

Multidimensional Risk Assessment

Modern Risk Analysis

- Has taken advantage of Epidemiology to derive true quantitative estimates of risk
- Has paid great attention to uncertainty and ways to quantify that
- We will argue we need to pay more attention to
 - Dose-Response
 - Equity

Estimated PM2.5-related premature mortality associated with incremental air quality differences between 2005 ambient mean pm2.5 levels and lowest measured level from the epidemiology studies or policy relevant background (90th percentile CI)

	Estimates Based on Krewski et al. (2009)		Estimates Based on
Air Quality Level	'79-'83 estimate (90th percentile confidence interval)	*99-'00 estimate (90th percentile confidence interval)	Laden et al. (2006) (90th percentile confidence interval)
10 μg/m ³ (LML for Laden et al., 2006)	26,000 (16,000—36,000)	33,000 (22,000—44,000)	88,000 (49,000—130,000)
5.8 μg/m ³ (LML for Krewski et al., 2009)	63,000 (39,000—87,000)	80,000 (54,000—110,000)	210,000 (120,000—300,000)
Policy-Relevant Background	110,000 (68,000—150,000)	140,000 (94,000—180,000)	360,000 (200,000—500,000)

Bold indicates that the minimum air quality level used to calculate this estimate corresponds to the lowest measured level identified in the epidemiological study

What's Missing?

- What if most of the excess deaths were in Diabetics?
- What if most of the excess deaths were in a few locations?
- What if the same people with high risk from particles had high risk from other exposures?

Assumptions in Risk Assessment

• Risk Independence

- Exposures and their effects are additive, no interactions
- Risk Averaging and Uniformity
 - Attributable Risk is enough, no susceptibility
- Risk Non-transferability
 - Risk applies to individual's exposure, not exposure of others
- Risk Synchrony
 - Effects don't depend on timing/cumulative exposure
- Risk Accumulation and Chaining
 - Overall risk in Population (from many exposures) matters

Dose-Response

- Recent NAS report recommends using Dose-Response curves instead of magic numbers
- Has important implications for risk assessment
- Many substances have no thresholds there are no magic numbers
- De Minimus is a fuzzy concept, depends on size of population exposed and who they are

Typically Assume





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Dose-Response between Blood Lead and IQ in 7 Pooled Birth Cohorts



What about Equity?

- Differential exposure can produce inequitable risk distributions
- Susceptibility can produce inequitable distributions of risk
- Differential exposure to susceptibility factors can increase the inequity
- High exposure to other risk factors can increase the inequity in environmental risk (cumulative risk)

Distribution of Risk by Location



Geographic Equity



Heart Attacks in Worcester



Intergenerational Risk



Bisphenol A



Factors Influencing Susceptibility

Lead Examples

Genetic Sources of Variable Response

•amino levulinic acid dehydratase: ALAD-2 allele
•apolipoprotein E (APOE): E4
•absence of dopamine receptor D4-7
•vitamin D B variant
•epigenetic processes:

•early life lead exposure over-expression in adulthood of amyloid precursor protein

•higher prenatal lead exposure level associated with reduced DNA methylation in cord blood

•Higher bone lead associated with reduced DNA methylation in blood in the elderly

Phenotypic Sources of Variable Response (host characteristics)

- Lead-associated decrement in renal function greater in patients with:
 pre-existing chronic kidney disease
 Diabetes
- Association between increased patella lead and autonomic dysfunction (heartrate variability) more pronounced in patients with metabolic syndrome

Psychosocial Sources of Variable Response

- In rats, maternal stress (novelty, restraint, cold):
 - impairs later learning in pups (schedule-controlled response)
 - increases pups' basal and stress-induced corticosterone response
- In nonhuman primates, stress increases mobilization of lead from deep body stores (e.g., bone)
- In humans:
 - Among men, inverse association between bone lead level and cognition more pronounced among those self-reporting greater stress
 - In older adults, inverse association between bone lead and cognition greater among those living in neighborhoods with more psychosocial hazards
 - In children, higher cord blood lead level associated with greater total peripheral (vascular) resistance response to acute stress

Socio-Economic Position As Source of Variable Response

 In rats, being raised in "enriched" environment mitigates lead-associated effects on spatial learning and normalizes gene expression in hippocampus (NMDA-R, BDNF)

• In humans:

- children from lower strata of SEP express leadassociated cognitive deficit at lower biomarker levels
- Impact of lead on children's end-of-grade reading scores more pronounced at lower than upper tail of distribution (i.e., among children other risk factors for poor performance)

Bi-directionality of Relationships

- contextual factors affect response to lead, but,
- lead exposure affects response to other factors:
 - as adults, rats exposed to lead in early life show reduced behavioral recovery to an induced ischemic stroke in hind-limb somatosensory cortex
 - early lead exposure impairs topographical reorganization of the barrel field (somatosensory) cortex following whisker follicle ablation

Air Pollution Examples

Effect of Particles on Heart Rate Variability by Genotype



Implications: A Simulation Study

- Take risk of MI by tertile of Income from Marmot analysis of Representative US sample
- Similarly Prevalence of Diabetes by tertile
- RR of MI for Diabetics from recent Danish Study
- Assume Diabetes doubles Particle risk, and so does some genetic profile

Distribution of Incremental Risk



Density

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MI Risk

Health/Equity/Cost Tradeoff



Figure 2. Annual mortality benefits and change in risk inequality for power plant control scenarios (A), along with distribution of risk for baseline conditions and selected control scenarios (B) (indicator = Atkinson index, $\varepsilon = 0.75$; pollutants = SO₂, NO₂, PM_{2.5}; baseline = PM-related mortality). Blue dots in A represent intermediate control scenarios, and letters represent defined scenarios listed in Table 1.

Methodological Issues

Effect modification: limits of conventional approach

- Low statistical power
- Limited functional forms
- Difficulty interpreting 3+ way interactions
- Misspecified "main" effects
- "Statistical interaction formulations are inadequate to capture the ecology of human development"* page 924

* Source: Evans GW. Dev Psychol 2003, 39:924-33.

Alternatives to interaction terms

- Cumulative risk model (Rutter 1983)
 - Sum discrete risk using standard threshold cutoffs
- Decision tree analysis (Breiman, 2001)
 - Assumes no explicit causal model, fully capture complex interactions
- Systems dynamics models (Galea, 2009)
 - Feed back, non-linearities
- Hierarchical (aka multi-level) models (Raudenbush & Bryk, 2002)
 - Nested data; cross-level interactions; random slopes to model risk heterogeneity
 - Model the social ecology of risk

Example: Multilevel (hierarchical models) for differential vulnerability

- Hypothesis: The effect of air pollution (PM₁₀) is exacerbated for residents of high crime neighborhoods due to prolonged exposure to psychosocial hazards
- Clustered data
 - 1000 individuals
 - 50 neighborhoods/communities
- Individually monitored PM₁₀ exposure – High (e.g., 90th percentile) vs. not-high



Visualizing random intercepts and slopes



Outcome variable Y_{ij}

Random intercepts and

 $\gamma_{10} = 5$

Model 2: Modeling cross-level interactions



Real world example: Environmental stress, lead and cognition

- Animal models show environmental stress worsens lead effect on brain/cognition
- The Baltimore Memory study
 - 1. 1140 community-dwelling adults aged 50-70 in 65 contiguous Baltimore neighborhoods
 - 2. Tibia lead measured using XRF spectroscopy
 - 3. Measure "environmental stress" (toxicology term) with a scale of neighborhood psychosocial hazards (social epidemiology term)
- Test this model:



Neighborhood psychosocial hazards exacerbate association of tibia lead on cognition



Source: Glass TA, et al. AJE 2009, 169:683-92.

_egend:

Highest tertile NPH score = _____ Middle tertile NPH score = _____ Lowest tertile NPH score = _____

Living beyond our means: Why not Measure what we Want?

- Traditional Regression analysis models the mean response in the population
- The risk in the population may be high for a small subset
- Quantile regression:
 - directly estimate the effect on 95th percentile of risk, rather than on the mean risk
 - Modeling multiple quantiles estimates the change in the distribution

Conclusions and Recommendations: Implications for Risk Assessment

 identification of most vulnerable subgroup of the population is a key step in risk assessment

•often, this is unknown or the subgroup is defined very broadly (e.g., the fetus, the young child)

•Our claim: finer distinctions in terms of magnitude or risk can and must be made within these broadly defined groups

•But better data are needed on the factors that modify vulnerability

What We Have Shown

- Substantial progress has been made in identifying factors that influence:
 - the magnitude of an individual's external dose to a toxicant
 - the association between external dose and internal or absorbed dose (toxicokinetics)
 - biological response at the critical target organ to the internal dose (toxicodynamics)
- Further, the the factors that influence these processes do not occur randomly in the population

Additional Implications for Risk Assessment

- uncertainty (or safety) factors are applied to a specified effect level (point of departure)
- purpose: to take account of considerations such as inter-species extrapolation (if relying on nonhuman data), inter-individual variability, database insufficiency, etc.
- specific value of the UF is arbitrary, defaults typically used (e.g., 10, 3, or 10⁻¹)
 - rather than applying an arbitrary UF, we need to move towards using data-driven estimates of this variability

Additional Implications for Risk Assessment

- in search for bases of inter-individual variability in vulnerability, most attention has focused on individual-level biological or genetic factors easy to measure, good tools available
- more attention is needed to "upstream" factors, the social, political, and economic processes that ultimately result in disparities in risks and health outcomes (i.e., multi-level thinking and modelling)