Human Health Research Program (2006-2013)

OVERVIEW OF LTG-2: Cumulative Risk

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BOSC Review, 2009

Background

- EPA is responsible for protecting public health from environmental stressors
  - Uses risk assessment to do this
    - Risk = Exposure x Hazard
  - Historically, very simplistic approach
    - Single chemical, single pathway ,deterministic
- What we had for early environmental problem – high concentration, high toxicity chemicals
- Not adequate for today's complex problems – low levels of many chemicals and other stressors

Background

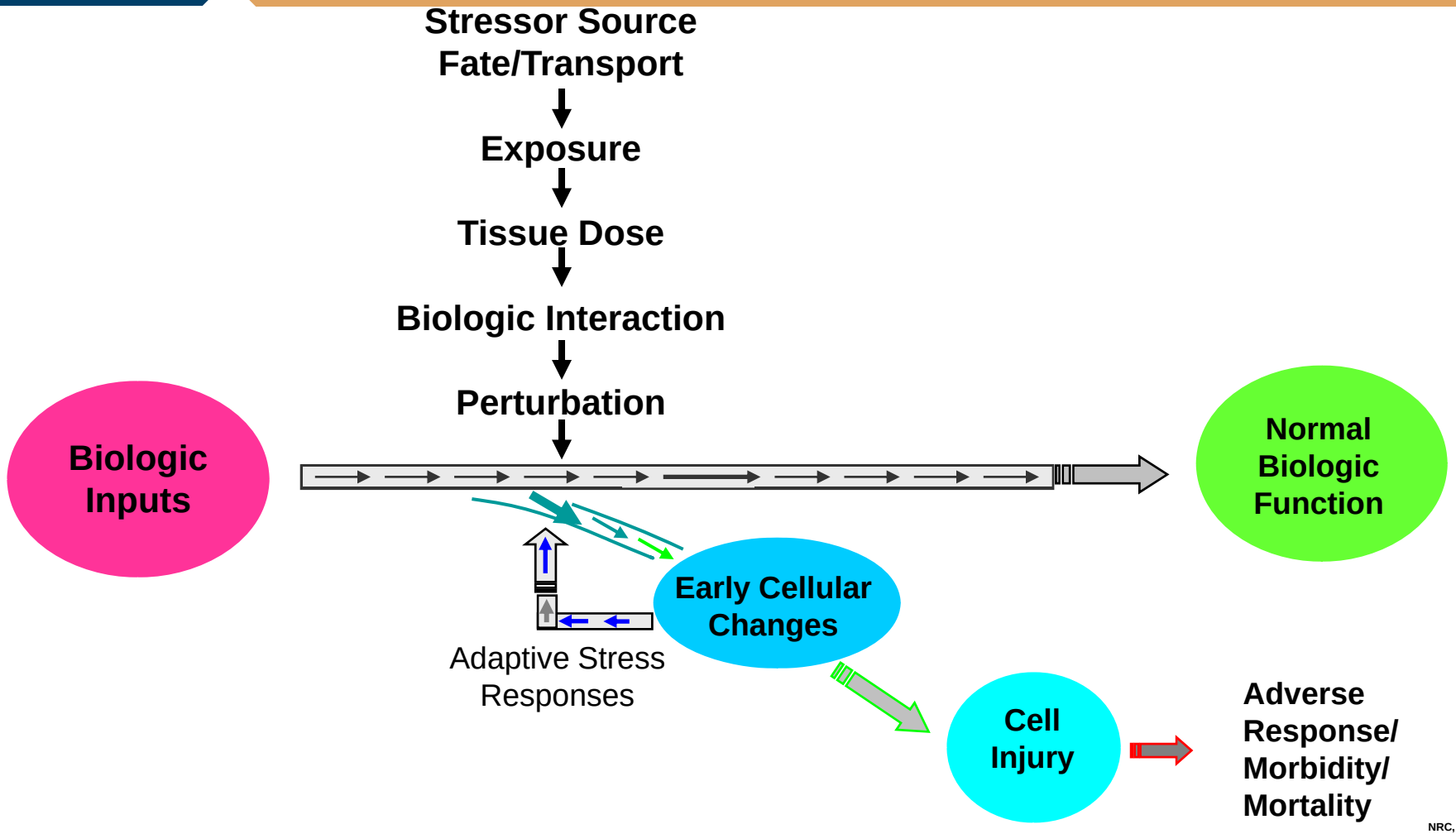
- Legislation in the late 1990's required us to move beyond this approach (FQPA, SDWA)
- Risk assessments must consider
  - Aggregate exposures – exposures from all sources, routes, and pathways for a single chemical
  - Cumulative risk -- risk from aggregate exposures to all chemicals with a common MOA
  - Special consideration for susceptible populations, including infants and children, elderly, groups with preexisting disease

Broader Scope of Cumulative Risk

- Risks associated with exposure to chemical and nonchemical stressors including social, economic, behavioral, etc
  - 1997 EPA administrator memorandum
  - National Academy of Public Administrators
  - Environmental Justice
  - EPA Risk Assessment Forum

Improved approaches are needed

- Currently blunt tools
  - For both health outcomes and exposure
  - Little linkage between the two
- Understanding Cumulative Risk will require us to move beyond these tools
- A ***systems approach*** is needed that
  - describes the processes
  - links the processes



For risk assessment, a systems approach is needed

***Toxicity Testing in the Twenty-first Century: A Vision and a Strategy,* NAS, June 2007.**

NRC- Toxicity Testing in the 21st Century

- Articulates the need for new tools and approaches for risk assessment
- Incorporates a systems approach
- LTG 2 research is consistent with this new vision
  - Research to understand and link the processes

A Systems Approach is Feasible

- New tools are available and constantly developing
  - Better and more sensitive analytical methods
  - New ‘omic tools
  - Advance computational methods
    - Development of databases
    - New analysis methods
  - Better computing power to develop and link models

LTG 2 Research Tracks

- Overall goal: develop scientific knowledge and tools to understand and predict cumulative risks that reflect real-world situations
  - Track 1 – science, modeling tools and data to conduct legislatively mandated cumulative risk assessment (CRA)
  - Track 2 – evaluates biomarkers for use in CRAs and in understanding the processes and linkages that lead to risk
  - Track 3 – evaluate cumulative risk from chemical and non-chemical stressors, moves beyond strict legislative mandates to evaluate risks in the real-world context of public health protection

Links to Other LTGs/MYPs

- Overall goals
  - understands the processes,
  - develops models that mathematically describe and link processes
- Data developed in LTG 1(biological mechanisms) and LTG 3 (Susceptible populations) used to develop and evaluate models
- Enhance science and tools used in LTGs 3 and 4 and other MYPs (air, EDCs, Safe Pesticides,etc,)
- Linked source-to-outcome models developed here are applied directly in LTG 4

Track 1: Conducting Cumulative Risk Assessments

- Overall goal: develop and enhance the scientific understanding, data, and modeling tools for CRAs focusing on chemicals with common MOA
- Science Questions
  - What new scientific knowledge is needed?
  - Can linked cumulative risk models be built?
  - How can tools be used to inform/or conduct enhanced cumulative assessment?

Track 1 Approach

- Iterative approach to develop and apply methods for specific risk assessments
  - OP pesticides
  - Carbamate pesticides
  - Pyrethroid pesticides
- Fundamental science
  - Biological – chemical interactions, mode of action, mechanism of interaction, low dose effects, linking toxicity with PBPK outputs
  - Exposure – exposure levels and cooccurence of chemicals, linked exposure/PBPK models

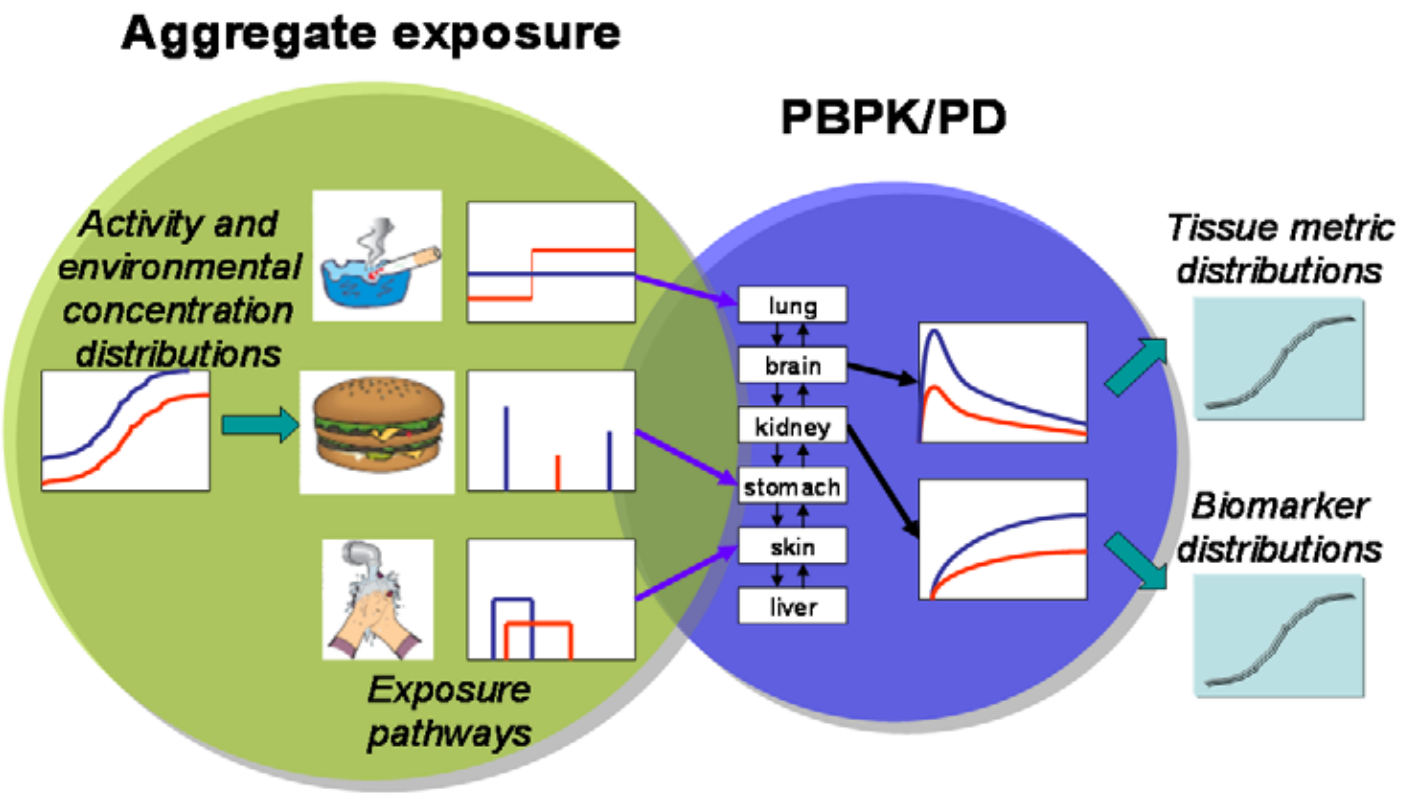


Figure 2. Schematic of linked Exposure and Dose Models

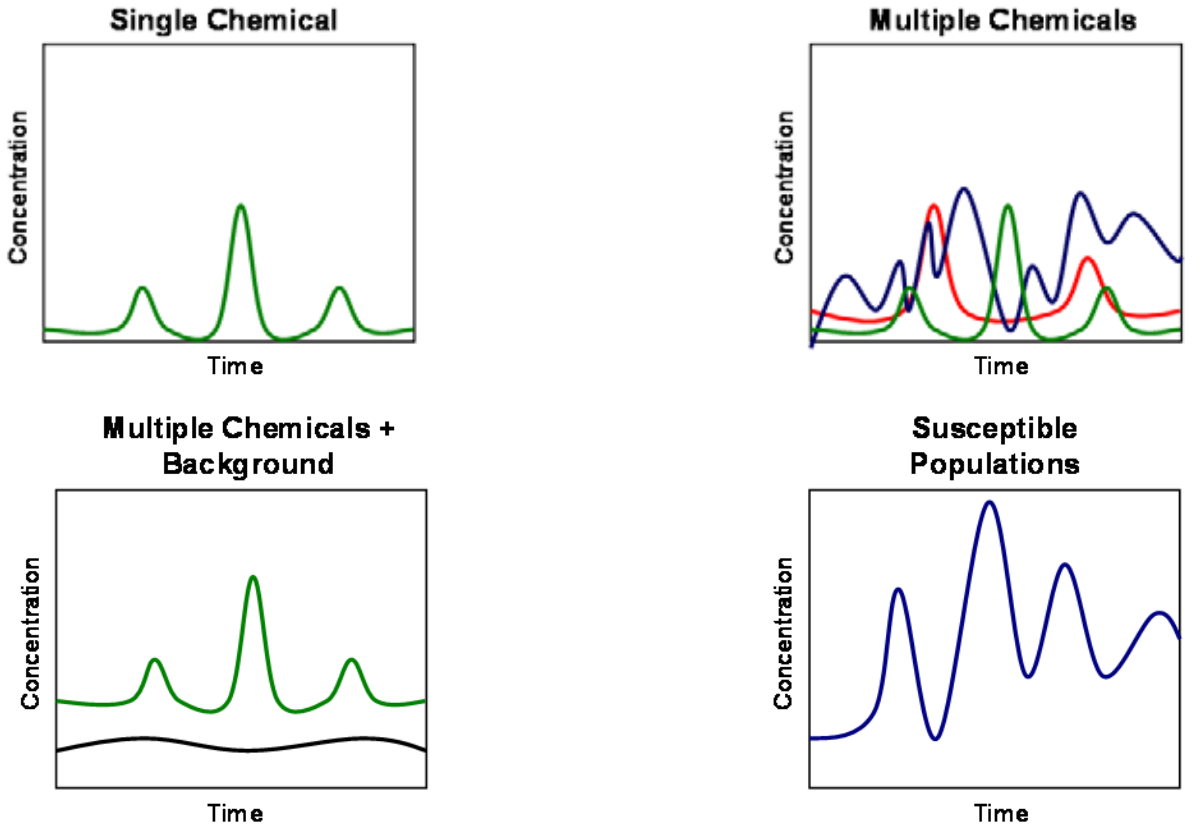


Figure 3 Outputs for linked exposure/dose model under different Scenarios

Track 2: Biomonitoring to Improve Risk Assessment

- Goal: Develop the scientific knowledge and tools that will allow us to use biomonitoring data to improve future cumulative risk assessment
- Science Questions
  - What is the state-of-the-science for using biomarkers in risk assessment
  - What new science and approaches can be used to enhance the use of biomarkers of exposure (and effects) in cumulative risk assessments?
  - How can environmental and biomarker measurements be linked in a conceptual model of exposure, dose, and susceptibility for identifying the toxicological pathways from stressor source to adverse health effect?

Track 2: Approach

- Exposure biomarkers in risk assessment

  exposure (human) ⟷ exposure (rat)

  biomarker (human) ⟷ exposure (rat)

  - Analyze existing databases for relationships
  - Develop exposure/PBPK models
  - Develop methods for reverse dosimetry
- Understand linkages between exposure and biomarker measurement
  - Exploratory measurement studies

Track 3: Cumulative Risk to Real World Stressors

- Goal: develop methods to evaluate risk for exposures to chemical and non chemical stressors
- Science Question:
  - How do we estimate cumulative exposures for various chemical and nonchemical stressors?
- Uses
  - Epidemiological Studies such as NCS
  - Cumulative Risk Assessments
  - Evaluating Risk Management options and outcomes

Track 3: Approach

- Focus on Community – fundamental issues occur within this domain
- Evaluation of state of the science
  - Tools and their applications
  - Effectiveness of tools
- Develop and application of tools
  - Models for NCS
  - Community risk tools including STAR grants
  - Applied to Accountability Projects in LTG 4

Outputs and Uses of Research

- CRA methods directly used by OPP in CRAs for pesticides
- Enhanced CRA methods used by other Agency risk assessors
- Tools for using biomonitoring in CRA will be used directly by EPA program offices in future risk assessments
- Guidance for collecting and using biomarkers will be used to improve future exposure and epidemiological studies
- Methods for assessing cumulative exposures in communities will be used
  - By researcher in future epidemiological studies,
  - CARE partners for community risk assessments
  - Regions and local communities to assess risk options