RELATIONSHIP BETWEEN TOXICITY VALUES FOR THE HEALTHY SUBPOPULATION AND THE GENERAL POPULATION

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ABSTRACT

The present chemical warfare (CW) agent toxicity estimates are not suitable for use with the general population (GP) because they are framed for male soldiers. A method was created to convert the median effective dose and probit (or Bliss) slope to estimates applicable to the GP. It was assumed that individual susceptibilities have a log-normal distribution. Two mathematical models were developed to describe a healthy or sensitive subpopulation (SP). In the tail model, the SP consists of all individuals having susceptibilities within a tail of the GP distribution. In the bell model, the SP has a lognormal distribution. The median and the probit slope of an SP were determined as a function of the SP size. The two models gave similar results. Historical military demographics were used to estimate the size of the healthy SP from which military personnel are drawn. Uncertainty factors were obtained from the tail and bell models. Uncertainty factors from both models were consistent with the results of two previous studies that quantified differences between populations. The model can be readily incorporated into an casualty assessment module to permit rapid recalculation of toxicity estimates. This will allow the commander or staff to better estimate the degree of collateral damage to civilian populations from CW agent attacks and incidents.

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The technical report has been approved for public release, distribution is unlimited. Registered users should request copies from the Defense Technical Information Center; unregistered users should direct such requests to the National Technical Information Center.

The following is a breakdown of the poster into individual slides.

CUM SCIENTIA DEFENDIMUS

Relationship Between Toxicity Values for the Healthy Subpopulation and the General Population

2002 Joint Service Scientific Conference on CB Defense Research
Hunt Valley, MD
20 November 2002

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Comparison of Populations via Mathematical Modeling

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- Goal: To develop a mathematical model to describe differences in agent toxicity between a healthy subpopulation (SP) and the general population (GP)
  - Parameter value conversion between populations—median dose/dosage values and probit slopes
  - No known work previously done on this subject
- Only one model parameter: SP Size
- Key assumptions
  - Individual susceptibilities for the GP have a normal distribution (bell-shaped curve) of Log (Effective Dose) or Log (ED) values
  - SPs (either healthy or sensitive) are represented by one of two models: Bell or Tail
- Disclaimer: The content of this poster is not to be construed as an official Department of the Army position unless so designated by other authorizing documents

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Application to Decision Support Methods

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Casualty estimations

Current CW agent toxicity values (LCT_{50} or ECT_{50} and probit slope) for military subpopulation are not appropriate for use in estimating casualties for the general population exposed to CW agent attacks or incidents

Using military toxicity values for the general population will result in the underestimation of civilian casualties

Method offers a simple means to arrive at reasonable approximation of civilian toxicity values based on an extrapolation using mathematical/statistical modeling from known military values

Algorithm for toxicity value conversion can be easily programmed into transport & dispersion models

Models Used to Compare Population Differences

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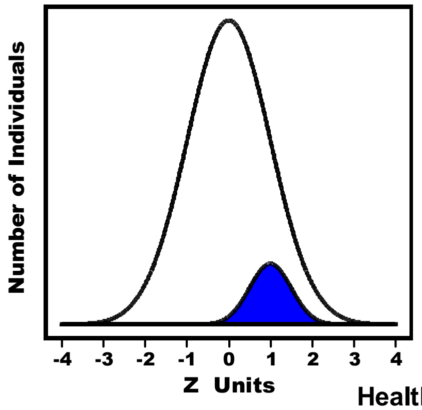
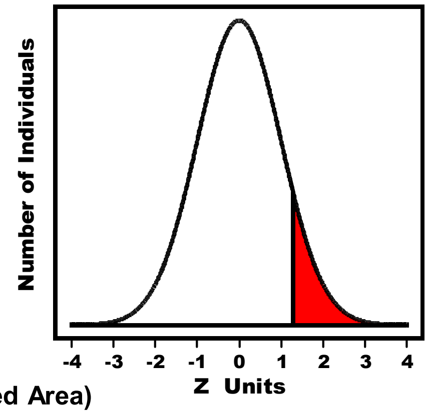
$Z = m_{GP}\,[\log(ED) - \log(ED_{50})]$

m_{GP} = Probit slope of GP

ED_{50} = Effective Dose 50% for GP



Bell & Centroid Model



Healthy Subpopulations (Shaded Area)
Size = 10% of Population

Defining a Subpopulation

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A Subpopulation can be defined in a variety of ways

- Healthy Subpopulations
  - Military
  - Workplace
- Sensitive Subpopulations
  - Infants
  - Elderly
  - People with chronic medical conditions
- Other Subpopulations
  - Gender
- Mathematical modeling can account for gender differences
  - Separately apply either Bell or Tail Model to each gender
- Use of demographics to estimate SP size
  - Existing chemical warfare (CW) agent toxicity values developed for military SP
  - Workplace SP used for industrial chemicals

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Demographics of U.S. WWII Military Subpopulation

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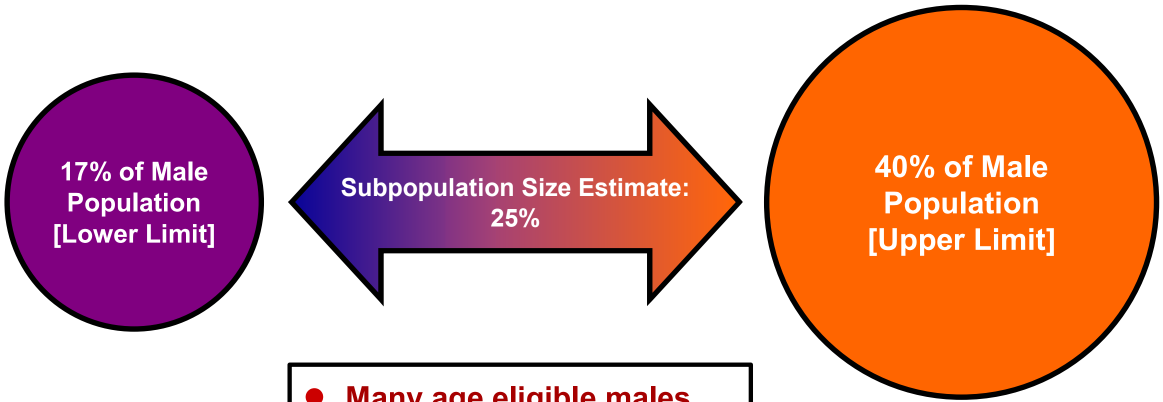

Peak Military Strength (1945)

- Many age eligible males medically unfit for service
- Some healthy males exempted from service

Age Eligible Males (18 to 45 years old)

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SP Size Role in Models and Conversion Process

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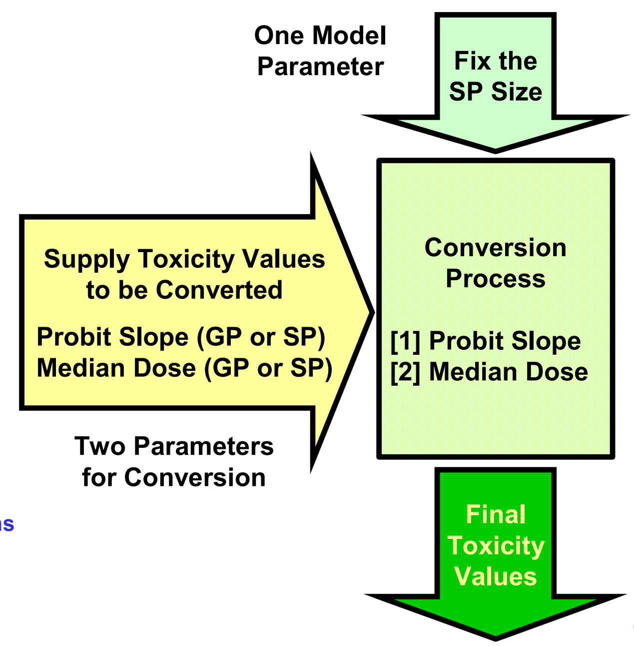
- Tail Model
  - Selection of SP size fixes mathematical relationship between SP and GP
  - Example: If Size = 10%, then ED_{50} of a sensitive SP is located at ED_{05} of the GP
- Bell and Centroid Models
  - Selection of SP size does not determine SP mean and standard deviation
  - SP bell curve must remain underneath GP bell curve
  - Range of feasible values exists for SP mean and standard deviation
    - Bell Model—Maximum difference in means of SP and GP
    - Centroid Model—Located at centroid of feasible range



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Feasible Region of Mean & Standard Deviation Values

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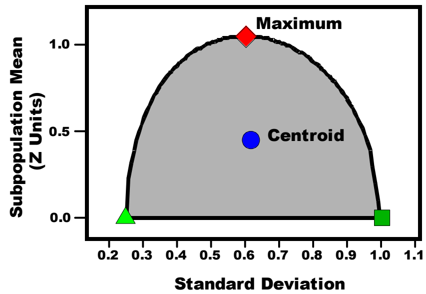
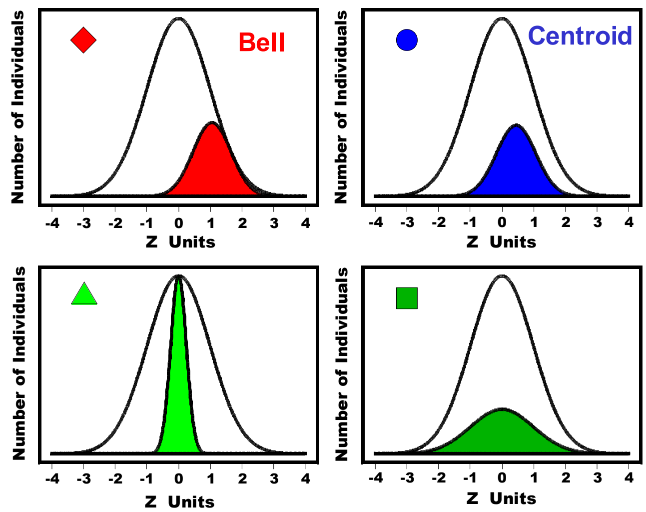
Region of Feasible Values for Healthy Subpopulation Size of 25%



Feasible value pairs do not always produce realistic distributions (see △)

Subpopulation Distributions (Shaded Areas) as Function of Location Within Region



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Subpopulation Model Statistics

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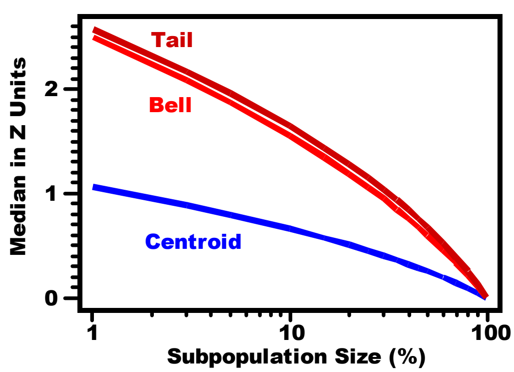
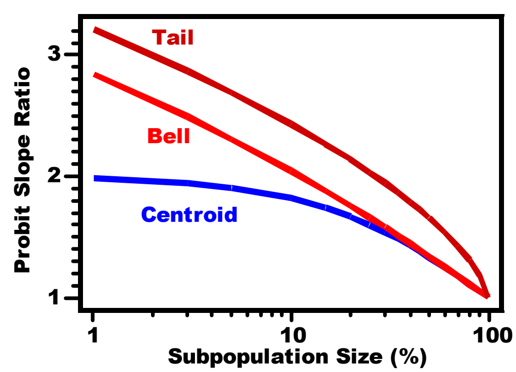
Median of a Healthy Subpopulation



For SP Size of 25%

Median (Tail) = 1.15
Median (Bell) = 1.06

Probit Slope Ratio
(For Healthy and Sensitive Subpopulations)



Probit Slope Ratio (PSR) = Slope (SP)/Slope (GP)
$= m_{SP} / m_{GP}$

For SP Size of 25%

PSR (Tail) = 2.03
PSR (Bell) = 1.66

Calculation of Effective Dose Ratio

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$$EDR = \left[\frac{ED_B}{ED_A}\right] = \text{antilog}\left[\frac{(Z_B - Z_A)}{m_{GP}}\right]$$

EDR = Effective Dose Ratio

ED_A and ED_B = Effective doses for Populations A and B

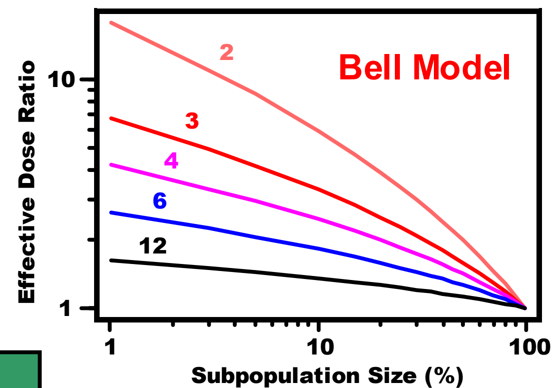
Z_A, Z_B = Distance (in Z units) of ED_A and ED_B from ED_{50} of GP

m_{GP} = Probit slope of GP

Only Three Values Needed

- Subpopulation Size
- Probit Slope (m_{SP} or m_{GP})
- Median Dose (for either SP or GP)

EDR Dependency on Probit Slope
Ratio of Medians for m_{GP}: 2, 3, 4, 6 and 12



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Comparison of EDRs from Different Models

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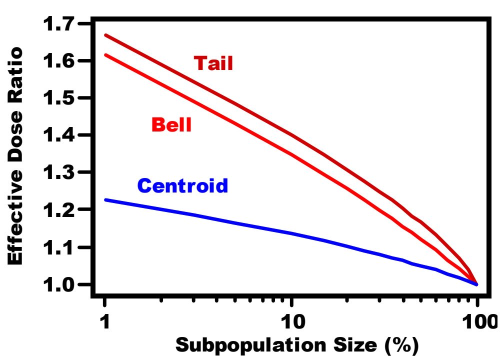
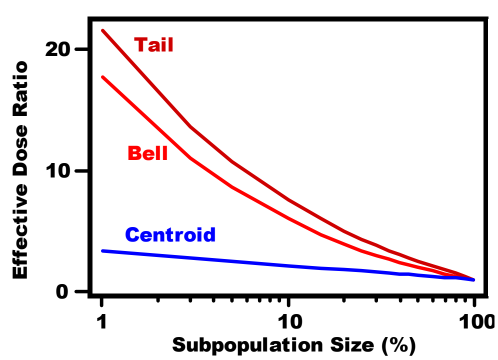
Relative Magnitude of Model EDRs
at a Fixed Probit Slope and SP Size

> Bell > Centroid

EDRs from Tail, Bell and Centroid Models
Ratio of Medians for m_{GP} = 12



EDRs from Tail, Bell and Centroid Models
Ratio of Medians for m_{GP} = 2



Sample Calculation—Chlorine Toxicity

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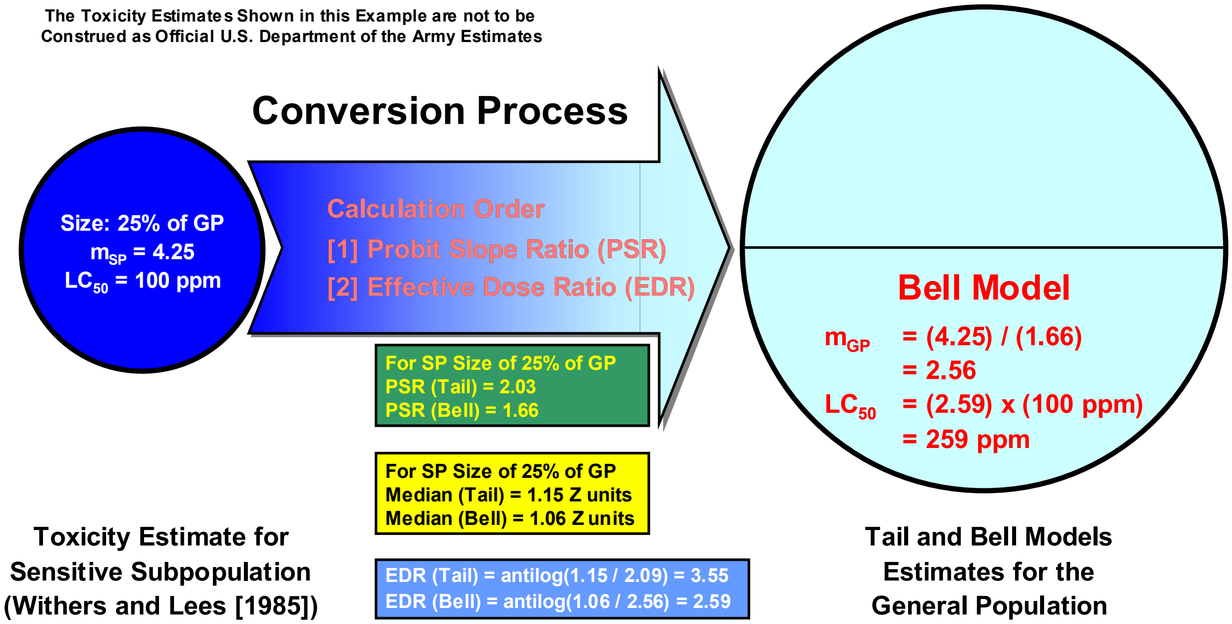
The Toxicity Estimates Shown in this Example are not to be Construed as Official U.S. Department of the Army Estimates



CW Agent Acute Exposure Guideline Levels (AEGLs)

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- Environmental Protection Agency (EPA) AEGLs–protection of health of sensitive individuals
  - AEGL-1: Threshold notable discomfort
  - AEGL-2: Threshold serious effects
  - AEGL-3: Threshold lethality
- CW agent AEGLs based on most toxic route: inhalation (IH)
- Proposed CW agent AEGLs (posted on EPA website)
  - G-type and VX Nerve Agents (Oct 2000)
  - Sulfur Mustard (HD) (January 2000)
  - Phosgene (CG) (August 2000)
  - Chlorine (October 1997)
- AEGL development involves use of Uncertainty Factors (UF) to account for various sources of uncertainty
  - UF values are usually 1, 3 or 10
  - Examples of UF applications in AEGLs:
    - Healthy to sensitive human (Intraspecies)
    - Laboratory animal to human
    - Incomplete to complete database
- Intraspecies UFs
  - Needed to account for response variability in the human population
  - Used to convert from a healthy human SP to a GP basis for threshold effects
    - Essentially ECT_{01} (healthy SP) to ECT_{01} (GP)

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Comparison of Intraspecies UFs for CW Agent AEGLs

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- Tail and Bell Models can be used to calculate intraspecies UFs
  - UFs based on EDR of LCT_{01} (healthy SP) to LCT_{01} (GP)
  - Military probit slope values from Grotte and Yang (2001)
  - Probit slopes for CG and Chlorine estimated from review of existing experimental data
  - Models provide mathematical basis for setting intraspecies UF values
- EPA AEGL-3 intraspecies UFs shown for comparison
  - Assignment of values more qualitative in nature

Agent	Route	Military Probit Slope	m_{GP}		Uncertainty Factors (Between 1st Percentiles)		
			Tail	Bell	Tail	Bell	EPA AEGL
G	IH	12.0	5.9	7.2	3.2	1.9	10
G	PC	5.0	2.5	3.0	16.7	4.6	
HD	IH	6.0	3.0	3.6	10.4	3.6	3
HD	PC	7.0	3.4	4.2	7.5	3.0	
VX	IH	6.0	3.0	3.6	10.4	3.6	10
VX	PC	6.0	3.0	3.6	10.4	3.6	
CG	IH		6.7	8.3	2.8	1.7	3
Chlorine	IH		5.9		3.2	2.2	3

IH — Inhalation

PC — Percutaneous

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Conclusions from Comparison of Intraspecies UFs

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UF Comparison Summary

Poor

G-Agents:
AEGL (10) >> Tail (3) & Bell (2)

Caution

VX:
AEGL (10) >> Bell (4)
AEGL (10) = Tail (10)

CG & Chlorine:
AEGL (3 & 3) > Bell (1.7 & 2.2)
AEGL (3 & 3) = Tail (2.8 & 3.2)

Excellent

HD:
AEGL (3) ≈ Bell (4)
AEGL (3) << Tail (10)

- Both models are conservative
  - Tail Model the most conservative
    - Sets an absolute upper limit on UF value
  - Bell Model gives more realistic SP distribution shape
    - Important for comparing the 1st percentiles of two distributions
- Suggested course of action on current CW agent AEGL intraspecies UF values
  - G-Agent should be strongly reconsidered
  - VX, CG and Chlorine should be reassessed
  - Strong mathematical support for HD—no change need be considered
  - Any changes should be kept in context of ALL other assumptions made in developing AEGLs for a particular agent

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Summary

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- New method developed for converting toxicity
  - Based on the mathematical modeling of a SP and its relationship to the GP
  - Conversion from SP to GP basis
  - Addresses a critical parameter gap (GP CW agent toxicity estimates)
- Method needs only three values:
  - Model parameter: SP size
  - Two toxicity values for conversion
    - Probit slope for either SP or GP
    - Median dose for either SP or GP
- Both healthy and sensitive SPs can be modeled with either of two models: Tail or Bell/Centroid
- Historical military demographics reviewed for modeling military SP
- Intraspecies UFs for EPA CW Agent AEGL-3s investigated with method
  - Method provides mathematical basis for calculation of intraspecies UF values
  - Strong argument exists for current G-agent UF being too high
  - Current VX UF value is questionably high

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Additional Information

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- Work documented in U.S. Army technical report
  - Crosier, RB and Sommerville, DR, *Relationship Between Toxicity Values for the Military Population and Toxicity Values for the General Population*, ECBC-TR-224. Edgewood CB Center, Aberdeen Proving Ground, MD, March 2002. UNCLASSIFIED/UNLIMITED. AD # A400214.
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