

Biologically based dose-response modeling. The potential for accurate description of the linkages in the applied dose-tissue dose-health effect continuum

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COMPUTATIONAL
TOXICOLOGY

Disclaimer

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

Outline

1. Why getting the biology right matters
2. Hand-in-hand, wet and in silico experiments
3. What's a mechanism? PBPK, BBDR, virtual tissues
4. Relevance to risk assessment

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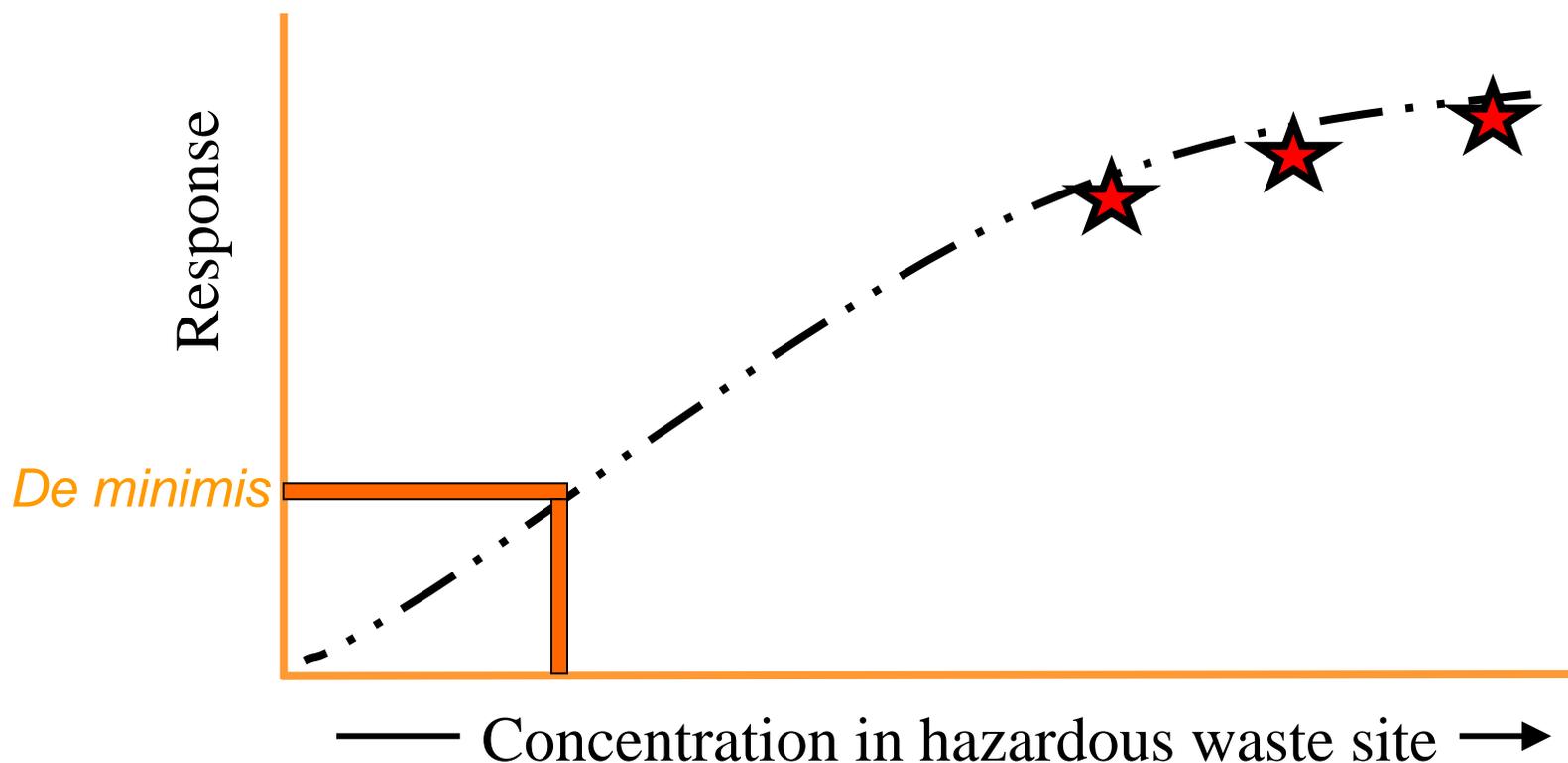


Scar tissue. A crisscross of roads and pits scars the surface of a former gold mine in Summitville, Colorado, while underground workings and tunnels allow acidic waste to drain into nearby watersheds. The Superfund site has cost more than \$150 million in remediation efforts and remains incomplete. (*Scott Fields, EHP 111, 154-161, 2003*)

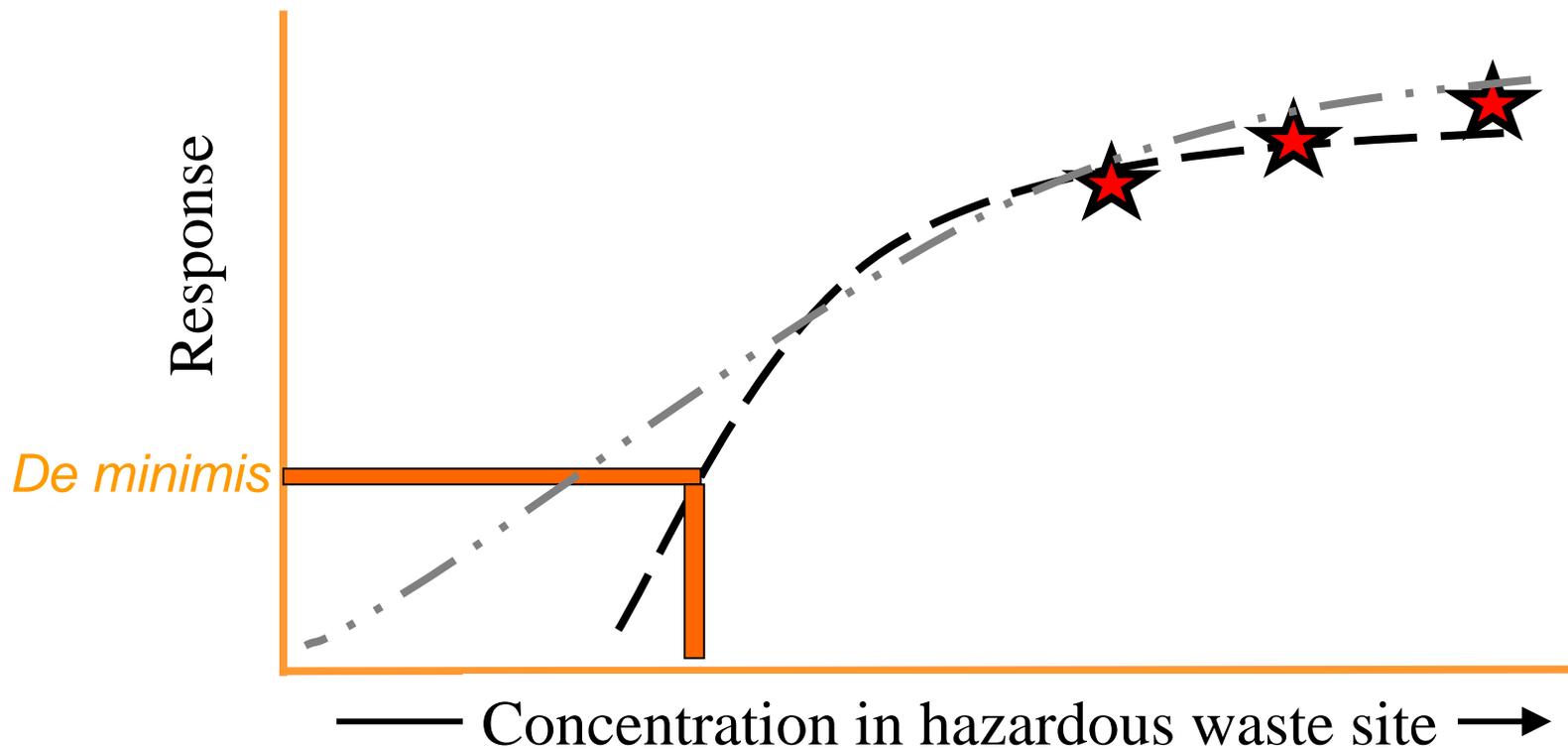
Although there is no good estimate of the cost to clean up abandoned mines, experts agree that in the United States alone the price tag reads tens of billions of dollars.

(Scott Fields, EHP 111, 154-161, 2003)

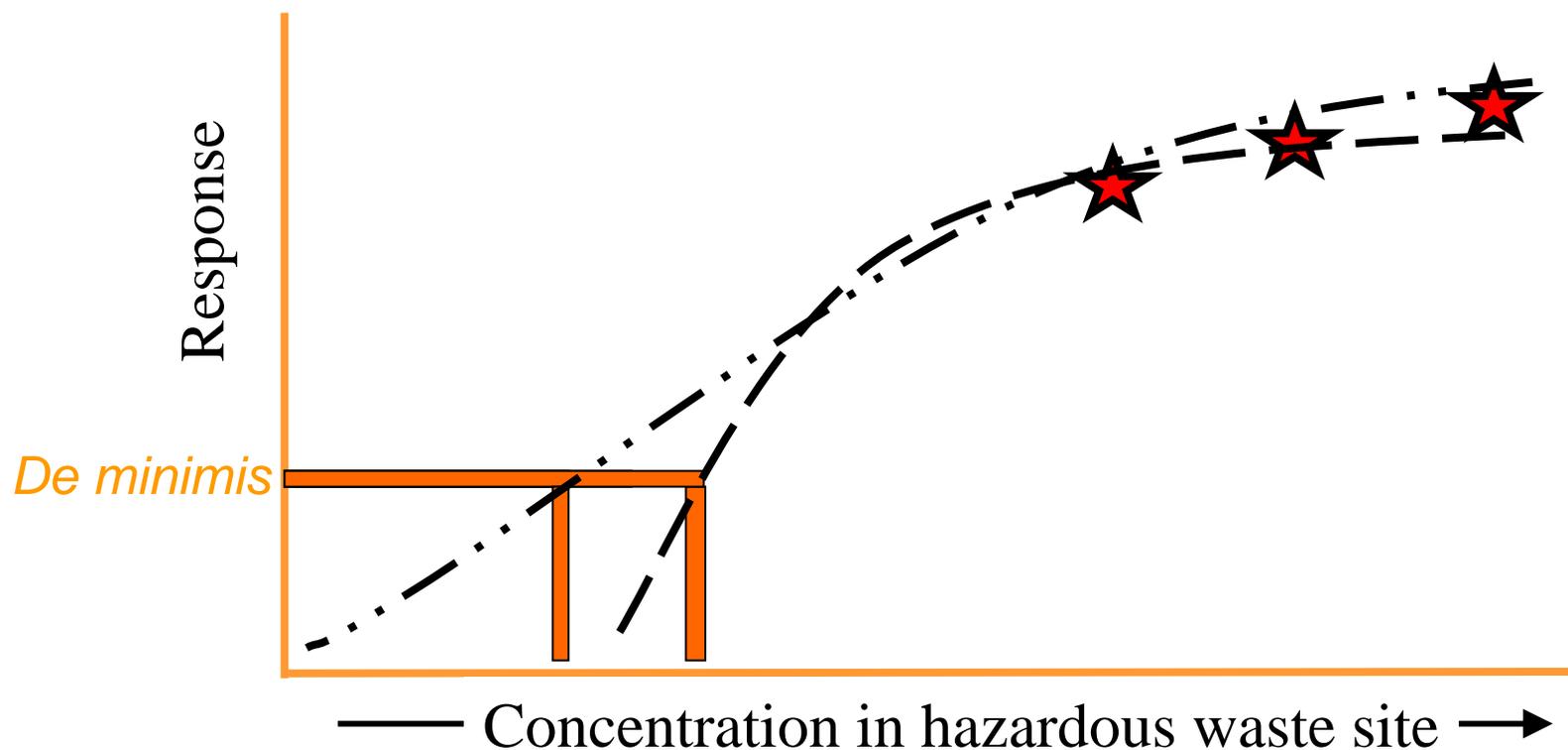
*Cost of cleanup is a
function of the shape of
the dose-response curve*



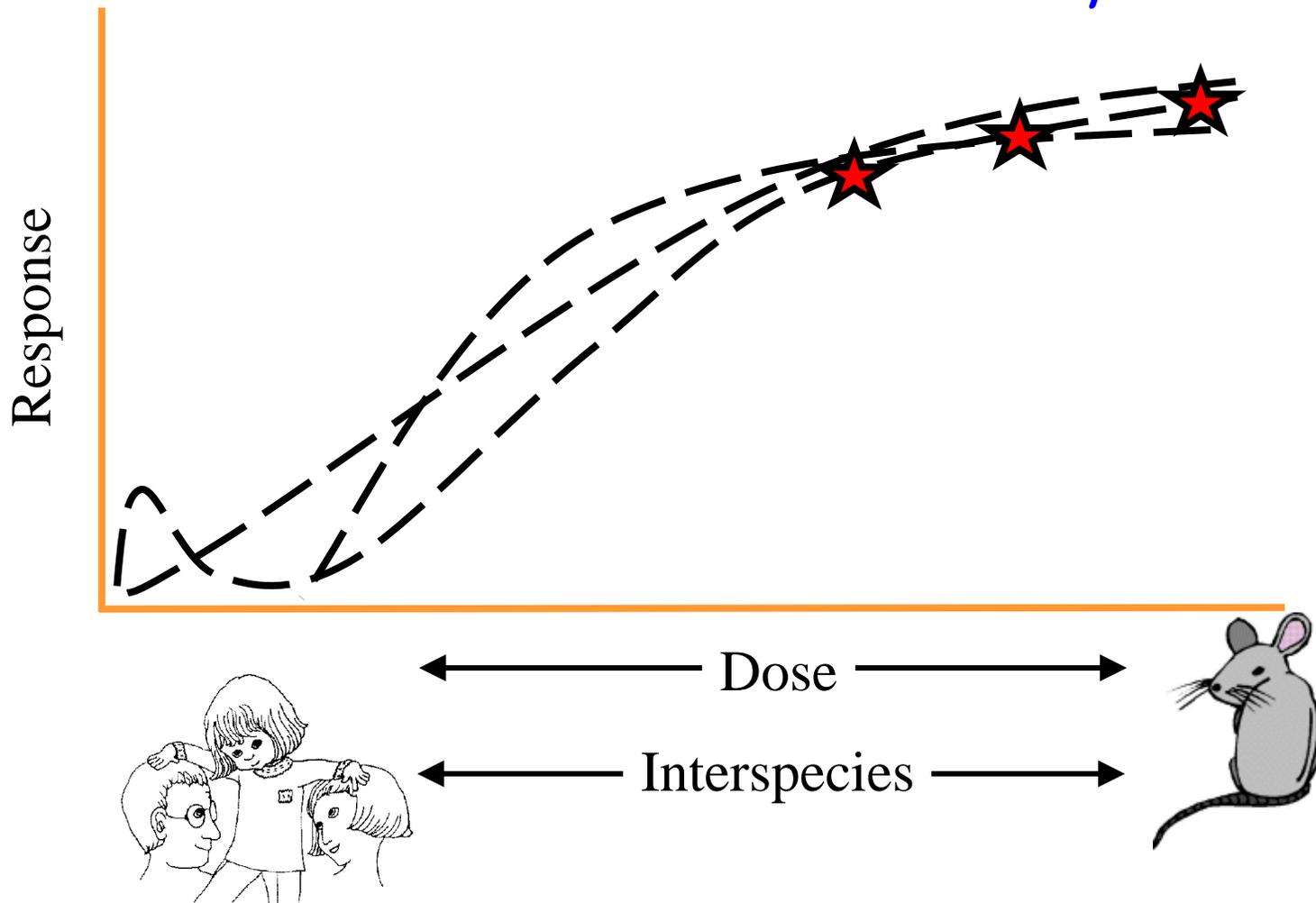
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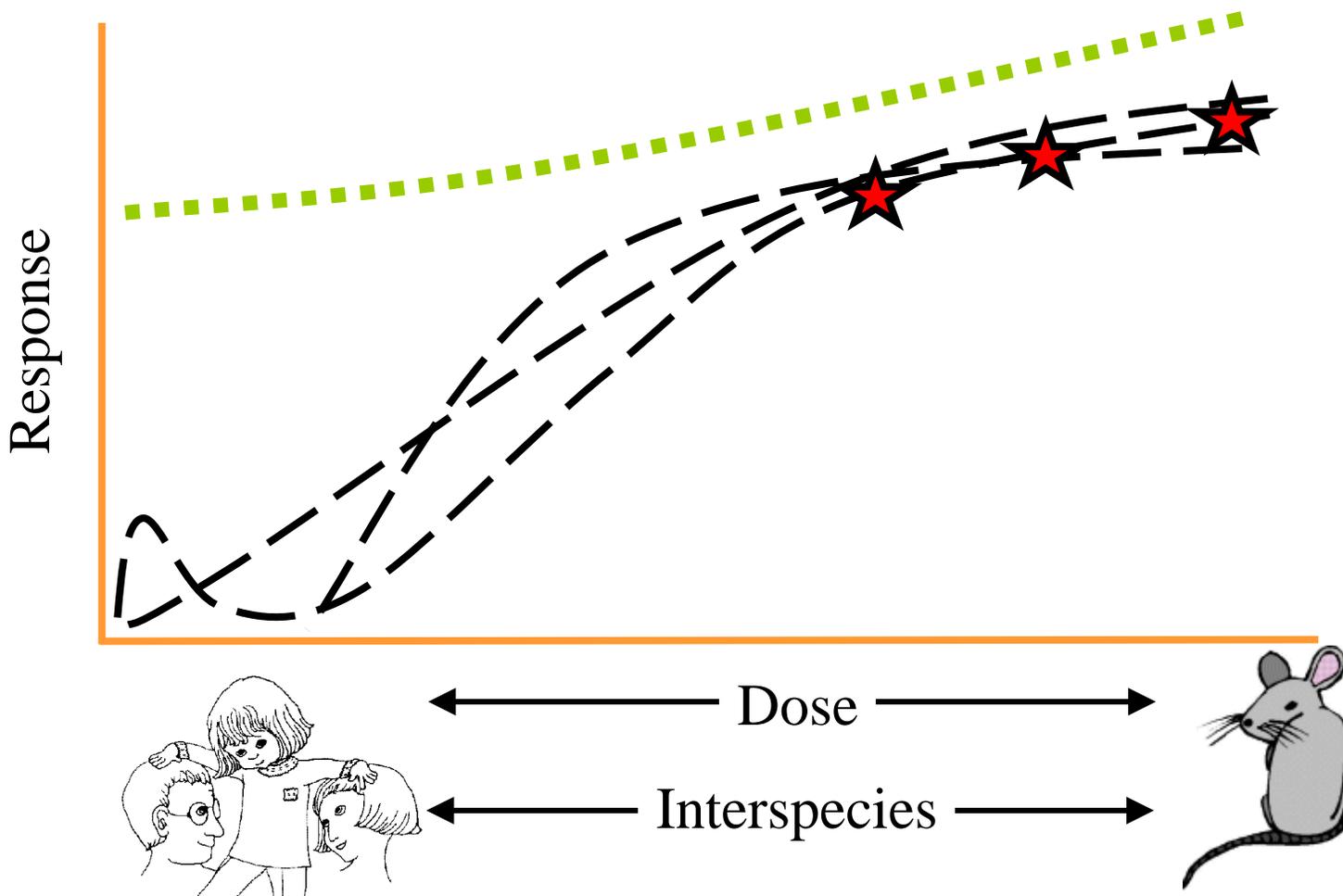
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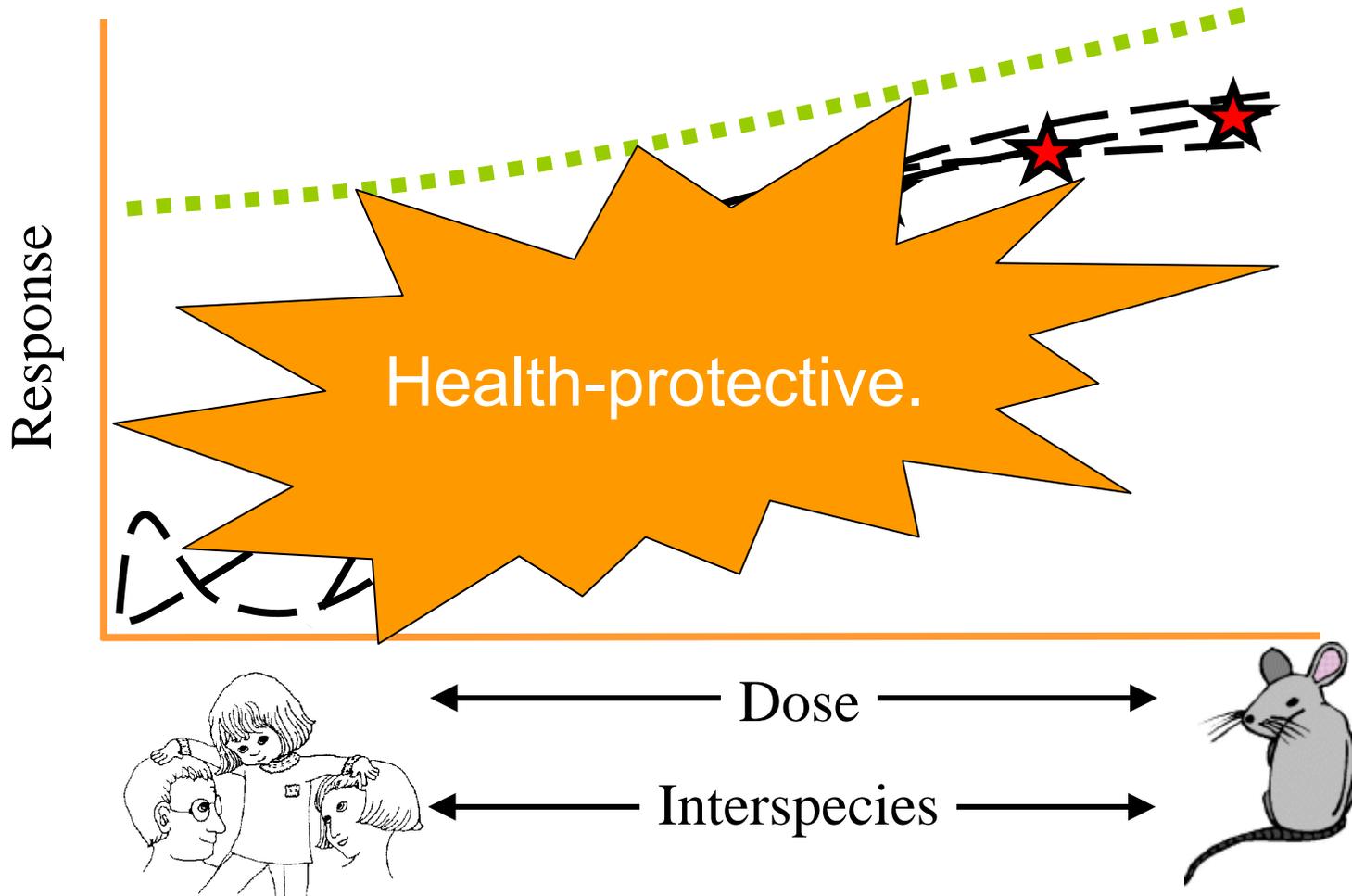
*Available data don't constrain
the dose-response curve at
relevant levels of exposure*



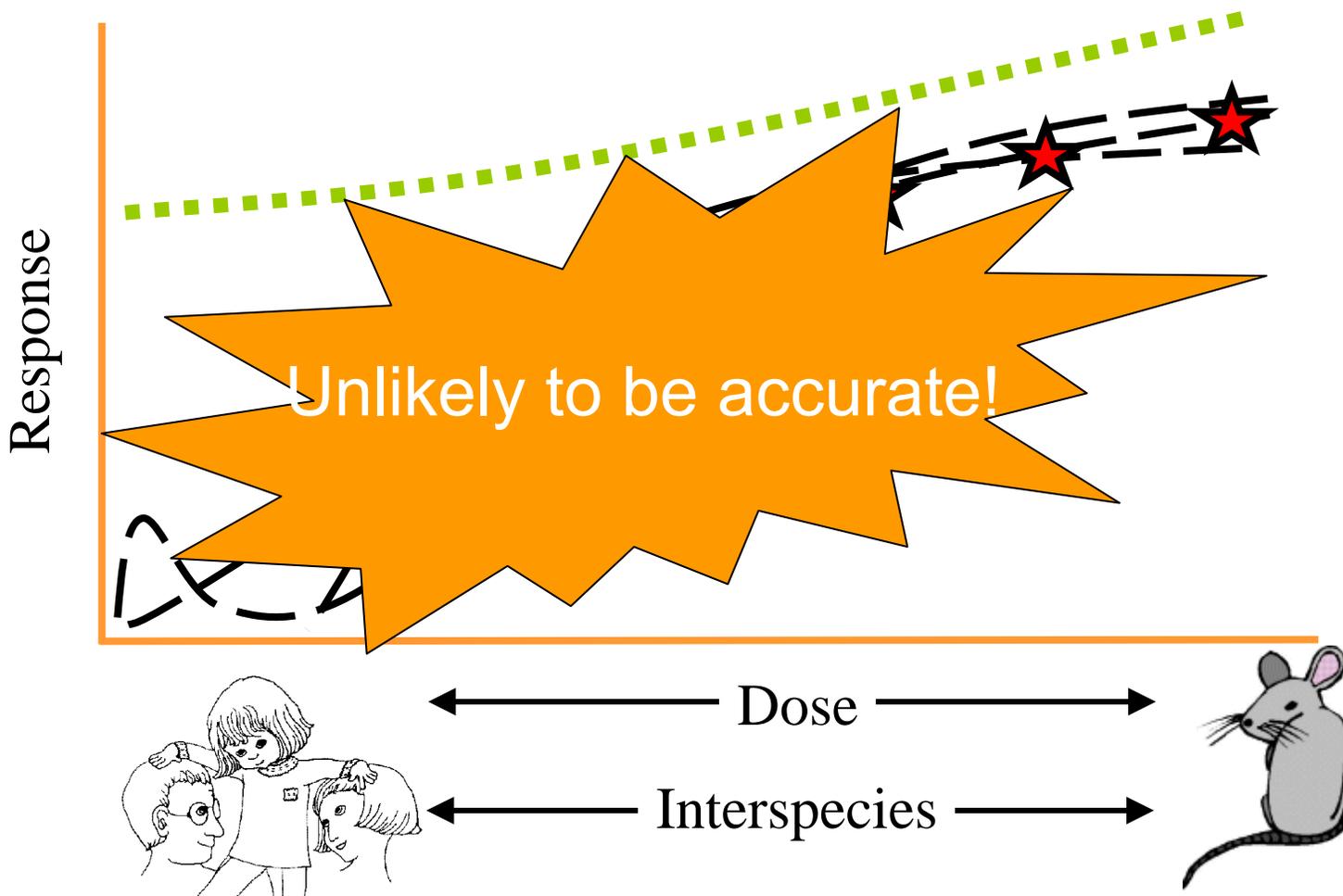
Default-based treatment



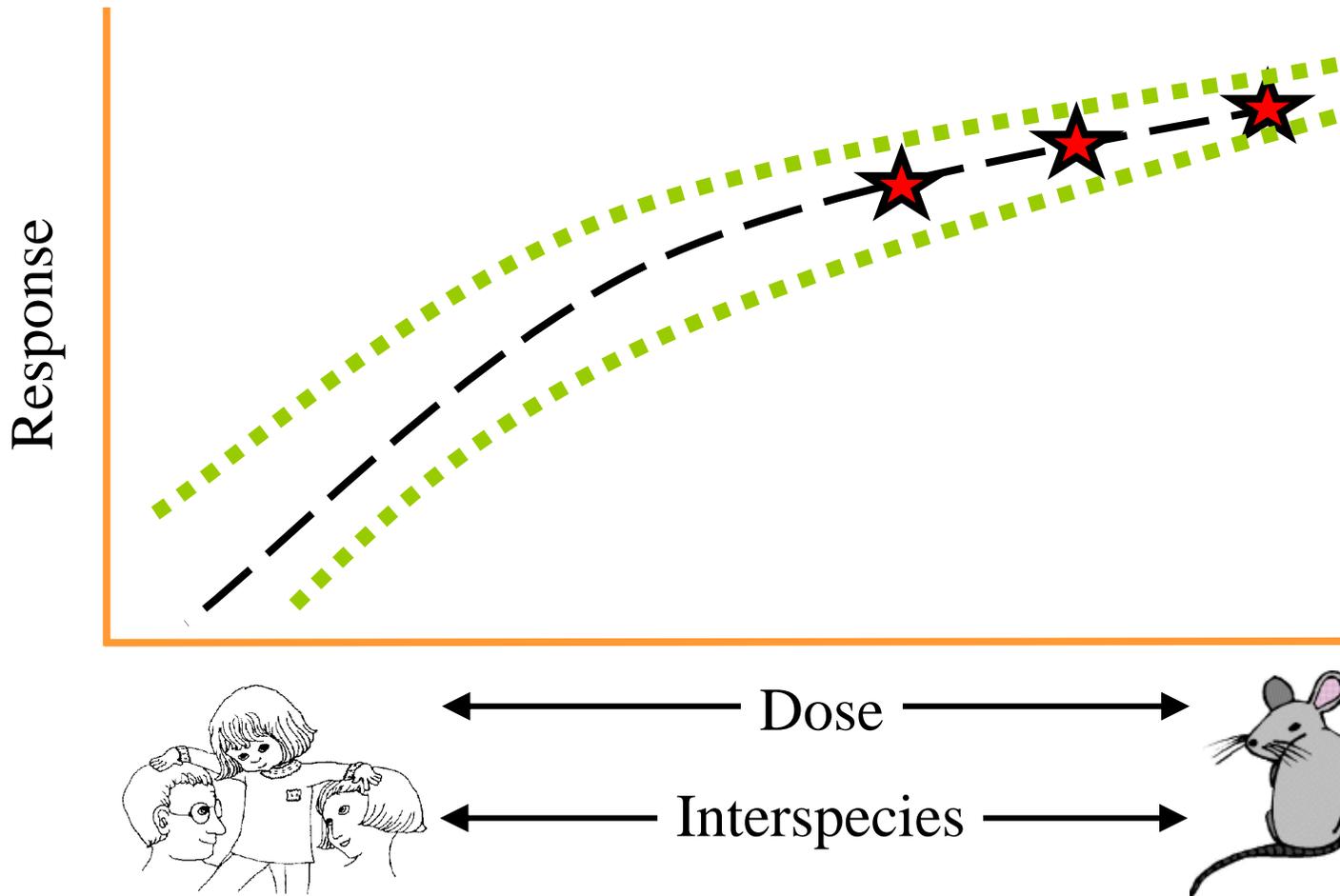
Default-based treatment



Default-based treatment

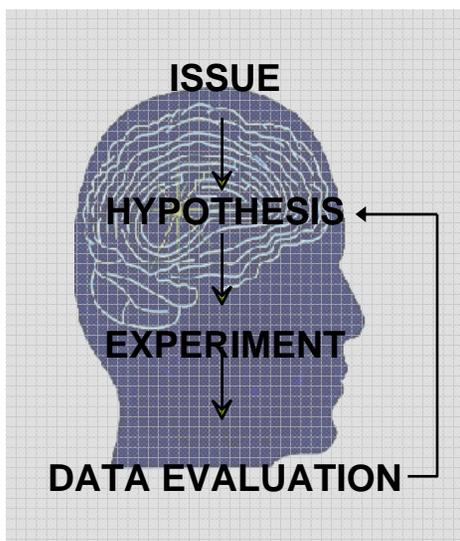


Accuracy

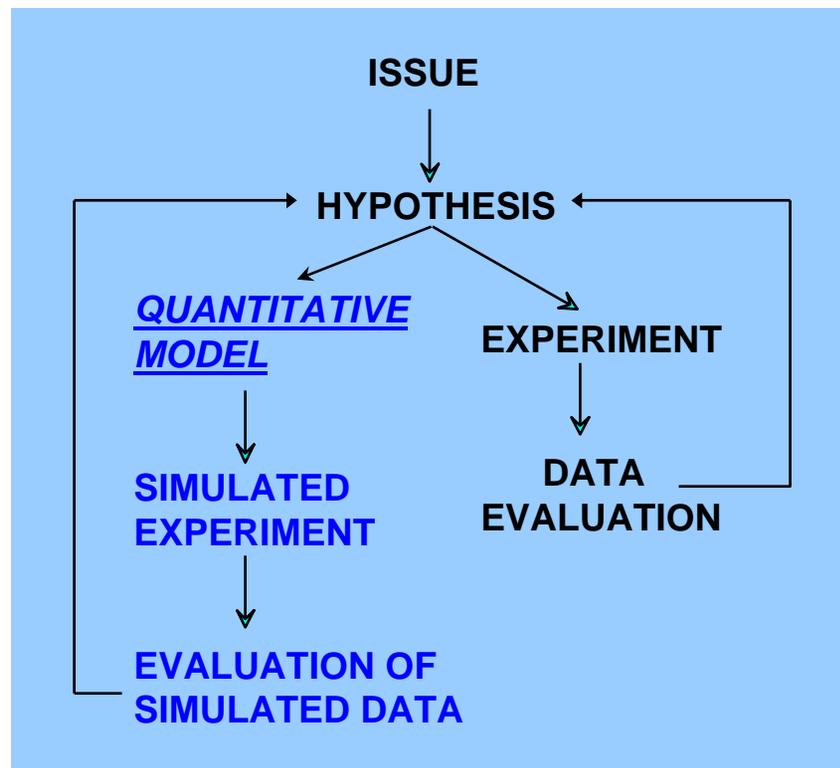
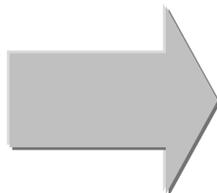


Outline

1. Why getting the biology right matters
2. Hand-in-hand, wet and in silico experiments
3. What's a mechanism? PBPK, BBDR, virtual tissues
4. The difference between being right and being useful
5. Path forward.

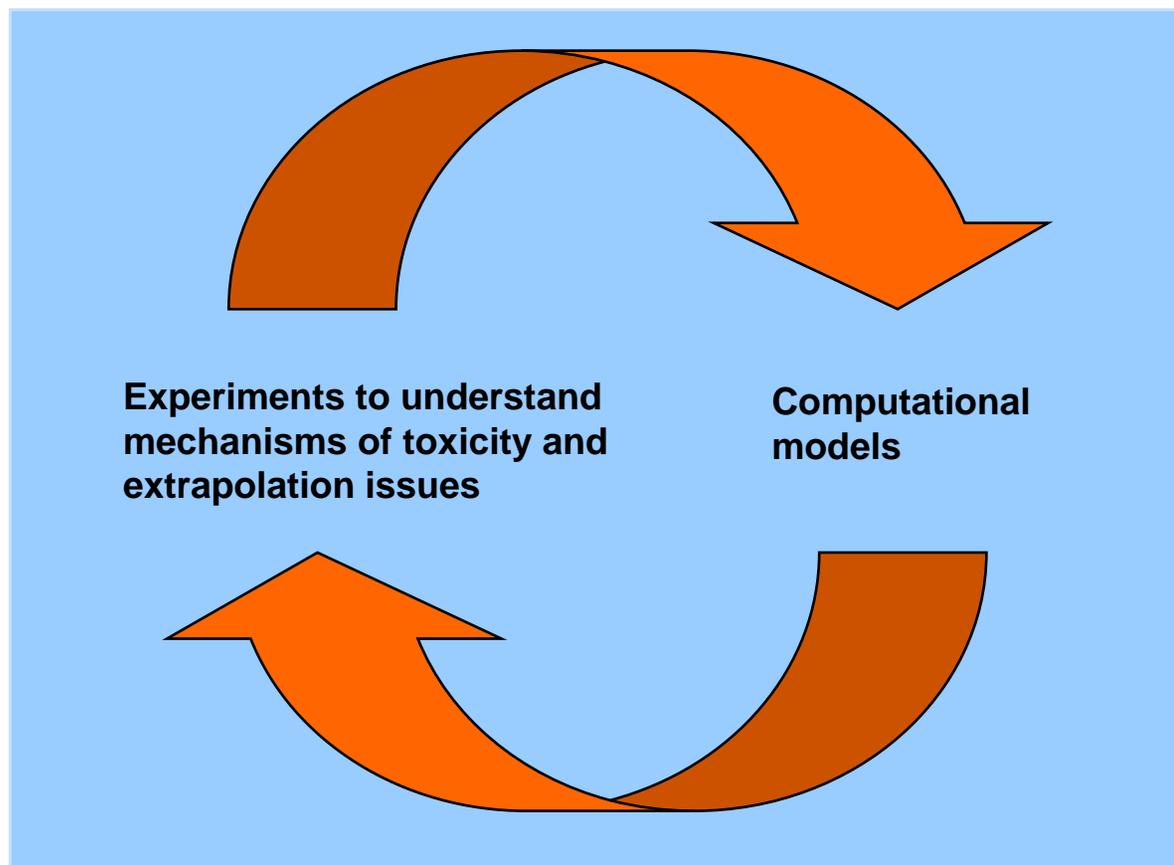


(Intuitive modeling)

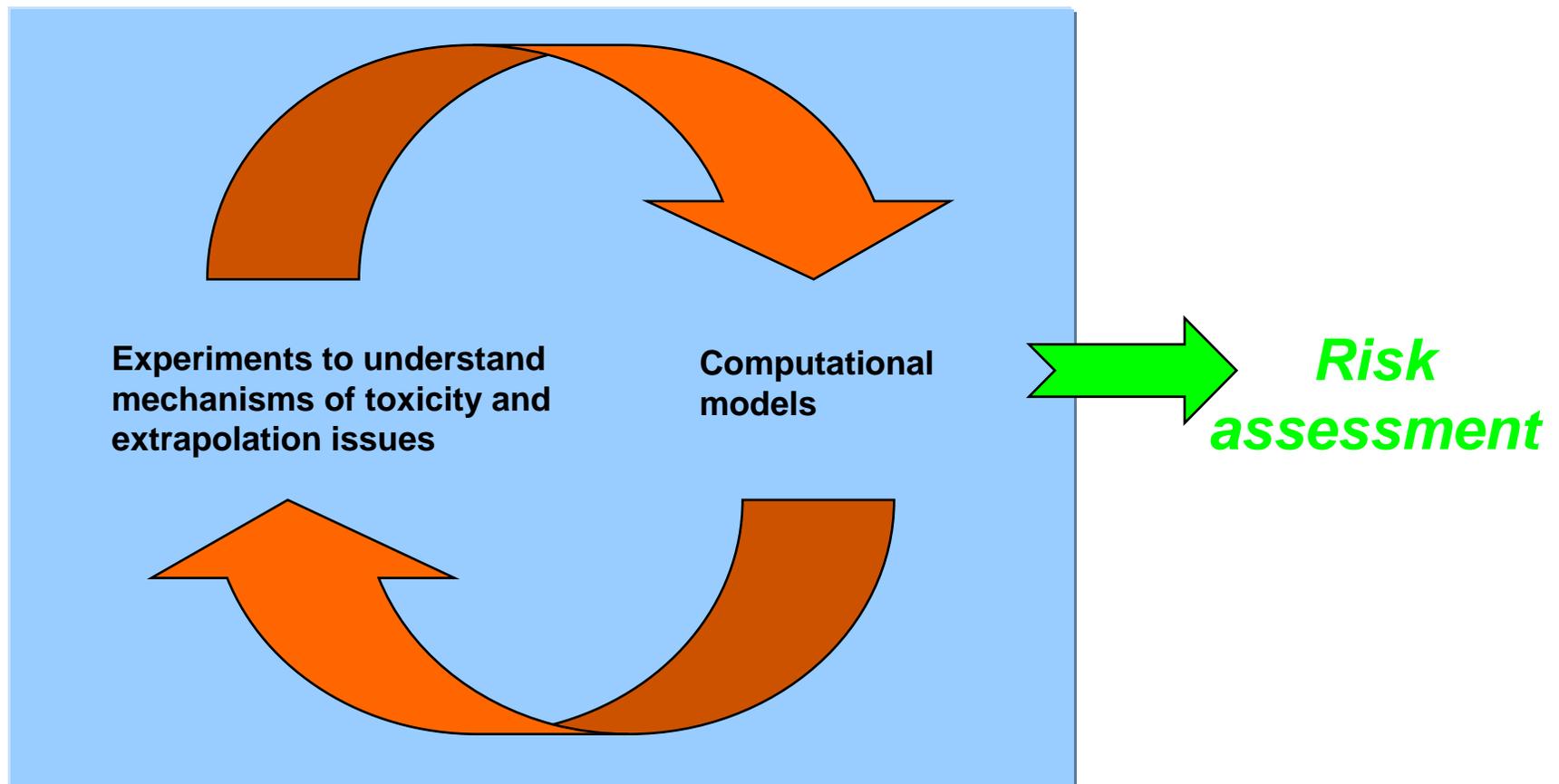


(Formal + intuitive modeling)

Computational modeling and lab experiments



Bridging to risk assessment



Learning from models

❖ *All models are wrong but
some are useful.*



George Box

Learning from models

- ❖ *All models are wrong but some are useful.*
- ❖ Ask, not if the model is right, but can we learn something useful from it?



George Box

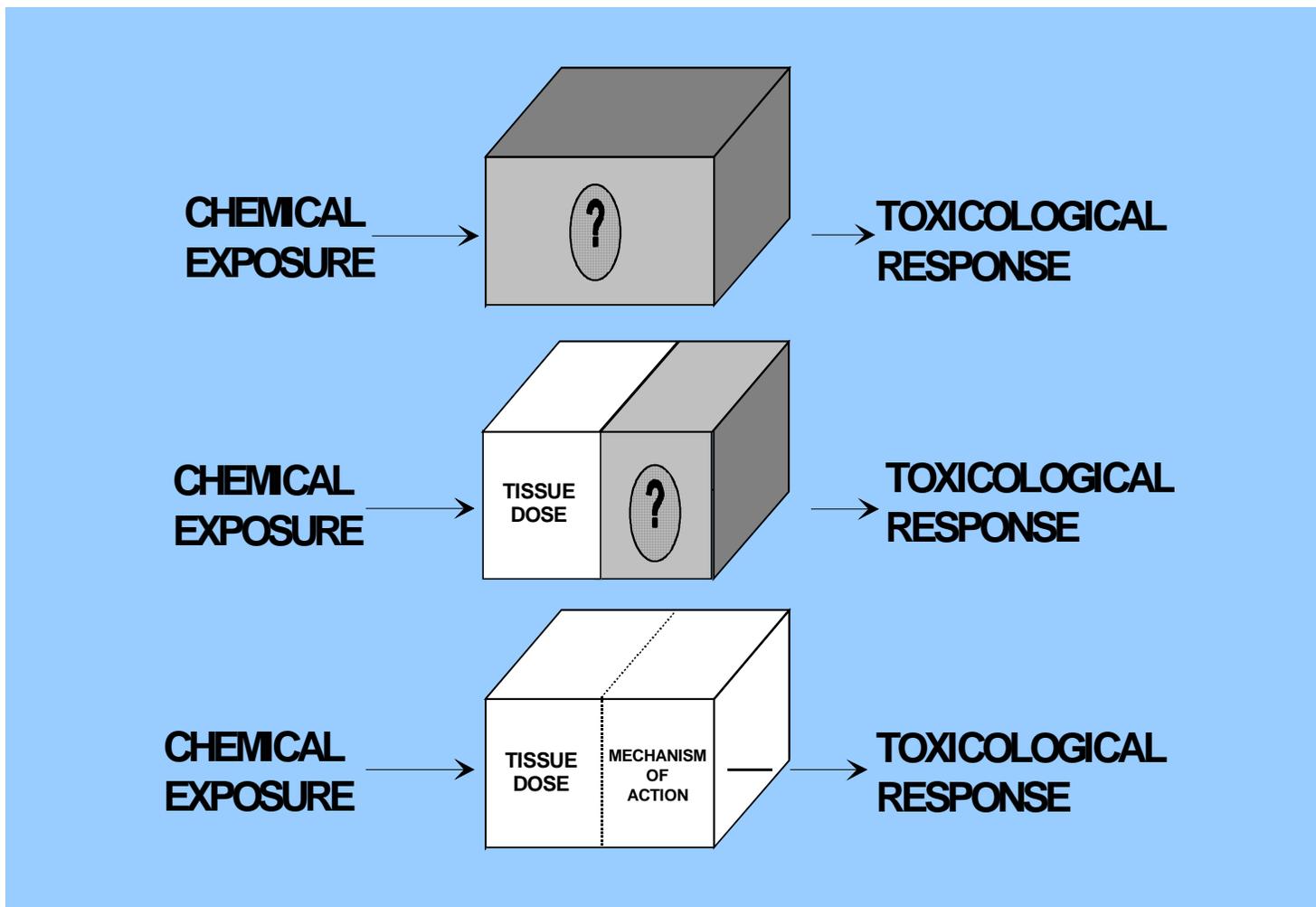
Philosophy

- ❖ Develop the model to help us better understand what the data can tell us.
- ❖ Model is interpretive and predictive.
- ❖ Using good practice, more likely to uncover uncertainty that introduce it.
- ❖ Not required to be “right”.
- ❖ Is required to be better than no model!

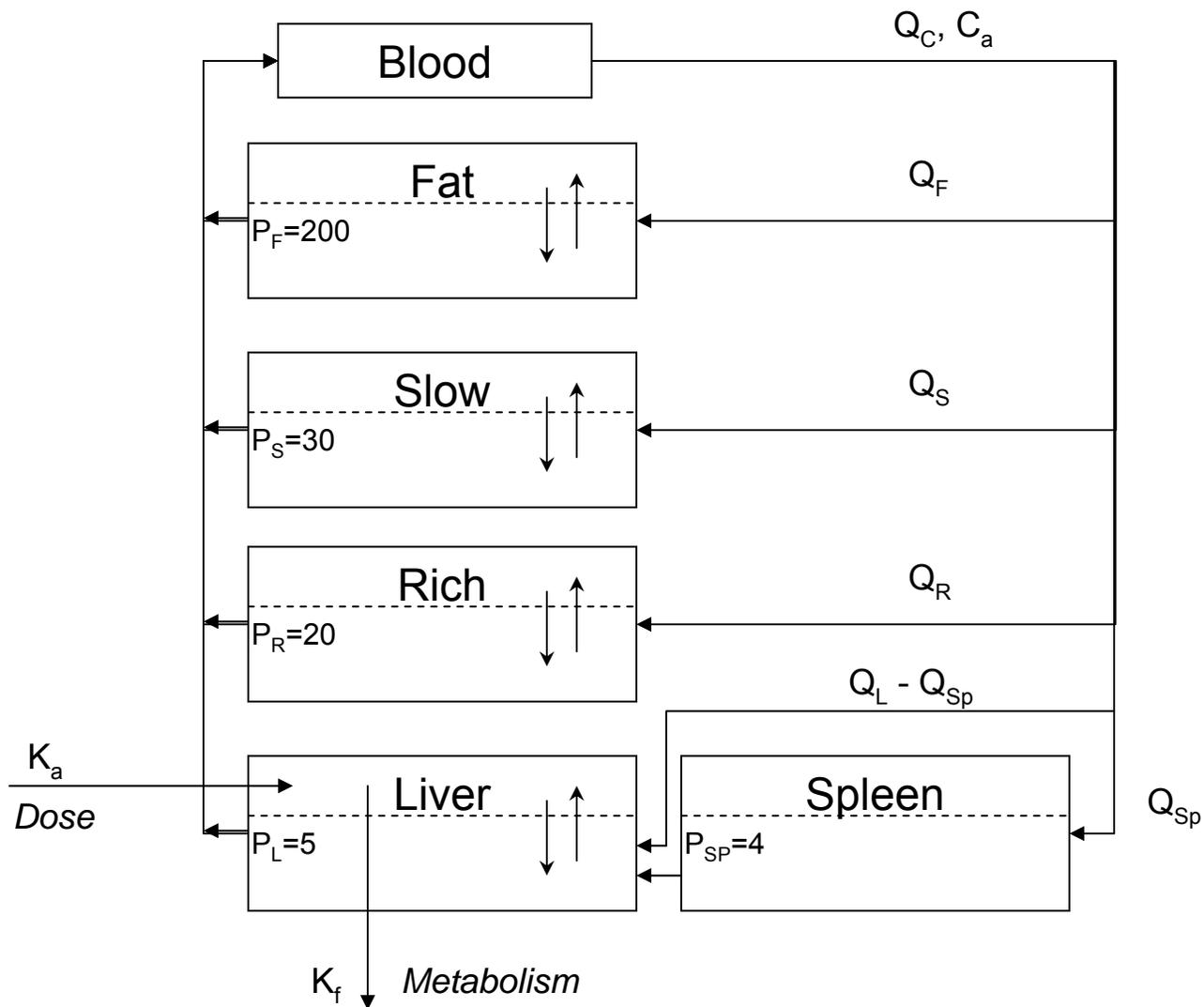
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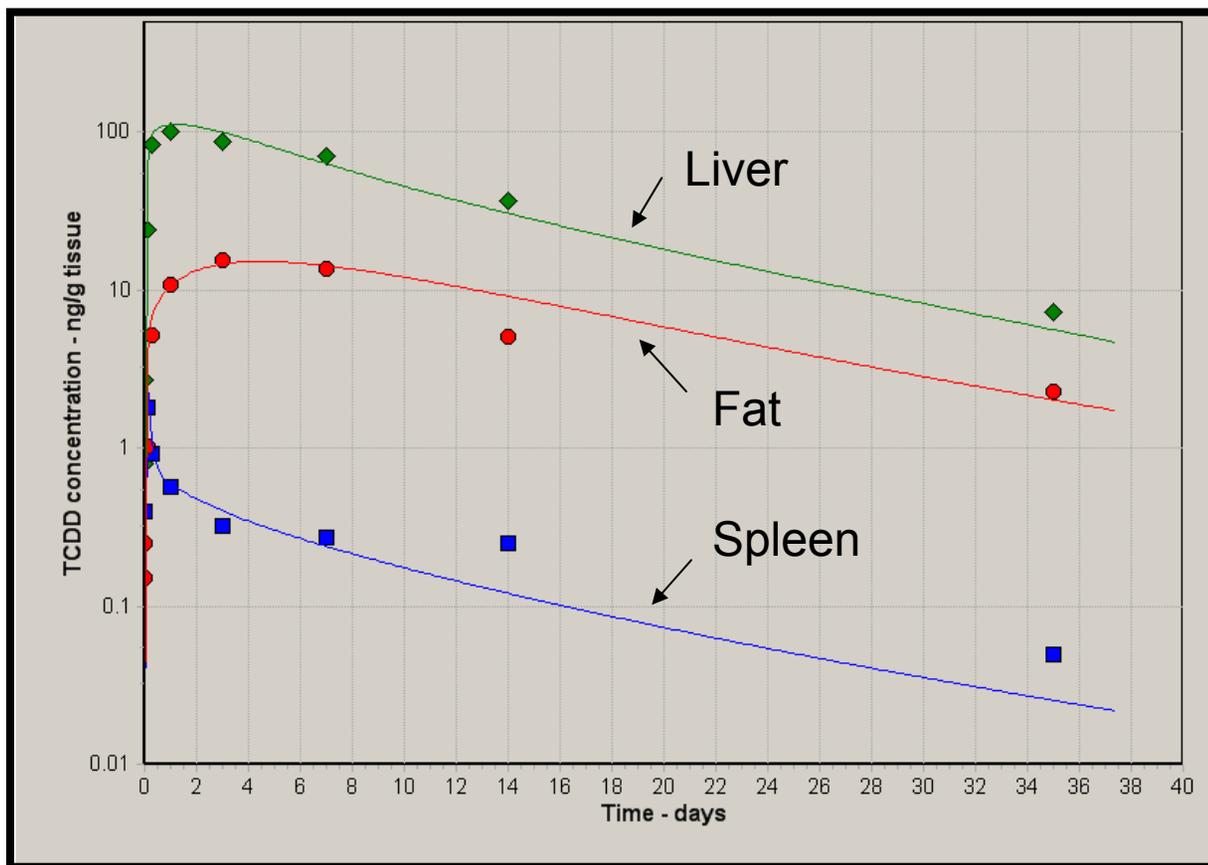
Biological mechanisms determine dose-response



Dioxin PBPK model



Dioxin PBPK Model with Spleen - Fitting time-course rat data



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

Occam's Razor



<http://www.aaai.org/aitopics/retired/assets/Page%20Art/razor.gif>

Occam's Razor

through the ages...



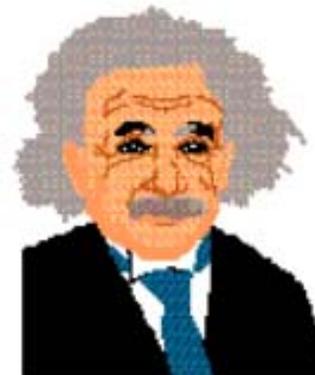
*Pluralitas non
est ponenda sine
necessitate.*

*(Plurality should not be
posited without necessity.)*

- William of Ockham

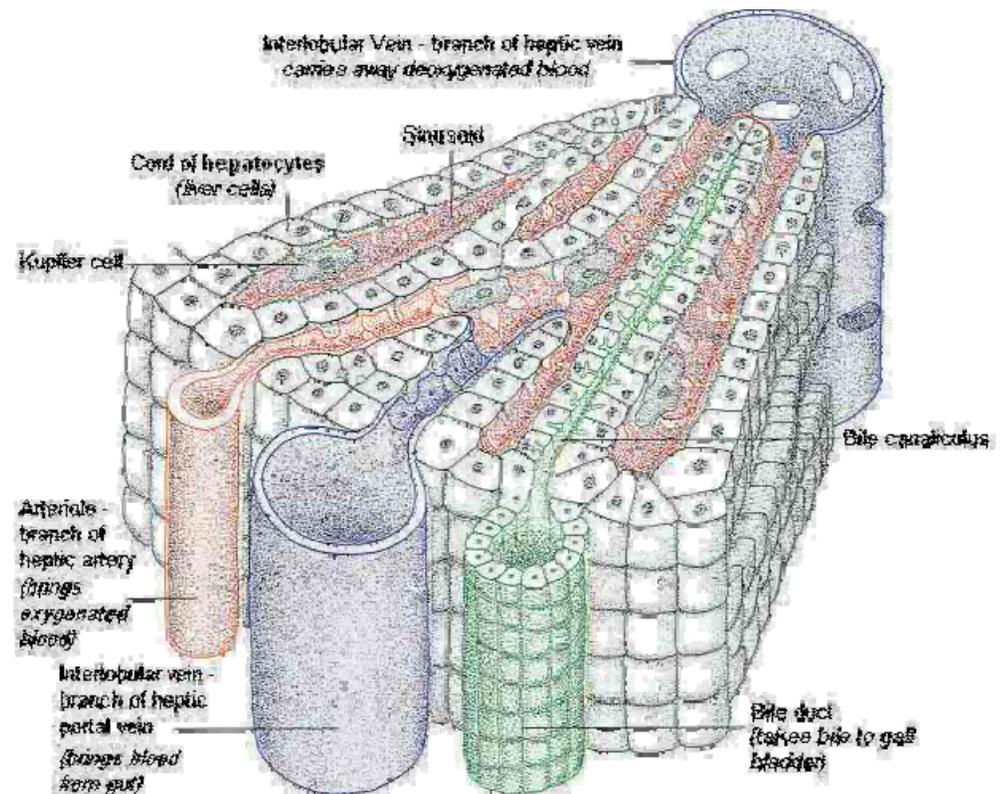
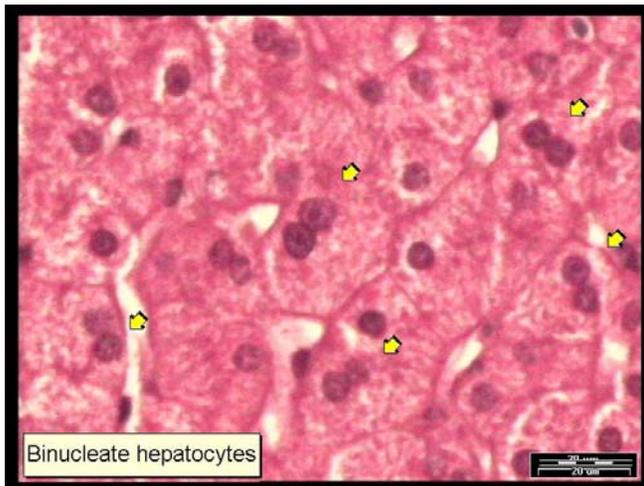
Everything should be
made as simple as
possible, but not
simpler.

- Albert Einstein

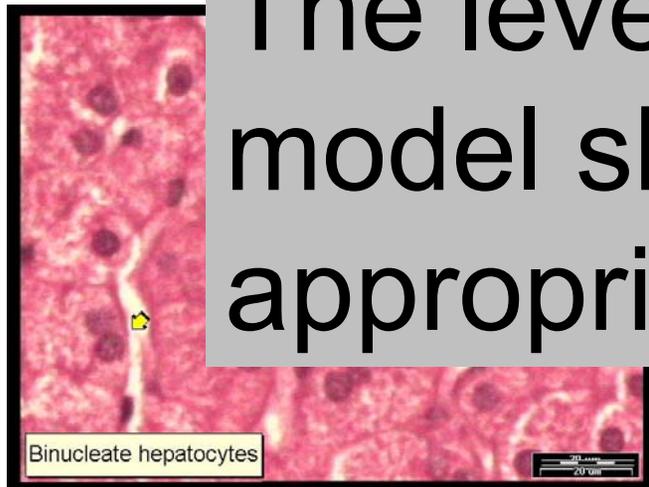


Kee
It
Simple,
Stupid !

Hepatic architecture at the cellular level



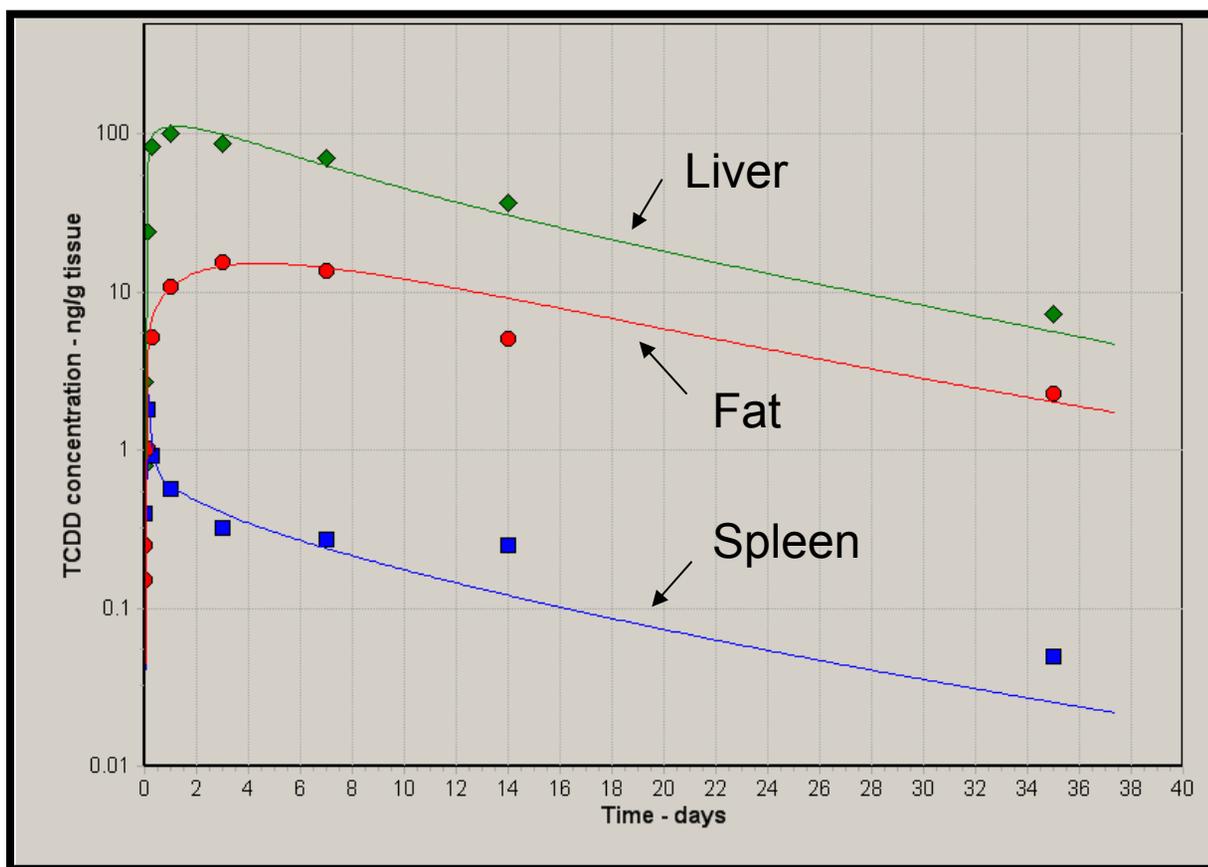
Hepatic architecture at the cellular level



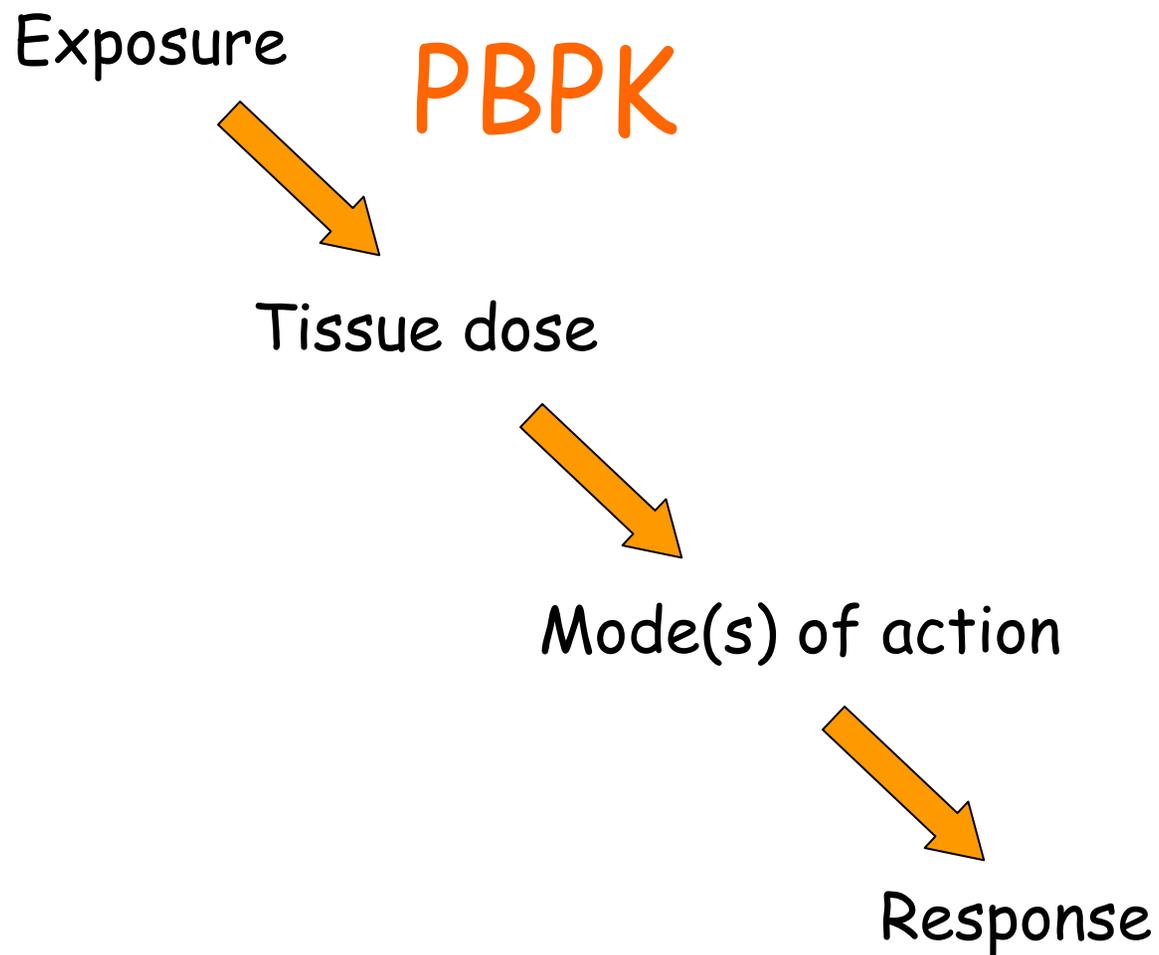
The level of detail in the
model should be
appropriate to the data

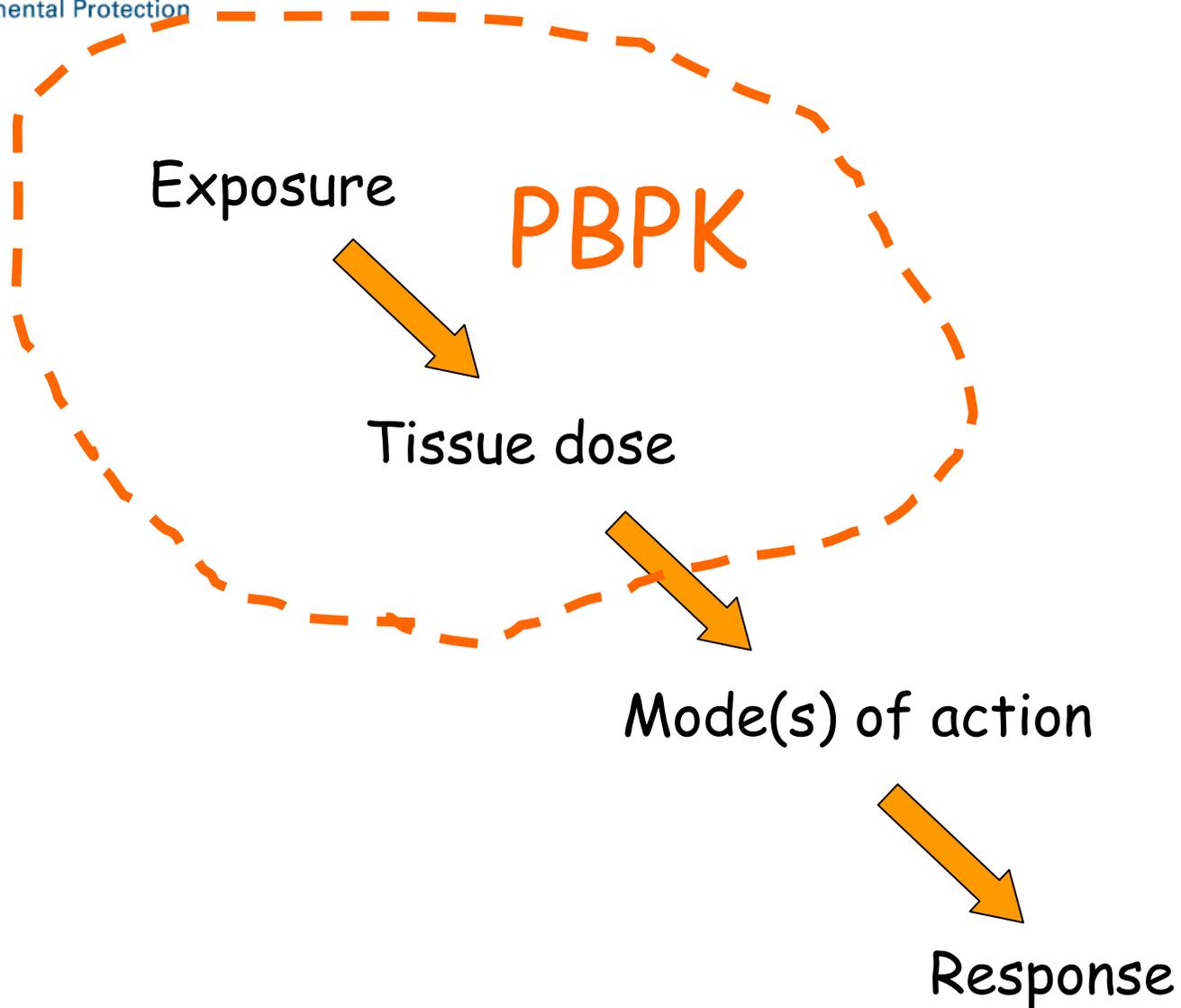


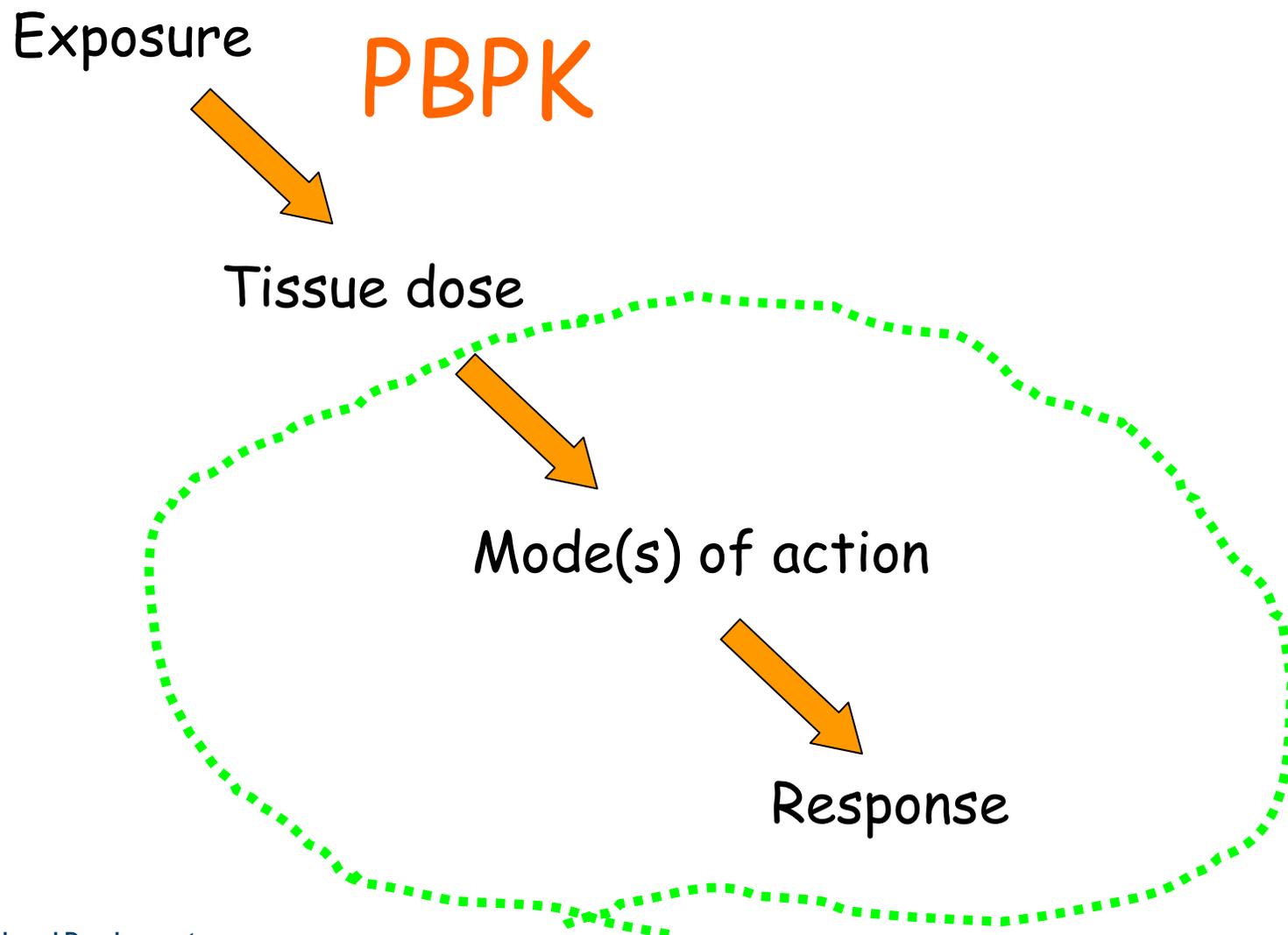
Dioxin PBPK Model with Spleen - Fitting time-course rat data



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







What is Mode of Action?

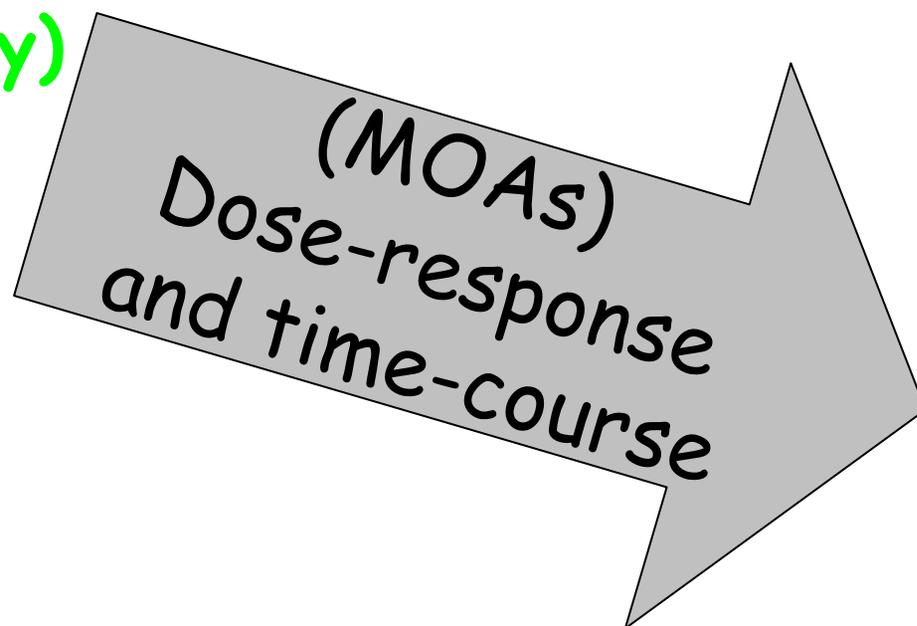
- ❖ . . . a sequence of **key events** and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. . . Mode of action is contrasted with "*mechanism of action*," which implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode of action.

(Rita Schoeny)

EPA Cancer Guidelines, 2005

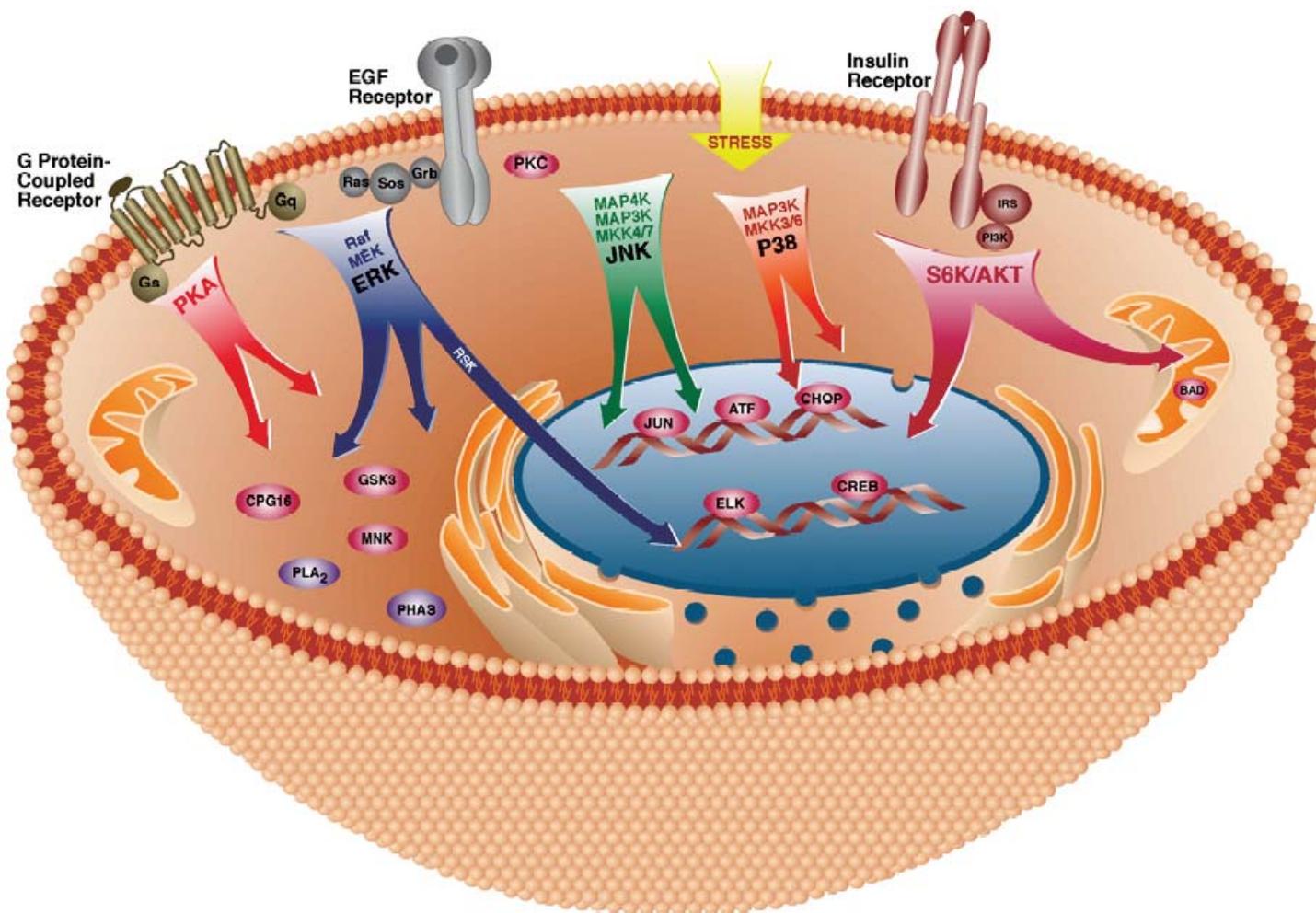
Goal is to understand mechanistic
basis of dose-response and time-
course relationships

(dosimetry)

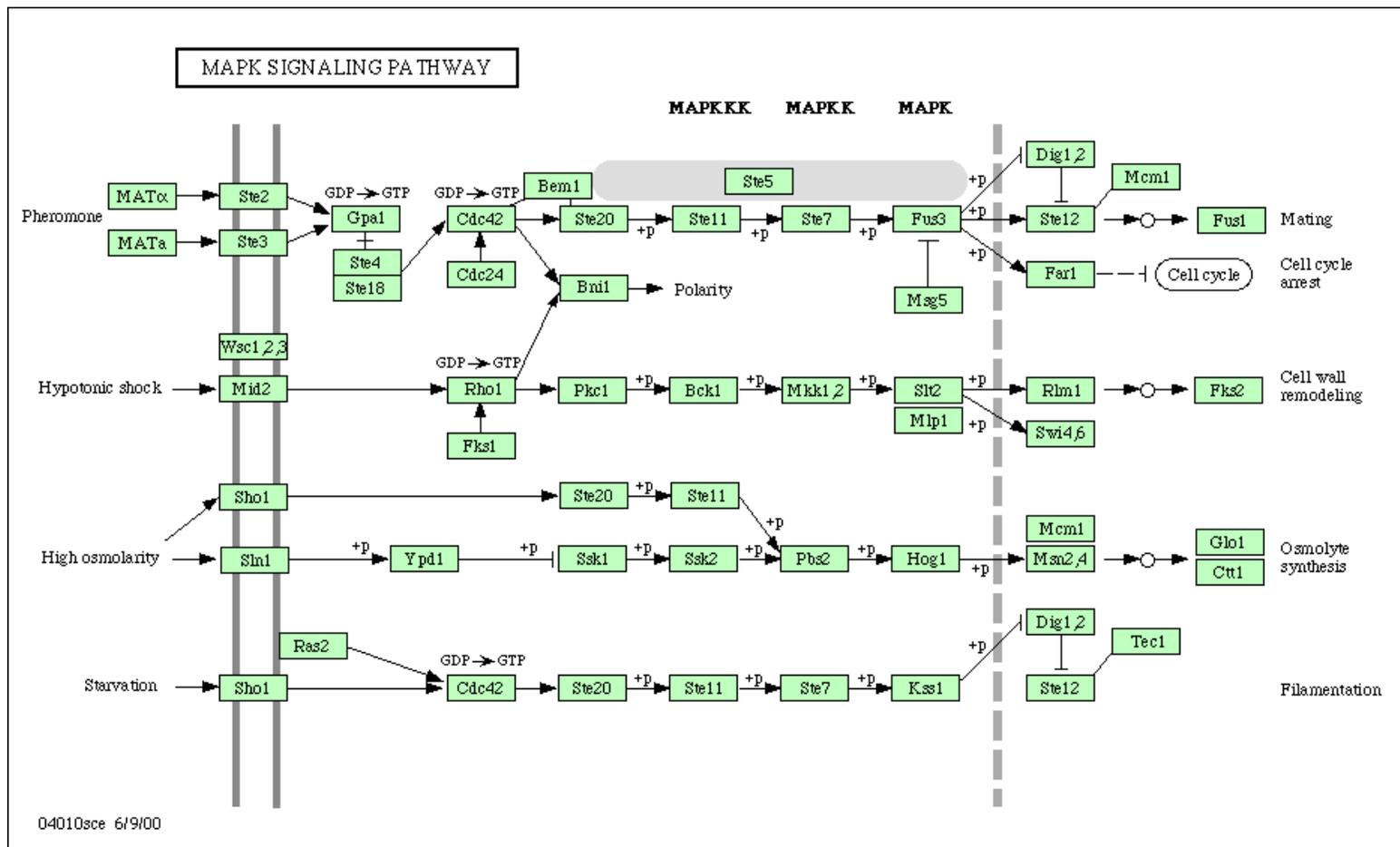


Regulatory
endpoint

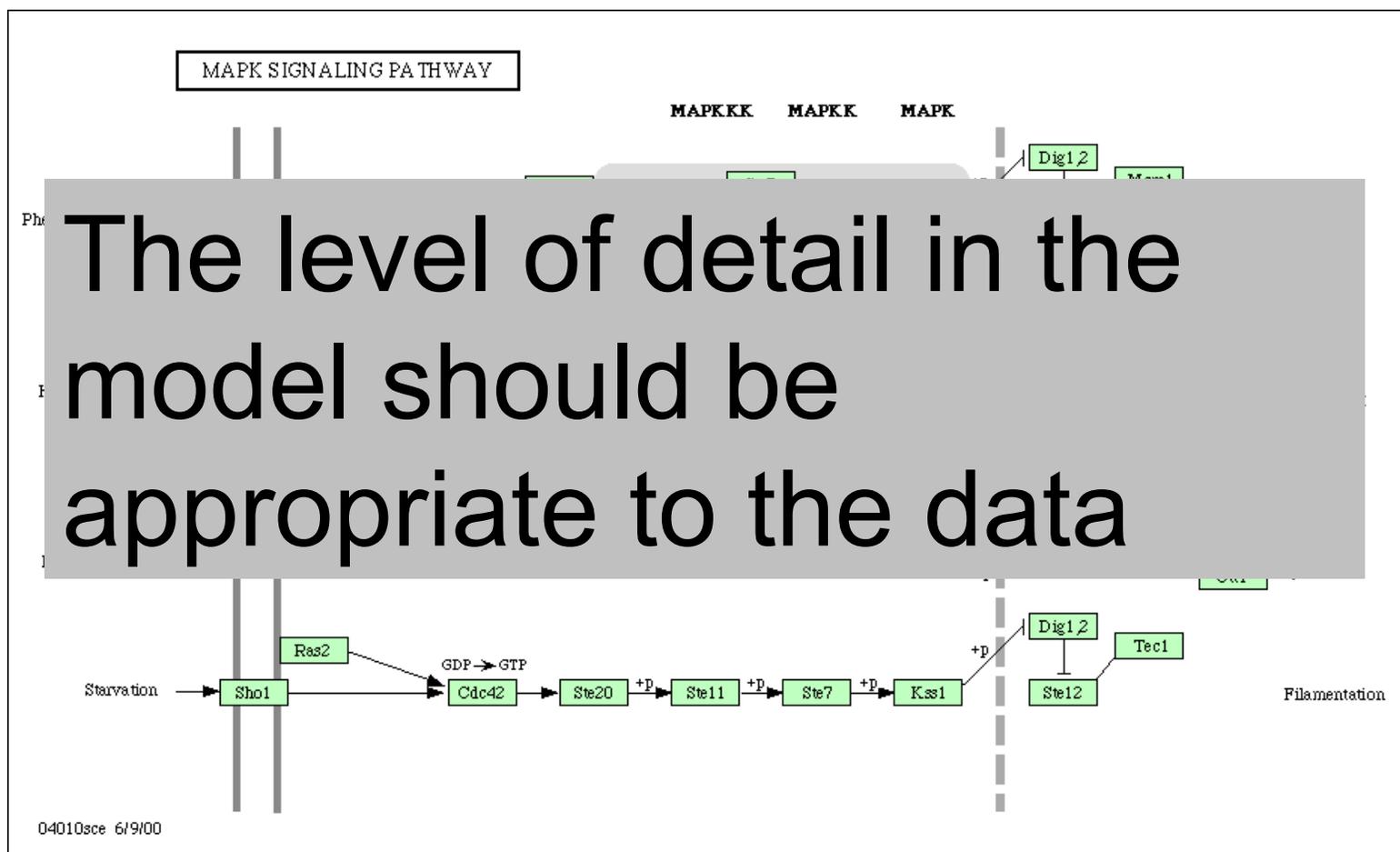
Intracellular signaling cascades



How do we model the signaling cascade?

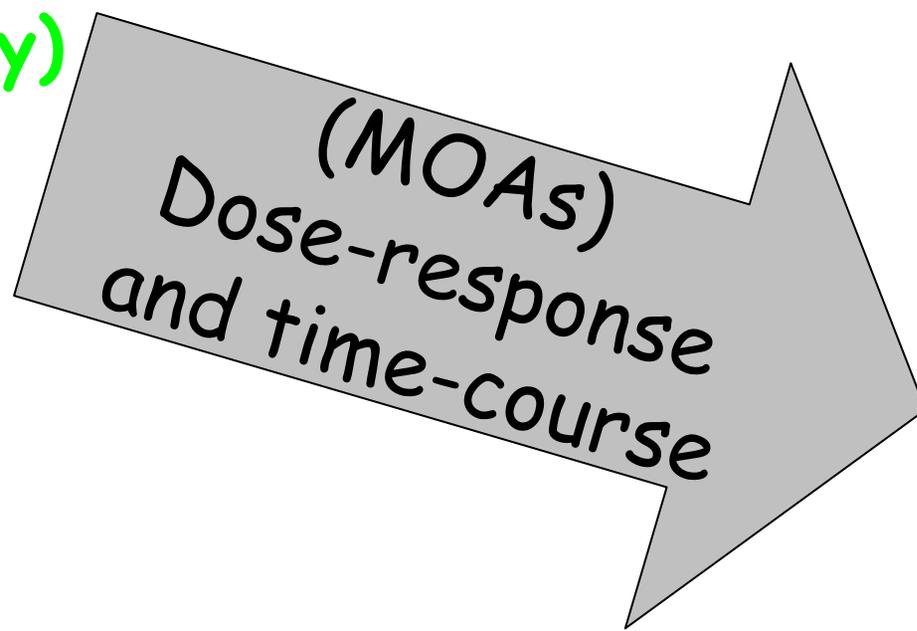


How do we model the signaling cascade?



Goal is to understand mechanistic
basis of dose-response and time-
course relationships

(dosimetry)



Regulatory
endpoint

Specify the sequence(s) of key events

(dosimetry)



MOA 1
Key event 1



MOA 1
Key event 2

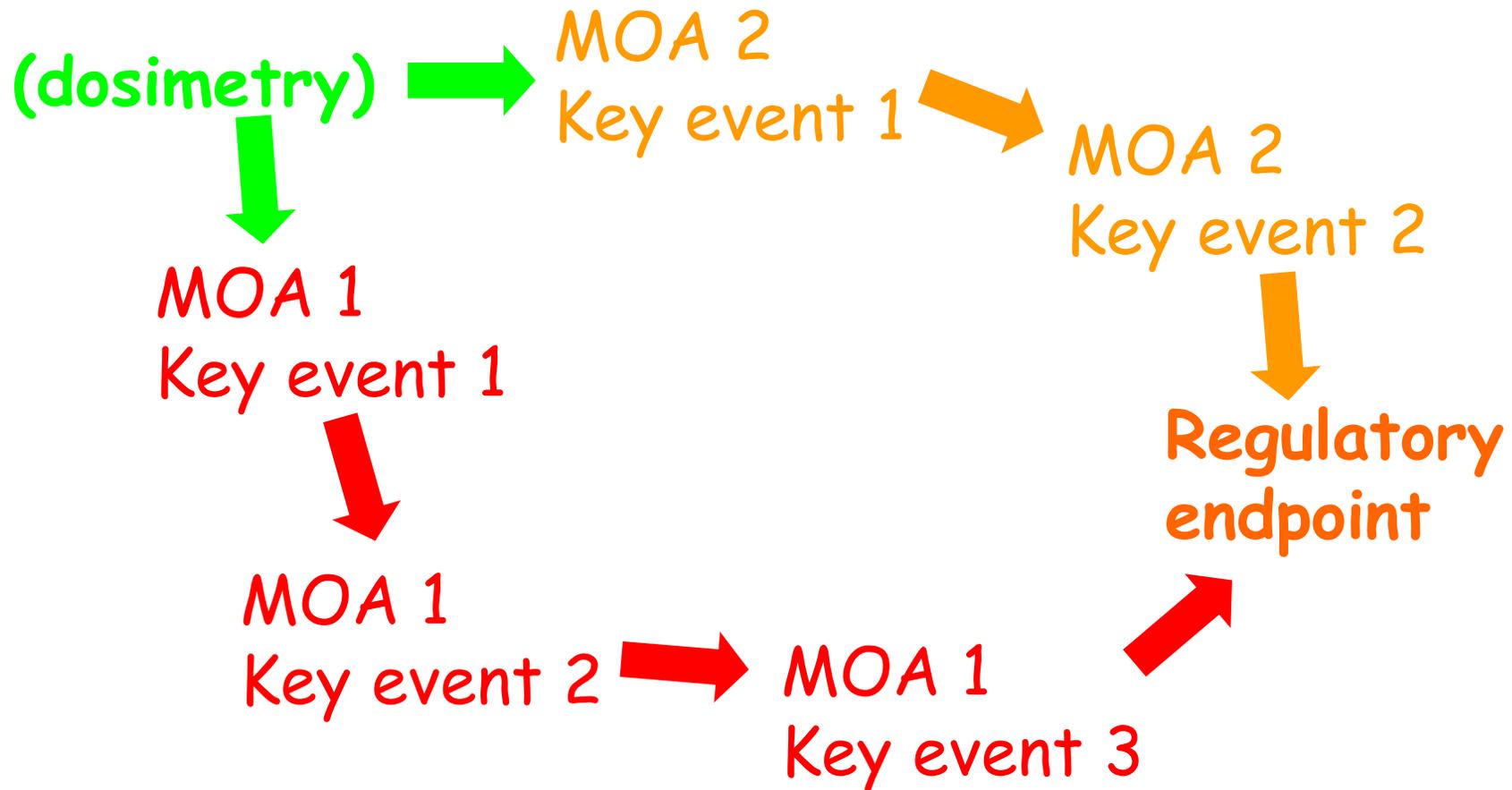


MOA 1
Key event 3

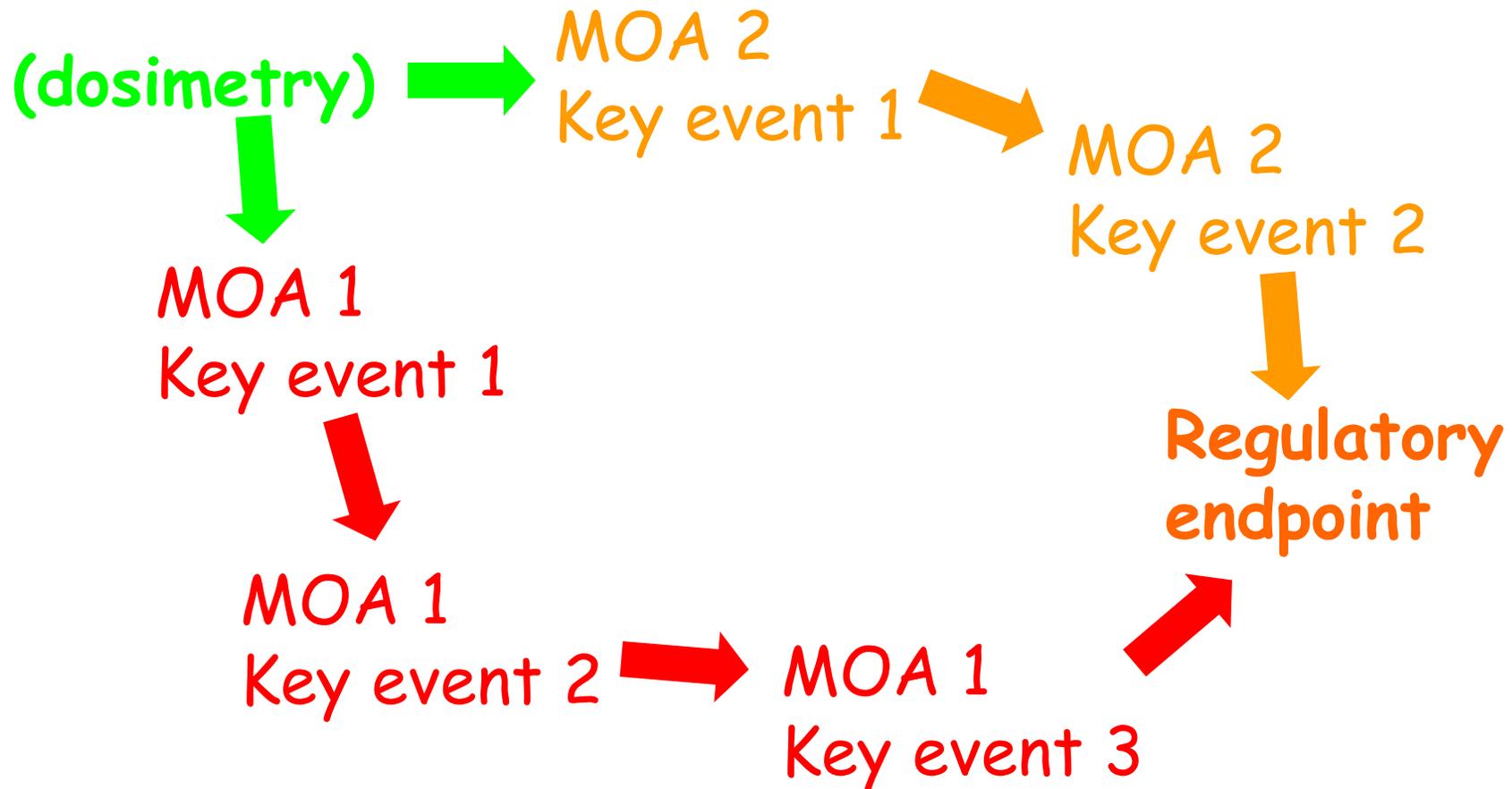


Regulatory
endpoint

Specify the sequence(s) of key events

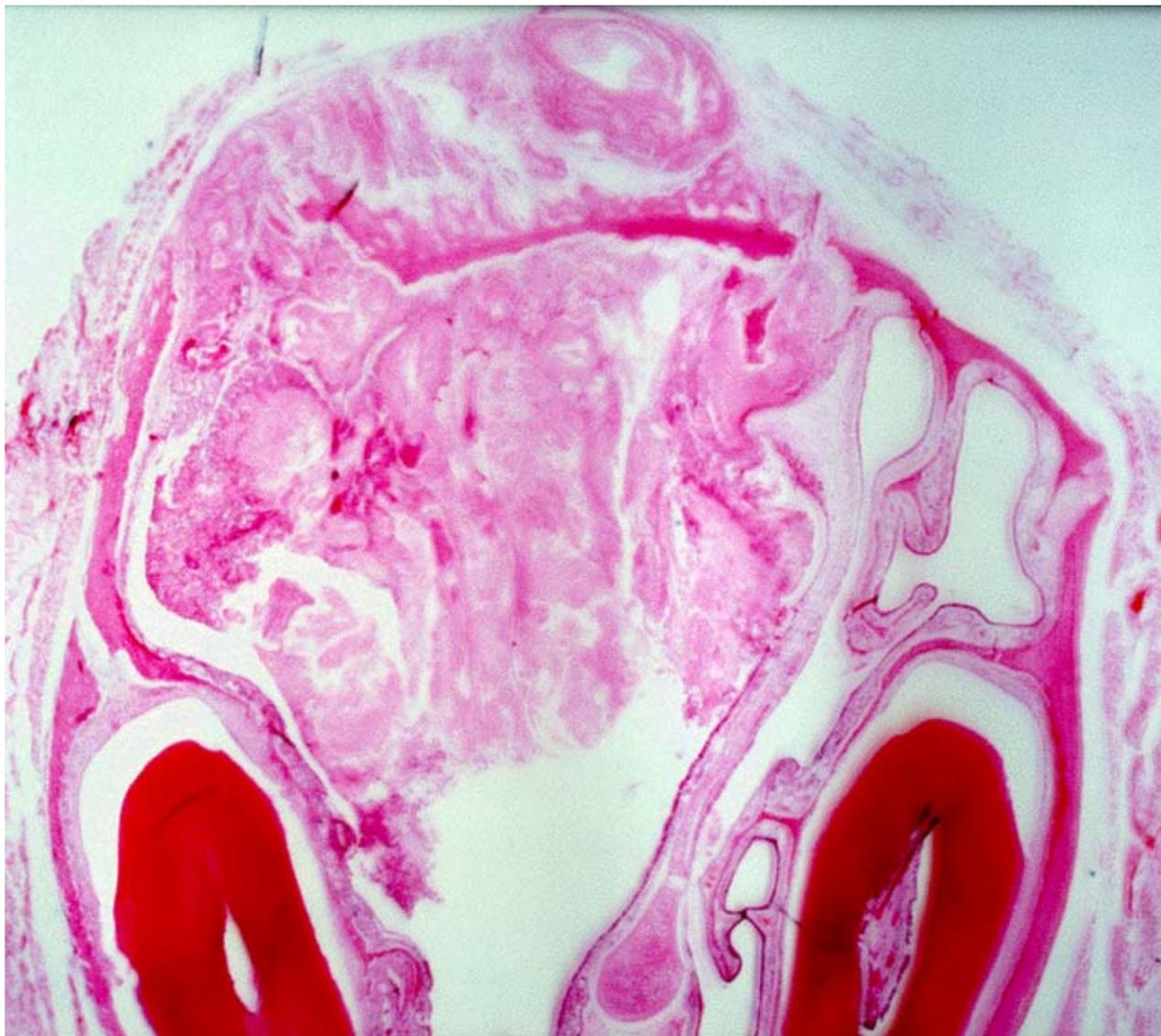


Then the dose-response and time course relationships

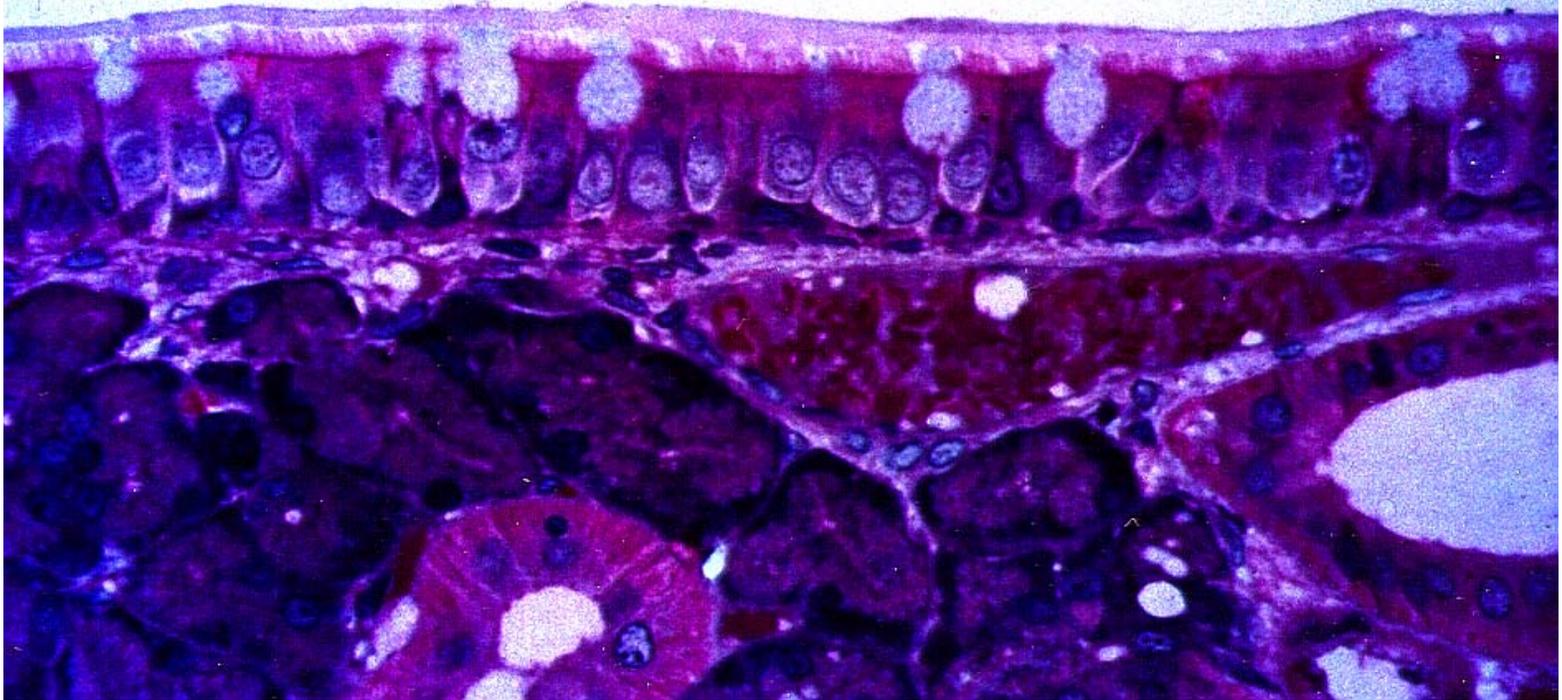


Example

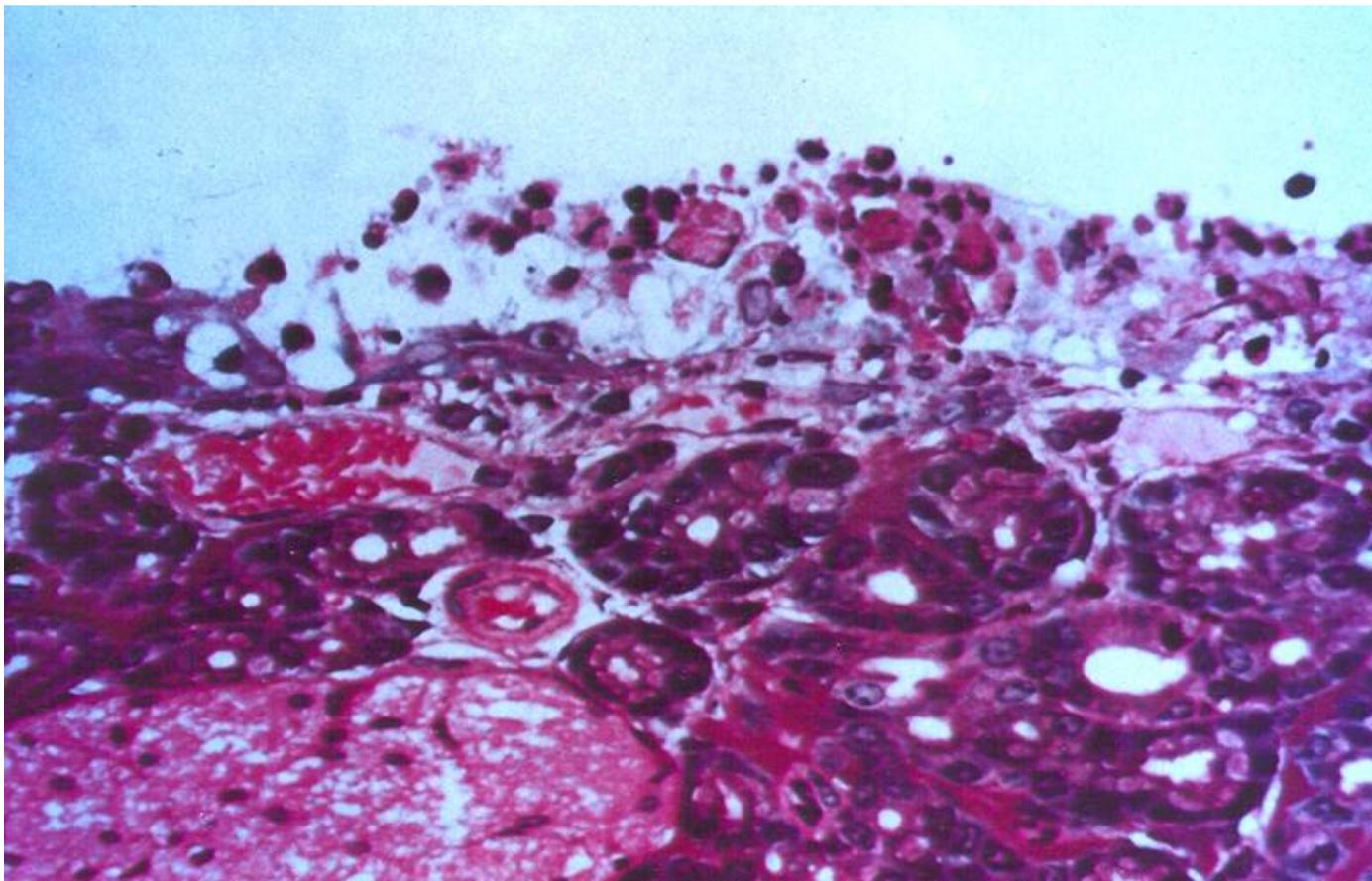
Formaldehyde BBDR model



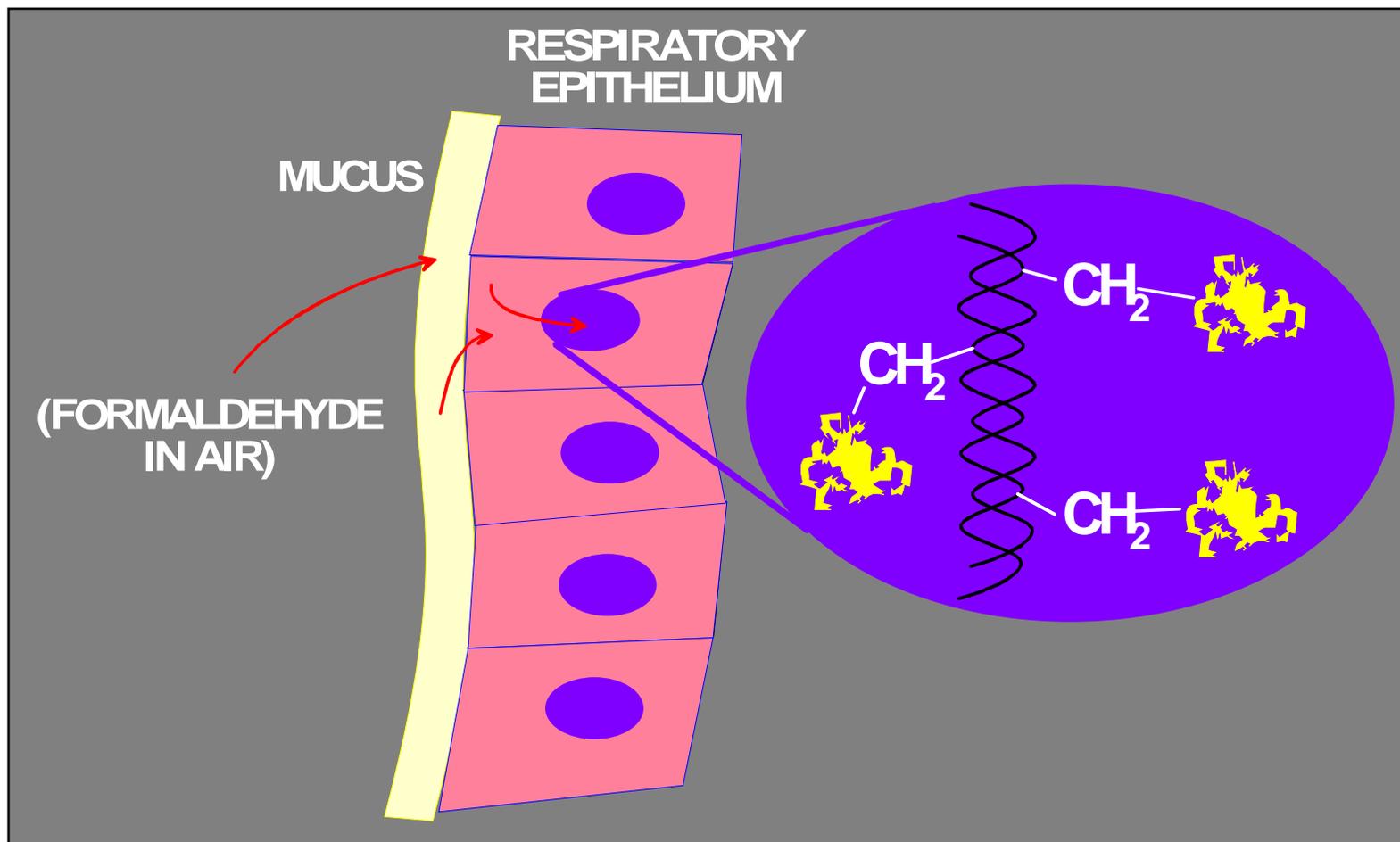
Normal respiratory epithelium in the rat nose



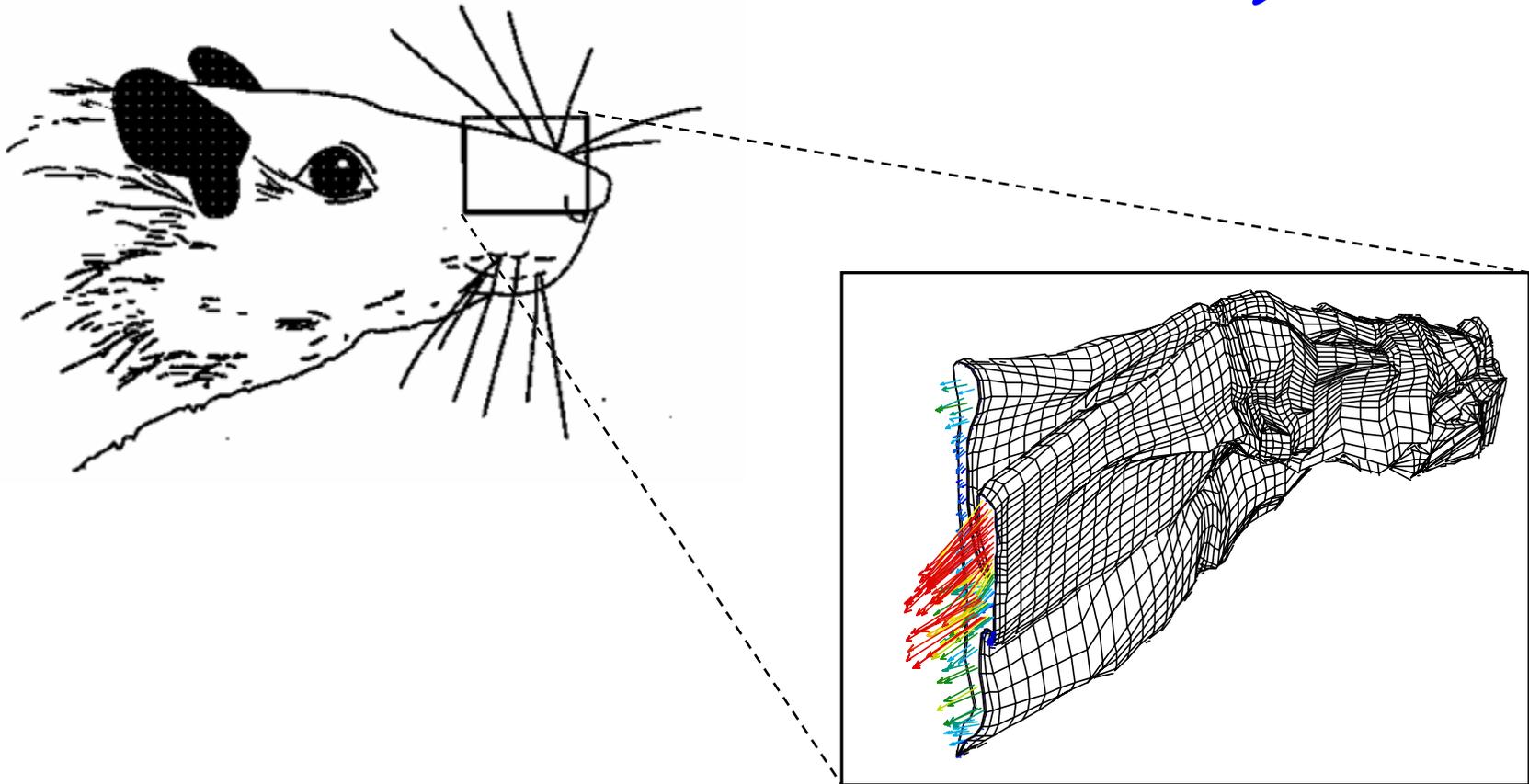
Effect of formaldehyde on respiratory epithelium in the rat nose (10+ ppm)



DPX



CFD simulation of nasal airflow (Kimbell et. al)



Main elements of the CIIT assessment

Inhaled formaldehyde



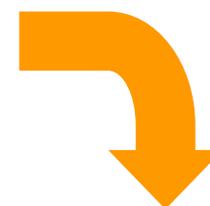
CFD modeling



Tissue dose



Cell proliferation



Mutagenicity
(DPX)

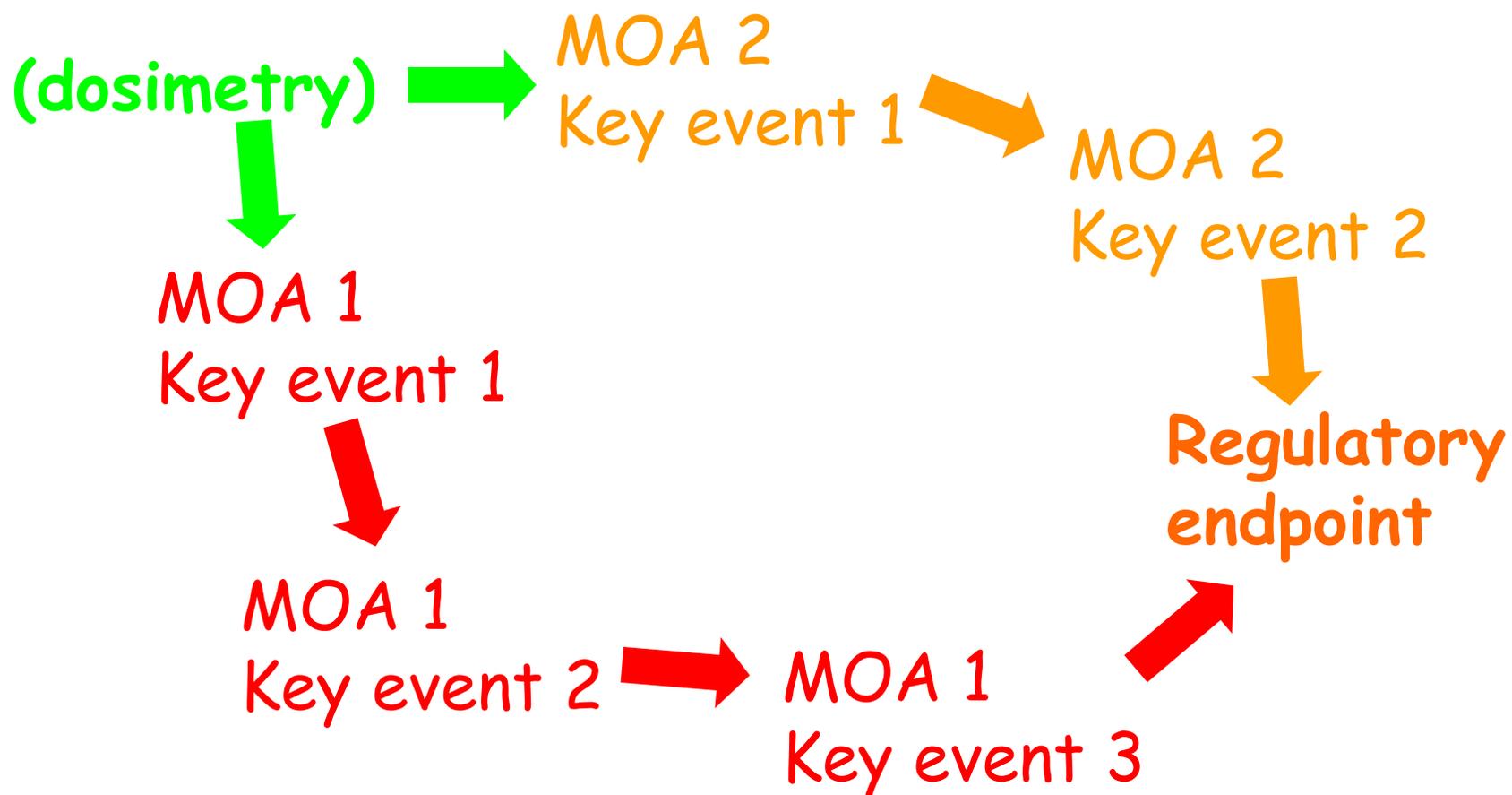


Clonal growth
model

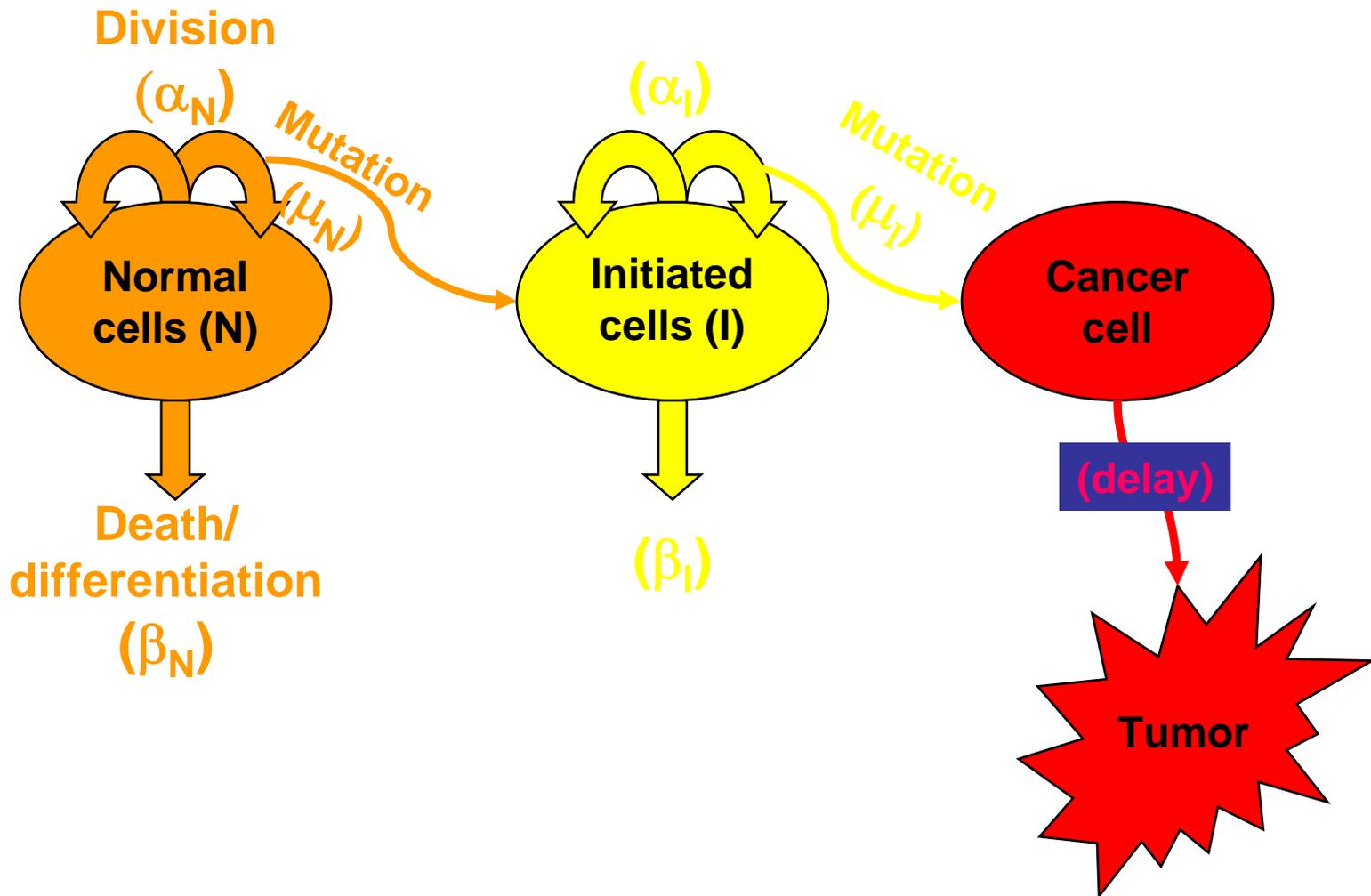


Tumor response

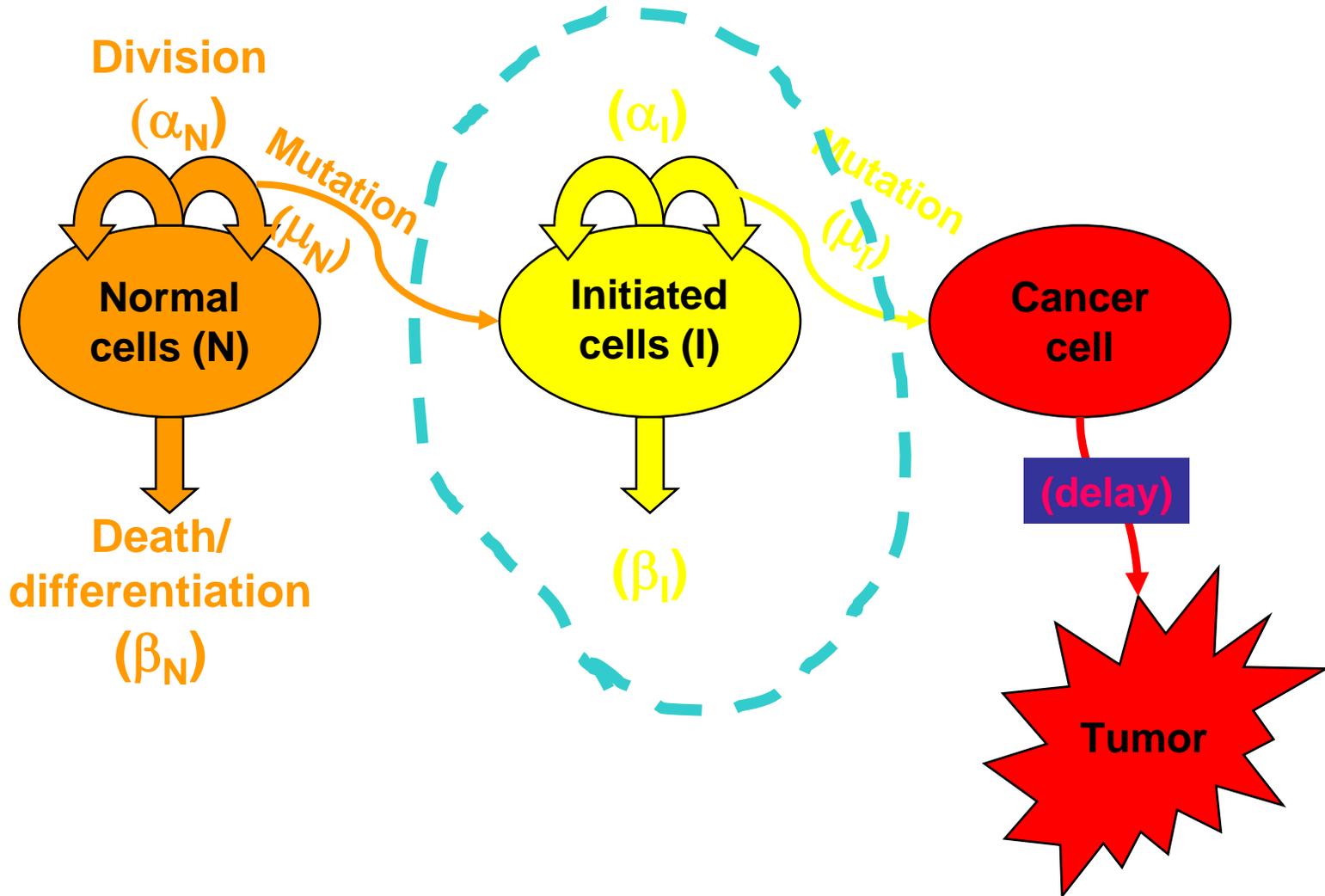
Then the dose-response and time course relationships



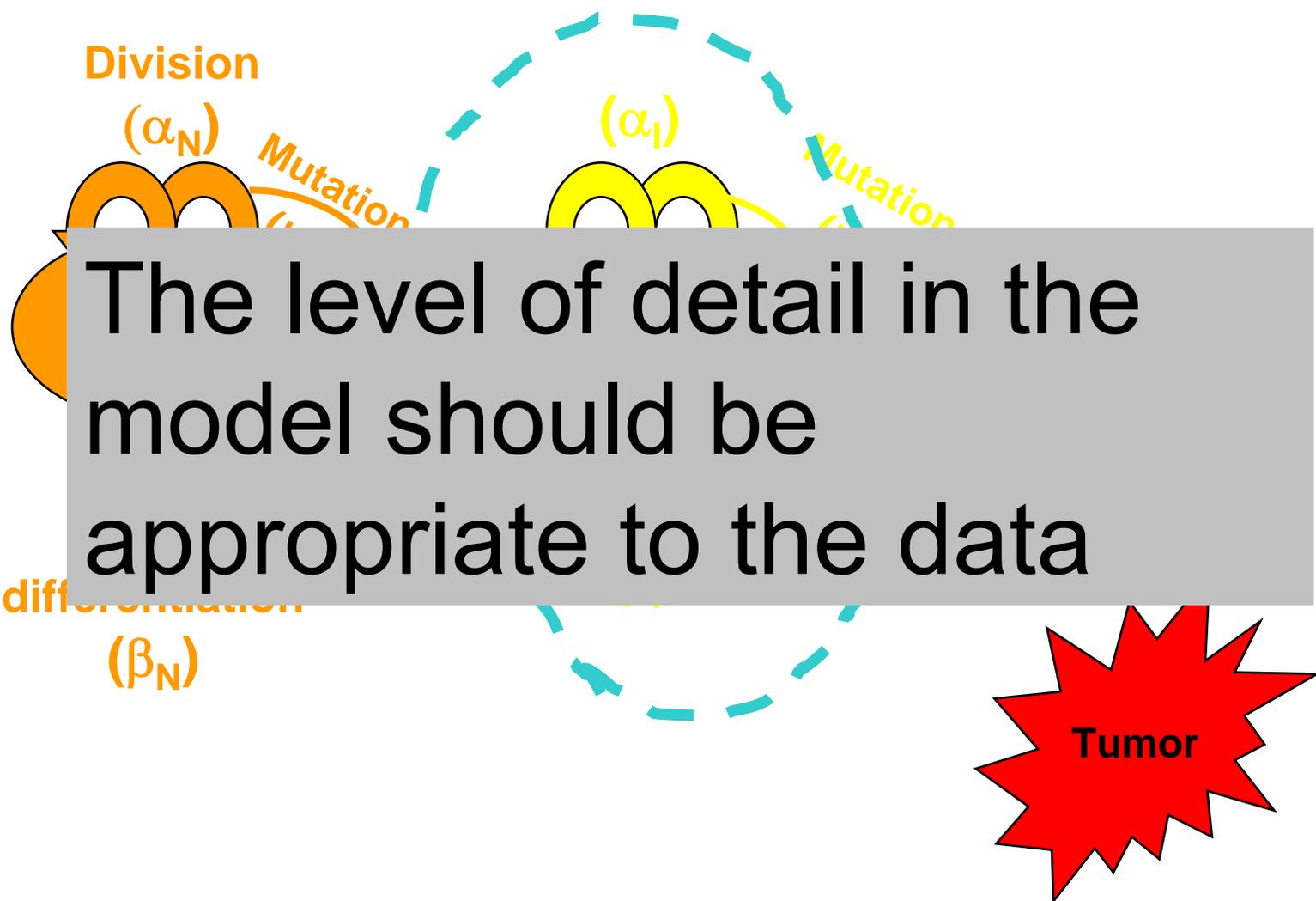
2-stage clonal growth (MVK) model



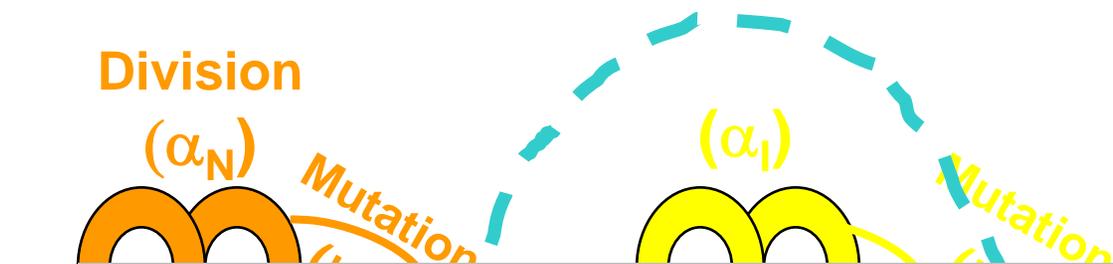
2-stage clonal growth (MVK) model



2-stage clonal growth (MVK) model



2-stage clonal growth (MVK) model



The level of detail in the

This doesn't mean that

every parameter value

must be measured in the
laboratory!

Parameter values for I cells

- ❖ No data, but good data for normal cells and tumors.
- ❖ Theory and experiment says that in general I cells have a growth advantage.
- ❖ Code model according to this context and optimize.
- ❖ Observe Occam's Razor - keep the description as simple as possible

Learning from models

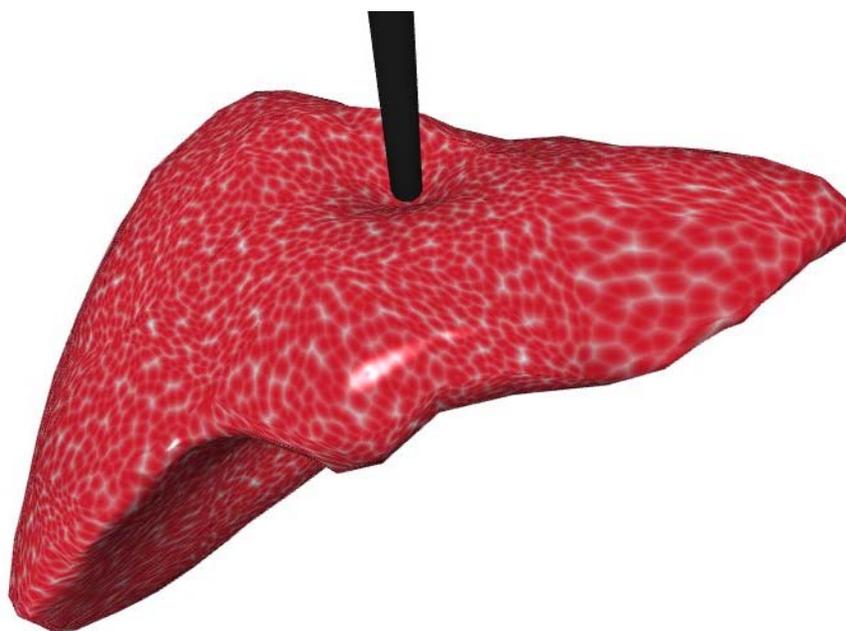
- ❖ *All models are wrong but some are useful.*
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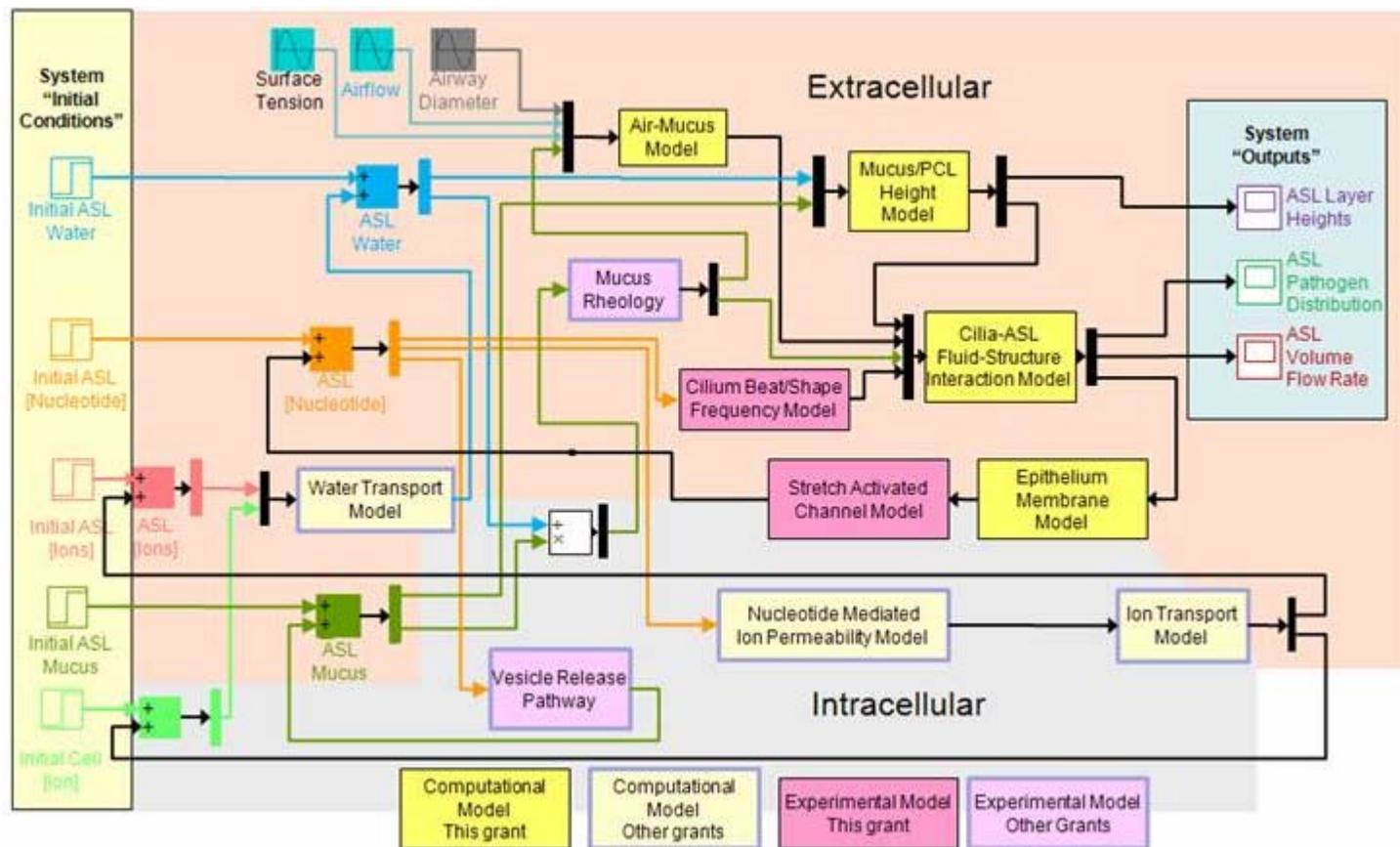
George Box

Virtual tissues

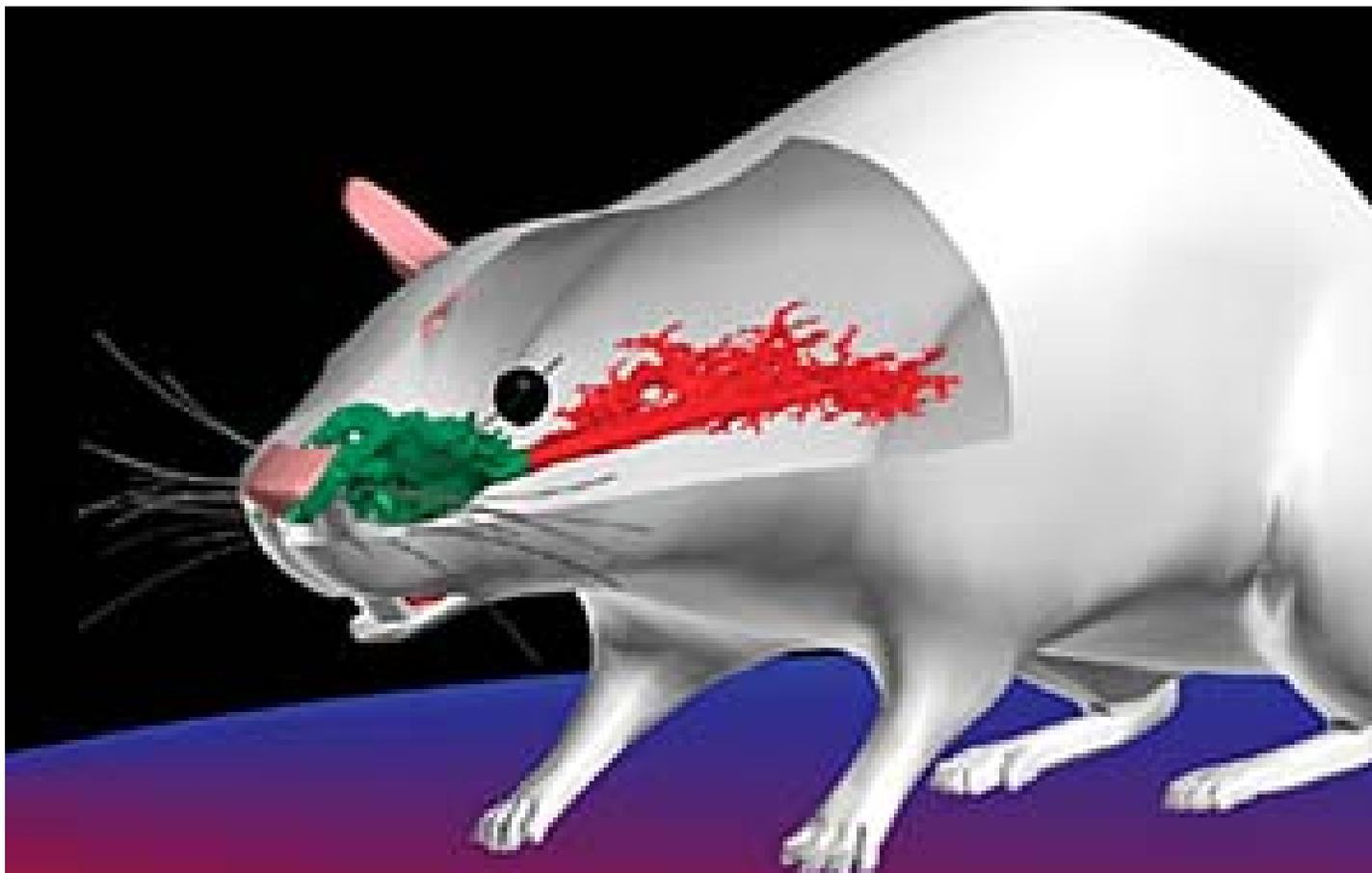
Liver

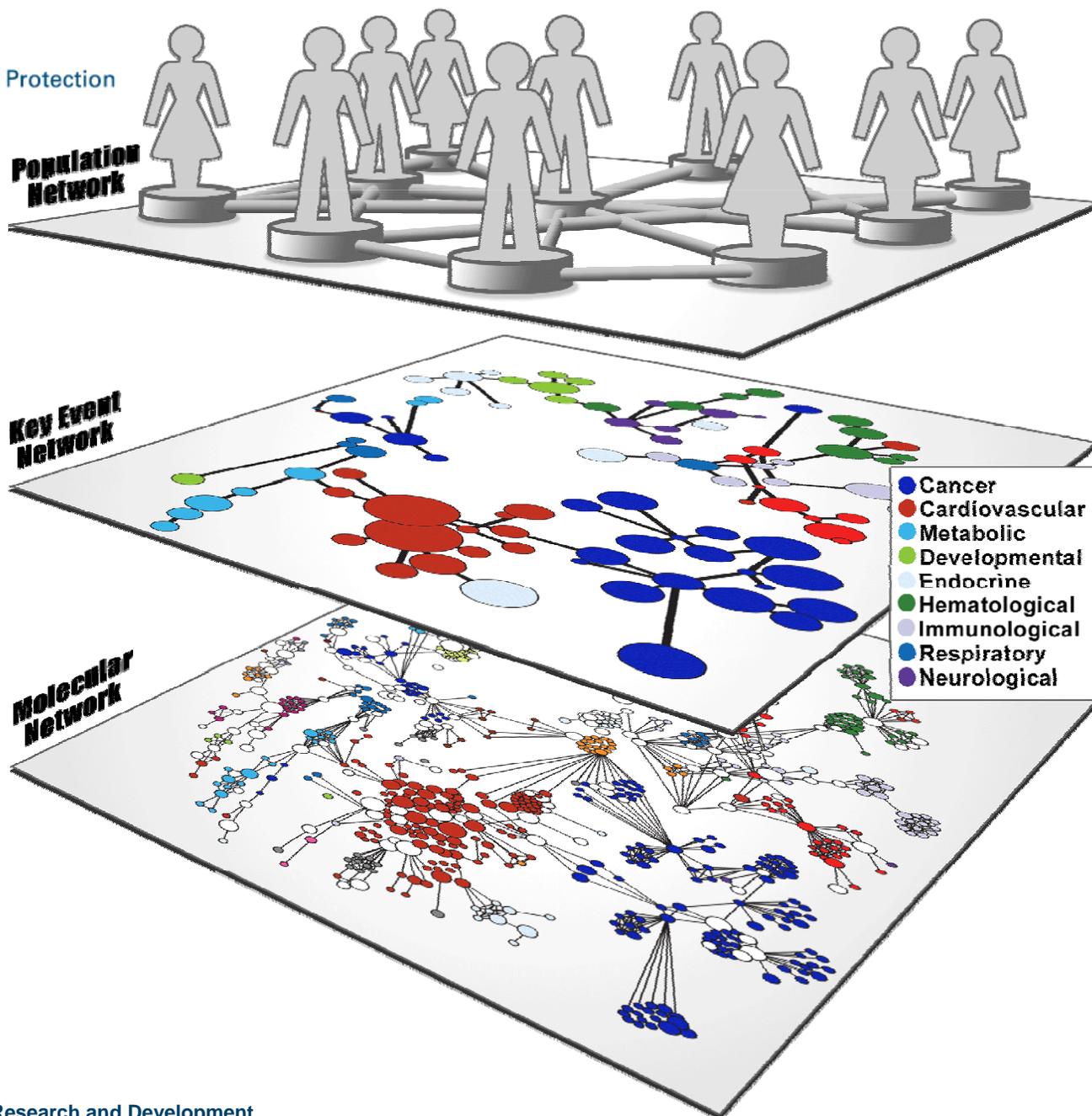


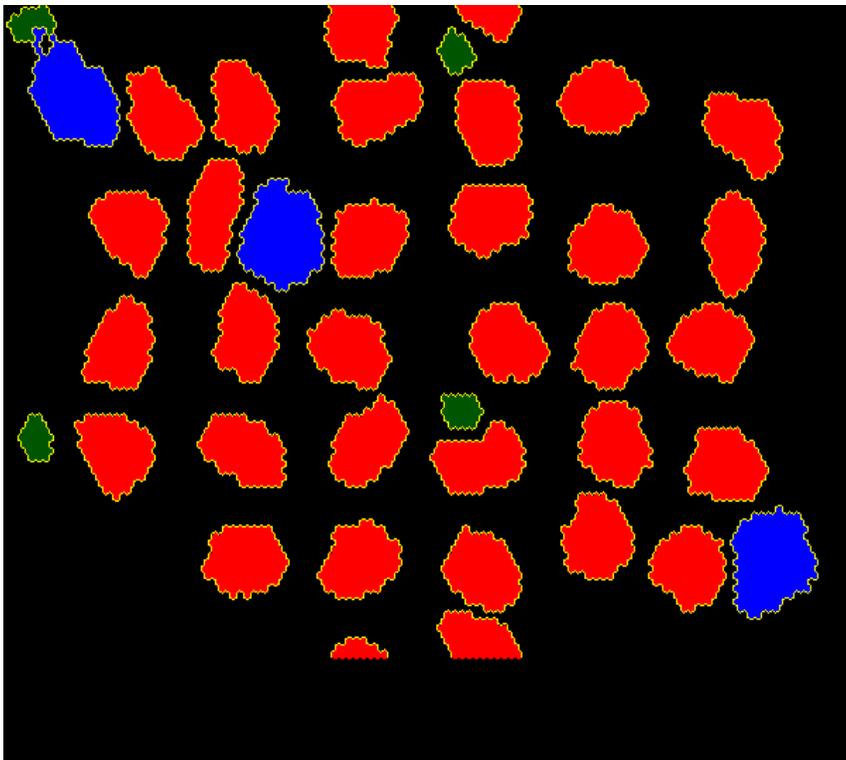
UNC Virtual Lung



PNNL Virtual Lung







Characteristics of VTs

- ❖ Spatial component
 - Spatial data
- ❖ Normal biology
 - Toxicity arises from perturbations
- ❖ Long-range goal: Sufficiently detailed biology that, for a given toxicant, prediction of PK and effect is possible.
 - In effect, the computer model replaces the animal model

How are VTs different?

	PBPK/BBDR	Virtual tissues
Spatial component	+	++++
Normal biology	++++	++++
Level of detail	++	++++
Multi-scale	+	++++
Prediction	++	++++
Maturity	+++	+

Whole organism models

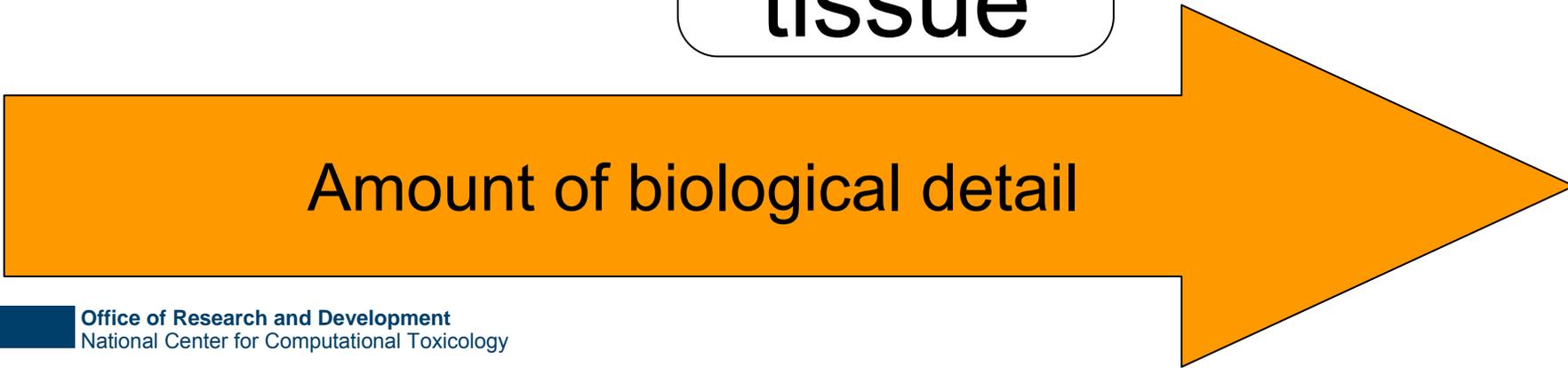
PBPK

BBDR

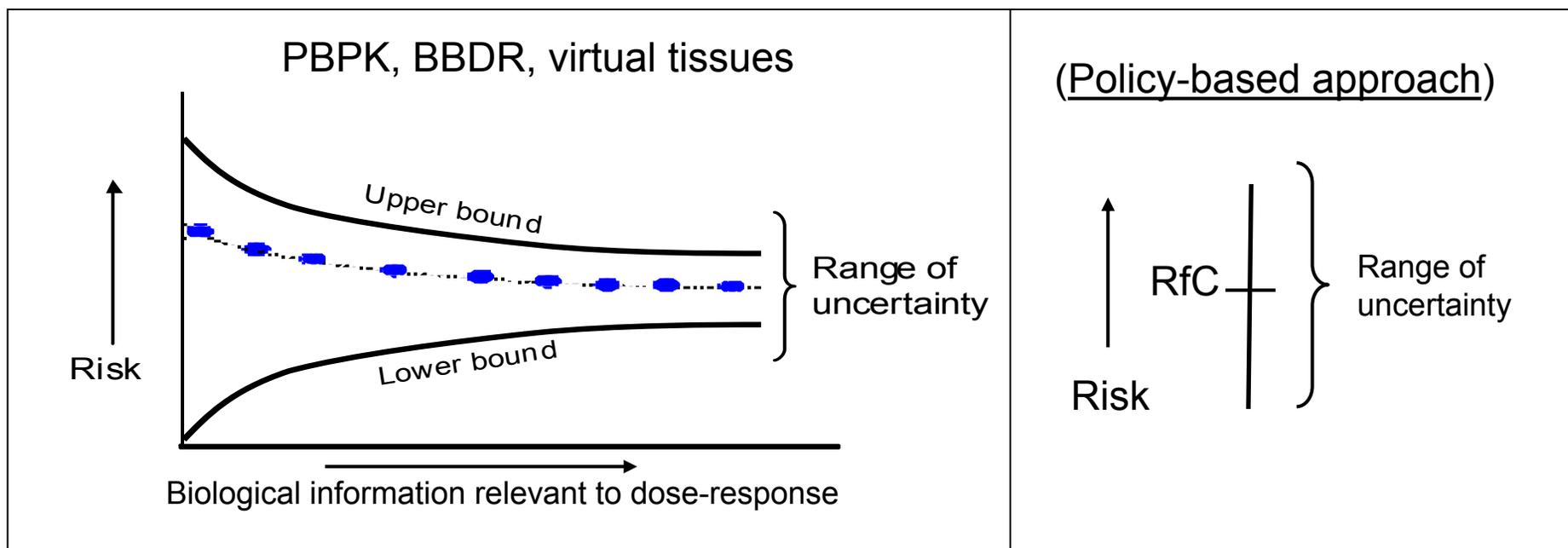
**Virtual
organism**

**Virtual
tissue**

Amount of biological detail

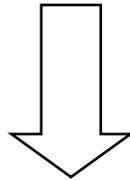


The risk prediction with the least uncertainty is preferable

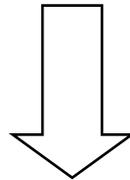


1987 U.S. EPA

Inhaled ppm

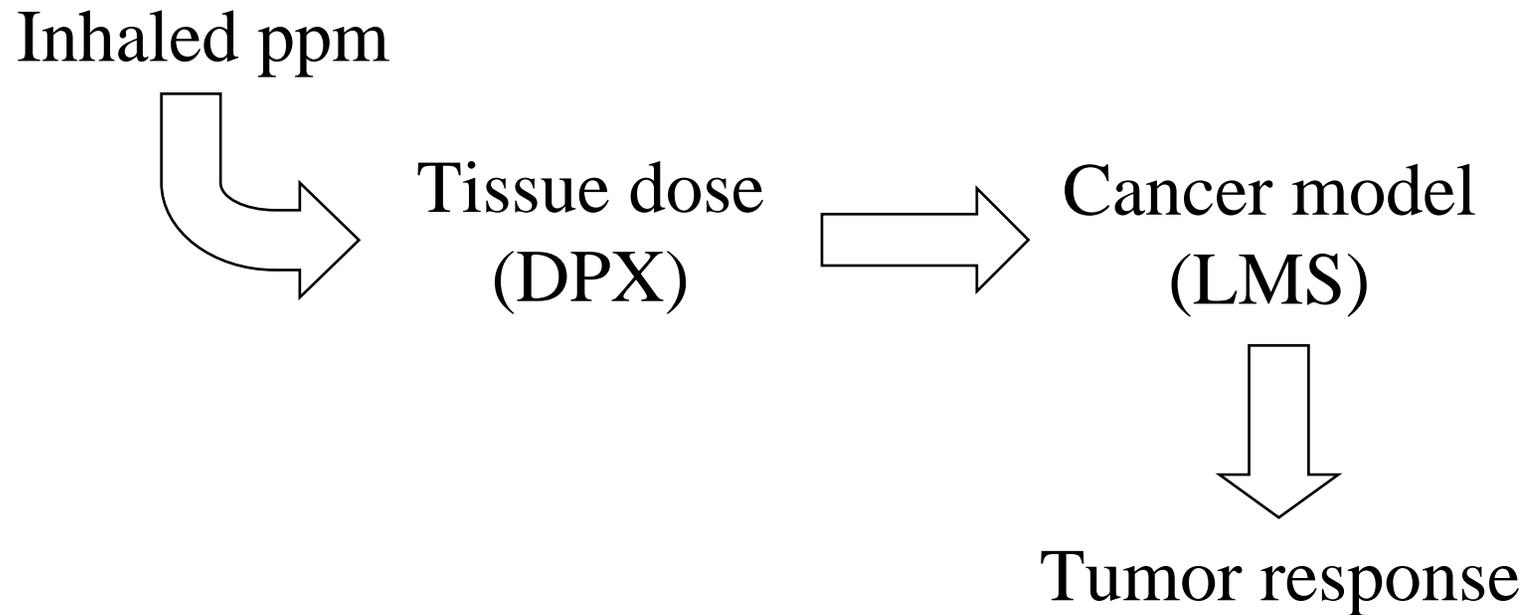


Cancer model
(LMS)



Tumor response

1991 U.S. EPA



Main elements of the CIIT assessment

Inhaled formaldehyde



CFD modeling



Tissue dose



Cell proliferation



Clonal growth
model

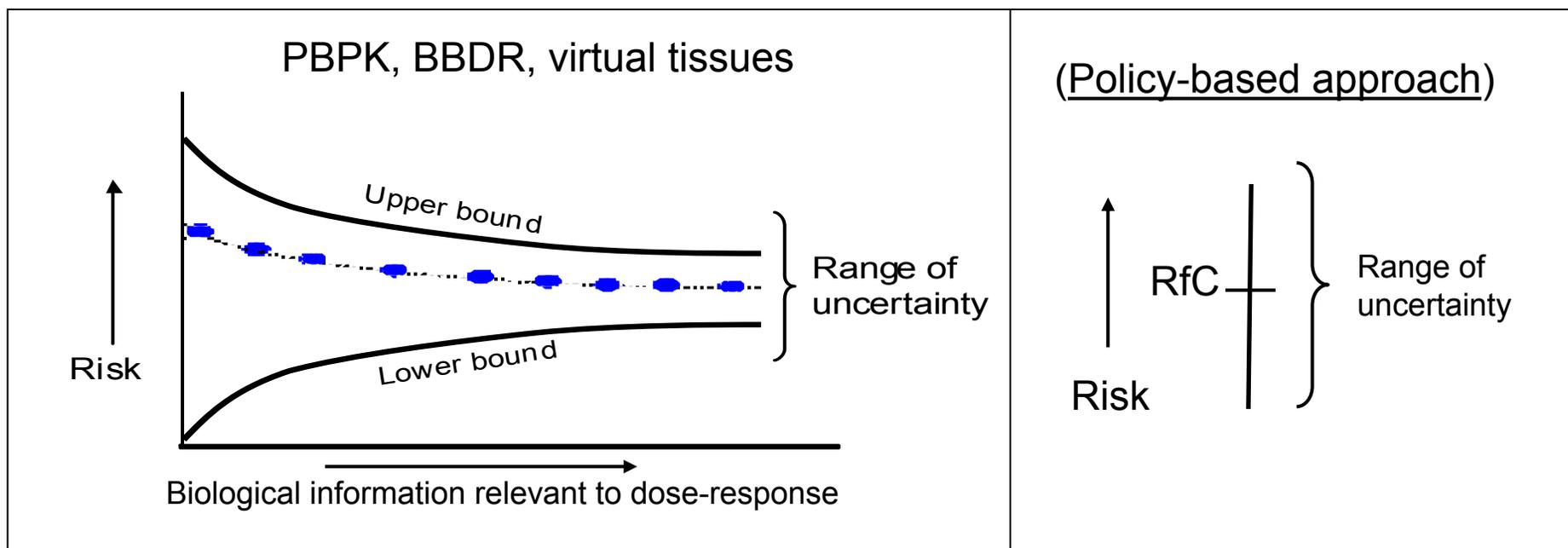


Mutagenicity
(DPX)



Tumor response

The risk prediction with the least uncertainty is preferable



Summary (1)

- ❖ Remediation is expensive, so accurate prediction of dose-response is important to help control costs.
- ❖ Dose-response is a function of biological mechanisms.
- ❖ Computational models of these mechanisms improve the efficiency of research and provide the capability for prediction.
- ❖ Modeling technology is evolving towards virtual tissues and organisms

Summary (2)

- ❖ General correspondence between level of detail in models and available data is important
 - Some optimization is OK
 - Observe Occam's Razor!
- ❖ Need transparent, usable means for evaluating relative uncertainty of models.

Acknowledgements

EPA National Center for Computational
Toxicology

Thomas Knudsen

Imran Shah

Michael Rountree

End