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**EVALUATION OF AIRBORNE EXPOSURE LIMITS FOR G-AGENTS:  
OCCUPATIONAL AND GENERAL POPULATION EXPOSURE CRITERIA**

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Aberdeen Proving Ground, MD 21010-5423



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## EXECUTIVE SUMMARY

### PURPOSE

The purpose of this document is threefold:

- (1) The adequacy of existing G-agent (GA, GB, GD) airborne exposure limits (AELs) for the occupational setting and general population are evaluated on the basis of currently accepted risk assessment approaches as well as through the incorporation of any relevant data which has become available since the time the existing AELs were first derived.
- (2) AELs are also derived for the nerve agent GF, for which there are no existing criteria.
- (3) Currently accepted risk assessment methodologies are also used to derive additional exposure criteria which did not previously exist. Specifically, short-term exposure limits (STELs) for the occupational setting as well as acute exposure guideline level one (AEGL-1) for the general population are derived.

### DISCUSSION

The G-type chemical warfare (CW) agents include Sarin (GB), Tabun (GA), Soman (GD) and GF, which are organophosphate ester derivatives of phosphoric acid. Small quantities of CW agents or agent by-products are used by various military and contract laboratories for defensive research purposes, and verification of Chemical Weapons Convention compliance. Although bulk quantities are no longer manufactured in the United States, they currently exist in military stockpiles where they await eventual destruction.

People whose work environment may include chemical weapon materials, whether in storage depots and demilitarization facilities, laboratory research, verification of the Chemical Weapons Convention, remediation and decontamination, or emergency response operations, face potential risks of accidental exposure to these materials. This risk is also shared to a much lesser extent by the general population in communities surrounding areas where chemical agents are stored, transported or processed for disposal. In addition, chemical weapons, whether in foreign or domestic stockpiles, are still considered potential military threats and terrorist targets. The most likely route of exposure is by inhalation, but also may include the direct effects of chemical agent vapor on the eyes.

Existing AELs for GA and GB were promulgated by the CDC (DHHS, 1988); DA PAM 40-8, and DA PAM 385-61 also provide AELs for GD. These AELs include 8 hr/day; 5 day/week TWA, and IDLH (30 min) guidelines for the occupational setting as well as a 72 hr TWA for the general population. However, it should be noted that the latter guideline (general population AEL) is, in fact, a 24 hr/day; 7 day/week TWA for an estimated lifetime exposure. The original AEL was expressed as a 72 hr TWA only to reflect sampling requirements at the time of the original CDC publication (DHHS, 1988).

The process used to derive the existing AELs did not necessarily conform to today's accepted methodologies. In addition, certain additional data and studies have become available since the time of their derivation. The use of additional data and methodologies presumably will allow greater certainty in estimating concentration guidelines which are protective of occupational personnel and the general population.

## **FINDINGS AND CONCLUSIONS**

Findings and conclusions resulting from recalculation of existing exposure criteria and development of new criteria include the following:

(1) The recalculation of existing occupational AELs resulted in concentration values with 2-3 fold differences. In terms of uncertainties inherent in the risk assessment process, these values are deemed within an acceptable range of each other. Therefore, the existing occupational AELs are deemed valid and adequately protective. Recalculated general population AEL values were also similar to existing criteria values. In order to differentiate between the long-term and short-term AELs, occupational worker AELs are referred to as worker population Limits (WPLs) and general population AELs are referred to as general population limits (GPLs).

### **Note:**

(a) The recommended AELs are estimates associated with "no observable adverse effects" in (i) the workforce for an 8 hr/day TWA; 40 hr week, for a lifetime, and (ii) in the general population for a 24 hr/day; 7 days/week, for a lifetime.

(b) Unlike the above "no observable adverse effects" for AELs, the biological endpoint selected for determining the IDLH estimate includes generalized weakness, and signs of systemic G-agent poisoning in addition to less serious effects including miosis, rhinorrhea, and tightness of the chest. IDLH estimates are limited to acute exposures (up to 30 min).

(2) The estimated STELs and AEGL-1 concentration values are presented in the Table below.

### **Note:**

(a) Exposures above the TLV-TWA up to the STEL should be no longer than 15 min, and should not occur more than four times per day. The developed STEL values are based upon acute human exposure data and estimate airborne concentrations associated with "no observable adverse effects" in humans (chemical workforce population).

**Recommended Airborne Exposure Limits (AELs) for GB, GA, GD, and GF in Occupational (WPL) and General Populations (GPL)**

Recommended AEL (mg/m <sup>3</sup> )				
GB	GA	GD	GF	Application
<b>Occupational Worker AELs (WPLs)</b>				
0.0001	0.0001	0.00003	0.00003*	WPL (TWA; 8 hr/day, 5 days/wk)
0.002*	0.002*	0.001*	0.001*	STEL (TWA; 15 min x 4/day)
0.1	0.1	0.05	0.05*	IDLH (30 min)
<b>General Population AELs (GPLs)</b>				
0.000003	0.000003	0.000001	0.000001*	GPL (TWA; 24 hr/day 7 days/wk)
0.0024*	0.0024*	0.0012*	0.0012*	AEGL-1 (30 min)
0.0012*	0.0012*	0.0006*	0.0006*	AEGL-1 (1 hr)
0.0003*	0.0003*	0.0001*	0.0001*	AEGL-1 (4 hr)

- = Developed (no existing criteria).
- WPL = Worker population airborne exposure limit or Occupational AEL (no observable adverse effects)
- GPL = General population airborne exposure limit or General population AEL (no observable adverse effects)
- IDLH- = Immediately Dangerous to Life or Health
- STEL = Short Term Exposure Limit
- AEGL-1 = Acute Exposure Guideline Level -1
- TWA = Time Weighted Average

(b) The acute exposure guideline levels limited to discomfort (AEGL-level 1) are estimates for acute (30 min, 1 hr, and 4 hr) exposure scenarios associated with the lowest observable adverse effects (miosis, rhinorrhea and tightness of chest) in humans (general population).

(3) The AELs for agent GF are presented in the Table below. These values will be necessary where GF is identified or potentially present.

## **RECOMMENDATIONS**

**Recommend continued use of existing occupational AELs (WPLs) for GA, GB, and GD, general population AELs (GPLs) for GA and GB, and incorporation of new AELs derived in this document and presented in the Table above.**

## PREFACE

The work described in this report was authorized under MIPR No. 94-237, Chemical Agent Health Criteria Document. This work was started in May 1994 and completed in February 1998.

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## EVALUATION OF AIRBORNE EXPOSURE LIMITS FOR G-AGENTS: OCCUPATIONAL AND GENERAL POPULATION EXPOSURE CRITERIA

### 1. PURPOSE

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- (3) Currently accepted risk assessment methodologies are also used to derive additional exposure criteria which did not previously exist. Specifically, short-term exposure limits (STELs) for the occupational setting as well as acute exposure guideline level one (AEG1-1) for the general population are established.

### 2. BACKGROUND

#### 2.1 Introduction.

The G-type chemical warfare agents include Sarin (GB), Tabun (GA), Soman (GD) and GF, which are organophosphate ester derivatives of phosphoric acid. Although they are no longer manufactured in the United States, they currently exist in military storage depots/stockpiles where they await eventual demilitarization/destruction. Small quantities are still used by various military and contract laboratories for defense research purposes. Chemical agents, whether in foreign or domestic stockpiles, are still considered as potential military/terrorist threats.

Determination of exposure criteria will depend upon whether the chemicals in question are threshold or non-threshold toxicants. The G-agents have been traditionally classified as "threshold" toxicants, *i.e.*, a minimum dose or level of exposure has been identified which is necessary before toxic responses are seen. This category is characteristic of non-carcinogenic chemicals. In contrast, carcinogens are usually considered 'non-threshold" toxicants, although it is now generally accepted that some carcinogens also have threshold limits.

Although G-agents were first synthesized in the 1940's, significant data gaps in their toxicology still exist. Given that the G-agents were developed for offensive purposes, most of the existing data are directly relevant to acute exposures using low (humans and animals) or high concentrations (animals). The database for GB is more complete than those for other G-agents. It is the only G-agent for which sufficient data exist for deriving AELs. The developed exposure criteria for GA, GD, and GF were based upon extrapolation involving "relative potencies" (ED50's

for mild effects) of these agents compared to GB as proposed by Reutter and Wade (1994). The exposure criteria developed here are based on empirically derived dose-response relationships, where the “response” is defined as the “lowest observed adverse effect level” (LOAEL) of chemical agent exposure in humans.

## 2.2 Chemical and Physical Properties.

The “G” nerve agents, sometimes referred to as “nerve gases”, are fluorine- or cyanide-containing organophosphates. In pure form they are colorless liquids. The nerve agents are all viscous liquids and not nerve “gas”, *per se*. However, the vapor pressures of the G series are sufficiently high for the vapors to be a toxic/lethal hazard. The volatility is an important physical factor to consider in evaluating health hazards criteria. GB is so volatile that small droplets sprayed from a plane or released from a shell exploding in the air may never reach the ground. This total volatilization means that GB is largely a vapor hazard. However, GB liquid can also be a potent percutaneous hazard, especially when exposure involves occlusion with clothing. GD is an intermediate volatility agent, and is therefore, considered both a vapor as well as a percutaneous hazard. GA and GF have the lowest volatility of this group and can be expected to contaminate surfaces for a sufficiently long time to provide a relevant contact (via skin) hazard. Clothing can off-gas G-agents for about 30 min after contact with vapor. The surface persistence of any G-agent can be increased by being thickened with various substances which increase the potential hazard of potential exposure via the intact skin (FM 3-9, 1990).

G-agent solubility in water ranges from complete miscibility for GB to almost total insolubility for GD and GF. The ability of GB and GA to mix with water means that: 1) these agents (and their hydrolysis products) can easily contaminate water sources, and 2) that they will not penetrate skin as readily as the more fat-soluble agents like GD and GF, but are nevertheless toxic by the percutaneous route of exposure. G-agents spread rapidly on surfaces, such as skin; while thickened agents spread very slowly. The moist surfaces in the lungs absorb all the agents very well. Further details of G-agent physical and chemical properties are listed in Table 1.

## 2.3 Biological Properties.

### 2.3.1 Mechanism of Action.

The most commonly accepted mechanism by which organophosphorus nerve agents cause toxic effects is through the phosphorylation of the active site of the enzyme acetylcholinesterase (AChE) resulting in a buildup of the neurotransmitter acetylcholine at cholinergic synapses. These include endings of the autonomic nerves to the smooth muscle of the iris, ciliary body, bronchial tree, gastrointestinal tract, bladder, blood vessels, salivary glands, secretory glands of the gastrointestinal and respiratory tracts, cardiac muscle and sweat glands. With loss of AChE activity, there is cholinergic overstimulation of nerve fibers resulting in uncontrolled, disorganized target organ responses. The accumulation of acetylcholine at these sites results in characteristic muscarinic signs and symptoms. The accumulation of acetylcholine at the endings of motor nerve to voluntary muscles and in some autonomic ganglia results in nicotinic signs and symptoms. Finally, the accumulation of excessive acetylcholine in the brain



and spinal cord results in characteristic CNS symptoms. Until the tissue cholinesterase enzymes are restored to normal activity, there is a period of increased susceptibility to the effects of another exposure to any nerve agent. This period of increased susceptibility occurs during the enzyme regeneration phase which could last from weeks to several months.

Theoretically, if the actions of nerve agents were limited to this mechanism of action, their acute effects should not outlast the inhibition of the enzyme at the target sites. Indeed, some systems develop tolerance rapidly, so function returns to normal even before there is substantial regeneration of measurable enzyme activity. Although the blood may be considered a target site, it is probably not a target of toxicity but more of a sink for anti-ChE agents. Measurements of plasma and erythrocyte acetylcholinesterase activities constitute a very sensitive index of exposure to AChE agents. However, they by no means imply anti-AChE intoxication (Koelle, 1994). It can be demonstrated that, even with over 99% inhibition of circulating cholinesterases, animals (and presumably humans) can survive without oxime or atropine treatment (Grob and Harvey, 1958). Recovery from the effects of inhibitors may depend on rapid regeneration of ChEs, particularly some AChE isoenzymes; desensitization of the postsynaptic membrane, a phenomenon that limits the response to accumulated AChE; or compensatory changes in presynaptic and postsynaptic receptors.

In addition to reacting with ChEs, organophosphates (OP's) can react with other components in nerves or in effector organs. OP materials may exert direct effects on the cholinergic receptor, or on its phospholipid environment, at both CNS and PNS synapses (Karczmar, 1967; Van Meter et al., 1978; Kuba et al., 1974; Gage, 1976; Baron, 1981). White and Stedman (1931) suggested that, in addition to inhibiting AChE, OP compounds have an effect on the site where the ACh molecule reacts at the neuromuscular junction. Similarly, Miquel (1946) suggested that OP compounds react with other sites on the muscle, in addition to the enzyme. Studies by Xavier and Valle (1963) disclosed that Phosdrin, an OP insecticide, was able to affect both the ACh receptor and the ion channel associated with it, without affecting AChE itself. They also found, using two different methods, that physostigmine and neostigmine, in addition to producing blockade of AChE, potentiated the muscle response to ACh when applied in the presence of complete AChE blockade.

### 2.3.2 G-agent Vapor Intoxication: Local vs. Systemic Responses.

The effects of acute intoxication with anticholinesterase agents are manifest by muscarinic and nicotinic signs and symptoms (Table 2). Effects primarily associated with local exposure result from the action of vapors or aerosols at their site of contact, for example, with the eyes or respiratory tract (Table 2). Effects which follow systemic absorption by any route occur at sites distant from their initial point of exposure.

#### 2.3.2.1 Local Responses.

Although lungs, eyes and skin can absorb G-agent vapor, the lungs and the eyes absorb nerve agent vapor more rapidly. Changes occur in the smooth muscles of the eye, resulting in miosis (constriction of the pupil) and in smooth muscle and secretory glands of the bronchi, producing bronchial constriction and excessive secretions in the upper and lower airways. In high vapor concentrations, the nerve agent is carried from the lungs throughout the circulatory system where widespread systemic effects may appear in less than 1 minute. The local effects given below are believed to be primarily due to inhibition of tissue cholinesterase at the site of action and may not correlate with inhibition of the blood cholinesterases.

Ocular Responses. The initial manifestation of responses are often a function of the most likely route(s) of exposure, especially at very low concentrations. After exposure to vapors or aerosols, ocular and respiratory effects generally appear first. The ocular effects are characterized by miosis (one of the earlier signs of exposure), conjunctival congestion, ciliary spasm, pain on accommodation, and eye-associated headache and browache.

Respiratory Effects. Respiratory effects include watery nasal discharge, tightness of the chest, and wheezing due to the combination of bronchoconstriction and increased bronchial secretion.

Percutaneous Effects. After percutaneous absorption of G-agent liquid/vapor, localized sweating and muscular fasciculation in the immediate vicinity are generally the earliest manifestations. However, under conditions in which there is no eye or respiratory protection, these effects would likely be preceded by local ocular and respiratory effects.

#### 2.3.2.2 Systemic Responses.

Generally speaking, systemic responses to G-agent vapor exposure will follow the initial local responses and are also correlated with dose and pharmacokinetic properties of the compound involved. However, of all the signs and symptoms, listed in Table 2, those associated with the central nervous system (*e.g.*, drowsiness, difficulty in concentrating, emotional lability, excessive dreaming, *etc.*) are among the earliest detected. Severe intoxication, however, is manifest by extreme salivation, involuntary defecation and urination, sweating, lacrimation, bradycardia, and hypotension, respiratory depression, collapse, convulsions and death. Muscarinic, nicotinic, and central nervous system effects all contribute to adverse respiratory effects; they include laryngospasm, increased tracheobronchial and salivary secretion, and peripheral and central respiratory paralysis. Although blood pressure may fall alarmingly and cardiac irregularities may intervene, these effects probably result as much from hypoxia as from the specific actions mentioned, inasmuch, because they can often be reversed by the establishment of adequate pulmonary ventilation.

Signs and symptoms of nerve gas poisoning as listed by Grob (1956) are given in Table 2. They include both local effects (eye, respiratory, and percutaneous) as well as systemic effects which can occur at sites distant from the site of absorption (*e.g.*,

central nervous system). The onset and sequence of their appearance varies with the dose and route of absorption.

### 2.3.3 Assessing the Severity of G-agent Intoxication.

G-agent vapor intoxication will likely involve ocular, nasal, and respiratory exposure in which signs and symptoms result from local as well as systemic effects. The sequence and intensity of particular signs will depend upon the exposure conditions, especially the concentration of agent and the exposure duration.

It is not uncommon to find responses to relatively short duration, high concentration G-agent exposures- categorized according to levels of severity, as given in Table 3 (Vojvodic, 1981). However, most such classification schemes were based upon a rather shallow probit slope of 7.3, calculated by averaging across species and across time (Christensen et al., 1958). Reutter et al., (1992); and Reutter and Wade, (1994) indicate that the slope calculated by Christensen et al., (1958) is not supported by the actual data and that the slope of the dose response curve is probably at least 12. They also state that given the steep dose- response curve, normal biological variation, and the potency of the G-agents, there is considerable overlap of the different categories, and it is not realistic to assign dose-bands. For example, there is no statistical difference between doses producing moderate-to-severe effects and those producing lethality (Cresthull et al., 1957).

### 2.3.4 Acute Toxic Effects of G-agents by Inhalation Exposure.

Although nerve gases may be absorbed through any body surface, the route through which absorption is most rapid and complete is the respiratory tract, resulting in dyspnea, rales, bronchorrhea, and tachypnea. The acute lethal action of the G-agents and other anti-AChE compounds results from their attack on the respiratory system at several levels: bronchoconstriction and excessive tracheobronchial secretion, paralysis of the diaphragm and other respiratory muscles, and depression of the respiratory center of the CNS. The predominant site of respiratory failure or malfunction varies with the species (Koelle, 1994) and route of exposure.

Exposure to a threshold lethal concentration of Sarin vapor, for example, would probably result in death within one to a few hrs. Exposure to several times the lethal concentration would probably be fatal within min. Estimates of lethal (LCt50) and effective (ECt50) concentration-time for responses in a human population to an acute exposure of G-agent vapors are listed in Table 4.

Table 2. Signs and Symptoms of G-agent Poisoning (From Grob, 1956)

Site of Action	Signs and Symptoms
<p style="text-align: center;"><u>Muscarinic</u></p> <p>Pupils Ciliary body</p> <p>Conjunctivae Nasal Mucous Membranes Bronchial Tree</p> <p>Sweat Glands</p>	<p style="text-align: center;"><b>Following Local Exposure</b></p> <p>Miosis, sometimes unequal Frontal headache; eye pain on focusing; dimness of vision; occasional nausea, vomiting Hyperemia Rhinorrhea; hyperemia Tightness in chest, prolonged wheezing on expiration, cough Sweating at site of exposure to liquid</p>
<p style="text-align: center;"><u>Nicotinic</u></p> <p>Striated Muscle</p>	<p>Fasciculations at site of exposure to liquid</p>
<p style="text-align: center;"><u>Muscarinic</u></p> <p>Bronchial Tree</p> <p>Gastrointestinal</p> <p>Sweat Glands Salivary Glands Lachrymal Glands Heart Pupils Ciliary Body Bladder</p>	<p style="text-align: center;"><b>Following Systemic Absorption</b></p> <p>Tightness in chest, prolonged wheezing on expiration, dyspnea, chest pain, increased bronchial secretion, cough, pulmonary edema, cyanosis Anorexia, nausea, vomiting, abdominal cramps, epigastric and substernal tightness with heartburn and eructation, diarrhea, tenesmus, involuntary defecation Increased sweating Increased salivation Increased lachrymation Slight bradycardia Miosis, occasionally unequal Blurring of vision Urinary frequency, involuntary micturation</p>
<p style="text-align: center;"><u>Nicotinic</u></p> <p>Striated Muscle</p>	<p>Easy fatigue, weakness, muscular twitching, fasciculations, cramps, generalized weakness including muscles of respiration Pallor, occasional elevated blood pressure</p>
<p>Sympathetic Ganglia <u>Central Nervous System</u></p>	<p>Giddiness, tension, anxiety, jitteriness, restlessness, emotional lability excessive dreaming, insomnia, nightmares, headache, tremor, apathy, withdrawal with depression, altered frequency spectrum of spontaneous EEG, drowsiness, difficulty in concentrating, slowness of recall, confusion, slurred speech, ataxia, generalized weakness, coma with absence of reflexes, Cheyns-Stokes respiration, convulsions, depression of respiratory and circulatory centers with dyspnea, cyanosis and fall in blood pressure</p>

**Table 3. Characteristic Clinical Signs/Symptoms Associated with Graded Levels of Severity of G-agent Toxicity (From Vojvodic, 1981)**

<b>Severity</b>	<b>Clinical Sign/Symptoms of Poisoning</b>
<b>Mild</b>	<p><b>CNS:</b> Restlessness, emotional lability, increased irritability, disturbances in sleep, frontal headache</p> <p><b>Visual:</b> slight reduction of vision, especially at dusk and in artificial light, pain in the eyes, especially on convergence Miosis, pupils react weakly to light, sometimes anisocoria. The changes in the eyes can be absent if the eyes are not directly exposed to the nerve gas.</p> <p><b>Respiratory:</b> sensation of pressure and tightness in the chest, slight difficulty in breathing, rhinorrhea.</p> <p><b>Cardiovascular:</b> pulse can be slightly slowed.</p> <p><b>Gastrointestinal:</b> pain in the region of the stomach, mild heartburn with disturbances in appetite, stool normal or watery, urination normal.</p>
<b>Moderate</b>	<p>In addition to the symptoms reported for mild poisoning, there is also a feeling of fear which can result in panic. Headache, inadequate reactions to the environment, increased reflex sensitivity, fibrillation, and fasciculation of the muscles. The pupils are narrowed to a "pin head," do not react to light, and lacrimation is increased. The other ocular symptoms are the same as in mild poisoning, but more pronounced. Rhinorrhea, labored breathing involving auxiliary respiratory musculature •The pulse is rhythmic, slow, and heart chamber filling is good. The blood pressure can be increased slightly. There are intensive gastric pains, nausea, increased salivation, and vomiting. The stool is liquid, and urination is frequent. The body temperature is decreased slightly.</p>
<b>Severe</b>	<p>The symptoms are the same as in moderate poisoning, but more pronounced. The feeling of fear is replaced by terror. Vertigo, headache, speech disturbances, loss of orientation, paresthesia, loss of consciousness. Signs include: muscular fibrillation, tremor which initially involves the head, then the upper extremities, and finally, the entire body. Muscular hypertonicity, spastic contractions of the individual muscles, then entire groups of muscles, and finally, generalized clonic-tonic convulsions. After a phase of central nervous system excitation, there is a phase of inhibition with coma. Copious-perspiration and pronounced cyanosis are visible on the skin. The changes in the eyes are initially the same as in the moderate form. However, as poisoning rapidly develops, miosis can be totally absent, replaced by mydriasis and exophthalmos. If miosis is present, it decreases gradually and disappears at death. The respiratory disorders are very pronounced, rhythm is disturbed, the respiratory excursions are irregular, respiration is noisy ("harsh and wheezing"). The pulse is initially slowed (sometimes accelerated when the blood pressure is slightly increased). As the intoxication progresses, the blood pressure drops, the pulse becomes weak, and filling decreases. The heart sounds are muffled and indistinct. Defecation and urination are involuntary. Blood cholinesterase activity is decreased to 10-20% of baseline (to 1-5% in the case of death), and serum activity is less than 10% of the normal value</p>

Table 4. Summary of Human Toxicity Estimates for G-Agent Vapor Exposure Recommended by Reutter and Wade (1994)

	GA	GB	GD	GF
Exposure Dose	Percutaneous Vapor (mg.min/m <sup>3</sup> )			
LCt50	15000	10000	2500	2500
ECt50 (mild effects)	2000	1200	300	300
	Vapor Inhalation (mg.min/m <sup>3</sup> )			
LCt50	70	35	35	35
ECt50 (severe effects)	50	25	25	25
	Ocular or Nasal Vapor (mg.min/m <sup>3</sup> )			
ECt50 miosis	0.50	0.50	0.25	0.25

### 2.3.5 Central Nervous System (CNS) Effects.

Even if the action of anticholinesterases were limited to the inhibition of postsynaptic AChE, the complex circuitry of the brain provides ample opportunity for effects at other sites. Because brain cholinergic pathways are diffuse and connect with many other systems, overactivity or blockade of cholinergic synapses can lead to abnormal activity in many other neurons. A number of transmitters and bioactive substances can be affected indirectly or directly by cholinergic agonists (Glisson et al., 1972). Among those in question are part of the GABA system, which are important in brain excitability and epileptogenesis (Bowery et al., 1976), as well as those involving peptide transmitters and bioactive peptides (O'Neill, 1981). It is unknown whether these effects are brief or long-lasting. However, the circuits are complex, and even a temporary perturbation might lead to reverberations that persist for a long time. The biological significance of such perturbations can only be speculated at this time.

#### 2.3.5.1 OP-type Pesticides.

Most of the human behavioral data obtained on the neurotoxicity of OP compounds have been recorded from occupational exposures to insecticides. The reason for discussing these data here is to briefly illustrate the possible scope of behavioral effects of OP compounds as a class. Whether or not members of this chemical class (nerve agents or various pesticides) possess similar or identical profiles in terms of both their CNS and behavioral effects is still being debated. Metcalf and Holmes (1969) tested industrial and agricultural workers with both behavioral and electrophysiological

techniques. The most obvious signs of intoxication were disturbed memory and difficulty in maintaining alertness and attention. The EEG showed waveforms suggestive of narcolepsy, perhaps corroborating the inability to maintain alertness. Levin and Rodnitzky (1976) reviewed the effects of OP compounds in humans, both in experimental and industrial settings, and came to the conclusion that the most important signs of intoxication were memory deficits, linguistic disturbances, depression, anxiety, and irritability. The long persistence of symptoms has also been reported by Coye *et al.* (1986) and Savage *et al.* (1988), even after serum cholinesterase levels had returned to normal. Headache, giddiness, paresthesia, and ocular symptoms were most commonly observed in workers exposed to Fenthion (O,O-dimethyl-O-(4-methylmercapto-3-methylphenyl)-phosphorothioate). These workers also had significantly reduced serum cholinesterase levels (Misra *et al.*, 1985). These studies suggest that the repeated exposure of human subjects to some OP pesticide compounds can have long-lasting effects, sometimes even after the usual biochemical indices of exposure, such as serum cholinesterase, have returned to normal. Behavioral tolerance to OP exposure develops rapidly, but this tolerance may hide to some extent the real intoxication that has already taken place. Annau (1992), reviewed open literature studies which provide evidence of the behavioral effects of OP compounds (nerve agents and insecticides) at low doses. Because most of these studies are clinical and epidemiological, their utility is limited to descriptions of responses rather than dose-response relationships.

#### 2.3.5.2 OP Nerve Agents.

Grob and Harvey (1953, 1958) described the CNS effects of human subjects exposed to repeated oral administration of Sarin. Signs of muscarinic poisoning (anorexia, nausea, and tightness of the chest, abdominal cramps, vomiting, diarrhea, salivation, and lacrimation) appeared along with CNS effects consisting of tension, anxiety, emotional lability, and insomnia. With more prolonged exposure, headache, drowsiness, mental confusion, and slowness of recall were additional symptoms recorded. Changes in the EEG consisting of a greater percentage of slow waves and increased amplitude were also seen. Bowers *et al.* (1964) studied the behavioral effects of VX in humans and noted responses very similar to those described above. Subjects had difficulty concentrating, remembering tasks they had to perform, and were somewhat irritable. Thought processes seemed to fade away continually during the exposure and, when present, were exceedingly slow. Duffy *et al.* (1979) showed that when EEG measures were taken, even 1 year after workers had been exposed to OP compounds, significant alterations could be seen in beta activity, as well as in several other frequencies. However, Duffy *et al.* (1979) wrote that he could not distinguish individual behavioral profiles (agent workers *vs.* control group) as being abnormal.

The results of previous human studies, (Grob *et al.*, 1953; Grob, 1956a; Grob, 1956b; Grob and Harvey, 1958), suggested that complete recovery from light or moderate nerve-gas poisoning was possible. However, Spiegelberg (1961, 1963) observed what he described as psychopathological-neurological delayed lesions in former workers in CW production plants for the Wehrmacht. Because the Spiegelberg reports were primarily clinical observations rather than a controlled scientific study (exposure conditions were

unknown and “control” groups were not mentioned) it is difficult to conclude whether or under what conditions nerve agent exposure may result in long term behavioral effects.

The Committee on Toxicology, National Research Council (NRC), was requested by the U. S. Army to study the possible chronic or delayed adverse health effects incurred by those who participated in chemical agent testing at Edgewood Arsenal during 1955-1975. The primary health concern regarding these subjects was that long-term health effects might occur in the form of subtle changes in EEG, sleep pattern, and behavior, such as increased irritability, inability to concentrate and depression that could persist for more than a year. In summary, the responses to a questionnaire about current health status by subjects exposed to these chemicals suggest that, as a group, these subjects were no different from a control comparison group or from the remainder of the test subjects. If subtle changes, occurred, they were not revealed by the subjects’ answers about their current health status. Post-test admission to Army or VA hospitals for mental disorders did not appear to be significantly increased, either during the years immediately following testing or later. There was a borderline significant increase in malignant neoplasms among soldiers who were admitted to VA hospitals (but not Army hospitals) and were exposed to anticholinesterases, compared with those who received no chemical testing. The neoplasms occurred at various sites, and no consistent pattern was seen. However, in interpreting these data, based upon a review of National Cancer Institute studies of animal bioassay for carcinogenesis at maximal tolerated doses of ten anticholinesterase organophosphate insecticides, the NRC panel stated that anticholinesterase compounds, as a pharmacologic class, were unlikely to have induced malignancies among Edgewood subjects (NRC, Final Report, 1985).

### 2.3.6 Delayed Neuropathy.

Degeneration of particular regions of the nervous system is a well characterized adverse health effect of human and animal exposure to many OP esters that may or may not also display anti-AChE properties (Johnson, 1975; 1981; Wagner, 1983; Faust and Opreko, 1988). Some neuropathic OP esters can precipitate prominent neurologic abnormalities after a single exposure (as well as after multiple exposures), the clinical disease usually beginning within 2-3 wks. At some time during this clinically quiescent period, a stereotyped sequence of neuropathology changes takes place that leads to the appearance of sensorimotor neuropathy. The degree of clinical impairment and the prognosis for functional recovery depend directly on the extent of nervous system damage, which in turn depends on the neuropathic potency of the responsible OP compound, as well as the dose and duration of exposure. Delayed neuropathy results from direct cellular damage caused by the inactivation of a specific enzyme, neuropathy target esterase (NTE) but not of AChE. This syndrome first received widespread attention in the 1920s, when some 20,000 cases developed in the southern United States among persons who drank “Jamaica Ginger” that was adulterated with an organophosphate ester TOCP (Smith et al., 1930). In delayed neuropathy, there is a symptomless period of 5 to 30 days followed by some initially mild symptoms, such as weakness, tingling, and muscle twitching in the legs. A flaccid paralysis eventually develops, first in the legs and then progresses to the hands and thighs. Not all animal species are susceptible to delayed

neuropathy. Mice and rats are resistant, whereas humans, chickens, cats, and sheep are susceptible to this effect of organophosphates (Abou-Donia, 1981). No neuropathies were reported by Weimer *et al.* (1979) following chronic exposure of mice, rats, and dogs to 0.001 and 0.0001 mg/m<sup>3</sup> GB for six hrs per day, five days per week for up to one year. In contrast, Husain *et al.* (1993) reported delayed neurotoxic effects in mice following repeated inhalation exposure to a nominal concentration of 5 mg/m<sup>3</sup> GB, for 20 min per day for 10 days. The hen (Olajos, 1979) and cat demonstrate syndromes similar to that seen in humans (Gordon *et al.*, 1983; Johnson, 1975). However Goldstein (1985) did not observe classical delayed neurotoxicity with single large doses (1 mg/Kg, s.c., pretreated with atropine and physostigmine) of both GB and GD in the cat. In subacute experiments with GB (2.5 or 5.0 µg/Kg/day to a total of 25 µg/Kg) and GD (3.5 or 7.0 µg/Kg/day to a total of 35 µg/Kg), no signs of neuropathy were found (Goldstein, 1985). Although there were functional changes in the primary sensory -neuron in the peripheral and central processes of the subacutely treated cats, there were no neurological deficits and no physiological changes in these animals, suggesting that the above alterations are reversible or, in the least, unable to affect the animals normal behavior (Goldstein, 1985).

Vranken *et al.*, (1982) studied the in-vitro inhibition of hen brain NTE activity by chemical agents Tabun (GA), Sarin (GB), Soman (GD), and VX. All of the agents studied inhibited NTE with the exception of VX. Gordon *et al.* (1983) estimated that doses of nerve agent that cause 70 to 80 % inhibition of NTE are necessary to produce experimental neuropathy. In the case of GB, the syndrome is produced by giving supralethal doses (30 x LD50) in combination with prophylactic protection against the acute effects of GB poisoning. Under such requirements, the probability of delayed neuropathy occurring as a result of exposures to threshold dose conditions of G agents is remote.

Tests of GA in chickens at 120 times the LD50 dose elicited mild neuropathic symptoms in one of two hens that survived the dosage divided into two daily injections, but no delayed neuropathy was observed in survivors of a single dose (Willems *et al.*, 1984). The authors concluded that even higher doses of GA would be needed to produce the clinical signs of delayed peripheral neuropathy. If human populations were ever exposed to these massive doses (greater than 120 times the LD50 value), the likelihood of death is very high, so the possibility of delayed neuropathy is not a relevant concern with GA exposure.

An "intermediate syndrome" of neurotoxic effects has been described in several cases of insecticide exposure (Senanayake and Karalliedde, 1987). The onset of the "intermediate syndrome" paralysis was 24 to 96 hrs after poisoning, well after the acute cholinergic crisis had ended and before the expected onset of delayed neuropathy. The muscles involved in the intermediate syndrome were different from those that are involved in delayed neuropathy and unfortunately included the respiratory muscles. Nothing is known about the ability of nerve agents to cause this intermediate neurotoxic syndrome.

### 2.3.7 Cardiac Complications.

G-agent-induced cardiac complications have been reviewed by Munro *et al.* (1994) and are summarized below. Because the database for such effects is very limited, it may be appropriate to consider data regarding such effects in organophosphate insecticides and their relevance as “potential” health problems with nerve agents. Among the list of possible delayed abnormalities that can result from a single exposure to organophosphate insecticides are serious and often fatal cardiac complications, which develop after apparent recovery from acute toxic effects (Hirshberg and Lerman 1984; Kiss and Fazekas 1979; Ludomirsky *et al.*, 1982). The cardiac complications presented most often are heartbeat irregularities (arrhythmias).

Electrocardiogram (EKG) abnormalities in a human that persisted for four weeks have been described in a single case of acute exposure to a nerve agent (Sidell, 1974). However, these may have resulted from myocardial infarction--perhaps hypoxia, as opposed to a direct toxic effect on the cardiac tissues. Additionally, cardiac lesions have been found in animals surviving “high” doses of nerve agents (McLeod 1985; Singer *et al.*, 1987). Studies on dogs (Jacobson *et al.*, 1954; and Weimer *et al.*, 1979) also suggest that EKG changes may occur following prolonged inhalation exposures to GB. However, all the aforementioned cardiac effects (arrhythmias, EKG changes, and lesions) may be secondary to primary effects on the brain (e.g., anoxia) following nerve agent and pesticide exposures (Weidler, 1974). Recently Arsura *et al.* (1987) described complications that can result from the use of anticholinesterase medication in patients who already have cardiac problems. A possibility exists, therefore, for the exacerbation of preexisting cardiac problems with nerve agent exposure, although there is no direct evidence for this.

### 2.3.8 Mutagenicity, Carcinogenicity, Teratogenicity and Reproductive Toxicity.

Except for an epidemiological follow-up survey of humans exposed to G-agents conducted by the NRC, no data could be found to assess mutagenicity, carcinogenicity, teratogenicity and reproductive toxicity in humans. Therefore the potential for such effects of G-agents will be inferred from animal and *in vitro* studies.

#### 2.3.8.1 Mutagenicity.

There are a number of tests that are designed to determine whether a chemical can damage deoxyribonucleic acid (DNA). Because DNA provides the fundamental code for normal cell function, permanent changes in DNA, called mutations, can result in cell death and permanent changes in cell function. If these mutational events occur in germ cells in the ovaries or testes, the results might be passed on to the next generation as inherited abnormalities. Damage to the DNA of other cells can result in the transformation of a normal cell into a malignant or cancerous cell (carcinogenesis). Damage to the DNA of cells in a developing fetus can result in death or transformation of a cell leading to abnormal development (teratogenesis) (Chemical Stockpile Disposal Program

Final Programmatic Environmental Impact Statement; Appendix B. Toxicity of Warfare Agents and Their Breakdown Products, January, 1988). For these reasons, the tests for DNA damage by nerve agents are important in assessing the possible human health hazards presented by nerve agents (Kimball and Munro, 1981).

Of the studies published to date, only those with GA (Wilson *et al.*, 1994) suggest some evidence of DNA damage. Five mutagenicity tests performed on GA resulted in indications of mutagenicity in Salmonella spp. assays with S-9 and it was a direct-acting mutagen to mouse lymphoma cells. GA did not promote unscheduled DNA synthesis in rat hepatocytes; it induced sister chromatid exchanges in mouse cells in-vitro but not in-vivo. The conclusion that GA is a weakly acting mutagen is supported by the fact that it was mutagenic in only three of the five assays, and that increases in mutagenicity were often less than 2-fold greater than that of the controls and occurred near toxic levels (Wilson *et al.*, 1994).

Organophosphate compounds related to nerve agents have given positive results in certain tests for DNA damage (Malhi and Grover, 1987; Nishio and Uyeki, 1981); however, with other assays and other compounds, there have been negative results (Velazquez *et al.*, 1987) or evidence of only weak mutagenicity (Velazquez *et al.*, 1986). It is important that the nerve agents be submitted to a variety of assays before conclusions are drawn as to their ability to damage DNA.

Goldman *et al.*, 1989 evaluated GA for mutagenicity by the bacterial (Ames) mutagenicity assay with and without metabolic activation. Without activation, GA was not mutagenic. With metabolic activation, GA was not cytotoxic at the levels tested and exhibited a slight but significant positive dose response in 8 of 11 trials using tester strains TA 98, 100, 1535 and 1537. None of the response curves showed a doubling of revertant rate over control values, and only 4 trials achieved as much as a 50 % increase. This finding supports similar results from in vitro mammalian cell assays and murine lymphoma cell mutations, leading to the conclusion that GA is a weak mutagen.

Nasr *et al.* (1988) evaluated GA for genotoxicity by the induction of chromatid exchanges in cultured Chinese hamster ovary (CHO) cells at concentrations up to 200 mU/mL with and without S-9. The results indicated that GA was both toxic to the cells at high levels and behaved as a weak mutagen in this assay. Chromatid exchanges increased linearly with GA concentration, but the number of exchanges was never more than twice the number of the controls.

GA was evaluated for mutagenicity by the point mutation assay at the thymidine kinase locus in the mouse lymphoma cell (L5178Y). Kawakami, *et al.*, (1989). The agent was tested at several concentrations 10 - 200 µg/L with and without rat liver S-9 activation. The study showed that there was a linear dose-mutation response in mouse lymphoma cells to GA without rat liver S-9 activation.

The mutagenic potential of agents GB (Sarin type I and type II) and GD was studied by Goldman, *et al.*, (1987). No significant evidence was produced which suggested that these agents might be mutagenic. Negative results were found in the

Ames Salmonella bacterial gene mutation assay using 5 different strains. When mammalian cells (mouse lymphoma) were exposed, no agent-related mutagenesis was found in CHO cells exposed *in vitro* to either agent. Sister chromatid exchanges scored in lymphocytes from mice exposed *in vivo* to the maximally tolerated dose of GB or GD also showed no mutagenic effect. Rat hepatocytes were used to detect possible DNA damage *in vitro* by measuring their unscheduled DNA synthesis following exposure to GB and GD. All of the *in vitro* assays were conducted with and without metabolic activation. The results lead to the conclusion that Sarin and Soman are not mutagenic.

#### 2.3.8.2 Carcinogenicity.

The only data describing the carcinogenic (cancer-causing) potential of GB comes from a study by Weimer *et al.* (1979) in which dogs, rats (colony and Fischer 344 strain) and mice ("A" strain-- chosen because of the susceptibility of this rodent species to certain types of tumors) were exposed to airborne GB. Exposure to low doses of GB for 6 hr/day, 5 days/week, for up to 52 weeks at concentrations of 0.001 or 0.0001 mg/m<sup>3</sup> (maximum cumulative exposure of 10.5 mg-min/m<sup>3</sup>) did not result in an increase of tumors and had no dominant lethal mutations nor adverse effect on reproductive performance through three generations. Note, however, that these doses were very low, and did not produce any overt signs of toxicity. Weimer *et al.* (1979) reported that the only identified tumor that could possibly be related to agent exposure was pulmonary adenoma which occurred in 3 of 19 *strain A* mice exposed to the 0.0001 mg/m<sup>3</sup> and in 3 of 20 *strain A* mice exposed to 0.001 mg/m<sup>3</sup>. Although the results suggest that GB is not carcinogenic, this study was not designed to be a definitive study of the carcinogenic activity of GB, particularly with the limited doses employed.

#### 2.3.8.3 Teratogenicity.

Agent GB has been tested for effects on the fetus or embryo by giving pregnant rats and New Zealand White (NZW) rabbits oral doses of GB during the period of major fetal organ development (LaBorde and Bates, 1986). Two forms of GB with either the tributylamine stabilizer (Type I) or the dicyclohexylcarbodiimide stabilizer (Type II) were tested. The pregnant animals were sacrificed on day 20 of their pregnancy, and the litters were examined for a number of biological effects: number and status of the fetal implants, individual fetal weight, and fetal malformations. No evidence of developmental toxicity was found with either Type I or Type II GB in either species, even at doses of GB that resulted in maternal toxicity or mortality. Mehl, *et al.*, (1994), found that in contrast to trichlorfon and dichlorvos, Soman did not reduce brain weight in offspring when administered to guinea pigs between day 42 and 46 of gestation.

Likewise, GD was also tested using the above methods (Bates, *et al.*, 1990). Maternal rats and rabbits in the high-dose groups exhibited statistically significant increases in toxicity and mortality when compared to controls. There were no significant dose-related effects among dose groups in the prevalence of postimplantation loss,

malformations, or in average body weight of live fetuses per litter. There was no evidence of increased prenatal mortality or fetal toxicity in the CD rat or the NZW rabbit following exposure to GD, even at a dose that produced significant maternal toxicity.

#### 2.3.8.4 Reproductive Toxicity.

Another study evaluated testicular atrophy in Fischer rats after a six-month exposure to low doses of GB: no differences were found between treated and non-treated animals (Morin and McKinley, 1976). Studies utilizing higher doses of GB to rats are needed to more accurately ascertain the risk of GB exposure on human reproductive parameters. Furthermore, because rats (and mice) show a relative resistance to the acute toxicity of GB (a factor that does allow testing at higher concentrations), it is also important to test an animal species that does not show the rapid detoxification of GB seen in rats and mice. These studies are further discussed in section 3.4 "Derivation of Airborne Exposure Levels for GB: The Critical Study". Goldman *et al.* (1988) tested Sarin and Soman in a battery of *in vitro* tests for mutagenicity and found no evidence of an effect.

Denk (1975) reported the results of another developmental study of GB in rats exposed to GB vapor (0.0001 and 0.001 mg/m<sup>3</sup>) for 6 hr/day, 5 days/wk, for varying time periods. In separate series of experiments, male rats were exposed for periods of 1 wk to 1 year and then mated to unexposed females; mated pairs of rats were exposed to GB for 1 - 3 weeks or until pups were whelped; and male and female rats were exposed to GB for 10 months and then mated. Both F1 and F2 generations were each mated. In summarizing the results, Denk (1975) reported that GB had no adverse effects with respect to dominant lethal mutations, reproductive performance, fetal toxicity, and teratogenesis at the doses and by the route used."

A study by the National Research Council (1982, 1985) on the long-term health effects of nerve agents administered to military volunteers found no evidence of carcinogenic or mutagenic effects associated with nerve agent exposure. Prior to 1986, DA Pamphlet 40-8, (Medical Services, Special Occupational Safety and Health Standard for the Evaluation and Control of Occupational Exposure to Agent GB, August 1982) identified the absence of an adequate toxicological database concerning the potential teratogenicity of agent GB, and directed that special considerations be enacted for employment of women in areas with potential for agent GB exposure. However, in 1986, available toxicological data on GB were reviewed by the Committee on Toxicology of the National Research Council, and the consensus of opinion was that restrictions on the employment of women in areas with potential GB exposure be discontinued because they could not be supported by the available data. The requirements for the development and implementation of a pregnancy surveillance program, as stated in AR 40-5, Medical Services, Preventive Medicine, 30 AUG 1986, are no longer in effect.

In a review of the hazardous substances databank (HSDB), Registry of Toxic Effects of Chemical Substances (RTECS) and Material Safety Data Sheets (MSDS) concerning the G-agents, no data applicable to the above topics were found, but

references were made regarding potential hazards of organophosphates in “general” which are summarized below under the following categories:

(1) Reproductive Hazards

- Of the OP compounds tested for teratogenicity in animals, most have proved negative, however, some have caused lower fetal birth weights and/or higher neonatal mortality.
- Sporadic reports of human defects related to organophosphates have not been fully verified.

(2) Carcinogenicity

Although the weight of evidence suggests that G-agents are not carcinogens, some controversy exists as to whether organophosphates, as a class, may be considered non-carcinogenic.

(3) Genotoxicity

- Cytogenetic studies of organophosphate-exposed workers have suggested possible increases in frequencies of chromosome aberrations, but the evidence is not compelling.
- Two generations of an Israeli family who had been chronically exposed to organophosphates had 100-fold amplification of the “silent” allele of the ChE gene on chromosome 3; the absence of amplification of other genes on chromosome 3 suggests that the amplification of the ChE gene was a specific response to OP exposure. Whether this was a beneficial compensatory response or adverse, and indicative of genotoxicity, is not clear.

2.3.8.5 Existing Exposure Limits and the Basis for Their Derivation.

2.3.8.6 Existing Airborne Exposure Limits (AELs) For G-agents.

Existing AELs for nerve agents GA, GB, and GD are summarized in Table 5. They can be found in 53 FR8504 (CDC/DHHS, 1988); DA PAM 40-8, 4 DEC 1990; and DA PAM 385-61, March, 1997. Existing exposure limits specific for GB vapor are summarized in Table 6, and include limits proposed by McNamara and Leitnaker (1971) as well as those described in DA PAM 40-8 for GB. No airborne exposure limits for GF could be found.

The Centers for Disease Control (CDC), Public Health Service, Health and Human Services, have developed ‘Final Recommendations for Protecting Human Health and Safety Against Potential Adverse Effects of Long-term Exposure to low doses of agents GA, GB, VX, Mustard Agent (H, HD, T) and Lewisite (L)’ (Federal Register, Vol., 53,

No. 50, pp. 8504- 8507, March 15, 1988), which is considered a primary source for existing exposure guidelines for the G-agents. Their conclusions were reached as a result of a review of the existing health standards for these agents as well as discussions held with invited consultants and the public. Published and unpublished reports of all potential adverse effects including carcinogenicity, mutagenicity, and teratogenicity for all agents were considered. The CDC concluded that “there appears to be little risk either of adverse health effects from long-term exposures to low doses or of delayed health effects from acute exposure in the case of the nerve agents. Human health would be protected from exposure to GA, GB, and VX vapor at the concentrations published in Federal Register, Vol., 53, No. 50, pp. 8504- 8507, March 15, 1988 (shown in Table 5). Even long term exposure to these concentrations would not create any adverse health effects. At these concentrations, no detectable reduction in resistance to organophosphate pesticides would occur.”

### **2 . 3 . 8 . 7    Basis For Existing Exposure Standards For G-agents.**

Following a review of both acute and sub-chronic exposure data (no chronic data were available) for GB in animals and acute exposure data in human subjects, McNamara and Leitnaker (1971) inferred the consequences of chronic exposure in humans.

In deriving guidelines for airborne exposures to GB for occupational workers as well as the general population, McNamara and Leitnaker (1971) considered that existing data involving “no-effect” levels in animals continuously exposed to G-agent vapor, may not apply directly to man if the kinetic parameters of recovery are markedly different. However, they proposed that, “. . .the effects of chronic exposure can be inferred mathematically from the kinetics of recovery from single and repeated exposures, given that the recovery process, itself, is not damaged by the insult. If this condition is not met, the application of the model for recovery from single, large doses to low level continuous exposures will predict greater effects than would actually occur, and the allowable concentration will be unnecessarily conservative. Also, tolerance may develop with chronic exposure. If inferred effects correspond to observed effects in animals, confidence is gained that a similar mathematical inference from human data will also be valid” (McNamara and Leitnaker, 1971).

The following discussion regarding a potential approach in developing health hazards criteria for GB is quoted from McNamara and Leitnaker (1971):

“Determination of maximum air concentrations are usually based on equilibrium conditions; i.e., recovery rate = injury rate, unless the time required to reach equilibrium exceeds the period of chronic exposure. In the latter case the accumulation expected during the total period of exposure is used. When an acute dose is administered, it may not exceed the threshold of a particular effect. When repeated doses are given, several conditions are possible. Repeated doses of equal size given at intervals shorter than complete recovery time may cause a build-up effect until equilibrium is reached, if the animal survives. If recovery is a linear function and the dose interval is less than the recovery time, an equilibrium will not be reached. On the other hand, if the dose interval exceeds the total

Table 5. Existing Airborne Exposure Limits (AELs) For G-agents

TYPE	Exposure Limits (mg/m <sup>3</sup> ) <sup>1</sup>		
	GD	GF	GB/GA
Agent Worker (8-hr TWA)	0.00003	•	0.0001
General Population: 72 hr TWA <sup>1</sup> Ceiling Value	0.000003 0.00003	•	0.000003 0.0001
Source Emission Limit	0.0001	•	0.0003
<i>Masked Personnel</i> in routine operations (8-hr TWA) a. A NIOSH/MSHA-approved, pressure demand full faceplate SCBA or supplied-air respirator with escape cylinder may be used b. Alternatively, a full facepiece, chemical canister, air-purifying protective mask (that is, M9, M17, M40 series mask, or other mask certified as equivalent) is acceptable	0.00003 – 50.06	*	0.0001– ≤0.2
<i>Personnel Conducting Emergency Operations</i> or operations in unknown but potentially high agent concentrations (8-hr TWA) a. A NIOSH/MSHA-approved, pressure demand full faceplate SCBA or supplied-air respirator suitable for use in high agent concentrations with protective ensemble b. The best available respiratory protection and personnel ensemble If protection in a above is not available, a full facepiece, chemical canister, air purifying protective mask with hood is acceptable Currently, only the M9 series protective mask with MI1 canister or M40 series mask is acceptable	>0.06	•	>0.2

1 - The existing general population AEL (DHHS, 1988) was expressed as a 72 hr TWA only to reflect sampling requirements at the time of the original CDC publication (DHHS, 1988).

• No AELs could be found

Source: 53 FR8504 (CDC/DHHS, 1988); DA PAM 40-8, 4 DEC 1990; and DA PAM 385-61, March, 1997

recovery interval, there will be no build up regardless of the recovery function. With a continuous, constant rate of injury that does not damage the recovery mechanism, and recovery is non-linear, the build-up to an equilibrium level is a smooth function.

Table 6. Summary of Existing Airborne Exposure Limits (AELs) for GB

Source	Airborne Concentration (mg/m <sup>3</sup> )/Exposure Criteria
DA-PAM 385-61, 1997	0.0001 (8-hr TWA) - Agent worker (during any single work shift) When known or suspected and/or foreseeable agent concentrations exceed these values, appropriate protective clothing will be worn.
	0.2 Unmasked personnel will not be allowed access to areas in which exposure limit concentration is exceeded, for any period.
	0.000003 (72-hr TWA) - General population This was expressed as a 72 hr TWA only to reflect sampling requirements at the time of the original CDC publication (DHHS, 1988).
	0.0003 (8-hr TWA) <u>Source Emission Limit</u> In no case will the concentration of GB at the point of deliberate release from engineering controls exceed the source emission limit.
DA PAM 40-8, 1990	0.0001 (8-hr TWA)- Agent worker (during any single work shift)
	0.000003 (72 hr TWA) - General population; This was expressed as a 72 hr TWA only to reflect sampling requirements at the time of the original CDC publication (DHHS, 1988).
	0.0001 <u>Ceiling-</u> Maximum exposure concentration for any time, for any duration (limited to minimum detection time required).
	0.0003 (8-hr TWA) <u>Source Emission Limit</u> Primarily an engineering device guideline.
Memorandum HQDA Subject: Chemical Agent Policy Issues, 13 JAN 92	0.2 (30 min) <u>IDLH</u> (Immediately Dangerous to Life or Health) Maximum concentration from which, in the event of respirator failure, one could escape within 30 min without experiencing any escape-impairing or irreversible health effects (adapted recommendations of OTSG).
53 FR8504 (CDC/DHHS, 1988)	0.0001 (8-hr TWA; 40 hr/wk ) - Agent Workers "Human health will be adequately protected at this limit - even long exposures are expected to be without effect"
	0.000003 (72 hr TWA) - General Population This was expressed as a 72 hr TWA only to reflect sampling requirements at the time of the original CDC publication (DHHS, 1988). Human health will be adequately protected at this limit.
	0.0003 <u>Source Emission Limit</u> Maximum allowable stack concentration.
McNamara and Leitnaker, 1971	0.001 (1-hr TLV) - Unmasked workers; One-time exposure
	0.0003 (8-hr TWA)- Unmasked workers 8 hr; One-time
	0.0001 (8-hr TWA) - Unmasked workers 8 hr/day (indefinitely)
	0.0001(1-hr TWA) - General population (Ceiling)
	0.000003 (72 hr TWA) - General population This was expressed as a 72 hr TWA only to reflect sampling requirements at the time.

If injury is applied at a constant rate and recovery occurs at a constant rate, build-up of effect will occur at a constant rate (described simply by a negative exponential function) and will never reach equilibrium if injury rate exceeds the recovery rate. If the recovery rate exceeds the injury rate, no build-up will occur."

After a review of both animal and human toxicological data, McNamara and Leitnaker (1971) focused on acute data reported by Nelson (1956) relating the recovery of GB toxicity in guinea pigs to blood and brain cholinesterase activity. Nelson (1956) reported that brain AChE and plasma ChE, but not RBC-AChE activity paralleled recovery of toxicity. McNamara and Leitnaker (1971) proposed that, in the absence of any data to the contrary, it was suitable for general application, including human estimates. A number of points regarding the characteristics of cholinesterases should be noted in order to evaluate their importance in OP poisoning: 1) human plasma ChE is comprised of butyrylcholinesterase (BuChE); 2) rodent plasma ChE contains both BuChE and AChE; 3) the function of both plasma and RBC ChE is obscure; 4) the rate of recovery of plasma ChE is dependent upon the synthesis of new enzyme; 5) the rate of recovery of RBC ChE is a function of the normal synthesis of new RBCs; and 6) the rates of recovery of both plasma and RBC ChE may not parallel the rate of recovery of AChE in target tissues. Indeed, McNamara and Leitnaker (1971) stated, "Since plasma ChE is butyrylcholinesterase or 'pseudo' cholinesterase, rather than acetylcholinesterase or 'true' cholinesterase, which is the enzyme of interest from the functional standpoint, correlation of the plasma ChE recovery with recovery from toxicity may seem fortuitous."

Using data primarily from human exposures to GB vapor (Johns, 1952; Harvey, 1952), McNamara and Leitnaker (1971) proposed that a Ct of 0.5 mg·min/m<sup>3</sup> should be considered a "no-effect" dose for acute exposures. This estimate was based on a straight-line extrapolation of the above data (Johns, 1952; Harvey, 1952) from which they calculated that an "estimated less than 1% of the working population can be expected to show miosis or the mildest of symptoms, rhinorrhea, or tight chest, even with an acute exposure to such a dose" (Figure 1).

It is noted that a recent comprehensive review of the larger body of human exposure data (Reutter and Wade, 1994) does not indicate that a Ct of 0.5 mg min/m<sup>3</sup> is a "no-effect" dose, particularly for short exposures. Indeed, McNamara and Leitnaker (1971) stated, "Fit of the data to a straight line is conceptually improper since a maximal constriction will occur beyond a dose increase which cannot produce additional effects. The scatter of points does not allow an estimate of the shape of the curve."

McNamara and Leitnaker (1971) were of the opinion that predicting long-term effects on the eye from continuous exposure to low concentrations of GB was difficult because "chronic exposures had not been studied quantitatively with precision. Miotic effects are influenced by exposure conditions and are difficult to reproduce". Therefore, they concluded that it was appropriate to use the same recovery function for miosis as for systemic (*i.e.*, plasma ChE depression) toxic effects. McNamara and

Leitnaker (1971) stated that it was highly unlikely that the fractional recovery rate of miosis was less than that for systemic effects,

McNamara and Leitnaker (1971) postulated that in order to test the fit of their enzyme-recovery and dose-effect accumulation model, developed primarily in the guinea pig, (Nelson *et al.*, 1956). In another species (human), a plasma ChE recovery curve (resulting from low-dose GB vapor exposure in humans) was extracted from data by Grob and Harvey (1953) and fit to a single exponential. They assumed that dose-effect accumulation was dependent on the rate of dosing and the rate of recovery, thus an accumulation model could be expressed as:

$$\begin{aligned} D &= D_0 e^{\lambda t} \\ E &= D_d / \lambda (1 - e^{-\lambda t}) \\ E &= D_d / \lambda, (t \rightarrow \infty) \\ D_d &= \lambda \times E \end{aligned} \tag{1}$$

where:

D	=	cumulative effect
D <sub>0</sub>	=	effect present at time, t = 0
D <sub>d</sub>	=	dosing per unit of time
λ	=	constant with reciprocal time units
E	=	the acute dose to produce the effect

The single exponential model seemed to fit the data of Grob and Harvey (1953) (Figure 2) the best of those considered. The half-life was 6.7 days and λ was about 0.105/day. Assuming that plasma ChE recovery in man corresponds to detoxification, as it does in the guinea pig, they (McNamara and Leitnaker, 1971) proposed that the constant daily dose would be about 10% of the equilibrium dose.

McNamara and Leitnaker (1971) considered the acceptable equilibrium level of effects as a Ct of 0.5 mg·min/m<sup>3</sup>, since less than 1% of the working population can be expected to show miosis or the mildest of symptoms, rhinorrhea, or tight chest, even with an acute exposure to such a dose [see above comments/. To avoid eventual build-up to the threshold of lethal doses (10 mg·min/m<sup>3</sup>), McNamara and Leitnaker (1971) proposed that daily doses should not exceed 1 mg·min/m<sup>3</sup>. To avoid build-up to the threshold of neuromuscular symptoms, they proposed that the daily dose must be limited to 0.46 mg·min/m<sup>3</sup>.

Given a Ct of 0.5 mg·min/m<sup>3</sup> as a “no-effect” dose (see above comments), and the prediction of the kinetic model which indicates a dose equivalent of 0.5 mg·min/m<sup>3</sup> may accumulate with a daily exposure of 0.05 mg·min/m<sup>3</sup>, McNamara and Leitnaker (1971) proposed a ceiling concentration of 0.001 mg/m<sup>3</sup> for unmasked workers for any period up to 1 hr TLVs were to be averaged for a maximum of 10 work periods per worker as long as he does not work more than seven shifts a week and is not exposed to more than 0.15 mg·min/m<sup>3</sup> in any one shift.

Figure 1. Minimal Signs/Symptoms of GB Vapor Exposure in Human Subjects  
 (From McNamara and Leitnaker, 1971)

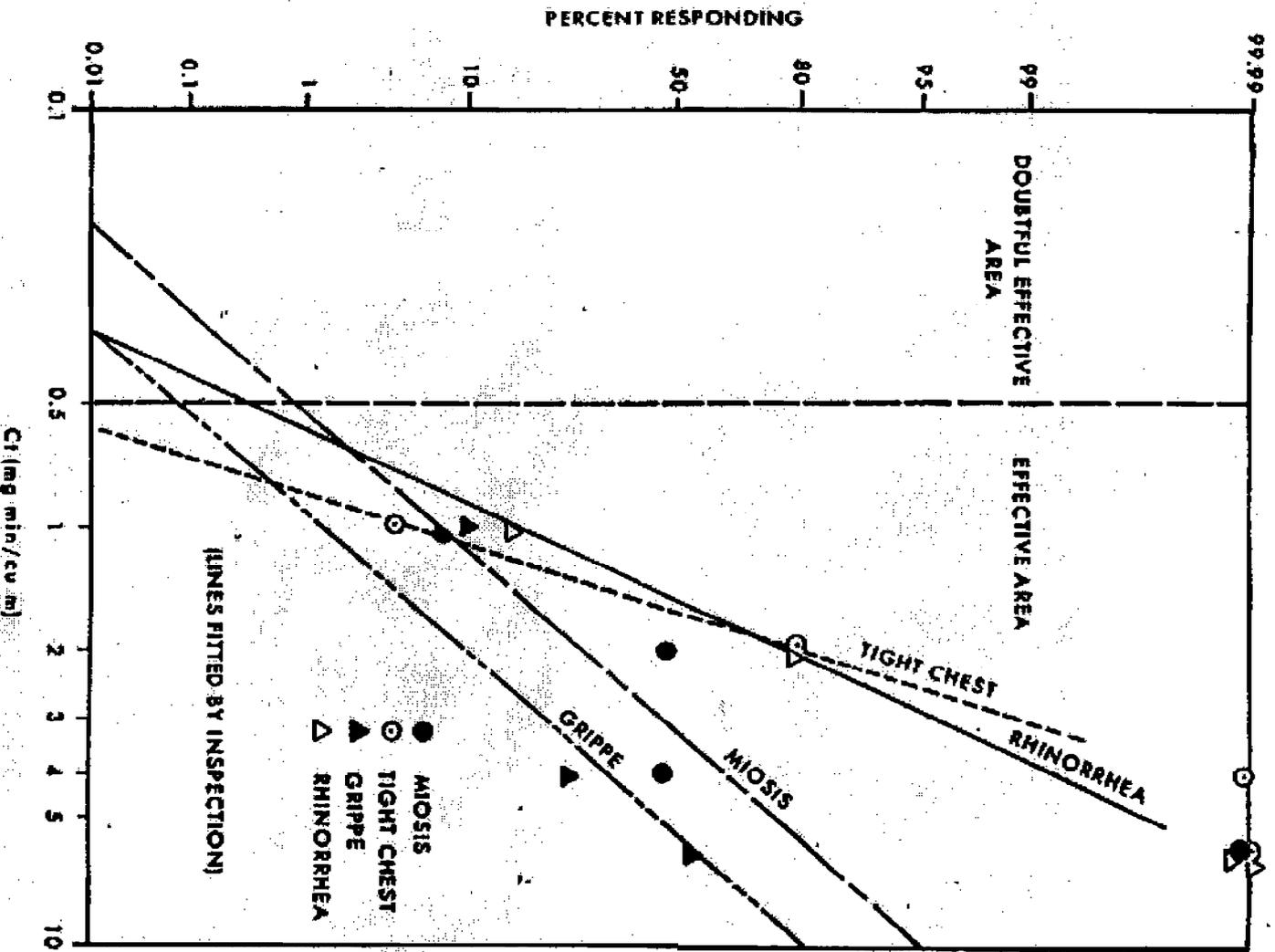
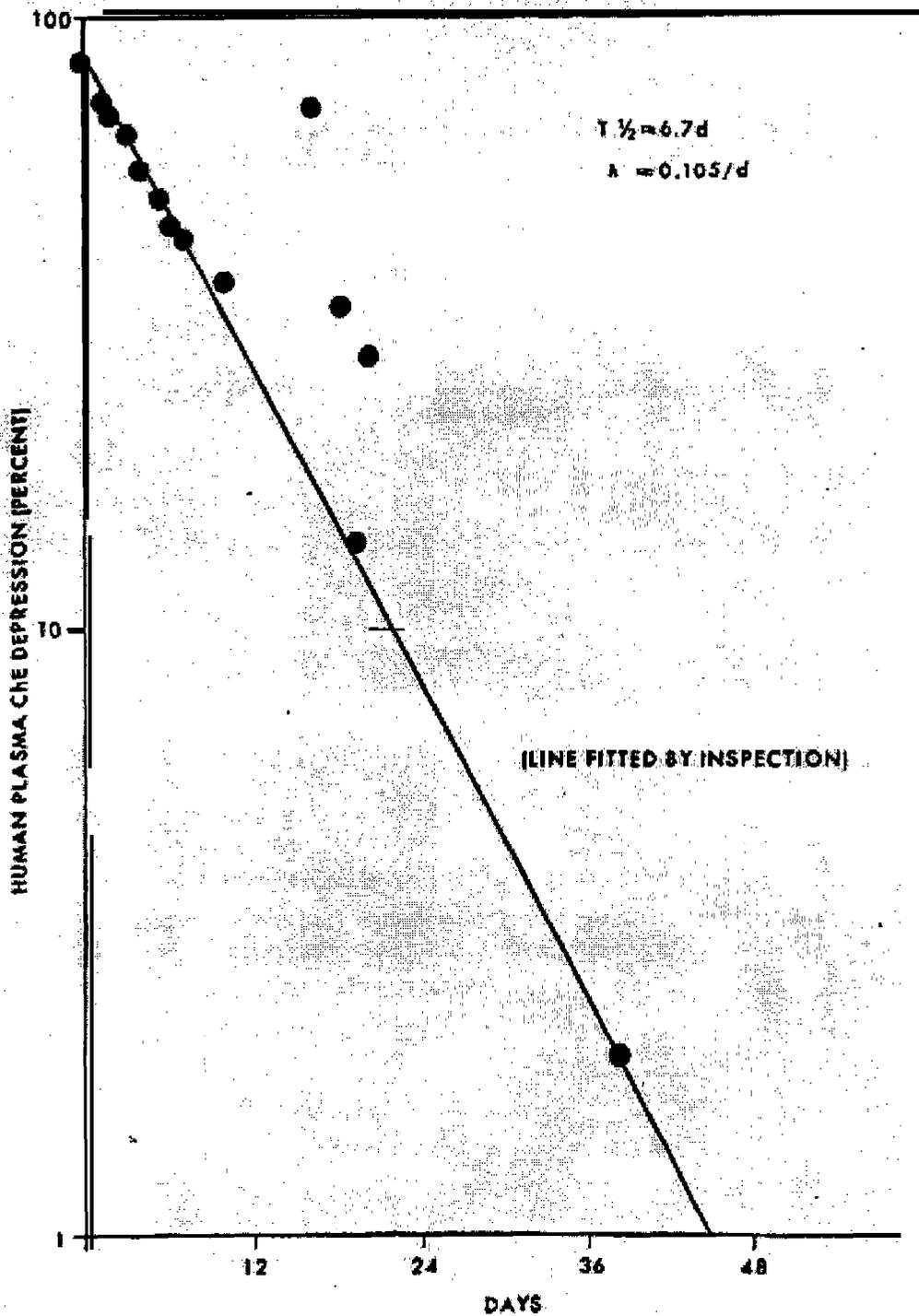


Figure 2. Rate of Recovery of Plasma ChE Activity Following GB Administration in Guinea Pigs (From McNamara and Leitnaker, 1971)



The following discussion in developing health hazards criteria for GB is quoted directly from McNamara and Leitnaker (1971).

“The threshold for miosis is obviously very low. Recovery occurs within 1 to 3 days with mild miosis recovering sooner. It is conceivable, but highly unlikely, that the fractional recovery rate, if the process is a negative exponential, is less than that for systemic effects. If the recovery rate is linear, the situation is even better for daily sub-threshold doses.

If a continuous concentration is assumed which delivers a subthreshold acute dose in 8 hrs, an additional confidence factor is created. Development of recognizable miosis, a sign of insignificant health importance should be highly improbable. Such a level is acceptable for a Workplace TLV predicated on the requirement that employees be examined for miosis at least twice daily, at the beginning at the end of each shift. Maximum allowable short term and 24 hr concentrations in the general environment must be proportionately lower. It is appropriate to use the same recovery function for miosis as for systemic toxic effects, in this case plasma ChE activity.

The expected level of plasma ChE inhibition at equilibrium from 0.05 mg min/m<sup>3</sup> per day would be, theoretically, the equivalent of a single exposure of 0.5 mg min/m<sup>3</sup>. Since initial depression of plasma and RBC is about the same, and since 10% RBC ChE depression occurs per 1 µg/Kg, and since 0.5 mg min/m<sup>3</sup> is equivalent to 0.075 µg/Kg, expected depression from a daily 8 hr exposure of 0.0001 mg min/m<sup>3</sup> would result in less than an average of 1% ChE depression (0.5 mg·min/m<sup>3</sup> /500 min = 0.001 x 0.10 = 0.0001). Theoretically, 50 % of the working population would have more ChE depression than this; i.e., perhaps up to 5%. But detection of such low levels of ChE depression would be impossible in an individual and, even detection of a mean depression of an exposed group, would be very difficult considering the magnitude of random fluctuations in level and error of procedure.

Variation of sensitivity to GB by age and sex, based on LD50, has been demonstrated in some species, but not others. Females and the young and old of both sexes may be more sensitive. Factors of two for age and sex represent the maximum influence observed (Oberst, 1961). No relevant data in humans are available. Although there are little data available, there are indications and theoretical reasons to believe that certain conditions and diseased states may increase susceptibility. For example, chronic disease of the bronchi, bronchioles, and lungs may reduce the threshold of observable respiratory effects of GB. It seems doubtful that this would reduce the threshold more than half. Individuals with blood ChE reduced congenitally or as a result of an identifiable disease (certain anemias) may lack the expected buffer that blood ChE apparently confers. Patients with severe liver disease may have a reduction in phosphofluorase and would thereby lose some ability to detoxify GB. Variation in recovery rate among normal

individuals undoubtedly exists, and some congenital conditions or diseases may represent a special population group at increased risk.

Considering all of these factors and unknowns, and considering the conservatism of the estimated safe level for occupational exposure, it is believed that an additional factor of 0.1 should protect all members of the general population. There is of course, an additional safety factor of occupancy in that no member of the general population would be continuously present in the area of the general environment where GB concentration would be highest.

It is proposed that the concentration in any area to which the general population has access must not exceed 0.0001 mg/m<sup>3</sup> averaged over any 1-hr period, and must not exceed 0.000003 mg/m<sup>3</sup> averaged over any 72-hr period or longer. The maximum concentration for this time period would therefore be 0.025 mg/m<sup>3</sup>. In reviewing various toxicity data, McNamara and Leitnaker (1971) concluded that GB inhibits cholinesterase activity at dose levels that cause no other physiological effects. In tests on humans, Grob and Harvey (1958) found that multiple doses of GB, totaling 0.007 mg/Kg over three days, did not produce any symptoms (or signs) of toxicity. There was a 27-33% reduction in RBC ChE activity.”

It should be noted that these exposures were intravenous and therefore, unlikely to show initial signs/symptoms characteristic of a whole-body vapor exposure in which local effects of G-agent exposure are initially routinely reported in both the eyes and respiratory tract.

### 3. FINDINGS/DISCUSSION

#### 3.1 Human Exposure Data.

Opresko (1988) suggested that “the most reliable basis for setting exposure standards is through the use of comprehensive studies on humans, identifying the maximum exposure levels having no adverse health effects under the expected exposure conditions. Given that adequate human data exist, such an approach eliminates the need for controversial cross-species extrapolation models.” This is not to suggest that animal data should be ignored; only that human data is preferred.

In light of the above, the present review of data sources focused primarily on human data. Human data are especially relevant for formulating exposure criteria because they are limited to non-lethal, mild-moderate effects, some of which involve behavior (e.g., motivation/emotional and task performance-related mental ability), and subtle symptoms of local and systemic effects (tightness of throat and chest, dimness of vision, *etc.*) which are not readily measured in animal models. Whereas “signs” of G-agent exposure can be observed in animals, generally speaking, only humans can report their subjective perception of “symptoms” in addition to displaying such clinical signs. Existing human

data, at least for GB, appear to be adequate and preferable for purposes of developing exposure criteria based upon the earliest and most subtle signs and symptoms. On the other hand, animal studies are the only source for existing long-term exposure to G-agents, and can help verify whether exposure limits based upon studies involving acute exposures are appropriate.

#### Mild Effects of Acute GB Exposure in Humans.

In estimating an AEL for GB, McNamara and Leitnaker (1971) considered miosis (Johns, 1952) as well as other threshold effects (e.g., tight chest, rhinorrhea, grippe) (Harvey, 1952) as LOAEs. Both of the above data sets originate from a common study in which volunteers were exposed to low Ct's (0 - 6 mg·min/m<sup>3</sup>) of GB vapor for 2 - 20 min in a chamber. Johns (1952) defined a "mild" miosis as a maximal decrease in pupil size of 1-2 mm diameter vs. a mean maximal decrease of 0.33-0.36 mm in control exposures. Signs of mild miosis were seen at the lowest Ct (1 mg·min/m<sup>3</sup> ; 0.05 mg/m<sup>3</sup> for a 20 min exposure, but not at 0.5 mg/m<sup>3</sup> for a 2 min exposure. This is interpreted as indicating that the above NOEL was not based solely on a single sign (miosis) but rather representative of a pattern of effects, both local and systemic, (Figure 1, Appendix A) typically seen after whole-body GB vapor exposures limited to the same low-level dosages.

Harvey (1952) described a variety of mild signs resulting from acute exposures to GB vapor in humans at Ct's ranging from 1-6 mg·min/m<sup>3</sup>. These data which are summarized in Table 7, were part of the database presented by McNamara and Leitnaker (1971) in developing exposure limit recommendations for GB which serve as the basis for current occupational standards for G-agent exposure. AChE levels were decreased in the above study an average of approximately 20 % at the highest exposure dose (6 mg·min/m<sup>3</sup>).

Mumford (1950) reported that GB vapor threshold for eye symptoms is produced by Ct's of 1.5 - 5.0 mg·min/m<sup>3</sup>, and a moderate to severe degree of discomfort, due primarily to miosis and concomitant frontal headache, persisting for 3 - 5 days, by dosages of 6 - 12 mg·min/m<sup>3</sup>. Ct's up to 6.4 mg·min/m<sup>3</sup> resulted in no significant change in levels of AChE, though characteristic local eye symptoms of miosis, etc. were marked. Ct's above 15 mg·min/m<sup>3</sup> produced a marked fall in AChE with concomitant pronounced symptoms of systemic nerve gas poisoning.

Fairley and Mumford (1948) tested the ability of volunteers to detect GB and GD vapor by smell. Men were exposed to GB (16 men) or GD (15 men) at a Ct of 0.15 mg·min/m<sup>3</sup> (0.3 mg/m<sup>3</sup>) for 0.5 min. They reported that for GB: 9/16 reported detection of agent by smell, 7/16 reported tight chest, and all 16 reported rhinorrhea. For agent GD: 14/15 reported that they could smell agent, 7/15 reported tight chest, and 11 /15 reported rhinorrhea.

Uhde and Moore, (1945) exposed volunteers to T2104 vapor (GA) at various Cts from 0.7 to 30 mg·min/m<sup>3</sup> (2 min exposure). In 4 men exposed to a Ct of 0.7 (0.35 mg /m<sup>3</sup> for 2 min), all detected the agent by smell and reported slight, transient tightness of the chest, but none displayed any change in pupil size. Ten men were exposed to a Ct

of 3.2 mg-min/m<sup>3</sup> and all could detect the agent by smell, reported tightness of chest, and displayed miosis.

Sim (1956) reported the results of a series of experiments (total of 246 human exposures) in which the time of onset of pupillary constriction was measured following GB vapor exposure. Exposure conditions included Cts ranging from 2.5 to 7.5 mg-min/m<sup>3</sup> (2 min exposure) and 5 - 15 mg-min/m<sup>3</sup> (1 min exposure). All volunteers whose eyes were uncovered experienced some degree of miosis at the above Cts.

Thienes and Haley (1972) reported that a single intravenous dose (0.002 mg/Kg) of GB caused excessive dreaming and talking in sleep; a dose of 0.02 mg/Kg caused insomnia, excessive dreaming, withdrawal, and depression in humans. Grob and Harvey (1958) reported that multiple doses of 0.002 mg/Kg totaling 0.044 mg/Kg over three days, produced mild symptoms of toxicity. Exposures had a cumulative effect and resulted in increased sensitivity to the chemical. Multiple doses, totaling 0.03 mg/Kg per day, caused mild symptoms on the second and third days while multiple doses totaling 0.04 mg/Kg per day produced mild symptoms on the first day and severe symptoms on the third day. A single oral dose of 0.22 mg/Kg produced mild toxic effects, while a 0.028 mg/Kg dose produced moderate effects.

Grob *et al.* (1959) reported that following systemic administration of GB, the plasma and RBC cholinesterase activity could be depressed considerably below normal without symptoms necessarily appearing. Following a single dose of GB, symptoms usually began coincident with the depression of plasma and RBC cholinesterase activity to approximately 34 and 22% of original activity, respectively. If the exposure is over a longer period of time, this guide is less reliable since the rate of restoration of AChE activity of red cells, as determined by the rate of RBC turnover, is very slow (1% of original activity/day), and is probably slower than that of the tissues. Thus, AChE could be gradually depressed towards zero by the administration of GB over a period of days without symptoms necessarily ensuing, or without any relation to the severity of the symptoms that occurred. In addition, the AChE activity remained at low levels long after the disappearance of symptoms and the presumed restoration of the ChE activity of the tissues. There is likewise no close correlation between symptoms and the precise level of ChE activity of the plasma probably because of the different sensitivity of the plasma (primarily BuChE), and tissue (AChE) cholinesterases to inhibition by GB, and perhaps also due to different rates of restoration of these enzymes. The absorption of GB via the respiratory tract or eye (conjunctivae) may produce local manifestations which are out of proportion to the systemic effects, including blood ChE depression. Grob *et al.* (1959) noted that the instillation of GB (in aqueous solution or in normal saline) into the conjunctival sacs of normal subjects resulted in striking and very prolonged miosis of the treated eye. The lowest concentration of GB producing persistent and marked (not maximal) miosis was 0.0003 mg, while 0.03 mg resulted in nearly maximal miosis lasting for 72 hr to some degree, disappearing after 90 hr.

Table 7. Effects of GB Vapor Exposure in Human Volunteers (From Harvey, 1952)

Ct (mg.min/m <sup>3</sup> )	0	0	1	1	2	2	4	4	6	6
C (mg/m <sup>3</sup> )	0	0	0.5	0.05	1.0	0.1	2.0	0.2	3.0	0.3
t (min)	2	20	2	20	2	20	2	20	2	20
No. of Subjects Exposed	4	4	15	14	9	34	15	11	10	12
<b>Signs and Symptoms</b>	<b>Number of Subjects Showing Response</b>									
Headache		1	4	2	1	1		1	4	8
Eye pain	1		3	2					6	6
Dimness of vision							4		7	7
Twitching of lids					2		2			2
Rhinorrhea			2	3	9	20	15		10	12
Salivation										2
Throat Irritation			1				3			5
Tightness in chest				1	6	12	11	2	4	9
Sweating										4
Cramps				1			1		2	6
Nausea	1			1			1			3
Vomiting							1			1
Giddiness										5
Concentration difficulty										8
Malaise				2			7		7	6

McKee and Woolcott (1949) carried out a series of experiments to determine the effect of “acute exposures” to low concentrations of GB on humans and rabbits, and to correlate the relative times of onset of miosis, which they defined as an obvious and well defined contraction of the pupil (< half of original size). They concluded that the nominal Ct of GB to produce threshold effects in men as a result of a *single exposure* is approximately 3.3 mg·min/m<sup>3</sup> (0.082 mg/m<sup>3</sup> for 40 min). The actual dosage as shown by chemical analysis or biochemical assay was approximately 3/4 (2.475) of the nominal Ct. Slight tightness of the chest was not a constant symptom, and when it occurred, was of a transient nature. This also applied to aching of the eyeballs, and no other symptoms were noted as a result of this single exposure. It is important to note, however with regard to a possible LOAEL in man, that miosis and tightness of the chest was reported with single doses of GB in this same study as low as 0.6 mg·min/m<sup>3</sup> (t = 1 min).

In addition, McKee and Woolcott (1949) reported the results of “repeated” exposures of men to GB vapor (20 and 40 min) at Cts of 1.65 to 6.6 mg·min/m<sup>3</sup> (nominal concentrations) over eight days. They reported that successive daily exposures to a Ct of 3.3 mg·min/m<sup>3</sup> (*i.e.* 0.0825 mg/m<sup>3</sup> for 40 min) produced threshold effects (miosis and tightness of the throat and chest) after the first exposure. These effects appeared to be additive with successive exposures resulting in discomfort. However, when the exposure time was limited to 20 min at the same concentration as above, threshold effects were not observed until the 4th day of exposure when additive effects were expressed but much less evident. They speculated that the above effects would not likely be seen under these conditions after a reasonable number of exposures.

Table 8. Threshold Effects of ‘Repeated Exposure of Humans to GB Vapor (From McKee and Woolcott, 1949)

Group	Subjects Exposed	Ct (mg·min/m <sup>3</sup> )	C (mg/m <sup>3</sup> )	t (min)	Day - 1 <sup>1</sup>	Day - 2 <sup>2</sup>	Day - 3 <sup>3</sup>	Day - 4 <sup>4</sup>
I	5	1.237	0.062	20	NR	NR	NR	miosis
II	4	2.475	0.062	40	miosis	miosis +	miosis +	not exposed
III	4	2.475	0.062	40	NR	miosis +	miosis +	miosis +

NR - No responses reported

<sup>1</sup> - Response (in all exposed subjects) reported on the 1st day of a repeated exposure

<sup>2</sup> - Response (in all exposed subjects) reported on the 2nd day of a repeated exposure

<sup>3</sup> - Response (in all exposed subjects) reported on the 3rd day of a repeated exposure

<sup>4</sup> - Response (in all exposed subjects) reported on the 4th day of a repeated exposure

+ -additional threshold responses beyond miosis (e.g., headache, blurred vision, eye pain)

C - Chamber concentration of GB

Ct - Concentration (C) x exposure time (t)

t - Duration of exposure (min)

### 3 . 2 Developing Exposure Criteria: a Traditional Approach.

The objective of traditional toxicological, non-cancer risk assessment is to establish a threshold dose below which adverse health effects are not expected to occur, or are extremely unlikely (NRC, 1993). Lehman and Fitzhugh (1954) proposed that an acceptable daily intake (ADI) could be calculated for contaminants in human food. That concept was endorsed by the Joint FAO-WHO (Food and Agricultural Organization and World Health Organization) Expert Committee on Food Additives in 1961 and subsequently adopted by the Joint FAO-WHO Meeting of Experts on Pesticide residues in 1962 (McColl, 1990). Formally, the ADI was defined by:

$$ADI = NOEL/SF, \quad (2)$$

where NOEL stands for the no-observed-effect level in toxicological studies (the highest exposure level at which there are no statistically or biologically significant increases in frequency or severity of effects between the exposed population and its appropriate control) and SF represents a safety factor to allow for variations in sensitivity to the test agent in humans as compared to experimental animals and for variations within the human population. Those two sources of variation often have been accommodated through the use of a 10 X 10 - 100-fold SF as reviewed by the NRC's Food Protection Committee (NRC, 1970). The basic approach described above has been modified (ADI has been relabelled by the EPA as a reference dose (RfD) which is ideally based upon a no-adverse-effects level (NOAEL); safety factors are now referred to as uncertainty factors (UFs); and a modifying factor (MF) has been added to account for specific scientific uncertainties in the experimental data base used to derive the RfD) (NRC, 1993).

The RfD is defined by the following equation:

$$RfD = NOAEL/ (UF \times MF) \quad (3)$$

An adverse effect is defined as any effect that contributes to the functional impairment of an organism or that reduces the ability of the organism to respond to additional challenges (Dourson, 1986). When the data do not demonstrate a NOAEL, a LOAEL (lowest-observed-adverse-effect level) may be used. A LOAEL is defined as the lowest experimental dose at which statistically significant adverse effects occur.

Five factors may contribute to the composite UF. The factors are (1) the need to accommodate human-response variability, including sensitive subgroups; (2) the need to extrapolate from animal data to humans when human data are unavailable or inadequate; (3) the need to account for uncertainties when extrapolating from a LOAEL a NOAEL; (4) the need to extrapolate from subchronic to chronic exposure data when the latter is unavailable; and (5) the need to extrapolate from a database that is inadequate or incomplete. An additional factor may be necessary, a modifying factor

(MF) may also be used to account for deficiencies not accounted for above. Factors between 1- and 10-fold commonly are used to account for each of those sources of uncertainty (NRC, 1993).

EPA has adapted the oral RfD method to estimate inhalation reference concentrations (RfCs) to be consistent in setting exposure levels for health effects other than cancer (U.S. Environmental Protection Agency, 1990). The inhalation RfC method departs from the oral RfD paradigm by using dosimetric adjustments to scale the exposure concentrations for animals to a human equivalent concentration.

Opresko (1988) discussed application of the above RfC method to developing AELs for chemical agents. He suggested that occupational exposure limits for nerve agents should be based on determination of the lowest observable adverse effect (LOAE) for threshold-type of toxicants such as the organophosphate nerve agents, and the direct or indirect determination of the maximum chronic exposure level which could be tolerated without producing that effect. Such levels would be used to determine no-observed-adverse effect levels (NOAELs) in establishing health hazards criteria, if NOAELs are not determined experimentally.

A variety of data are available for use in establishing the human LOAEL for GB exposure. In cases where human data do not exist (e.g. chronic exposures), toxicity data derived from animal studies is the next best alternative requiring equivalent human dose levels to be calculated. For human as well as animal studies, the data must be adjusted to reflect the expected exposure conditions (exposure route, duration, frequency, and total exposure period). Such extrapolations are based on empirically derived data and on dose-response relationships (Opresko, 1988).

### 3.3 Selecting the “Critical Adverse Effect(s)” for G-Agent Airborne Exposure Criteria.

Current noncancer risk assessment models generally assume that 1) a population threshold exists, 2) estimates of safe exposure criteria represent subthreshold doses and 3) preventing the “critical” effect protects against all effects. The “critical effect” is either an adverse effect or a known precursor to an adverse effect (U.S. EPA, 1987). In considering airborne exposure limits (AELs) for the G-agents, it should be noted that the LOAE of organophosphate nerve agent vapors will include both local and systemic effects. It is unlikely that the LOAE for all routes of exposure or even a single exposure route would be limited to a single effect. It is more likely that the LOAE for nerve agents are manifest as a spectrum of “mild” effects characterized as biochemical (e.g., blood cholinesterase inhibition), physiological (e.g. miosis, respiratory tract secretions/constriction) or behavioral changes (e.g., malaise, irritability, insomnia, excessive dreaming). A determination must be made, relevant to the route of exposure, as to which of these might be the lowest observable adverse effect. In the case of acute human whole-body exposures to GB vapor, local effects on the eyes (miosis, eye-related discomfort) and respiratory tract (rhinorrhea, bronchosecretions, tightness of the chest) are likely to be noted earliest and at the lowest exposure concentrations.

Although blood cholinesterase inhibition has been used as the critical adverse effect in setting exposure standards (RfD) for organophosphate pesticides, its utility may be limited to identifying past exposure incidence (i.e., as a biomarker of exposure in the absence of clinical effects) within a limited timeframe and not as a barometer of functionality or severity of intoxication. In reference to the utility of AChE activity in considering LOAELs, the Technical Panel on Risk Assessment for the EPA (unpublished report) considers that, “. . . unequivocal correlation of a particular level of enzyme (cholinesterase) inhibition with an observable biological effect is not well supported by either the clinical or experimental literature. The interpretation of biological significance for ChE inhibition begins initially with the point at which enzyme inhibition becomes significantly different (statistically,  $p < 0.05$ ) from an individual baseline value or the value in a concurrent laboratory control group. The decision as to whether a statistically significant decrease in either RBC or plasma cholinesterase activity is ‘adverse’ (i.e. of biological significance) depends upon a case by case determination. Factors in this evaluation may include dose-response relationships, comparative pharmacokinetics, and elements of study design. Statistically significant inhibition of brain AChE is an adverse effect.”

#### **3.4 Derivation of Airborne Exposure Levels for GB: Considerations in Selecting a Critical Study,**

Selecting “the” critical study for deriving a WPL and GPL is determined by the availability of appropriate data. In some cases, the database may be insufficient for deriving any extrapolations regarding chronic health hazards, but in other cases there may be several studies which are worthy of consideration. Since the database for GB falls in the latter category, it may be useful to compare the results of three studies, each having characteristics which are unique but acceptable for risk assessment purposes. Although human chronic exposure data are preferred in establishing AEL guidelines, all of the available human data are limited to short-term exposures. In addition, a study of chronic GB vapor in animals is also available. Three studies (2 human and one animal) are discussed below:

a) The data of Harvey (1952) and Johns (1952), based upon a common experiment. Human volunteers underwent a single exposure to GB vapor (whole-body) and were monitored for onset of “mild” signs and symptoms (Harvey, 1952), including eye and visual effects (Johns, 1952). The LOAEL for threshold effects (miosis, rhinorrhea, tight chest, etc.) in their combined studies was  $0.05 \text{ mg/m}^3$  for a single 20 min exposure.

b) It was also of interest to utilize the human data of McKee and Woolcott (1949), for comparison. The latter study incorporated a repeated exposure over four consecutive days in which threshold signs and symptoms of GB exposure ( $0.062 \text{ mg/m}^3$  (LOAEL), 20 min) appeared to be cumulative and were manifest only on the fourth day of exposure. While short-term exposure data are not generally used for developing chronic reference values (RfC, RfD), there are examples of RfD values derived from acute

and subacute human exposures to OP pesticides in the IRIS database (U.S. EPA, 1988, 1992, 1993).

c) The data of Weimer *et al.*, (1979), the only known chronic study of GB vapor exposure, were selected for comparing AELs derived from a chronic study with those calculated using human short-term exposures. Weimer *et al.*, (1979) exposed rats, mice and dogs to whole-body GB vapor repeatedly at concentrations of either 0.0, 0.001 or 0.0001 mg/m<sup>3</sup> for 6 hr/day, 5 days/week for up to 52 weeks). Animals were monitored for clinical signs of intoxication daily but none were reported. Blood AChE was monitored in all species during the length of the study, and no significant changes in AChE activity were noted at any sampling time. Although 5/20 dogs exhibited abnormal EKGs at the time of sacrifice, pre-test measurements were not performed and there were no signs of physical abnormalities noted in the heart tissue at the time of necropsy. Atrophy of seminiferous tubules was noted in the Fischer 344 strain of rats, which is known for its susceptibility to genetically based defects, particularly under stress conditions. A second study (Morin' and McKinley, 1976) was performed in Fischer-344 rats receiving equivalent doses of GB for 3 or 6 months via intraperitoneal and subcutaneous injection, and no testicular atrophy was observed. A third study (Weimer *et al.*, 1979) was performed in which Fischer rats were exposed to GB vapor for up to 24 weeks; again, no testicular atrophy was observed. Throughout the study, histopathological examination indicated various degrees of tracheitis in rats mice and dogs, as compared to control animals. At six months post-exposure, it was still reported in both strains of rat and in the mice, The interpretation listed in the histopathology data table suggested that it was considered to be agent-related in the colony rats, and possibly agent-related in the Fischer rats and colony mice. In contrast, Weimer *et al.*, (1979) did not conclude that any effects they saw were agent-related. They suggested that such effects could be related to differences in animal exposure and housing conditions between control and treated animals. Nevertheless, the histopathology in their study should not be ignored. The biological significance of such a sign in rats is likely to be the object of debate as to whether it should be considered a "critical adverse effect", a lowest observed effect (LOE) or whether it is related to agent exposure or the result of differences in the housing of treated vs. control animals, as implied by the authors. Nevertheless, of primary concern is the potential for such a lesion to progress to a more serious effect. Therefore, in the absence of information to the contrary, tracheitis is considered an adverse effect and the lowest concentration (0.0001 mg/m<sup>3</sup>) of GB vapor used in the chronic animal study of Weimer *et al.* (1979) is considered the LOAEL.

### 3.4.1 Calculating the AEL for Occupational Workers (Worker Population Limit or WPL) for GB Vapor.

#### Using Acute Human Exposure Data as the Critical Study:

The AEL for occupational exposures (WPL) may be calculated according to the following formula.

$$WPL = LOAEL_{inhal} \times \frac{Resp_{exptl.} \times Exp_{exptl.}}{Resp_{occup} \times Exp_{occup}} \times \frac{1}{UF's \times MF} \quad (4)$$

For short-term human exposure data:

- WPL = Concentration in ambient air.  
 LOAEL<sub>inhal</sub> = Lowest observed adverse effect level (mg/m<sup>3</sup>).  
 Resp<sub>exptl.</sub> = Experimental subject minute volume (10 L/min).  
 Resp<sub>occup</sub> = Occupational minute volume (20.8 L/min over 8 hrs)  
 Exp<sub>occup</sub> = Occupational exposure (480 min/day x 5 days/week).  
 Exp<sub>exptl.</sub> = Experimental exposure (20 min/day x 1 day/ week or 4 days/week).

Note: 20 m<sup>3</sup>/day (13.9 L/min) has been adapted as a standard inhalation rate for humans (USEPA, 1996). This value is widely used to determine the inhaled dose for a given air pollutant for adults. For an occupational exposure, one-half of the daily ventilation (i.e., 10 m<sup>3</sup>) is considered to occur during an 8 hr work shift (10 m<sup>3</sup>/8 hr) at an average minute ventilation of 20.8 L/min

Uncertainty Factors (UF):

- UF<sub>1</sub> = 10 (short term to long term exposure extrapolation).  
 UF<sub>2</sub> = 1 (average human to sensitive human population).  
 UF<sub>3</sub> = 1 (animal to human extrapolation).  
 UF<sub>4</sub> = 3 (LOAEL to NOAEL extrapolation).  
 UF<sub>5</sub> = 1 (minimum to complete database).  
 MF = 1 (not necessary).

A value of 10 was selected for UF<sub>1</sub> because the data from short-term exposures is extrapolated to a working lifetime. A value of 1 was selected for UF<sub>2</sub> because the occupational population is not considered to include sensitive subpopulations. A value of 1 was selected for UF<sub>3</sub> based upon the use of human data. A value of 3 was used for UF<sub>4</sub> because the level of effect for the LOAEL was minimal. Finally, a value of 1 was chosen for both the UF<sub>5</sub> and the MF because no corrections for the completeness or quality of the database was necessary.

Using chronic animal data as the critical study:

On the other hand, if chronic animal data are used for deriving the occupational exposure criteria, the experimental exposure concentration for the animal is adjusted to a "human equivalent" concentration according to the following formula:

$$C_{exp\ Human} = \frac{Resp_{Animal} \times C_{exp\ Animal} \times BW_{Human}}{Resp_{Human} \times BW_{Animal}} \quad (5)$$

where:

$C_{expAnimal}$  = animal (rat) exposure concentration.  
 $BW_{Human}$  = human body weight (70 Kg).  
 $Resp_{Human}$  = human respiratory volume (10 L/min, resting).  
 $BW_{Animal}$  = animal (rat) bodyweight (0.35 Kg).

The chronic animal data of Weimer et al., (1979) were selected for comparison to the above short-term human exposures. Tracheitis was found in treated animals at 0.0001 and 0.001 mg/m<sup>3</sup> exposure concentrations and is considered the lowest observed adverse effect (LOAE). Using the above formula to determine the  $C_{Human}$  or "human equivalent LOEL":

$$\begin{aligned}
 C_{exp Human} &= \frac{(0.21 \text{ L/min}) \times (0.0001 \text{ mg/m}^3) \times (70 \text{ Kg})}{(10 \text{ L/min}) \times (0.350 \text{ Kg})} \quad (6) \\
 &= 0.00042 \text{ mg/m}^3 \\
 &= LOEL_{Inhal} \text{ ("human equivalent")}
 \end{aligned}$$

$LOEL_{Inhal}$  ("human equivalent") is applied to the following formula for calculating the WPL for occupational exposures:

$$WPL = LOEL_{Inhal} \text{ ("human equiv.")} \times \frac{Resp_{exptl} \times Exp_{exptl}}{Resp_{occup} \times Exp_{occup}} \times \frac{1}{UFs \times MF} \quad (7)$$

For chronic inhalation exposures in rats:

$WPL$  = Concentration in ambient air.  
 $LOEL_{Inhal}$  = Lowest observed adverse effect level (mg/m<sup>3</sup>).  
 $Resp_{exptl}$  = Experimental subject respiratory volume (10 L/min, resting).  
 $Resp_{occup}$  = Occupational respiratory volume (20.8 L/min).  
 $Exp_{occup}$  = Occupational exposure (480 min/day x 5 days/week).  
 $Exp_{exptl}$  = Experimental exposure (360 min/day x 5 days/week).

Uncertainty Factors (UF):

$UF_1$  = 1 (short term to long term exposure extrapolation).  
 $UF_2$  = 1 (average human to sensitive human population),  
 $UF_3$  = 10 (animal to human extrapolation).  
 $UF_4$  = 3 (LOAEL to NOAEL extrapolation).  
 $UF_5$  = 1 (for minimum to complete database).  
 $MF$  = 1 (not necessary).

A value of 1 was selected for  $UF_1$  because the data represent the effects of chronic exposure (1 yr.). A value of 1 was selected for  $UF_2$  because the occupational population is screened to exclude sensitive subpopulations. A value of 10 was selected for  $UF_3$  because humans are considered to be the most sensitive species. A value of -3 was used

population is screened to exclude sensitive subpopulations. A value of 10 was selected for UF<sub>3</sub> because humans are considered to be the most sensitive species. A value of 3 was used for UF<sub>4</sub> because the level of effect (tracheitis) was minimal. Finally, a value of 1 was chosen for both the UF<sub>5</sub> and the MF because no corrections for the completeness or quality of the database was necessary.

The following worksheet compares occupational AELs (WPLs) calculated using equation (4) for data from acute human exposures or equation (7) for data from chronic animal exposure studies:

Data Source	LOAEL <sub>Inhal</sub> (mg/m <sup>3</sup> )	Exp <sub>exptl</sub>	EXP <sub>exptl</sub>	Resp <sub>exptl</sub>	1		WPL (mg/m <sup>3</sup> )
		(min/day)	(days)	Resp <sub>occup</sub>	UF	MF	
		Exp <sub>occup</sub> (min/day)	EXP <sub>occup</sub> (days)				
1	0.05	0.042	0.2	0.5	0.033		0.000007
2	0.06	0.042	0.8	0.5	0.033		0.000033
3	0.00042	0.750	1.0	0.5	0.033		0.000005

<sup>1</sup> Harvey (1952), Johns (1952) - one-time 20 min exposure, humans.

<sup>2</sup> McKee and Woolcott (1949) - 20 min. exposure repeated over 4 days, miosis on 4th day in humans.

<sup>3</sup> Weimer et al., (1979) - chronic exposure (6 hrs/day x 5 days/week) in rats.

The AELs calculated above compare reasonably well (all are within an order of magnitude of each other). For the purpose of establishing exposure criteria, McKee and Woolcott (1949) was selected as the most appropriate "critical study" for calculating the occupational AEL because these data represent the effects of repeated exposure in humans showing cumulative build-up of mild effects.

Using the above risk assessment formula (including the breathing rates, exposure times and uncertainty factors discussed above for acute human inhalation exposures), the AEL for occupational worker exposure (WPL) is:

$$\begin{aligned}
 \text{WPL} &= \text{LOAEL}_{\text{Inhal}} \times \frac{\text{Resp}_{\text{exptl.}} \times \text{Exp}_{\text{exptl.}}}{\text{Resp}_{\text{occup}} \times \text{Exp}_{\text{occup}}} \times \frac{1}{\text{UF's} \times \text{MF}} \quad (8) \\
 &= 0.06 \text{ mg/m}^3 \times \frac{10 \text{ L/min} \times 80 \text{ min}}{20.8 \text{ L/min} \times 2400 \text{ min}} \times \frac{1}{30} \\
 \text{WPL} &= 0.000033 \text{ mg/m}^3 \text{ (recalculated)}
 \end{aligned}$$

The above AEL agrees with the existing AEL for GB (0.0001 mg/m<sup>3</sup>), only varying by a factor of 3. Generally speaking, risk assessment guidelines are considered “reasonable estimates” (with an uncertainty spanning perhaps an order of magnitude). Therefore, the existing AEL for GB appears to be adequately protective for the workforce, and no change to the existing occupational exposure criteria for GB is recommended.

$$\text{WPL} = 0.0001 \text{ mg/m}^3 \text{ (existing; recommended)}$$

**3.4.1 .1 Calculating the short-term exposure limit (STEL) for GB.**

The American Conference of Government Industrial Hygienists (ACGIH) defines STEL as “a 15-minute time weighted average (TWA) exposure which should not be exceeded at any time during a workday even if the 8-hr TWA is within the threshold limit value (TLV)-TWA. Exposures above the TLV-TWA up to the STEL should be no longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range. An averaging period other than 15 min may be recommended when this is warranted by observed biological effects.”

In calculating a short-term exposure limit (STEL) for GB, data from acute (McKee and Woolcott, 1949) human exposures (40 min) were selected and adjusted for a 60 min exposure time (15 min repeated up to 4 times/day). These data are summarized in Table 8 (Group II). The same formula was used as that for calculating the AEL for occupational workers.

The STEL for occupational exposures may be calculated according to the following formula:

$$\text{STEL} = \text{LOAEL}_{\text{Inhal}} \times \frac{\text{Resp}_{\text{exptl.}} \times \text{Exp}_{\text{exptl.}}}{\text{Resp}_{\text{occup}} \times \text{Exp}_{\text{occup}}} \times \frac{1}{\text{UF's} \times \text{MF}} \quad (9)$$

$$\text{STEL} = 0.06 \text{ mg/m}^3 \times \frac{10 \text{ L/min} \times 40 \text{ min}}{20.8 \text{ L/min} \times 60 \text{ min}} \times \frac{1}{10}$$

$$\text{STEL} = 0.00192 = 0.002 \text{ mg/m}^3$$

This represents a NOAEL concentration (LOAEL x UF) which is adjusted for 20.8 L/min ventilation rate and exposure totaling 60 min, i.e., up to 4 x 15 min exposures in a day, It is also assumed that the possibilities of exposure may occur multiple times during a working lifetime)

Cumulative effects of G-agent exposure would be expected at the developed STEL concentrations because they are in the same concentration range as those (0.06

GB ( $0.06 \text{ mg/m}^3$ ) was repeated the following day, additional mild signs (*e.g.*, headache, blurred vision, eye pain) were noted in the exposed humans.

For short-term human exposure data:

- STEL = 15-minute time weighted average (TWA) exposure concentration ( $\text{mg/m}^3$ ) which should not be exceeded more than four times per day.
- LOAEL<sub>Inhal</sub> = lowest observed adverse effect level ( $\text{mg/m}^3$ ).
- Resp<sub>exptl.</sub> = Experimental subject minute volume (10 L/min).
- Resp<sub>occup</sub> = Occupational minute volume (20.8 L/min)
- Exp<sub>occup</sub> = Occupational exposure (15 min x (4)/day)
- Exp<sub>exptl.</sub> = Experimental exposure (40 min/day).

Uncertainty Factors (UF):

- UF<sub>1</sub> = 3 (short term to long term exposure extrapolation).
- UF<sub>2</sub> = 1 (average human to sensitive human population).
- UF<sub>3</sub> = 1 (animal to human extrapolation).
- UF<sub>4</sub> = 3 (LOAEL to NOAEL extrapolation).
- UF<sub>5</sub> = 1 (minimum to complete database).
- MF = 1 (not necessary).

A value of 3 was selected for UF<sub>1</sub> because the data from an acute exposure is applied to a short-term exposure which may potentially be repeated occasionally in the workplace. A value of 1 was selected for UF<sub>2</sub> because the occupational population is not considered to include sensitive subpopulations. A value of 1 was selected for UF<sub>3</sub> based upon the use of human data. A value of 3 was used for UF<sub>4</sub> because the level of effect for the LOAEL was minimal. Finally, a value of 1 was chosen for both the UF<sub>5</sub> and the MF because no corrections for the completeness or quality of the database was necessary.

**3.4.1.2 Calculating the Immediately Dangerous to Life and Health (IDLH) Concentration for GB.**

The Existing IDLH Concentration and Its Derivation.

The existing IDLH for GB ( $0.2 \text{ mg/m}^3$ ) was proposed in Memorandum, 25 JUN 1991, and Memorandum 13 JAN 1992 and is based upon an *estimated* effective Ct (ECT) ( $15 \text{ mg}\cdot\text{min/m}^3$ , 2-min exposure; minute volume of 10L/min) for causing “miosis, runny nose, tightness of chest, and headache” in humans. Silver (1953) estimated the lethal concentration (LCt50) of GB in man by extrapolation from intravenous exposure data involving several animal species. Christensen et al., (1958) estimated various less-than-lethal ECTs in humans based upon Silver’s (1953) human LCt estimate. In addition, Cresthull et al., (1957) and Callaway and Crichton (1954) estimated that the ECT50 for severe effects (convulsions and collapse often including death) for the monkey, which they

Cresthull et al., (1957) and Callaway and Crichton (1954) estimated that the ECt50 for severe effects (convulsions and collapse often including death) for the monkey, which they referred to as the ICt50 for severe incapacitation, is approximately 70 percent of the LCt50 value, and that the percent severe effects- Ct curve of monkeys was parallel to the percent lethality-Ct curve. Based upon the studies of Wood (1949) and Mumford (1950), Silver (1953) expressed the opinion that the ICt50 estimate for resting man (breathing at 10L/min) may be in the range of 15 to 40 mg·min/m<sup>3</sup>. Christensen et al., (1958) interpreted this as 15 mg·min/m<sup>3</sup> for mild incapacitation/effects (miosis, rhinorrhea, tight chest, headache), and 40 mg·min/m<sup>3</sup> for moderate incapacitation/effects (signs and symptoms for mild incapacitation plus tremors, muscular weakness, incoordination, and ataxia). Christensen et al., (1958) assumed that the ICt50/LCt50 ratio for incapacitated man is of the same order of magnitude as that found in the monkey. Furthermore, Christensen et al., (1958) assumed that percent incapacitation-ICt50 curves for mild and moderate incapacitation/effects were also parallel to the lethal dose-response curve. Christensen et al., (1958) presented the plots of LCt50 against exposure times between 0.3 and 60 min for eight animal species to be approximately parallel. The slope of these curves is K/7.01 where K = Log LCt50 (t = 1 min) for a particular animal species. K for man was calculated to be 1.918 where the LCt50 estimate based on a 2-min exposure was 100 mg·min/m<sup>3</sup>. It should be noted that since the time the existing IDLH values were proposed (Memorandum, 25 JUN 1991, and Memorandum 13 JAN 1992), Reutter and Wade (1994) reviewed the animal data from which Christensen et al., (1958) extrapolated human percent lethal and incapacitation - Ct curves. Reutter and Wade (1994) concluded that LCt vs. ICT; and LCt50 vs. exposure time for several animal species were not parallel. Reutter and Wade (1994) proposed significantly higher slopes for lethality and severe effects of GB in humans. Christensen et al., (1958) reported that the estimated slope of the plots of ICt's and LCt's for man against exposure times above 2 min is 0.274. The following formula (which describes the relationship between ECt50 vs. exposure time) was developed by Christensen et al., (1958) to estimate the ECt50 for various exposure periods (0.3 to 60 min).

$$\log ECt = \frac{K (\log t + 7.01)}{7.01} \quad (10)$$

$$\log 15 = \frac{K (\log 2 + 7.01)}{7.01}$$

$$K = 1.128$$

K was used to extrapolate from the 2 min ECt of 15 mg·min/m<sup>3</sup> to 30 min:

$$\log ECt = \frac{1.128 (\log 30 + 7.01)}{7.01}$$

$$\log ECt = 1.366$$

$$ECt = 23.2 \text{ mg}\cdot\text{min}/\text{m}^3$$

The extrapolated ECt of 23.2 mg·min/m<sup>3</sup> represents the 30 min Ct for producing effects as defined above, at a minute volume of 10L/min for resting man. To convert the ECt to a minute volume of 42 L/min (moderate activity):

$$23.2 \text{ mg}\cdot\text{min}/\text{m}^3 \times 10/42 = 5.5 \text{ mg}\cdot\text{min}/\text{m}^3$$

Converting the 30 min ECt to the EC (i.e., IDLH, 30 min):

$$5.5 \text{ mg}\cdot\text{min}/\text{m}^3 / 30 \text{ min} = 0.18 \text{ mg}/\text{m}^3$$

IDLH, 30 min  $\approx$  0.2

The current NIOSH definition for an immediately dangerous to health or life condition (NIOSH Respirator Decision Logic, 1987) is a situation “that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment.” It is also stated that the purpose of establishing an IDLH is to “ensure that the worker can escape from a given contaminated environment in the event of failure of the respiratory protection equipment.”

The most recently revised criteria (NIOSH Publication No. PB-94-1950471, for determining an IDLH involve a tiered approach with:

- 1) acute human toxicity data being used preferentially followed next by
- 2) acute animal inhalation toxicity data (lethal concentrations adjusted to an equivalent 30 min exposure, if necessary); lethal concentrations are divided by a safety factor of 10
- 3) acute animal oral toxicity data; the lethal dose is used to determine the equivalent total dose to a 70 Kg worker and the air concentration containing this dose was determined by dividing by 10 cubic meters - IDLH was determined by dividing these air concentrations by a safety factor of 10, and 4) chronic toxicity data are considered if no relevant acute toxicity data exist although they may have little relevance to acute effects.

In the OSHA regulation (29 CFR 1910.146) on permit-required confined spaces, an immediately dangerous to life or health condition is defined as follows:

“Any condition that poses an immediate or delayed threat to life or that would cause irreversible adverse health effects or that would interfere with an individual’s ability to escape unaided from a permit space.”

It would appear that miosis, runny nose, tightness of chest, and headache may be likely to occur both below and above an IDLH concentration, but are not normally considered as life-threatening, escape-impairing, serious, or irreversible. However, a Ct of

15 mg·min/m<sup>3</sup> may be near the threshold for effects which are considered incapacitating, with regard to escape (Mumford, 1950).

#### The Recalculated IDLH.

In selecting a critical study for deriving the IDLH estimates for GB, two studies were considered. The first, Baker and Sedgwick (1996) reported that human subjects exposed to Sarin vapor (Ct = 15 mg·min/m<sup>3</sup>, 0.5 mg/m<sup>3</sup> for 30 min) experienced only mild clinical signs (miosis, transient hyperpnea) and subclinical signs consisting of small changes in single fiber electromyography (SFEMG) which is a sensitive technique for measuring subclinical changes at the neuromuscular junction. Small changes in SFEMG were seen at three hrs and three days after an exposure sufficient to cause a reduction in red cell acetyl cholinesterase to 60% of normal. The SFEMG changes were not accompanied by any clinical neuromuscular symptoms or signs and returned to normal 2 years after exposure. Their (Baker and Sedgwick, 1996) results suggest that there are reversible subclinical changes compatible with the development of nondepolarizing neuromuscular block without frank clinical expression. Although the exposure time used in this study would be ideal for application to an acute exposure scenario (i.e., IDLH-30 min) the level of responses reported were not of sufficient severity to be life threatening, irreversible or potentially impair escape without the aid of a protective mask.

Another choice for the critical study in deriving an IDLH is that of Mumford (1950). Mumford reviewed data from acute human exposures to GB vapor (ranging from 1.5 - 8 min), and concluded that Ct's above 15 mg·min/m<sup>3</sup> produced a marked fall in blood AChE with concomitant pronounced symptoms of systemic nerve gas poisoning, including generalized weakness, nausea and vomiting in addition to eye and respiratory effects. This is inconsistent with the increased severity and types of signs and symptoms noted by Harvey (1952), up to a Ct of 6 mg·min/m<sup>3</sup> (2 and 20 min exposures) in humans. Mumford (1950) estimated 15 mg·min/m<sup>3</sup> (10 mg/m<sup>3</sup> for a 1.5 min exposure) to be the lower border of physical incapacitation.

The severity of clinical signs for a Ct of 15 mg·min/m<sup>3</sup> are obviously different between the Baker and Sedgwick (1996) study (30 min exposure) and the Mumford (1950) study (1.5 min exposure). This may be another example that Ct is not constant and that exposure concentration may be more important than exposure time in determining the severity of acute effects. Whereas the same Ct is used in both the Mumford (1950) and the Baker and Sedgwick (1996) studies, the vapor concentrations and exposure times are very different resulting in signs which are consistent with those considered appropriate for an IDLH (Mumford, 1950) vs. mild clinical and subclinical signs (Baker and Sedgwick, 1996). Therefore, it may be more prudent to use data involving relatively high vapor concentrations (10 mg/m<sup>3</sup> and short exposure times 1.5 min (such as that of Mumford, 1950) and extrapolate to a 30 min exposure in deriving a human IDLH value.

It is proposed that the IDLH concentration (30 min) for GB be based upon short-term human exposure data (Mumford, 1950). In accordance with NIOSH guidelines (NTIS Publication No. PB-94-195047), acute human toxicity data (Mumford, 1950) were

selected for developing IDLH values and adjusted to a 30 min exposure period. The minute volume in this study (15 L/min) was adjusted to 42 L/min to approximate increased respiratory volumes anticipated during escape conditions (ICRP, 1975; USEPA, 1996). The basic information describing the Mumford (1950) report is listed below:

- Effective concentration (EC) for borderline incapacitation (pronounced symptoms of systemic nerve gas poisoning, including generalized weakness, nausea and vomiting in addition to eye and respiratory effects) = 10 (mg/m<sup>3</sup>)
- Exposure Time = 1.5 min
- Experimental Minute Volume = 15 L/min (estimated for subjects walking within exposure chamber)

Adjusting the EC for a 30 min exposure;

$$\begin{aligned}\text{EC (30min)} &= \text{EC} \times (1.5 \text{ min}/30 \text{ min}) \\ &= 10 \text{ mg/m}^3 \times (0.05) \\ \text{EC (30min)} &= 0.5 \text{ mg/m}^3\end{aligned}$$

Adjusting the EC (30 min) for 42 L/min (minute volume anticipated during escape activity) to calculate IDLH (30 min);

$$\begin{aligned}\text{IDLH (30 min)} &= \text{EC mg/m}^3 (30 \text{ min}) \times (15 \text{ L/min}/42 \text{ L/min}) \\ &= 0.18 \text{ mg/m}^3 \\ \text{IDLH (30 min)} &= 0.2 \text{ mg/m}^3\end{aligned}$$

Because the above IDLH value for GB is identical to the existing value, it would not appear necessary to recommend changes, however additional information was found in the literature to suggest the possibility that gender differences in sensitivity to G-agent vapor may exist.

Some data in animals (Callaway and Blackburn, 1954) suggests that small but statistically significant differences in sensitivities to the toxic effects of GB, GD, and GF may exist between males and females when considering the inhalation route of exposure. Callaway and Blackburn (1954) found that female rats were almost two-fold as sensitive to toxic effects (lethality) of GB, GD, and GF vapor as compared to male rats. McPhail (1953) also found that the female rat and hamster were more susceptible to Sarin than the males with intravenous and inhalation exposures. However, Callaway (1950) found no sex differences in the susceptibility of lethal effects of GB (including slopes of lethal dose-response curves) in rats and guinea pigs when GB was administered subcutaneously. Likewise, Coleman and Patton (1969) reported that LD50 values of Soman and Tabun in mice, hamsters and rats indicate that these two agents demonstrate no significant difference in toxicity between males and females. Furthermore, with Sarin

and DSDP in rats and hamsters, no significant difference was noted in toxicity between the sexes but both agents were significantly more toxic in the male mouse than in the female (although the LD50s differ by only 10-20%).

According to Wills (1972), plasma and RBC-ChE activities are generally lower in females than in males. However, with regard to less-than-lethal effects of Sarin, Woodward et al., (1994) examined erythrocyte and plasma cholinesterase activity in male and female rhesus monkeys before and after an acute intravenous exposure to Sarin. Their rationale for selecting the above endpoints resulted from speculation that the combined effects of hydrolysis, phosphorylation, as well as plasma protein binding, may reduce the amount of OP capable of reaching the AChE of the nervous system. In order to determine whether significant differences may exist between males and females in their physiological mechanism(s) which protect the nervous system, they examined gender differences in circulating cholinesterase levels in the atropinized monkey, the responses to Sarin (0.75 LD50) intoxication, and the reactivation of plasma BuChE and RBC AChE by pyridine-2-aldoxime methyl chloride (pralidoxime, 2-PAM). Intra-animal, intra-sex, and cyclic variability during one complete menstrual cycle (28 days) baseline values of BuChE variations were found to be minimal. Following Sarin intoxication and 2-PAM treatment, no significant differences were seen between the sexes in the rate of reactivation of BuChE or AChE by 2-PAM. The rate of aging of Sarin phosphorylated RBC AChE between sexes was also similar. *De novo* regeneration of RBC AChE and plasma BuChE after Sarin intoxication was different between the male and female monkeys. The female plasma BuChE recovery rate was 48% slower than the male recovery rate, while the early (first 63 days) RBC AChE recovery rate was 24.5% faster in the females. Woodward et al., (1994) concluded that there probably are not any clinically significant differences between male and female rhesus monkeys acutely intoxicated with Sarin. However, on subsequent exposure, clinical differences may be observed due to substantial differences in the rate of *de novo* synthesis of both plasma BuChE and RBC AChE.

Holmstedt (1963) reviewed studies of OP pesticides toxicity which indicated that the male rat is less susceptible to poisoning from Malathion, Diazinon, Dimethyl 2, 2-dichlorovinyl phosphate (DDVP), and Parathion, although the female is less susceptible to Chlothion. Frequently, when the study was extended to other species and the route of exposure changed from oral to other routes, no sex difference could be established. Some compounds, like Parathion are more toxic in female than male rats by the oral route, but not by the intraperitoneal route. Since Paraoxon showed no differences in acute intersex toxicity in mouse, rat, rabbit, guinea pig or cat by the oral route, the observed differences in Parathion toxicity in rats is felt to reside in the different capacities of male and female rats to convert Parathion to the more toxic Paraoxon. Furthermore, castration of male rats lead to an increase in toxicity of Parathion to a value similar to that seen in the female, However differences in the metabolism of agents cannot explain the increased resistance of female rats over males in the case of Chlorthion, nor can the mechanism be used to predict a sex difference in toxicity with other compounds which undergo activation in the liver. Very little information has been published on intersexual differences in acute toxicities of OP compounds which do not require metabolic conversion to active cholinesterase inhibitors. Tetraethyl pyrophosphate (TEPP) (Frawley et al., 1957) is

reported to be less toxic to male than female rats. By the oral route, Diisopropyl phosphorofluoridate (DFP) is almost twice as toxic to female rats as it is to males (Frawley et al., 1957).

In conclusion, a review of the literature of both G-agent and OP pesticide toxicity in animals suggests that sex differences in lethal susceptibility may depend upon the type of OP, the species, and the route of exposure. In applying such information to the derivation of an IDLH value for humans, it would be prudent to assume that the sex differences in G-agent sensitivity seen in rats might also be possible in humans. This is especially important because the critical effect selected for establishing an IDLH value is considerably more serious than the “no effect” or “mild/threshold effect” (e.g. miosis, rhinorrhea, tight chest etc.) endpoints used for establishing other AELs. It is also pertinent to consider the current more frequent inclusion of women in potential chemical exposure scenarios.

Callaway and Blackburn, (1954) found that female rats were as much as twice as sensitive to the lethal toxicity of GB as males by the inhalation route. Therefore, the IDLH for GB (based on human male responses) was adjusted by factor of 2 to estimate the IDLH value which addresses a female occupational worker population which is potentially more sensitive than males to GB vapor.

IDLH (30 min) for GB (based on male human data)

IDLH = 0.18 mg/m<sup>3</sup> or 0.2 mg/m<sup>3</sup>

IDLH (30 min) for GB (male + female workforce):

IDLH = 0.2 mg/m<sup>3</sup> ÷ 2

IDLH = 0.1 mg/m<sup>3</sup> (calculated; recommended)

In this case, although the calculated IDLH (0.1 mg/m<sup>3</sup>) differs from the existing IDLH value (0.2 mg/m<sup>3</sup>) by a factor of 2, this difference is considered sufficient to warrant recommending a change from existing IDLH criteria for the following reasons. First, because the uncertainty of estimates derived using the currently accepted risk assessment method are considered to span perhaps an order of magnitude or greater, it was recommended that several of the existing AEL values for GB, GA, and GD remain unchanged since they vary from the recalculated values by only a factor of 2-3, and thus are not considered to be different. However, such estimates (GPLs and WPLs) are based upon a “no observable adverse effect” level of response to a potential chemical exposure. In contrast, IDLH estimates represent airborne concentration thresholds for responses severe enough to potentially prevent escape within 30 min without the aid of a protective mask. Secondly, IDLH recommendations are based upon acute human exposures resulting in observable adverse effects. They represent estimates which are limited to acute 30 min exposure scenarios which potentially may also result in adverse effects. Thus, the level of

“uncertainty” associated with these IDLH estimates is much less than those criteria (e.g., WPLs of GPLs ) in which some combination of extrapolation for: adverse to no adverse effects, acute to lifetime exposure, or animal to human response may be involved.

It should also be noted that inhalation rates were used to derive the above IDLH estimates and AEGL-1 criteria which are discussed later. In the Exposure Factors Handbook, Volume 1 (1996) (USEPA), Chapter 5, Inhalation Route, it is stated that:

“...inclusion of this chapter in the Exposure Factors Handbook is not meant to imply that assessors will always need to select and use inhalation rates when evaluating exposure to air contaminants. In fact, it is unnecessary to calculate inhaled dose when using dose-response factors from Integrated Risk Information System (IRIS). This is due to the fact that the “dose-response” relationships recommended in IRIS for air contaminants are not really based on dose, but rather concentration. Such “dose-response” relationships require only an average air concentration to evaluate health concerns. For non-carcinogens, IRIS uses Reference Concentrations (RfC) which are expressed in concentration units. Hazard is evaluated by comparing the inspired air concentration to the RfC.”

Whereas RfCs in the IRIS database are primarily concerned with the relative hazards of air contaminants, it may not be critical to consider the actual dose received in estimating an exposure hazard to such chemicals. However, because nerve agents are more toxic than most chemicals listed in IRIS, the amount (dose) of “air concentration”, i.e., as a function of respiratory ventilation rate and exposure duration should be considered. For example, tripling the minute ventilation during exposure to the typical IRIS chemical may not result in much of a difference in toxicity, but if it happened with a G-agent, an increase in the severity of toxic signs and symptoms would be expected due to greater dose-response slopes for the latter category of hazardous chemical. If such differences in defining “dose” distinguish AELs from RfCs, the proposed AELs for G-agents may not be considered equivalent to RfCs.

If inhalation is the major route of exposure of a vapor, then the dosage of vapor is going to be influenced, at least to some degree by both the rate and volume of respiration. Given the above, it is anticipated that the confidence in estimates of exposure criteria will be maximized by utilizing available ventilation rates for levels of activity expected to occur in different populations and for various activities. Therefore, minute ventilation information was incorporated into the method for deriving exposure criteria proposed throughout this document.

#### 3.4.2 Calculating the AEL for General Population (General Population Limit or GPL) for GB Vapor.

The AEL for general population (GPL) is calculated using the same basic risk assessment approach as that described for the occupational population. Furthermore, the sources of data are identical to those discussed above (3.4.1). The same LOAEL used for deriving occupational exposure criteria for GB vapor are adjusted for general population respiratory volumes (13.9 L/min), exposure periods (24 hr/day, 7 day/week) and uncertainty factors to take into account a greater range of sensitivity of individuals to chemical exposure within the general population.

The AEL for general population exposures (GPL) is calculated according to the following formula:

$$GPL = LOAEL_{inhal} \times \frac{Resp_{exptl.} \times Exp_{exptl.}}{Resp_{occup} \times Exp_{occup}} \times \frac{1}{UF's \times MF} \quad (11)$$

For short-term human exposure data:

- GPL = Concentration in ambient air.
- LOAEL<sub>inhal</sub> = Lowest observed adverse effect level (mg/m<sup>3</sup>).
- Resp<sub>exptl</sub> = Experimental subject minute volume (10 L/min).
- Resp<sub>GP</sub> = General population minute volume (13.9 L/min over 24hrs).
- Exp<sub>GP</sub> = General population exposure (1440 min/day x 7 days/week).
- Exp<sub>exptl</sub> = Experimental exposure (20 min/day x 1 day/week or 4 days/week).

Note: 20 m<sup>3</sup>/day (13.9 L/min) has been adapted as a standard inhalation rate for humans (USEPA, 1996). This value is widely used to determine the inhaled dose for a given air pollutant for adults.

Uncertainty Factors (UF):

- UF<sub>1</sub> = 10 (short term to long term exposure extrapolation).
- UF<sub>2</sub> = 10 (average human to sensitive human population).
- UF<sub>3</sub> = 1 (animal to human extrapolation).
- UF<sub>4</sub> = 3 (LOAEL to NOAEL extrapolation).
- UF<sub>5</sub> = 1 (minimum to complete database).
- MF = 1 (not necessary).

A value of 10 was selected for UF<sub>1</sub> because the data from short-term exposures is extrapolated to a working lifetime. A value of 10 was selected for UF<sub>2</sub> because the general population includes sensitive subpopulations. A value of 1 was selected for UF<sub>3</sub> based upon the use of human data. A value of 3 was used for UF<sub>4</sub> because the level of effect for the LOAEL was minimal. Finally, a value of 1 was chosen for both the UF<sub>5</sub> and the MF because no corrections for the completeness or quality of the database was necessary.

On the other hand, if chronic animal data are used for deriving the occupational exposure criteria, the experimental exposure concentration of the animal is adjusted to a “human equivalent exposure” concentration according to the following formula:

$$C_{\text{exp Human}} = \frac{\text{Resp}_{\text{Animal}} \times C_{\text{exp Animal}} \times \text{BW}_{\text{Human}}}{\text{Resp}_{\text{Human}} \times \text{BW}_{\text{Animal}}}$$

where:

- $C_{\text{exp Human}}$  = human equivalent exposure concentration.
- $\text{Resp}_{\text{Animal}}$  = animal (rat) respiratory volume (0.21 L/min, resting).
- $C_{\text{exp Animal}}$  = animal (rat) exposure concentration.
- $\text{BW}_{\text{Human}}$  = human body weight (70 Kg).
- $\text{Resp}_{\text{Human}}$  = human respiratory volume (10 L/min, resting).
- $\text{BW}_{\text{Animal}}$  = animal (rat) body weight (0.35 Kg).

The chronic animal data of (Weimer *et al.*, 1979) were selected for comparison to the above short-term human exposures. Tracheitis was found in treated animals at 0.0001 and 0.001 mg/m<sup>3</sup> exposure concentrations and is considered the lowest observed adverse effect (LOAE). Using the above formula to determine the  $C_{\text{Human}}$  or “human equivalent LOEL”:

$$C_{\text{exp Human}} = \frac{(0.21 \text{ L/min}) \times (0.0001 \text{ mg/m}^3) \times (70 \text{ Kg})}{(10 \text{ L/min}) \times (0.350 \text{ Kg})}$$

$$C_{\text{exp Human}} = 0.00042 \text{ mg/m}^3 = \text{LOEL}_{\text{Inhal}} \text{ (“human equivalent”)}$$

$\text{LOEL}_{\text{Inhal}}$  (“human equivalent”) is applied to the following formula for calculating the GPL for general population exposures:

$$\text{GPL} = \text{LOEL}_{\text{Inhal}} \text{ (“human equiv.”)} \times \frac{\text{Resp}_{\text{exptl.}} \times \text{Exp}_{\text{exptl.}}}{\text{Resp}_{\text{GP}} \times \text{Exp}_{\text{GP}}} \times \frac{1}{\text{UFs} \times \text{MF}}$$

For chronic inhalation exposures in rats:

- GPL = Concentration in ambient air.
- $\text{LOEL}_{\text{Inhal}}$  = Lowest observed adverse effect level (mg/m<sup>3</sup>).
- $\text{Resp}_{\text{exptl}}$  = Exptl. subject respiratory volume (10 L/min, resting).
- $\text{Resp}_{\text{GP}}$  = Gen, population respiratory volume (13.9 L/min)

Exp<sub>GP</sub> = Gen. population exposure (1440 min/day x 7 days/week).  
 Exp<sub>exptl</sub> = Exptl. exposure (360 min/day x 5 days/week).

Uncertainty Factors (UF):

UF<sub>1</sub> = 1 (short term to long term exposure extrapolation).  
 UF<sub>2</sub> = 10 (average human to sensitive human population).  
 UF<sub>3</sub> = 10 (animal to human extrapolation).  
 UF<sub>4</sub> = 3 (LOAEL to NOAEL extrapolation).  
 UF<sub>5</sub> = 1 (minimum to complete database).  
 MF = 1 (not necessary).

A value of 1 was selected for UF<sub>1</sub> because the data represents the effects of chronic exposure (1 yr). A value of 10 was selected for UF<sub>2</sub> because the general population includes sensitive subpopulations. A value of 10 was selected for UF<sub>3</sub> based upon the use of animal data which are not as sensitive as humans. A value of 3 was used for UF<sub>4</sub> because the level of effect (tracheitis) was minimal. Finally, a value of 1 was chosen for both the UF<sub>5</sub> and the MF because no corrections for the completeness or quality of the database was necessary.

The following worksheet compares occupational AELs (GPLs) calculated using equation (11) for data from acute human exposures or equation (7) for data from chronic animal exposure studies:

Data Source	LOAEL <sub>inhal</sub> (mg/m <sup>3</sup> )	$\frac{\text{Exp}_{\text{exptl}}}{\text{Exp}_{\text{GP}}}$ (min/day) (min/day)	$\frac{\text{Exp}_{\text{exptl}}}{\text{Exp}_{\text{GP}}}$ (days) (days)	$\frac{\text{Resp}_{\text{exptl}}}{\text{Resp}_{\text{GP}}}$	$\frac{1}{\text{UF} \times \text{MF}}$	GPL (mg/m <sup>3</sup> )
1	0.05	0.014	0.142	0.72	0.0033	0.0000002
2	0.06	0.014	0.571	0.72	0.0033	0.0000011
3	0.00042	0.250	0.714	0.72	0.0033	0.0000002

<sup>1</sup> - Harvey (1952), Johns (1952) - one-time 20 min exposure, humans.

<sup>2</sup> - McKee and Woolcott (1949) - 20 min exposure repeated over 4 days, miosis on 4th day in humans.

<sup>3</sup> - Weimer et al., (1979) - chronic exposure (6 hrs/day x 5 days/week) in rats,

The AELs calculated above compare reasonably well (all are within an order of magnitude of each other). For the purpose of establishing exposure criteria, McKee and Woolcott (1949) was selected as the most appropriate "critical study" for calculating the occupational AEL because these data represent the effects of repeated exposure in humans showing cumulative build-up of mild effects.

Using the above risk assessment formula (including the breathing rates, exposure times and uncertainty factors discussed above for acute human inhalation exposures), the AEL for general population exposure is:

$$\text{GPL} = \text{LOAEL}_{\text{inhal}} \times \frac{\text{Resp}_{\text{exptl.}} \times \text{Exp}_{\text{exptl.}}}{\text{Resp}_{\text{GP}} \times \text{Exp}_{\text{GP}}} \times \frac{1}{\text{UF's} \times \text{MF}}$$

$$= \frac{0.06 \text{ mg/m}^3 \times 10 \text{ L/min} \times 80 \text{ min}}{13.9 \text{ L/min} \times 10,080 \text{ min}} \times \frac{1}{300}$$

$$\text{GPL} = 0.0000011 \text{ mg/m}^3 \text{ (recalculated)}$$

The above AEL appears to agree reasonably well with the existing general population AEL for GB (0.000003 mg/m<sup>3</sup>), only varying by a factor of 3. Generally speaking, risk assessment guidelines are considered “reasonable estimates” (with an uncertainty spanning perhaps an order of magnitude). Therefore, the existing AEL for GB appears to be adequately protective for the workforce, and no change to the existing general population exposure criteria for GB is recommended.

$$\text{GPL} = 0.000003 \text{ mg/m}^3 \text{ (existing; recommended)}$$

#### 3.4.2.1 Calculation of Acute Exposure Guideline Levels (AEGs) for the General Population.

According to the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (Federal Register, Oct. 30, 1997, Vol. 62, Number 210) the AEGs represent short-term threshold or ceiling exposure values intended for the protection of the general public, including susceptible or sensitive individuals, but not hypersusceptible or hypersensitive individuals. The AEGs represent biological reference values for this defined human population and consist for each of four exposure periods of 30 min, 1 hr, 4 hr, and 8 hr. The AEGL-1 biological endpoint is the airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance at or above which it is predicted that the general population, including “susceptible” but excluding “hypersusceptible” individuals, could experience notable discomfort. Airborne concentrations below AEGL-1 represent exposure levels that produce mild odor, taste or other sensory irritations. AEGs may be adopted by Federal and State agencies for chemical emergency programs.

The data of Harvey, 1952 was selected as the critical study for determining Acute Exposure Guideline Levels limited to discomfort (AEGL-level 1) for the general population. These data (Harvey, 1952) are based upon acute human exposures (2 and 20 min) to GB vapor. Harvey reported that between 1 and 3 out of a total of 14 human volunteers exposed to GB vapor (0.05 mg/m<sup>3</sup>) for 20 min reported some combination of

symptoms and signs including headache, eye pain, rhinorrhea, tight chest, cramps, nausea, and malaise.

In order to derive estimates for AEGL-1 criteria, the above airborne concentration ( $0.05 \text{ mg/m}^3$ ) reported by Harvey (1952) was temporally scaled to estimate AEGL-1 values for 30 min, 1 hr and 4 hr and further adjusted for a minute ventilation rate appropriate for the general population. Finally, this value was further adjusted by a factor of 10 to account for the increased sensitivity of general population versus the military volunteer population used in the Harvey (1952) study.

The National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances applies a non-linear method of temporal scaling routinely based upon a model described by ten Berge et al., (1986). ten Berge et al., (1986) states that "the product of concentration and exposure time (Ct) is not always a good parameter for predicting the mortality response (Haber's rule). On the contrary, the term  $C^n t$ , in which the exponent n is different from 1, often predicts the response very well" (ten Berge et al., 1986).

The value of the exponent (n) for each chemical must be calculated from data in which both concentration and exposure time are variables. Information in the ten Berge et al., (1986) paper, which was used to demonstrate the model, only involved data from several volatile industrial chemicals with mechanisms of action different from the organophosphates. Thus, in order to apply the ten Berge model, it would be necessary to find data (G-agent) in animals or humans in which both concentration and exposure times were varied. Another study which addresses this problem was published by Yee (1996). Yee (1996) also proposed that the toxicity of rapidly acting inhaled toxic materials is usually highly nonlinear and described the use of a nonlinear toxic load to quantify this effect. Yee (1996) cited the ten Berge et al., (1986) model as the basis for a model for describing the nonlinearity of the toxic response to GB vapor. His (Yee, 1996) reanalysis of raw data from a large-scale experiment of the toxicity of GB in rats, mice, guinea pigs, and pigeons for which both concentration and exposure time were varied, indicated that the nonlinear dose-response model ( $C^n t$ ) provided good descriptions of the animal toxicity data. The value for the exponent (n) in the  $C^n t$  model was determined to be 1.5, based upon data from the four species stated above. He interpreted this to mean that the degree of harm from GB exposure varies in a nonlinear fashion with the concentration.

In considering whether to use such a nonlinear model for temporal scaling in estimating AEGL levels for GB, additional information is presented:

- First, it should be noted that the value (1.5) of the nonlinear model exponent n is based upon data in which very short exposure times (e.g., as low as 2 sec) were used (Yee, 1996). In fact, the majority of data in all 4 species involved exposure times less than 2 min. Only 2 data points/species involved longer exposure times (including 2 and 10 min). Whether such ultra-short exposure data are adequate for deriving values for a nonlinear dose-response model is likely to be the subject of debate by

toxicologists and risk assessors. Yee and Bide (1997) caution that this method, like its predecessors, is empirical and bounded by the experimental data.

• Secondly, in searching the literature for additional data applicable for evaluating the nonlinear model exponent, it was discovered that Mumford (1949) commented on what appears to be an identical model proposed by Canada at the 1949 Tripartite Conference. Canada reported the results of an investigation (Suffield TM-1 39) on the effect of concentration on the toxicity of inhaled GB, which indicated that for four different species (rats, mice, guinea pigs and pigeons) the LCt50 decreased progressively as t dropped from 12 min to 3.5 sec, according to a relation of the type  $C^{1.5}t$ . However, Mumford (1950) stated that:

“preliminary work with rats and mice, using a simple technique in which a known concentration of GB was set up in a 1m<sup>3</sup> chamber and circulated at 500 l/min through a small exposure chamber for a given time, failed to confirm the Canadian findings in detail, though they did indicate a general tendency for the LCt50 to fall with very short times of exposure. It will be seen that whilst the Porton values agree qualitatively with the Canadian in indicating that the LCt50 for short exposure times is materially lower than the standard 10 min value, the two sets of data differ in respect of the extent of diminution and the t value at which it begins to be manifest. The Porton data indicate that LCt50 is roughly constant from 10 to 1 min but thereafter diminishes according to an equation similar to that of the Canadians. ” Mumford also states that “the apparent irregularity at the very short exposure times is not surprising, as individual variations in breathing rate and breath-holding will play an important part under these conditions.”

The precise reason why the LCt50 rises with decreases in the concentration of G vapor and vice versa, is conjectural. It is at least probable that the fall in the rate of absorption that must parallel any decrease in concentration plays a part, and favors dilution, detoxification, more equal distribution in tissues, and excretion. It is possible too that, with longer exposure, the agent alters the animal's respiration and circulation so that absorption is lessened: Further, there is evidence that enzymes (fluorophosphatases) exist in animal tissues capable of destroying G agents. The value to the organism of these detoxifying mechanisms will be greater the more slowly the toxic agent is absorbed, and a threshold concentration for each agent may exist below which the agent can be breathed indefinitely.

Although it is likely that Cts involving exposures times significantly beyond 10 min follow a nonlinear model (it can be demonstrated that Haber's rule is not appropriate for exposure duration beyond 10 min), the quantification of such a nonlinear model is still in question. It is not recommended that  $C^{1.5}t$  be used for temporal scaling for AEGL-1 (30 min - 4 hr) guidelines until appropriate data (involving exposure durations beyond 10 min have been identified- so that the value of the exponent (n) may be based upon data having exposure durations similar. to those times for which interpolations will be

made using this empirical nonlinear model. Validating such a model requires considerable time and resources and is beyond the present scope of this criteria document. Nevertheless, it is recommended that this project be pursued in the future.

In the absence of empirical data to define the value of the exponent (n) for C<sup>n</sup>t, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances uses a default value of 2 for temporal scaling in deriving AEGL criteria. Another alternative for temporal scaling is to apply a linear model (i.e., Haber's rule). AEGL-1 values derived using this linear method of temporal scaling would be expected to be more conservative than a non-linear model with the largest differences expected at the 4 hr time.

AEGLs derived using a nonlinear model (ten Berge) and a linear model (Haber's rule) are compared below:

<u>Nonlinear model</u>	<u>Linear model</u>
Assumes that concentration and exposure duration are not equally important in determining the severity of toxic response i.e., toxic response = C <sup>n</sup> x t ; n = 2 (default)	Assumes that concentration and exposure duration are equally important in determining the severity of toxic response i.e., toxic response = C x t
<u>Exposure dose predicted with non-linear model:</u>	<u>Exposure dose predicted with linear model:</u>
(0.05) <sup>2</sup> mg/m <sup>3</sup> x 20 min = 0.05 (mg·min/m <sup>3</sup> )	(0.05) mg/m <sup>3</sup> x 20 min = 1 (mg·min/m <sup>3</sup> )
<u>Temporal scaling of concentration (C)</u>	<u>Temporal scaling of concentration (C)</u>
<ul style="list-style-type: none"> <li>• In order to maintain the same dosage (proportional to level of effect), calculate value of C necessary to keep dosage constant for different duration of exposure</li> <li>• Adjust for difference in ventilation (10 L/min ÷ 13.9 L/min) for general population.</li> <li>• Adjust for increased sensitivity of general population (1/10).</li> </ul>	<ul style="list-style-type: none"> <li>• In order to maintain the same dosage (proportional to level of effect), calculate value of C necessary to keep dosage constant for different duration of exposure.</li> <li>• Adjust for difference in ventilation (10 L/min ÷ 13.9 L/min) for general population.</li> <li>• Adjust for increased sensitivity of general population (1/10).</li> </ul>
<u>AEGL-1 (30 min)</u>	<u>AEGL-1 (30 min)</u>
C <sup>2</sup> x 30 min = 0.05 (mg·min/m <sup>3</sup> ) C = 0.04 mg/m <sup>3</sup> Adjusting for ventilation and sensitivity: C = 0.04 mg/m <sup>3</sup> (10/13.9) (1/10) <u>C = 0.003 mg/m<sup>3</sup></u>	C x 30 min = 1 (mg·min/m <sup>3</sup> ) C = 0.033 mg/m <sup>3</sup> Adjusting for ventilation and sensitivity; C = 0.033 mg/m <sup>3</sup> (10/13.9) (1/10) <u>C = 0.0024 mg/m<sup>3</sup></u>
<u>AEGL-1 (1 hr)</u>	<u>AEGL-1 (1 hr)</u>
C <sup>2</sup> x 60 min = 0.05 (mg·min/m <sup>3</sup> ) C = 0.029 mg/m <sup>3</sup> Adjusting for ventilation and sensitivity;	C x 60 min = 1 (mg·min/m <sup>3</sup> ) C = 0.016 mg/m <sup>3</sup> Adjusting for ventilation and sensitivity;

$$C = 0.029 \text{ mg/m}^3 (10/13.9) (1/10)$$
$$C = 0.002 \text{ mg/m}^3$$

AEGL-1 (4 hr)

$$C^2 \times 240 \text{ min} = 0.05 \text{ (mg}\cdot\text{min/m}^3\text{)}$$
$$C = 0.014 \text{ mg/m}^3$$

Adjusting for ventilation and sensitivity;

$$C = 0.014 \text{ mg/m}^3 (10/13.9) (1/10)$$
$$C = 0.001 \text{ mg/m}^3$$

$$C = 0.016 \text{ mg/m}^3 (10/13.9) (1/10)$$
$$C = 0.0012 \text{ mg/m}^3$$

AEGL-1 (4 hr)

$$C \times 240 \text{ min} = 1 \text{ (mg}\cdot\text{min/m}^3\text{)}$$
$$C = 0.004 \text{ mg/m}^3$$

Adjusting for ventilation and sensitivity;

$$C = 0.004 \text{ mg/m}^3 (10/13.9) (1/10)$$
$$C = 0.0003 \text{ mg/m}^3$$

Relatively small differences in concentrations were found comparing AEGL-1 values derived from the above two methods. The largest difference was found at the 4 hr time in which AEGL values differed by a factor of 3. As expected, the linear model resulted in the most conservative predictions. Given that G-agents are considerably more toxic than most hazardous compounds in which the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances estimates AEGL values, AEGL-1 values derived using the more conservative approach (linear model) are recommended for G-agent vapor until further data can be found to validate the value of the concentration exponent most appropriate for use in the nonlinear model.

3.4.3 Summary of Airborne Exposure Levels for GB Vapor.

Existing, recalculated/developed and recommended AELs for GB in occupational and general populations are summarized in Table 9.

3.5 Derivation of Airborne Exposure Levels for GA, GD, and GF.

Because the toxicological database for GA, GD, and GF is incomplete compared to GB, it is proposed that exposure criteria for GA, GD, and GF, be based upon their "relative" potency (for inducing the mildest effects e.g., miosis in humans) to GB. One of the mildest of responses (miosis) was selected for the purpose of comparing G-agent potency because it is more closely associated with the biological endpoints used as the basis for deriving AEL, STEL, and AEGL-1 criteria, i.e. a biological response consistent with the "lowest observable adverse effects" resulting from G-agent exposure. This should also be appropriate for deriving relative potencies of G-agents in determining IDLH exposure criteria even though the IDLH is associated with a greater severity of response (e.g., weakness) which could compromise escape in the event of protective mask failure.

**Table 9. Existing, Recalculated/Developed, and Recommended Airborne Exposure Limits (AELs) for GB in Occupational and General Populations**

Criteria	Occupational (mg/m <sup>3</sup> )	General Population (mg/m <sup>3</sup> )
Existing	0.0001 - (TWA; 8 hr/day, 40 hr/week) 0.2 - IDLH (30 min)	0.000003 -(TWA; 24 hr/day, 7 days/wk)
Recalculated o r Developed •	0.000033 - WPL(TWA;8 hr/day, 40 hr/week) 0.1 - IDLH (30 min) 0.002 - STEL* (TWA;15 min x 4/day)	0.0000011 - GPL (TWA; 24 hr/day,7 days/week) 0.0024 - AEGL-1 • (30 min) 0.0012 - AEGL-1 • (1 hr) 0.0003 - AEGL-1 • (4 hr)
Recommended	0.0001 - WPL (TWA; 8 hr/day 40 hr/week) 0.1 - IDLH (30 min) 0.002 - STEL* (TWA; 15 min x 4/day)	0.000003 - GPL (TWA; 24 hr/day, 7 days/week) 0.0024 - AEGL-1 • (30 min) 0.0012 - AEGL-1 • (1 hr) 0.0003 - AEGL-1 • (4 hr)

- = Developed (no existing criteria)
- WPL = Occupational AEL (no observable adverse effects)
- GPL = General Population AEL (no observable adverse effects)
- IDLH- = Immediately Dangerous to Life or Health
- STEL = Short Term Exposure Limit
- AEGL-1 (30 min) = Acute Exposure Guideline - Level 1
- AEGL-1 (1 hr) = Acute Exposure Guideline - Level 1
- AEGL-1 (4 hr) = Acute Exposure Guideline - Level 1
- TWA = Time Weighted Average

The recommendations of Reutter and Wade (1994) were used in assigning potencies of GA, GD and GF vapor relative to GB. Specifically, the estimated EC<sub>50</sub>s (miosis) in humans for ocular and nasal exposure (Table 4) proposed by Reutter and Wade (1994) is considered the most applicable to estimating relative G-agent potency in deriving airborne exposure criteria. The rationale used by Reutter and Wade (1994) is discussed below:

“Old estimates for the potency of G-agent mild effects (miosis, rhinorrhea, and tight chest) were assumed valid unless the assumptions on which they were based were inappropriate for the scenario at hand

or were not supported by the available data. The data from a classified source indicated that potency or GA vapor exposure to induce mild effects in human subjects paralleled those reported by others for GB vapor exposure. Thus, at least at this level of response (mild signs), GA and GB vapors were estimated to be equipotent in humans. Callaway and Dirnhuber (1971) reported that the ECt50 (50% reduction in pupil area) for GB vapor exposures of rabbits (eyes only, using goggles) was approximately twice that for GD vapor. There were no human data found for estimation of the mild effects dosage following inhalation or ocular exposure to GF. The potency of percutaneous liquid GF was compared to that of GD for mitotic potency and no difference was found. Based upon these findings, the mitotic potency of GF vapor is assumed to be comparable to that for GD. "

Table 10. Recommended Airborne Exposure Limits (AELs) for GB, GA, GD, and GF in the Occupational and General Population

Recommended AEL (mg/m <sup>3</sup> )				
GB	GA	GD	GF	Application
<b>Occupational</b>				
0.0001	0.0001	0.00003	0.00003*	WPL (TWA; 8 hr/day, 5 days/wk)
0.002*	0.002*	0.001*	0.001*	STEL (TWA; 15 min x 4/day);
0.1	0.1	0.05	0.05*	IDLH (30 min)
<b>General Population</b>				
0.000003	0.000003	0.000001	0.000001*	GPL (TWA; 24 hr x 7 days/wk)
0.0024*	0.0024*	0.0012*	0.0012*	AEGL-1( 30 min)
0.0012*	0.0012*	0.0006*	0.0006*	AEGL-1( 1 hr)
0.0003*	0.0003*	0.0001*	0.0001*	AEGL-1( 4 hr)

- \* = Developed (no existing criteria).
- WPL = Occupational AEL (no observable adverse effects)
- GPL = General Population AEL (no observable adverse effects)
- IDLH- = Immediately Dangerous to Life or Health
- STEL = Short Term Exposure Limit
- AEGL-1 (30 min) = Acute Exposure Guideline - Level 1
- AEGL-1 (1 hr) = Acute Exposure Guideline - Level 1
- AEGL-1 (4 hr) = Acute Exposure Guideline - Level 1
- TWA = Time Weighted Average

The recommended (Reutter and Wade, 1994) EC<sub>t</sub>50s (miosis) in humans are 0.5 mg·min/m<sup>3</sup> (GA and GB) and 0.25 mg·min/m<sup>3</sup> (GD, and GF). Therefore, AELs recommended for GA, and GB, are estimated to be a multiple (2) of those recommended for GD and GF, and are summarized in Tables 10 and 11.

Recalculated WPLs for GA and GB (0.000033 mg/m<sup>3</sup>) were not considered to be different from their respective existing AELs (0.0001 mg/m<sup>3</sup>) (Table 11), because the uncertainty of estimates derived using the currently accepted risk assessment method is considered to span perhaps an order of magnitude or greater. Thus, if WPLs for GA and GB remain at 0.0001 mg/m<sup>3</sup>, the expected WPLs for GD and GF should be 0.00005 mg/m<sup>3</sup>, based upon their relative potency to GB. However, this value 0.00005 mg/m<sup>3</sup> would be greater than the existing WPL for GD (0.00003 mg/m<sup>3</sup>). Therefore, it is recommended that the WPL for GD remain at the existing level (0.00003 mg/m<sup>3</sup>), since it is slightly lower (more protective) than 0.00005 mg/m<sup>3</sup>. In the case of GF, it is recommended that the WPL be equal to that of GD (0.00003 mg/m<sup>3</sup>), as suggested in Table 4. Thus, the recommended WPL values for GA and GB are three times those for GD and GF.

In order to be consistent with the above recommended relative potency of GA and GB to GD and GF for WPLs, the same relative potencies of these agents is recommended for GPL criteria. However, for all criteria other than WPLs and GPLs, ratios of 2:1 (GA and GB: GD and GF) were applied .

#### 4. CONCLUSIONS

The existing, recalculated/developed, and recommended exposure criteria for GA, GB, GD, and GF are summarized in Table 11 and discussed below.

- The existing exposure criteria for GB and GA were promulgated by the CDC (DHHS, 1988). They are based upon recommendations proposed by McNamara and Leitnaker (1971) using a combination of acute human exposure data as well as acute animal pharmacokinetic data to predict cumulative effects of GB exposure in humans. Exposure guidelines for GD were set forth in DA PAM 40-8 (1990). No exposure guidelines exist for GF.

- In deriving recalculated/developed criteria, data from human short-term GB vapor exposures (single as well as repeated) and chronic GB vapor exposures in animals were compared. The recalculated/developed AELs for GB, which appear in Tables 9 -11, were derived from repeated human exposure data of McKee and Woolcott (1949). The latter was selected as the “critical study” for deriving AELs because signs of a cumulative build-up of mild effects was seen only after repeated exposure of humans to GB vapor.

Table 11. Existing, Recalculated/Developed, and Recommended Airborne Exposure Limits (AELs) for GA, GB, GD, and GF for Occupational and General Populations

Criteria	GA	GB	GD	GF	Application
<b>Occupational Worker Population AEL (WPL) (mg/m<sup>3</sup>)</b>					
Existing	0.0001	0.0001	0.00003	NF	WPL (TWA, 8 hr/day, 40 hr/wk)
	0.2	0.2	0.06	NF	IDLH (30 min)
Recalculated or Developed*	~0.000033	0.000033	0.000016	0.000016'	WPL (TWA; 8 hr/day, 40 hr/wk)
	0.1	0.1	0.05	0.05'	IDLH (30 min)
	0.002'	0.002'	0.001 .	0.001 .	STEL (TWA; 15 min x 4 /day)
Recommended	0.0001	0.0001	0.00003	0.00003	WPL (TWA 8 hr/day; 40 hr/wk)
	0.1	0.1	0.05	0.05	IDLH (30 min)
	0.002	0.002	0.001	0.001	STEL (TWA; 15 min x 4 /day)
<b>General Population AEL (GPL) (mg/m<sup>3</sup>)</b>					
Existing	0.000003	0.000003	0.000003	NF	WPL (TWA; 24 hr x 7 days/wk)
Recalculated or Developed .	0.0000011	0.0000011	0.0000006	0.0000006	WPL (TWA; 24 hr x 7 days/wk)
	0.0024*	0.0024'	0.0012'	0.0012'	AEGL-1(30 min)
	0.0012*	0.0012*	0.0006*	0.0006*	AEGL-1( 1 hr)
Recommended	0.0003'	0.0003'	0.0001 .	0.0001 .	AEGL-1 ( 4 hr)
	0.000003	0.000003	0.000001	0.000001	WPL (TWA; 24 hr x 7 days/wk)
	0.0024	0.0024	0.0012	0.0012	AEGL-1(30 m i n )
	0 . 0 0 1 2	0.0012	0.0006	0.0006	AEGL-1( 1 hr)
	0.0003	0.0003	0.0001	0.0001	AEGL-1( 4 hr)

- NF = No AELs were found.
- ' = Developed (no existing criteria)
- NF = No criteria for this exposure time could be found
- WPL = Occupational AEL (no observable adverse effects)
- GPL = General Population AEL (no observable adverse effects)
- IDLH- = Immediately Dangerous to Life or Health
- STEL = Short Term Exposure Limit
- AEGL-1 = Acute Exposure Guideline - Level 1
- TWA = Time Weighted Average

Derivation of criteria for GA, GD, and GF is based upon relative potencies (ECt50s) of these agents vs. GB for inducing mild effects (e.g., miosis) in humans. Agents GA and GB are considered equipotent in this regard and half as potent as agents GD and GF, as recommended by Reutter and Wade (1994).

- The recommended criteria represent the results of a final comparison of existing vs. recalculated or developed airborne exposure guidelines based upon an evaluation of whether a real difference exists between the two. Because the uncertainty of estimates derived using the currently accepted risk assessment method are considered to span perhaps an order of magnitude or greater, it is recommended that several of the existing AEL values for GB, GA, and GD remain unchanged since they vary from the recalculated values by only a factor of 2-3, and thus are not considered to be different.

Generally speaking, criteria applicable to long-term exposures (WPLs and GPLs), and derived from the risk assessment formula used in this document, are routinely associated with an uncertainty spanning perhaps an order of magnitude or greater. Thus, they are reasonable estimates of airborne concentrations which are considered thresholds for given levels of human toxic response. The formula used to derive recalculated/developed criteria in this document is part of a currently accepted risk assessment method which includes adjustments for maximal projected exposure duration, exposure dose (as influenced by airborne concentration and ventilation rate), and several “uncertainty factor” adjustments to take into account various limitations of the database.

## 5. RECOMMENDATIONS

Recommend continued use of existing occupational AELs (WPLs) for GA, GB, and GD, general population AELs (GPLs) for GA and GB, and incorporation of new AELs derived in this document and presented in the Table above.

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## GLOSSARY

### Acute Exposure Guideline Level -1 (AEGL-1)

The airborne concentration (expressed as ppm or mg/m<sup>3</sup>) of a substance at or above which it is predicted that the general population, including “susceptible” but excluding “hypersusceptible” individuals, could experience notable discomfort. Airborne concentrations below AEGL-1 represent exposure levels that produce mild odor, taste or other sensory irritations. These guidelines are established by the National Advisory Committee to develop AEGLs under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972. The AEGL-1 defined herein is applicable to 30-minute, 1- and 4-hr exposures, as indicated.

### Airborne Exposure Limits (AELs)

**Workplace:** Atmospheric concentration levels (mg/m<sup>3</sup>) for the workplace, which would not result in adverse health effects, based upon an 8 hr TWA for unprotected workers who may be repeatedly exposed for 8 hr/day, 40 hr/week, for a working lifetime. **General Population:** Atmospheric concentration levels (mg/m<sup>3</sup>) allowable for the general population (including sensitive subpopulations) for indefinite, unprotected lifetime exposure where no adverse health effects are expected as a result of exposure. The existing general population AEL (DHHS, 1988) was expressed as a 72 hr TWA only to reflect sampling requirements at the time of the original CDC publication (DHHS, 1988).

### Acute Toxicity

Toxic effects resulting from a single exposure to a toxicant occurring within a 24 hr time frame from the exposure period.

### Adverse Effect

Refers to either biochemical change, functional impairment, or pathologic lesion which impairs performance and reduces the ability of an organism to respond to additional challenge.

### Critical Effect

The first adverse effect or its known precursor that occurs as dose rate increases.

### General Population Limit (GPL)

Airborne exposure level (AEL) for long-term general population exposure expressed as an atmospheric concentration.

**Immediate versus Delayed Toxicity**

Immediate effects occur or develop rapidly after a single administration of a substance, while delayed effects are those that occur after a lapse of some time.

**Immediately Dangerous to Life or Health (IDLH)**

Immediately dangerous to life or health concentrations represent the maximum concentration from which, in the event of respirator failure, one could escape within 30 min without a respirator and without experiencing any escape-impairing (e.g. severe eye irritation) or irreversible health effects.

**Local versus Systemic Toxicity**

Local effects refer to those that occur at the site of entry (e.g., respiratory tract, eyes) of a toxicant into the body; systemic effects are those that are elicited after absorption and distribution of the toxicant from its entry point to a distant site.

**Lowest Observed Adverse Effect Level (LOAEL)**

The lowest exposure level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between exposed population and its appropriate control group.

**No Observed Adverse Effect Level (NOAEL)**

The exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control; some effects may occur at this level, but they are not considered as adverse, nor precursors to specific adverse effects. In experimental studies in which several NOAELs are determined, the regulatory focus is primarily on the NOAEL seen at the highest dose. This leads to the common usage of the term NOAEL to mean the highest exposure without adverse effect.

**Reference Concentration (RfC)**

An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious non-cancer effects during a lifetime. The EPA has adapted the reference dose method for oral exposures to set airborne exposure levels for health effects other than cancer.

**Severity**

The degree to which an effect changes and impairs the functional capacity of an organ system.

**Short-Term Exposure Limit (STEL)**

The concentration to which workers can be exposed continuously for a short period of time without suffering

from 1) irritation, 2) chronic or irreversible tissue damage, or 3) narcosis of sufficient degree to increase the likelihood of accidental injury, impair self-rescue or materially reduce work efficiency, and provided that the daily TLV-TWA s not exceeded. The STEL category of the TLV-TWA was developed by the American Conference of Governmental Industrial Hygienists (ACGIH) to define a 15 minute time weighted average (TWA) exposure which should not be exceed at any time during a workday even if the 8 hr TWA is within the threshold limit value (TLV) TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.

**Threshold**

A dose level below which a response is unlikely, because homeostatic, compensatory and adaptive mechanisms in the cell or organism protect against toxic effects.

**Threshold Limit Value (TLV)**

A copyrighted term of the Committee of the American Conference of Governmental Industrial Hygienists (ACGIH) which refers to airborne concentrations of substances and represents conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse health effects. TLVs are based upon available information from industrial experience; from experimental human and animal studies; and when possible, from a combination of the three. The bases on which the values are established may differ from substance to substance; protection against impairment of health (those that shorten life expectancy, compromise physiological function, impair the capability for resisting other toxic or disease processes, or adversely affect reproductive function or developmental processes) may be a guiding factor for some whereas reasonable freedom from irritation, narcosis, nuisance, or other forms of stress may be the basis for others.

**Threshold Limit Value-Time Weighted Average (TLV-TWA)**

The time-weighted-average concentration for a normal 8-hr workday and a 40 hr work week to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

**Threshold Limit Value - Ceiling (TLV-C)**

The concentration that should not be exceeded during any part of the working exposure. In conventional industrial hygiene practice, if instantaneous monitoring is not

feasible, then the TLV-C can be assessed by sampling over a 15-minute period except for those substances that may cause immediate irritation when exposures are short.

**Time Weighted Average (TWA)**

An averaging of exposure concentration over exposure time.

**Uncertainty Factor (UF)**

One of several factors used in operationally deriving the Reference Dose (RfD) or Reference Concentrations (RfC) from experimental data. UFs are intended to account for 1) the variation in sensitivity among the members of the general human population; 2) the uncertainty of extrapolating animal data to humans; 3) the uncertainty in extrapolating from data obtained in a study that is of less-than-lifetime exposure; 4) the uncertainty in using LOAEL data rather than NOAEL data; and 5) the inability of a single study to address adequately all possible adverse outcomes in man.

**Worker Population Limit (WPL)**

Airborne exposure level (AEL) for long-term occupational worker population exposure expressed as an atmospheric concentration.