

Overview of Health-Based Provisional Advisory Levels (PALs)

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Background

- Homeland Security Presidential Directives (HSPD) 7 & 8 for National Emergency Preparedness require that:
 - Federal agencies develop methods and technologies for protecting critical infrastructures and resources
 - U.S. EPA provides technical assistance to support national emergency response preparedness





Existing Health-Based Exposure Guidelines

	Reference Value	Organization	Exposure Duration
Occupational	PEL - Permissible Exposure Limit	OSHA	8-hour
	Ceiling	OSHA	Up to 10-minute
	REL - Recommended Exposure Limit	NIOSH	8-hour
	IDLH - Immediately Dangerous to Life and Health	NIOSH	Up to 30-minute
	STEL - Short Term Exposure Limit	NIOSH	15-minute
	TLV - Threshold Limit Value	ACGIH	8-hour
	TLV-STEL - TLV Short Term Exposure Limit	ACGIH	15-minute
Emergency Response	AEGL - Acute Exposure Guideline Level (air only)	NAC/AEGL; NRC/AEGL	10- and 30-minute; 1-, 4- and 8-hour
	DW HA – Drinking Water Health Advisory (water only)	EPA/OW	1-day; 10-day; longer-term
	ERPG – Emergency Response Planning Guideline	AIHA	1-hour
	TEEL – Temporary Emergency Exposure Level	DOE	1-hour
	ERG – Emergency Response Guidebook	DOT	Specialized application
Public Health	MRL - Minimal Risk Level (air and water)	ATSDR	1-14 days (acute); 15-364 days (intermed.); >365 days (chronic)
	CA-REL - Reference Exposure Level	Cal-EPA OEHHA	1-8 hours
	EPA – Acute RfC, short-term and subchronic RfC, RfC/RfD (air and water)	US EPA / IRIS	1-, 4-, 8-, and 24-hr, 30-d, 7-yr, lifetime
	MEG – Military Exposure Guideline (air and water)	DOD-CHPPM	1, 8, 24-h, 14-d, 1-yr (air); 5, 14-d, 1-yr (water)
Military			

The Need for Appropriate Exposure Levels

The Issues:

- Existing exposure guidelines are not sufficient to enable decision-making in short-term (24 hours to 2 years) timeframe. They do not ...
 - Address prioritized CBR (chemical, biological, radiological) agents of concern related to terrorist incidents
 - Characterize breakdown products in environmental media
 - Identify health hazards of environmental breakdown products
 - Assess health effects for different exposure pathways and exposure durations



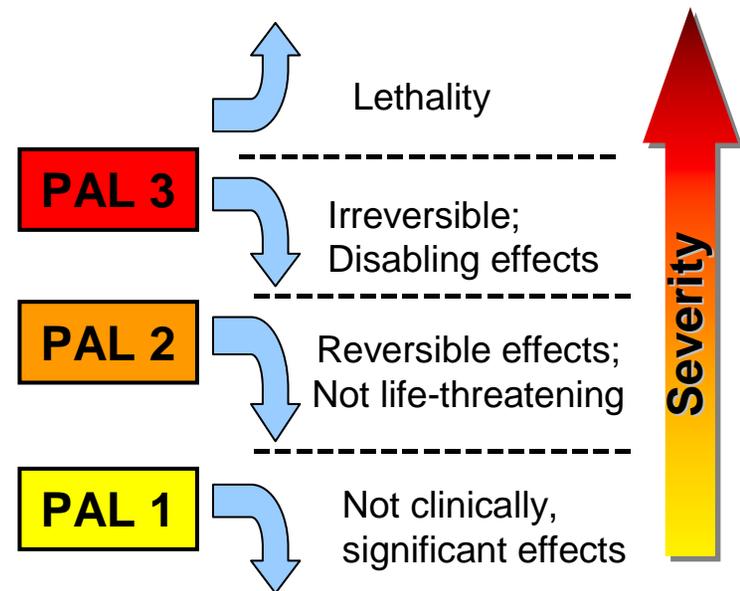
The Solution: **Provisional Advisory Levels (PALs)**

What

- Threshold exposure limits for general public for use in national emergency response programs and community planning
- Exposure levels for industrial chemicals and warfare agents in air and water
- Correspond to three severity levels (PALs 1, PAL 2, PAL 3) for 24-hr, 30-day, 90-day, and 2-year exposure durations

Application

- Acute- and Short-term exposure levels to:
 - Help identify situations where building re-entry or water use is possible
 - Aid decision-makers during cleanup operations

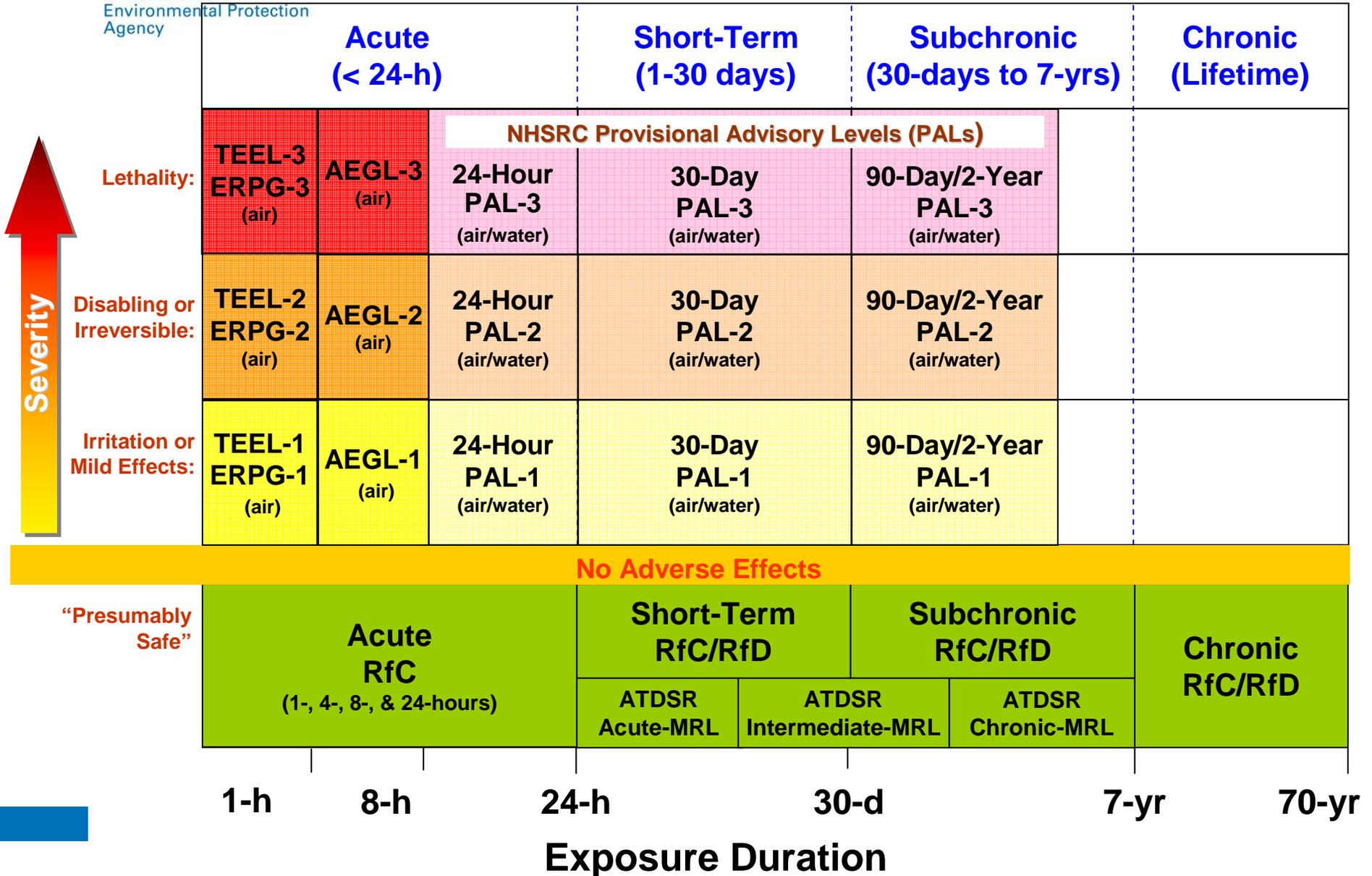


Definition of PALs

- **PAL 1**: Assumed continuous exposure concentration in air or drinking water ***above which*** changes from baseline of specific biomarkers or physiological responses could have adverse health effects in the general population
- **PAL 2**: Assumed continuous exposure concentration in air or drinking water ***above which*** serious, irreversible, or escape-impairing effects could result in the general population
- **PAL 3**: Assumed continuous exposure concentration in air or drinking water ***above which*** lethality in the general population could occur



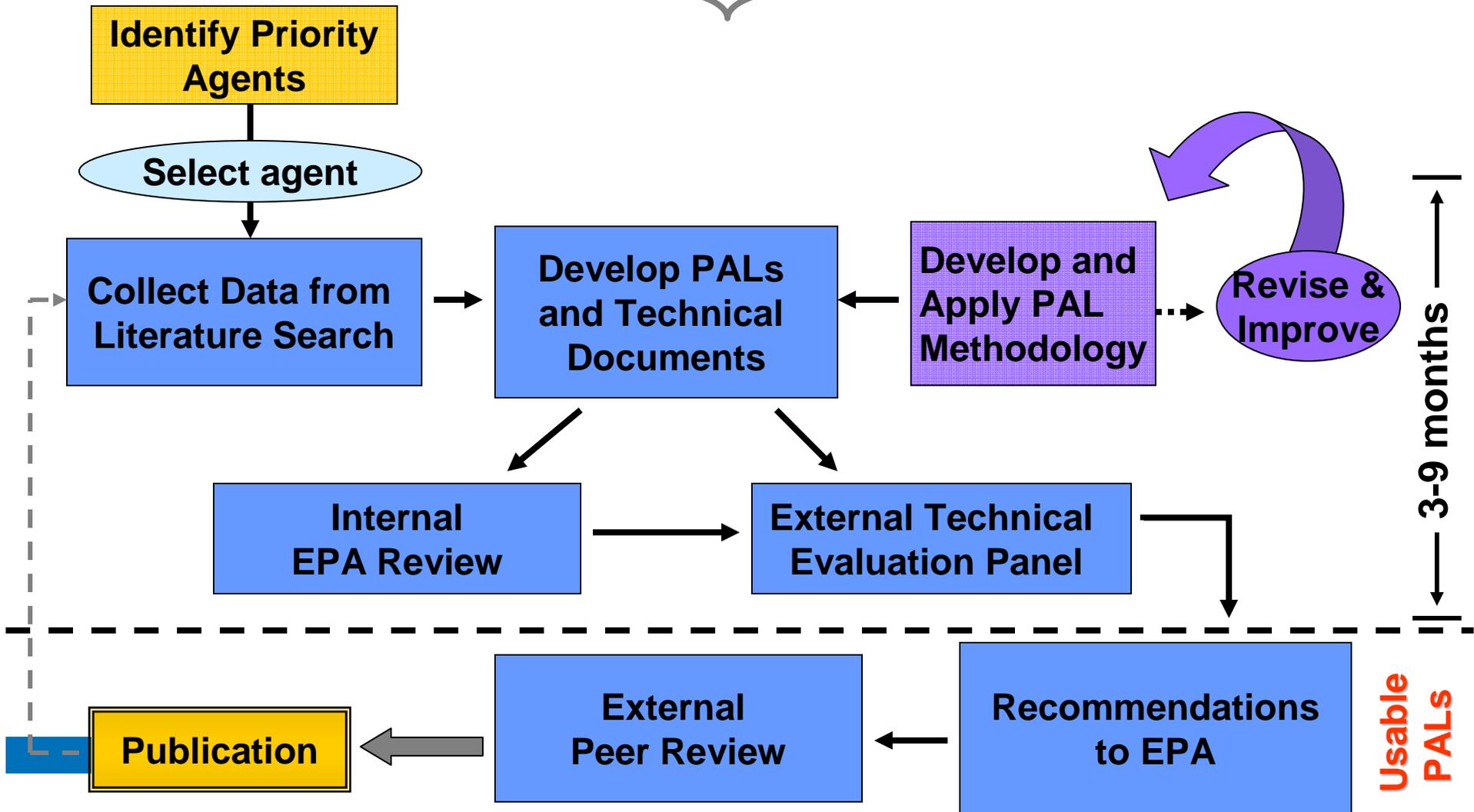
Integrating PALs with Other Exposure Levels





PAL Development Process: An Interagency Collaboration

- ORD
- OSWER
- OPPTS
- OAR
- OW
- Other Agencies



Derivation of PALs

- **Literature search** – Collect published/ unpublished toxicity information; assess toxicokinetic and toxicodynamic data; identify target organs
 - ***Identify critical effect:*** the response, consistent with the PAL tier level, which serves as the basis for deriving a specific PAL value
 - ***Identify point-of-departure:*** actual dose, exposure concentration, or calculated benchmark and respective exposure duration associated with a critical effect. This is used quantitatively in deriving PAL values



Derivation of PALs (cont'd.)

- **Exposure duration** – Extrapolate toxicity data using known methodologies (e.g., $C^n \times t = k$; ten Berge variation of Haber's Rule)
- **Uncertainty factors** – Apply a number of 10-fold factors to toxicity indices (e.g., NOAEL, LOAEL, BMD) in addressing data uncertainties



Haber's Rule: ten Berge and Exposure Duration Extrapolation

- Haber's Rule

$$C \times T = k$$

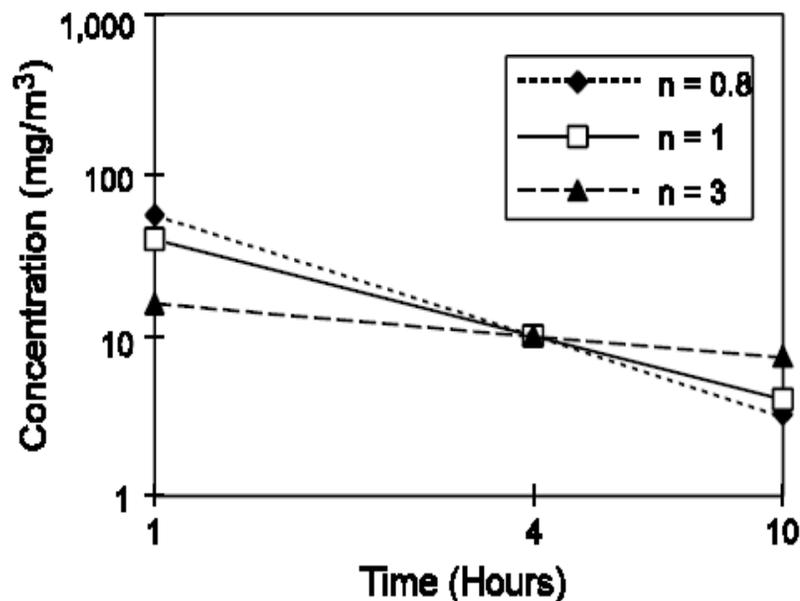
- ten Berge Variation

$$C^n \times T = k$$

Basis for Extrapolation:

Endpoint Specific >> Lethality > Default

(Default: $n = 3$ for shorter durations;
 $n = 1$ for longer durations)



Major Issues in PAL Development

- Selection of priority list of agents
- Lack of toxicity data for agents of concern
- Use of human equivalent concentration (HEC) adjustment
- LOAEL  NOAEL
- Use of uncertainty factors
- Dose and Exposure duration extrapolations
 - Application of PBPK and QSAR models
 - Application of ten Berge variation of Haber's Rule



Major Issues in PAL Development (cont'd.)

- **Uncertainty Analysis**
 - Comparative analyses
(NOAEL/LOAEL vs BMD vs CatReg)
 - BMD range
 - Different species, studies, endpoints

- **Carcinogen Assessment**
 - Limited data from cancer produced from single or few exposures
 - Acute and short-term effects are of more concern in an accidental release scenario than chronic life-time effects
 - Extrapolation from high to low doses
 - Cancer risk levels range from 10^{-4} to 10^{-6}





Major Application of PALs

- EPA/NHSRC is directed by HSPD 7 & 8 to develop national emergency preparedness exposure guidelines for terrorist events and incidents of national significance
- To facilitate health risk-based management and communication for reducing impact of threat agents on general public
- To address decision needs for controlling acute- and short-term exposures to chemical agents via different exposure pathways and exposure durations
- To develop appropriate emergency exposure guidelines that will be applicable at Federal, State, and local levels

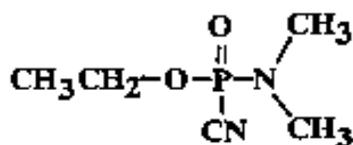




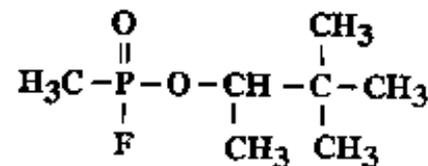
EXAMPLE: CALCULATION OF PAL VALUES



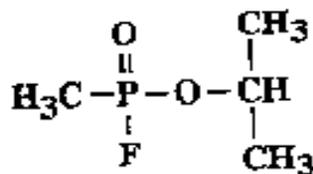
G-Series Nerve Agents (Organophosphate Derivatives)



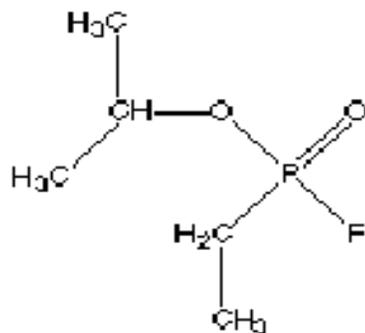
GA (Tabun)



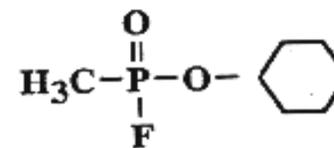
GD (Soman)



GB (Sarin)



Agent GE



GF (Cyclosarin)



Characterization of G-Agents

- Warfare agents; developed in WWII-era Germany
- Agents GA, GB, GD considered potential military or terrorist threats
 - GA and GB; -- U.S. unitary stockpile destroyed by Congressional order
 - GB single major G-agent in unitary stockpile
- Agent GB (impure formulations) deliberate releases of lethal concentrations
 - Potential releases
 - vapor or aerosol to air
 - liquid to soil or water if spilled, ruptured, or corroded container/munition
- Chemical terrorism
 - June 1994: night attack on residents of Matsumoto apartment complex (pumped agent vapor release to occupied space)
 - March 1995: chemical terrorist attacks on commuters in Tokyo subway system (passive volatilization)



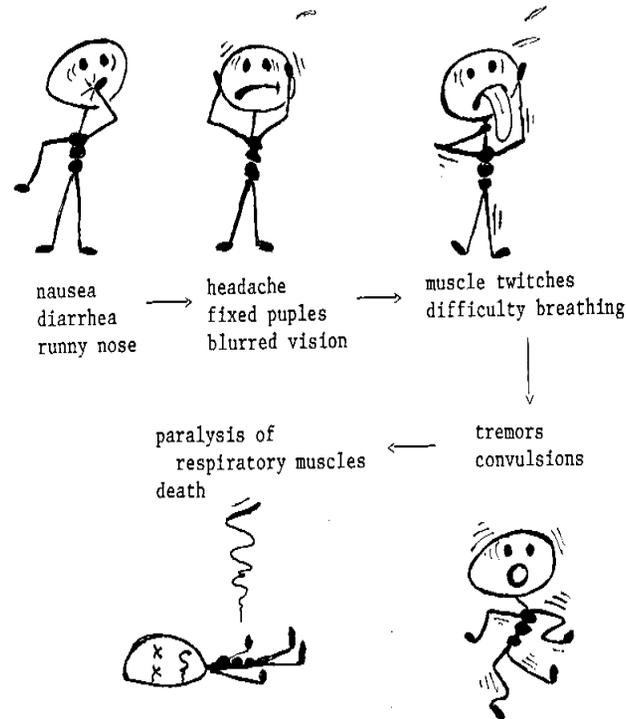
Toxic Effects of G-Agents

- Cholinesterase inhibitors; acetylcholine (Ach) accumulation produces continuous post-synaptic action potentials; adverse PNS and CNS cholinergic effects + end organ stimulation
- Affects nerve impulse transmission by additional mechanisms at neuromuscular junctions and neurotransmitter receptor sites in CNS
- No evidence of chronic neurological disorders after asymptomatic exposures; no established neuropathy potential
- Limited data on possible neurophysiological deficits following 1995 terrorist GB attack in Tokyo subway (psycho-motor performance, “postural sway,” event-related and visual evoked potentials in asymptomatic persons) or cases of accidental occupational exposure (no clinical significance); no dose-response data
- No selective reproductive or developmental toxicity; no carcinogenicity evidence; GB not genotoxic in bioassays; GA considered weakly mutagenic



Toxicity Signs/Symptoms of G-Agents

Pupillary muscles very sensitive to vapor contact; miosis -- early local sign of vapor exposure



Respiratory failure is chief cause of death; due to systemic effect cascade



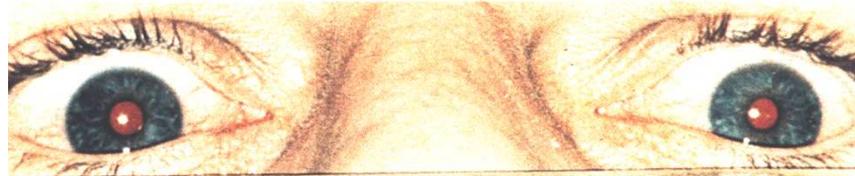
Critical Toxicity Endpoint – Miosis

- Miosis = reduction in post-exposure pupil diameter
- EC₅₀ for miosis is defined as chemical concentration causing post-exposure pupil diameter 50% or less of pre-exposure pupil diameter in 50% of exposed population; measured 30 min post-exposure
- EC₅₀ for miosis is reversible, local, transient, and non-disabling



Miosis – Recovery After Exposure to G-Agent Vapor

3 days



13 days



62 days



Fig. 5-4. This man was accidentally exposed to an unknown amount of nerve agent vapor. The series of photographs shows his eyes gradually recovering their ability to dilate. All photographs were taken with an electronic flash (which is too fast for the pupil to react) after the subject had been sitting in a totally dark room for 2 minutes. These photographs were taken (from top to bottom) at 3, 6, 13, 20, 41, and 62 days after the exposure. Subsequent photographs indicate that the eyes did not respond fully to darkness for 9 weeks; maximal dilation was reached on day 62 after the exposure. Reprinted with permission from Sidell FR. Soman and sarin: Clinical manifestations and treatment of accidental poisoning by organophosphates. *Clin Toxicol.* 1974;7:11.

Interspecies Variability for Miosis

- Compared miosis data for multiple species
 - Marmosets, guinea pigs, rabbits, human volunteers
 - Contact investigators at Porton Down and TNO
- Investigators and NRC/COT independently concluded that mitogenic response of mammalian eye to GB vapor is local response and quantitatively similar across species
- Concluded that interspecies UF for miosis endpoint in mammals is equal to 1 (this is consistent with NRC 2003 position on miosis as AEGL-1 critical effect)





24-Hour Inhalation PAL 1 for Agent GB

Key study	Mioduszewski et al. 2002b
Toxicity endpoint	Miosis in female rats. 4-hr EC ₅₀ = 0.012 mg/m ³
Scaling	C ⁿ x t = k, where n = 1. Therefore, C ¹ = (0.012 mg/m ³ x 4 hr)/24 hr = (0.048 mg/m ³ •hr)/24 hr = 0.002 mg/m ³
POD	0.002 mg/m ³ is considered a no-effect level for PAL 1 effects
UF = 10	10: intraspecies for sensitive subpopulations 1: interspecies because miosis response does not vary between species
Calculation	$PAL1 = \frac{0.002 \text{ mg/m}^3}{10 \times 1}$ PAL 1 = 0.0002 mg/m ³



24-Hour Inhalation PAL 2 for Agent GB

Key study	Baker and Sedgwick 1996
Toxicity endpoint	Human males (exercising at 96 paces/min) exposed whole body to 0.5 mg/m ³ for 0.5 hr: Miosis in 8/8; dyspnea and photophobia in some, RBC-ChE activity inhibition to approx. 60% baseline in 8/8, measurable (nonclinical) changes in single fiber electromyography (SFEMG) of forearm in 5/8 detectable in lab 4 and 15 mo post. Respiratory effects resolved in minutes; ocular effects within hrs. No permanent effects.
Scaling	$C^n \times t = k$, where $n = 1$. Therefore, $C^1 = (0.5 \text{ mg/m}^3 \times 0.5 \text{ hr})/24 \text{ hr} = (0.25 \text{ mg/m}^3 \cdot \text{hr})/24 \text{ hr} = 0.010 \text{ mg/m}^3$
POD	0.010 mg/m ³ resulting in long-lasting SFEMG change subclinical and reversible but steep dose response
UF = 10	10: intraspecies for sensitive subpopulations 1: interspecies because human data used
Calculation	$\text{PAL 2} = \frac{0.010 \text{ mg/m}^3}{10 \times 1}$ $\text{PAL 2} = 0.001 \text{ mg/m}^3$



24-Hour inhalation PAL 3 for Agent GB

Key study	Mioduszewski et al. 2002, 2001, 2002a
Toxicity endpoint	Experimentally derived 6-hr LC ₀₁ in female rats = 1.76 mg/m ³
Scaling	C ⁿ x t = k, where n = 1. Therefore, C ¹ = (1.76 mg/m ³ x 6 hr)/24 hr = (10.56 mg/m ³ •hr)/24 hr = 0.44 mg/m ³
POD	0.44 mg/m ³ is considered a threshold for lethality
UF = 30	10: intraspecies for sensitive subpopulations 3: interspecies for animal-to-human because mechanism of toxicity, anticholinesterase, does not vary greatly
Calculation	$PAL\ 3 = \frac{0.44\ mg/m^3}{10 \times 3}$ $PAL\ 3 = 0.015\ mg/m^3$



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Note: Miosis photo prepared with support of US Army Center for Health Promotion and Preventive Medicine (CHPPM)

