

Using Human Experimental Data to Derive Acute Exposure Concentrations for HD, GB and VX

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Background

- Chemical Weapons Convention Treaty
- 164 Signatories
- Destroy Stockpiles by 2007
- 9 US Sites, Bulk and Munitions
- Greatest Risk: Continued Storage
- Challenge: Disassembling Munitions
- CDC Oversight Responsibility (workers, residents)
- Criteria Based on Extrapolation from NOAEL/LOAEL (as with AEGs)

NOAEL/LOAEL APPROACH

- Select a LOAEL or NOAEL
- Most relevant studies and receptors
- Apply a series of uncertainty factors as divisors to the LOAEL or NOAEL to derive a theoretically “safe-sided” allowable exposure level.
 - 5 uncertainty factors and an additional modifying factor that are multiplicative.
 - By convention each of the factors is generally assigned a value of 1,3, or 10.
- The product of these factors generally reduce the NOAEL/LOAEL value by about 1-4 orders of magnitude (i.e., the original values are divided by a factor of 10 to 10,000).

US EPA 1999

“While it is appropriate to err on the side of protection of health and the environment in the face of scientific uncertainty, common sense and reasonable application of assumptions and policies are essential to avoid unrealistic estimates of risk.”

USEPA 1998

“A major criticism of the NOAEL/LOAEL paradigm is that its reliance on a single data point as the basis of the derivation does not allow for specific consideration of the shape of the dose-response curve, the number of animals in the group, or the statistical variation in the response and its measurement...The methods making use of mathematical dose-response models, Benchmark Concentration and categorical regression (as opposed to NOAEL method), are preferred when the toxicological data are sufficient to support these methods...because they use information from the entire dose-response curve rather than from a single experimental point”

Implications of Extrapolating from NOAEL/LOAEL

Unrealistic estimates of risk may result in

- exposure levels below the limits of dependable analytical quantification,
 - excessive numbers of false alarms, and
 - increased community risk because of program delays.
-
- 2000 CDC revisited data

Model: CatReg

- US Environmental Protection Agency
- <http://cfpub2.epa.gov/ncea/cfm/recordisplay.cfm?deid=18162>

USEPA SAB 1998

”The [categorical regression] process makes use of every bit of data available...The underlying premise of the approach is that the severity of the effect, not the specific measurement or outcome incidence, is the information needed for assessing exposure-response relationships for non-cancer endpoints....All the available data are graphed on a single chart and one can immediately get a rough picture of the level of the concentration multiplied by time values that can be expected to cause adverse effects of varying severity.”

Data of Interest

- Unclassified data
- Controlled exposures only
- Acute exposures (e.g., leaks, spills)
- C and t well characterized
- Thorough characterization of severity of the observed health endpoints

Then:

- Identify key health endpoint
- Define response categories
- Use categorical regression to analyze results by time, concentration and severity

Compounds

- HD
- GB
- VX

HD ($C_4H_8Cl_2S$)

- Bis(2-chloroethyl) Sulfide
- Vesicant or 'Blister' Agent
- Sulfur Mustard (Distilled)
- Yperite, Senfgas, Lost, Gelbes Kreuz
- First Used in 1917
- Used in Iran-Iraq War 1980-88
- Low mortality, highly incapacitating
- Irritation or damage to eyes, respiratory tract and skin

Why Human Experiments With HD?

- No adequate animal model because:
 - Blistering response is uniquely human
 - Humans are most sensitive species for critical effect (ocular)
- Primary objective of tests:
 - Identify means of protecting Allied soldiers
- Human experimental data first documented with investigator self-exposure in 1918 (US)

Reed 1918

“After exposure, no symptoms of note appeared until after six hours, when there set [in] rather suddenly a several conjunctival irritation with photophobia and blepharospasm which increased in severity until, at the end of 12 hours, it was found impossible to see anything. There was from this time progressive improvement until, at the end of 18 hours, it was possible to distinguish, with great effort, the faces of persons in the room. The pain was so severe as to prevent sleep for about 30 hours...By the end of the third day an intense prurience had developed on the trunk, following moderate exercise, which increased in severity so as to be almost intolerable...It was possible to read with comfort on the sixth day. The conjunctival injection did not clear up entirely in a month....hypersensitiveness of the eyes was noticeable for six weeks.”

HD Experiments

- Continued with lab staff, soldiers, "volunteers"
- US, UK, India, Australia, Canada
- Until at least 1965
- Significant no. of controlled experiments where reliable D-R curves can be established
- Categorization of effects remarkably similar

HD Experiments

Human experimental data were also amenable to CatReg analysis because of:

- Focus on receptors with the greatest potential for exposure (workers).
- Experiments conducted under relevant exposure conditions (i.e., involving exposure concentrations resulting in severe but largely reversible effects, rather than emphasis on no-response levels)
- Experimental exposure conditions similar to actual field conditions (acute, accidental, high-level exposures rather than intentional, continuous, low-level exposures)
- Experimental effects data already categorized into None, Mild, Moderate and Severe. Reduces uncertainty introduced by professional judgment. Several investigators returned similar results, reinforcing the consistency of the pathological response to sulfur mustard.
- Categorization of like effects based largely on objective signs rather than subjective symptoms.

HD Data

- Ct (mg-min/m³) is linear between ca. 2 min and 20 hr (Haber's Law)
- Ocular effects are the critical toxic effect
- No systemic involvement is seen without effects on the eye
- Deaths from mustard exposure tend to be a result of secondary infections involving the respiratory tract

HD Severity Categories

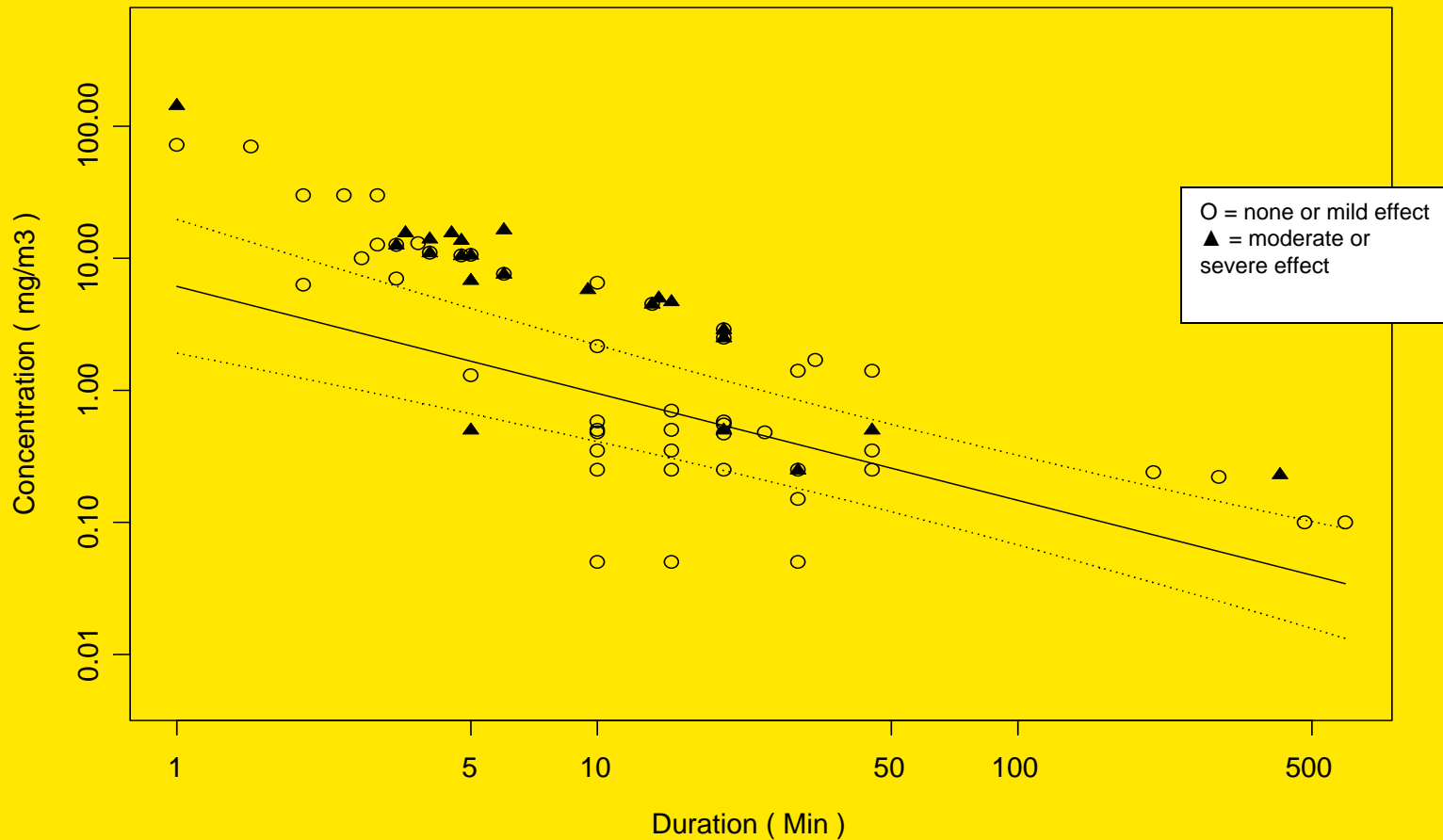
- 183 observations
- 4 categories
 - None
 - Mild but not adverse or irreversible
 - Moderate
 - Severe
- **Confidence in the demarcation between categories was increased by collapsing the data into two categories rather than four.**
 - “No” or “mild” (but not adverse) effects
 - “Moderate” or “severe” effects (which could be uncomfortable or impair escape but are not irreversible).

Categorization of Effects

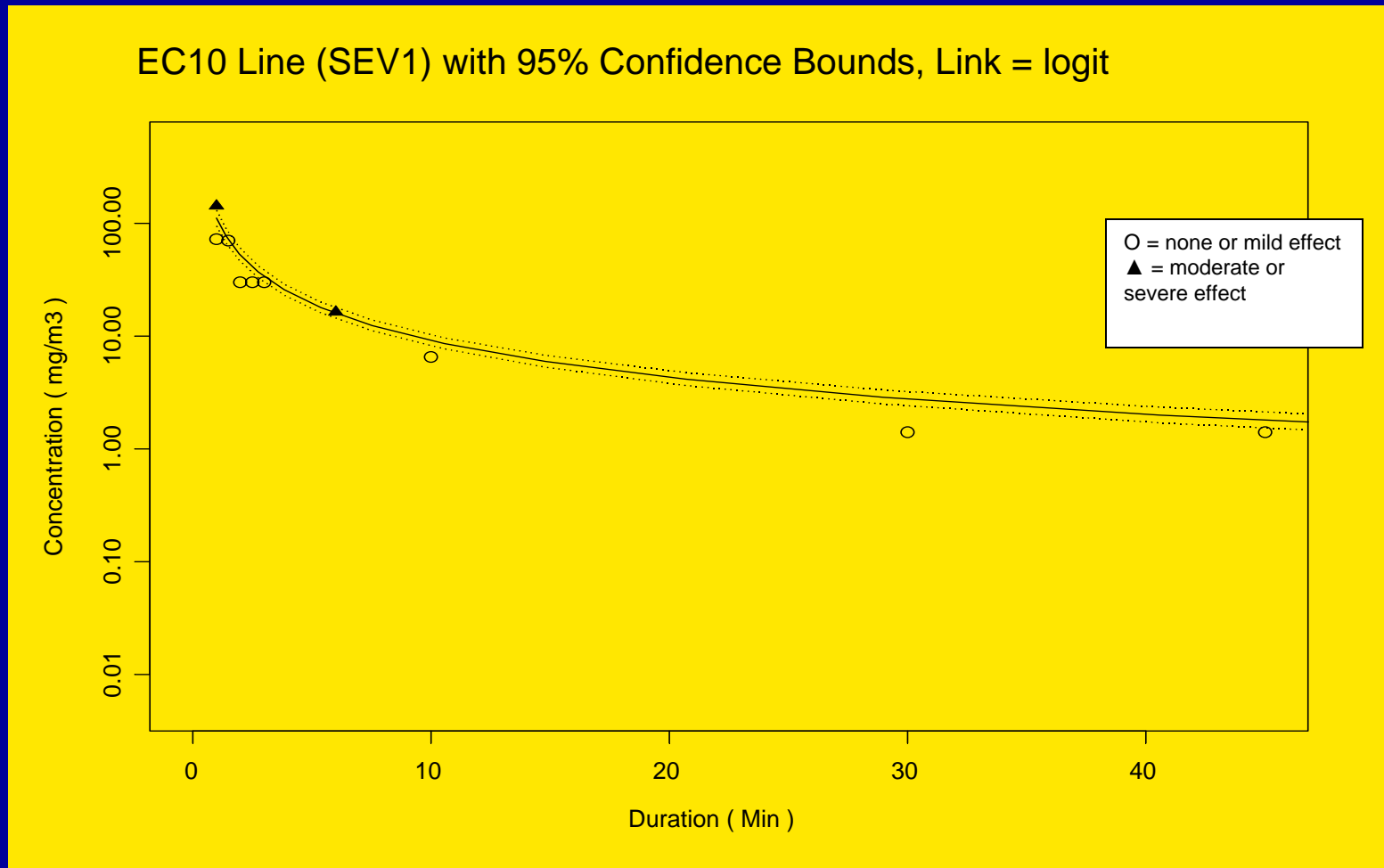
Signs/Symptoms	0=None	1=Mild	2=Moderate	3=Severe
<i>Primary Effects</i>				
Blepharospasm	N*	N	N	Moderate
Corneal effect	N	N	N	First 24 hours
Interference with vision	N	N	N	Slight
Photophobia	N	N	Slight or mild	Casualty level, well-marked
Edema	N	N	Slight	Well developed
Chemosis	N	N	Trace	Moderate
Conjunctivitis	N	Trace	Marked, widespread	Moderately severe to severe, widespread and intense redness
Casualty level/ treatment required	N	N	None, or may have required a few days treatment	Casualty
<i>Secondary Effects</i>				
Discomfort	N	N	Eye soreness for up to a few days	Severe
Angular/conjunctival congestion	N	Slight or discernible	Well-marked, moderate	Intense or severe
Lacrimation	N	Mild	Moderate	Severe
Injection band	N	Fine, mild, or moderate but comfortable	Well-marked, visible after 14 days	Severe, both lids

HD Results (All Studies)

EC10 Line (SEV1) with 95% Confidence Bounds, Link = logit



HD Results (Guild Study, 5-30 Min Exp)



Resulting Exposure Concentrations

Minutes of Exposure	EC ₁₀	Ct	95% LCL (=NOAEL)	95% UCL
5	19.35	96.8	17.35	21.59
15	5.87	88.1	5.2	6.62
30	2.77	83.0	2.39	3.20
480	0.03	14.4	0.01	0.1

Current HD Exposure Criteria

Mustard (H, HD, HT) Criteria	Worker Population Limit (WPL) (=TWA TLV)	General Population Limit (GPL) (=RfC)
Army/CDC Current (mg/m³)	0.003	0.0001
Concentration x Time (Ct)	1.4	0.4
Averaging Time	8 hours (TWA)	72 hours (TWA)

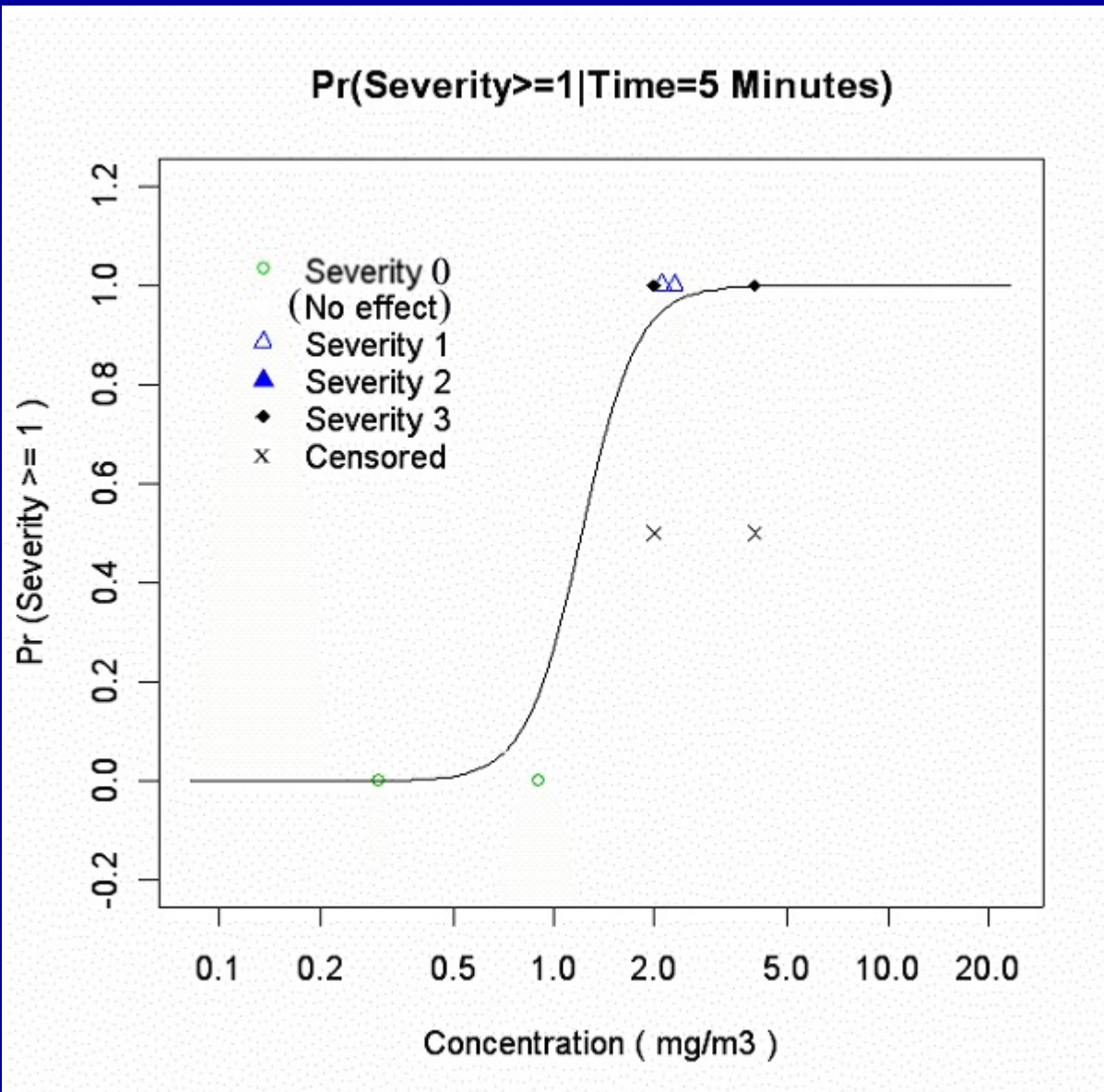
GB

- Nerve agent
- Inhibits acetylcholinesterase
- $C_4H_{10}FO_2P$, isopropyl methylphosphonofluoridate
- Sarin, Zarin
- Tokyo subway 1995 (Aum Shinrikyo)
- Major Data Challenge:
 - Exposure measured as reduction in RBC-AChE but
 - No correlation found between reduction in RBC-AChE and clinical manifestation

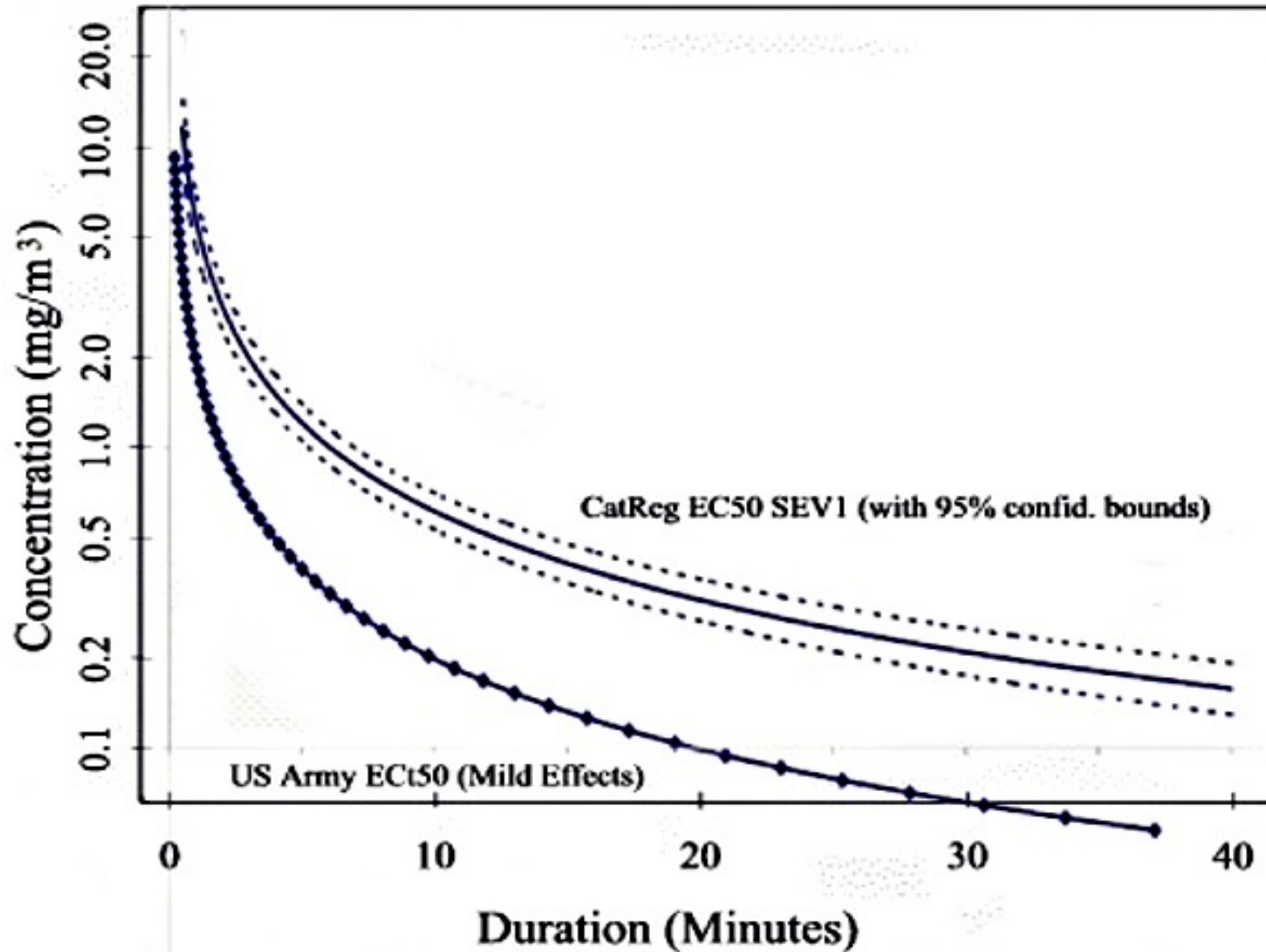
GB Severity Categories

- 4 studies, 150 observations
- 4 severity levels:
 - 0= No observable effect, or **mild** signs and symptoms.
 - 1= **Moderate**. Mild but definite harassment. Symptoms increase over time, persist up to several days.
 - 2= **Severe**. Symptoms of systemic poisoning with a marked fall in RBC AChE.
 - 3= **Lethal**.

GB Results



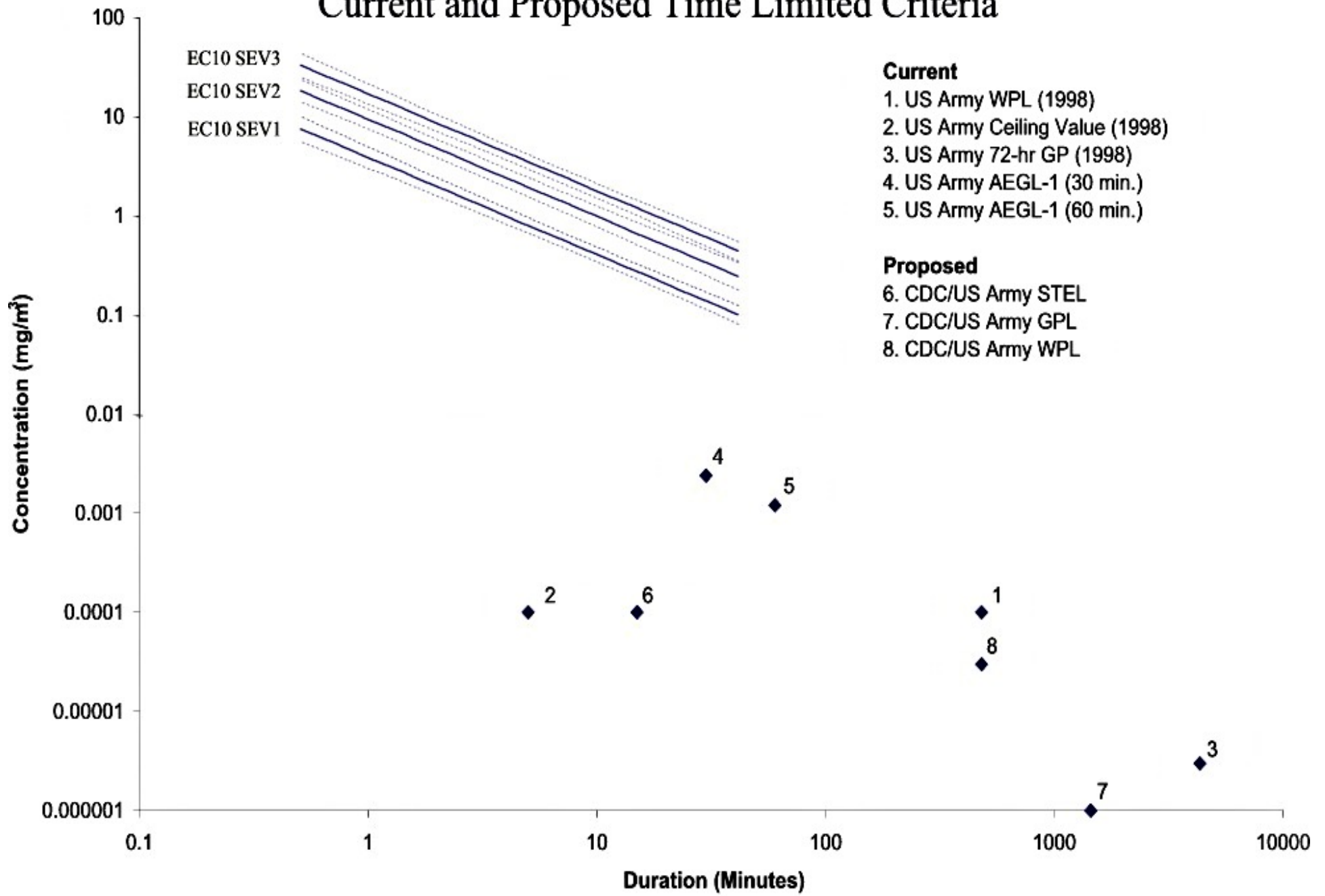
Comparison of CatReg Derived EC50 SEV1 Lines to the US Army ECt50 (Mild Effects) Criterion



Current GB Exposure Criteria

	Worker Population Limit (WPL) (=TWA TLV)	General Population Limit (GPL) (=RfC)	Short-Term Exposure Limit (STEL) (Workers)	Immediately Dangerous to Life and Health (IDLH) (Workers)
Army/CDC Current (mg/m³)	0.00003	0.000001	0.0001	0.1
Concentration x Time (Ct)	0.014	0.004	0.0015	<3.0
Averaging Time	8 hours (TWA)	72 hours (TWA)	15 min	<30 min

CatReg EC10 SEV1, 2 and 3 Lines Compared to Current and Proposed Time Limited Criteria



GB Results

- Ordered logit model, with logarithmic transformation of C and t, yielded the minimum deviance of the 3 models available under CatReg
- CatReg vs. GAUSS: Show substantial agreement (calculated values agree to at least 6 significant digits).
- C-t curves parallel for moderate and severe categories

Other Observations

- GB – no difference in responses among healthy soldiers or highly susceptible subjects
- x10 UF for sensitive populations may not apply to GB

What's Next

- EPA/Homeland Security supportive
- Prioritizing 130 compounds
- Perhaps 20% have adequate human data

- In US, existing values unlikely to become less conservative; more likely, CatReg used to confirm current values
- WHO/IPCS role will be key for new criteria development based on human data

Conclusions

- When available, human experimental data should be considered in development of human exposure and effects criteria
- CatReg can be a useful tool in developing soundly defensible criteria

Where to Find Papers

- No immediate plans for publication
- Posted at www.deltatoxicology.com

