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Alternatives to Pollutant-by-Pollutant Dose-Response Estimation

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From Insight to Impact – Worldwide

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Goals--Explore Methods to Overcome Barriers to the Quantification of Non-Cancer Risks

- Reduce Perceived Needs for Overwhelming Amounts of Chemical-Specific Health Risk Testing Information
- Create a Framework for Understanding and Quantifying "Missing Data" Uncertainties that Can be the Basis for Value-of-Information Analyses
- Help Facilitate Apples-to-Apples Comparisons and Priority Setting for Control of Exposures to Different HAPs with a Few Basic Types of Modes of Action

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Regulatory Toxicologists Can Make Better Use of Two Kinds of Information

- "Prior" information from reference sets of putatively analogous chemicals--leads to the "straw man" probabilistic system for assessments of traditional individual-threshold toxic effects.
- "Upstream" biomarkers in people that can be more readily connected to human exposures on the one side, and have established relationships to "downstream" quantal outcomes of ultimate concern on the other side--e.g.
  - Birth weight as a predictor of infant mortality and other consequences of impaired development
  - Motile sperm counts as a predictor of male fertility effects
  - Changes in cardiovascular risk factors as predictors of cardiovascular morbidity and mortality

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Chemical-Specific Data are Nice, But…

- They limit your creativity;
- They are not strictly necessary;
- *Straw man model*: General approach to proceed with only the most basic chemical-specific data:
  - It is ultimately hopeless to try to fairly and accurately represent the compounding effects of multiple sources of uncertainty as a series of point estimate "uncertainty" factors.
  - characterize the uncertainties created by missing chemical-specific data by drawing an analogy to a reference set of previously studied chemicals that are putatively analogous to the one being studied.
  - This essentially converts an uncertainty to an observable variability among the cases of the reference set represent the prior experience in evaluating each type of uncertainty.

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Traditional Toxicological Model Leading To General Expectations of Thresholds in Dose Response Relationships for Toxicants

- Biological systems have layers on layers of homeostatic processes (think of a thermostat)
- Any perturbation automatically gives rise to offsetting processes that, up to a point, keep the system functioning without long term damage.
- After any perturbation that does not lead to long term damage, the system returns completely to the *status quo* before the perturbation.
- Note: These assumptions can provide a reasonable basis to infer individual thresholds for stressors that act via homeostatic-system-overwhelming. Individual thresholds will differ, however, and the overall population may contain people with very small thresholds.

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However--There might not be no-adverse-effect thresholds for:

- Tasks that challenge the maximum capacities of the organism to perform
  - (e.g., 100 yard dash; perhaps learning to read)
- Circumstances where some pathological process has already used up all the reserve capacity of the organism to respond to an additional challenge without additional damage
  - (e.g. infarction causes heart muscle cell death that may be marginally worsened by incremental exposure to carbon monoxide)

On a population basis, interactions with background pathological processes may often be important.

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A New Mandate

- **National Research Council (2008). *Science and Decisions: Improving Risk Analysis***
  - Dose response relationships for traditional toxic effects should be based on mechanistic/mode of action ideas where possible
  - human interindividual variability in susceptibility and interactions with “background” disease processes in people should be incorporated
  - Recommends probabilistic system--replacing single-point “uncertainty” factors with distributions; redefining traditional “reference doses” and “reference concentrations” with undefined but putatively low risks with “risk specific doses”--assessed as having less than Y risk with Z confidence
  - Does provide straightforward ways of estimating risk and uncertainty of toxic hazards for use in comparing results of different policy options

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Key Idea for Transforming Risk Assessment for Traditional Toxic Effects

- Quantitatively characterize each uncertainty (including those currently represented by “uncertainty factors”) *by reducing the uncertainty to an observable variability among putatively analogous cases*.
  - Human interindividual variability--kinetic and dynamic
  - Variation in sensitivity between humans and test species
  - Adjustment for short- vs. longer periods of dosing and observation
  - Adjustment for database deficiencies (e.g. missing repro/developmental studies)

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Key Idea-Difficulties with the Proposed Approach

- This general approach is not without difficulty—need rules for making the analogies
  - e.g. defining the reference groups to derive uncertainty distributions for particular cases.
- It does provide a way forward for health scientists to learn to reason quantitatively from available evidence relevant to specific uncertainties.

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Examples of Data Bases Assembled/Analyzed

Type of Projection	Parameters	Original Authors
General Human Interindividual	Pharmacokinetic and Pharmacodynamic Parameters	Hattis et al. 2002 "Straw Man" Proposal
Adult/Child	Classical Drug PK (T1/2, Clearance, Vd) 27-41 drugs; 366 data groups	Ginsberg et al., 2002; Hattis et al., 2003
Young Adult/Elderly	Classical Drug PK (AUC, T1/2, Clearance, Vd) 17-44 drugs 215 data groups	Hattis and Russ 2004 Report to EPA
Interspecies—Acute Toxicity	LD50 10,160 Species-Pairs	Rhomberg and Wolff (1998)

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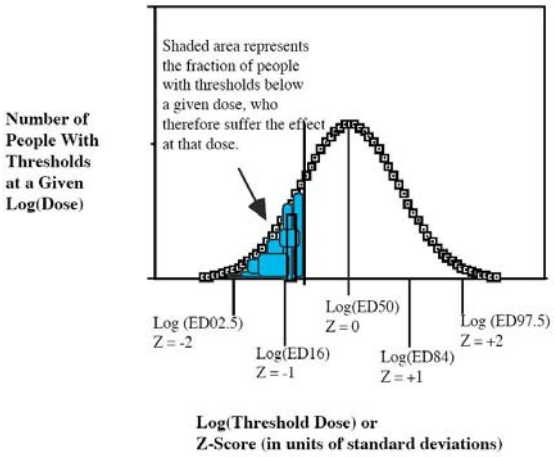
Interpretation of Dose Response Information for Quantal Effects in Terms of a Lognormal Distribution of Individual Threshold Doses



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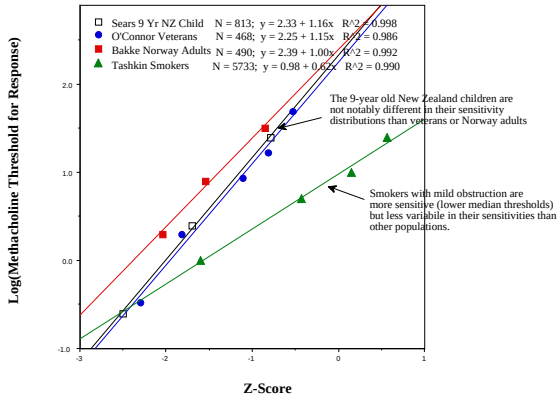
Lognormal Plots Of Methacholine Concentrations Needed To Cause A 20% Reduction in FEV1 In Different Populations



--Correspondence of Points to the Line Indicates Fit to Lognormal Distribution
--Steepness of the Slope of the Line Indicates the Breadth of the Lognormal Distribution of Individual Thresholds

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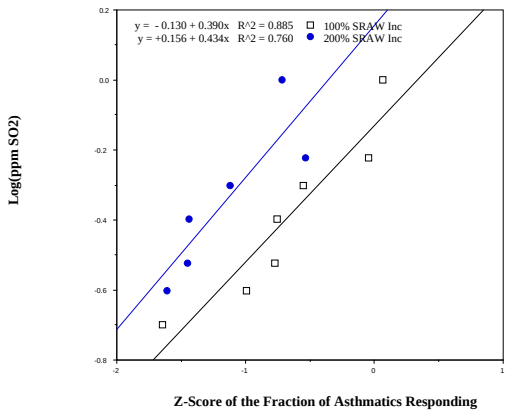
Distribution of Thresholds in Asthmatics for a Doubling or a Tripling of Specific Airway Resistance by SO2



Different Intercepts Indicate Different EC50's for Different Severities of Response

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Tentative "Straw Man" Proposal for Re-Defining RfDs and RfCs in Terms of a "Risk-Specific Dose"

- Tentatively it is suggested that the RfD/RfC be the lower (more restrictive) value of:
  - (A) The daily dose rate or air concentration that is expected (with 95% confidence) to produce less than 1/100,000 excess incidence over background of a minimally adverse response in a standard general population of mixed ages and genders, or
  - (B) The daily dose rate that is expected (with 95% confidence) to produce less than a 1/1,000 excess incidence over background of a minimally adverse response in a definable sensitive subpopulation.

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Warning: Estimates of Risks for Individual Agents are Highly Uncertain, and Depend Greatly on the Extent of Interacting Background Pathological Processes

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Effect of Interacting Background on 95th Percentile Estimates of the Incremental Risk from 2,4,6-Trinitrotoluene*

Interacting Background Risk	Risk Over Bkgd at .1*RfD	Risk Over Bkgd at RfD	Risk over Bkgd at 10*RFD
1.0E-40	3.6E-08	1.1E-04	3.1E-02
1.0E-10	7.8E-08	1.1E-04	3.2E-02
1.0E-08	2.7E-07	1.3E-04	3.2E-02
1.0E-07	6.5E-07	1.4E-04	3.1E-02
1.0E-06	2.3E-06	2.0E-04	3.4E-02
1.0E-05	8.3E-06	3.0E-04	3.3E-02
1.0E-04	3.4E-05	6.5E-04	3.9E-02
1.0E-03	1.4E-04	1.8E-03	5.2E-02

Risk of Mild Adverse Effects from Chronic Human Dosage Near the Current EPA Reference Dose

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It is also possible to use a similar technique to provide starting distributions of expected potencies for different kinds of effects based on experience with all previously studied chemicals or all chemicals with particular chemical groups or quantitative characteristics.

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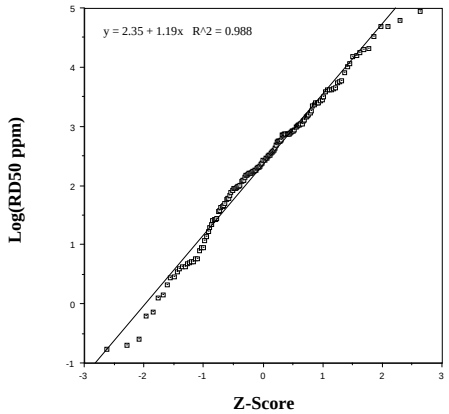
Lognormal Plot of 145 RD50 Values Compiled by Alarie et al. (1998)



Lognormal Variability Among Chemicals in RD50 Potencies Is a Measure of the Uncertainty In Irritant Potency for an Untested Chemical

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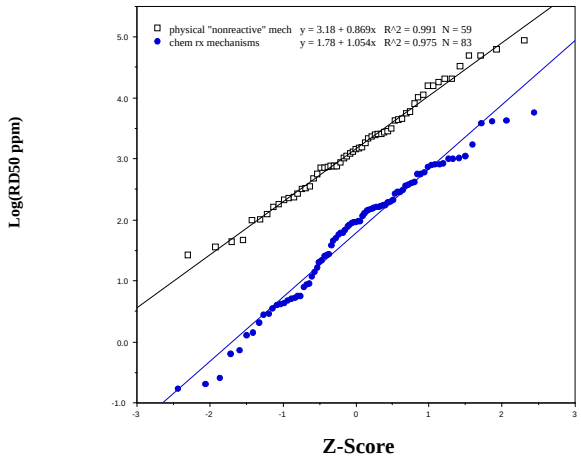
Distributions for Chemicals Likely to Have Physical vs. Chemical Reaction Mechanisms Determine Their RD_{50} values



Chemicals Physical Vs Chemical Reaction Irritant Mechanisms as Classified by Alarie et al. (1998)

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The Promise of Early Effect Biomarkers for Two-Step Assessments of Risks

Exposure → **Change in Biomarker of Early Effect** → **Change in Incidence of Ultimate Effect**

(Continuous Parameter, Statistically Powerful)

(Rare Quantal Effect, Important but Statistically Noisy; Hard to Measure)

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Taxonomy Based on What Organisms Need to Accomplish to Develop and Maintain Functioning, and What Can Go Wrong

- Establishment and Maintenance of Homeostatic Systems at Different Scales of Distance, Time, Biological Functions, Involving
  - Sensors of Key Parameters to Be Controlled
  - Criteria (E.g. “Set Points”) for Evaluating Desirability of Current State
  - Effector Systems That Act to Restore Desirable State With Graded Responses to Departures Detected by the Sensors
- Some Examples of Perturbations:
  - Hormonal “Imprinting” by Early-Life Exposure to Hormone Agonists
  - The “Tax” Theory of General Toxicant Influences on Fetal Growth, and Possible Consequences

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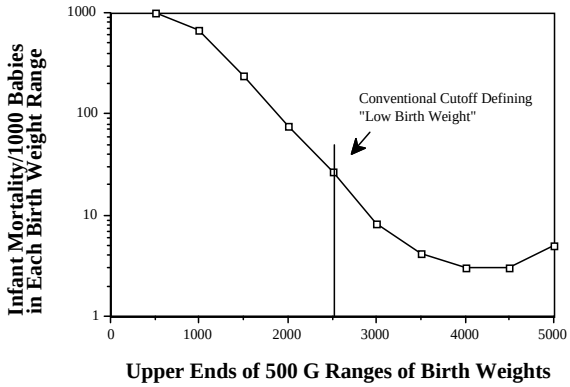
Relationship Between Weight at Birth (in 500 Gram Increments) and Infant Mortality



Differences In Birth Weight Have Appreciable Implications for Infant Mortality Both Above and Below the Conventional Clinical Criterion for “Low Birth Weight”

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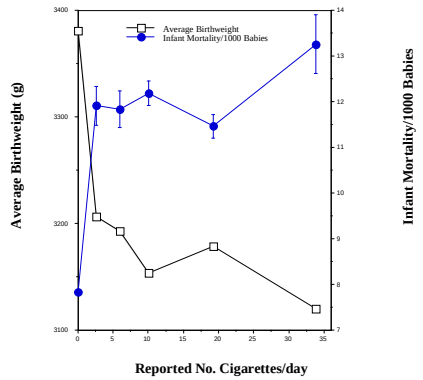
Relationship Between Reported Cigarettes/Day Smoked, Average Birthweight, and Infant Mortality



Similar "Saturating" Patterns of Dose Response for Relationships of Both Birth Weight and Infant Mortality to Reported Direct Smoking--U.S. National Center for Health Statistics 1990 Data

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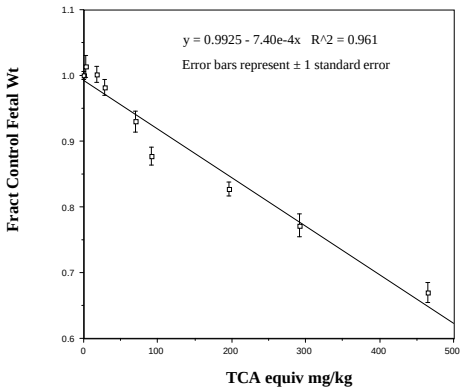
Results of Regression Analysis of the Fraction of Control Fetal Weight Response in Grouped Categories of TCA Equivalents – Interpretation with a Linear Model



Dose Response Relationships for Fetal Growth Inhibition in Conventional Toxicological Studies Are Often Nearly Linear

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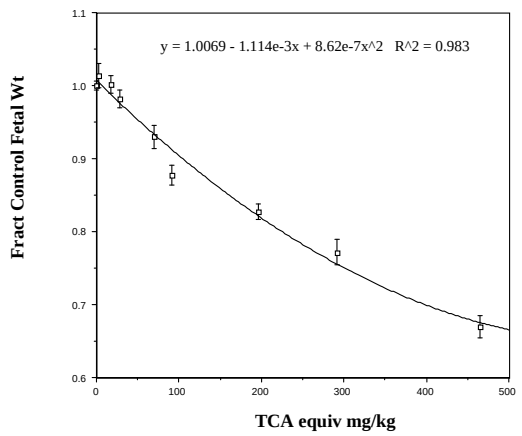
Results of Regression Analysis of the Fraction of Control Fetal Weight Response in Grouped Categories of TCA Equivalents – Interpretation with a Quadratic Model



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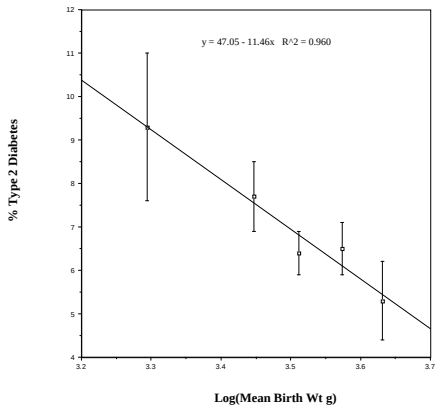
Plot of the Incidence of Type 2 Diabetes in Relation to Log (Mean Birth Weight) – Data of Forsen et al., 2000



Birth Weights are Correlated with Some Important Imperfections of Homeostatic Control in Later Life

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Basic Birth Weight Reduction Results of Bell et al. (2007)

Based on County-Average Air Pollutant Exposures During Gestation for 358,504 Babies in Massachusetts and Connecticut, Evaluated with Single-Pollutant Models, Controlling for Confounders

Air Pollutant	Grams Reduction Birth Weight per Interquartile Exposure Range	Lower 95% Confidence Limit (g)	Upper 95% Confidence Limit (g)	Mean and Std Dev Exposure	Interquartile Exposure Range	Exposure units
NO2	8.9	7	10.8	17.4 ± 5.0	4.8	ppb
CO	16.2	12.6	19.7	656 ± 180	303	ppb
SO2	0.9	-2.6	4.4	4.7 ± 1.2	1.6	ppb
PM10	8.2	5.3	11.1	22.3 ± 5.3	7.4	µg/m3
PM2.5	14.7	12.3	17.1	11.9± 1.6	2.2	µg/m3

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Implications for Population Aggregate Birth Weight Changes of the Bell et al. (2007)

Results for Pollutant Potencies (gram Reduction in Mean Baby Weights Per Unit Exposure During Gestation) and Suggested Population Aggregate Impacts on Birth Weights

Air Pollutant	Indicated Potency in g Birth Weight Reduction per ppb Gas or (for Particles) µg/m3	Lower 95% Confidence Limit on Potency	Upper 95% Confidence Limit on Potency	Suggested Population Aggregate Effect (g/baby) (Potency X Mean Exposure)
NO2	1.85	1.46	2.25	32
CO	0.053	0.042	0.065	35
SO2				
PM10	1.1	0.7	1.5	25
PM2.5	6.7	5.6	7.8	80

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Implications for Information Inputs to Risk Management Decision-Making

- Increasingly cases such as airborne particles, ozone, and lead are forcing the recognition that even for non-cancer effects, some finite rates of adverse effects will remain after implementation of reasonably feasible control measures.
- Societal reverence for life and health means “doing the very best we can” with available resources to reduce these effects.
- This means that responsible social decision-making requires estimates of how many people are likely to get how much risk (for effects of specific degrees of severity) with what degree of confidence—in cases where highly resource-intensive protective measures are among the policy options.
- The traditional multiple-single-point uncertainty factor system cannot yield estimates of health protection benefits that can be juxtaposed with the costs of health protection measures.

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Motivation to Move On

- Younger generation of analysts will ultimately not tolerate older procedures that fail to provide a coherent way to use distributional information that is clearly relevant to the factual and policy issues.
- Younger generation of analysts will have greater mathematical and computational facility, particularly as biology becomes quantitative “systems biology” with quantitative feedback modeling--increasingly an applied engineering-like discipline.
- Legal processes will ultimately demand use of the “best science” as this becomes recognized in the technical community.
- Newer information/communication tools will foster increasing habits and demands for democratic accountability; experts worldwide will increasingly be required to expose the bases of their policy recommendations—leaving less room for behind-the-scenes exercise of “old boy” safety factor judgments.

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