Basics and Applications of Risk Assessment in Environmental Challenges

Abdel-Razak Kadry, DVM, PhD, DABT
Center of Computational Toxicology and Exposure, ORD, USEPA, Washington, DC, USA

International Conference on Risk Assessment of Environmental Genotoxicants, Cairo, Egypt
December 21, 2019

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency

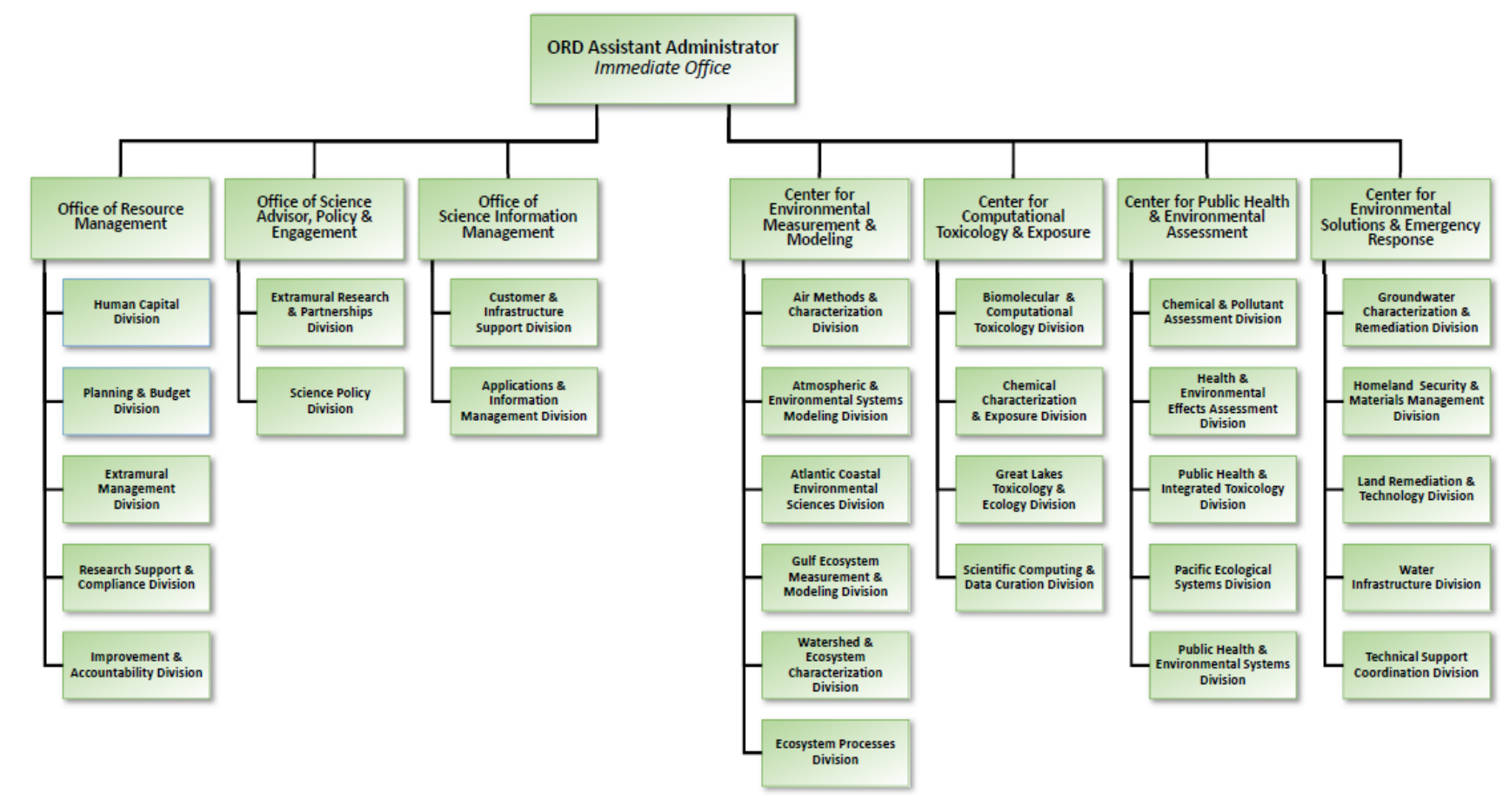
The mission of the Environmental Protection Agency is to protect human health and the environment.

EPA's Office of Research and Development (ORD)

- ORD provides the data, tools, and information that form the sound scientific foundation the Agency relies on to fulfill its mission to protect the environment and safeguard public health.

- The office is organized into four different research Centers and four different Offices that work collaboratively to facilitate a seamless, efficient structure focused on delivering research results that have immediate impact for our partners across EPA and the nation.

EPA's Office of Research and Development (ORD)



The Center for Computational Toxicology & Exposure (CCTE)

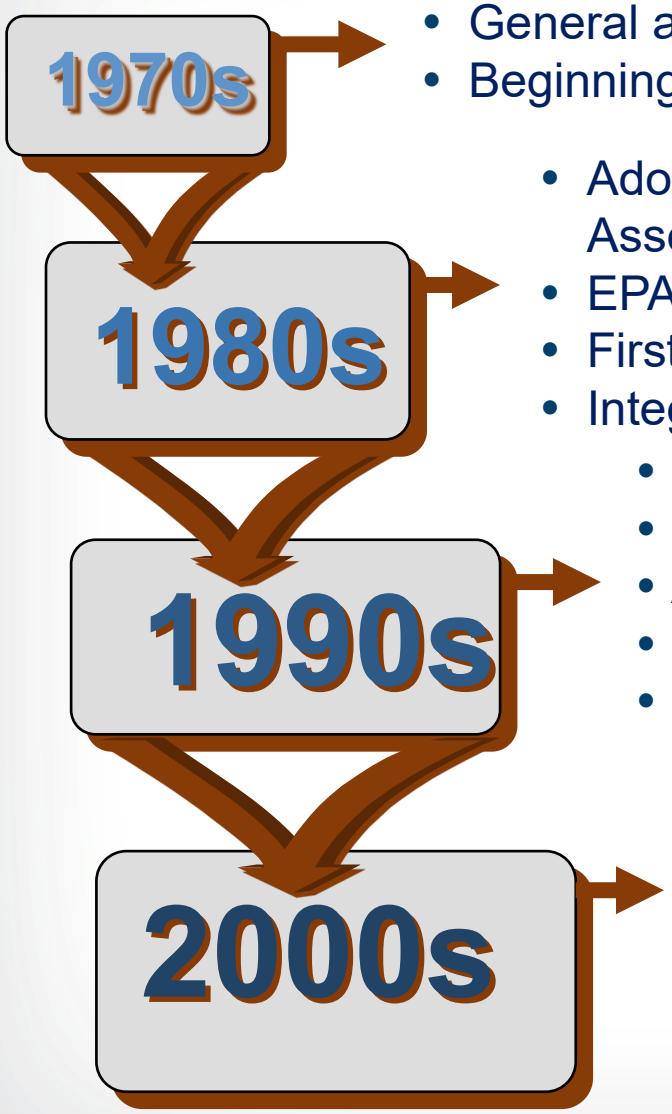
CCTE research strives to:

- Reduce the time required to thoroughly test chemicals and other emerging materials for human health and ecological toxicity from years to months.
- Expand our understanding of quantitative human and ecological exposures for thousands of chemical substances and emerging materials.
- Develop a comprehensive information system that contains relevant actionable chemical safety and ecological data with the software tools to integrate them for a range of human health and environmental decisions.
- Reduce the time required to characterize freshwater ecosystems and project the future state of ecological condition and ecosystem services from decades to years.
- Demonstrate translation of CCTE data, models, and tools into regulatory decisions by EPA Program Offices, EPA Regions, and States to protect human health and the environment.

Risk Assessment is Critical to U.S. EPA Regulatory Decision-Making

- U.S. EPA is both a regulatory agency and a science agency
- U.S. EPA operates under many laws that require the assessment of potential risk from exposure to environmental contaminants (*e.g.*, Clean Air Act, Safe Drinking Water Act)
- Risk assessment remains fundamental to major programs in the Agency (water, air, waste)
- Evolving in the face of new understandings about uncertainty, mode of action, metabolism, susceptibility, etc.
- Addressing emerging science and new science challenges

Risk Assessment -- Maturing and Evolving



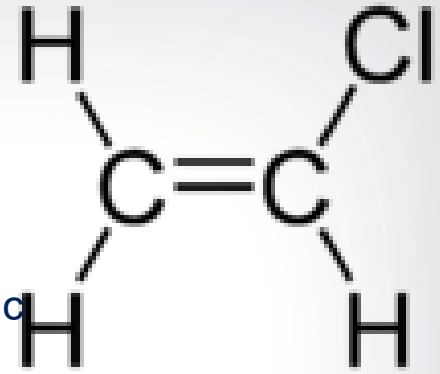
- Beginnings of the field of risk assessment
- Emphasis on oral route
- General acceptance of Safety Factors (10x10)
- Beginnings of cancer guidelines

- Adopt National Academy of Sciences' Risk Assessment/Risk Management paradigm
- EPA publishes five risk assessment guidelines
- First paper on Reference Dose (RfD)
- Integrated Risk Information System (IRIS)
  - Inhalation Reference Concentration (RfC)
  - Oral RfD methodology
  - Applications of PBPK models
  - BBDR models developed
  - BMD models developed and applied

- Examination of non-cancer methods
- Revised cancer guidelines, including MOA
- Susceptible populations
- Cumulative assessment approaches
- Probabilistic approaches
- Uncertainty analysis
- ***Emerging issues: biofuels, nanoparticles, "omics"…Next Generation Risk Assessment***

National Research Council (NRC) Publications on Risk Assessment

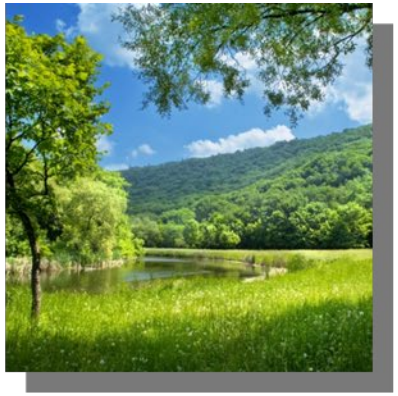
- 1983: *Managing the Process* – the "Red Book"
- 1989: *Improving Risk Communication*
- 1994: *Science and Judgment* – the "Blue Book"
- 1996: *Understanding Risk*
- 2007: *Toxicity Testing in the 21st Century*
- 2008: *Phthalates and Cumulative Risk Assessment*
- 2009: *Science and Decisions* – the "Silver Book"
- 2011: Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde
- 2013: Environmental Decisions in the Face of Uncertainty
- 2014: Review of EPA's Integrated Risk Information System (IRIS) Process



- 1970: EPA established
- Most vinyl chloride is used to make polyvinyl chloride (PVC) plastic and vinyl products.
- Reports of cases of liver cancer (many resulting in death) in workers at vinyl chloride facilities were reported in the media in the early 1970s. Some cases of angiosarcoma were reported in people who lived in the vicinity of facilities producing vinyl chloride.
- 1975: First EPA chemical assessment (vinyl chloride)
- OSHA lowered permissible levels protecting workers, and EPA assessed the need to limit emissions of vinyl chloride into the air from these facilities.
- EPA published the "Quantitative Risk Assessment for Community Exposure to Vinyl Chloride."
- Current OSHA is 1 ppm . 5 ppm [15-minute]
- Followed in 1976 by "Interim Procedures and Guidelines for Health Risk and Economic Impact Assessments of Suspected Carcinogens" published by EPA Administrator (these were not formal guidelines or policy, but were the beginnings of such guidelines)

"Risk Assessment" is Contextual

Engineering/
Structural



Ecological

Financial/
Business

Security:
Vulnerability
and Threat

Human
Health

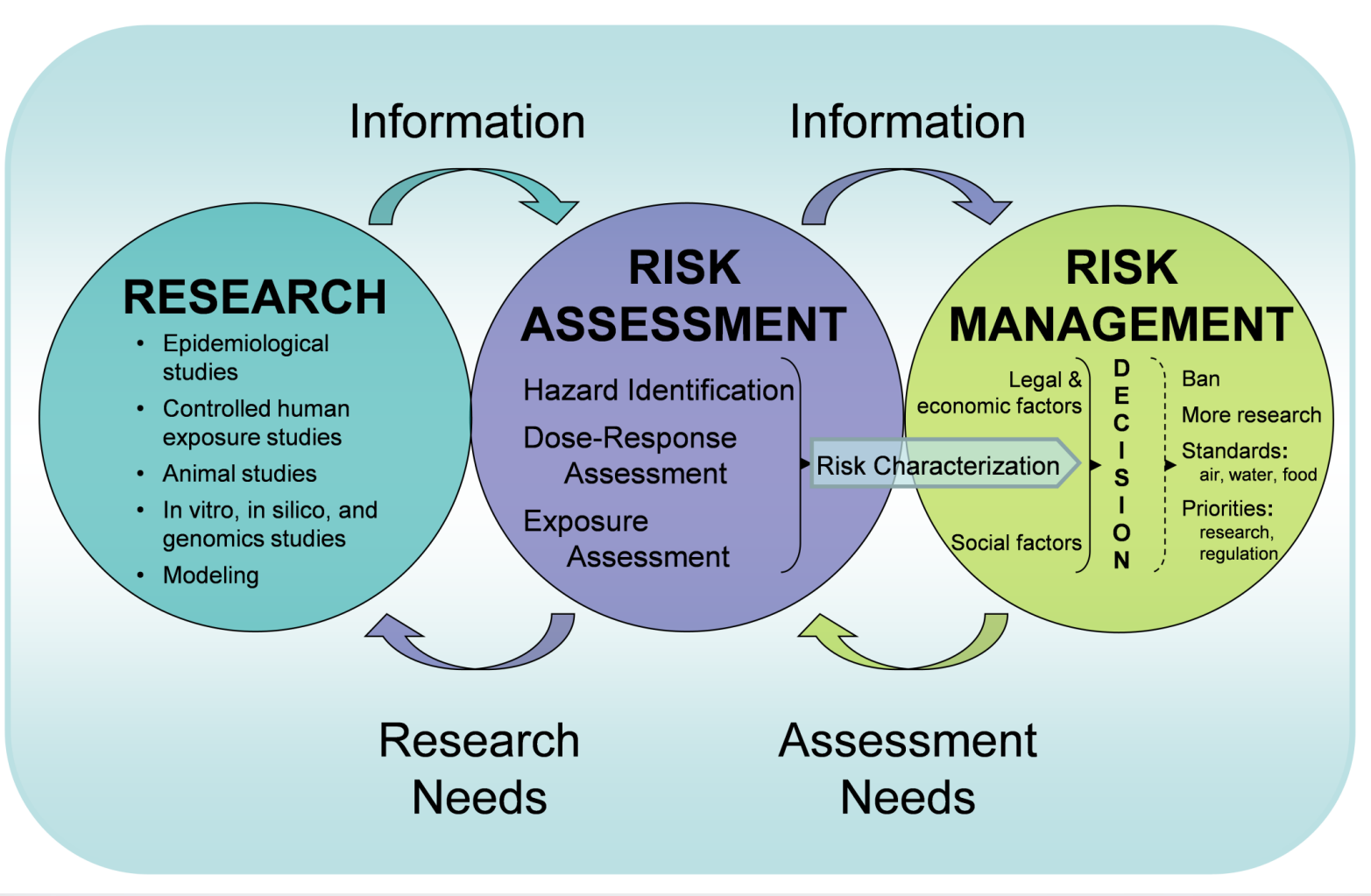
EPA Definition of Risk Assessment

Risk assessment:

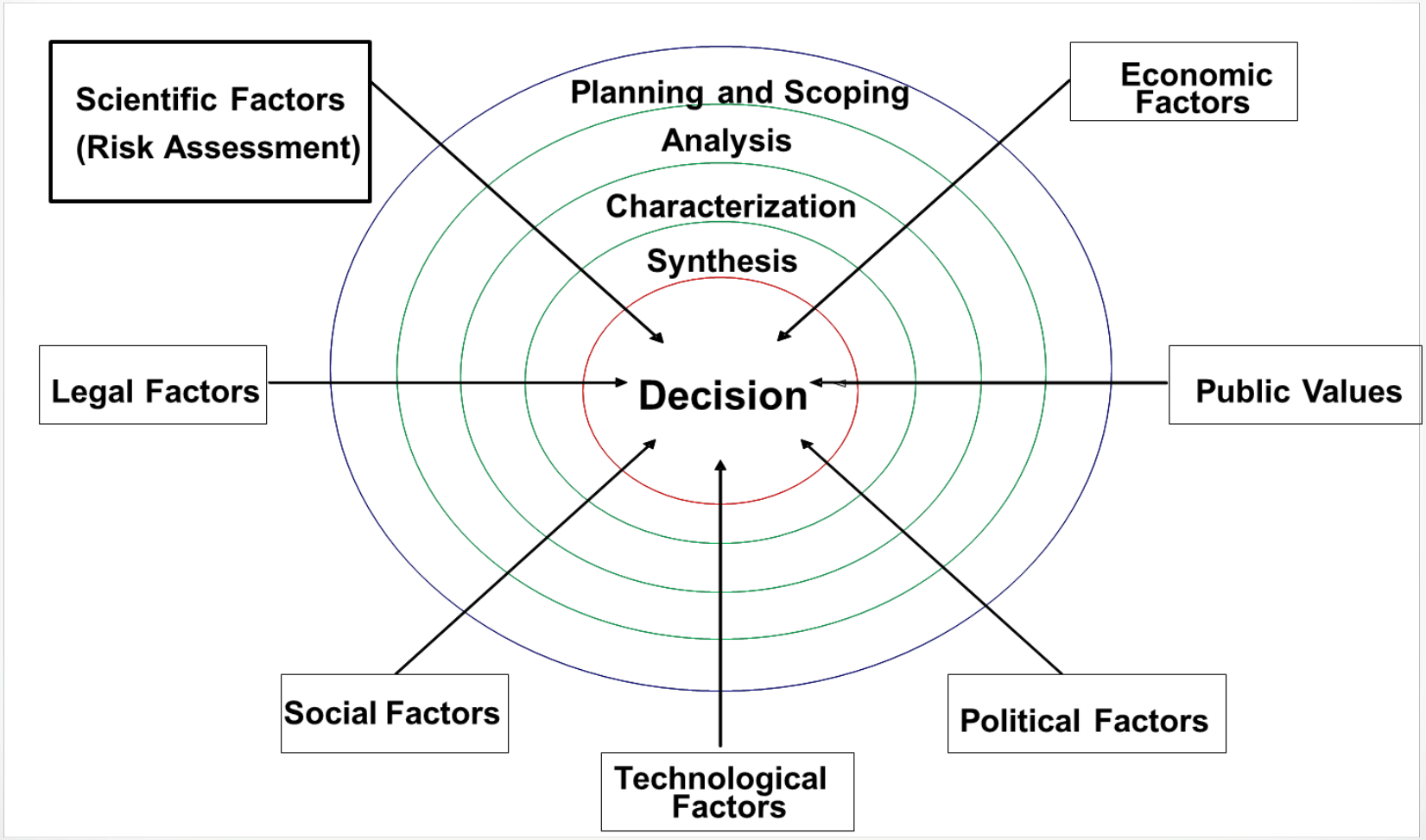
Qualitative and quantitative evaluation of the risk posed to human health and/or the environment by the actual or potential presence and/or use of specific pollutants

From EPA's "Terms of Environment" Glossary

Risk Analysis Paradigm



Risk Management Decision Framework



For a Risk to Occur…

1. A hazard must exist, and

2. Exposure must take place

Integrated Risk Information System (IRIS)

IRIS assessments:

- Provide scientific information on potential adverse health effects that may result from exposure to chemical substances found in the environment; developed according to EPA guidelines for health risk assessment.
- Include oral reference doses and inhalation reference concentrations for non-cancer endpoints.
- Provide a weight of evidence descriptor (e.g., carcinogenic to human) and include oral slope factors and inhalation unit risks for cancer endpoints.
- EPA risk assessors combine IRIS toxicity values with scenario-specific exposure values to estimate risk; used for risk-based decision-making.
- Foster consistent risk assessments across EPA Programs and Regions; available to U.S. States and local communities, international community and private sector

www.epa.gov/iris

Integrated Science Assessments (ISA)

Integrated Science Assessments:

- Provide the scientific basis for the National Ambient Air Quality Standards (NAAQS) for the six criteria air pollutants.

- Evaluates and integrates evidence from across scientific disciplines – atmospheric sciences, dosimetry, exposure, toxicology, controlled human exposure, epidemiology, ecology or welfare effects.

- Conclusions, causal judgments (e.g., “causal relationship,” “likely to be a causal relationship,” “suggestive evidence of a causal relationship,” “inadequate to infer a causal relationship,” and “not likely to be a causal relationship”) drawn for health and ecological or environmental effects.

- Are vetted through a rigorous peer review process, including review by the Clean Air Scientific Advisory Council and public comment periods.

Provisional Peer Reviewed Toxicity Values (PPRTVs)

- Provide hazard and dose-response assessments for chemicals of concern at Superfund sites when values are not available in the IRIS database

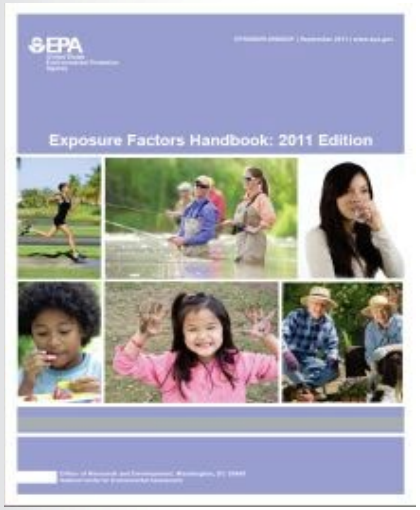
- Are used to support decisions on acceptable levels of human exposure, establish remediation strategies, and set clean-up goals that are appropriate for protecting human health while not overly conservative and costly.

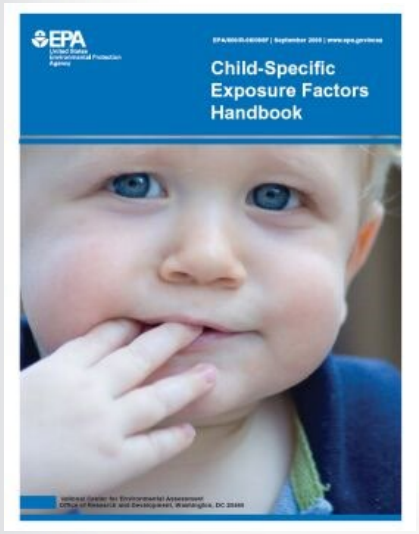
- May produce up to 6 toxicity values per assessment, including: a subchronic and chronic RfD and RfC, cancer oral slope factor and inhalation unit risk.

- Use the same technical guidance as IRIS assessments and undergo independent external peer review.

http://hhpprtv.ornl.gov

Exposure Factors Program





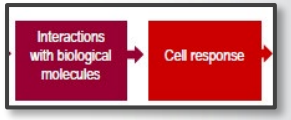
<u>Exposure Factors Handbook</u> (2011)

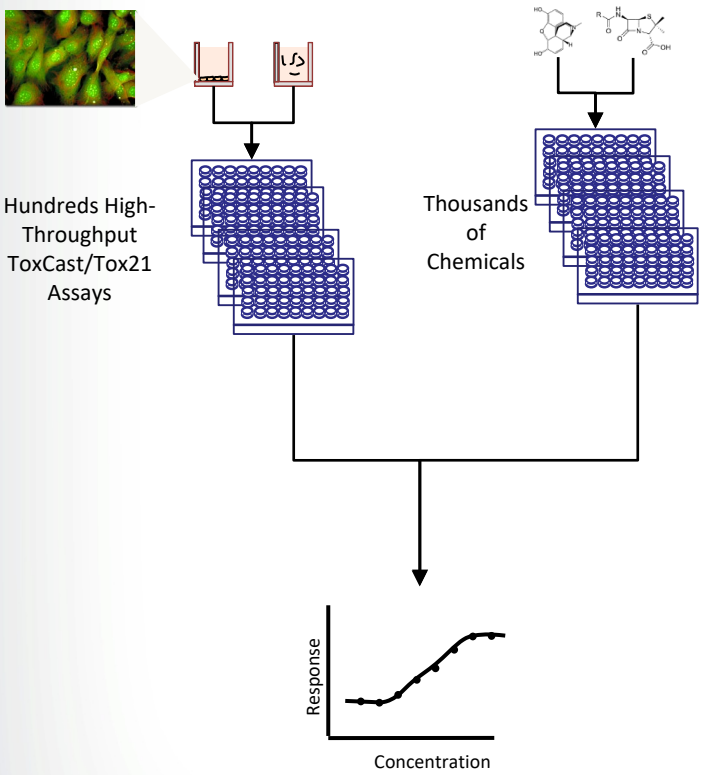
- Summarizes available data on factors used for assessing exposure:
  - Drinking water consumption, soil ingestion, inhalation rates, dermal factors including skin area and soil adherence factors
  - Consumption of fruits and vegetables, fish, meats, dairy products, homegrown foods, human milk
  - Activity patterns, body weight, and consumer products.

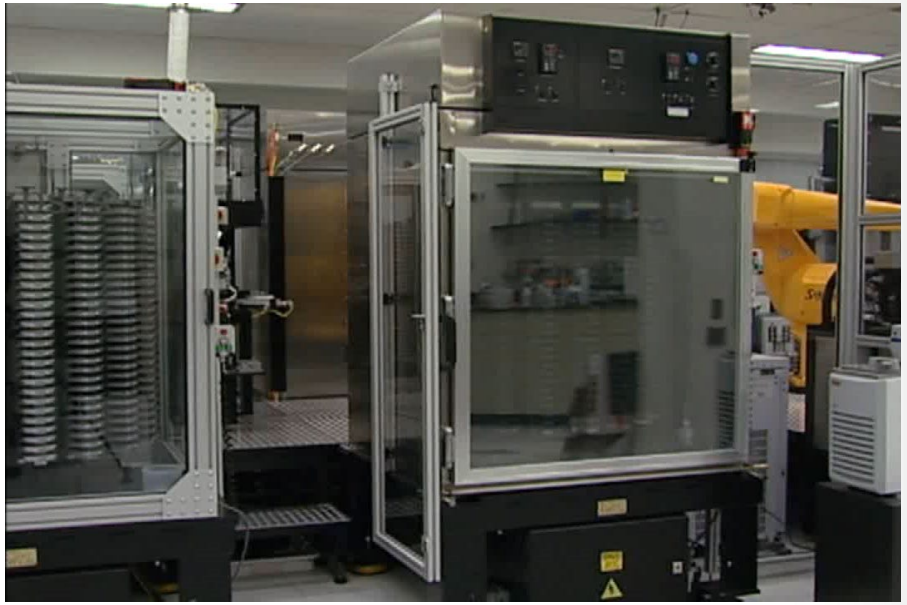
<u>Child-Specific Exposure Factors Handbook</u> (2008)

- Consolidates all child exposure data into single document

High-Throughput Assays Used to Screen Chemicals for Potential Toxicity



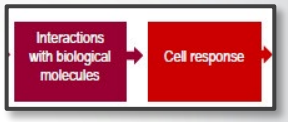




- Understanding of what cellular processes/pathways may be perturbed by a chemical
- Understanding of what amount of a chemical causes these perturbations

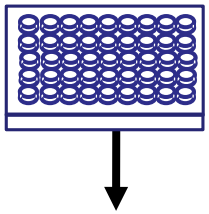
Courtesy from Dr Maureen Gwinn, EPA

Innovations in Incorporating Xenobiotic Metabolism

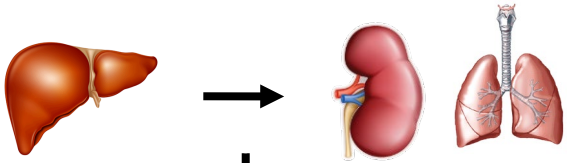


"Extracellular" Approach

Chemical metabolism in the media or buffer of cell-based and cell-free assays

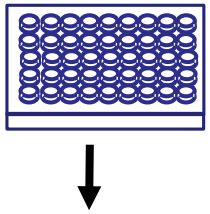


More closely models effects of hepatic metabolism and generation of circulating metabolites

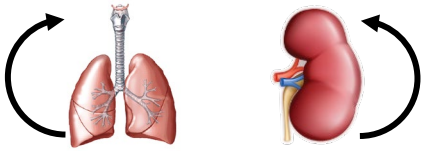


"Intracellular" Approach

Chemical metabolism inside the cell in cell-based assays



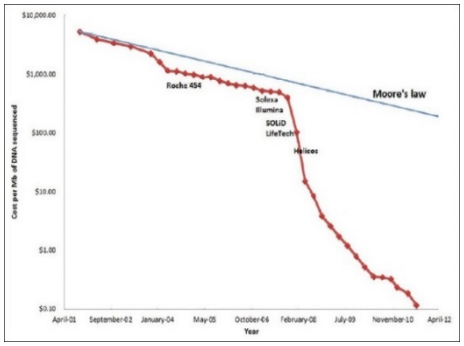
More closely models effects of target tissue metabolism



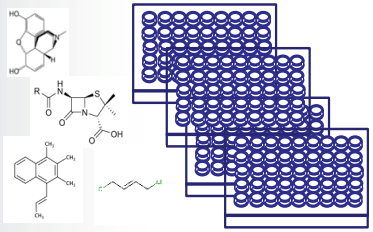
Integrated strategy to model *in vivo* metabolic bioactivation and detoxification

Courtesy from Dr Maureen Gwinn, EPA

High-Throughput Transcriptomics and Phenotypic Profiling

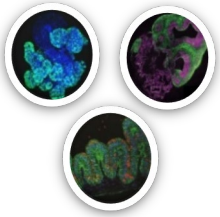


Thousands of chemicals



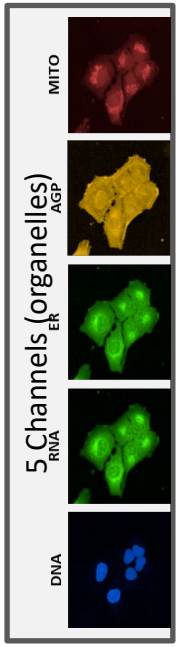
X

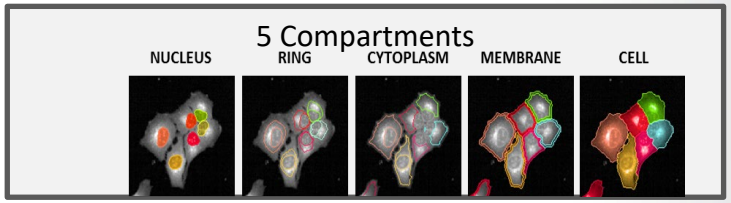
Multiple Cell Types

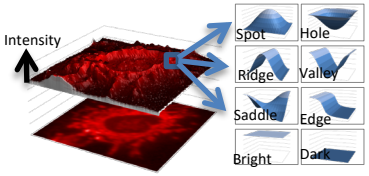


Requirements:

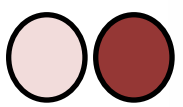
- Low cost
- Whole genome
- 384 well
- Automatable





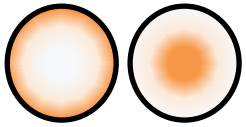


Texture

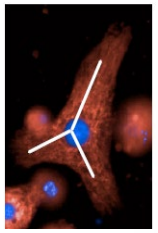


Intensity

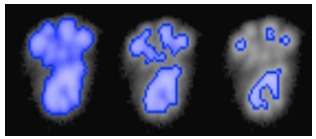
Axial



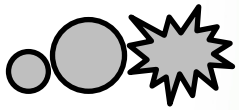
Radial distribution



Symmetry



Compactness



Shape

Profile

Illustrations from Perkin Elmer

~ 1300 endpoints
(tcpl: "components")

Courtesy from Dr Maureen Gwinn, EPA

Health and Environmental Research Online (HERO) Database – Making Risk Assessments Transparent

- **HERO** is a database of scientific studies used to develop EPA risk assessments.
  - Is used for IRIS, ISAs and PPRTVs
  - Allows the public to readily access studies on which decisions are based
- **HERO** provides:
  - Citation
  - Abstract
  - Topic areas that describe the reference
  - Assessment for which reference was used
- **HERO** is an ***EVERGREEN*** database – new studies are continuously added

www.epa.gov/hero

Risk Assessment Training and Experience (RATE)

The RATE program:

- Provides comprehensive risk assessment instruction in a classroom setting; and web-based platform.
- Includes modules on the fundamentals of risk assessment; hazard identification; dose-response; exposure assessment; and risk characterization, communication and management.

This innovative program :

- Helps ensure that state-of-the-art methods are incorporated into risk assessment practice.
- Trains the next generation of risk assessors and environmental leaders, ensuring that decisions are based on sound science and the most current risk assessment practices.

Genetic Toxicology Data in IRIS Assessments: Current uses

- Genetic toxicology data contribute to the hazard evaluation and influence dose-response by informing:
- The occurrence of precursor events in humans that are attributable to the agent
- The relevance of animal evidence to humans
- The existence of susceptible subpopulations (genetic polymorphisms) or lifestages (ADAFs applied for mutagenic carcinogens) in humans
- Mutagenic MOA or unable to determine MOA: linear extrapolation

U.S. EPA (2005). Guidelines for carcinogen risk assessment. (EPA/630/P-03/001F)
U.S. EPA (2005). Supplemental guidance…(EPA/630/R-03/003F)

Courtesy of Dr Catherine Gibbons, EPA

Studies available in genotoxicity database

- Regulatory
- Standard testing battery
- Important for identifying gene mutations, chromosomal mutations, and aneuploidy in vitro and in vivo
- Narrow focus on mutagenic potential
- Academia
- Valuable for investigating mechanistic detail
- Follow grant funding trends
- Industry
- Extremely useful but similarly must follow funding trends

Courtesy of Dr Catherine Gibbons, EPA

Genetic Toxicology Data in IRIS Assessments: Current uses

- Genetic toxicology evidence can lead to the highest cancer classification of Carcinogenic to humans:
- Strong human evidence for cancer or precursors
- Extensive animal evidence
- Mode of action and key precursors have been identified in animals
- Strong evidence that precursors are anticipated to occur in humans and progress to tumors
- Used for benzo[a]pyrene assessment

U.S. EPA (2005). Guidelines for carcinogen risk assessment. (EPA/630/P-03/001F)
U.S. EPA (2005). Supplemental guidance…(EPA/630/R-03/003F)

Courtesy of Dr Catherine Gibbons, EPA

Challenges Facing the Risk Assessment Community

- Toxicity values; in many cases, if no value is available, we assume zero risk.
- To understand what science an assessment is based on.
- Clear guidance for conducting risk assessments.
- Consistent training in hazard, dose-response, exposure assessments, risk assessment, and risk communication – for this and the next generation of risk assessors.
- To learn about innovations in risk assessment science and methods.

Conclusions

- Risk Assessment is a powerful decision-support tool for a public health regulatory agency
  - Useful when there is not complete knowledge
  - Taking full advantage of information and data by integrating it into a systematic framework
  - Several applications

- Risk analysis encompasses:
  - risk assessment;
  - involves communicating the risk to a broader audience; and
  - ensures that policy considers the public health impact (e.g., decrease in the risk of foodborne illness) of intervention strategies

Conclusions (Continue)

Risk assessment is the integration of qualitative and quantitative information on:

- toxicity
- severity of effects
- geographic extent
- exposure
- magnitude of response
- and many other factors

It is an integrated and dynamic process that utilizes scientific estimates to inform environmental and public health risk management decisions.

Risk assessment is not just dose-response assessment alone.

Acknowledgment

- Reeder Sams, Ph.D, EPA-CCTE
- Maureen Gwinn, Ph.D, EPA-CCTE
- Catherine Gibbons, Ph.D, EPA-CPHEA
- Regina Milbeck, EPA-CCTE


спасибо
谢谢
GRACIAS
THANK YOU
ありがとうございました
MERCI
DANKE
धन्यवाद
شُكراً
OBRIGADO