Chemical Warfare Operational Toxicity Exposure Standards - Their Care, Feeding and Husbandry!

Protection and Decontamination Conference
22-26 October, 2007

Dr. Steve Channel, DRIV (GS15), USAF
PM, Operational Toxicology, BioAgent Fate
AFRL/HEPC@APGEA, MD
DSN584-8872, Comm: 410-436-8872
Stephen.channel@us.army.mil

Operational Toxicology Research Program

- **How did we come to this??**
  - The drivers and history of the Low Level Tox Research Program
- **What do we need in an operational exposure std?**
  - Operational applications vs. general civilian population
  - Essential elements in a military application
- **What have we done to address the problem?**
  - LLCWA Operational Toxicology Research Program
- **So What? Translating the science**
  - There are standards and there are standards…what????

Operational Toxicology Research Program

How did we come to this?

- 1990-1991: Persian Gulf Crisis/ Gulf War
  - Kamasia; Gulf War Illness (GWI)

What do we REALLY know about the effects of exposure to Chemical Warfare Agents?

Post-deployment

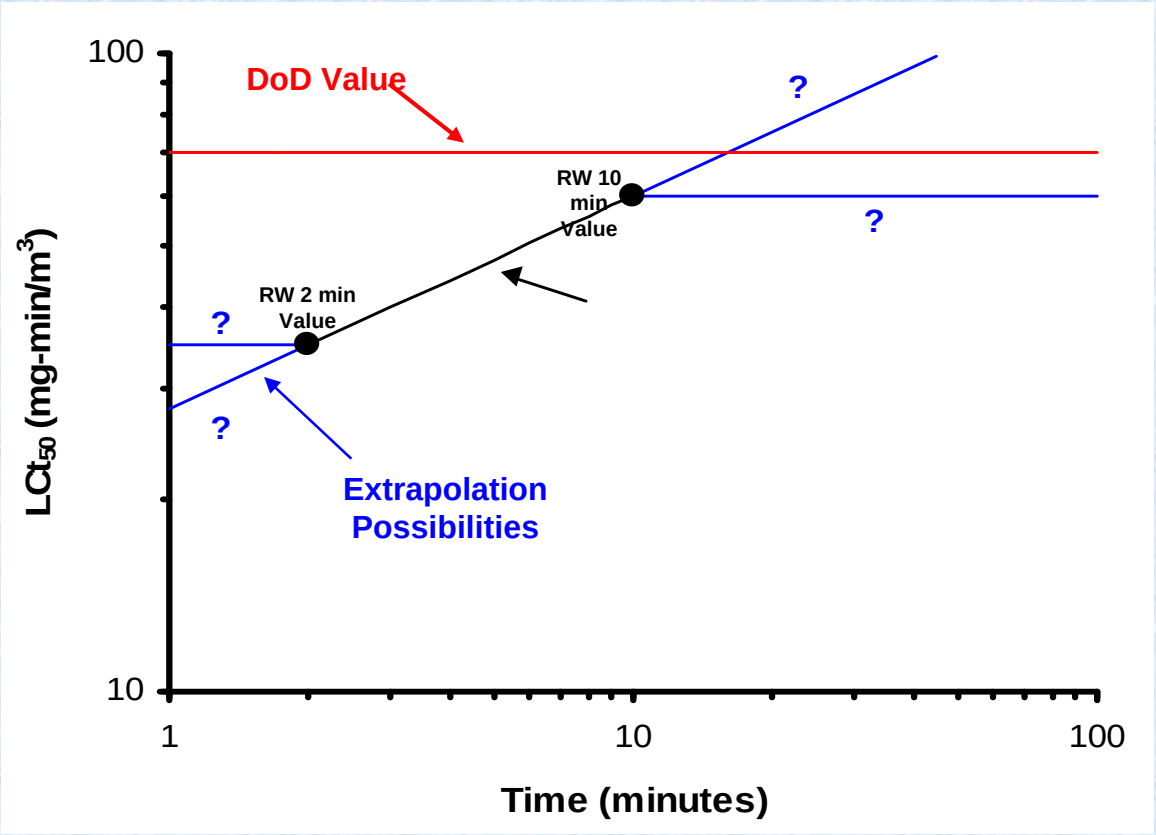
- **Military and Veterans Health Coordinating Board**
- **Veterans Affairs**
- **GWI Research Program**
- **Deployment Health and Medical Surveillance**

Operational

- **Army Chemical Defense Equipment Process Action Team (CDEPAT) tasked by USA SG to:**

  “ review the toxicity data for… nerve agents (GA,GD,GD,GF,VX)….and the vesicant agent sulfur mustard (HD) and to establish a set of exposure limits that would be useful in protecting soldiers from toxic exposure to those agents.”

How did we come to this?



Limited Dataset

- 2-10 Minutes
- Lethality endpoint
- Persistent Effects?

Model assumptions

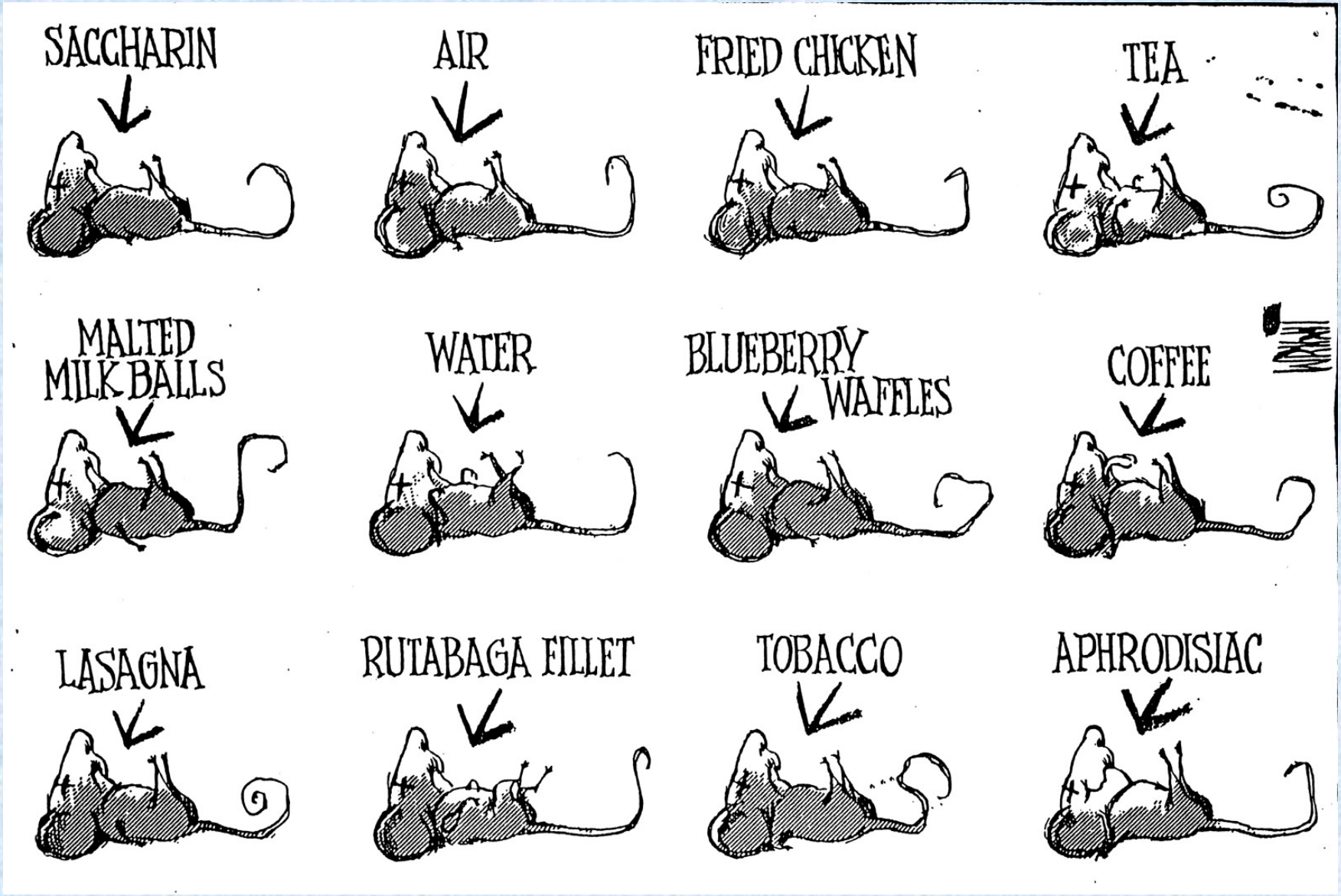
- Linear (Haber's Law)

Bottom Line?

We REALLY didn't know, or have data to support appropriate operational exposure values!!

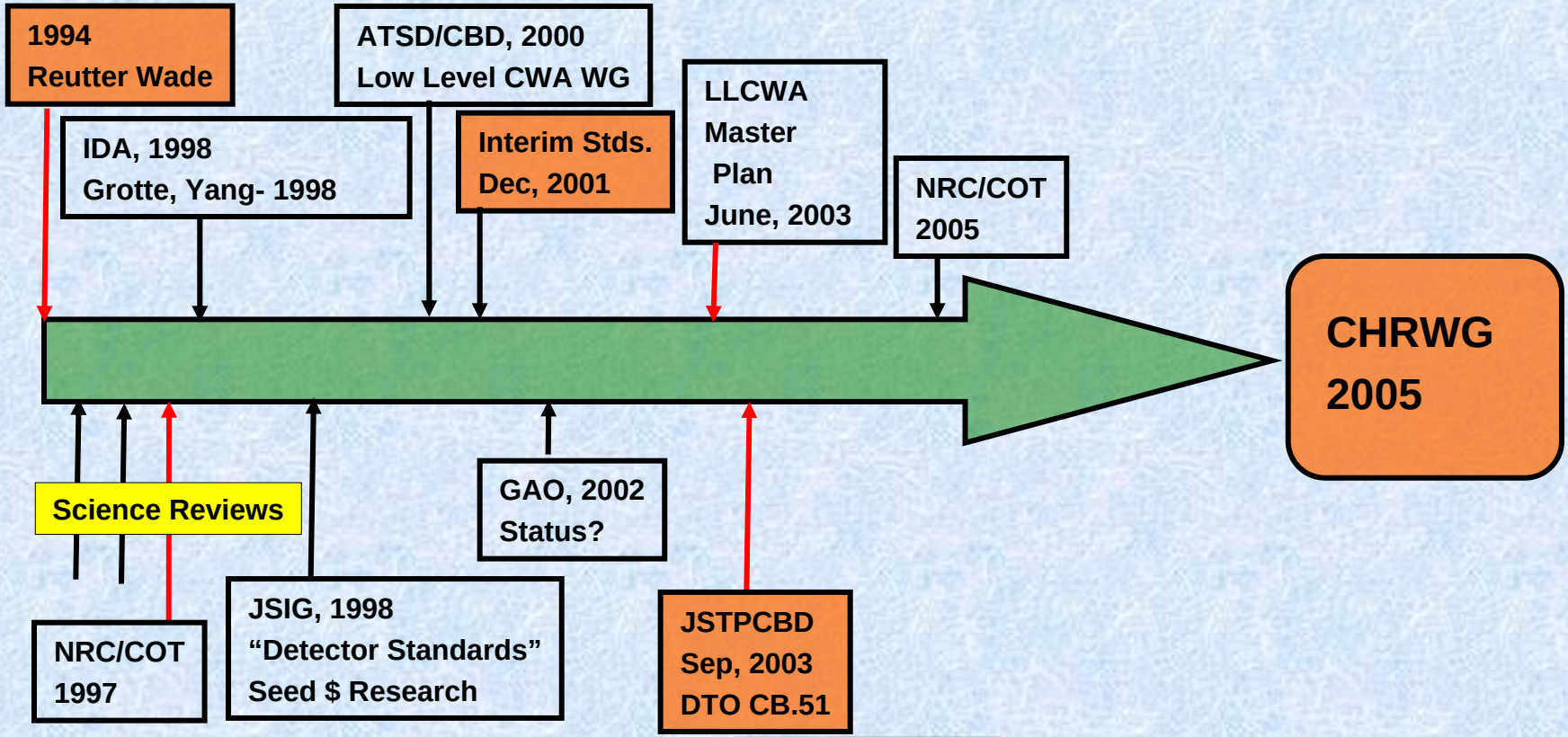
Operational Toxicology Research Program

How did we come to this?



Operational Toxicology Research Program

How did we come to this?



Science Reviews TARA, SME, NBC Sci Conf, SOT

Deliverables:

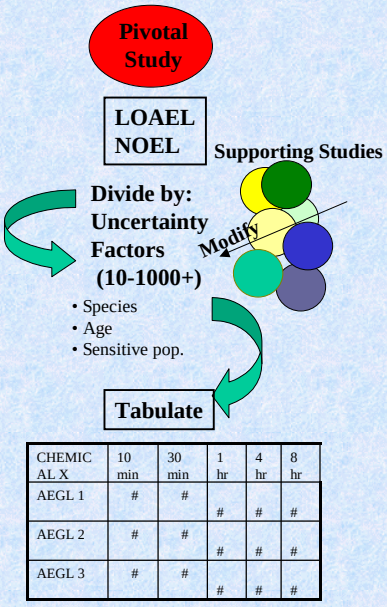
FM 3-11.9
JPID, SUSTAIN ICT
AFMAN 10-2602
Annual Rpt of Program

What do we need in an Operational Exposure Std??

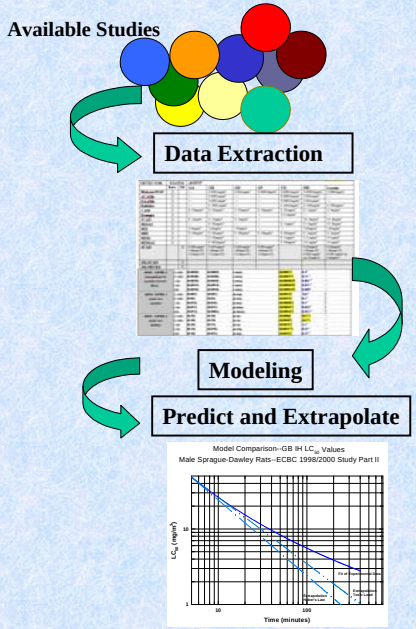
Essential elements in a military application:

- The ability to extrapolate in time to address mission profiles!
- The ability to predict casualties and their probability
- The ability to anticipate consequences at various levels of risk
- The ability to associate the variability with a prediction

"Point Source" or "Threshold" Standards do not Allow the above Flexibility!



CHEMICAL X	10 min	30 min	1 hr	4 hr	8 hr
AEGL 1	#	#	#	#	#
AEGL 2	#	#	#	#	#
AEGL 3	#	#	#	#	#



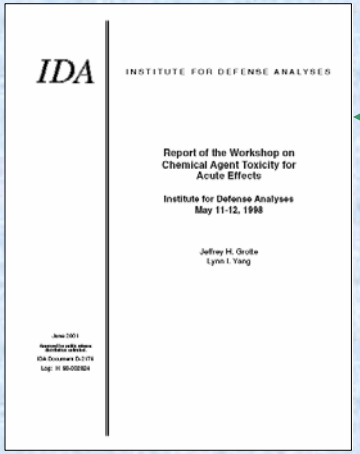
Result: Evacuation!

Metanalysis and statistical analysis modeling, when linked to targeted and focused studies provides maximum flexibility

Result: Continue mission with appropriate TTP

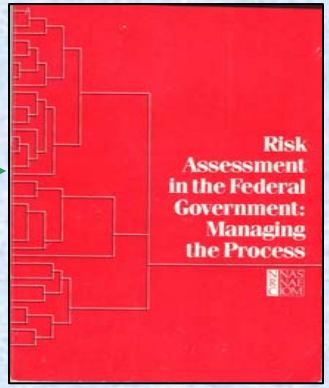
What Have We done to address the Problem?

How did we know the what was necessary?

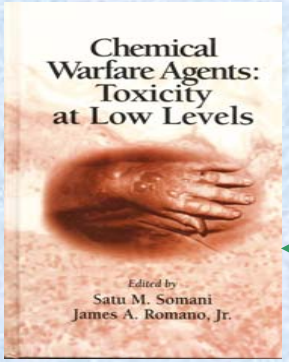


We knew the gaps!

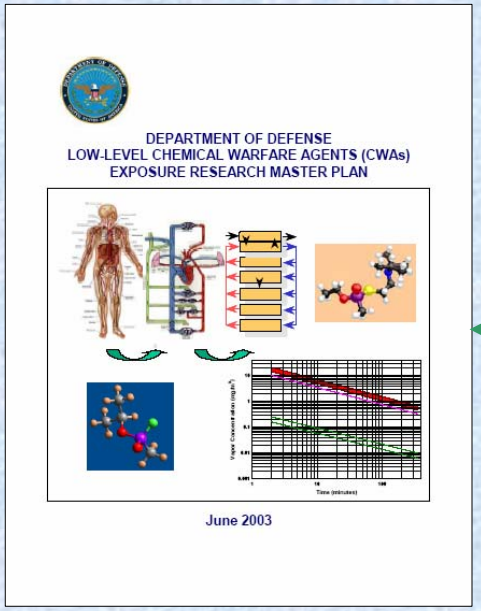
We had the process!



National Academy Press, 1983



We'd done the background science!

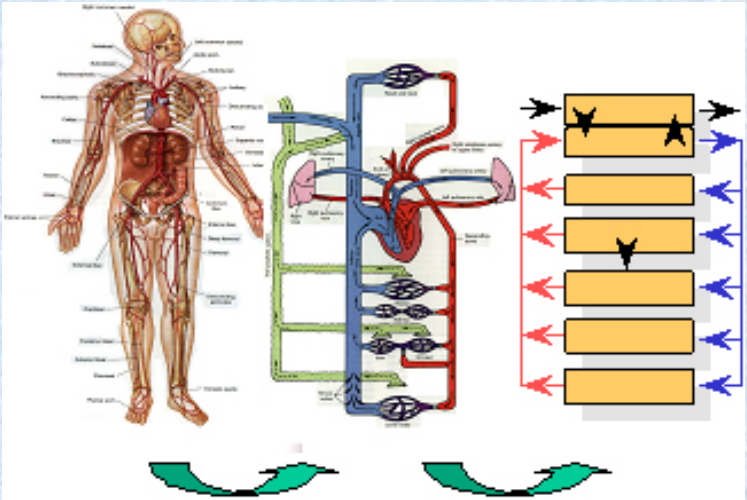


We had the plan!

What Have We done to address the Problem?

Inhalation Studies

- Dose-Response
- Conc-Time Profile
- Miosis and ChE



Health Effects

- Parenteral studies
- Sublethal, Systemic
- Persistent/Delayed Effects
- Medical Countermeasures

Three Major Thrusts

Integration Studies

- Biomarkers/Physiologically Based Pharmacokinetics (PBPK)
- Route/Species Extrapolation
- Risk Assessment application

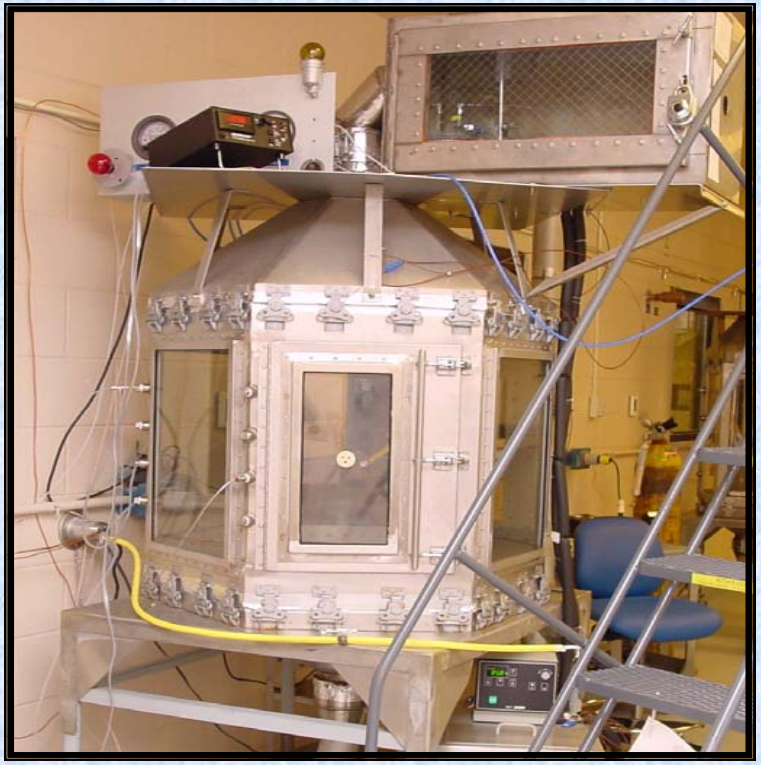
One Product

Science-Based Exposure Standards for Deployed Forces

What Have We done to address the Problem?

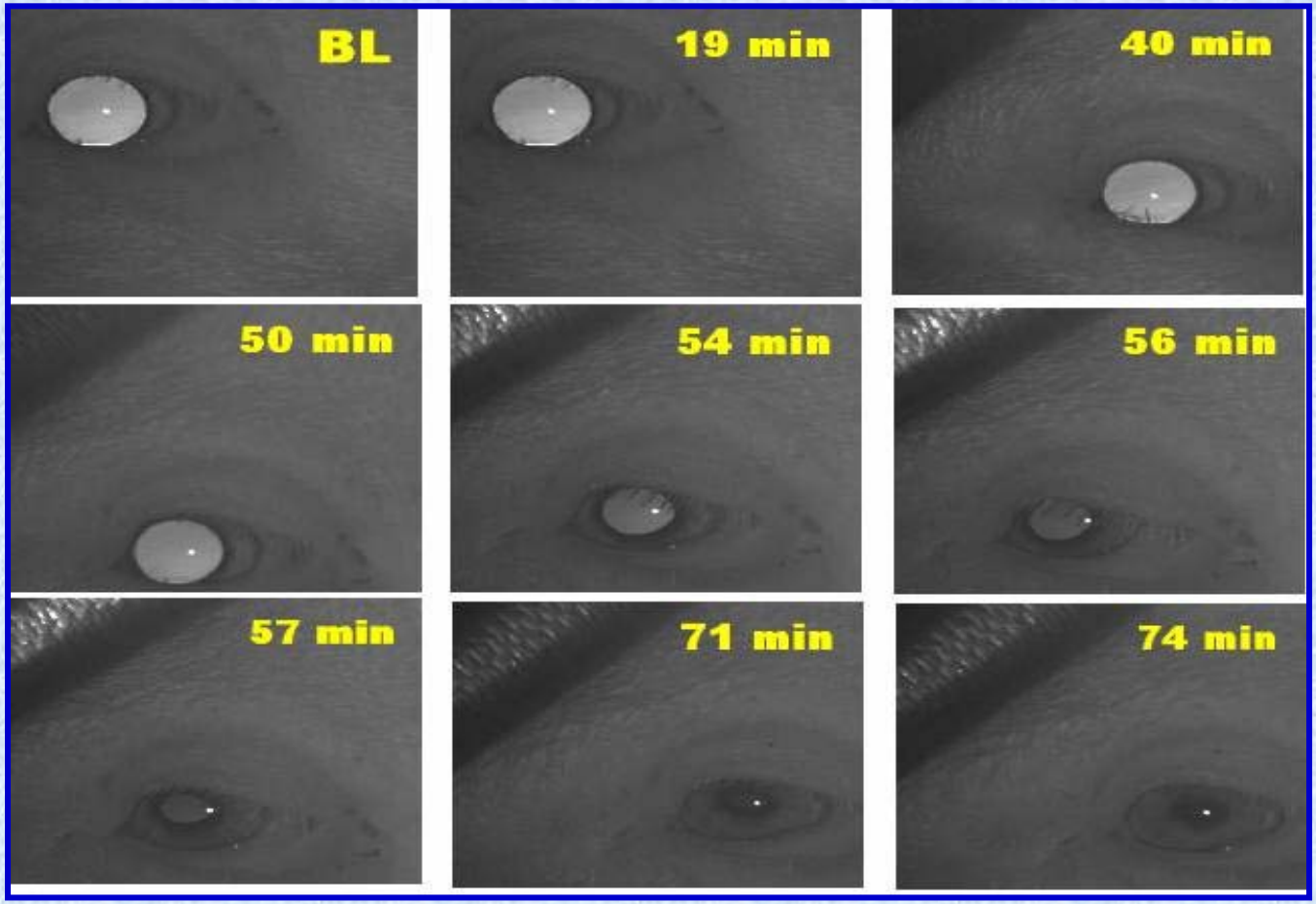
Whole-body VX Vapor Exposure in Swine

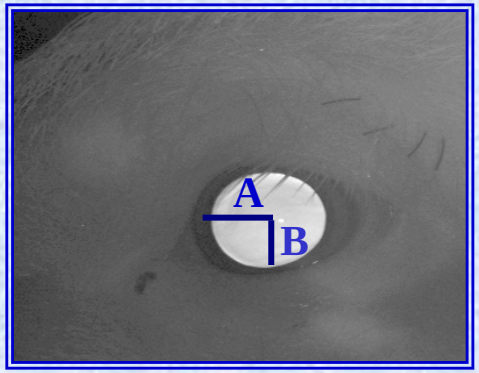
- 1000 L dynamic airflow chamber
- VX generation system contained in glove box
  - Vapor Sampling / GC Analysis
- Pig placed in sling
- Respiratory belt and ECG leads attached to pig and leading to Bio-logic headbox.
- Jugular catheter passed through ports
- IR images of pupil taken through Plexiglas



What Have We done to address the Problem?

Example of Nerve Agent Vapor-Induced
Pupil Size Changes Over Time in Swine

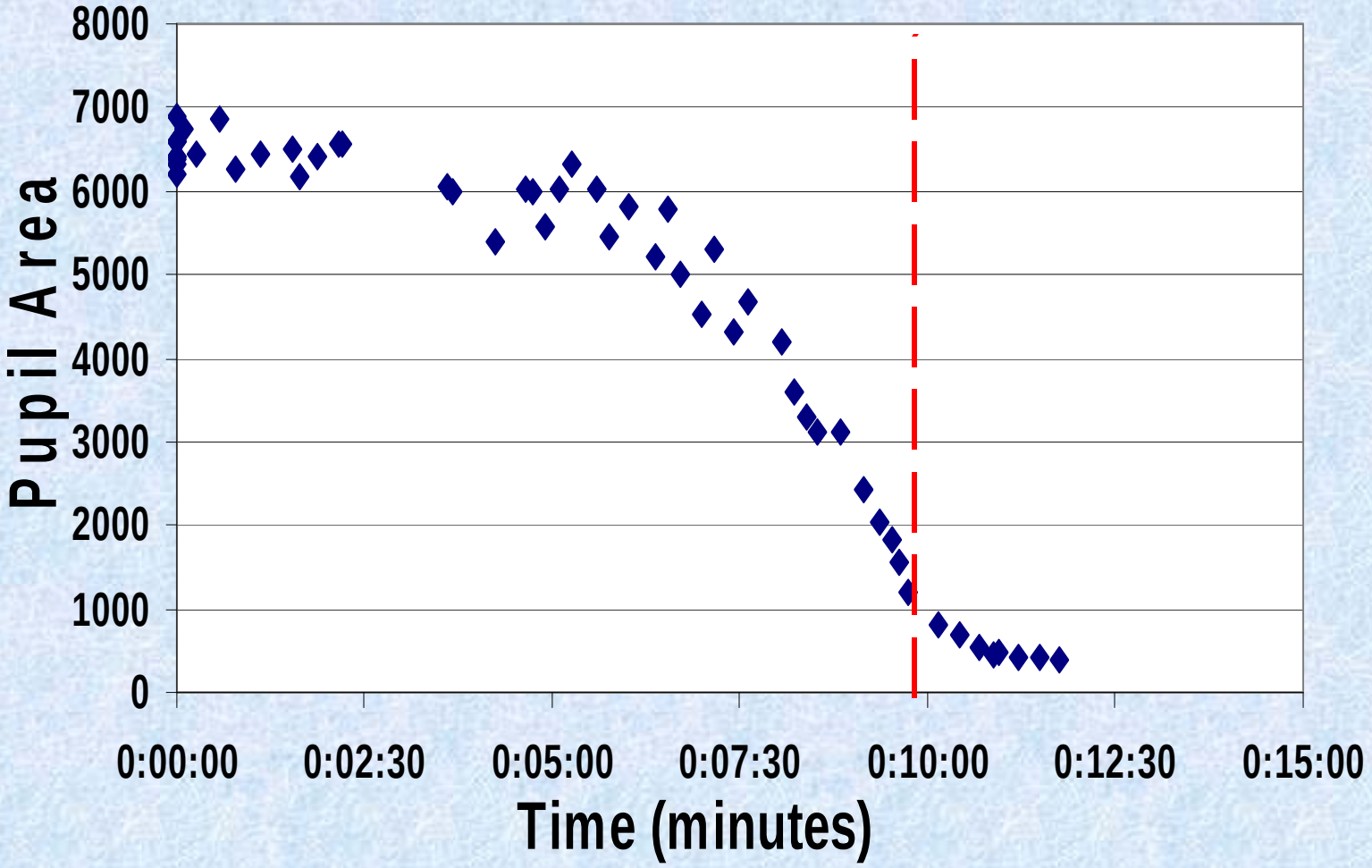




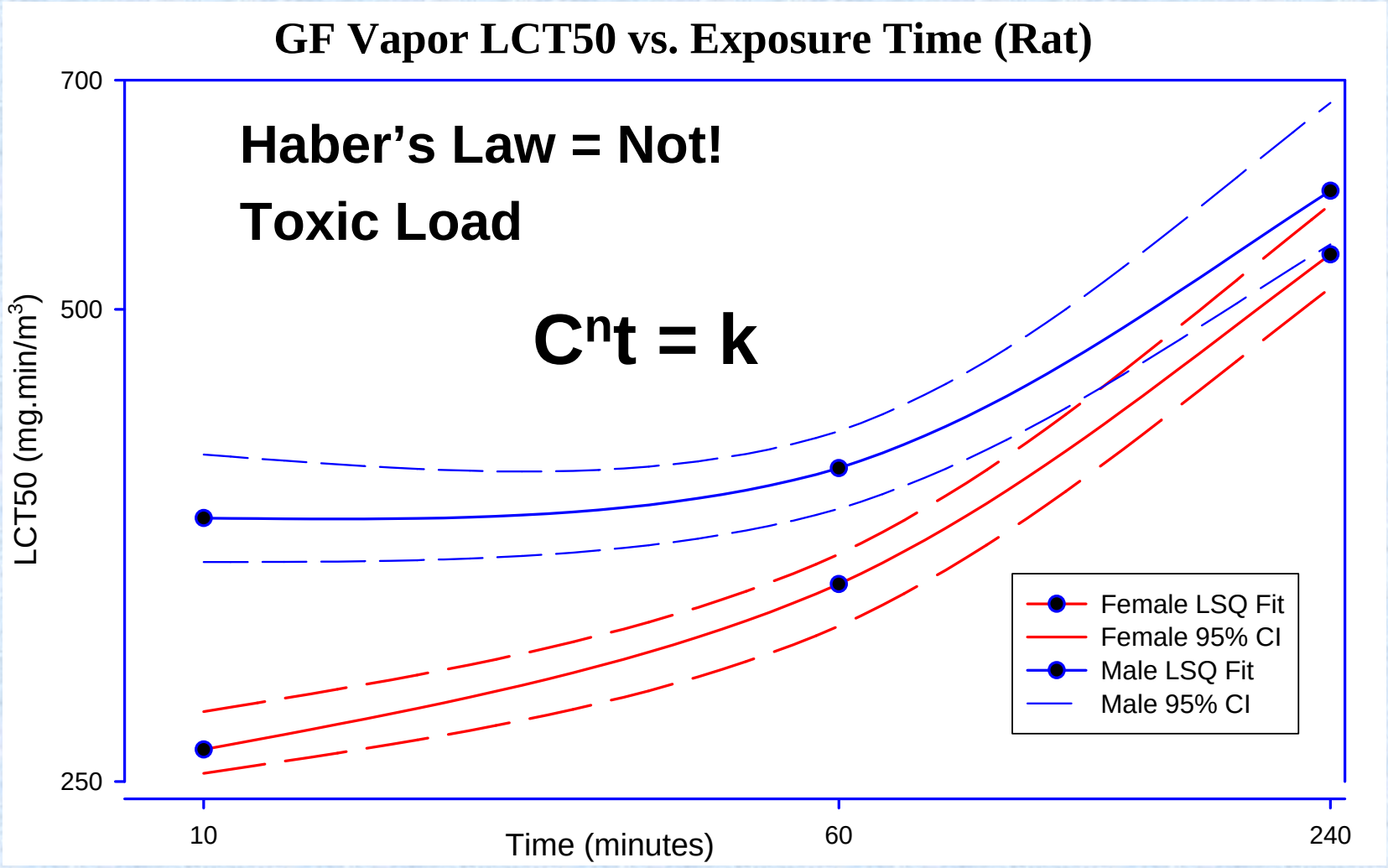
- Infrared light reflects off of the retina
- Pupil area = $A*B*\pi$

What Have We done to address the Problem?

Time Course of Nerve Agent Vapor-Induced Pupil Constriction in Swine



What Have We done to address the Problem?



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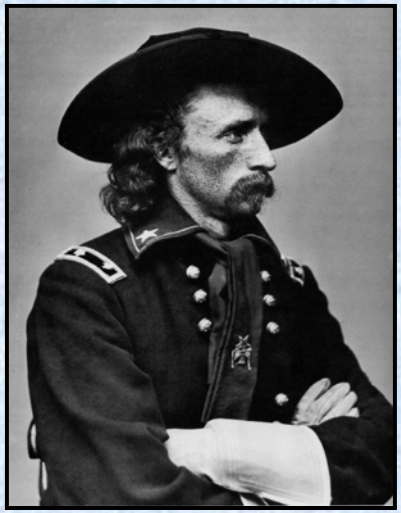
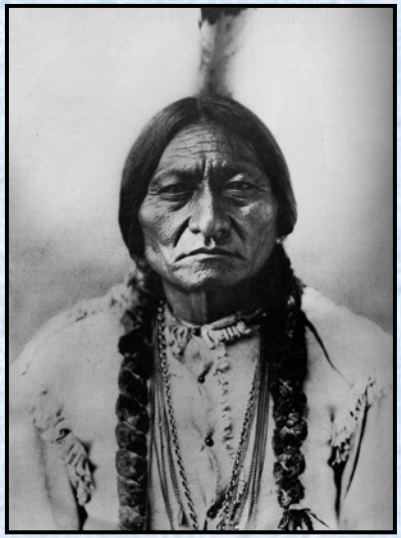


Gen.G. A Custer

C^nT = Annihilation!

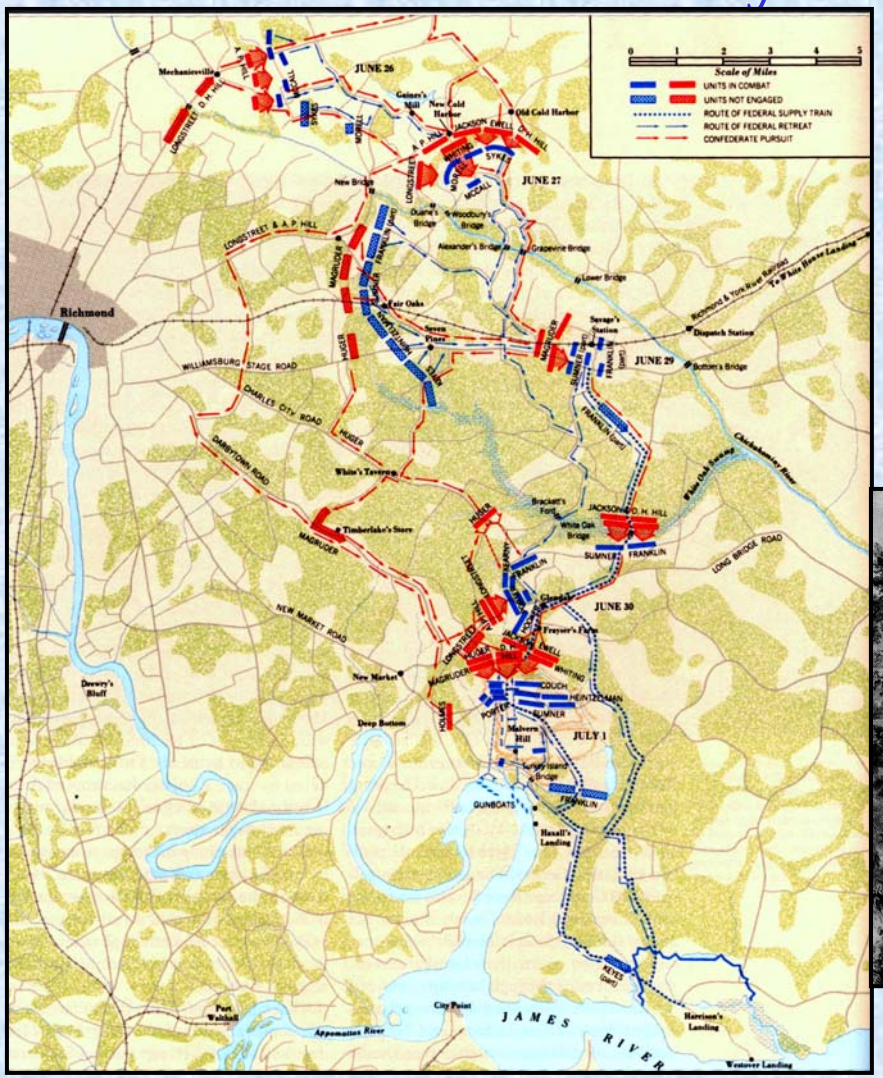


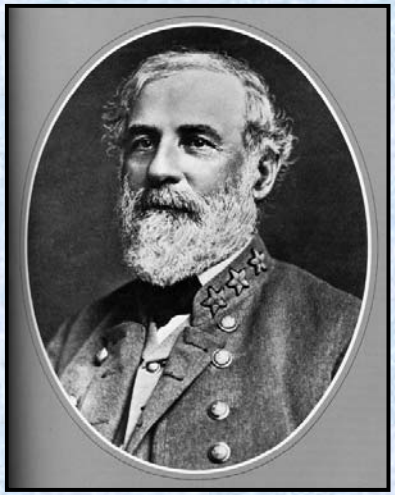
Sitting Bull

What Have We done to address the Problem?

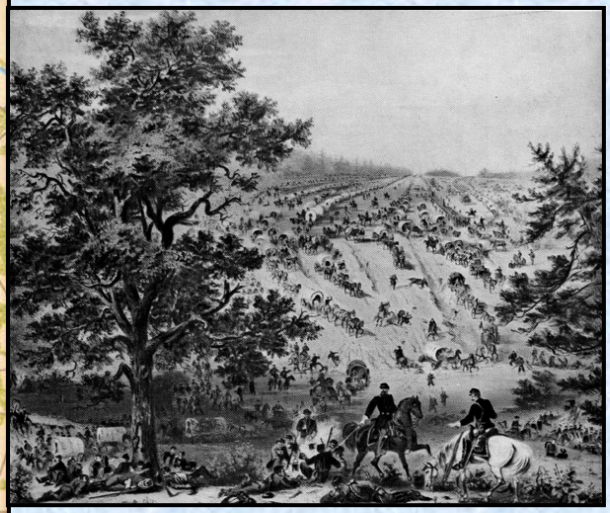
C^nT = Stalemate…maybe?

Gen. Geo. McClelland





Gen. Rbt. E. Lee

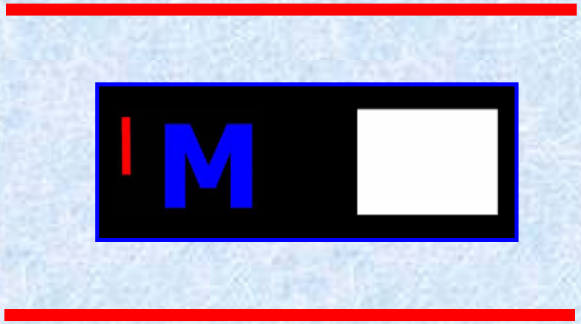


The Retreat!

What Have We done to address the Problem?

Performance Endpoint: Serial Probe Recognition Test (SPR)

Up to three stimuli (character pairs) are presented on the screen sequentially (stimuli are randomly chosen from a pool of 200)



A "probe" screen is then presented that contains a character stimulus and a white square stimulus.

If the character stimulus was presented in the preceding sequence, then it is the correct choice. If the character stimulus was not presented in the preceding sequence, then the white square is the correct choice.

- Major dependent measures for the test are <u>accuracy</u>, <u>response time</u>, and <u>number of trials completed</u> during a fixed length session.

- Yields a powerful measure of cognition and has been used with human and non-human primates. It has also been used previously to evaluate the effects of CWNAs.

What Have We done to address the Problem?

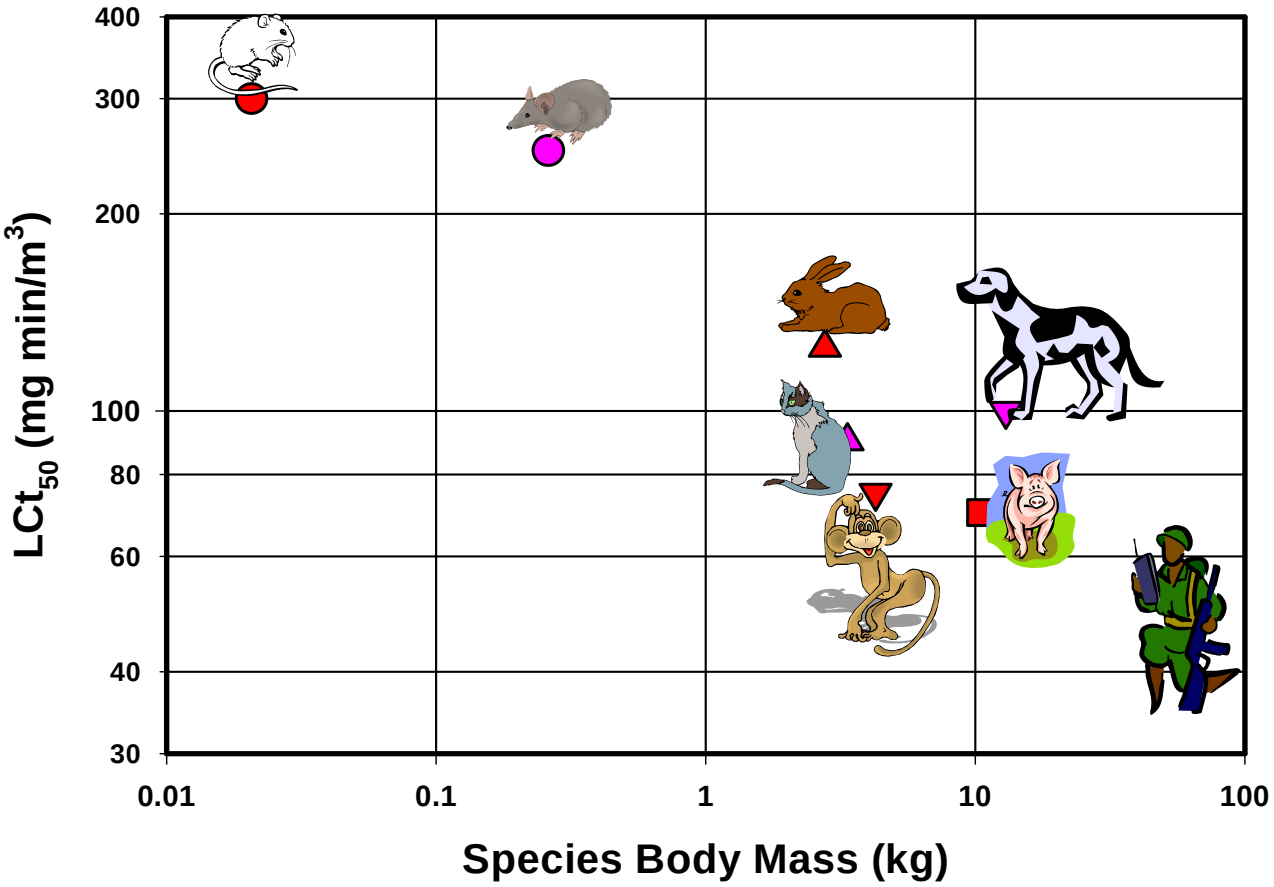
African Green Monkey – SPR, IM GB

Single trial on the SPR, List Length=3, test stimulus is from list, correct choice response

Operational Toxicology Research Program

What Have We done to address the Problem?

- **Body Mass/LCt_{50} Relationship for GB (10-Minute Exposure)**

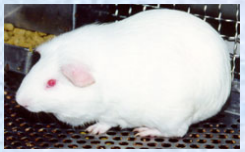


Operational Toxicology Research Program

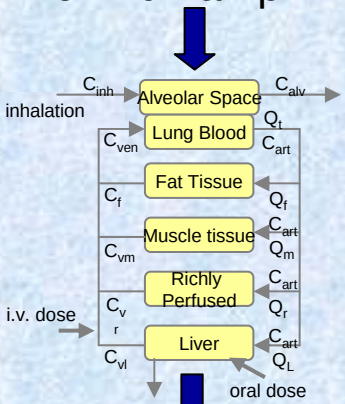
What Have We done to address the Problem?

Göttingen minipig

Non-human primate



Guinea Pig



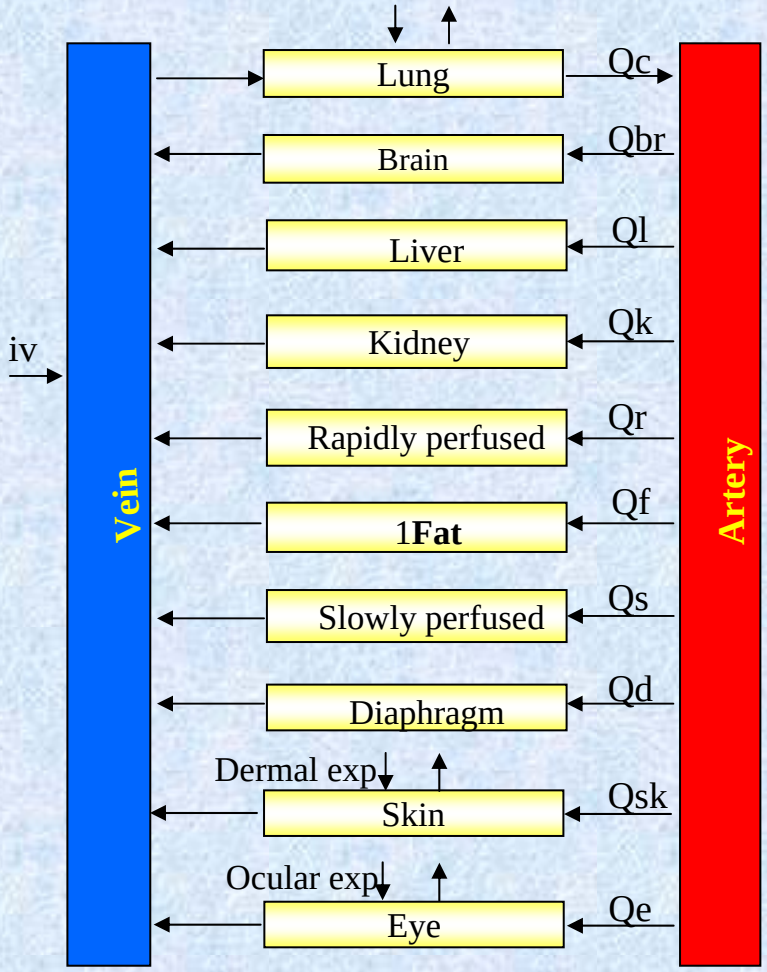
Warfighter

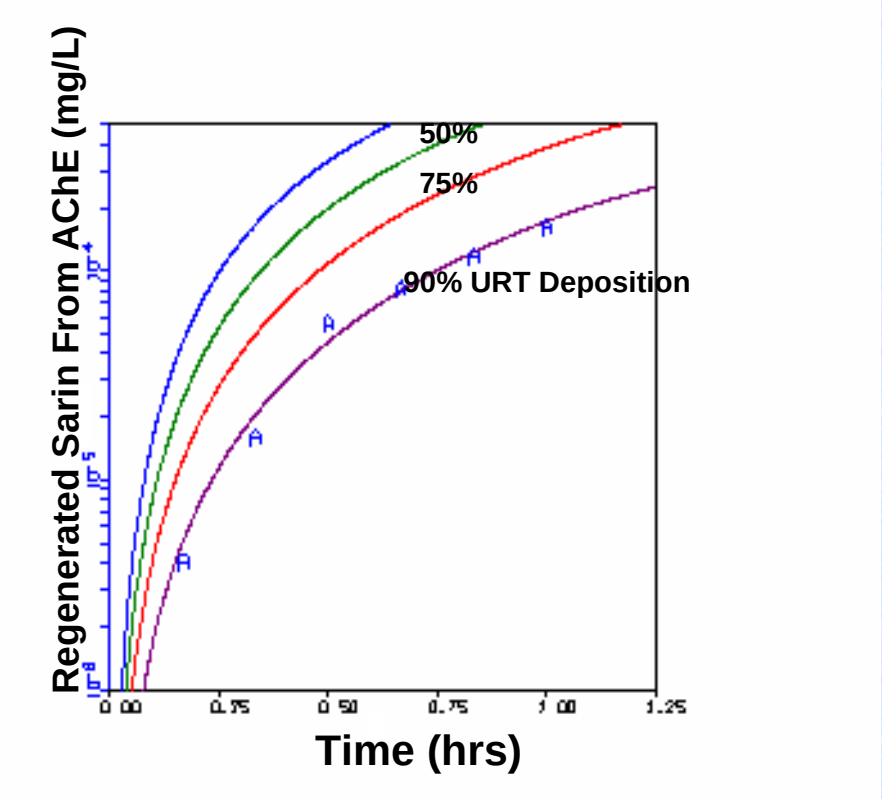
Extrapolating
The data to inform
A human hazard
Risk assessment

Multispecies
Dose Route
Equivalency
Using PBPK/PD

What Have We done to address the Problem?

Physiologically based Pharmacokinetic/Pharmacodynamics

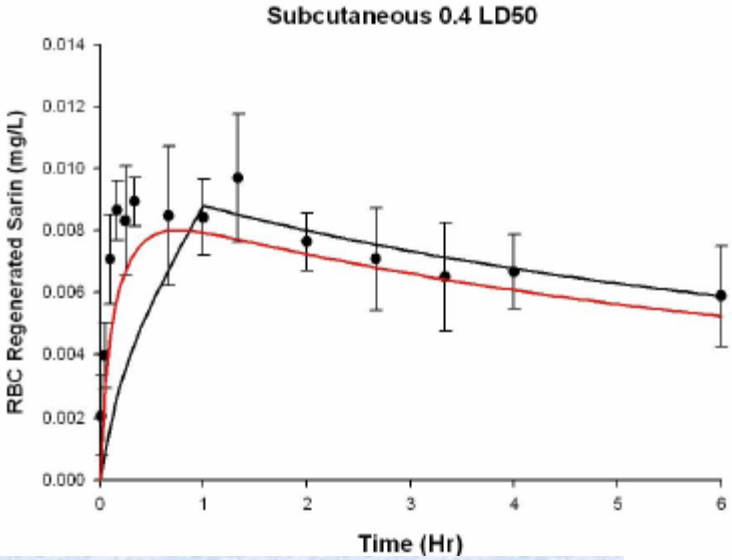




M. Jakobowski, ECBC, RDECOM and J. Gearhardt, AFRL/HEPB

- Quantitative route/species extrapolation Based on PBPK/PD studies

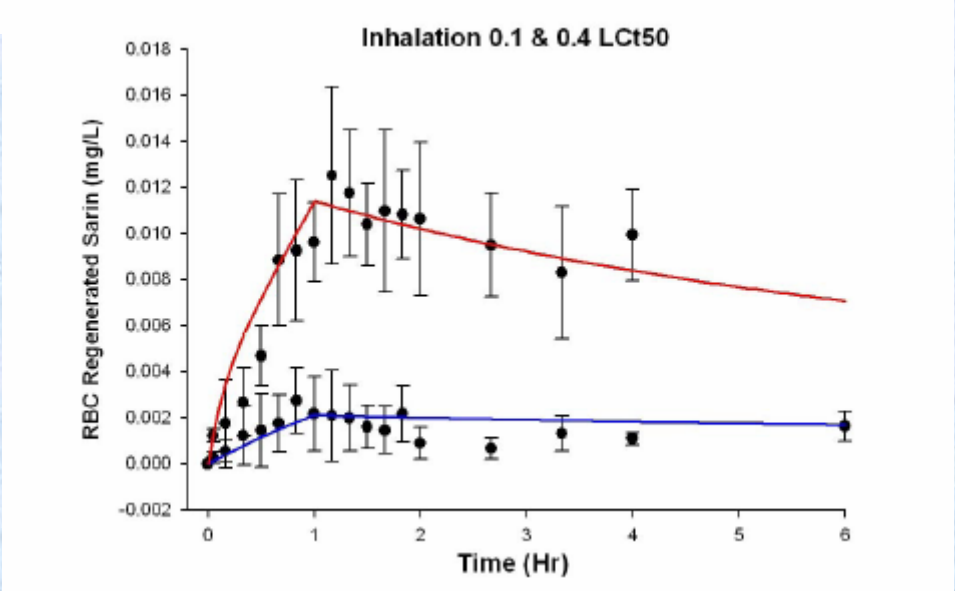
What Have We done to address the Problem?



Cross Route Exposure Validation

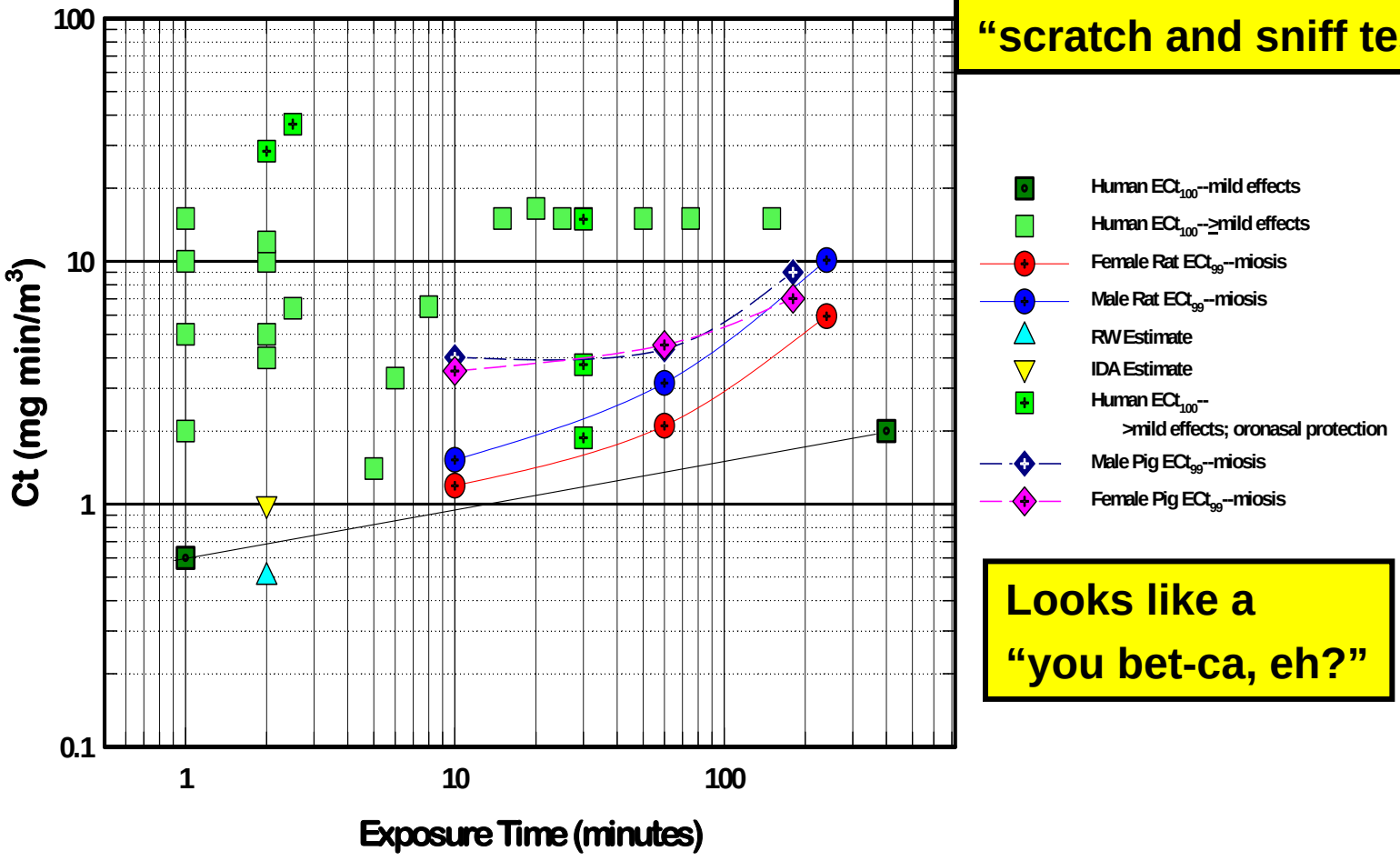
- **Physiologically based Pharmacokinetic/Dynamic Model (PBPK/PD) predictions (lines) vs. dose-metric data (points; regenerated agent, blood)**

- **Subcutaneous exposure route kinetics can now be described as an equivalent inhalation challenge! PBPD models will relate kinetic profiles to probability of effect.**



What Have We done to address the Problem?

Do the results pass the "scratch and sniff test!



Looks like a "you bet-ca, eh?"

Operational Toxicology Research Program

So What: Translating the Science!

Table 5. VX Toxicity Values

Agent	Parameter	Route of Entry	Value/Probit Slope
VX	LCt50	Percutaneous vapor	150/6 {12}
VX	LCt50	Inhalation vapor	15/6 {1}
VX	ECt50, threshold {2}	Percutaneous vapor	10/6 {3}
VX	ECt50, severe {4}	Percutaneous vapor	25/6
VX	ECt50, severe {4}	Inhalation vapor	10/6
VX	ECt50, mild {5}	Inhalation vapor	0.1/4 {3}{14}
VX	LD50	Percutaneous liquid	5/6 {1}
VX	ED50, severe {4}	Percutaneous liquid	2/6 {1}

Table 6. HD Toxicity Values

Agent	Parameter	Route of Entry	Value/Probit Slope
HD	LCt50	Percutaneous vapor	10000/7 {15}
HD	LCt50	Inhalation vapor	1000/6 {1}{16}
HD	ECt50, threshold, moderate temperature {13}	Percutaneous vapor	50/3 {17}
HD	ECt50, threshold, hot temperature {13}	Percutaneous vapor	25/3 {17}
HD	ECt50, severe, moderate temperature {18}	Percutaneous vapor	500/3 {17}
HD	ECt50, severe, hot temperature {18}	Percutaneous vapor	200/3 {17}
HD	ECt50, severe {19}	Ocular vapor	100/3 {3}
HD	ECt50, mild {19}	Ocular vapor	25/3 {3}
HD	LD50	Percutaneous liquid	1400/7 {1}
HD	ED50, severe {18}	Percutaneous liquid	600/3 {1}{20}

NOPE!

Operational Toxicology Research Program

So What: Translating the Science!

Endpoint	Approved Interim (2min) Exposure{Slope}	Revised (2min) Exposure{slope}	Time Extrapolation Exponent
Operational Exposure Values - Inhalation Vapor GB			
Lethality - LCt50 mg*min/m3	35{12}	35{12}	1.5
Severe (Incapacitation) - ECt50 mg*min/m3	25{10}	25{12}	1.5
Mild (Threshold) - ECt50 mg*min/m3	1{5}	0.4{10}	1.5
Operational Exposure Values - Inhalation Vapor GF			
Lethality - LCt50 mg*min/m3	35 {12}	43{12}	1.25
Severe (Incapacitation) - ECt50 mg*min/m3	25{10}	31{12)	1.25
Mild (Threshold) - ECt50 mg*min/m3	0.4 {14}	0.4{10}	1.5
Operational Exposure Values - Inhalation Vapor VX			
Lethality - LCt50 mg*min/m3	15{6}	15{10}	1
Severe (Incapacitation) - ECt50 mg*min/m3	10{6)	10{10}	1
Mild (Threshold) - ECt50 mg*min/m3	0.1 {4}	0.04 {4}	1
Operational Exposure Values - Inhalation Vapor GD			
Lethality - LCt50 mg*min/m3	35 {12}	FY07	FY07
Severe (Incapacitation) - ECt50 mg*min/m3	25{10}	FY07	FY07
Mild (Threshold) - ECt50 mg*min/m3	0.4 {6}	FY07	FY07
Operational Exposure Values - Inhalation Vapor HD			
Lethality - LCt50 mg*min/m3	1000{6}	As Stated	As Stated
Severe (Incapacitation) - ECt50 mg*min/m3	100 {3} occ	As Stated	As Stated
Mild (Threshold) - ECt50 mg*min/m3	25{3) occ	As Stated	As Stated

So What: Translating the Science!

Begin with the end in MIND!!!

Stephen Covey

Exposure Estimates for Joint Platform Interior Decontamination (JPID) Operational Requirement Document (ORD) Efficacy Review

12 October 2004
Updated: 31 October 2006)

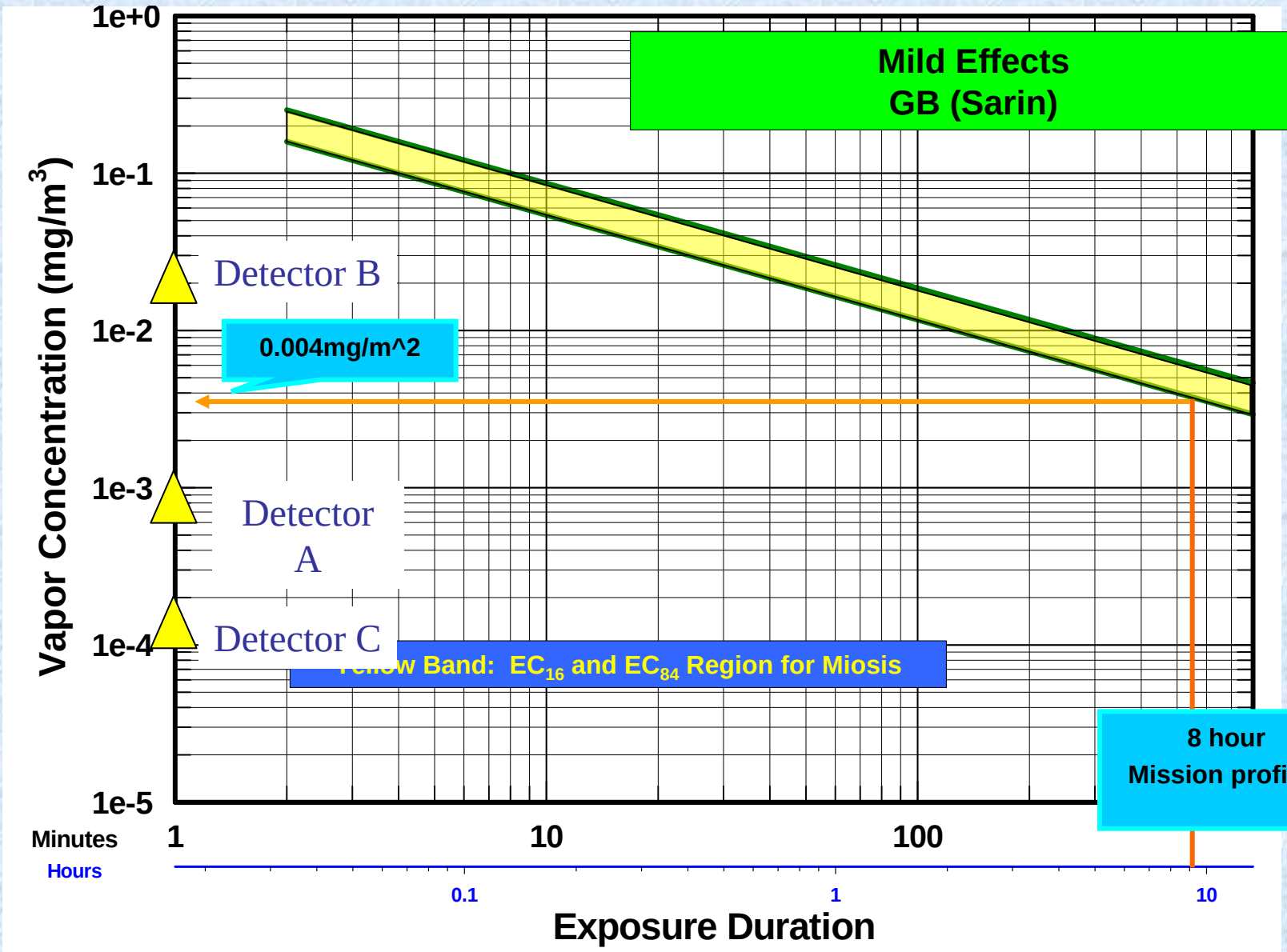
Dr. Steve Channel, USAF, AFRL
Dr. Sharon Reutter, RDECOM, ECBC
Mr. Doug Sommerville, RDECOM, ECBC
Ms. Erin E. Shockley, RDECOM, ECBC

Example Questions:

- **I have a piece of equipment (aircraft) that is contaminated at (XXmg/m2); Can it be used effectively? For how long? (hazard)**
- **Will personnel require some form of protection? (mitigation)**

Operational Toxicology Research Program

So What? Translating the science!



So What: Translating the Science!

Here is reality!

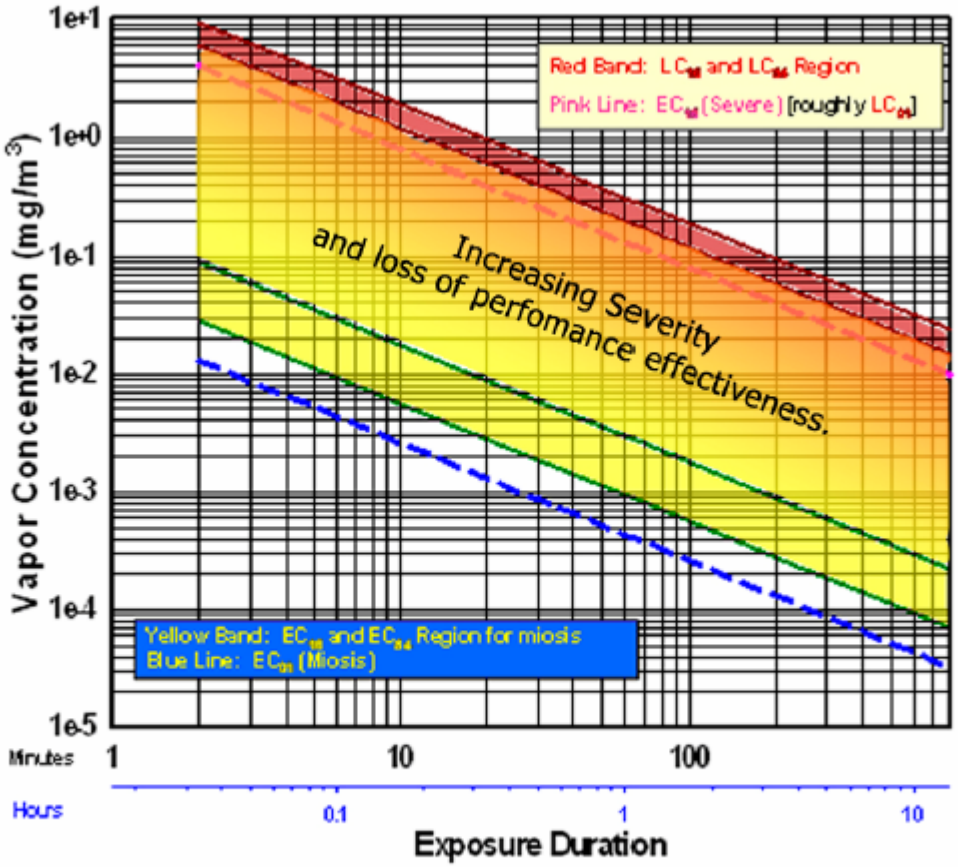
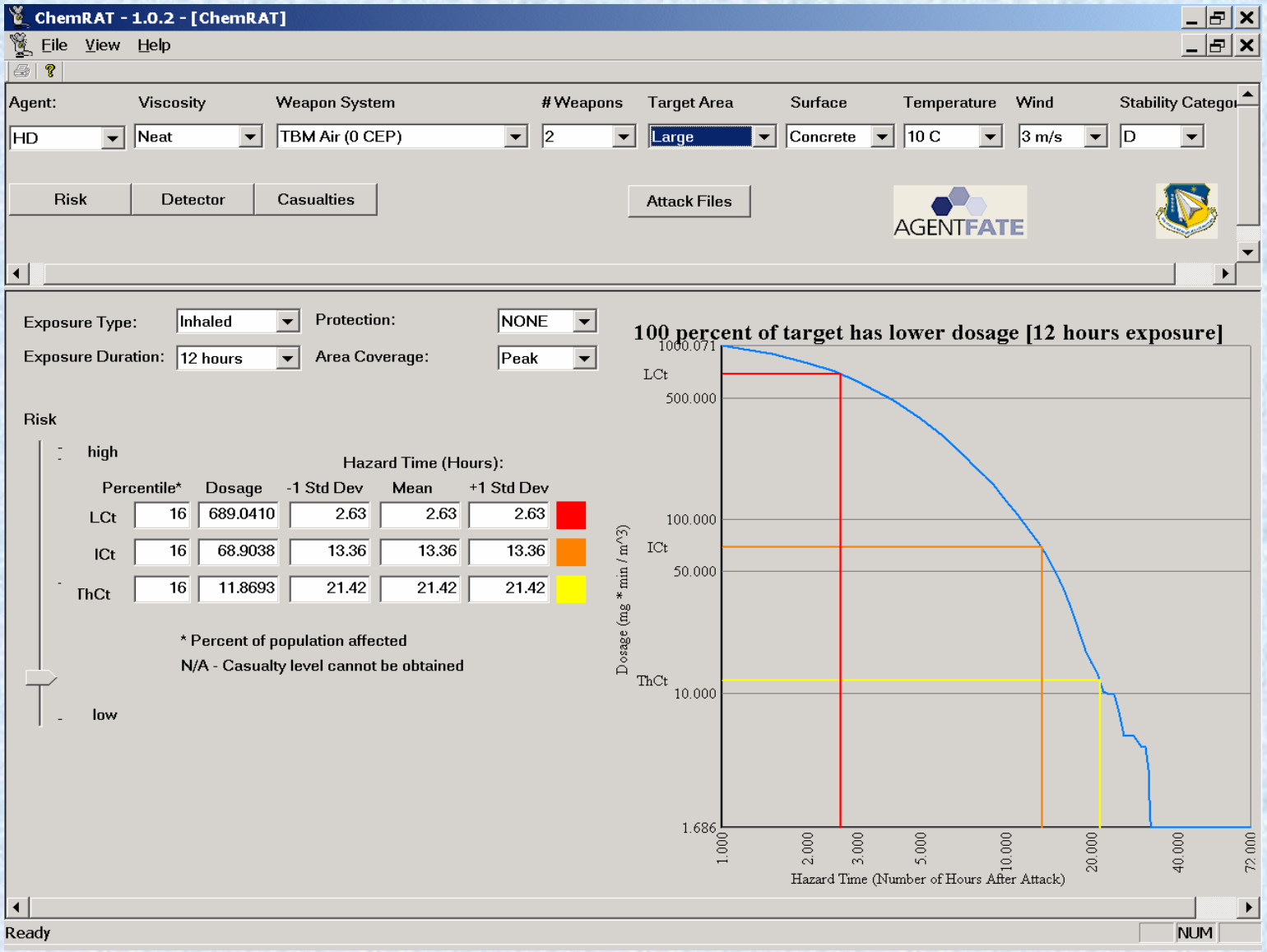


Figure E.2.3 Graphical Representation of VX Vapor Dose Profile (Inhalation/Ocular Exposure) LCtxx and ECtyy vs. Exposure Duration

Operational Toxicology Research Program

So What: Translating the Science!



Conclusions and Discussion

What is it we are after here?

Operational exposure standards?

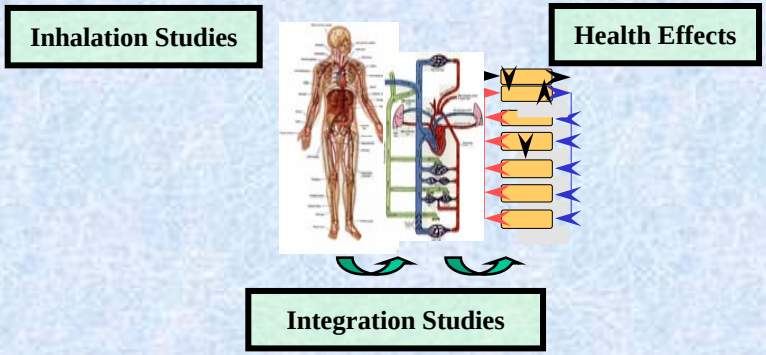
- Higher levels of acceptable risk {the “Dirty Harry” factor}
- Mission imperative; just “quitting” isn’t an option
- Trained, equipped and healthy military population
- Classified data is absolutely OK!

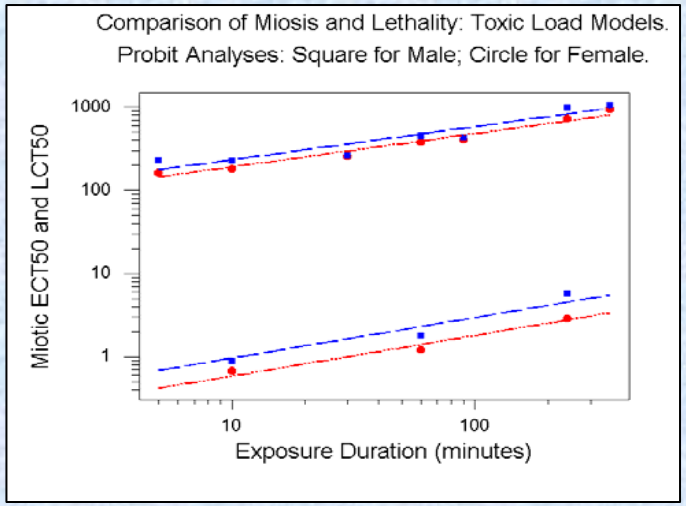
Restoration/Remediation standards?

- Must consider the end use and exposure population
- Evaluation and removal from exposure is very OK!
- May have to survive the public review process
    - Excludes the larger data set available
- Primary focus is on planning and monitoring

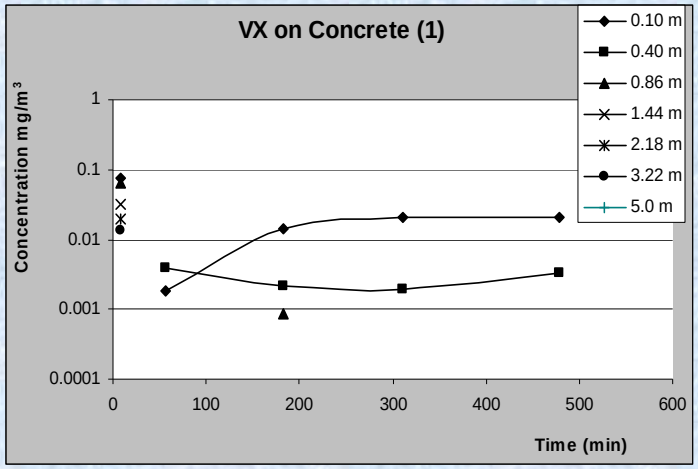
Both are part of a spectrum and policy will determine the wavelength!

Operational Toxicology Research Program





Agent Fate Research Program



Backups

Effect

Route

- Oral
- Inhalation
- Parenteral

Dose

- Mass
- Time

Exposure does not = Dose!!

"And who are you who are so wise in the ways of science??!!" *Sir Bedemir*

Technical Approach – Performance Evaluations - SPR

Single trial on the SPR, List Length=3, test stimulus not from list, correct choice response

What's Next??

CB.69 *Chemical Warfare Agent Operational Exposure Hazard Assessment Research*

Transformational Capabilities: 1c. Chemical Defense (Primary)

3d. Warfighter Readiness, Survivability, and Sustainment

Supported Functional Concept(s): Protection (Primary)

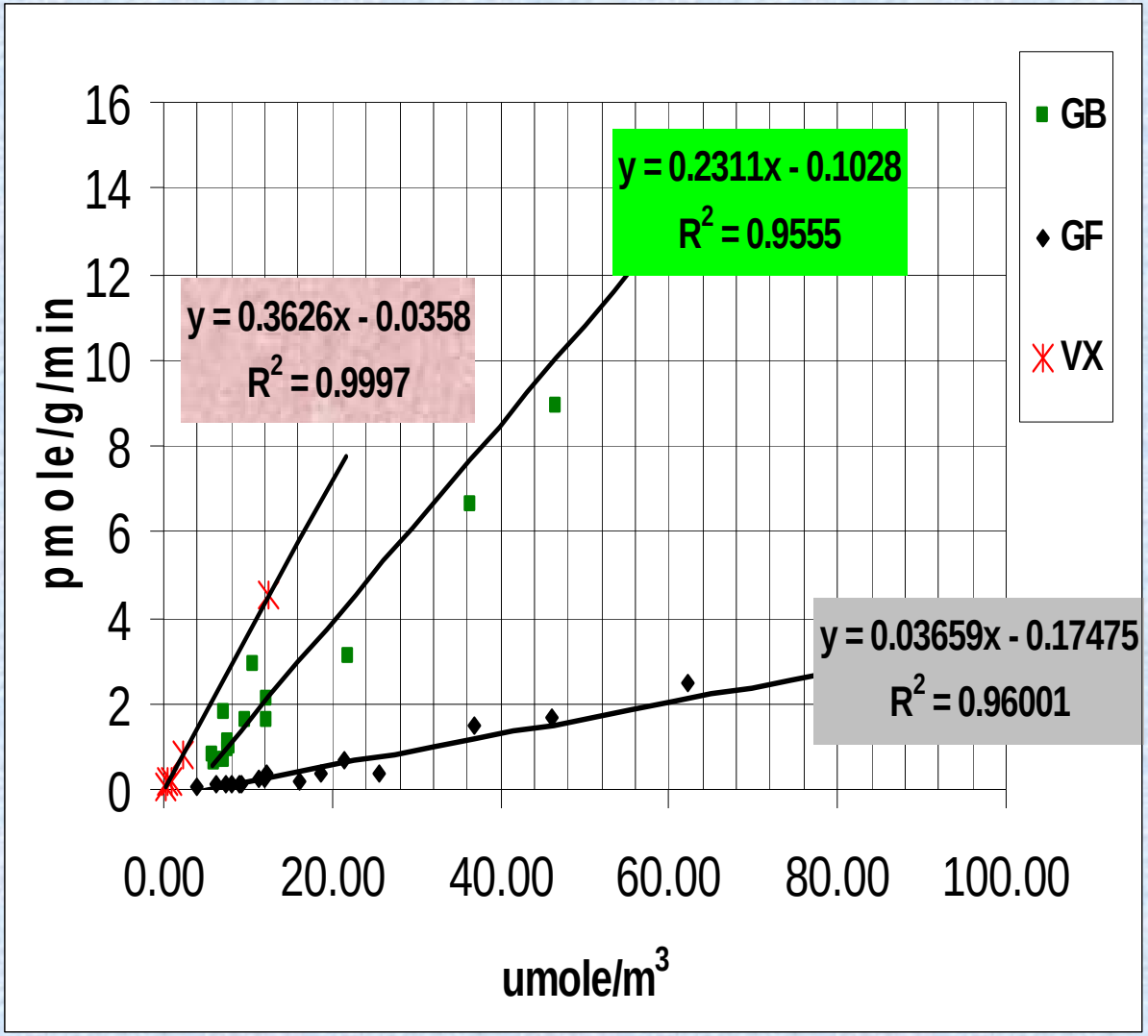
Objectives. **This DTO will deliver data sets on operationally-relevant health effects of low-level exposure to the class of chemical warfare agents (CWAs) termed "Non-Traditional Agents (NTAs)".**

CB.69 S&T Funding (Dollar Amounts in Millions)

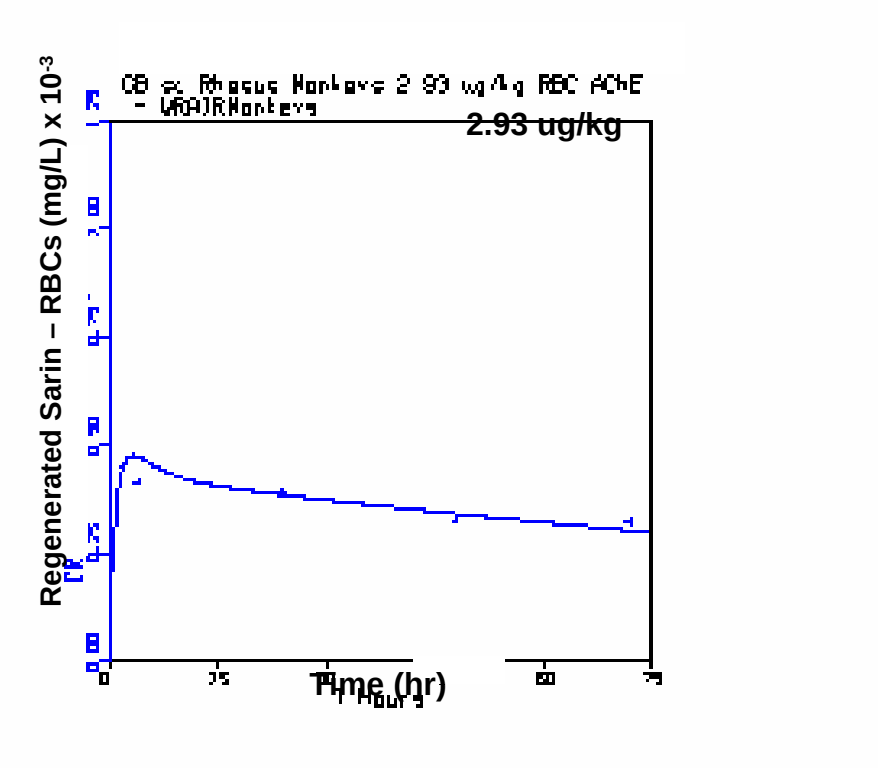
PE	Project	FY07	FY08	FY09	FY10	FY11
0602384BP	CB2	6.0	8.0	8.0	8.0	8.0
0602384BP	TC2	1.0	1.0	1.0	1.0	1.0
	DTO Total	**7.0**	**9.0**	**9.0**	**9.0**	**9.0**

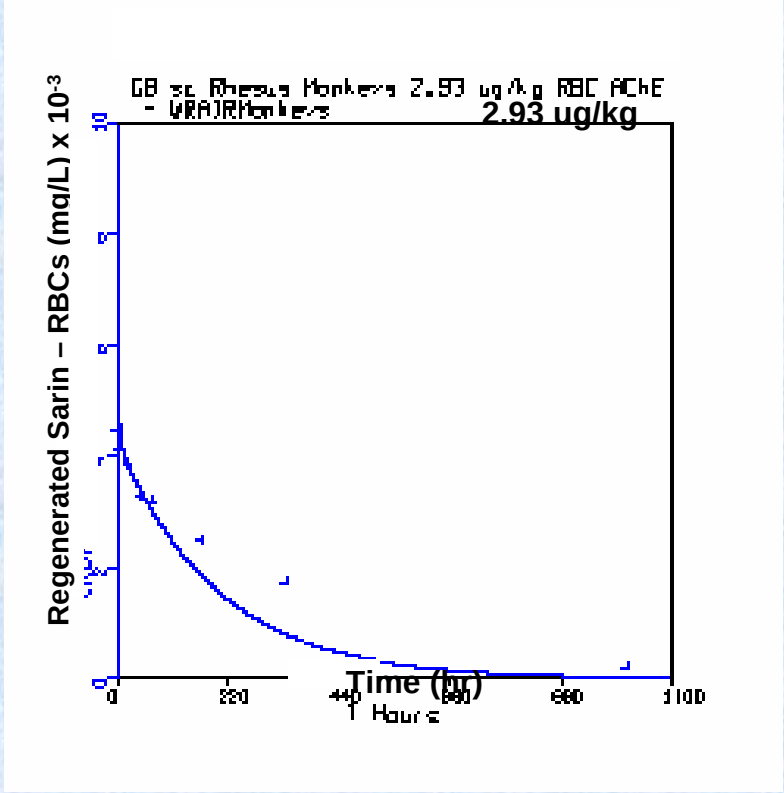
The dose-metric: Regenerated Agent

There is a definite linear correlation between the amount of GVX/RGB/RGF seen in the RBC per minute of exposure and the exposure concentration in male minipigs at lethal levels. Molar units present a more accurate picture.



GB i.m. Rhesus Monkey

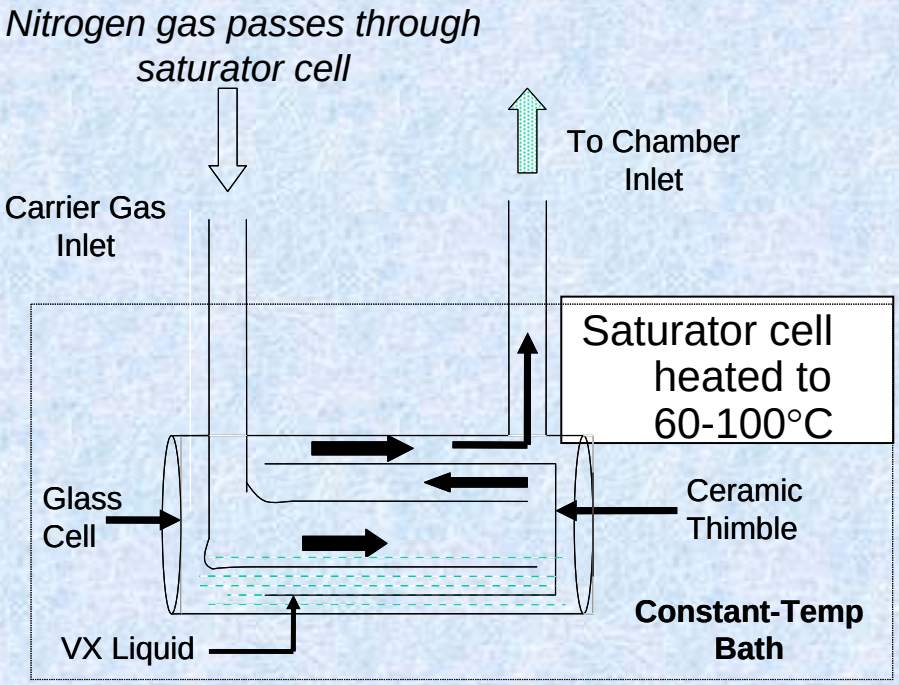




Dr. Genovese, WRAIR

VX Vapor Generation: Stable, Verifiable of Concentrations

Generation of stable/ verifiable exposure atmospheres



Saturator Cell

	GB	VX
Molecular Formula	$C_4H_{10}PO_2F$	$C_{11}H_{26}NO_2PS$
Molecular Wt. (g/ mol)	140	267
Vapor Pressure @ 20 °C	2.1 mm Hg	0.0007 mm Hg
Vapor Density (Air = 1 STP)	4.86	9.2
Liquid Density (g/mL)	1.10 @ 20 °C	1.008 @ 20 °C
Volatility (mg/m^3)	22000@ 25 °C	10.5 @ 25 ° C