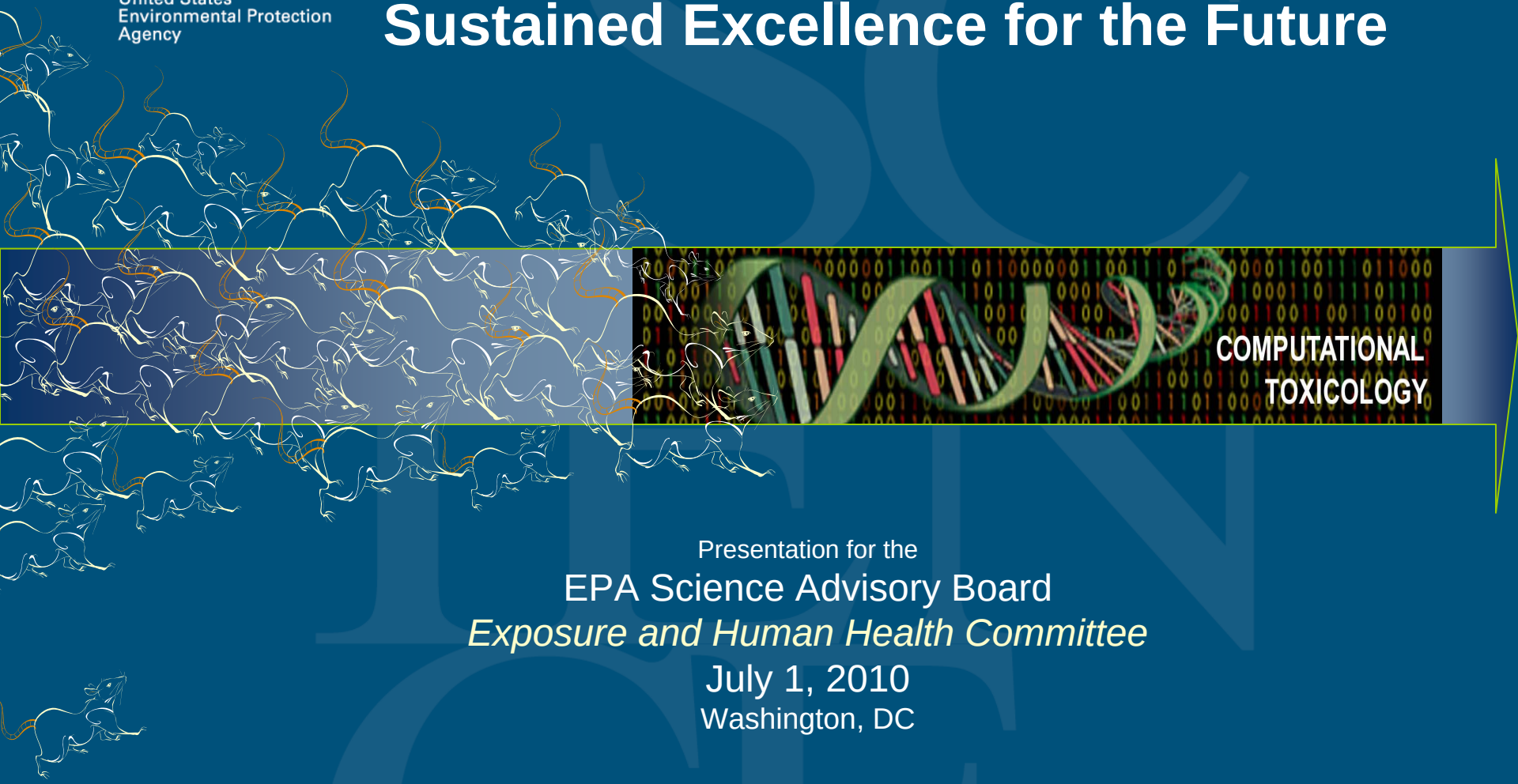
Human Health Risk Assessment: Sustained Excellence for the Future



Presentation for the

EPA Science Advisory Board

Exposure and Human Health Committee

July 1, 2010

Washington, DC

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National Center for Environmental Assessment

Office of Research and Development

United States Environmental Protection Agency

United States Environmental Protection Agency

NCEA's Work – Critical for Agency Decision-Making

Risk Paradigm Alignment in ORD

National Health and Environmental Effects Research Laboratory

Research on mechanisms and susceptibility to identify hazards and dose-response

National Exposure Research Laboratory

Research to measure, characterize and assess exposures and to support compliance with environmental regulations and policies

National Risk Management Research Laboratory

Research and technology transfer to prevent, mitigate and control pollution

National Center for Computational Toxicology

Application of computational tools and models to improve understanding of toxicity and risks posed by environmental agents.

National Center for Environmental Assessment

Development of human health assessments, research on risk assessment methods, and guidance development

National Homeland Security Research Center

Research to help decision-makers prepare and respond to chemical and biological attacks

National Center for Environmental Research

Extramural program - grants, fellowships, and national centers of excellence - to complement ORD's in-house research program

Human Health Assessment Activities

IRIS and other priority health hazard assessments:

- Developing human health assessments (e.g., tetrachloroethylene, trichloroethylene, formaldehyde)
- Provisional Peer Reviewed Toxicity Values (PPRTVs) for EPA's waste site clean-up program (Superfund): PPRTVs for 69 chemicals completed in FY2009
- Incidence Response Assessments (e.g., Hurricane Katrina health impact assessment of debris incineration, impacts assessment of dust from collapse of the World Trade Center)

State-of-the-science risk assessment models, methods, and guidance:

- Uncertainty analysis
- Identification of possible modes of action
- Physiologically-Based Pharmacokinetics (PBPK) Modeling
- Approaches for Assessing Risk of Environmental Exposures to Age-Susceptible Populations
- Approaches for cumulative risk assessment
- Approaches to unifying dose response
- Incorporating background vulnerability into risk assessment

Air Quality Integrated Science Assessments (ISA):

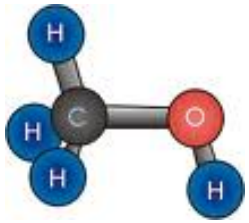
- Producing ISAs which provide the scientific bases for EPA's air quality decision-making
  - *Ozone – completed February 2006; underway – 1st draft Nov. 2010*
  - *Lead – completed September 2006; Lead ISA Information Call-in – 2010*
  - *Particulate Matter – Completed 2009*
  - *Nitrogen Oxides – ISA – Health and Environmental Criteria – both final in 2008*
  - *Sulfur dioxide – ISA – Health and Environmental Criteria – both final in 2008*
  - *Carbon Monoxide – Completed 2010*

Integrated Risk Information System

- IRIS provides qualitative and quantitative health effects information on over 540 substances
- Many high-profile, first applications of risk assessment guidelines and science policy
- Reference Dose (RfD)/Reference Concentration (RfC) for non-cancer effects
- Cancer risk: Hazard characterization, oral slope factors, and oral and inhalation unit risks
- Improvements in transparency, consistency, and timeliness

www.epa.gov/iris

Current IRIS Agenda



- Approximately 80 chemicals on the current IRIS agenda.
  - Some high profile chemicals like tetrachloroethylene, trichloroethylene, formaldehyde, arsenic, and others.
- About 30 chemicals are at the early stages of work
  - Recently conducted priority setting exercise with Programs and Regions
  - Also asked for information to help us better understand the need for these chemical assessments across the Agency

IRIS Assessments Recently Posted:

- **Acrylamide** – *Posted March 2010*
  - Includes RfD for chronic oral exposure, RfC for chronic inhalation exposure
  - Includes carcinogenicity assessment for lifetime exposure *("likely to be carcinogenic to humans")* with oral slope factor and inhalation unit risk
- **Carbon tetrachloride** – *Posted March 2010*
  - Includes RfD for chronic oral exposure, RfC for chronic inhalation exposure
  - Includes carcinogencity assessment for lifetime exposure *("likely to be carcinogenic to humans")* with oral slope factor and inhalation unit risk
- **Ethylene glycol monobutyl ether (EGBE)** – *Posted March 2010*
  - Includes RfD for chronic oral exposure, RfC for chronic inhalation exposure
  - Includes carcinogencity assessment for lifetime exposure *("not likely to be carcinogenic to humans at environmental exposures")*

Status of Key Health Assessments

(expected dates)

- ***Trichloroethylene (TCE)***
  - External Review Draft released for public review and comment (Nov. 2009)
  - SAB peer review meeting (May 2010)
- ***Dioxin***
  - Draft response to the NAS comments released for public review and comment (May 2010)
  - External peer review meeting (July 2010)
- ***Tetrachloroethylene (PERC)***
  - Final assessment anticipated 1st quarter FY2011
- ***Formaldehyde***
  - Begin external peer review by NAS (June 2010)
- ***Phthalates*** – Cumulative risk assessment underway
- ***Chromium VI***
  - Begin external peer review (3rd quarter FY2010)
- ***Arsenic (inorganic)***
  - Cancer: Released revised draft for public comment and SAB peer review in Feb. 2010; Final assessment anticipated 4th quarter FY 2010
  - Non-cancer: Final assessment anticipated 4th quarter FY 2011
- ***Chloroform***
  - Inhalation route only
  - Interagency review anticipated 4th quarter FY 2010
- ***1,4-dioxane***
  - Final assessment anticipated 3rd quarter FY 2010
- ***PAH Mixtures***
  - Draft relative potency factor analysis released for public comment, Feb. 2009
  - Begin SAB peer review (June 2010)

Please check IRISTrack for latest status:
www.epa.gov/ncea/iristrac

Health and Environmental Research Online (HERO) Database

- HERO – a database of scientific studies used to develop EPA risk assessments aimed at understanding the health and environmental effects of pollutants and chemicals
  - Created for the Integrated Science Assessment Program
  - Will be expanded to include IRIS assessments and PPRTVs
- 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

IRIS Update Project

- Update assessments that are more than 10 years old and have new studies that may impact a toxicity value or a cancer weight of evidence descriptor.
- Assessments requiring extensive analysis go into standard IRIS process; those with no new data will be updated to indicate they are still current.
- Assessments requiring limited analysis will go into update process (chemicals will be batched).
- Project started in FY2009; First batch of assessments anticipated to start review process in 4th quarter 2010.

The update process:

- FRN announcing IRIS Update Project agenda and calling for scientific information
- Comprehensive search of scientific literature on each chemical
- Draft health assessment development
- Combined simultaneous review of the draft by EPA and other Federal Agencies via the Federal Standing Science Committee
- Public comments on draft assessments, followed by independent external peer review under the Federal Advisory Committee Act
- Final IRIS assessment reflecting public comments and independent external peer review will replace old assessments on IRIS database.

Exposure Factors Program

Exposure Factors Handbook 2009 Update

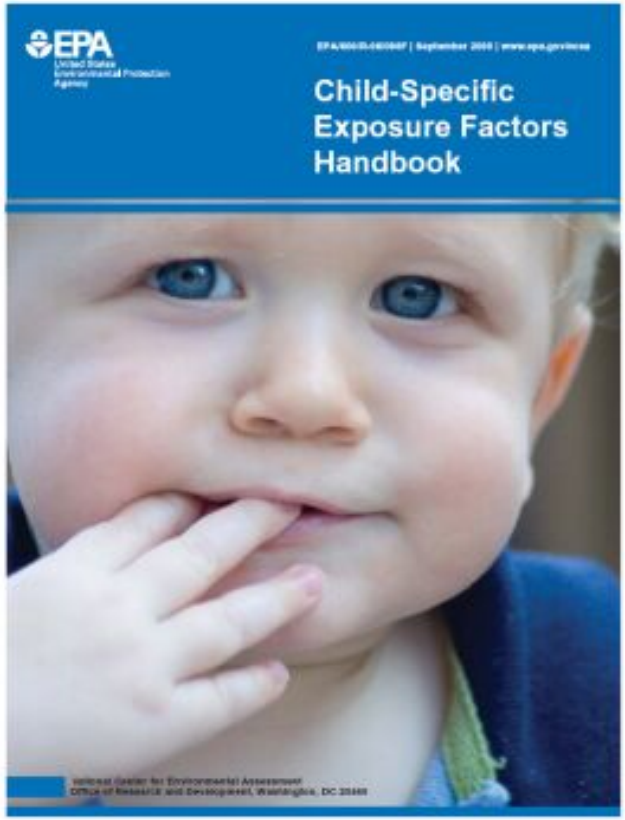
(External Review Draft Oct. 2009)

- 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.

Child-Specific Exposure Factors Handbook

(Final Report Sept. 2008)

- Consolidates all child exposure data into single document



Technical Support

NCEA scientists provide technical support to users of assessments, guidance and tools:

- Support to OAR through the entire NAAQS rulemaking process
- Programmatic support on various rulemakings
- Support to Regions (PCBs, dioxin, etc.)
- Assistance for States with difficult problems (hexavalent chromium, volcanic ash in Hawaii)

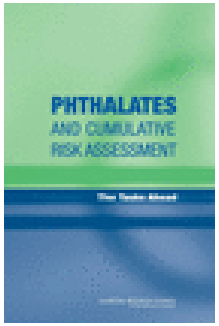
United States Environmental Protection Agency

Sustained Excellence for the Future of Risk Assessment

National Research Council Reports

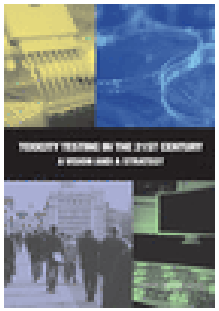
Toxicity Testing in the 21st Century

- Toxicity testing and assessment is approaching a scientific pivot point
- Advances in toxicogenomics, bioinformatics, systems biology, epigenetics, and computational toxicology.



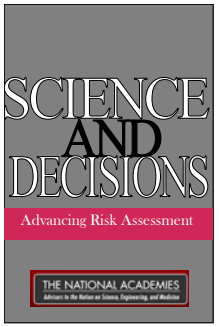
Science and Decisions: Advancing Risk Assessment

- Utility of risk assessment
- Uncertainty and variability
- Unified approach to dose response assessment
- Cumulative risk assessment



Phthalates and Cumulative Risk: The Tasks Ahead

- Group chemicals that cause common adverse outcomes and not focus exclusively on structural similarity or on similar mechanisms of action.



Type of Assessment Can Depend on its Use

- Need to consider use and then **balance**
  - Thoroughness
  - Complexity
  - Timeliness
- Need to consider and then **avoid**
  - Paralysis by analysis - how much effort is needed?
  - Arguments about science can lead to protracted and unacceptable delays
  - If assessment is need for a regulatory decision, may miss window for is usefulness to the Agency
- Difficult for an agency to be responsive if substantial time and resources are needed for each assessment

Benchmark Dose Modeling Methods

- Benchmark Dose (BMD) Modeling provides a common method for deriving a point of departure for cancer and noncancer health assessments.
- NCEA's practice is to use BMD modeling to derive a point of departure when the data are available and adequate – whether a linear or nonlinear low-dose extrapolation is used.
- Benchmark Dose Software developed in 1995 by NCEA
- Most recent version contains 30 different models that are appropriate for analysis of dichotomous data.
- NCEA provides technical support and training to others in the use of BMD Software and using BMD modeling for risk assessment.

Summer 2010 - EPA will distribute final release of Version 2.1.2 (Build 60) of the Benchmark Dose Software (BMDS).

Cumulative Assessment of Phthalates

- IRIS human health assessment for six phthalates with a cumulative assessment based on common adverse outcome
  - dibutyl phthalate (DBP), di(2-ethylhexyl)phthalate (DEHP), butyl benzyl phthalate (BBP), di-isobutyl phthalate (DIBP), di-isononyl phthalate (DINP), and dipentyl phthalate (DPP)
  - Individual summaries and one cumulative assessment

- Workshop summer/fall 2010 to evaluate NAS recommendations related to methods for performing a cumulative assessment for these phthalates
  - Determine which options for conducting a cumulative risk assessment for the phthalates should be included in the assessment and the strengths and limitations of these options.
  - First step in considering risks of exposure to multiple chemicals
  - May serve as a framework for extension to other compounds in the future

Moving Science Forward with New Methods

- Physiologically-Based Pharmacokinetic (PBPK) Modeling
  - PBPK Models are becoming increasingly complex
    - *Many thousands of lines of computer code*
    - *Significant uncertainty from estimated parameters*
  - Developing guidance for deciding when complex models are necessary, and when simpler models will suffice
- Integrated probabilistic assessment
  - Harmonized approach for cancer and non-cancer health endpoints
  - Replace “dividing by uncertainty factors” with coherent probabilistic approach using distributions
  - Improve characterization of uncertainty and variability

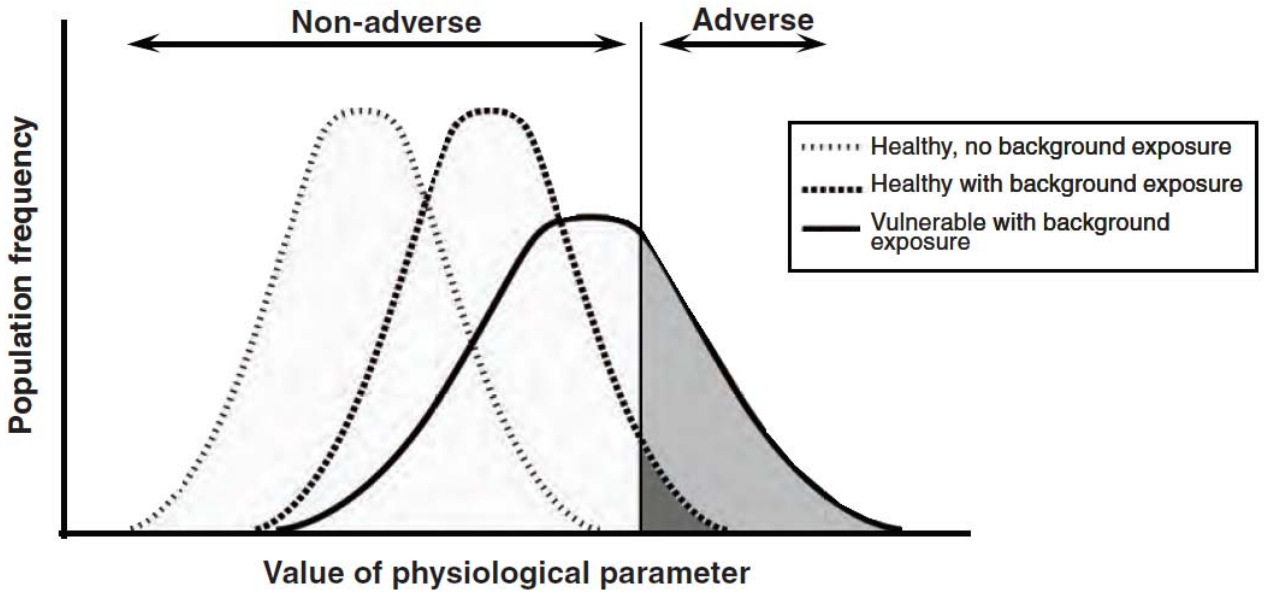
Improving Quantitative Characterization of Uncertainty and Variability

- Many requests/demands to address quantitative uncertainty and variability in human health risk assessment
- Development of methods to conduct this type of analysis have been slow
- A number of different approaches for addressing qualitative uncertainty and variability have been developed
- IPCS project to develop general framework/approach for applying probabilistic methods for hazard characterization
  - Initial draft in collaboration with RIVM
  - Emphasizes explicit, quantitative characterization of the degree of severity, population variability, and uncertainty based on available data
- However, new methods are needed, particularly for extrapolation of dose-response to doses below the range of the available data

Variability in Population Response

Populations responses depend on a variety of factors:

- Endogenous and exogenous exposures
- Health status
- Other biologic factors



Science and Decisions, NRC 2009

Human Health Risk Assessment

Transforming to address emerging science and new science challenges

- Tens of thousands of chemicals untested and lack assessment of potential for human toxicity.
- Current toxicology testing methods:
  - ➢ too expensive
  - ➢ too slow
  - ➢ cope with too few chemicals.
- Toxicology approaches – evolving away from *in vivo* testing of laboratory animals
- Approaches must be modified to deal with more chemicals; innovative approaches
  - – Screening
  - – Fingerprinting
  - – Toxicity pathways
  - – Focused high-throughput assessments
- Risk assessment approaches must be developed that can use the new generation of data types and arrays; “omics”

NextGen Risk Assessment

Human Health Assessment Issues

Mechanistic Considerations in Human Health Risk Assessment

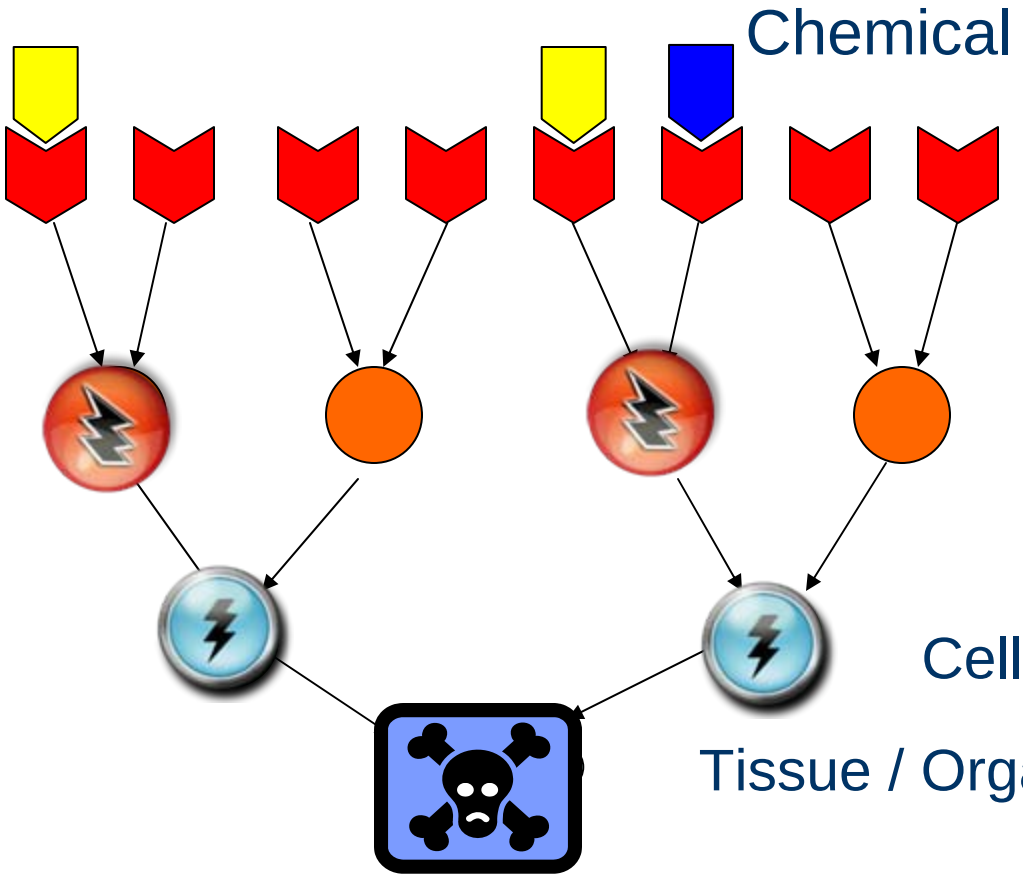
- Increased need to characterize:
  - A wider array of hazard traits
  - More chemicals (no data on most chemicals in commerce)
- Human carcinogens increasingly recognized to impact:
  - Multiple toxicity pathways, mechanisms affected
  - These mechanisms could inform new predictive approaches
    - *In vitro assays*
    - *Human biomarkers*
- Dose-response curve:
  - In an individual: can take multiple forms depending on genetic background, target tissue, internal dose
  - In a population: variability in susceptibility in response are key determinants

Source: Guyton et al. Improving prediction of chemical carcinogenicity by considering multiple mechanisms and applying toxicogenomic approaches. Mutat Res. 681(2-3):230-40, 2009.

Focus on Mechanisms of Human Disease

- Increases appreciation of individual and population heterogeneity of disease mechanisms
- Improves prediction of interactions across environmental exposures
- Addresses mechanism-based likelihood of other outcomes
- Identifies mechanism-based sources of human variability/susceptibility (e.g., background diseases and processes, genetic polymorphisms, age, co-exposures)
- Uses systems biology level tools and data
- Advances high throughput methodologies (microarray, proteomics)
- The use of mechanistic data will play a key role in the future of risk assessment to:
  - Aid in identification of sources of human variability/susceptibility (e.g., background diseases and processes, co-exposures, etc) and early stage disease biomarkers.
  - Address likelihood of other outcomes
  - Improve prediction of interactions across environmental and endogenous exposures
  - Indentify mechanistic drivers of response at low doses.

Toxicity Pathways



NexGen Assessments:

From Now Until the Future -- Possible Approaches

1. High priority list and streamlined process

- High priority list
  - *Screen based on readily available data*
  - *High production volume and released to environment (e.g., U.S. EPA's Toxic Release Inventory [TRI])* ***and/or***
  - *Biomonitored (e.g., U.S. Centers for Disease Control [CDC])*
  - *Integrated hazard and exposure High-Throughput Screening*
- Streamlined process
  - *Narrower scope: policy relevant information only*
  - *Basic "off the shelf" risk assessment methods; no methods development*
  - *More focused and coordinated stakeholders reviews*

2. Broaden Scope to Synthesize More Information in Each Assessment

- Cumulative effects - organized around different agents that cause the same effects, e.g. phthalates, air pollutants
- Families of chemicals – organized around agents that are physically similar, e.g. nanomaterials, fibers
- Topics – organized about agents that intersect due to the problems they create or problems they are intended to solve, e.g. climate change, biofuels
- Inherency – take into account both desired and undesired properties when designing chemical materials…*"inherently non-hazardous as possible"*

(Anastas and Zimmerman, Design through the Twelve Principles of Green Engineering, ES&T, 2003)

Human Evaluation and Quantitative Risk Assessment

No alert
No additional assessment

Tier 1 Assessments

- Screening and prioritization
- HTS, Virtual Systems, QSAR
- False negatives minimized)

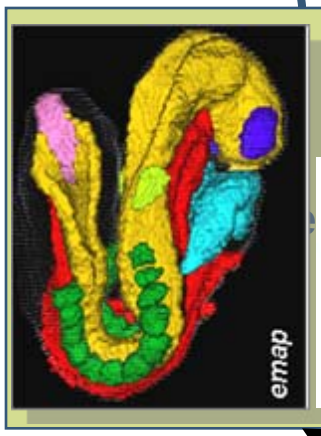
Alert

Tier 2 Assessments

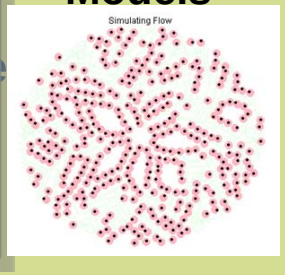
- Many (hundreds) chemicals - limited hazard and exposure
- HMT reliant and policy relevant data
- Science-based defaults and upper confidence limits risk estimates

Tier 3 Assessments

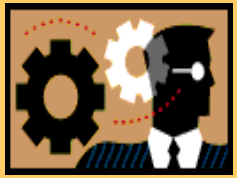
- Few (dozens) chemicals – high hazard and exposure
- Based on all policy relevant data and emerging science
- Best estimates of risk and uncertainty analyses



Predictive Systems Models



Test Data (REACH or TSCA)



Regulatory decision-making and policy

FASTER SCIENCE FOR BETTER DECISIONS: CHARACTERIZING ENVIRONMENTAL CONTAMINANT RISK FROM HIGH THROUGHPUT DATA

NexGen Assessments:
Our Strategy for the Future

- We must thoughtfully position environmental health assessors for the future and be prepared to contribute to meaningful change within the larger risk assessment/risk management community.
- The environmental health community is embarking on an exploration of new science, methods and policies that could be incorporated into currently emerging and future risk assessments.
- This strategy will help us map a course forward, focusing on creating prototype NexGen risk assessments, learning from these efforts and, then, refining the next versions based on this new knowledge.
- This possible strategy focuses on development of:
  1. *A pilot implementation of a new approach for risk based decision-making, including characterization of risk management needs, policy relevant questions and implications for NexGen risk assessments;*
  2. *An operational scale knowledge mining, creation and management system to support risk assessment work and interface with gene environment data bases.*
  3. *Prototype examples of increasingly complex assessments responsive to the risk context and refined through discussions with scientists, risk managers, and stakeholders.*

The ORD Path Forward

Integrated – Environmental and human health issues have become more complex….systems thinking and integrative approaches are needed.

Transdisciplinary – We must involve the widest span of disciplines to bring different perspectives to the table

Innovative – Addressing environmental challenges (water quality/quantity; ubiquitous toxics, etc.) will require innovation. ORD must help drive that innovation.

Catalytic – We need to act catalytically and spark further action among others.

Visible – Great work, done invisibly, cannot have an impact. Communication is essential in the design, definition, conduct, transfer, and implementation of the work we do if we are to have an impact.

Sustainability

Solution-Oriented

Timeliness

Relevance

Responsiveness

Integrity

The Future of Risk Assessment

Summary

- The landscape of risk assessment is changing to an extent that significant modernization of risk assessment is necessary.
- These changes are driven largely by advances in understanding the gene environment; the important input and advice from expert science panels; and volumes of new test data from Europe.
- We must thoughtfully position environmental health scientists and assessors for the future and contribute to meaningful change within the larger risk assessment/risk management community.
- The goal of the NextGen strategy is to map a course forward, focusing on creating 1st approximation NexGen risk assessments, learning from these efforts and, then, refining the next versions based on this new knowledge.
- It may take a decade before risk assessment can rely primarily on new advances in science
- It is necessary, however, to begin <u>now</u> to address needed changes.

Thank You!

Questions?