Development and Use of Biologically-Based Dose Response (BBDR) Models

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Contributing Organizations: ORD: NHEERL, NCCT

LTG 1 Poster 13

Science Questions

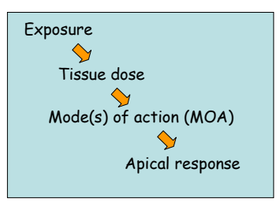
- How do we measure, model, or predict the key attributes of the MOA that could impact risk assessment?
- How do we incorporate *in vitro* data into future toxicity testing in a way that will support risk assessment?

Research Goals

- To identify toxicity pathways underlying adverse outcomes relevant to risk assessment
- To elucidate the quantitative relationship between *in vitro* toxicity pathway assays and adverse outcomes in humans
- To create models of human tissues, organs, and systems to enable quantitative risk assessment based on toxicity pathway information

What is a BBDR model?

Health risk is a function of toxicant exposure and of the shape of the dose-time response surface. When both exposure and the response surface are well characterized then risk can be predicted accurately. BBDR modeling attempts to maximize the accuracy of the description of the dose-time response surface. Relevant information on the biological mechanisms of target tissue dosimetry and on the mode or modes of action linking the target tissue dose with the apical health effect of interest are used. BBDR modeling thus depends on targeted data collection in the laboratory that is coordinated with computational modeling.



Generic structure of a BBDR model

This poster represents a survey of ongoing and future projects utilizing quantitative approaches to develop biologically-based dose response (BBDR) models. The outcome of these models are used to numerically define dose-time response surfaces related to health risks.

BBDR modeling of an environmental pollutant represents an avenue of research to identify and, in some instances, quantify uncertainties in relationship to mode of action (MOA) by which compounds elicit adverse health effects. Results from ongoing research and their impact on risk assessments are presented in the following internal and peer reviewed publications:

Findings and Conclusions

"Strategic Plan for the Future of Toxicity Testing and Risk Assessment at the U.S. EPA", FTT Working Group, EPA white paper under review by the Science Policy Council.

"Incorporating Hepatotoxicity as a Mode of Action for Several chemicals in a Generalized Quantitative Model for Tumor incidences in Mice." Luke, N.,DeVito, M. J., Conolly R., and El Masri, H. Abstract. *The Toxicologist* (2009).

"Employing a Mechanistic Model for the MAPK Pathway to Examine the Impact of Cellular All or None Behavior on Overall Tissue Response" Luke, N. S., Devito M. J., Portier, C. J. and, El-Masri, H. A. Submitted. *J. Comp. Biol.* (2008)

Experimental and mathematical modeling methods for the investigation of toxicological interactions. El-Masri, H. A. *Toxicol Appl Pharmacol* **223**, 148-154. (2007).

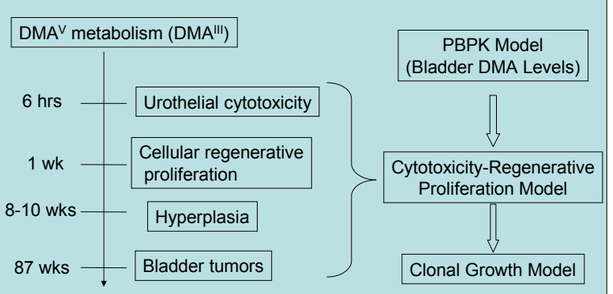
BBDR modeling and uncertainty in risk assessment

When should a BBDR model be used in place of default approaches? This is an easy question to ask but in practice is often difficult to answer. Since default approaches typically use little or no mechanistic data relevant to the toxicant in question, alternative approaches that are more data-based would seem to be preferable. However, BBDR models can have uncertainties associated with their relatively complex structures and with their large numbers of parameters. Acceptance of BBDR models for use in risk assessment is thus an ongoing challenge. Well-defined criteria for model validation and for the evaluation of the uncertainties of BBDR models relative to that of defaults are important research needs.

Examples of ongoing and future research in BBDR Modeling

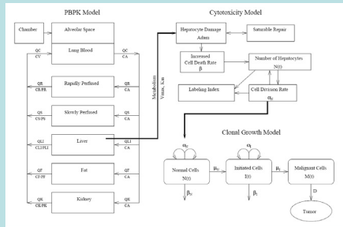
(1) BBDR model for dimethyl arsenic

- Putative mode of action is cytotoxicity and regenerative cell proliferation
- BBDR Model is developed to quantitatively address:
  - Differences in bladder tumor incidences among species:
    - Rat bladder urothelium is highly responsive by several endpoints
    - Mouse is almost non-responsive (some evidence of cytotoxicity)
  - Possible human relevance of rat bladder tumors for exposure to inorganic arsenic (known inducer of bladder cancer in humans)

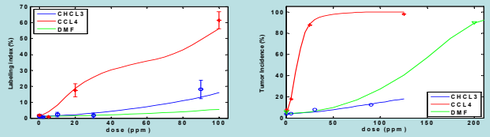


(2) BBDR model for cytotoxic carcinogens

Cytotoxicity leads to a compensatory increase in cell proliferation, which is a risk factor for cancer. BBDR modeling is used to examine how the dose-responses for key cytotoxic effects of chloroform, carbon tetrachloride, and dimethylformamide influence the corresponding dose-responses for their carcinogenic effects.



Schematic of the overall BBDR Model



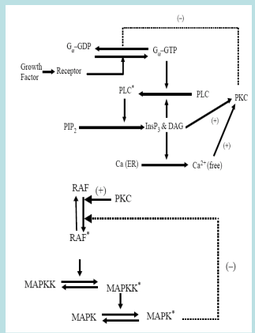
BBDR model simulations against data for three chemicals

Table 1: Parameter values for Chemical Specific Parameters in model. Values with asterisks were optimized to data

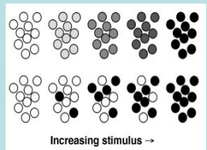
Parameter	Function	CHCL3	CCL4	DMF
$V_{max,c}$	maximal rate of metabolism	0.642	0.0605	1.0855*
$K_{m,c}$	half maximal concentration	0.77	0.46	14.2
k_{dam}	proportionality constant relating rate of metabolism to damage	1	8.152*	0.5255*
DI	chemical dependent increase in the death rate of initiated cells	4.7132*	0.45224*	0.4834*

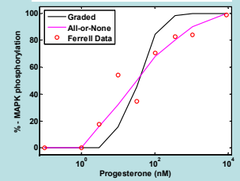
(3) Signaling model for all or none MAPK activation

A Biologically based computational model incorporating key events in the activation of MAPKinase is used to determine if "all or none" or graded cellular response can best describe tissue dose response relationship between Progesterone levels and MAPK phosphorylation in *Xenopus* oocytes



Schematic of MAPK activation Model



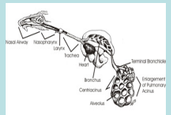


Graded response – as stimulus increases, each cell reacts in the same, graded fashion.

All or None response – Each cell has two states, off and on. As stimulus increases, more cells reach their on state. Tissue level (average) is analogous to graded response.

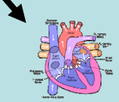
(4) BBDR Model of Cardiopulmonary System (Inhaled Reactive Gases and PM)

Internal dose of inhaled Cl_2, O_3 or PM dictated by species-specific ventilation rate and airway architecture



Compartmental model of PM deposition and clearance in major respiratory tract regions used to compute retained dose

Cardiopulmonary and Systemic Disposition Models



- Cardiac Tissue Model
  - Physiological
    - Electrocardial
    - Compliance/Heart rate
  - Biochemical
    - Oxidative stress

Further details are given in LTG 1 Poster 14

Impact and Outcomes

- This research effort will integrate computational modeling and data generation to support the development of BBDR models for use in risk assessment.
- BBDR Models will provide unique and useful tools for science-based derivation of risk posed by exposure to environmental pollutants.
- BBDR models will be used to quantify any new toxicity pathways available from Toxcast and Tox21. These pathways will be linked to key events in the mode of action employed by the model
- BBDR models will comprise different modules describing biological events that can be incorporated into virtual tissues (see LTG1 Poster 12).

Future Key Products

- Analysis of genetic-cellular networks underlying the normal biology of the system to identify critical events in toxicity pathways to be included in BBDR models for selected environmental pollutants (short term)
- Identification of data gaps to provide numerical estimates for parameters implemented in BBDR models (short term).
- Generation of *in vitro* data to support the quantitative development of BBDR models of selected toxicity pathways (mid term)
- Quantitative models linking toxicity pathway data to adverse outcomes in humans (long term)
- Model-generated data to support the use of resulting quantitative models in risk assessment (long term)

Researchers Involved

BBDR Modeling Participants

NHEERL: Michael DeVito, Nicholas Luke, Elaina Kenyon, Stephen Edwards, Andrew Geller
NCCT: David Dix, Imran Shah, Keith Houck, Richard Judson, Thomas Knudsen, Robert Kavlock
NHEERL/NCEA: Annie Jarabek

Tox21 Memorandum of Understanding (EPA participants)

NHEERL: Chris Corton, Julian Preston, Kevin Crofton, Michael DeVito, Ram Ramabhadran, Stephanie Padilla, Stephen Edwards, Steve Simmons, Vickie Wilson, William Mundy

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