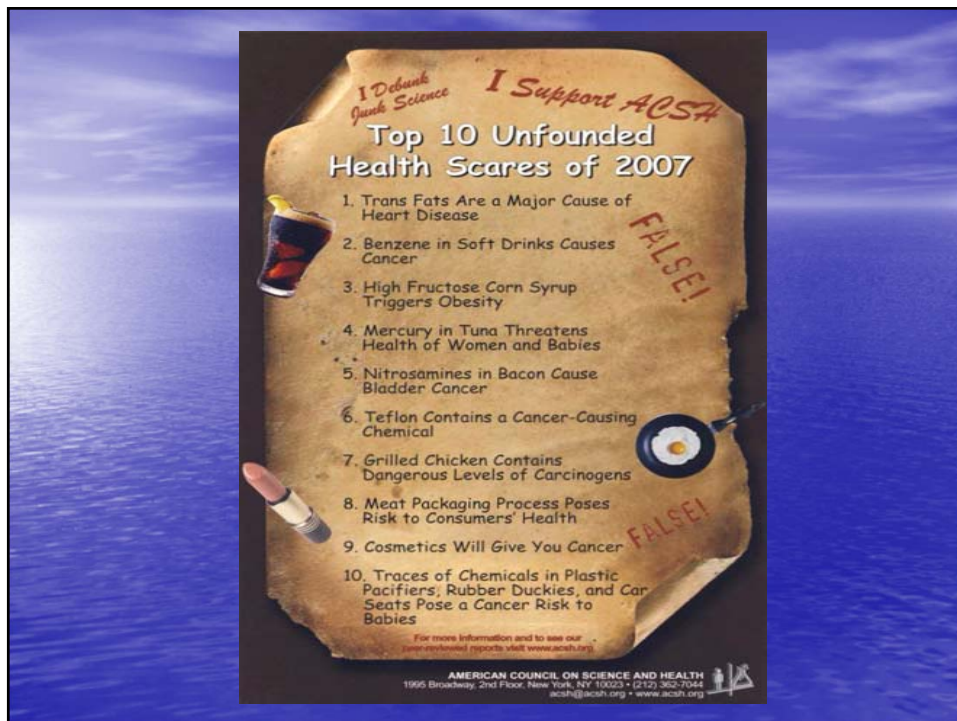


The Role of Science, Toxicology, and Risk Assessment in Evaluating Environmental Health Concerns

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Today's Focus

- Principles of toxicology/risk assessment
- Approaches to scientific study interpretation
- Causation vs association
- Regulatory frameworks

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Dose THE KEY CONCEPT in Toxicology



Father of Modern Toxicology

Paracelsus—1564

"All things are poisonous, only the dose makes it non-poisonous."

All chemicals—synthetic or natural—have the capacity to be toxic

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Dose

Determines Whether a Chemical Will Be Beneficial or Poisonous

	Beneficial Dose	Toxic Dose
Aspirin	300 – 1,000 mg	1,000 – 30,000 mg
Vitamin A	5000 units/day	50,000 units/day
Oxygen	20% (Air)	50 – 80% (Air)



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Dose

Woman Dies after Water-drinking Contest: Water Intoxication eyed in 'Hold Your Wee for a Wii' contest Death

SACRAMENTO, California—A woman who competed in a radio station's contest to see how much water she could drink without going to the bathroom died of water intoxication, the coroner's office said Saturday.

AP Associated Press

Updated: 10:24 p.m. ET Jan 13, 2007



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Risk

The likelihood of injury or disease resulting from exposure to a potential hazard

Evaluation of risk embodies all the basic concepts of toxicology



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Risk Assessment Paradigm

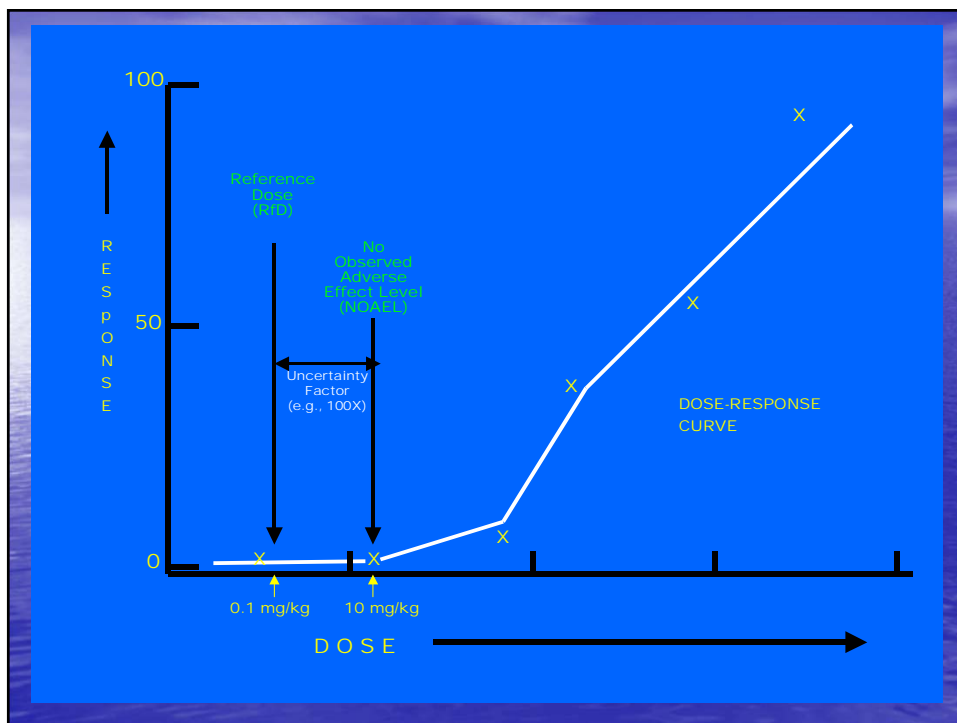
- Hazard identification
- Dose-response
- Exposure assessment
- Risk characterization

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Hazard Identification

- Every chemical has a toxicological profile
- Chemicals are not capable of causing everything
- Benzene causes leukemia, not lung cancer
- Thalidomide is a teratogen, not a neurotoxicant

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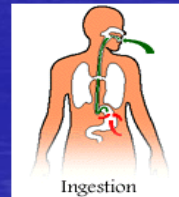
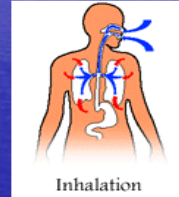
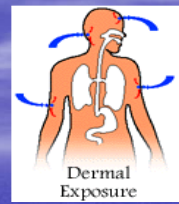


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Exposure

Route of Exposure

- The **route** (site) of exposure is an important determinant of the ultimate **dose**—different routes may result in different rates of absorption.
 - Dermal (skin)
 - Inhalation (lung)
 - Oral ingestion (Gastrointestinal)
 - Injection
- Toxic effects may be local or systemic



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Exposure

Sources of exposure to chemicals

- Environmental, including home and school
- Occupational
- Therapeutic
- Dietary
- Accidental
- Deliberate



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Naturally Occurring Mutagens and Carcinogens in Foods

- Aflatoxin (nuts) - mutagen/rodent and human carcinogen
- Benzene (butter, coffee, roast beef) – rodent carcinogen
- Coumarin (cinnamon) – rodent carcinogen
- Ethyl alcohol (bread, red/white wine) – rodent/human carcinogen
- Furan and derivatives (onions, celery, mushrooms) - mutagens
- Heterocyclic amines (roast beef, turkey) – mutagens, rodent carcinogens
- D-limonene (black pepper, mangoes) – rodent carcinogen
- Psoralens (celery, parsley) – mutagens; rodent/human carcinogens
- Quercitin glycosides (apples, tea, tomatoes) – mutagens/rodent carcinogens
- **Dose levels/exposures to humans typically do not reach those required to elicit toxicological effects in laboratory animals**

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International Agency for Research on Cancer – List 1 Known Human Carcinogens

- Alcoholic beverages
- Mineral oils
- Outdoor air pollution
- Painters (workplace exposures)
- Processed meat
- **IARC uses hazard only - exposure not considered as is done by EPA**

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Current Health Concerns

- Glyphosate
- Bisphenol A
- PFAS compounds
- Pharmaceuticals in the environment
- Vaccines (autism)
- Heavy metals, PCBs, dioxins, asbestos

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Chemical X in the Environment – How do we Evaluate Health Risk

- Toxicological Profile – animal studies
- Epidemiological evidence
- Exposure to humans – routes/amount
- Metabolism/detoxification
- Mode of action – relevance to humans

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Evaluating a Scientific Study

- Are the study data accessible?
- Peer-reviewed publication
- Sound methodology (GLP)
- Do conclusions reflect the data
- Reproducibility/verification

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The Importance of Context

- Evidence – in vitro, animal, human
- Experimental doses vs. human exposure
- Relevant route of exposure?
- Relevant toxicological mechanism?

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Saccharin – Relevance for Humans?

- Bladder cancer in male rats – high doses
- FDA urges ban
- Congress requires warning labels
- *However...*
- *Human evidence fails to link saccharin and cancer*
- *Rat-specific mechanism demonstrated, one not relevant to humans*

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Scientific Weight of Evidence

- Considers all available data (+ and -)
- Human, animal, in vitro, in silico evidence
- Consistency in reporting
- Human exposure levels
- Exposures relative to regulatory limits

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Causation

- Not the same as association
- Associations are the norm
- Separating fact from speculation
- Causation based on successfully meeting specified criteria

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Demonstrated Causal Effects

- Lung cancer (tobacco smoke)
- Skin cancer (excessive uv rays)
- AIDS (virus)
- Heart disease (diet, genetics)

Linkage between risk factor and effect

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Love Canal (1978)

- Odor complaints from landfill
- Unsubstantiated health claims; EPA reports chromosome damage
- Media frenzy; 2500 residents relocated - \$30 million
- EPA studies determined to be flawed; NYDOH, CDC, AMA, and NRC could not demonstrate abnormal health trends
- Causation not demonstrated
- Spurred the birth of Superfund

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Remembering Regulations

- Regulation by EPA, FDA, USDA
- Extensive toxicological testing
- Risk assessments performed
- Safety factors for inter/intraspecies differences and extra factor for women/children (pesticides)
- Significant margins of exposure/safety

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Safety Embedded in Regulation

- Bisphenol A (BPA):
 - Acceptable chronic daily exposure is 0.5 mg/kg/day
 - Includes a 1000-fold MOE (safety factor) below the LOEL in animal studies
- PBDE (BDE-99) flame retardant:
 - Acceptable chronic daily exposure is 0.0001 mg/kg/day
 - Includes a 3000-fold MOE (safety factor)
 - Based on study employing single oral doses of pure material by gavage

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PFAS

- Thousands of compounds – little toxicity, exposure, risk information
- Top priority for EPA
- Traditional approaches for toxicity evaluation along with NAMs
- Animal studies indicate reproductive, developmental, liver, kidney, immune endpoints
- Epidemiology studies - increased cholesterol with limited findings for thyroid, birth weights, immune effects
- EPA research focused on high-throughput assays for a range of endpoints and then targeted in vivo studies based on screening results, exposure, prioritization
- <https://www.epa.gov/pfas>

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PFAS – EPA Research Program

- [Environ Health Perspect.](#) 2019 Jan;127(1):14501. doi: 10.1289/EHP4555.
- **A Chemical Category-Based Prioritization Approach for Selecting 75 Per- and Polyfluoroalkyl Substances (PFAS) for Tiered Toxicity and Toxicokinetic Testing.**
- [Patlewicz G](#)¹, [Richard AM](#)¹, [Williams AJ](#)¹, [Gulke CM](#)¹, [Sams R](#)¹, [Lambert J](#)², [Noyes PD](#)³, [DeVito MJ](#)⁴, [Hines RN](#)⁵, [Strynar M](#)⁶, [Guisseppi-Elie A](#)⁶, [Thomas RS](#)¹.
- ORD – National Center for Computational Toxicology

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Advancements in Toxicology and Risk Assessment

- Problem formulation
- 3R Principles – New approach methods
- Genomics
- Mode of action research
- Refined exposure
- Modeling/Monitoring/Biomonitoring

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Summary

- Omnipresent environmental and health concerns that demand input from science
- Seek objective, verifiable data
- Risk = Hazard + Exposure
- Always consider human context/exposure
- Regulatory limits include significant MOEs