

Risk Assessment – Recognizing Hormesis

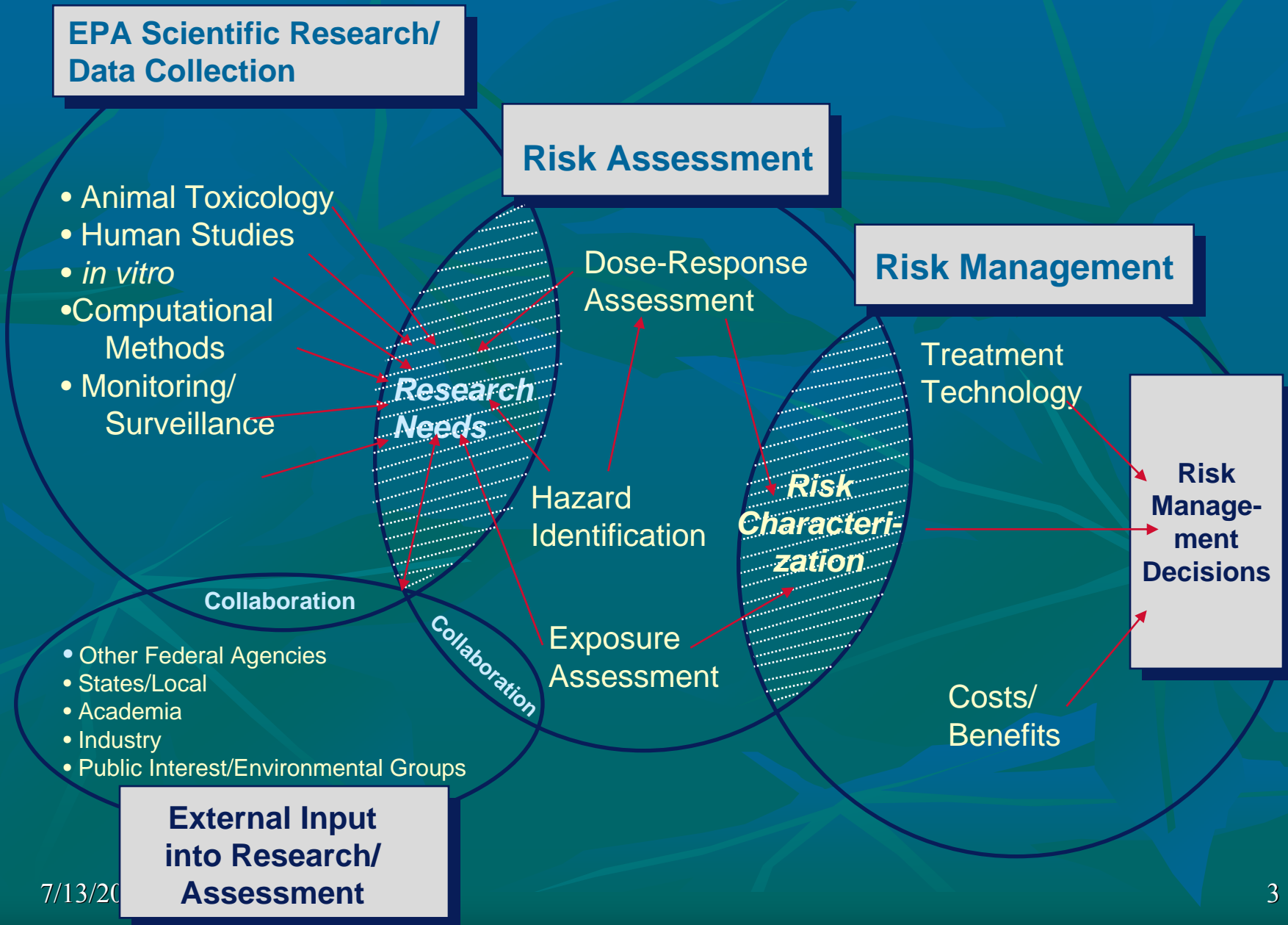
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Disclaimer

- The views expressed in this presentation are those of the author and do not represent the policy of the U.S. EPA.
- And this author stole the interesting material from Joyce Donohue, Ph.D., R.D.

Research ↔ Assessment ↔ Management



So What Is Science Policy?

- Science Policy is a means to carry on assessments in the absence of all the data one would wish
- It is not witchcraft, arbitrary and capricious, just made up



Science Policy at EPA

- Defaults, methods, Guidelines
- Used when there are data gaps
- Set by Science Policy Council – advised by Risk Assessment Forum, Programs, others
- Generally peer reviewed
- Lots of documentation, which is publicly available

Cancer Guidelines -- What's New

- Analyze data before invoking default options.
- **Mode of action is key in decisions**
- Weight-of-evidence narrative replaces the previous “A-B-C-D-E” classification scheme.
- Two step dose response assessment
 - Model in observed range
 - Extrapolate from point of departure
- Consider linear and non-linear extrapolation
- Address differential risks to children
 - Concurrent release of *Supplemental Guidance for Assessing Cancer Risks from Early-life Exposures*
 - Supplemental Guidance will be revised periodically

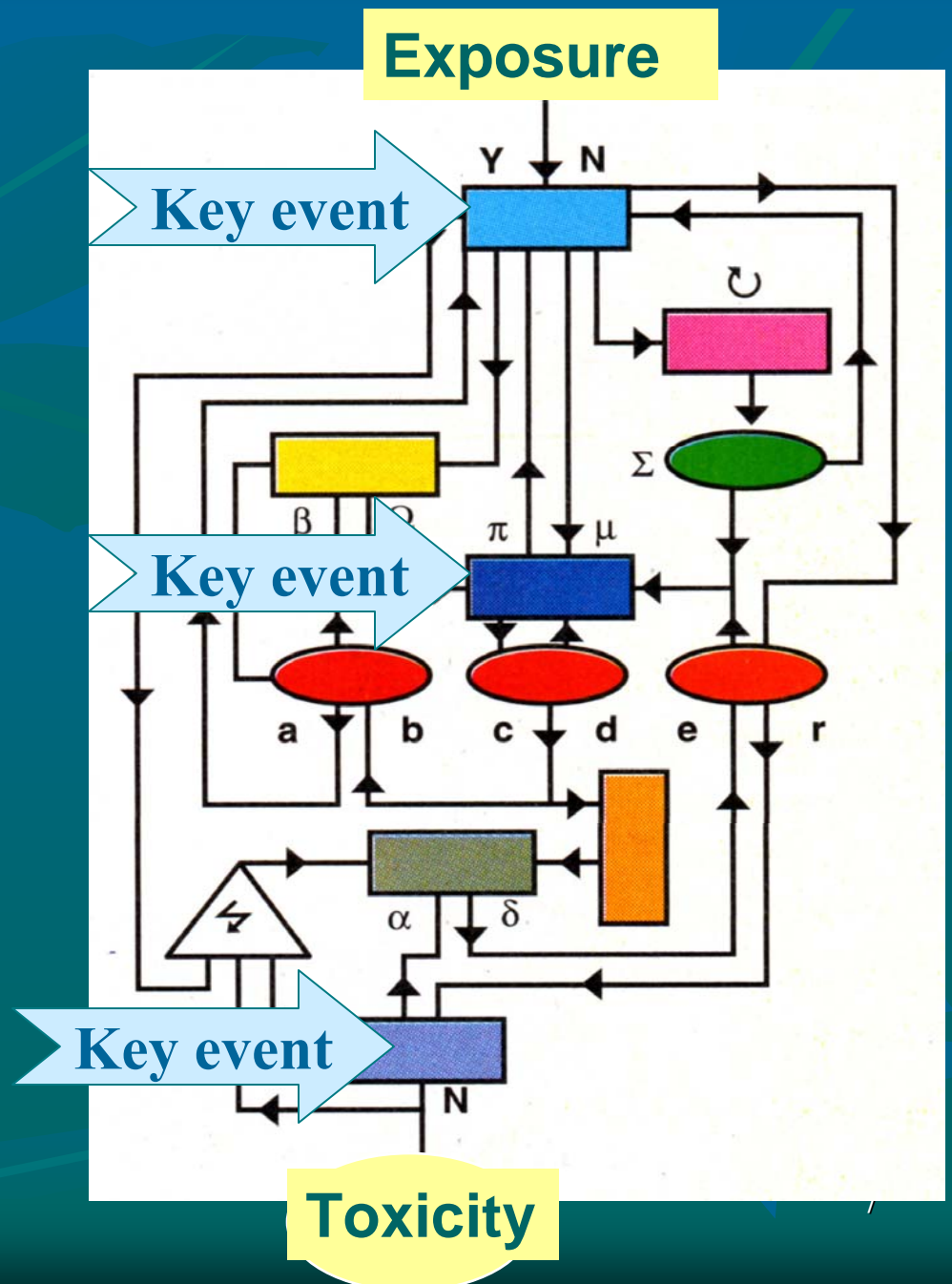
“Mechanism of action”

(more detailed understanding at biochemical & molecular level)

VS

“Mode of action”

(identification of **key** & **obligatory** steps)



What is Mode of Action?

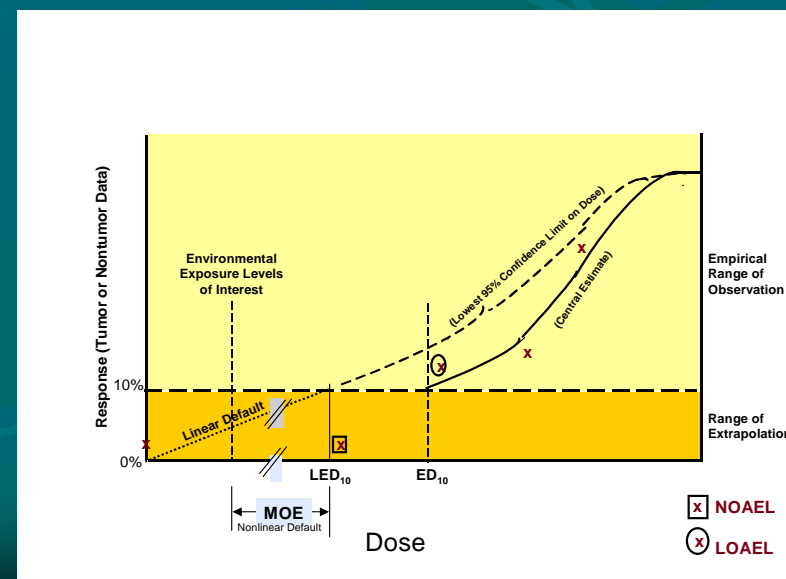
- . . . a sequence of **key events** and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. . . Mode of action is contrasted with “*mechanism of action*,” which implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode of action.

Mode of Action Framework

- Hypothesized MOA: summary description and identification of **key events**
- Experimental support:
 - Strength, consistency, specificity of association
 - Dose-response concordance
 - Temporal relationship
 - Biological plausibility and coherence
- Consideration of the possibility of other MOAs
- Relevance to humans

Why Do You Care about MOA

- MOA is key in Hazard Identification
 - Helps describe circumstances under which agent is carcinogenic (High dose? Route?)
 - Relevance of data for humans
- MOA determines choice of Low Dose Extrapolation



And You Care About Kids

- Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens – aka “Kid Guidance”
 - Effects observed in childhood
 - Early life exposures that contribute to later life effects



Kid Guidance – the Punch Line

- Use age-specific values for exposure and potency
- When data permit, develop separate potency estimates for childhood exposure
- In risk characterization, mutagenic MOA risk is increased by age-dependent adjustment factor (used with exposure info for age group)
 - <2 yrs old, 10 fold
 - 2 to < 16yrs, 3 fold
- No MOA, use linear extrapolation without ADAF; non-linear MOA, do not use ADAF

Use of Default Options

Analyze all data before using defaults

Analyze the available data

Is there too much uncertainty
or is critical information
lacking?

Invoke a
default option*

Y

N

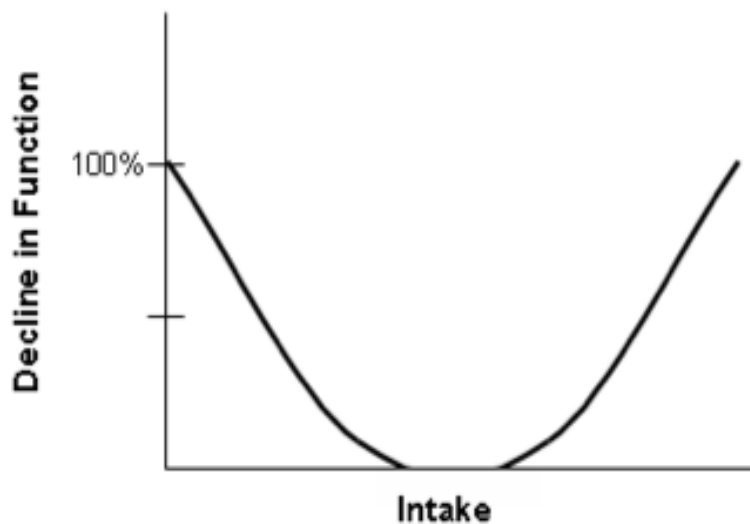
* *“The primary goal of EPA actions is public health protection, accordingly, as an agency policy, the defaults used in the absence of scientific data to the contrary³ should be health protective (SAB 1999).”*

Nutritionally Active Chemicals and Water

- Essential trace elements
 - e.g. Cu, Zn, Se, F, Cr, Mn, Fe
- Nonessential intermediary metabolites
 - Formaldehyde, acetaldehyde, glyoxal, Meglyoxal
- Alcohols, aldehydes and ketones that generate ATP
 - Ethanol, acetone, isopropyl alcohol
- Electrolytes (Na, SO₄)

The Hormetic Dose Response

Figure 1: Generalized Dose-response Curve for an Essential Nutrient

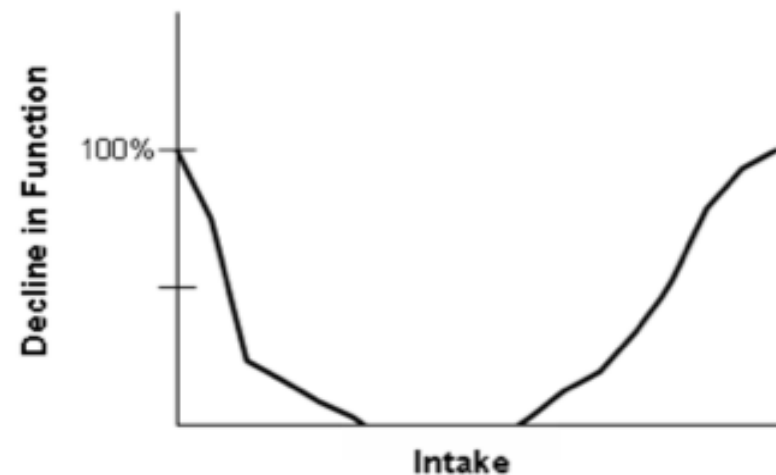


- The typical U-shaped DR curve does not show the severity of effect or organ system involved
- Endpoints are not necessarily symmetric

Conceptual Asymmetric DR Curve for Essential Nutrients

- Slopes of DR for endpoints may vary
- Progression from one measure of impairment to another may not be smooth.

Figure 2: Conceptual Asymmetric Dose-response Curve for an Essential Nutrient



Toxicity – What Is Acceptable?

- Only defined in law for cancer risk
 - Depending on statute and population, range is 10^{-7} to 10^{-4}
- For non-linear dose response, generally a safety assessment
 - RfDs, TDIs, ADIs, MRLs try to define level with no appreciable risk of deleterious effect
- For linear dose response for non-cancer . . . ?

Nexus of Nutrition and Toxicity

- Not likely to consider hormesis for mutagenic MOA carcinogens
- Point of departure for both will be some biomarker for adverse effect
 - Deficiency or
 - Toxicity
- Dietary Reference Intakes and toxicity (safety) assessment both proceed under data limitations and apply some variation of **uncertainty factors**
 - But adjustments are in the opposite direction

IOM Nutritional Guidelines

- RDA: avg daily intake sufficient for nutrient requirement of **97-98% of healthy people** (within life-stage, gender).
- EAR: avg daily intake to meet requirement for **specified indicator of adequacy** for 50% of healthy people (within life-stage, gender).
- AI: avg daily dietary intake for healthy people (within life-stage, gender). Done when **insufficient data for RDA**
- Tolerable Upper Intake Level

Differences between Nutritional and Toxicity Guidelines

- Nutritional
 - Directed toward specific life-stage, gender
 - Designed for healthy population
 - Daily intake
 - Developed only for necessary nutrients
- Toxicity
 - Specific exposure duration
 - Exposure in mg/kg body weight/day
 - Developed for any material likely to be toxic

Some Difficulties

- Differing philosophies of nutrition and toxicology communities complicates process of setting reasonable intake guidelines for essential nutrients
- If standard risk assessment procedures are applied without consideration of MOA, can get RfDs close to the RDA

Comparison: RfD and DRI

Table 1: Comparison of the Reference Dose with the Adults Recommended Dietary Allowance or Adequate Intake for Selected Trace Mineral Nutrients

Nutrient	RfD mg/kg/day	RDA or AI*	
		Adult mg/kg/day	Child (Age 1-3) mg/kg/day
Boron	0.2	NE	NE
Chromium (III)	1.5	0.0005*	0.0009*
Fluoride	0.06	0.05*	0.07*
Manganese	0.14	0.03	0.1
Molybdenum	0.005	0.0006	0.02
Nickel	0.02	NE	NE
Selenium	0.005	0.0007	0.002
Zinc	0.3	0.2	0.2

NE = None established

Body weights used for dose conversion :76 Kg for adults; 13 kg for a child.

Values for the RDA/AI have been rounded to one significant figure.

Whence Came these RfDs?

- RfDs for F, Mo, Mn, Se all based on human data
- All UF adjusted to avoid RfD lower than RDA or AI

RfD Examples

- **Mn**, POD is NOAEL for dietary study; no UF, even though this would be SOP. But would have resulted in $RfD < RDA$.
- **Zn**, several short term studies, LOAEL. UF of 300 would have been standard, but $UF = 3$, so RfD would not be $< RDA$
- Common sense vs common practice

RfD Examples: Comparison with Dietary Intake

■ Bo

- RfD = 0.2 mg/kg/day (rat fetal wt decrease)
- Dietary intake = 0.01 to 0.019 mg/kg/day
- UL = 0.33 mg/kg/day (for pregnant females)

■ Ni

- RfD = 0.02 mg/kg/day = 20 ug /kg /day (rat ↓ BW)
- Dietary intake = 1.1 to 5.8 ug /kg /day
- No UL

Why Are UL \neq RfDs ?

- ULs are somewhat higher than RfDs
- Slightly different methodology
 - IOM uses UF based on professional judgment
 - EPA uses \log_{10} or fractions thereof
 - Which is subject to the evolution of data derived UF
- IOM (1998) opined that large human database on levels of nutrients in foods allows for relatively low UF.

Joyce Recommends 1

- Consider whether nutrient is essential
- Determine range of dietary intake accommodated by homeostatic controls
- Use data-derived uncertainty factors rather than defaults

Joyce Recommends 2

- Avoid conflict between normal intake / nutritional guidance and safety assessment
 - Consider scenarios for which toxicity value does not apply
 - Describe those exceptions or
 - Use dietary intake data to determine uncertainty factors
- Recognize that non-essential nutrients in excess can have adverse effects
- Differentiate between point of contact effects and toxic dose

Joyce Recommends 3

- Consider relative source contribution
 - RfD is for the entire oral exposure
 - DRIs may benefit from consideration of source
 - Risk management should consider role of biouptake, bioaccumulation of mineral nutrients / contaminants
- Collaborate

Difficulties in Making Informed Adjustments to RfD

- Data at low dose are lacking for most chemicals other than essential nutrients
- Data are unlikely to be forthcoming
 - Would require major modifications to standard study designs – some of which are enshrined in either policy or regulation
 - Difficult to evaluate if a chemical is having a good effect in a standard testing protocol
 - Positive change in one parameter may be outweighed by negative change in another.

Questions?

- Please ask Beth Doyle or Joyce Donohue