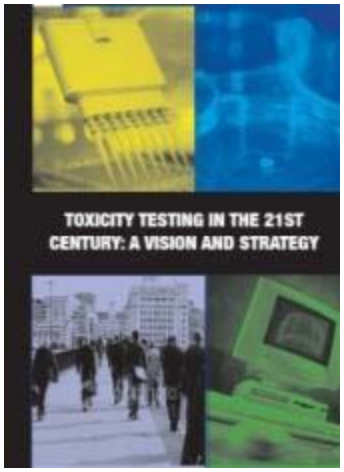
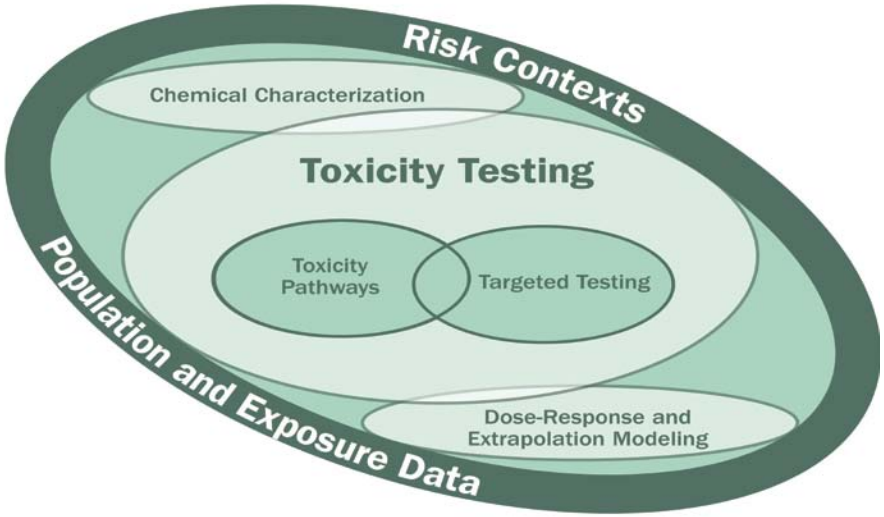
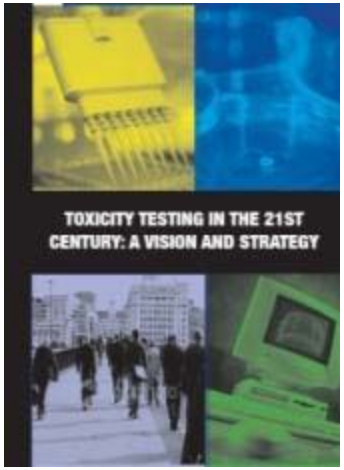


Implications of the NAS Report depend on how the program is implemented

International Implications of the NAS Report: Challenges and Opportunities
Ottawa, CA
June 29, 2009

Comments following Keynote
Melvin Andersen, PhD
The Hamner Institutes





Toxicity Testing in the 21st Century

… a not-so-distant future where all routine toxicity testing will be conducted in human cells or cell lines ***in vitro*** by evaluating perturbations of cellular responses in a suite of toxicity pathway assays.

Andersen and Krewski (2009). Toxicity Testing in the 21st Century: Bringing the Vision to Life. Tox. Sci., 107, 324-330.

In the report (Figure 5-1) implementation as a linear, comprehensive overhaul plan -but

i

1

- Elucidate toxicity pathways.
- Establish data-storing and -management systems.
- Establish practices for assay conduct and reporting.
- Plan human-surveillance and -biomonitoring strategy.

2

- Develop suite of representative human cell lines and cultures.
- Develop and validate high- and medium-throughput assays.
- Develop biomarkers for exposure, susceptibility, and effect for human surveillance and biomonitoring.

3

- Gain experience though testing mechanistic assays
  - In parallel with traditional apical tests.
  - On chemicals with large datasets of apical tests.
  - By screening chemicals that would not otherwise be tested.
- Begin biomonitoring and surveillance of human populations.

4

- Propose then validate suites of assays for use in place of identified apical tests.

Moves to the mainstream after all steps are in place – maybe 20 years
Risk Assessment approaches only vaguely identified

An Alternative – Parallel topics Approach

- **Phase I**: Select a series of prototype compounds/pathways whose targets are well-understood; use these to cover key technology areas – assay design, computational/dose response modeling, in vitro-in vivo extrapolation, etc.; **show how the process works for risk/safety assessment; compare to current methods;** make mid-course corrections.

- **Phase II**: Extend quickly to other materials and expand assays evaluated in current high throughput projects – giving more attention to assay design and pathway validation.

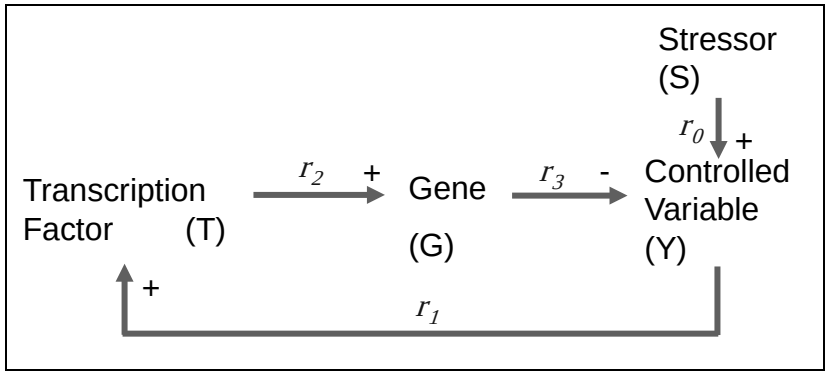
- Formalize process and approaches for using the information for safety/risk assessment

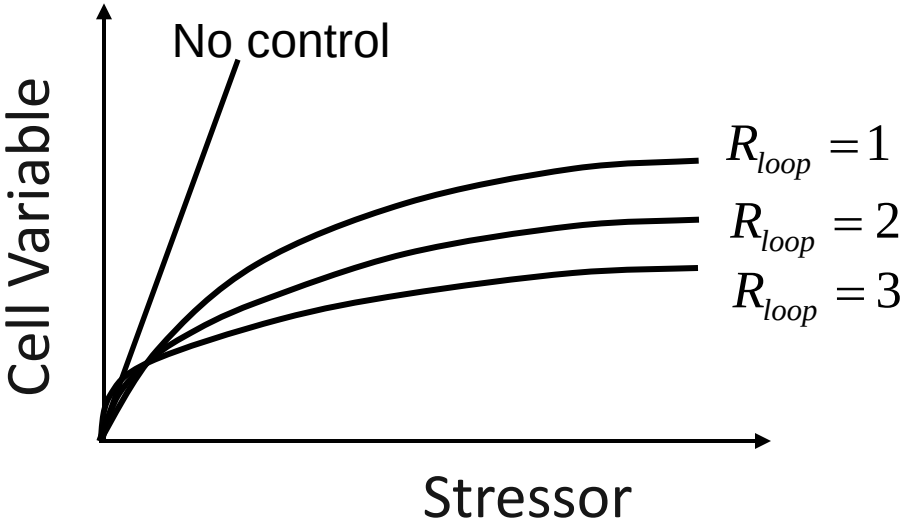
Understanding Toxicity Pathway Function/Design to guide assay design and dose response tools

Perturbations to Cellular Responses

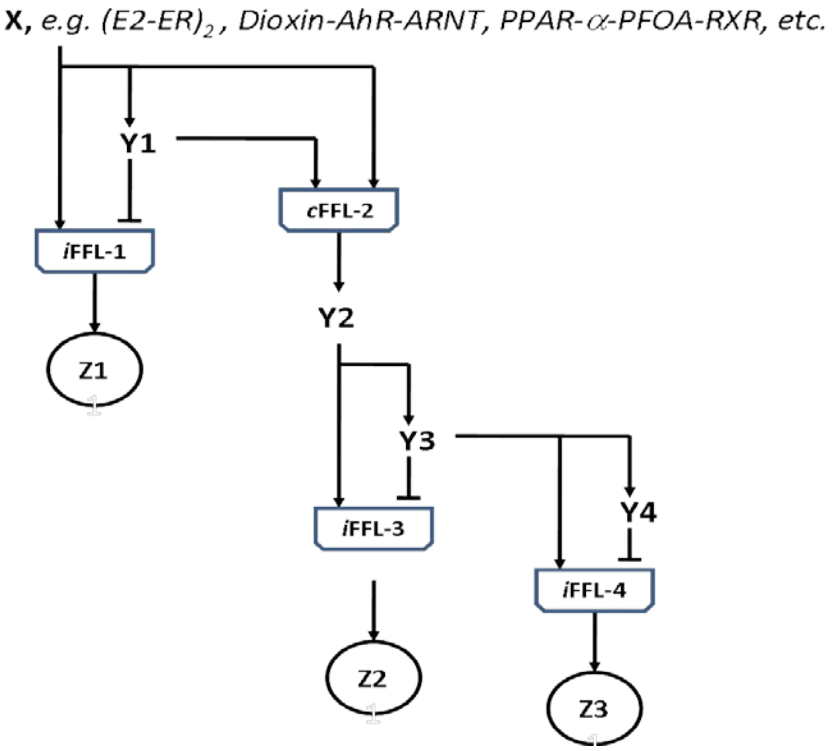
- Oxidative stress
- Genotoxic stress (DNA damage)
- Heat shock (Unfolded protein response)
- Endoplasmic reticulum stress
- Hypoxia
- Inflammation response
- Heavy metal stress
- Osmotic stress

Generic Controller Structure and Dose Response



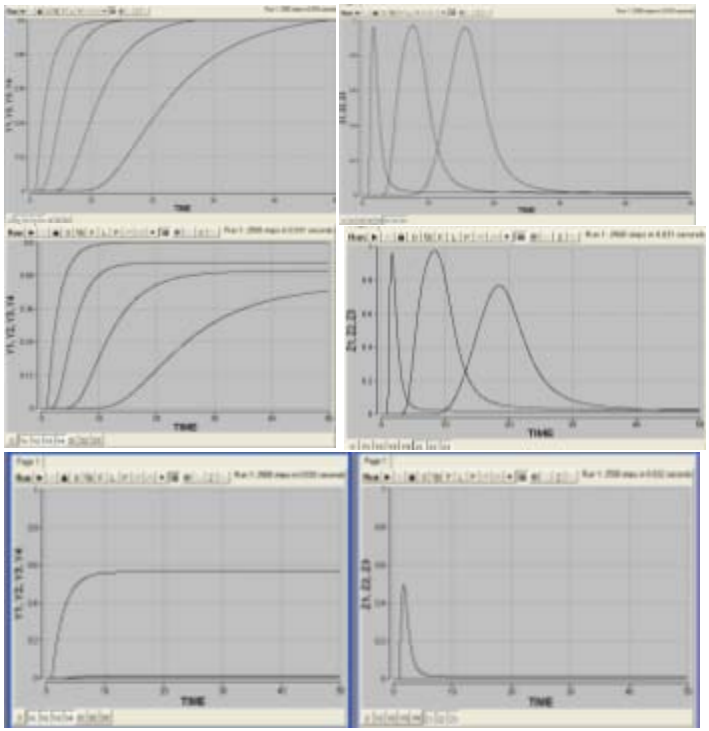


Similar considerations for receptor mediated perturbations



dose

Genes Y1- Y4 ***Genes Z1- Z3***



Depicts a series of genes in a ***network*** – Y_i and Z_i - with aspects their dose relationships to the right

Toxicity Pathway Results and Quantitative Safety/Risk Assessments – The alternative

Use prototypes, with rich data sets, that affect specific pathway targets.

Develop tools and models for pathway analysis and application in risk assessment

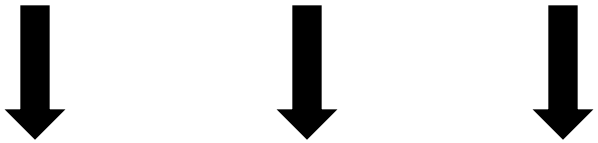
Refine as we move along with examples.

I. in vitro rapidly performed toxicity pathway test battery for *n*-assays in human cells , cell lines, or tissue aggregates

ii. Computational systems biology description of pathway circuitry for creating biologically realistic dose response models

iii. Dose dependent transition studies for sequential pathway activation to understand linkage to cell and tissue level responses (perturbations to adversity)

iv. PBPK Modules – for *in vitro- in vivo* extrapolation, and inferring human population exposures for specific use patterns



Do representative risk/safety assessments

Can a transition be accomplished in a reasonable timeframe? How?

- Need a clearly articulated plan to move new methods into practice while moving away from present, animal-intensive approaches
- Do sequentially in the beginning for well-defined pathways with well-studied prototype compounds
- Process has to be defined with sufficient clarity about implementation to have a sense of the implications