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Improving Exposure Science and Dose Metrics for Toxicity Testing, Screening, Prioritizing, and Risk Assessment

ILSI Health and Environmental Sciences Institute
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Tucson, Arizona

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Disclaimer

Although this work was reviewed by EPA and approved for presentation, it may not necessarily reflect official Agency policy.

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Goal Statement

Advance the characterization of exposure and dose metrics required to ***translate*** advances and findings in computational toxicology to information that can be directly used to support exposure and risk assessment for decision making and improved public health.

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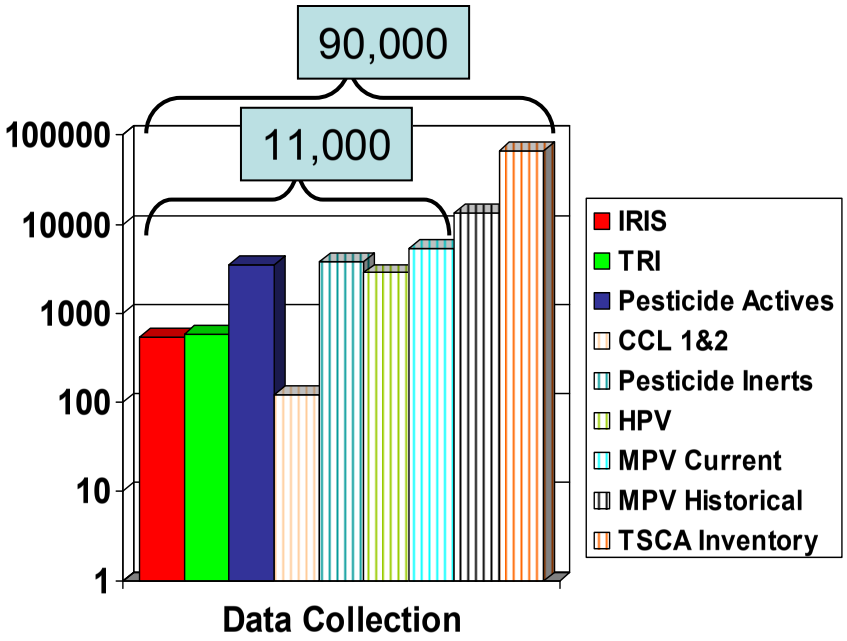
Mandate to Assess Thousands of Chemicals

Clear need to develop methods to evaluate a large number of environmental chemicals for their potential toxicity



- CEPA Prioritization Program (DSL)
- REACH
- HPV
- Endocrine Disruptor Screening Program (EDSP)
- Chemical Assessment and Management Program (ChAMP)

Richard Judson

Transforming Toxicology

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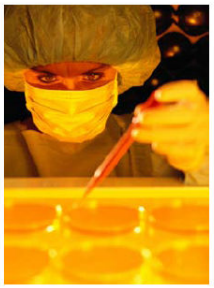
July 2007

REPORT IN BRIEF

Toxicity Testing in the 21st Century: A Vision and a Strategy

Advances in molecular biology, biotechnology, and other fields are paving the way for major improvements in how scientists evaluate the health risks posed by potentially toxic chemicals found at low levels in the environment. These advances would make toxicity testing quicker, less expensive, and more directly relevant to human exposures. They could also reduce the need for animal testing by substituting more laboratory tests based on human cells. This National Research Council report creates a far-reaching vision for the future of toxicity testing.

Toxicity tests on laboratory animals are conducted to evaluate chemicals—including medicines, food additives, and industrial, consumer, and agricultural chemicals—for their potential to cause cancer, birth defects, and other adverse health effects. Information from toxicity testing serves as an important part of the basis for public health and regulatory decisions concerning toxic chemicals. Current test methods were developed incrementally over the past 50 to 60 years and are conducted using laboratory animals, such as rats and mice. Using the results of animal tests to predict human health effects involves a number of assumptions and extrapolations that remain controversial. Test animals are often exposed to higher doses than would be expected for typical human exposures, requiring assumptions about effects at lower doses or exposures. Test animals are typically observed for overt signs of adverse health effects, which provide little information about biological changes leading to such health effects. Often controversial uncertainty factors must be applied to account for differences between test animals and humans. Finally, use of animals in testing is expensive and time consuming, and it sometimes raises ethical issues.



Today, toxicological evaluation of chemicals is poised to take advantage of the on-going revolution in biology and biotechnology. This revolution is making it increasingly possible to study the effects of chemicals using cells, cellular components, and tissues—preferably of human origin—rather than whole animals. These powerful new approaches should help to address a number of challenges facing the

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We propose a shift from primarily in vivo animal studies to in vitro assays, in vivo assays with lower organisms, and computational modeling for toxicity assessments.

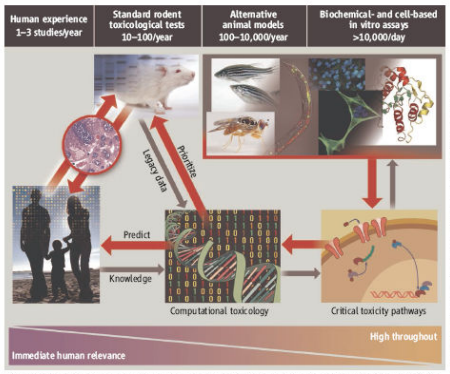
Francis S. Collins,*† George M. Gray,‡* John R. Bucher§*

In 2005, the U.S. Environmental Protection Agency (EPA), with support from the U.S. National Toxicology Program (NTP), funded a project at the National Research Council (NRC) to develop a long-range vision for toxicity testing and a strategic plan for implementing that vision. Both agencies wanted future toxicity testing and assessment paradigms to meet evolving regulatory needs. Challenges include the large numbers of substances that need to be tested and how to incorporate recent advances in molecular toxicology, computational sciences, and information technology; to rely increasingly on human as opposed to animal data; and to offer increased efficiency in design and costs (*1*–*5*). In response, the NRC Committee on Toxicity Testing and Assessment of Environmental Agents produced two reports that reviewed current toxicity testing, identified key issues, and developed a vision and implementation strategy to create a major shift in the assessment of chemical hazard and risk (*6*, *7*). Although the NRC reports have laid out a solid theoretical rationale, comprehensive and rigorously gathered data (and comparisons with historical animal data) will determine whether the hypothesized improvements will be realized in practice. For this purpose, NTP, EPA, and the National Institutes of Health Chemical Genomics Center (NCGC) (organizations with expertise in experimental toxicology, computational toxicology, and high-throughput technologies, respectively) have established a collaborative research program.

EPA, NCGC, and NTP Joint Activities

In 2004, the NTP released its vision and roadmap for the 21st century (*1*), which established initiatives to integrate high-throughput screening (HTS) and other automated screening assays into its testing program. In 2005, the EPA established the National Center for Computational Toxicology (NCCT). Through these initiatives, NTP and EPA, with the NCGC, are promoting the evolution of toxicology from a predominantly observational science at the level of disease-specific models in vivo to a predominantly predictive science focused on broad inclusion of target-specific, mechanism-based, biological observations in vitro (*1*, *4*) (see figure, below).

Toxicity pathways. In vitro and in vivo tools are being used to identify cellular responses after chemical exposure expected to result in adverse health effects (*7*). HTS methods are a primary means of discovery for drug development, and screening of >100,000 compounds per day is routine (*8*). However, drug-discovery HTS methods traditionally test compounds at one concentration, usually between 2 and 10 μM, and tolerate high false-negative rates. In contrast, in the EPA, NCGC, and NTP combined effort, all compounds are tested at as many as 15 concentrations, generally ranging from ~5 nM to ~100 μM, to generate a concentration-response curve (*9*). This approach is highly reproducible, produces significantly lower false-positive and false-negative rates than the traditional HTS methods (*9*), and facilitates multiassay comparisons. Finally, an informatics platform has been built to compare results among HTS screens; this is being expanded to allow comparisons with historical toxicologic NTP and EPA data (http://ncgc.nih.gov/pub/openhts). HTS data collected by EPA and NTP, as well as by the NCGC and other Molecular Libraries Initiative centers (http://mli.nih.gov/), are being made publicly available through Web-based databases [e.g., PubChem (http://pubchem.ncbi.nlm.nih.gov)]. In addition,



Transforming toxicology. The studies we propose will test whether high-throughput and computational toxicology approaches can yield data predictive of results from animal toxicity studies, will allow prioritization of chemicals for further testing, and can assist in prediction of risk to humans.

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*The views expressed here are those of the individual authors and do not necessarily reflect the views and policies of their respective agencies.

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Toxicity Testing in the Twenty-first Century

- The key aspect of the NRC vision and the proposed paradigm shift in Toxicity Testing is that new tools are available to examine toxicity pathways in a depth and breadth that has not been possible before.

- Efforts underway to apply high-throughput-screening (HTS) approaches for chemical prioritization and toxicity testing have been accelerated in response to NRC reports.

- An explosion of HTS data for *in vitro* toxicity assays will become available over the next few years.

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Toxicity Testing in the Twenty-first Century: A Vision and a Strategy

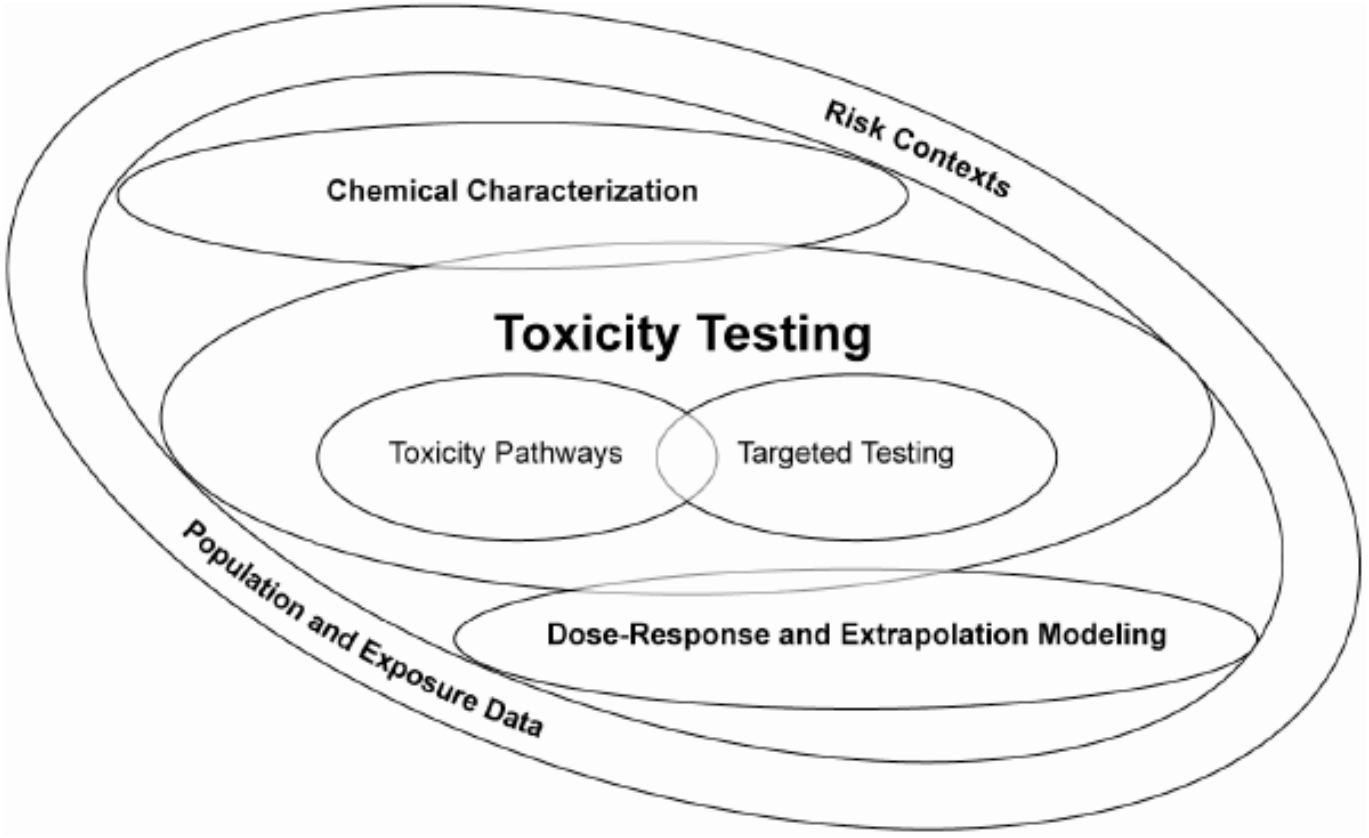

FIGURE 2-3 The committee's vision is a process that includes chemical characterization, toxicity testing, and dose-response and extrapolation modeling. At each step, population-based data and human exposure information are considered, as is the question of what data are needed for decision-making.

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Extrapolation Modeling in NRC Vision

- Three primary components of extrapolation modeling critical for vision.
  - Toxicity-pathway models to provide quantitative, mechanistic understanding of dose-response relationship for perturbations by environmental agents.
  - PBPK modeling to predict human exposures leading to tissue concentrations comparable to concentrations causing perturbations in vitro.
  - Human data on background chemical exposures and disease processes that affect the same toxicity pathways and provide a basis for addressing host susceptibility.

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Exposure Science in NRC Vision

- Population-based data and human exposure information required at each step of vision; critical role in both guiding development and use of the toxicity information. Components include:

  - Use of information on host susceptibility and background exposures to interpret and extrapolate *in vitro* test results.
  - Use of human exposure data to select doses for toxicity testing so we develop hazard information on **environmentally-relevant effects**.
  - Use of biomonitoring data to relate real-world human exposures with concentrations that perturb toxicity pathways to identify potentially important (**biologically-relevant**) exposures.

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ToxCast ™ Program for Prioritizing Toxicity Testing of Environmental Chemicals

- In 2007, EPA launched ToxCast™ in order to develop a cost-effective approach for prioritizing the toxicity testing of large numbers of chemicals in a short period of time.
- Using data from state-of-the-art high throughput screening (HTS) bioassays developed in the pharmaceutical industry, ToxCast™ is building computational models to forecast the potential human toxicity of chemicals.

http://epa.gov/ncct/toxcast/

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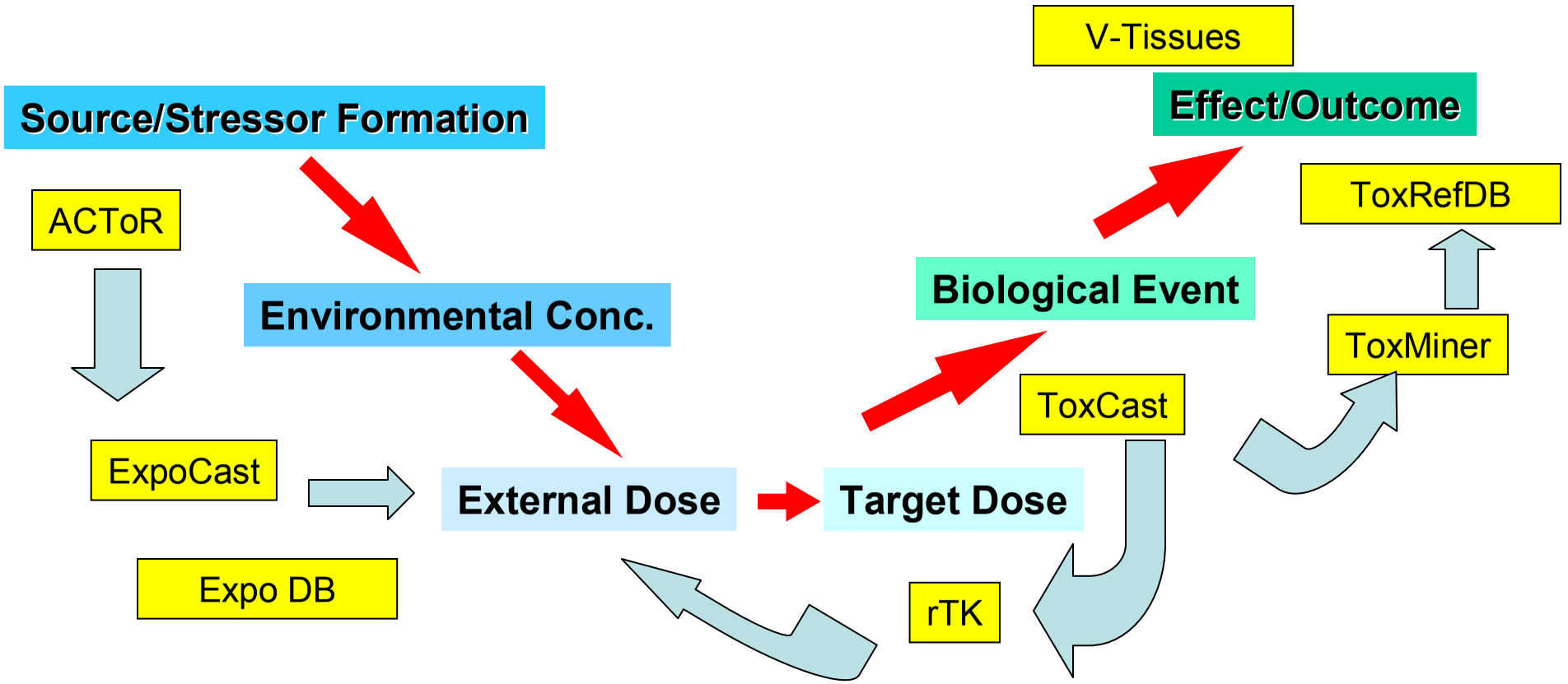
Source to Outcome Continuum



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Exposure Science for Toxicity Testing

- How can we characterize exposure efficiently and support development of toxicity information to facilitate prioritization of thousands of compounds?

- Paradigm shift in exposure science required
  - From resource and time intensive measurement and modeling
  - To rapid, inexpensive approaches for characterizing and predicting **biologically-relevant** exposure.
  - Leverage advanced and emerging technologies and approaches

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EPA Community of Practice: Exposure Science for Toxicity Testing, Screening, and Prioritization

- The primary purpose of the EPA Exposure Science Community of Practice (ExpoCoP) is to provide a forum for promoting the advancement and utilization of exposure science to address Agency needs for chemical screening, prioritization and toxicity testing.

- Membership of well over 40 individuals from over 15 public and private sector organizations

- http://epa.gov/ncct/practice_community/exposure_science.html

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ExpoCoP Presentations

- Chemical selection for ToxCast, Richard Judson, NCCT
- Exposure categorization of the Domestic Substances List: current status, future activities, Bette Meek, University of Ottawa
- Exposure data: structure annotation for improved access and linkage, Ann Richard, NCCT
- ECETOC Targeted Risk Assessment Tool for REACH, Rosemary Zaleski , ExxonMobile Biomedical Sciences
- Using Publicly Available Information to Prioritize Chemicals (ComET plus), Michael Jayjock, The LifeLine Group
- Characterizing Exposure to Volatile and Semi-Volatile Contaminants in Indoor Sources using Simple Mass-Transfer Models, John Little, Virginia Tech
- Assessing the Exposure-Dose-Toxicity Relationship within the EPA's ToxCast Program, Rusty Thomas, The Hamner

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ExpoCoP Presentations

- Chemical Assessment and Management Program (ChAMP), Cathy Fehrenbacher, US EPA/OPPT
- Multimedia Multipathway Modeling of Emissions to Impacts: screening with USEtox and advanced spatial modeling with IMPACT, Olivier Jolliet, University of Michigan

- GExFRAME – a Web-Based Framework for Accessing Global Exposure Data, Scenarios and Models, Muhilan Pandian, Infoscientific
- Genomics Applications: Detecting Human Exposures and Predicting Inter-individual Susceptibilities, Rebecca Fry, UNC Chapel Hill
- Biological Equivalents (BEs) and Their Use in Risk Assessment Screening and Risk Management Prioritization, Shawn Hays, Summit Toxicology
- Integrated Strategies for Exposure and Toxicity Assessment of Chemical Substances and Mixtures, Denis Sarigiannis, European Commission - Joint Research Centre
- PReParE: Physiologically Relevant Parameter Estimation for PBPK Modeling, Rocky Goldsmith, NERL

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A Path Forward: Anchoring Stressors to Real-World Human Exposure

- The NRC Vision of a shift to characterizing toxicity pathways requires a commensurate shift to characterizing exposure across all levels of biological organization.

- Interpretation of toxicogenomic hazard data requires contextual relevance. Pathways identified using HTS approaches are being anchored to apical endpoints using conventional toxicity data.

- Similarly, understanding relevant perturbations leading to these toxicogenomic endpoints requires anchoring stressors to real-world human exposure.

- New approaches to risk assessment require exposure science to predict exposures down to the molecular level. Requires systems-based consideration of interactions between exposure and effect.

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Systems-Based Exposure Science

"…systems biology will progressively complement the conventional mode **of** study by facilitating the understanding **of biological** networks and mechanisms in terms **of** their dynamic system behavior on different **levels of organization." Dubitzky, 2006**

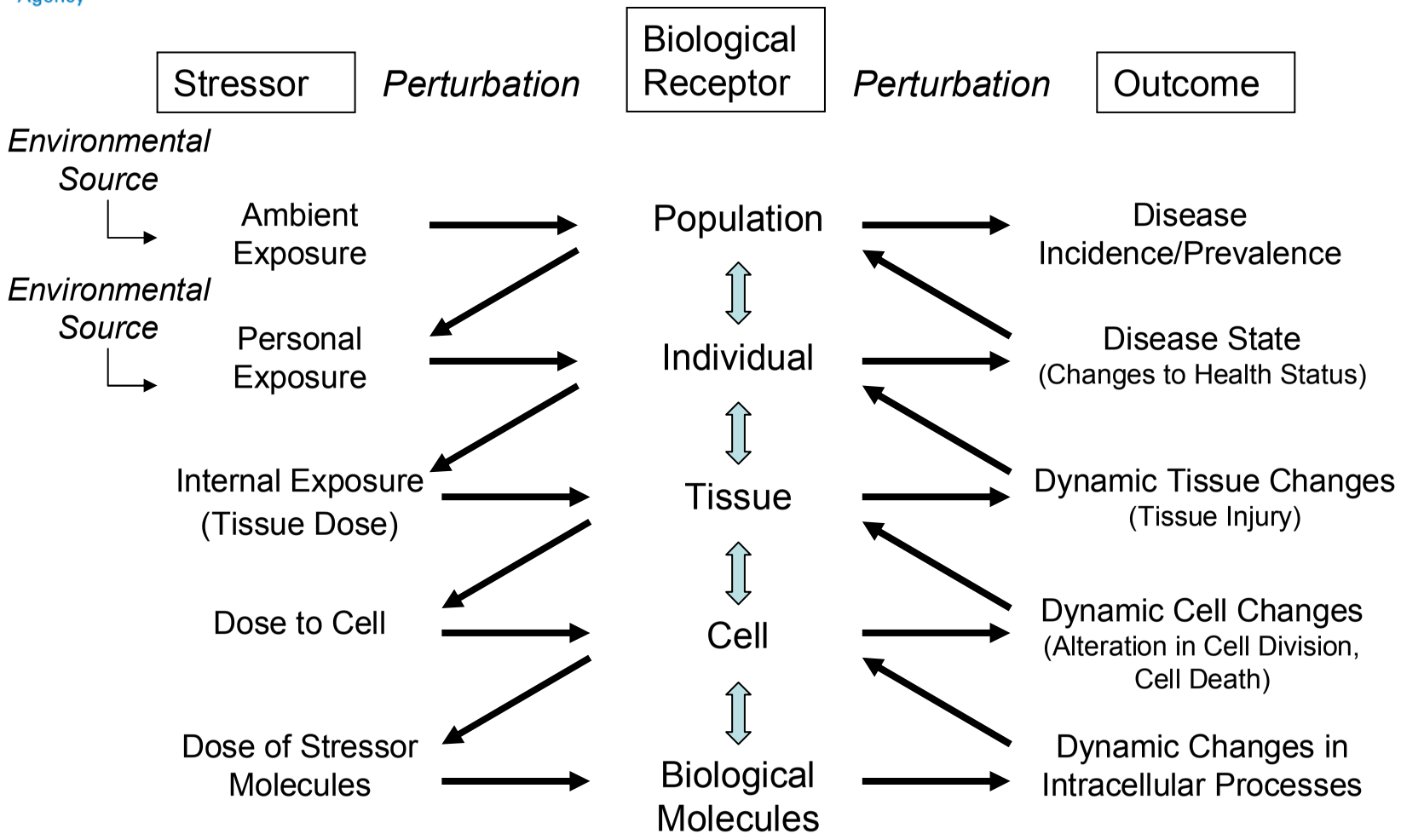
Stressor
Perturbation
Biological Receptor
Perturbation
Outcome
Environmental Source
Environmental Source
Ambient Exposure
Personal Exposure
Internal Exposure (Tissue Dose)
Dose to Cell
Dose of Stressor Molecules
Population
Individual
Tissue
Cell
Biological Molecules
Disease Incidence/Prevalence
Disease State (Changes to Health Status)
Dynamic Tissue Changes (Tissue Injury)
Dynamic Cell Changes (Alteration in Cell Division, Cell Death)
Dynamic Changes in Intracellular Processes

Figure 1