PUTTING EXPOSURE BACK IN RISK ASSESSMENT
OR: THE DOSE MAKES THE POISON

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Presented to The International Society of Exposure Science and The Society of Toxicology

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WHAT I WILL DISCUSS TODAY

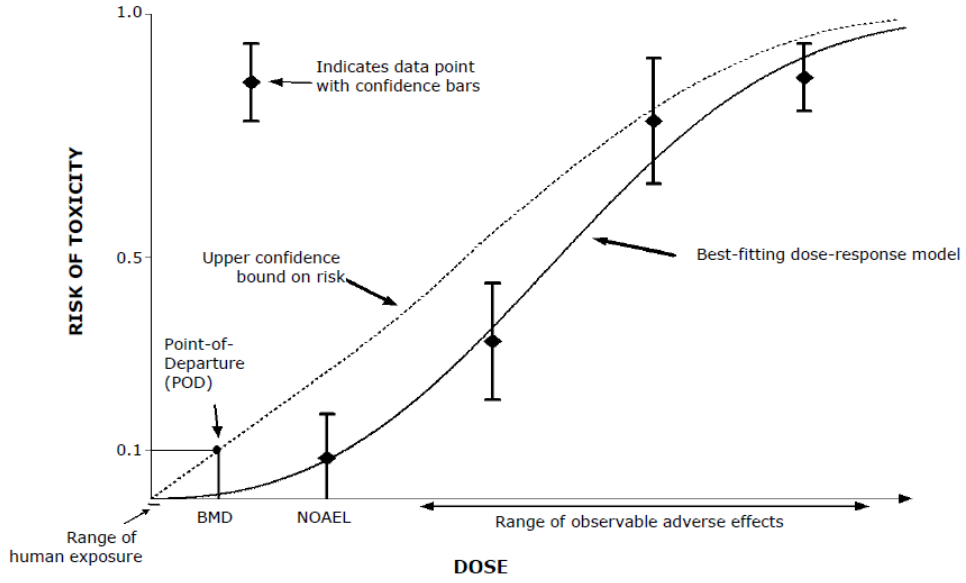
1. Origin and evolution of risk-based decision making for chemicals management
2. Growing appeal of hazard-based approaches
3. The important role of exposure in the risk assessment process
4. The pros and cons of risk- vs hazard-based assessments

SAFETY ASSESSMENT: FOOD SAFETY LAWS INTRODUCED A "BRIGHT LINE" APPROACH TO RISK-BASED DECISIONS

- Introduced in the 1950's by USFDA scientists
- Intended for decisions about:
  - Substances intentionally introduced into foods
    - Food additives
    - GRAS substances
  - Substances, the intentional use of which led to their presence in foods
    - Pesticides
    - Veterinary drugs for food-producing animals (introduction)
    - Components of food contact material

SAFE DOSES: ORIGINAL GUIDING PRINCIPLES FOR SAFETY ASSESSMENT

- Virtually all chemicals can cause some type of toxicity at sufficiently high doses
- Evidence can come from observational human studies (epidemiology), clinical studies (less common), animal studies, cell-based studies
- The rate of occurrence and severity of toxicity increases with increasing exposure (dose)
- Methods are available to identify doses at which toxicity is unlikely to be expressed ("safe dose")



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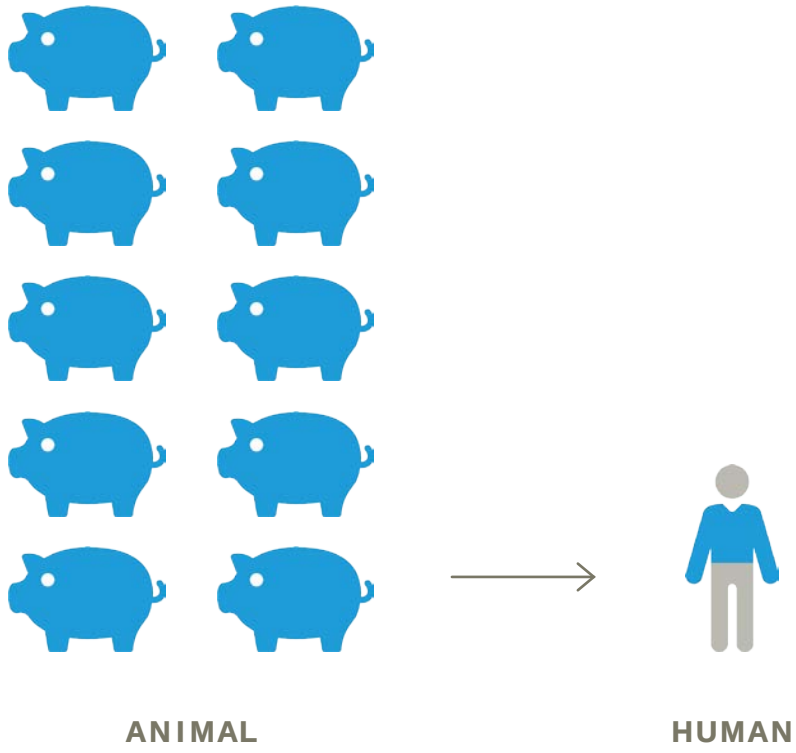
THE NOAEL (ORIGINALLY NOEL)

- Derived from empirical toxicity data showing the existence of thresholds for toxicity
- Various “safety factors” applied to come up with “allowable daily (human) intakes” (ADI)
- Allows for a threshold taking into account the diversity of sensitivity within the population
  - **10X**: animal to human
  - **10X**: susceptible populations



SAFETY APPLICATION

- When exposures exceed the ADI, they are considered to be a hazard
- Risks associated with the ADI were not quantified
- An important exception: **carcinogens!**
- USFDA took the position that this safety assessment model was not to be applied to carcinogens
  - Delaney clause (1958): No carcinogen could be introduced into food, directly or indirectly

EVOLUTION

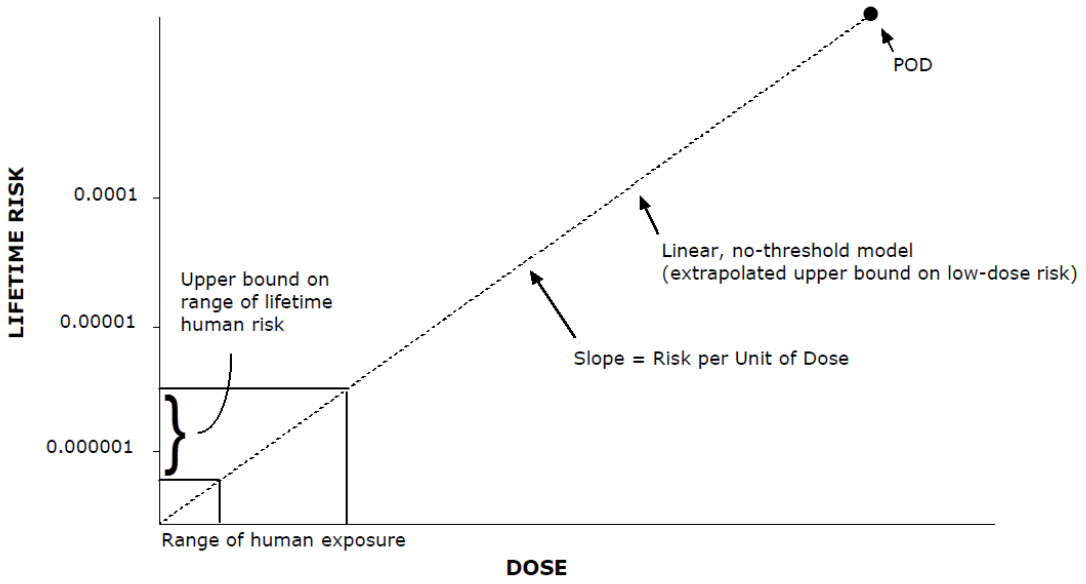
- The "**no safe level**" approach for carcinogens does not work well, as there are many, many known carcinogens
- Most exposures cannot be controlled as easily as intentional additions to food
- Early approaches: Best available control technologies (BACT)

- For non-carcinogens, how do you apply a simple "**bright-line**" approach to contaminants?
- What about substances that indirectly become components of food? Need to understand "**safe level**" in order to develop sufficiently sensitive analytical detection methods.

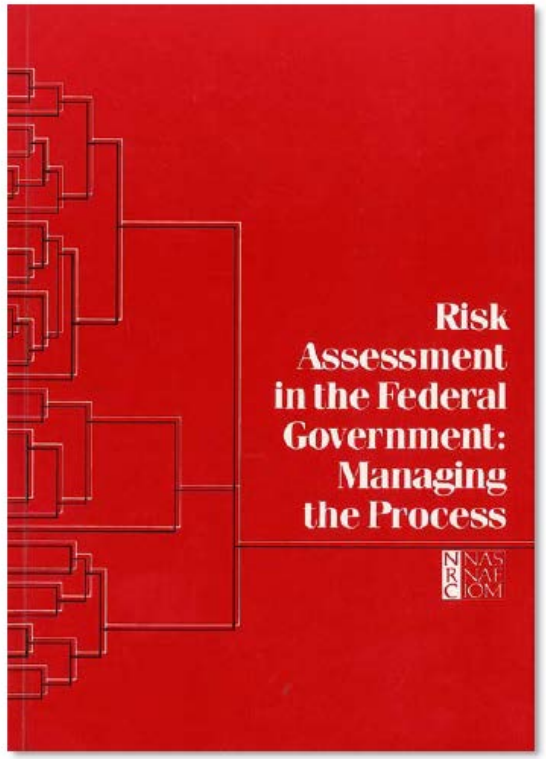
MID-1970'S: QUANTITATIVE RISK ASSESSMENT (QRA)

- In 1979, Interagency Regulatory Liaison Group set forth a method to conduct QRA for carcinogens.
- Safety defined by specifying residual risk that would be tolerated in different regulatory circumstances
  - Assumes no-threshold
  - Assumes linear dose-response
  - Develops upper-bound for cancer risks
- Leads to risk-based decision making

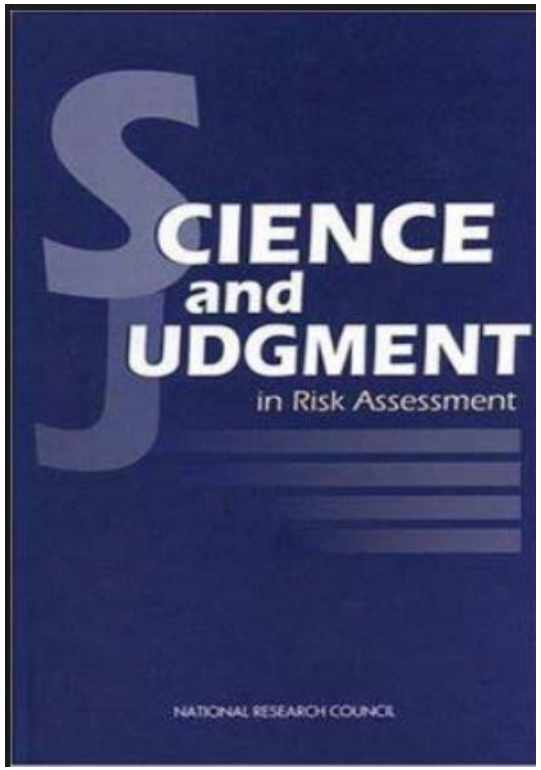
Close-up of extrapolation into low-dose region



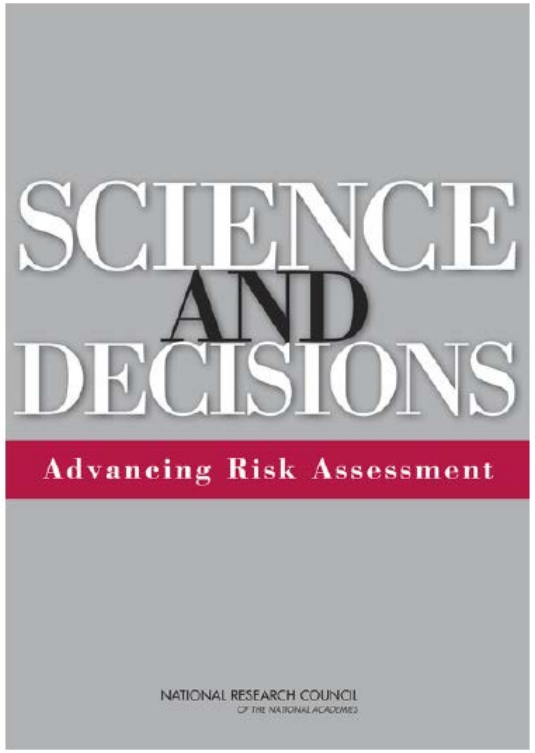
NAS: THE EVOLUTION OF RISK ASSESSMENT METHODS



1983



1994



2009

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IMPROVEMENTS ON BASIC RISK ASSESSMENT METHODS

- Incorporation of exposure science
- Risk assessment conduct
- Risk management principles
- Risk communications
- Systematic reviews and evidence integration approaches
- Problem formulation
- Use of mechanistic data
- Use of mode-of-action for toxicity
- Descriptions of uncertainties in risk calculations

BASIC RISK ASSESSMENT COMPONENTS
EXPOSURE & POTENCY

Exposure:

- The state of being in contact with something
- The degree of exposure

HAZARD ID RISK = f(EXPOSURE) X Potency

- How will people contact the chemical?
- What is the magnitude, frequency and duration of contact?

- What are the chemical's health effects?
- What is the relationship between exposure and health effects?

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THE SIMPLISTIC DEFINITIONS
CHEMICALS HAVE HAZARDS/HUMANS HAVE RISKS

Hazard (chemical):

- Source of potential damage, harm or adverse effects
  - Intrinsic characteristic or property of chemical
  - Independent of use or exposure

Risk (danger) for individual or population:

- Chance (probability) that a person or population will experience an adverse effect if exposed
  - Dependent on exposure occurrence
  - Characteristic of finished property or use

SHORT-CUT TO RISK

RISK ~ Any EXPOSURE OR Any HAZARD

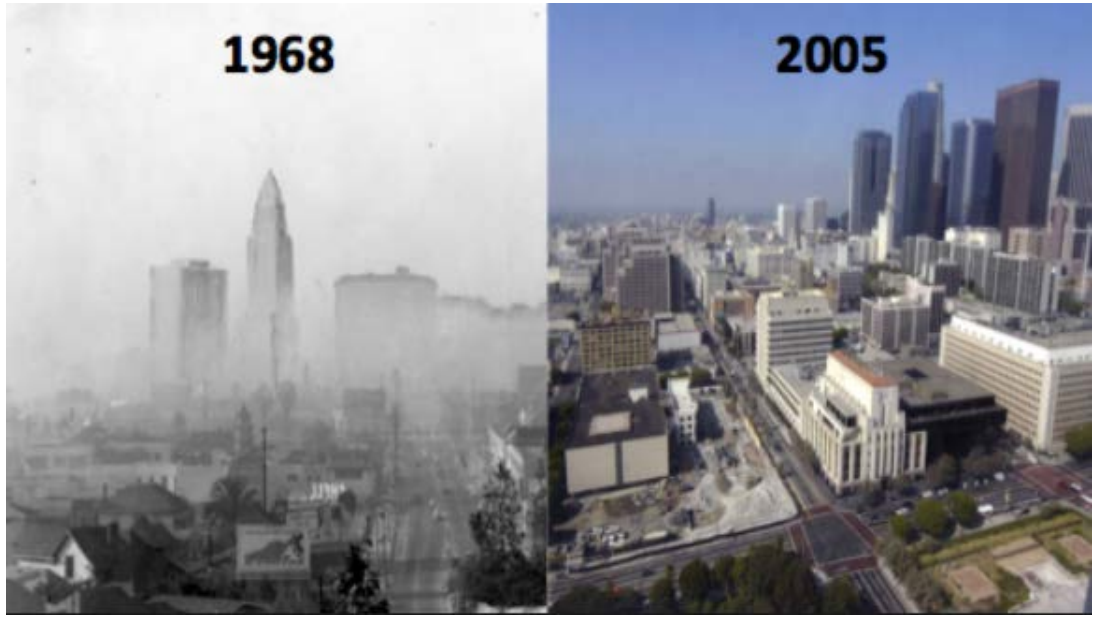
- How will people contact the chemical?
- What is the magnitude, frequency and duration of contact?

- What are the chemical's health effects?
- What is the relationship between exposure and health effects?

BUT HOW GOOD IS THIS ESTIMATE?

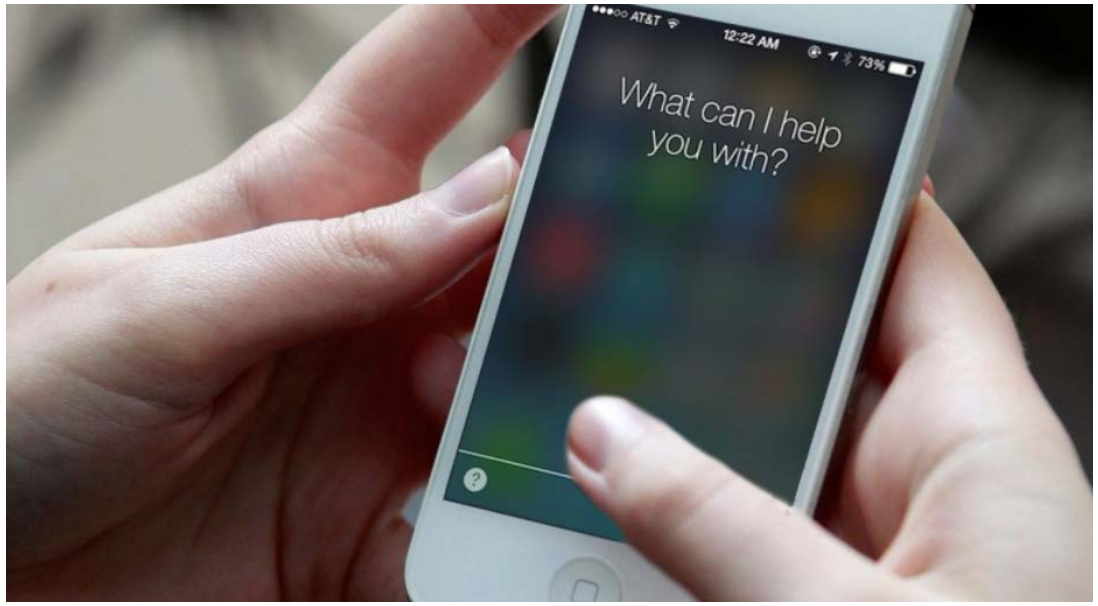
OUR WORLD IS BECOMING SAFER, BUT THAT IS NOT ALWAYS THE PERCEPTION

- US Programs show steady progress
  - Clean Air Act
  - Clean Water Act
  - Superfund
- But (in the US) common perception that the world is becoming **less** safe
  - Chemicals seen as among most significant hazards threatening health
    - Especially persistent chemicals, synthetic chemicals
  - Often just based on hazard (not exposure)



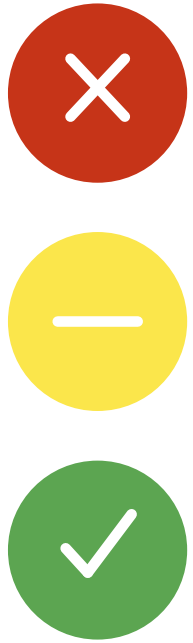
PERCEPTION AS THE NEW REALITY

- Misunderstanding of what hypothetical risks actually mean
- Credibility of government and science
  - Conflicting sound bites
- Uncommon incidents extrapolate to common
- Flow of information



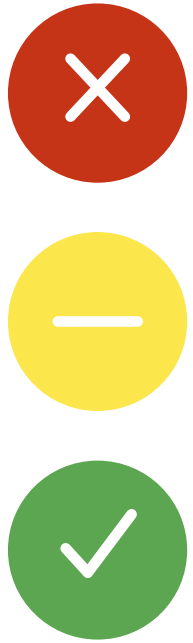
SO, SIMPLIFY!

- Remove the biggest complexity from the equation
  - Avoiding estimation of exposure and anticipated uses of products simplifies things
- Can characterize chemicals based on:
  - Type of health response (Carcinogenic, Mutagenic, Reprotox [EU])
  - Chemical properties (persistence, bioaccumulation)
  - Potency (relative toxicity) (Some do not even consider this: IARC, NTP)
- Create a list of “hazardous” chemicals
  - Simple
  - Easy to explain
  - Good/bad; red/yellow/green
- Eliminates discussions and debate about the complexities of risk



LEVELS OF HAZARD-BASED ASSESSMENTS

- Lists
  - Simplest chemical assessment mechanism
  - Specifies a number of chemical lists from several regulatory and/or nonregulatory sources.
  - Scoring a consumer product with a list-based tool straightforward
- Frameworks
  - Apply documented procedure for technical evaluation and systematic assessment, usually performed by tox experts
  - Identify endpoints for evaluation and use both lists and tox data
  - Strength of evidence approaches which only consider the positive evidence fit here (IARC, NTP) expert analysis
- Tools that rely on tox professionals to conduct the hazard assessment (manually or through software tied to database)



IN THE BEGINNING…

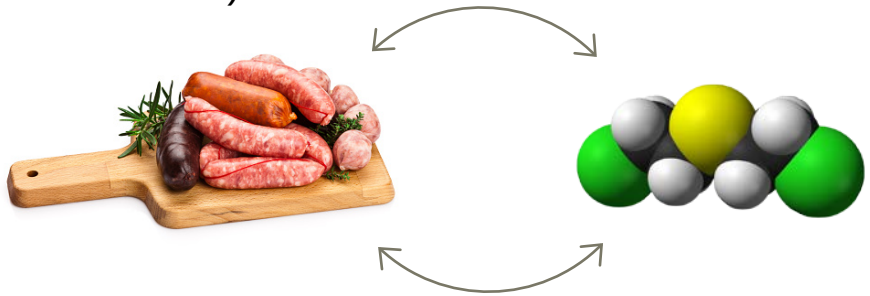
- Original intention of hazard-based approaches: raise warning flag for chemicals of potential concern: **Screening**
- Would lead to further evaluation
- However, warning flags may never be removed
  - Sometimes, even appear after more complete evaluation determines adequate risk management
- Evaluation often stops at classification; acceptability based only on hazard with no consideration of the potential risk under even extreme (though remotely possible) human exposures

THE PROBLEM…

- Places chemicals with widely differing potencies and very different modes of action into same categories
- Categorization can lead to unnecessary public anxiety
  - Divert resources better used addressing more substantial problems
  - Safe and useful products come under unnecessary and excessive scrutiny
  - Safe and useful products may even be replaced by other less characterized and potentially less safe products

Example

- Processed meat (consumption) and sulfur mustard gas are placed into the same category (Group 1) for cancer (by IARC)
- Leads to confusion: should we treat processed meat as we do sulfur mustard gas (reduce exposure to zero) or should we treat sulfur mustard gas as we do red meat (consider it part of a healthy lifestyle in moderation)?



THE PROBLEM…

- Ignores exposure potential
- Dose/response gets entirely left out of the picture
- Less informative; less detail to help decision makers

Examples

- Botulinum toxin (BoTox)
- Alcohol
- Water

INTERNATIONAL TREND TOWARD HAZARD-BASED DECISIONS

Evolution: the "**precautionary principal**"

- Starting in the mid-2000's
  - REACH-EU regulatory overhaul
  - Greener products initiative (EU)
  - Safer Choice (USEPA)
  - Consumer demand: marketing advantages, "seal of approval"
- Recent examples of more widespread use:
  - BPA (consumer driven)
  - Fracking (politically driven)

…BUT REALITY IS MORE COMPLICATED

- There is that pesky exposure element….

  …and the dose-response considerations!

- Does it really reduce risks?
  - What impacts on function, durability, cost, sustainability?
- There are trade-offs beyond toxicity of chemical:
  - Controlling pests that carry hazards of their own (Zika)
  - Keeping safety equipment affordable (car seats)
  - Making food affordable

- Resources spent replacing ingredients that might have already been safe
- **Even IARC's approach is criticized for being outdated***

*(Boobis, A.R., et al., Classification schemes for carcinogenicity based on hazard-identification have become outmoded and serve neither science nor society, Regulatory Toxicology and Pharmacology (2016), http://dx.doi.org/10.1016/j.yrtph.2016.10.014)

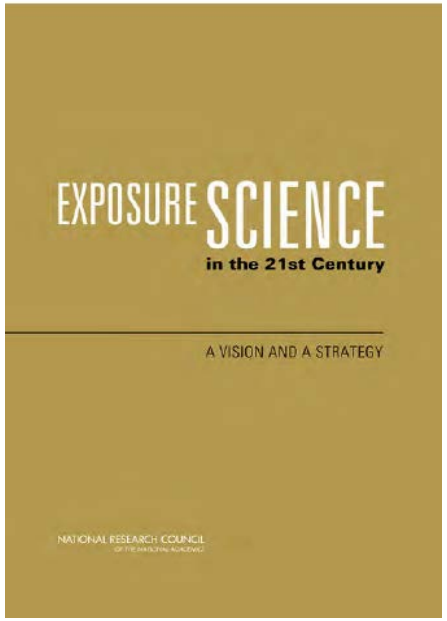
OVERVIEW OF RESULTS: DIFFERENCES IN TOOL FRAMEWORKS LEAD TO DIFFERENT SCORES

TOOL	GreenWERCS Walmart Scoring Model	GreenWERCS ChemRisk Model	GreenWERCS GreenScreen Scoring Model	GreenWERCS GreenScreen List Translator	GreenScreen Full assessment	GreenSuite adjusted	USEPA DfE AA Criteria	SciVera Lens
CHEMICAL	Generic Hazard Designation							
Caffeine	Low	Low	Moderate	Very high	High	Very high	High	High
Citric Acid	Low	Low	Low	Uncertain	High	High	Low High	High
Ethylene Glycol	Low	Moderate	Moderate	High	Very high	Very high	Moderate	Moderate
Glycolic Acid	Low	Low	Low	Uncertain	Very high	High	High Very high	Very high
DBP	Low	Moderate	Moderate	Very high	Very high	Very high	High Very high	High
BIT	Low	Low	Low	Uncertain	Uncertain	Very high	High Very high	Very high
HBCD	Low	Low	Low	Very high	Very high	Moderate	High Very high	Very high

Notes: 1. Tool names are those offered by the provider

Panko et al. 2016. Published open access in Integrated Environmental Assessment & Management at http://onlinelibrary.wiley.com/doi/10.1002/ieam.1757/abstract

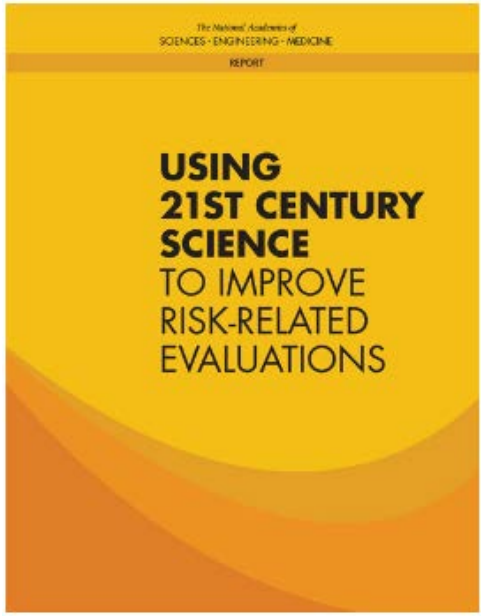
21ST CENTURY EXPOSURE SCIENCE



2012

Develops a framework for bringing exposure science to a point where it fully complements the hazard parameter of risk assessment

Focus is on advances in tools and technologies including sensor systems, analytical methods, molecular technologies, computational tools, bioinformatics



2017

Integration of new technologies into evaluating chemical risk

Discusses how traditional human health risk assessment will need to change to reflect new exposure science

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EXPOSURE AND ITS ROLE IN UNDERSTANDING RISKS

- Exposure science is the study of stressors, receptors and their interactions
  - Includes temporal and spatial aspects
- May take many forms:
  - Concentration
  - Duration
  - Dose (exposure dose, target dose, or external dose)

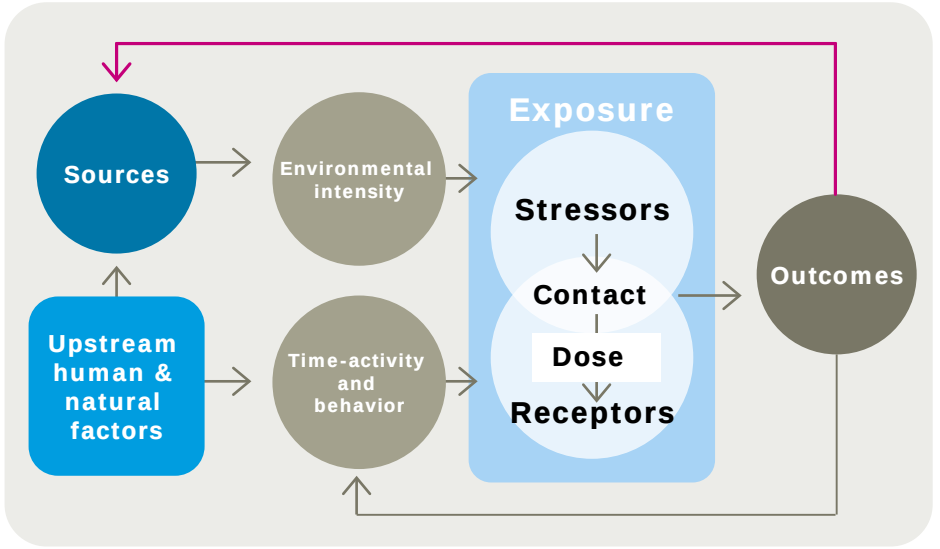

Figure 1-1 The classic environmental-health continuum.

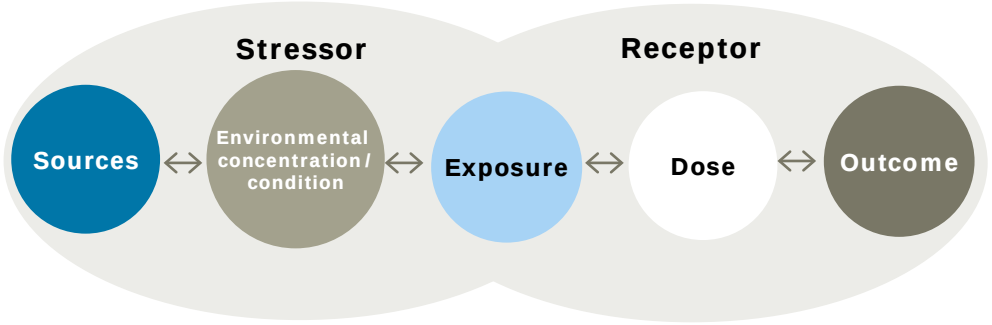

Figure 1-2 illustrates the revised version discussed in the present report.

Source: adapted from USEPA 2009a.

EXPOSURE SCIENCE IN THE 21ST CENTURY

Exposure science informs…

- Health and environmental sciences → require reliable quantitative data on human, ecosystem exposures
  - Air pollution epidemiology, risk assessment, health tracking, accountability assessments
- Market → require identification and control of exposures from the manufacture, distribution, and sale of products and services
  - Energy, transportation, healthcare
  - Limits liability for health and environmental damages; minimizes regulatory oversight
- Societal → aspirations of individuals and communities to maintain local environments, personal health, worker health (those who make consumables), health of global environment
  - Relies on health, safety and sustainability information
- Advances build confidence in exposure estimates used to support risk-based decision making by enhancing quality, expanding coverage and reducing uncertainty

BUT ALL OF THIS TAKES TIME AND DATA…

HAZARD-BASED APPROACHES

Pros

- Appear simpler (may not be)

No Hazard = Better

- Depends on easy-to-state (but difficult-to-achieve) element of scientific methodology
- May be a good screening step along the way (but not as an end game)
- Appealing to many; appear to be gaining strength

Cons

- Incomplete picture
- Characterizing hazard can mischaracterize risks
  - Example: “hazardous” substance that is in component or form where there are no exposures (internal component; polymer form)
- May make decision based on incomplete information
  - *In vitro* hazard evaluation? SAR?
- No information for decision-makers to assess ease/cost/variability of substitution
- **Unintended consequences!**

HAZARD-BASED APPROACHES
CONTINUED

Pros

Cons

- Eliminating or restricting chemical base on hazard does not necessarily mean product is safer
- Does not differentiate the seriousness of type of hazard (irritation versus cancer)
- Does not address comparison of chemical with risks at high dose from those with risks at low dose. All are equal!
- Does not work well for environmental contamination

Hazard ≠ Risk

HAZARD-BASED APPROACHES
CONTINUED

Pros

Cons

- Most legal requirements are risk based
- Deciding if a chemical is hazardous is a matter of judgement and science policy
- Conflicting information and data complicate the task
- Different experts can come to different conclusions with the same data

RISK-BASED APPROACHES

Pros

- Takes exposure into account
- Takes dose/response into account
- "**All things are poison and nothing is without poison; only the dose makes a thing not a poison.**" – Paracelsus
- Allows for a description of uncertainty
- Helps focus on the highest priorities
- Allows for a comparative toxicity approach

Cons

- Requires more data and analysis
- Offers more opportunities for scientific disagreement and debate → delays
- Depends on often-limited or absent data on human exposure
- Requires discussion of scientific uncertainty → difficult to do and hard for the public to understand
- Overall, difficult to communicate to the public

RISK-BASED APPROACHES
CONTINUED

Pros

- Minimizes the chances of substitutions causing unintended consequences
- Reduces opportunity costs in innovation
- More consistent with regulatory frameworks and legal liability standards
- Quantitative expressions of risk have more utility for decision making

Cons

CONCLUSIONS

Risk assessment has evolved over the years, starting formally in the 1950's

1

Risk assessment has matured, grown, as we understand the process and have more data

2

The complexity of risk assessment can be perceived as more "black box" – difficult to comprehend as well as explain – leading (in part) to increasing use of hazard-based approaches

3

Such hazard-based approaches leave out important considerations such as exposure, dose/response, and are inadequate to guide risk-management decisions

4

Modern strategies in a risk-decision framework provide clearer guidance, allowing informed risk-management decisions

5

Risk assessment approaches avoid unintended downsides of hazard-based decisions

The dose makes the poison!

6

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THANK YOU!

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Thanks to Bob DeMott, Joseph Rodricks and Robinan Gentry for content and discussion.

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