and Sidell and Groff (1974) studies showing that potency of agent VX is approximately 4 times that of agent GB for AEGL-2 effects (please see derivation for GB AEGL-2).</p> <p style="padding-left: 40px;">Total uncertainty factor: 30</p> <p style="padding-left: 80px;">Interspecies: 1 (human data).</p> <p style="padding-left: 80px;">Intraspecies: 10—for possible susceptible human individuals. Some individuals possess abnormally low levels of blood cholinesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (Morgan 1989; Wills 1972; Opresko et al., 1998). Therefore, a factor of 10 was retained.</p>
<p>Modifying factor: 3 (for sparse VX database).</p>
<p>Animal to human dosimetric adjustment: None applied (human data)</p>
<p>Time scaling: Based on relative potency from Grob and Harvey (1958) and Sidell and Groff (1974)—potency of agent VX is approximately 4 times that of agent GB for AEGL-2 effects (please see derivation for GB AEGL-2) and $C^n \times t = k$ where $n = 2$ and $k = 8.6 \times 10^{-6} \text{ mg/m}^3 \times \text{h}$.</p>
<p>Data adequacy: Based on relative potency estimate from Grob and Harvey (1958) and Sidell and Groff (1974)—potency of agent VX is approximately 4 times that of agent GB for AEGL-2 effects (please see derivation for GB AEGL-2). The scarcity of dose-response data for agent VX forces the AEGL analysis to rely on assumptions of relative potency. Thus, AEGL values for agent VX are derivative. The relative potency assumptions for estimating AEGL-2 values for agent VX from the available database for agent GB need experimental confirmation.</p>

AEGL-3				
10 min	30 min	1 h	4 h	8 h
0.0027 ppm (0.029 mg/m ³)	0.0014 ppm (0.015 mg/m ³)	0.00091 ppm (0.010 mg/m ³)	0.00048 ppm (0.0052 mg/m ³)	0.00035 ppm (0.0038 mg/m ³)
<p>Key reference: Mioduszewski et al. 2002a. Interaction of exposure concentration and duration in determining acute toxic effects of sarin vapor in rats. <i>Toxicol. Sci.</i> 66: 176-184.</p> <p>Secondary references: (1) Grob, D., and Harvey, J.C. 1958. Effects in man of the anticholinesterase compound Sarin (isopropyl methyl phosphonofluoridate). <i>J. Clin. Invest.</i> 37:350-368. (2) Sidell, F.R., and Groff, W.A. 1974. The reactivability of cholinesterase inhibited by VX and sarin in man. <i>Toxicol. Appl. Pharmacol.</i> 27:241-252.</p>				
<p>Test species/strain/gender/number: Based on assumptions previously stated from Grob and Harvey (1958) and Sidell and Groff (1974)—potency of agent VX is approximately 4 times that of agent GB (please see derivation for GB AEGL-3 derived from female Sprague-Dawley rat data) and RBC-ChE₅₀ is part of an anticholinesterase response continuum.</p>				
<p>Exposure route/concentrations/durations: Based on assumption previously stated from Grob and Harvey (1958) and Sidell and Groff (1974)—that the potency of agent VX is approximately 4 times that of agent GB (please see derivation for GB AEGL-3) and the study of rat inhalation toxicity in dynamic mode exposure chamber (Mioduszewski et al. 2000, 2001, 2002a).</p>				
<p>Effects: Derivation of AEGL-3 values based on assumption previously stated from Grob and Harvey (1958) and Sidell and Groff (1974) studies showing that potency of agent VX is approximately 4 times that of agent GB (please see derivation for GB AEGL-3) and from GB vapor exposure study (Mioduszewski et al. 2000, 2001, 2002a) in which lethality and sublethal clinical signs were monitored during and after exposure. Only lethality data reported at this time.</p>				
<p>End point/concentration/rationale: Derivation of AEGL-3 values based on assumption previously stated from Grob and Harvey (1958) and Sidell and Groff (1974) studies showing that potency of agent VX is approximately 4 times that of agent GB (please see derivation for GB AEGL-3) and from GB vapor exposure study (Mioduszewski et al. 2000, 2001, 2002a) of female SD rats exposed to GB vapor. Gender differences for lethality are significant. The LC₀₁ values for GB exposure were multiplied by a factor of 0.25 to estimate the LC₀₁ value for agent VX. These estimated concentrations for VX</p>				

AEGL-3 Continued
LC ₀₁ in female SD rats (the susceptible gender) are the points of departure for agent VX AEGL-3 estimations, which are thus protective. The AEGL values are estimates for VX vapor exposures only.
<p>Uncertainty factors/rationale: Based on assumption previously stated from Grob and Harvey (1958) and Sidell and Groff (1974) studies showing that potency of agent VX is approximately 4 times that of agent GB (please see derivation for GB AEGL-3).</p> <p>Total uncertainty factor: 100</p> <p style="padding-left: 40px;">Interspecies: 3—female rat data. The full default value of 10 is not considered appropriate because the mechanism of toxicity in lab rodents and humans is ChE inhibition.</p> <p style="padding-left: 40px;">Intraspecies: 10—for possible susceptible human individuals. Some individuals possess abnormally low levels of blood cholinesterase and carboxylesterase activity that may make them especially susceptible to the effects of cholinesterase inhibitors such as nerve agents (Morgan 1989; Wills 1972; Opresko et al. 1998). Therefore, a factor of 10 was retained.</p>
Modifying factor: 3 (for sparse VX database).
Animal to human dosimetric adjustment: None applied (insufficient data)
Time scaling: $C^n \times t = k$ where $n = 2$ and $k = 1.16 \times 10^{-4} \text{ mg/m}^3 \times \text{h}$, based on the assumption that the scaling function for agent VX is similar to that derived for agent GB from the experimental rat data of Mioduszewski et al. (2000, 2001, 2002a,b). Extrapolation from 6-h experimental value to 8-h AEGL-3.
Data adequacy: The scarcity of dose-response data for agent VX forces the AEGL analysis to rely on assumptions of relative potency. Thus, AEGL values for agent VX are derivative. The relative potency assumptions for estimating AEGL-3 values for agent VX from the available database for agent GB need experimental confirmation.