

Chemical Risk Assessment and Virtual Tissues

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY



**COMPUTATIONAL
TOXICOLOGY**

Disclaimer

- ❖ *This work was reviewed by EPA and approved for presentation but does not necessarily reflect official Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation by EPA for use.*



The mission of the
Environmental Protection
Agency is to protect human
health and the environment.

Challenges

TOXICITY TESTING IN THE 21ST CENTURY

A VISION AND A STRATEGY

Committee on Toxicity Testing and
Assessment of Environmental Agents

Board on Environmental Studies and Toxicology

Institute for Laboratory Animal Research

Division on Earth and Life Studies
NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

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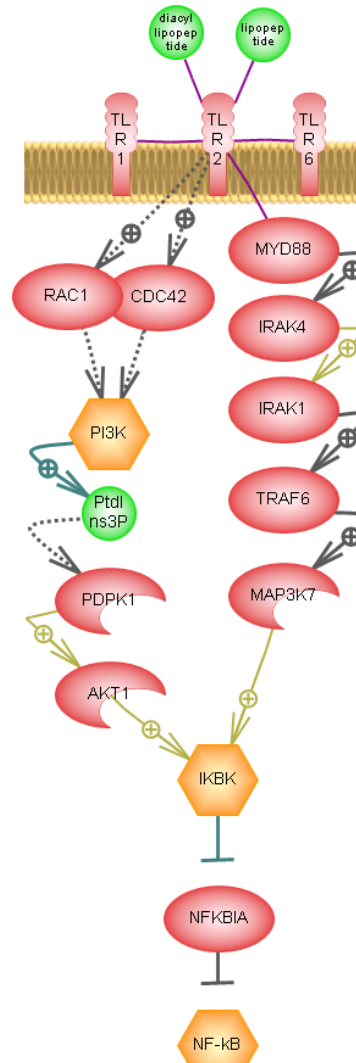
Examples of toxicity pathways

**B-cell
activation**



**Plasma
cell**

**Toll-like
receptor
signaling**

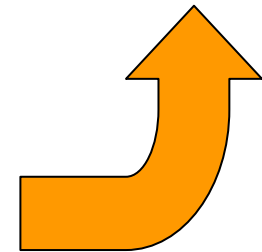
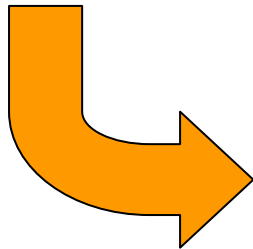
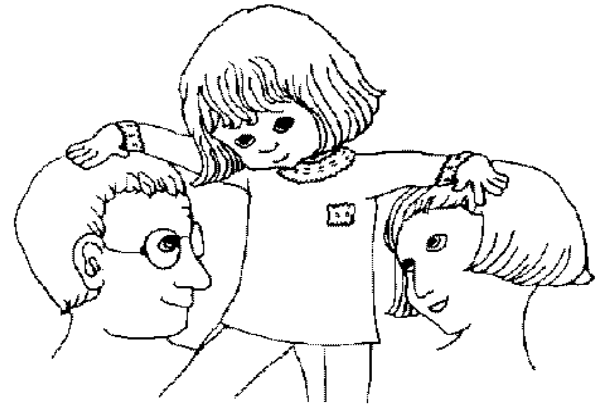
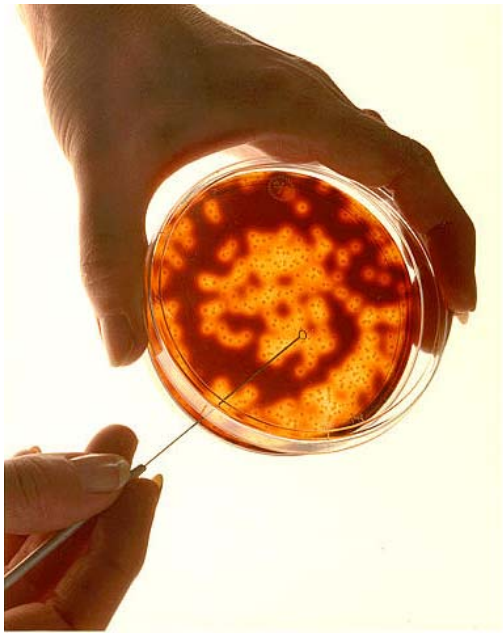


**Innate
immunity**

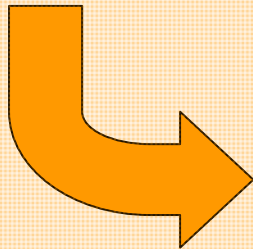
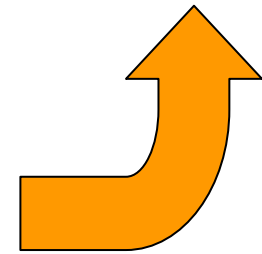
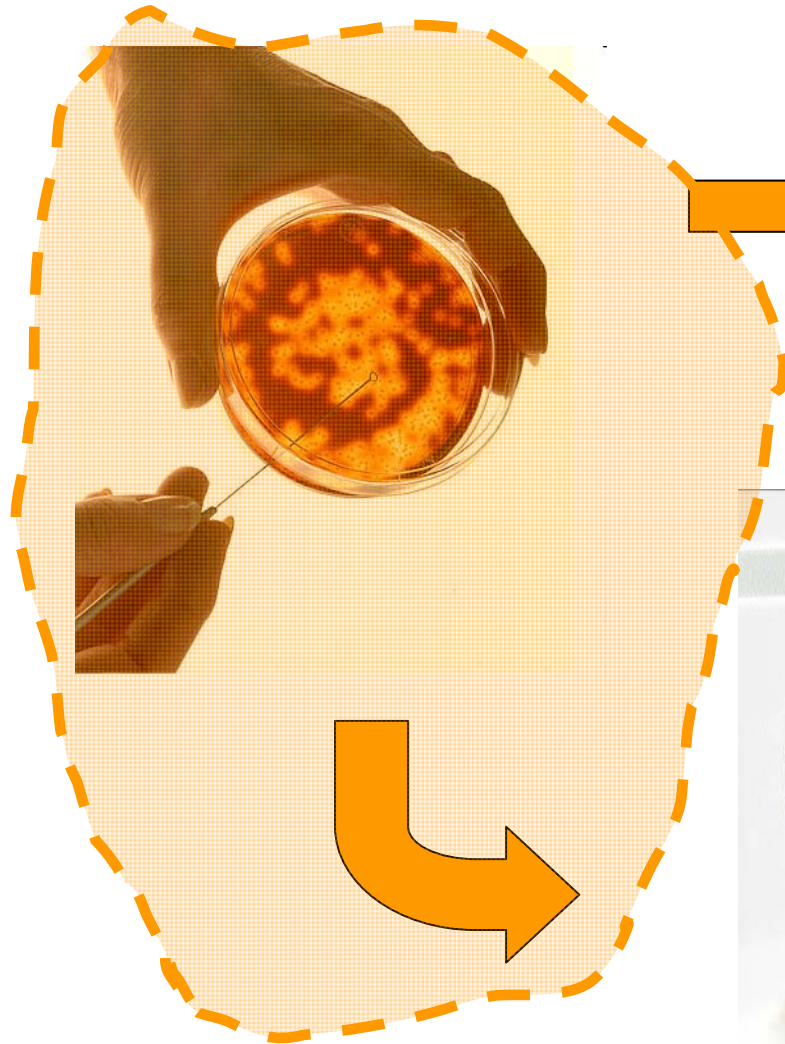
NAS paradigm

- ❖ Evaluate perturbations of toxicity pathways at relevant doses
 - Move away from traditional high dose, laboratory animal-based toxicity testing
- ❖ Concentrations to use *in vitro*?
- ❖ Qualitative and quantitative linkages to *in vivo* effects?

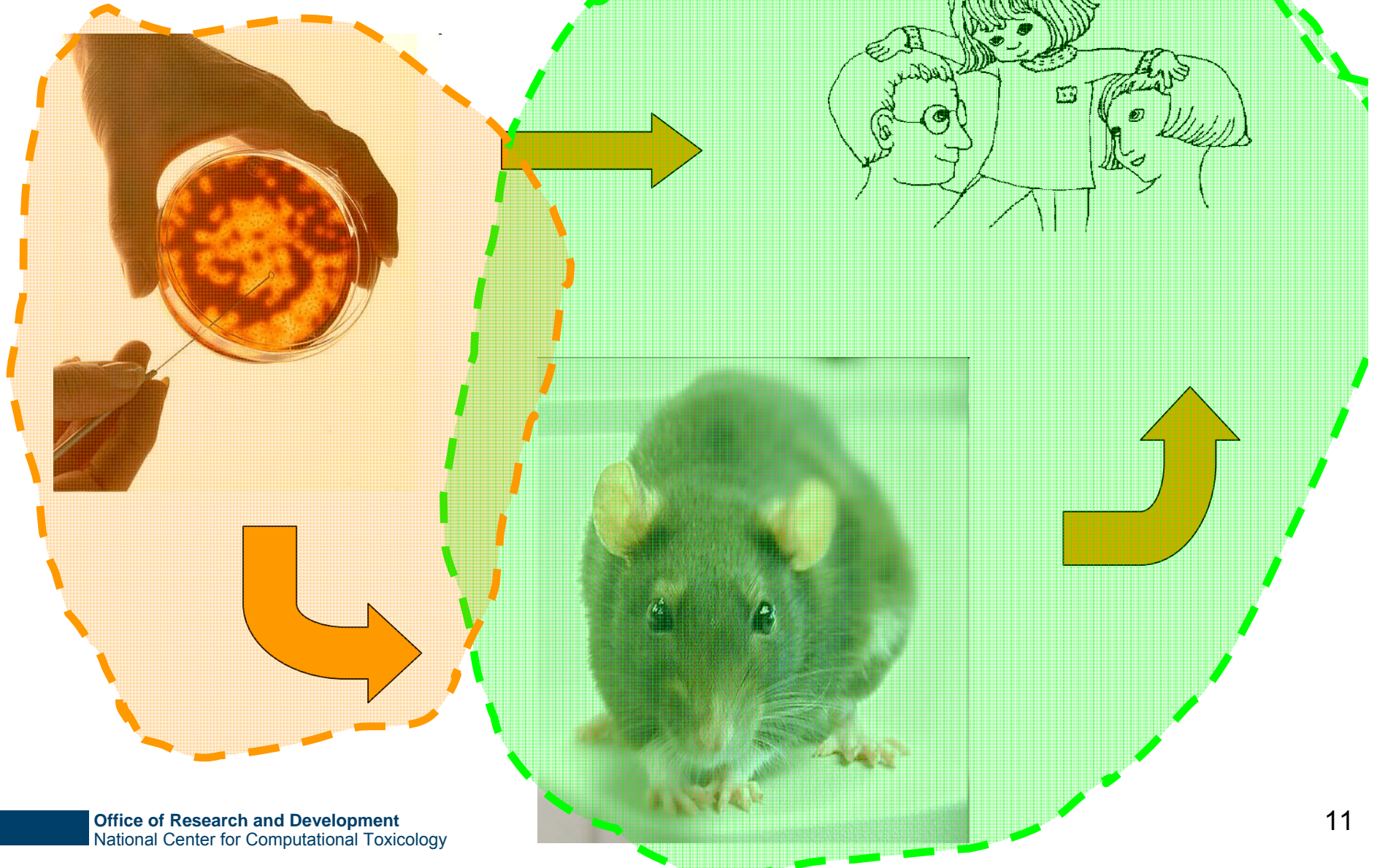
Extrapolations



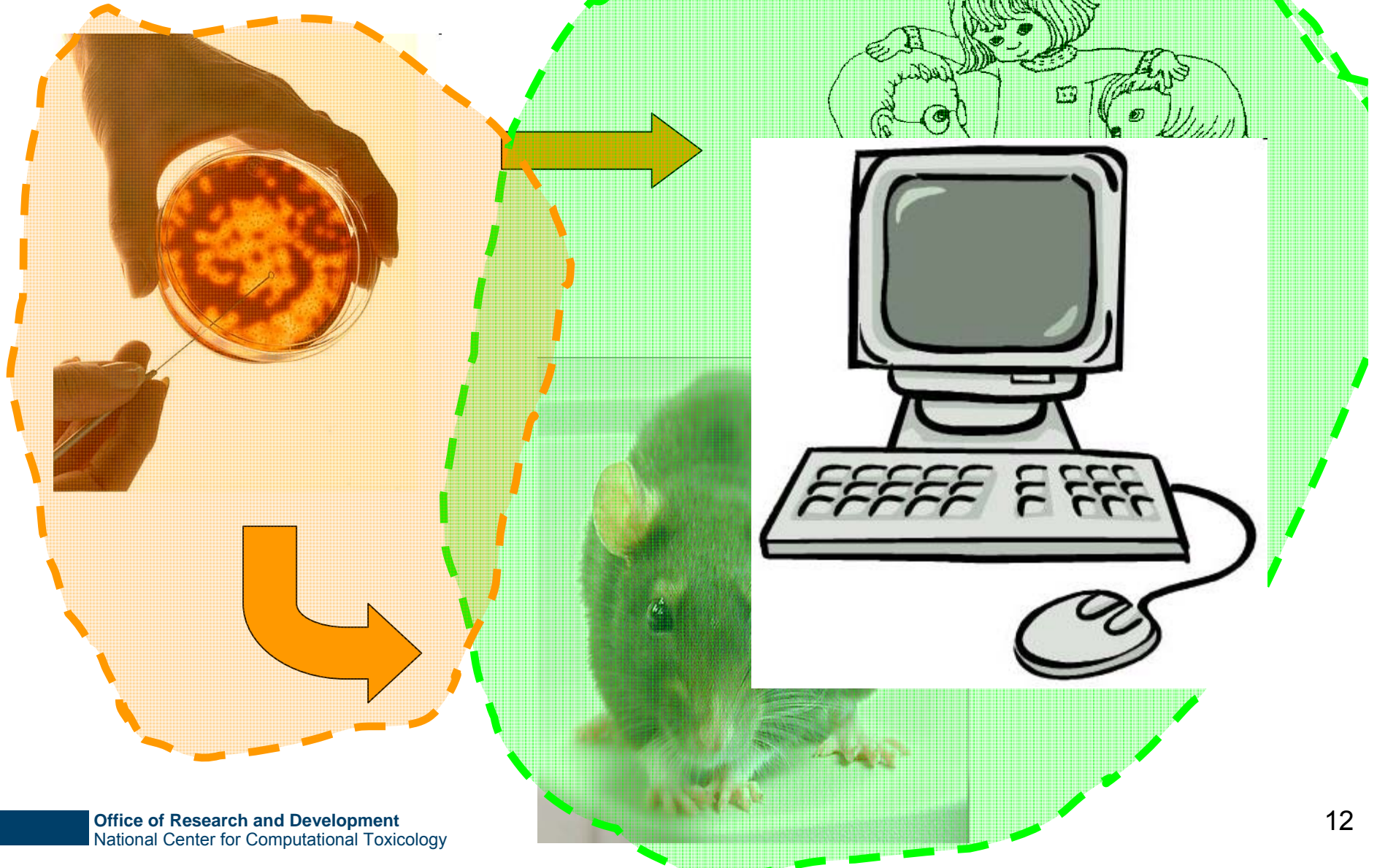
Extrapolations



Extrapolations

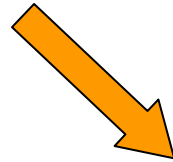


Extrapolations

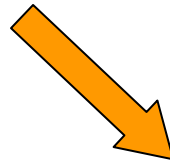


Data needs for extrapolations

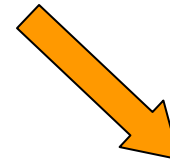
Exposure



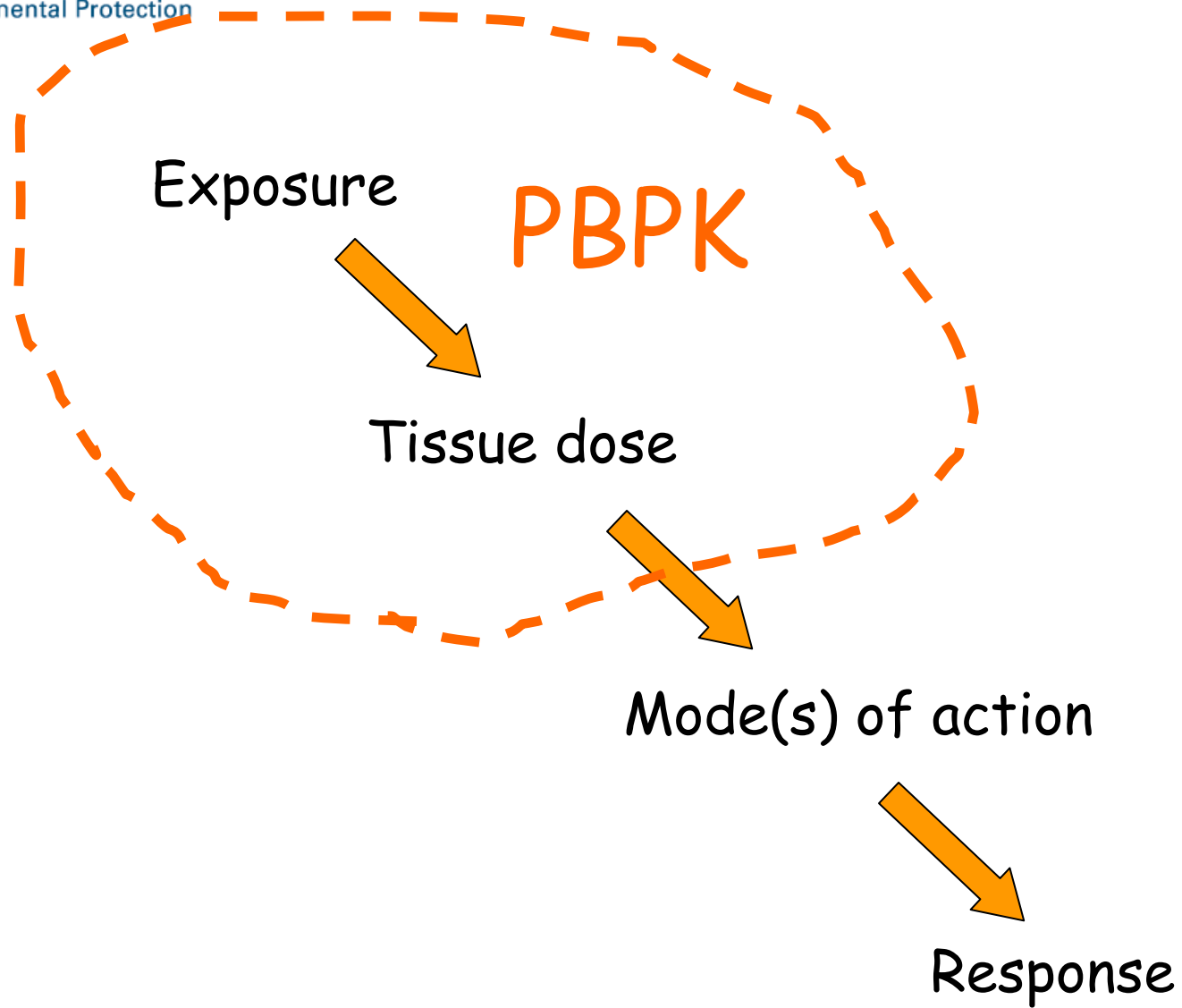
Tissue dose



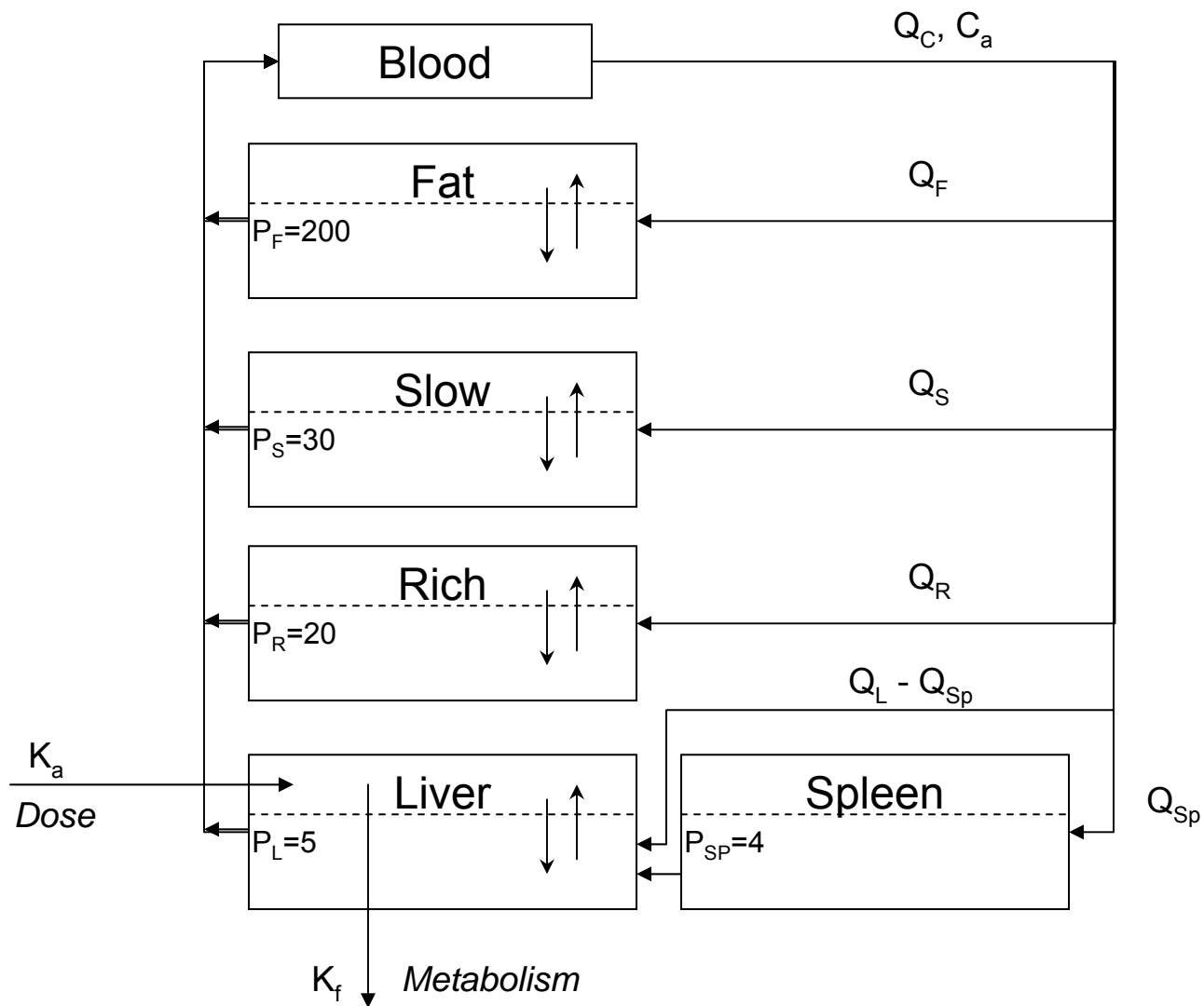
Mode(s) of action



Response

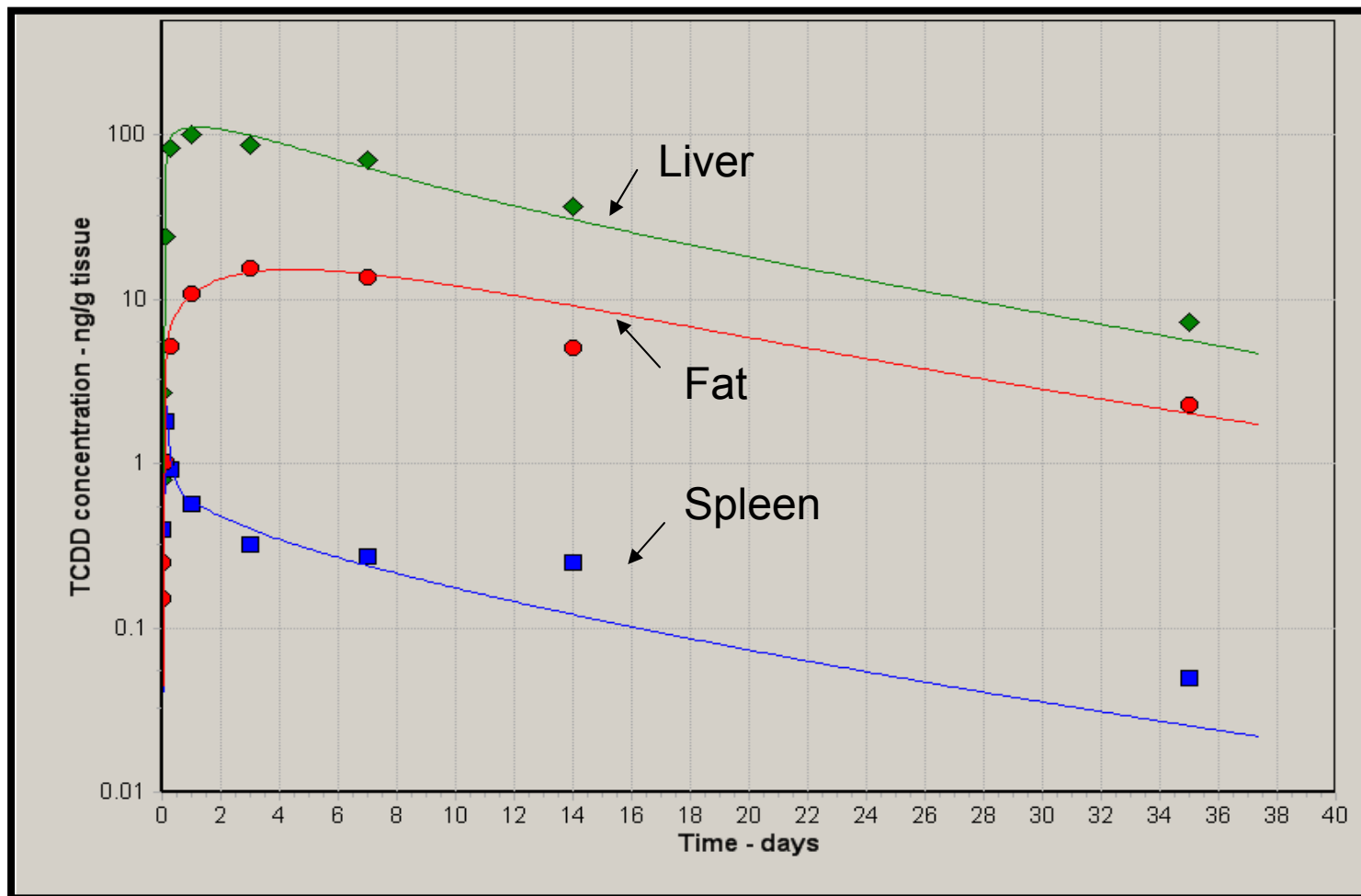


Dioxin PBPK model



Dioxin PBPK Model

Fitting time-course rat data

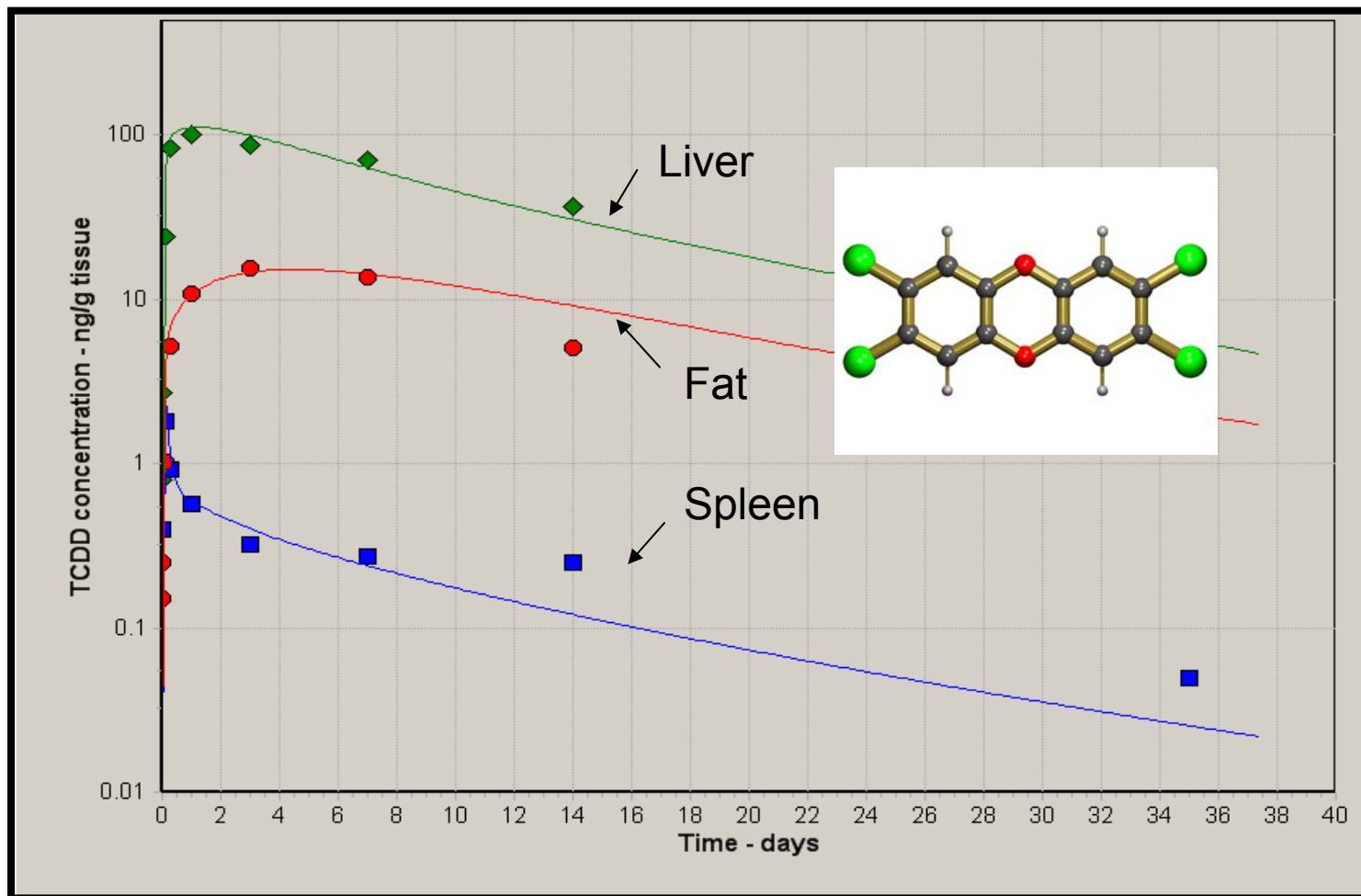


Oral dose: 10 $\mu\text{g}/\text{kg}$

(Wang et al. '97)

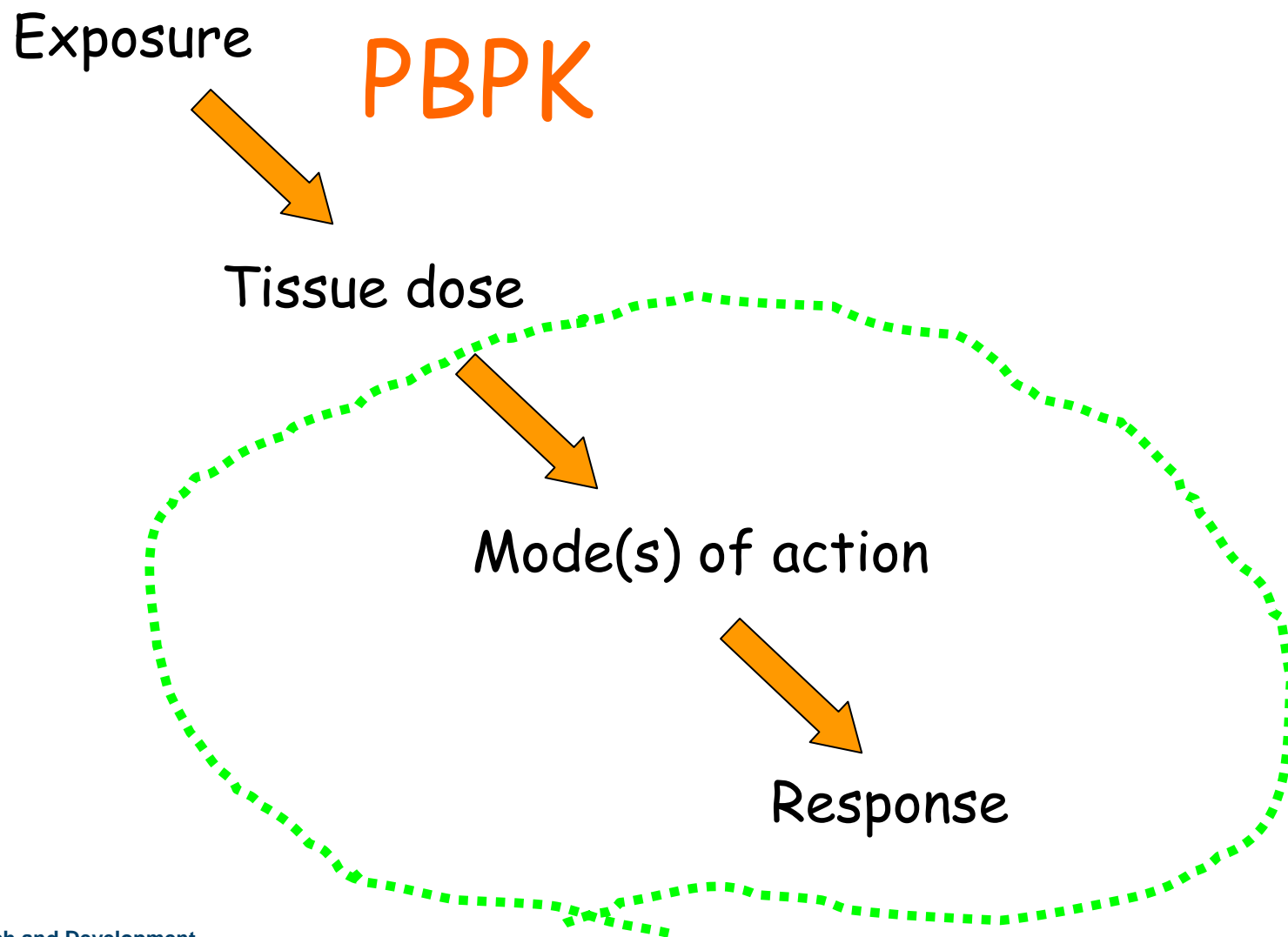
Dioxin PBPK Model

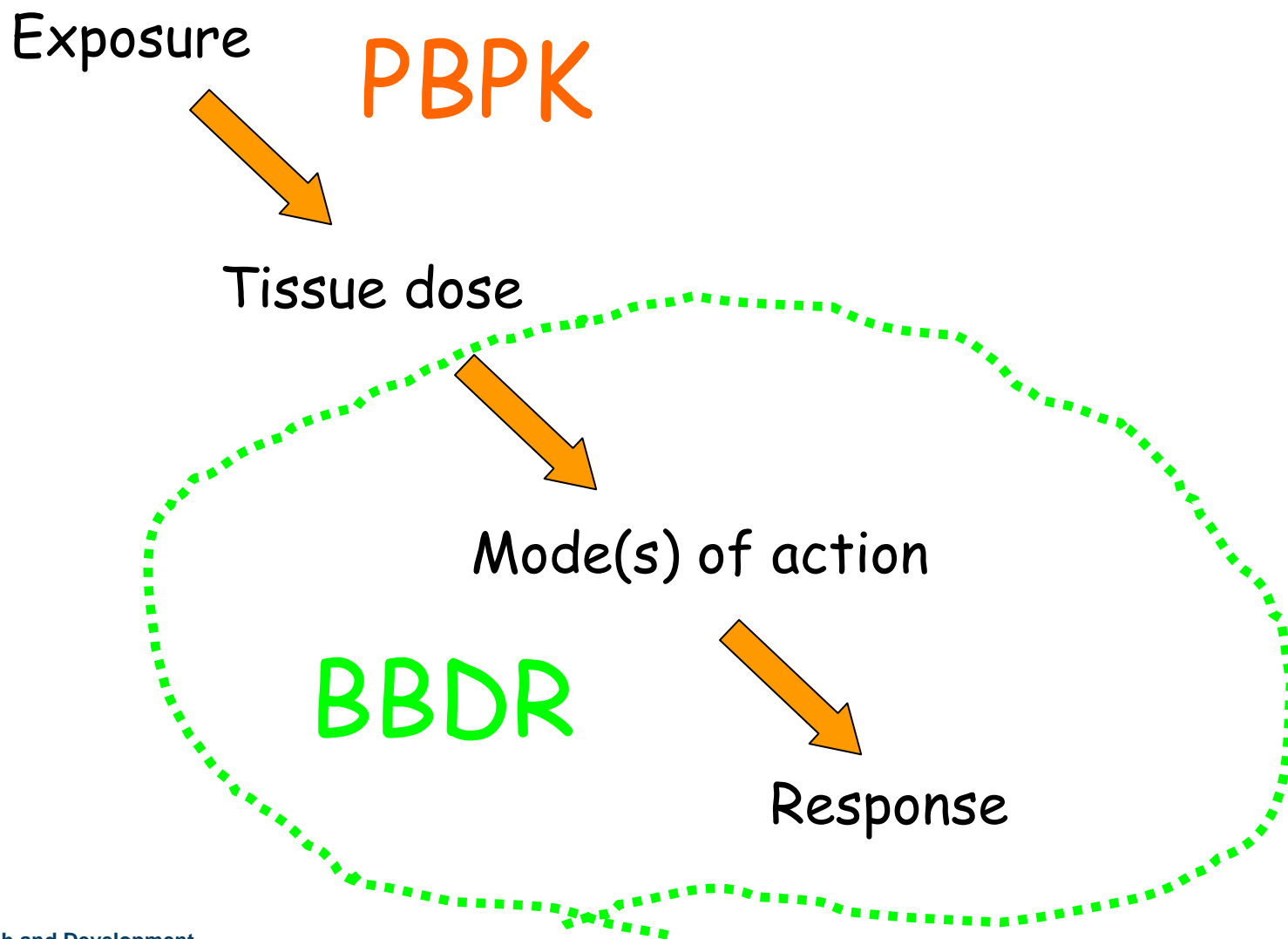
Fitting time-course rat data



Oral dose: 10 $\mu\text{g}/\text{kg}$

(Wang et al. '97)₈





Mode of Action

- ❖ . . . a sequence of **key events** and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. . .

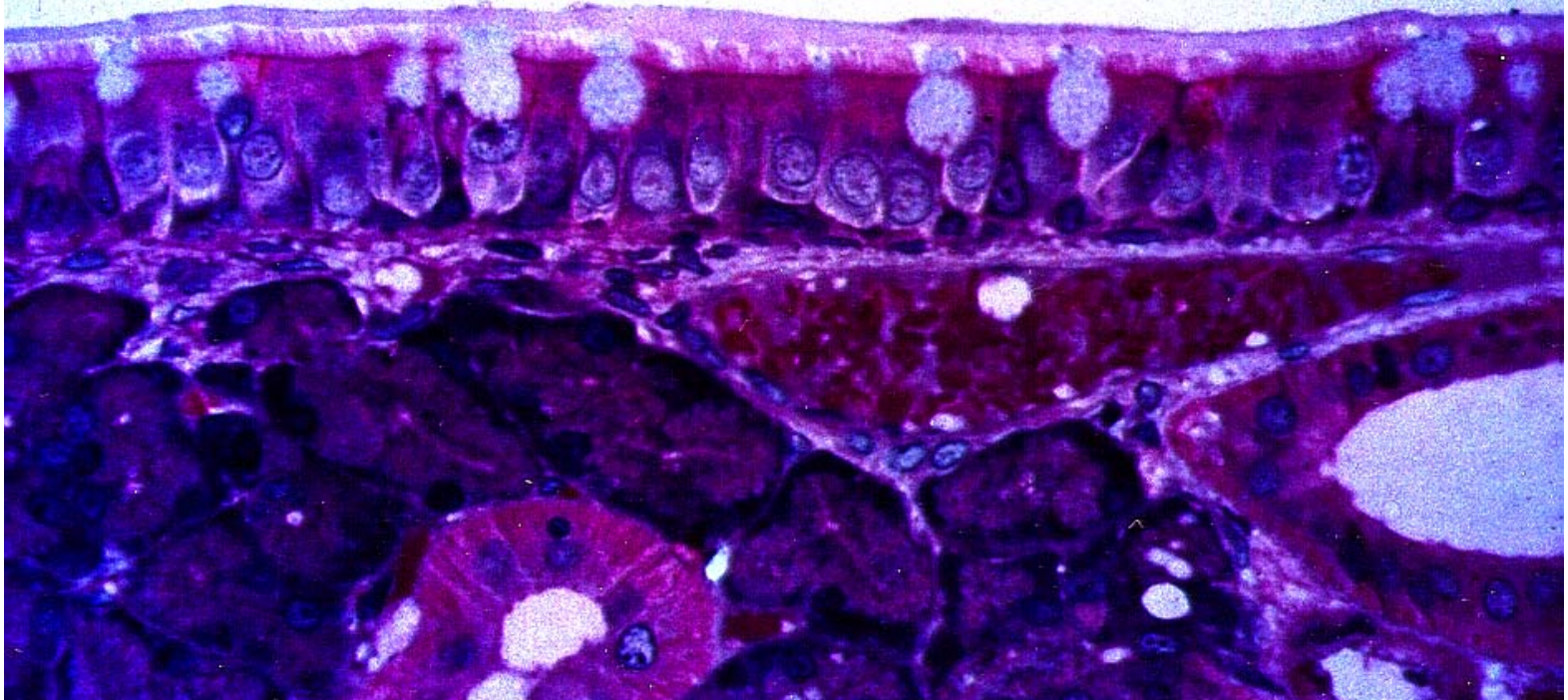
(Rita Schoeny)

EPA Cancer Guidelines, 2005

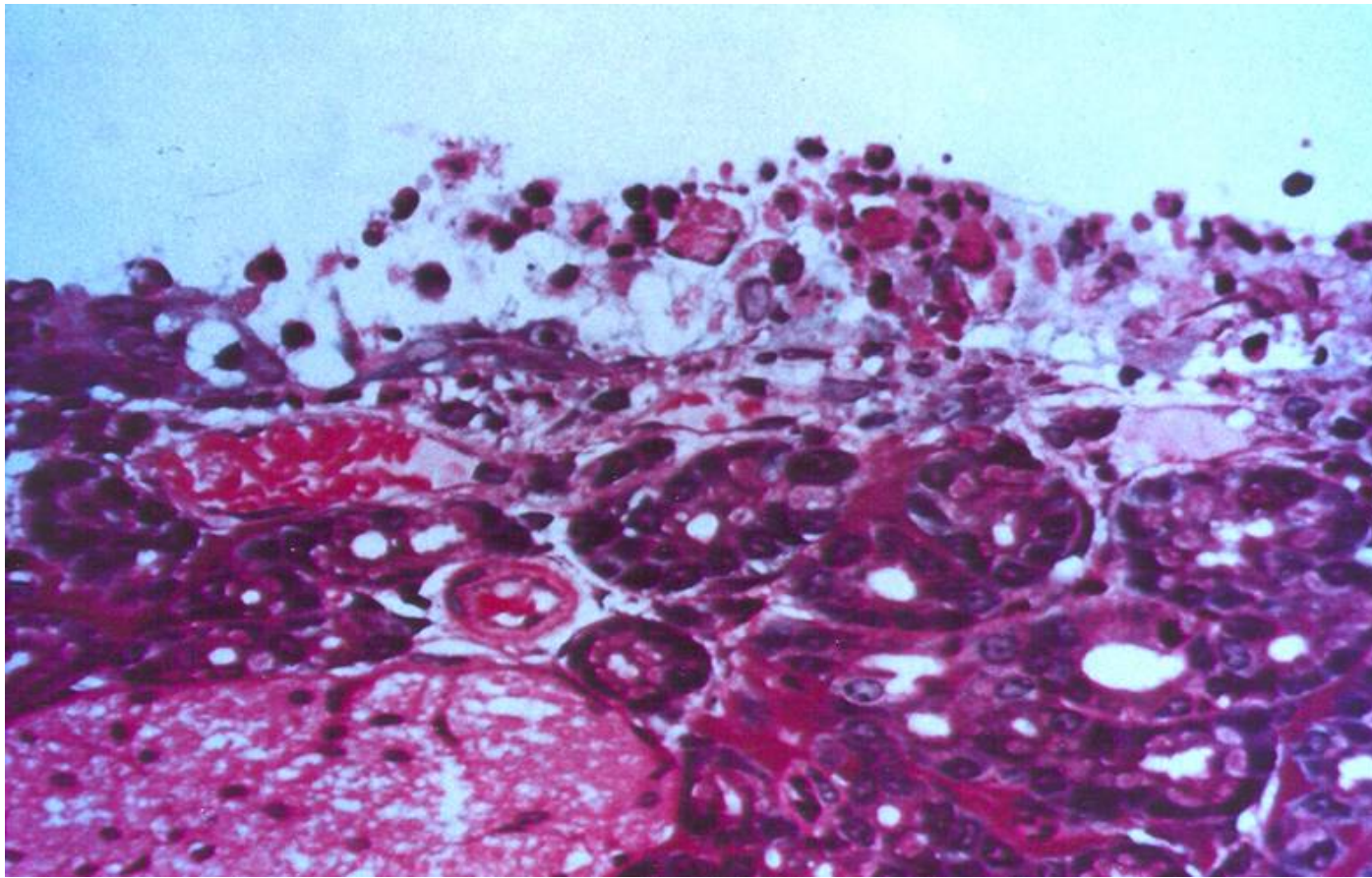
Formaldehyde



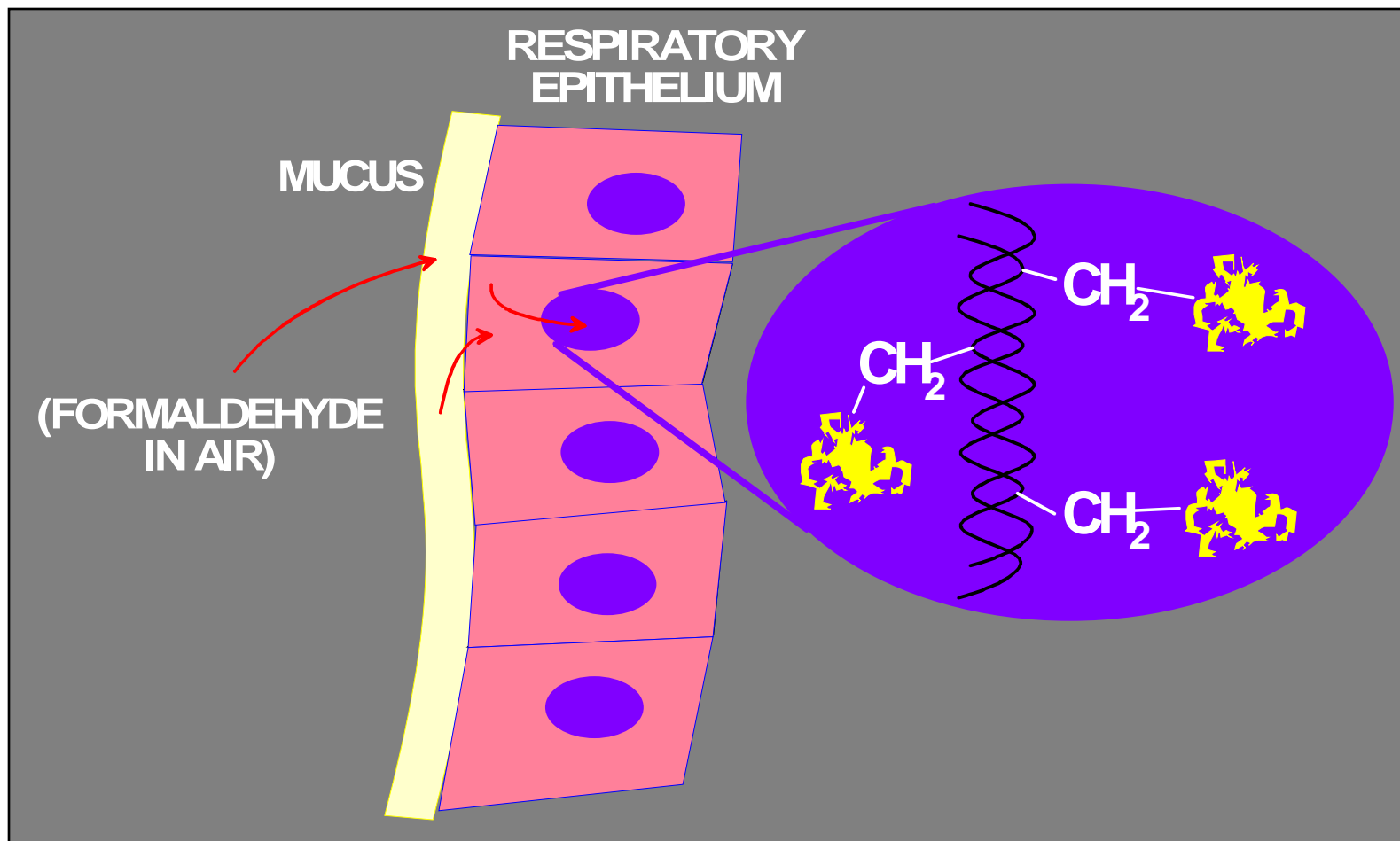
Normal respiratory epithelium in the rat nose



Key event: Cell killing → regenerative proliferation

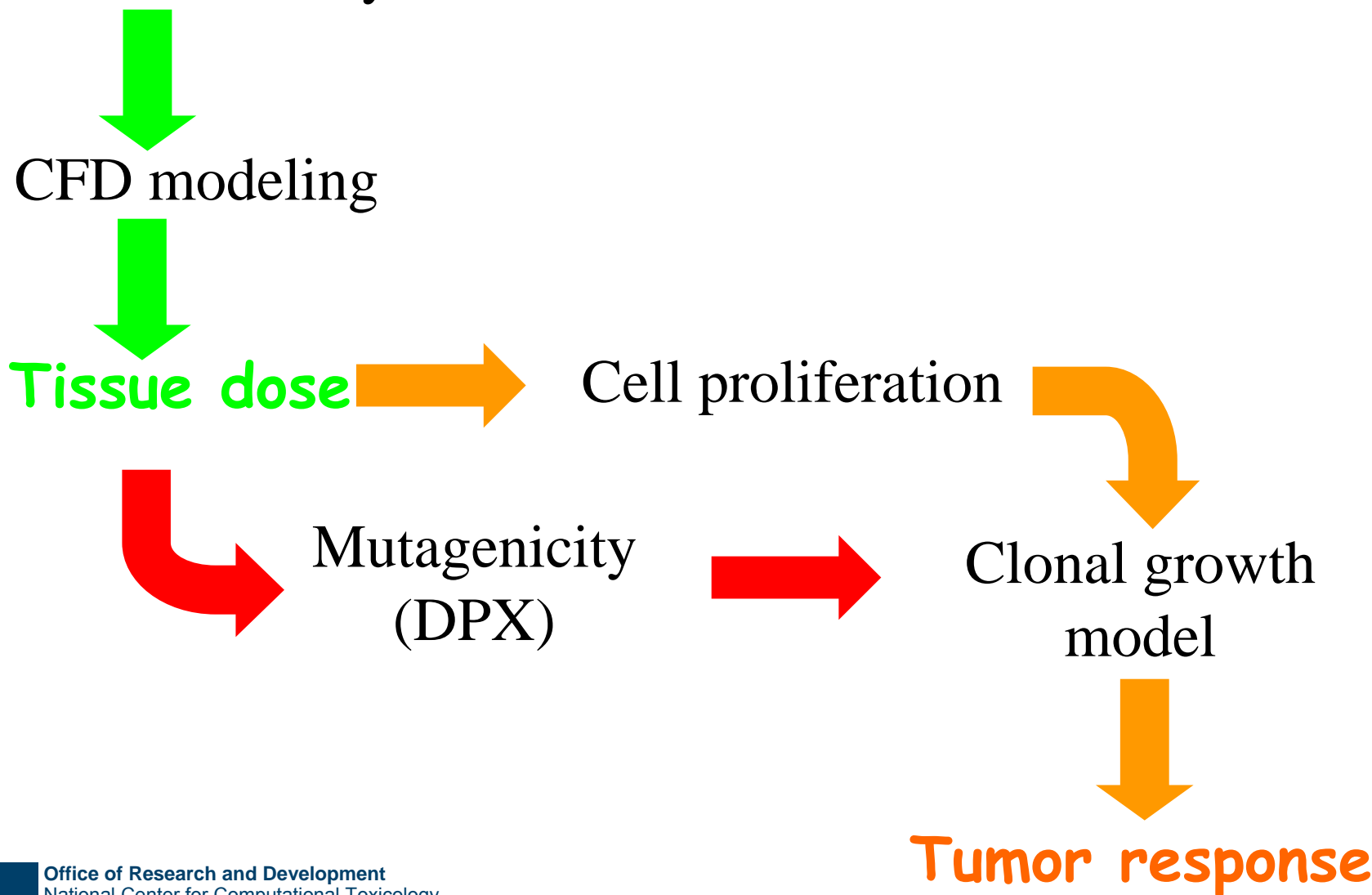


Key event: DNA-protein cross-links (DPX)

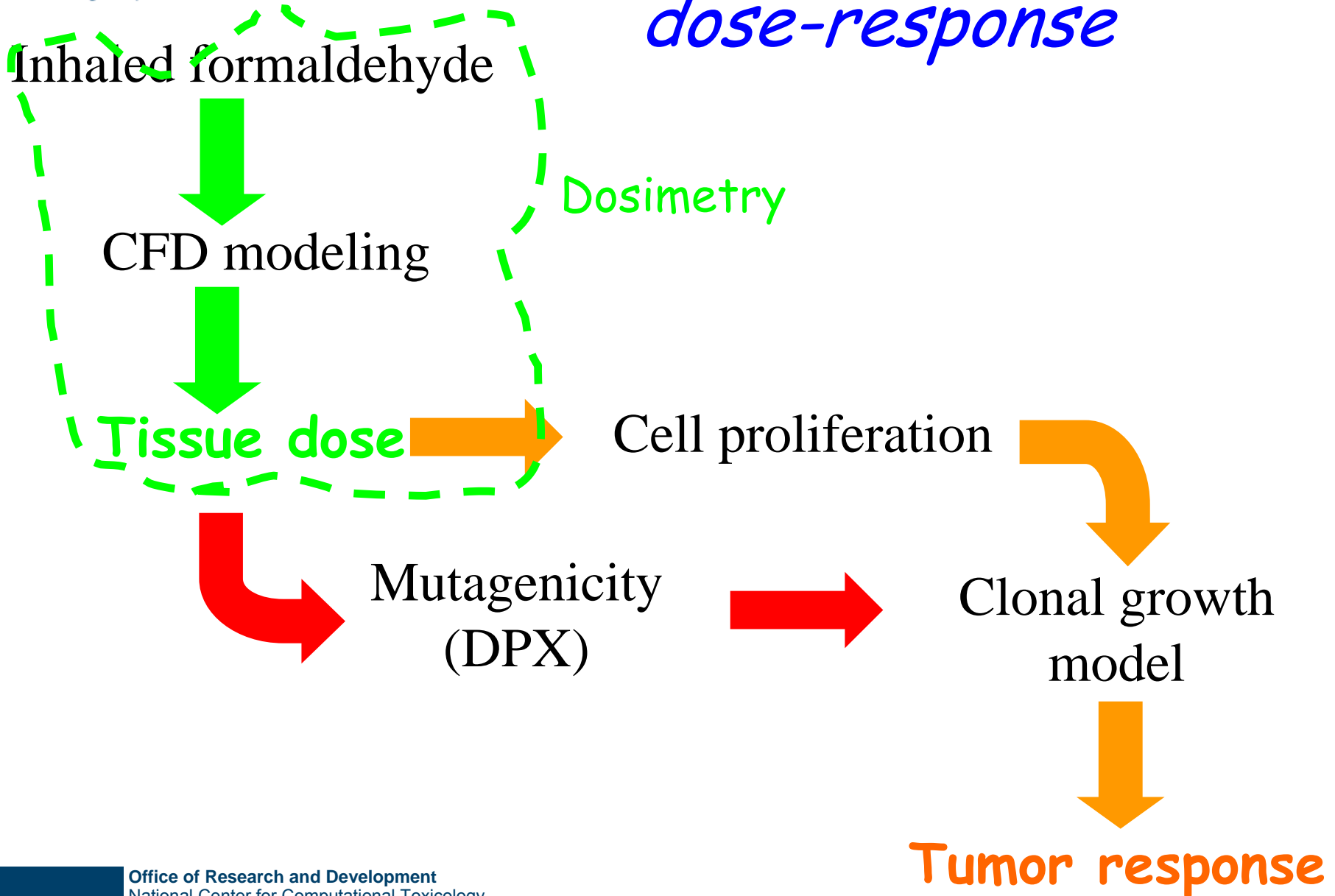


MoA -based assessment of dose-response

Inhaled formaldehyde

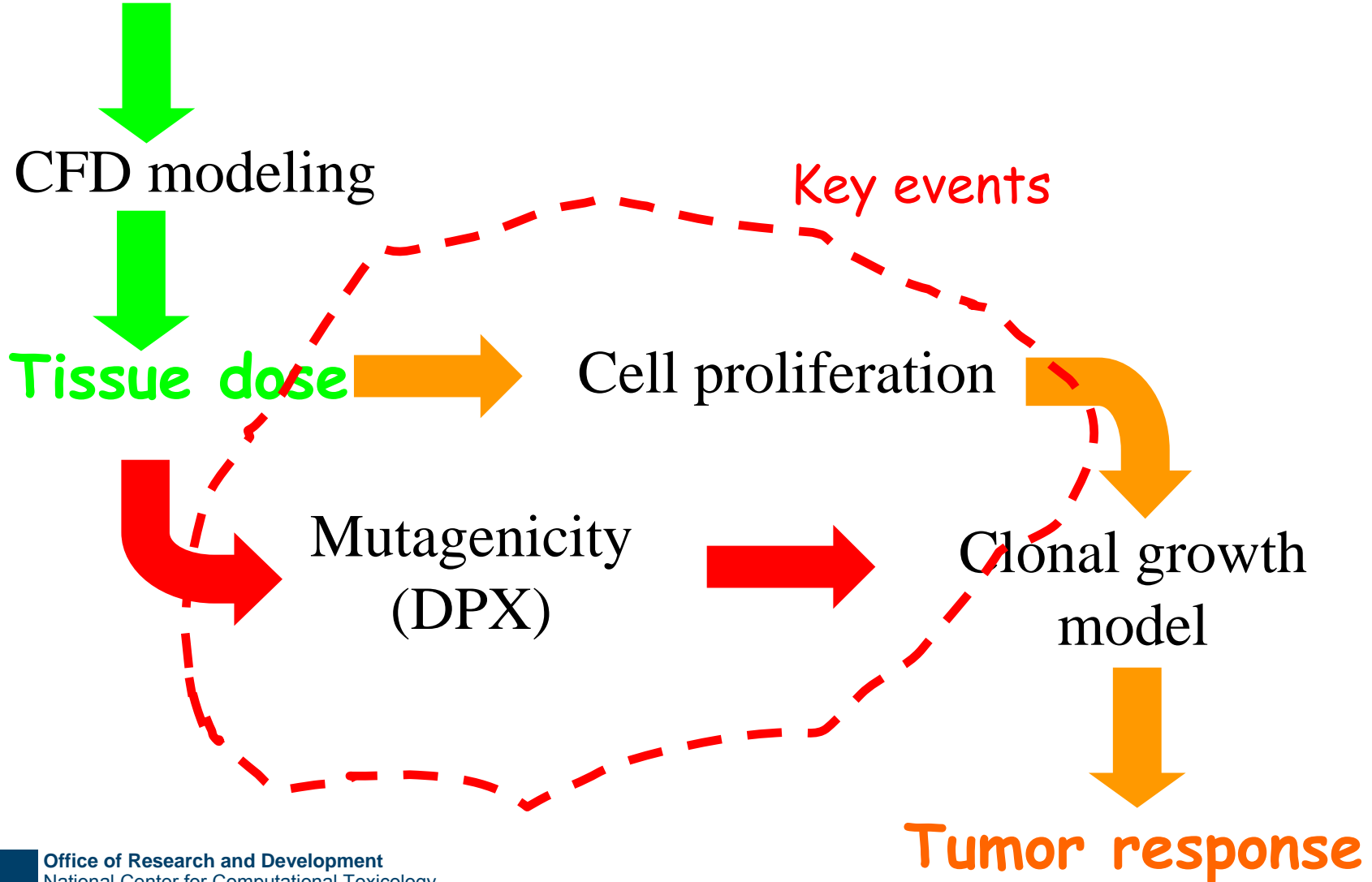


MoA -based assessment of dose-response



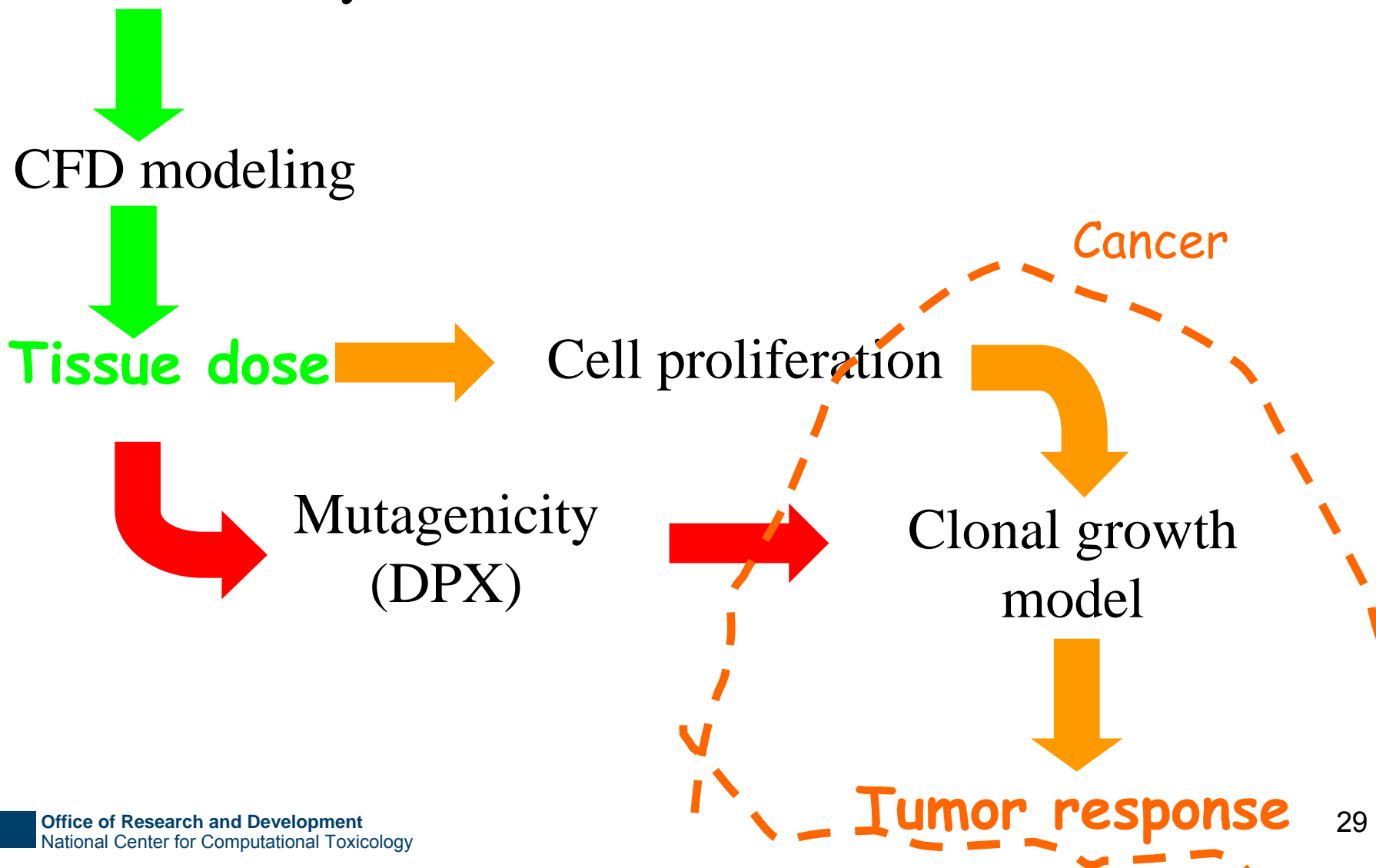
MoA -based assessment of dose-response

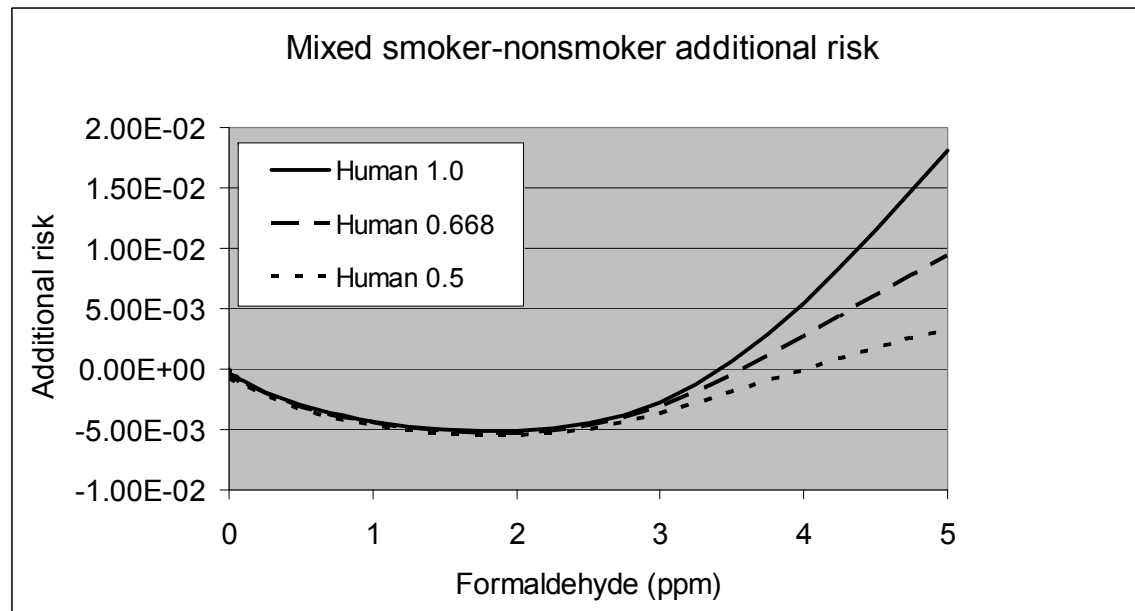
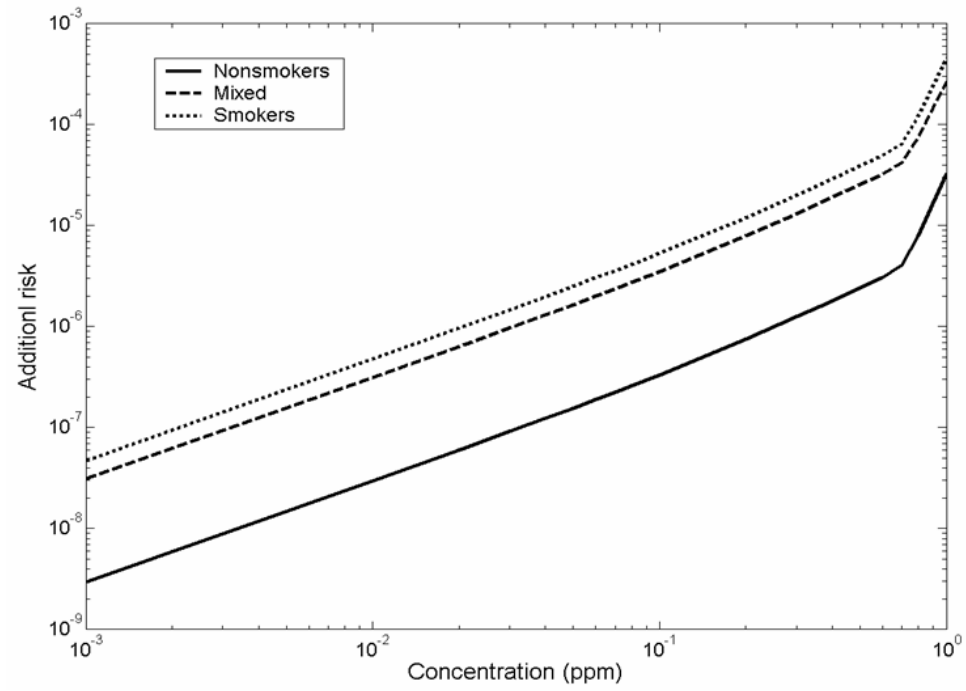
Inhaled formaldehyde



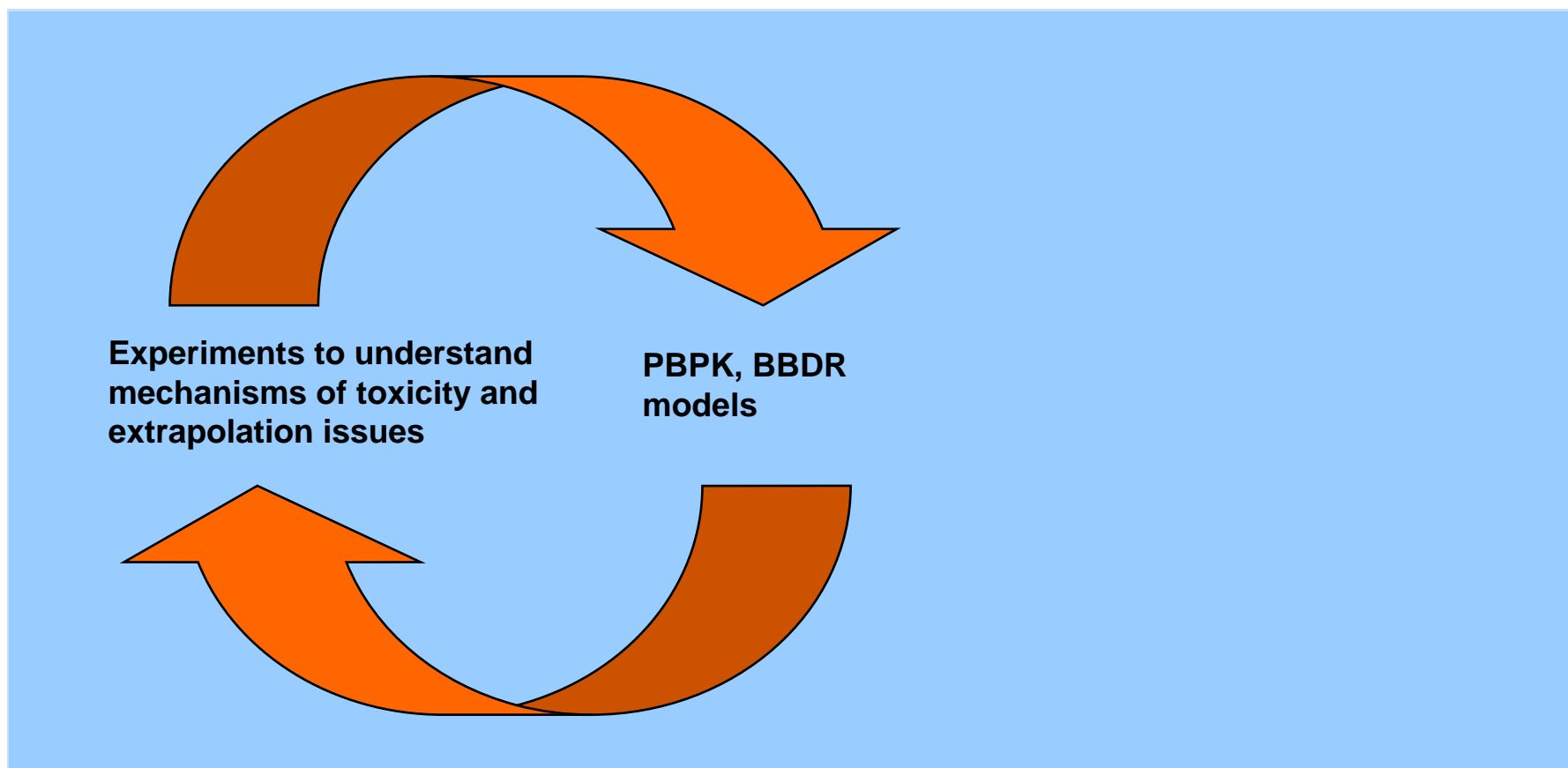
MoA -based assessment of dose-response

Inhaled formaldehyde

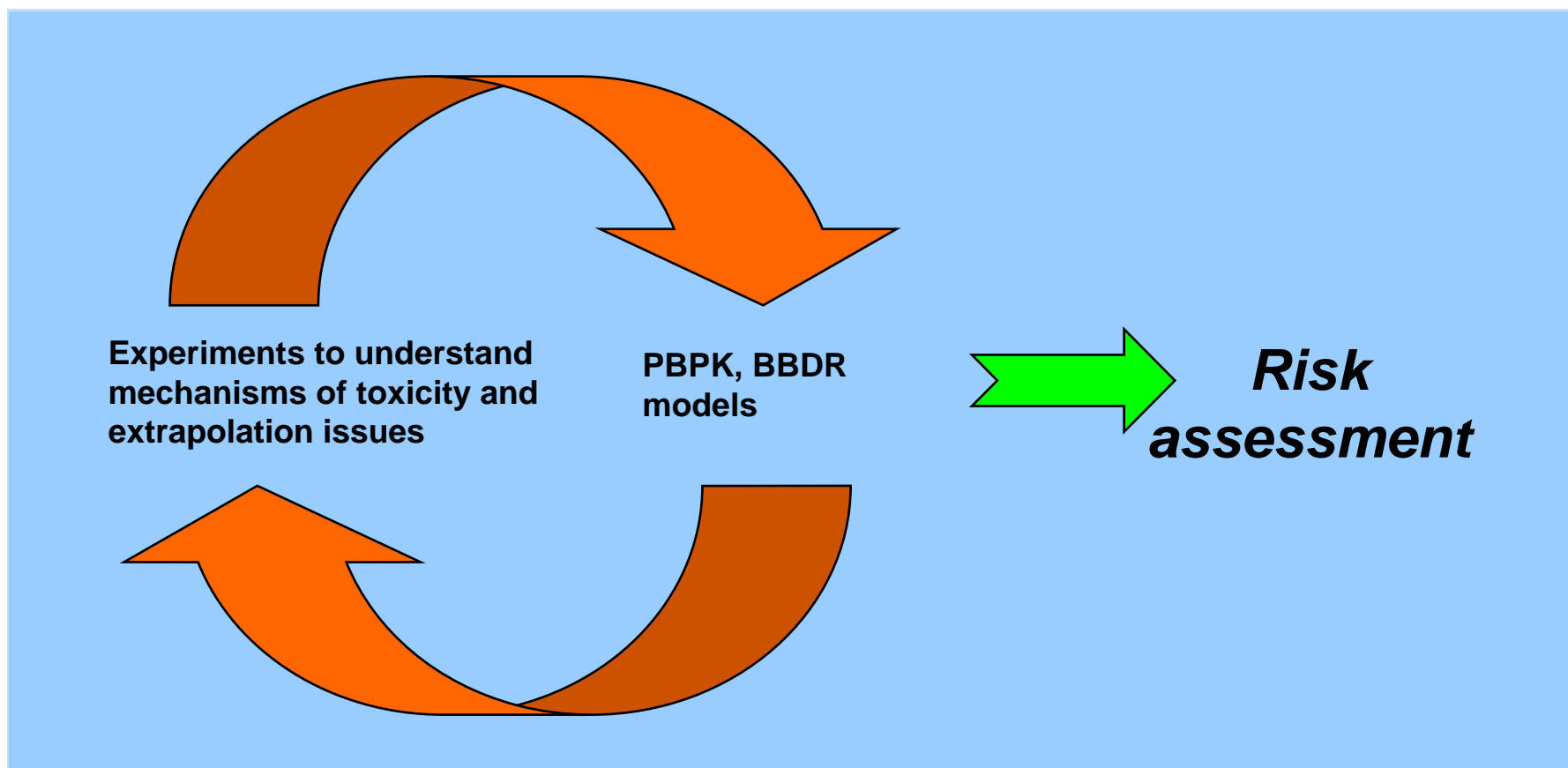




PBPK & BBDR modeling: Iteration between laboratory and computer



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Virtual tissues

EPA virtual tissue projects

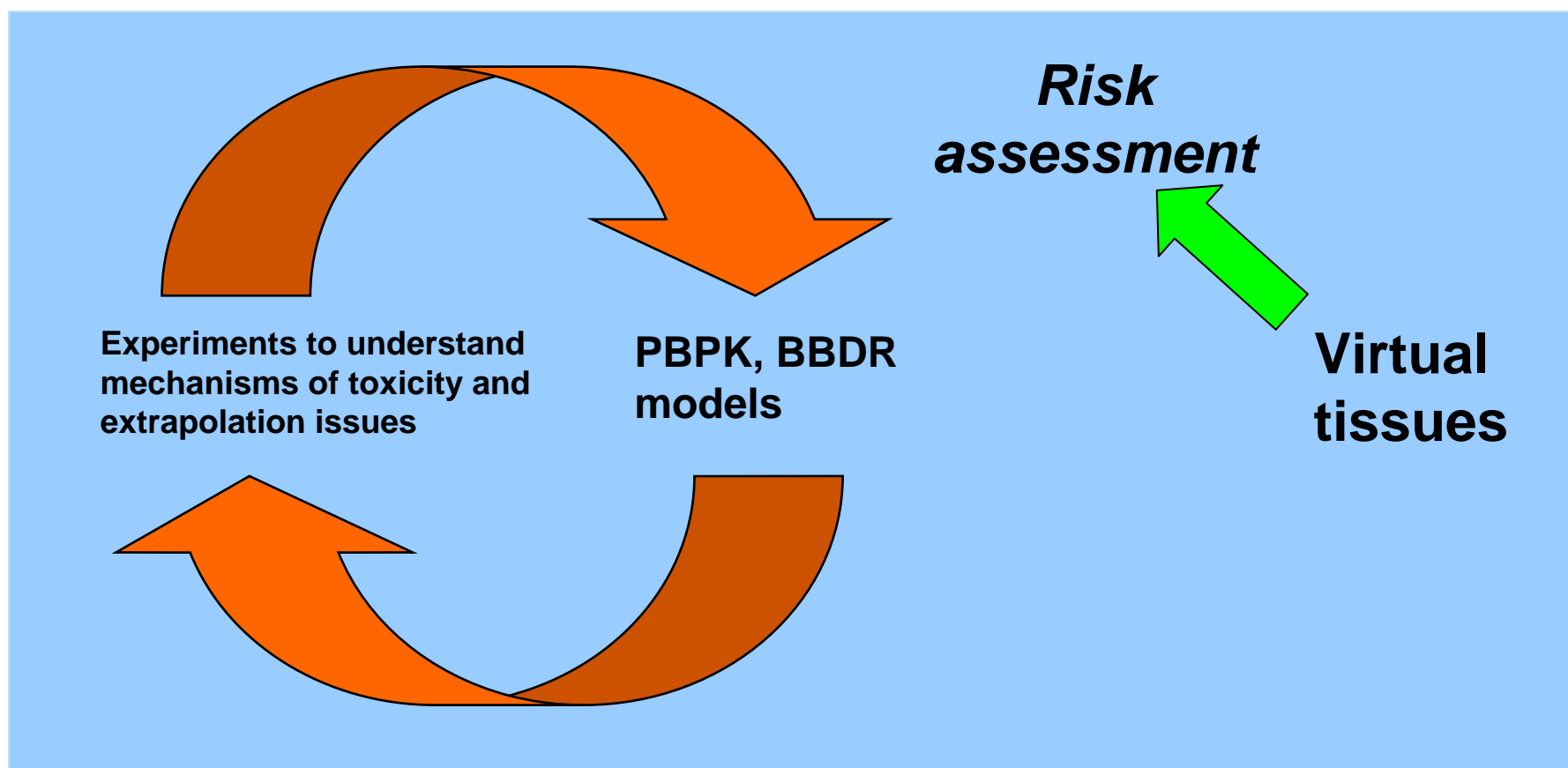
**The Virtual Liver Project (v-Liver™):
A computational system for simulating
chemical-induced injury in hepatic tissues**



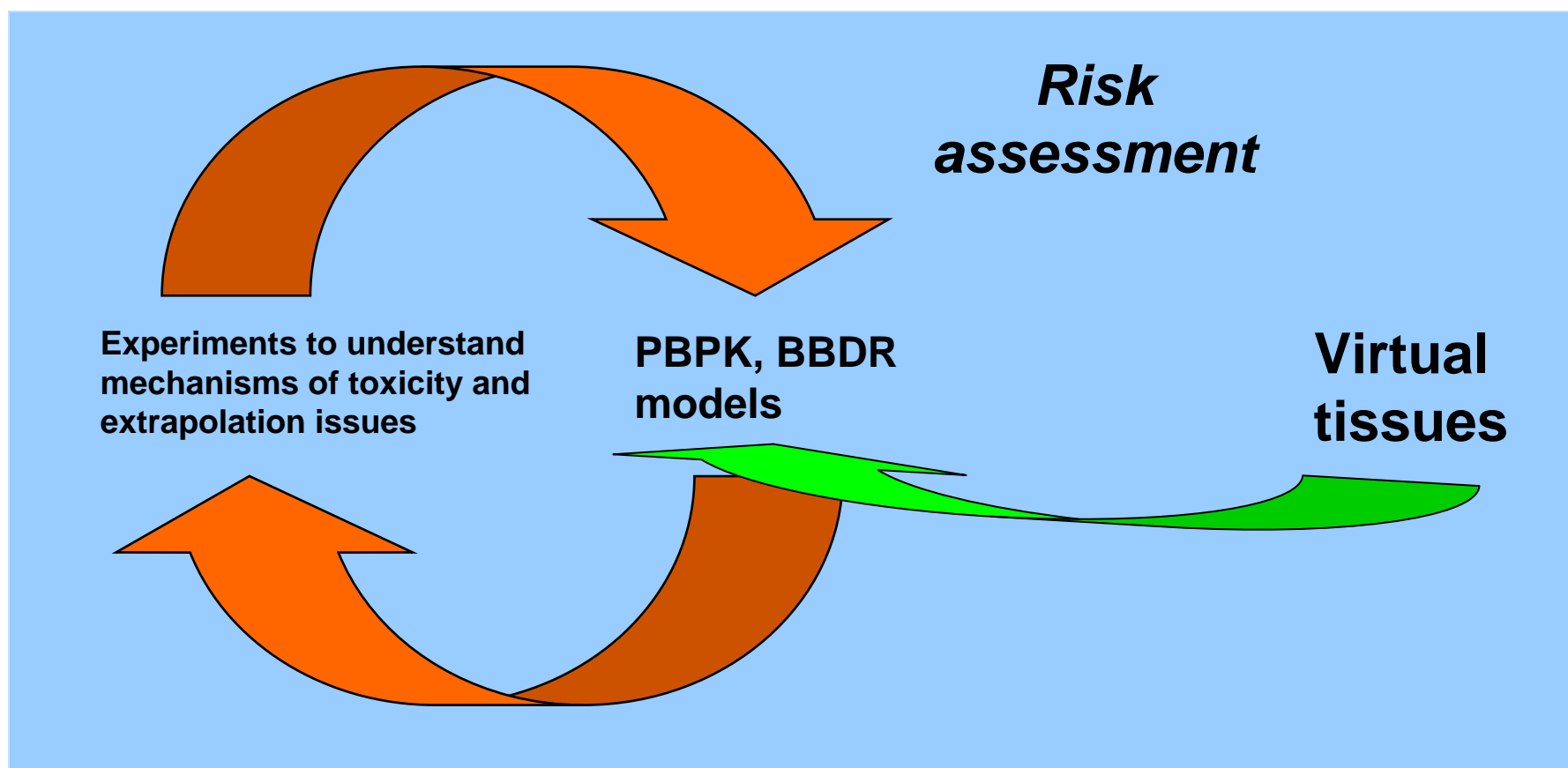
How are VTs different?

- ❖ Sufficiently detailed biology that, for a given toxicant, prediction of PK and effect is possible.
 - In effect, the computer model replaces the animal model
 - On-going need for targeted lab studies?
 - How far into the future are we looking?

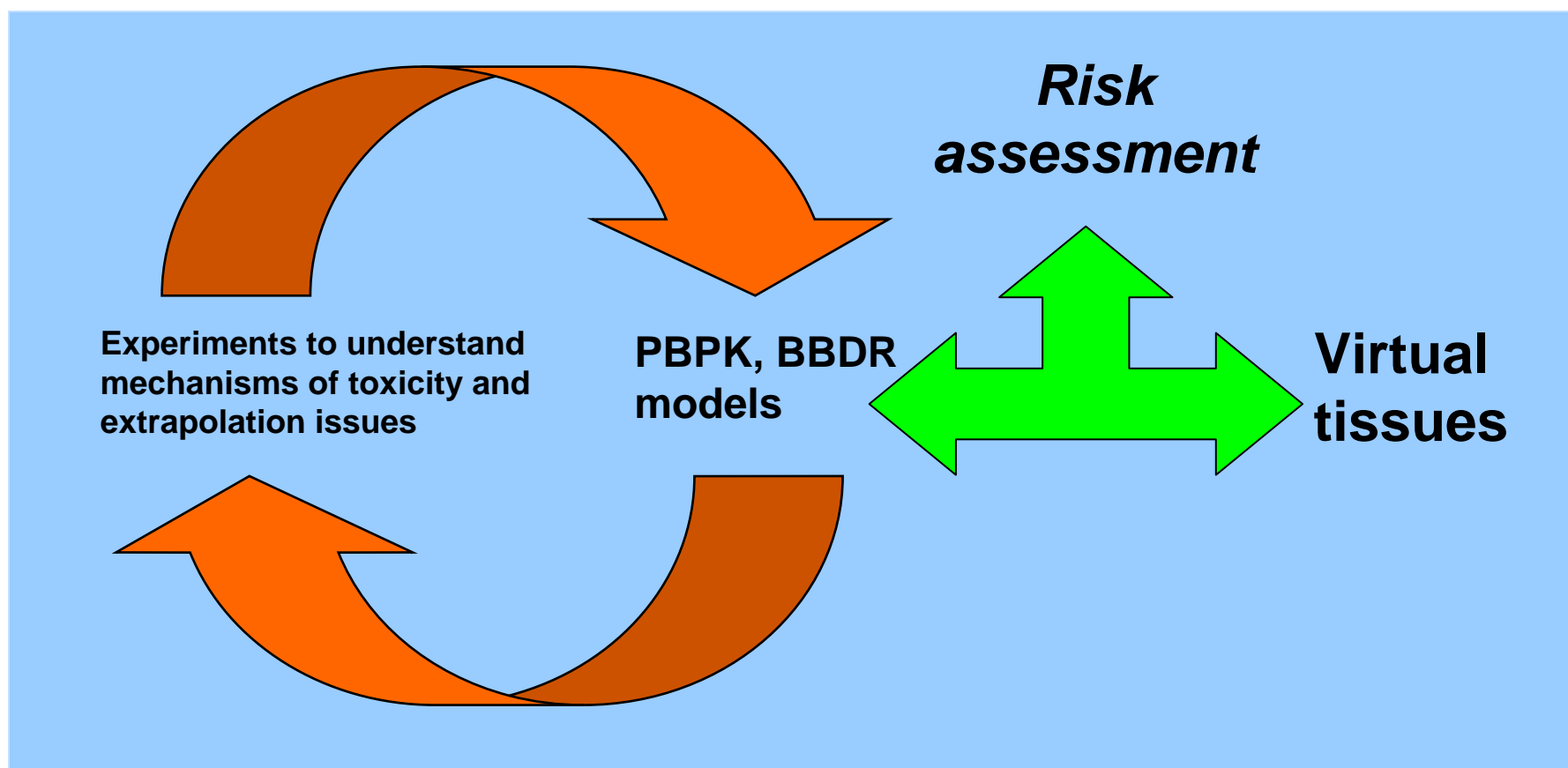
Virtual tissues: Better predictive capabilities? Emergent behavior?



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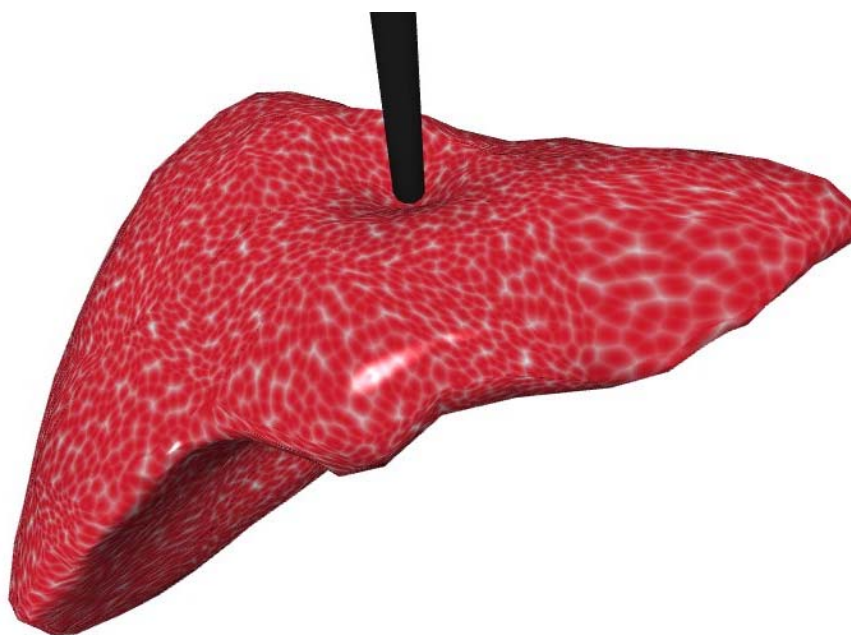
Virtual tissues: Better predictive capabilities? Emergent behavior?



What do we need?

- ❖ Prediction of tissue dose.
 - *In vivo* → *in vitro*
- ❖ Insight into normal biological processes.
 - Development
 - Homeostasis
 - Etc.
- ❖ Prediction of how toxicants perturb the biology.
 - Key events → endpoints

Which one is real?



Acknowledgements

❖ Imran Shah

❖ Thomas Knudsen

End