Integration of biomarkers in risk assessment; a toxicological perspective

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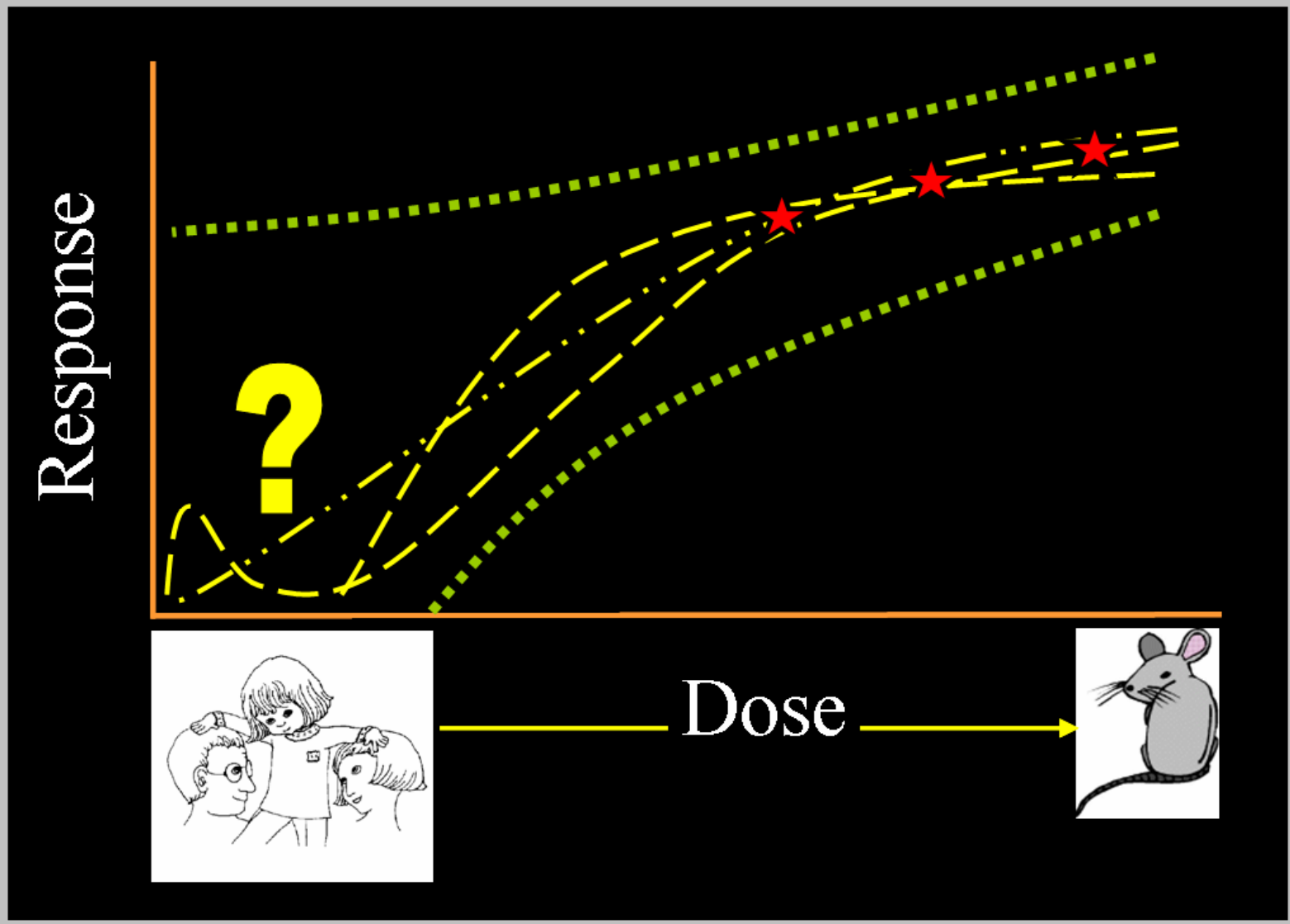
Thursday, October 19, 2006

Outline

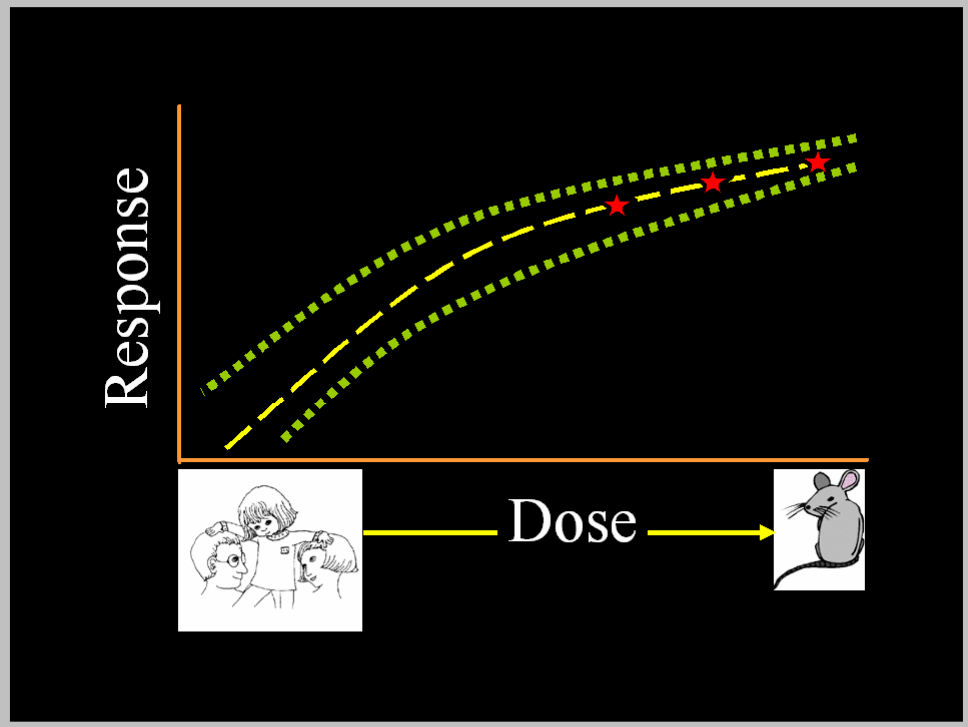
- Using mechanistic data to reduce uncertainty in risk assessment
- Formaldehyde nasal SCC in rats
- Mechanistic studies of the rat tumors
- Risk assessment driven by the data
- IARC



The problem

Mode-of-action analysis

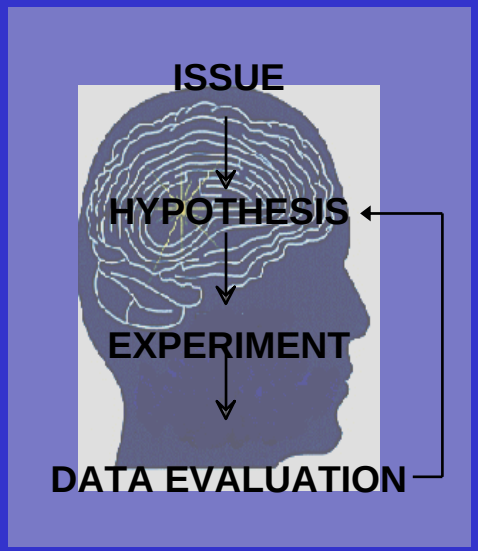
Biologically-based computational modeling



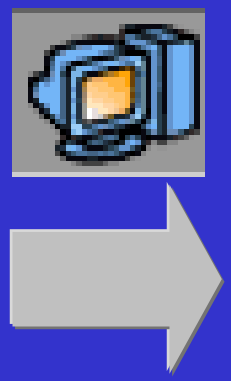
The solution

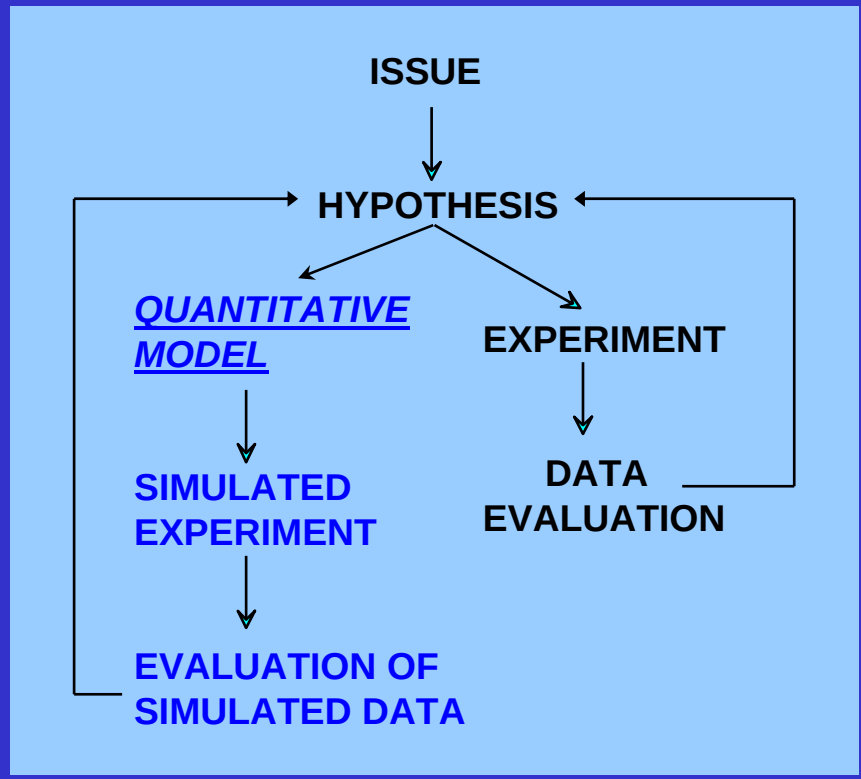
Approach

Quantitative modeling of the mode or mechanism of action to predict dose-response and time-course behaviors



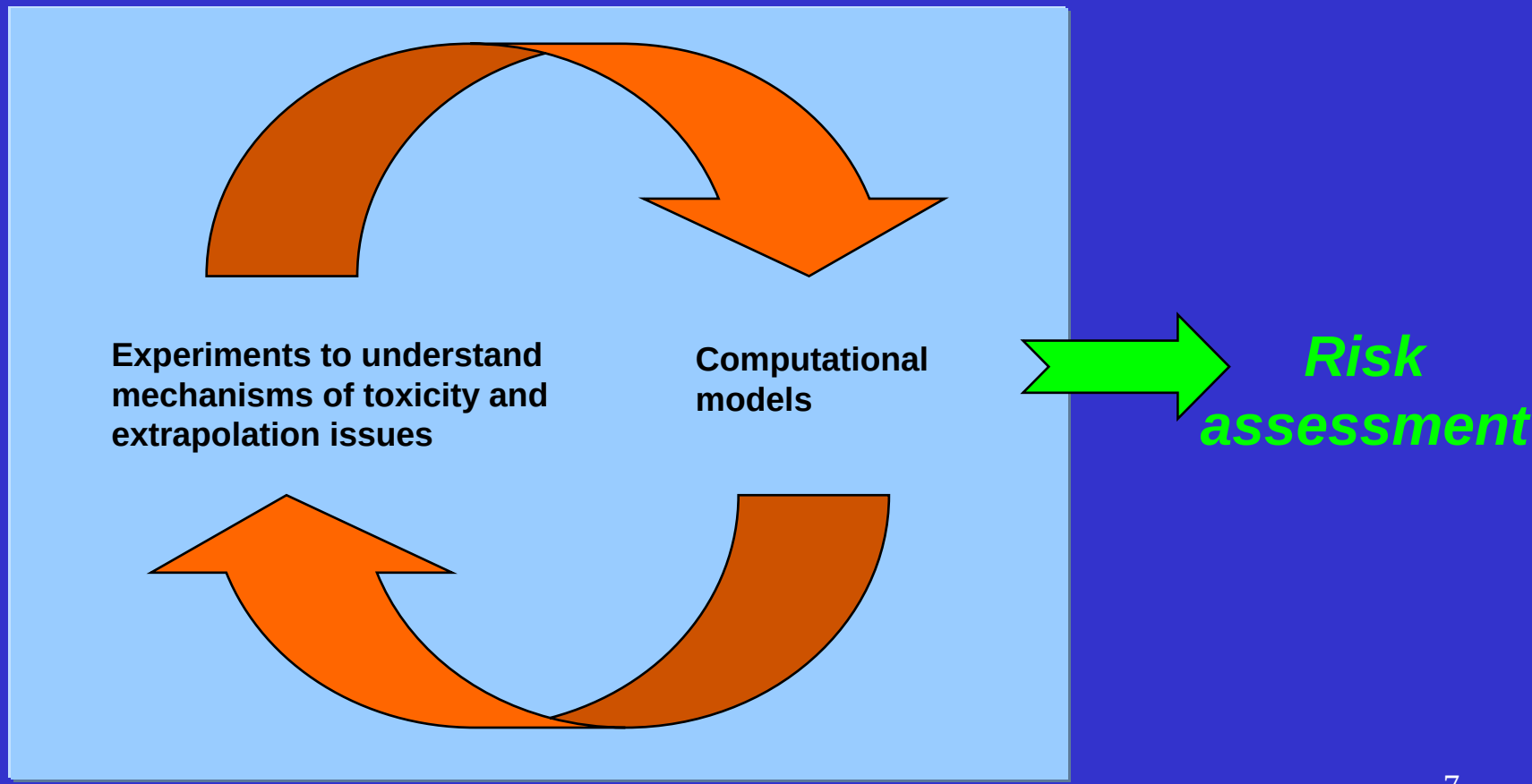
(Intuitive modeling)



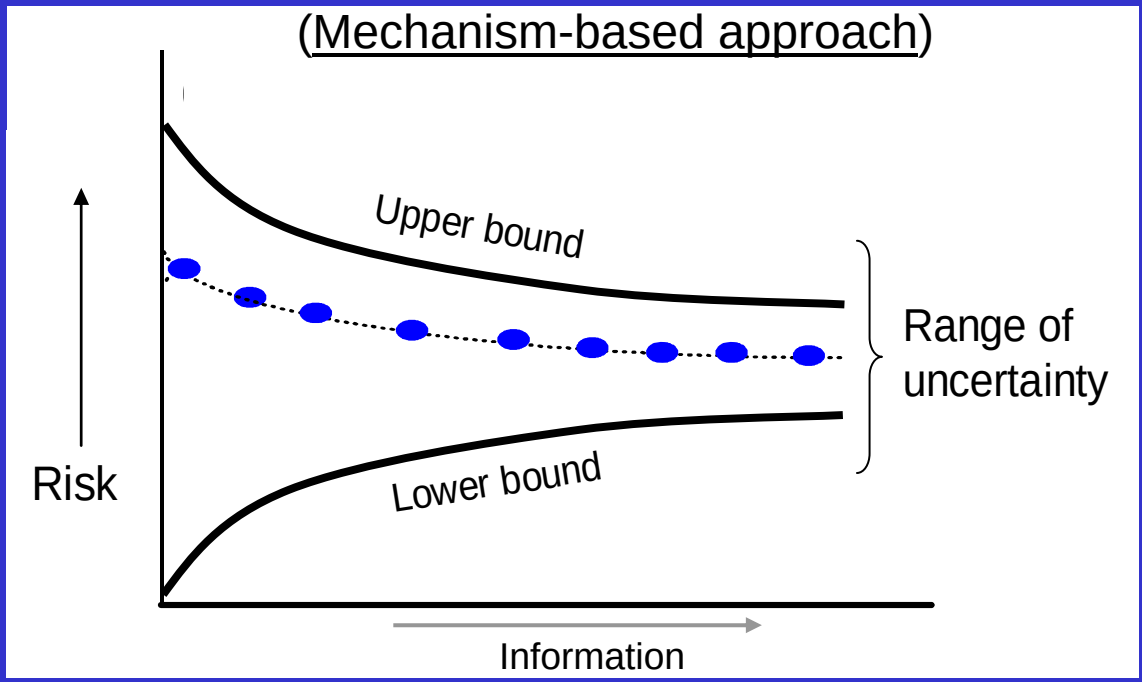


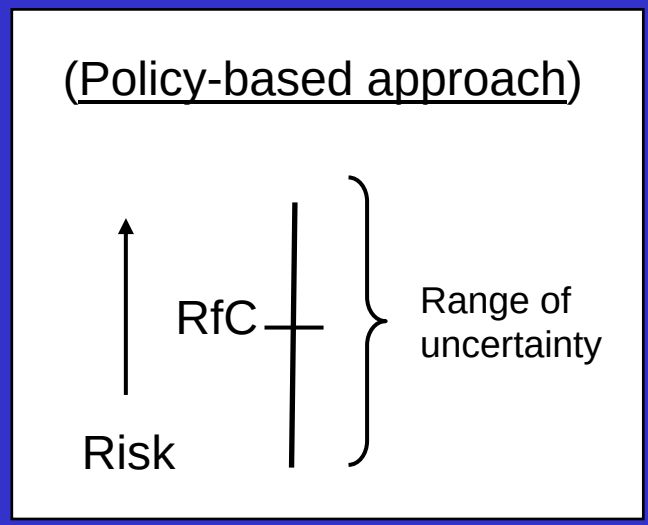
(Formal + intuitive modeling)

Biologically based computational models form natural bridges between research and risk assessment

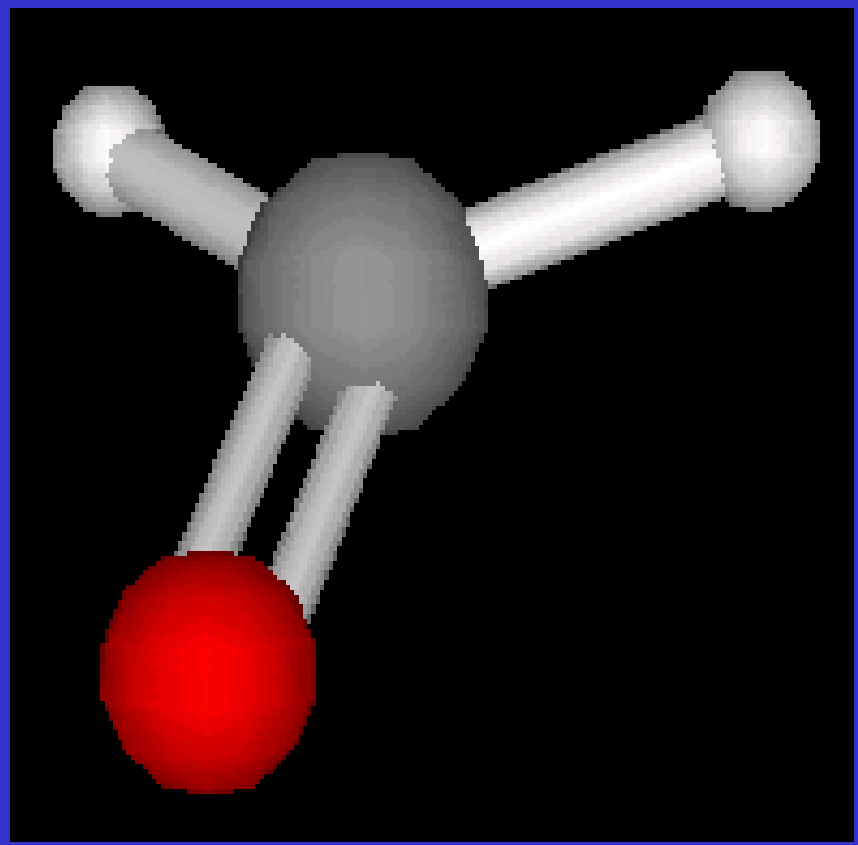


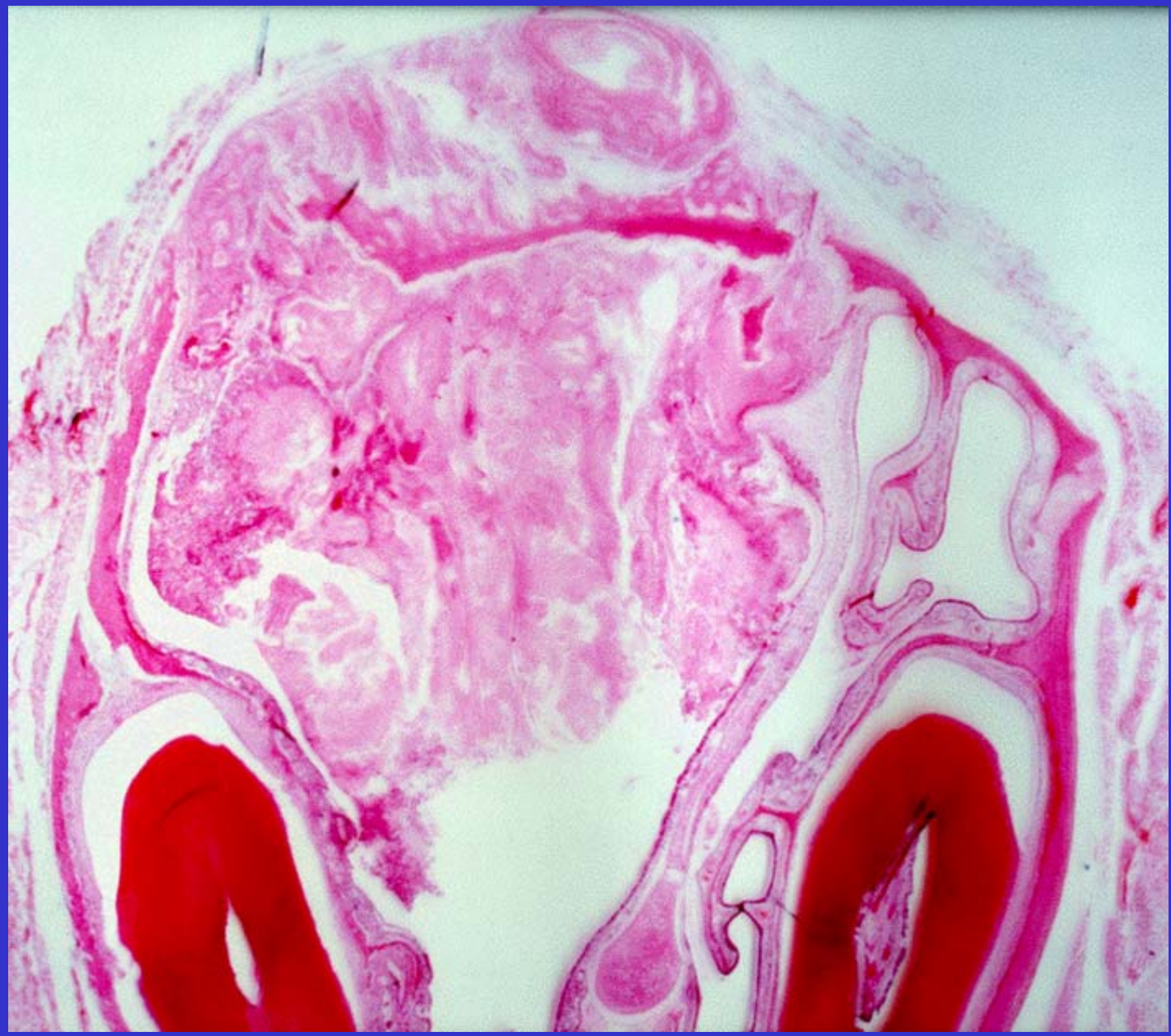
Reduction of uncertainty in risk assessment



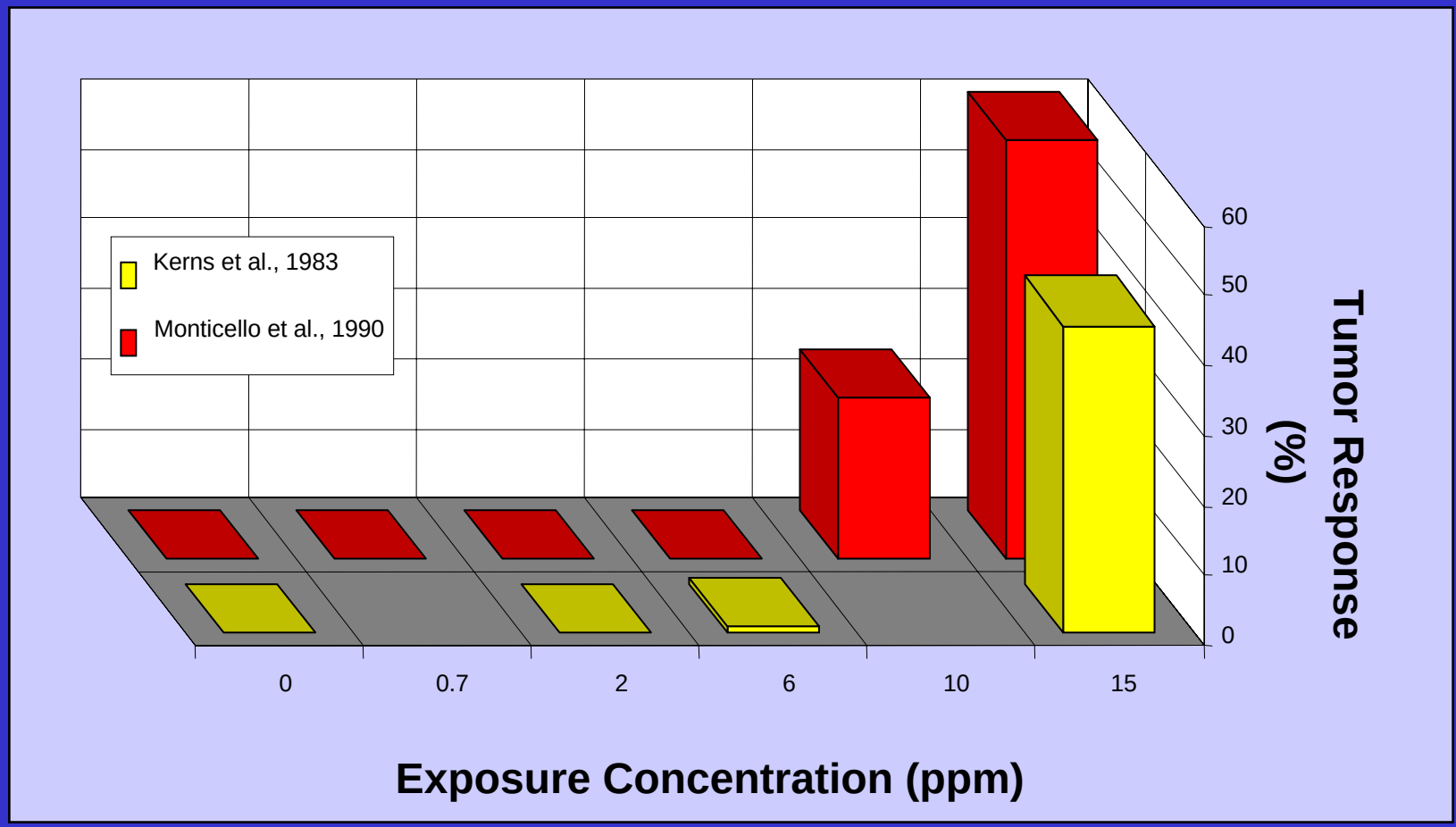


Dose-response assessment for formaldehyde

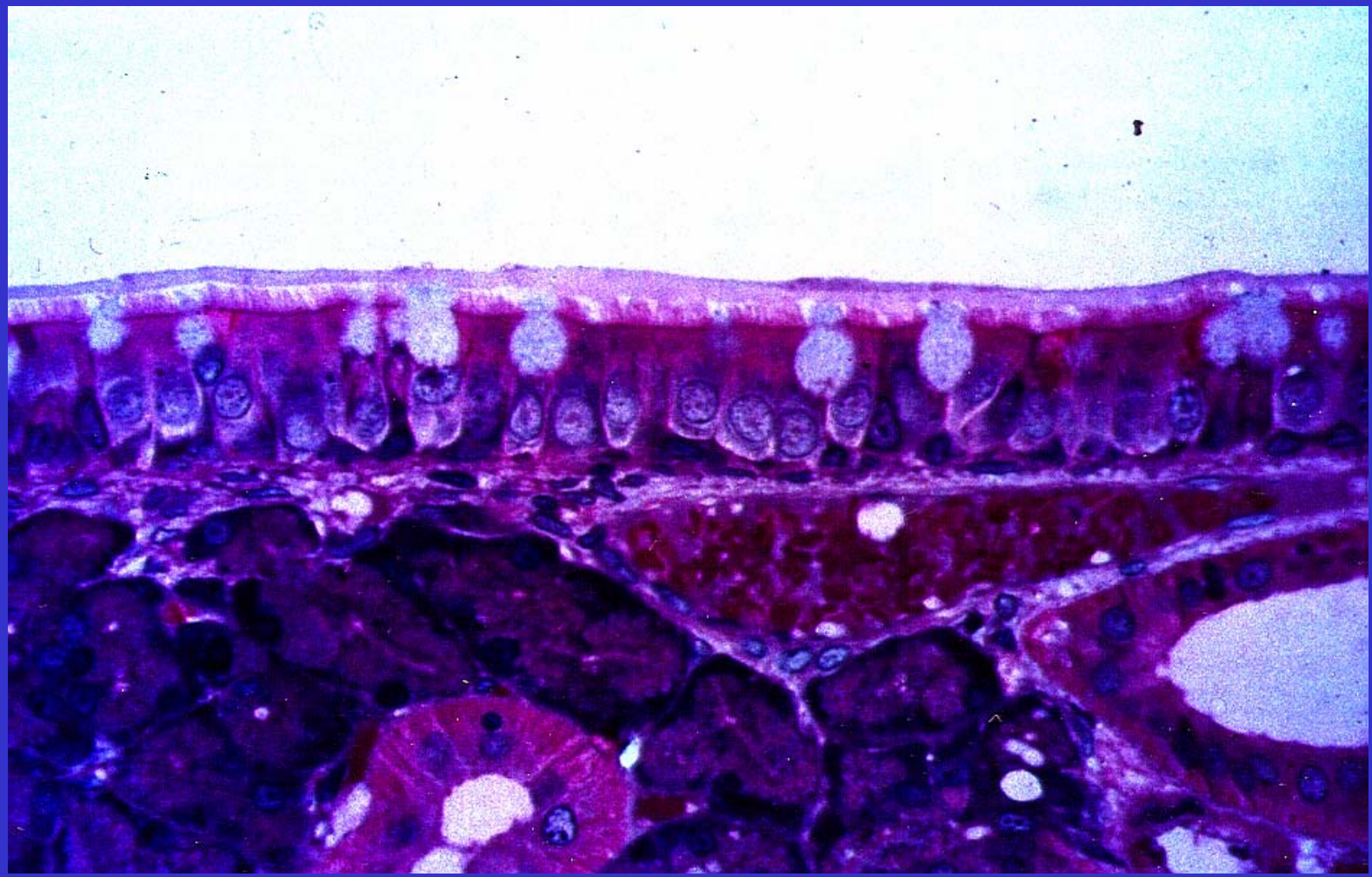




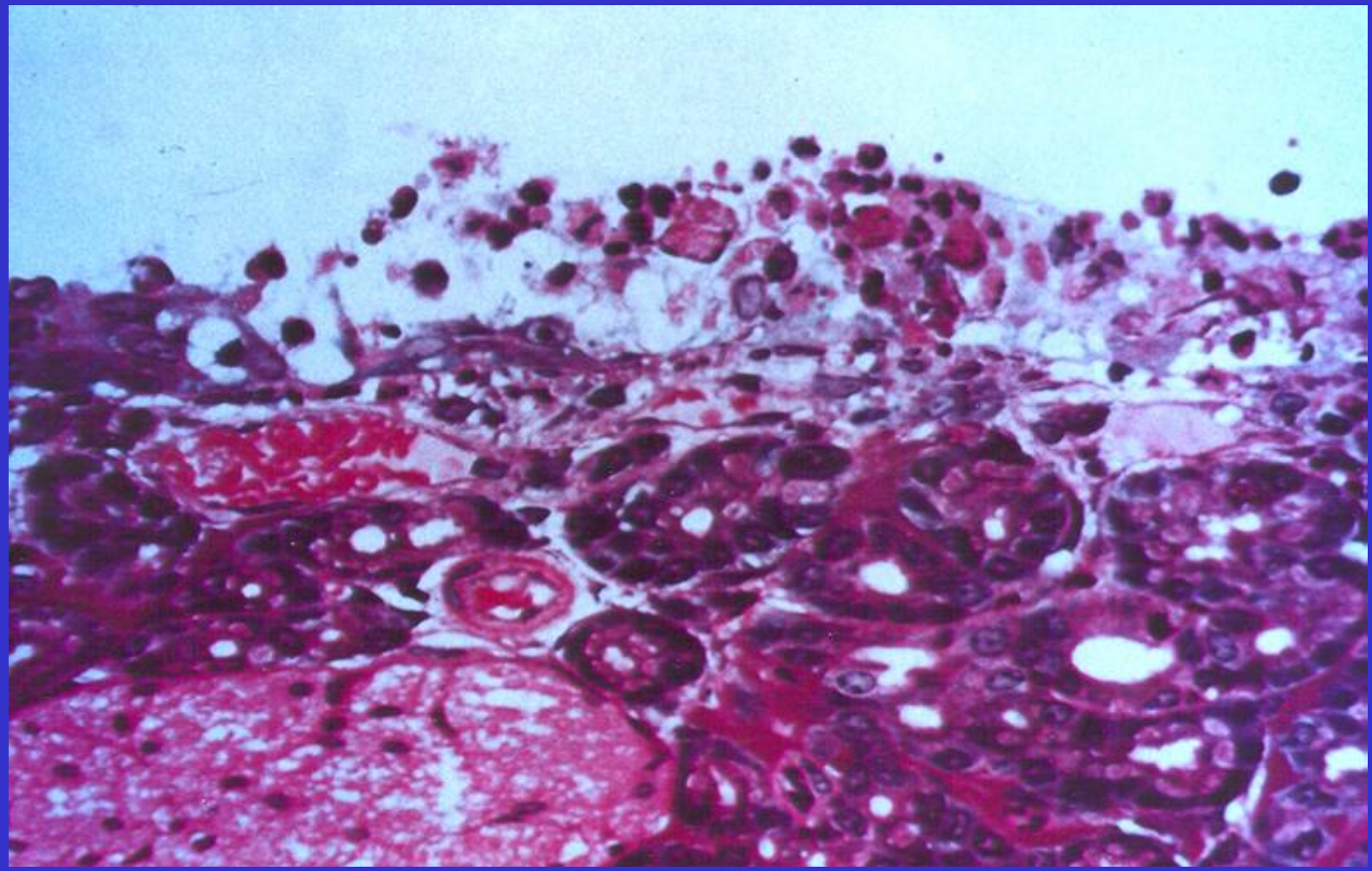
Formaldehyde bioassay results



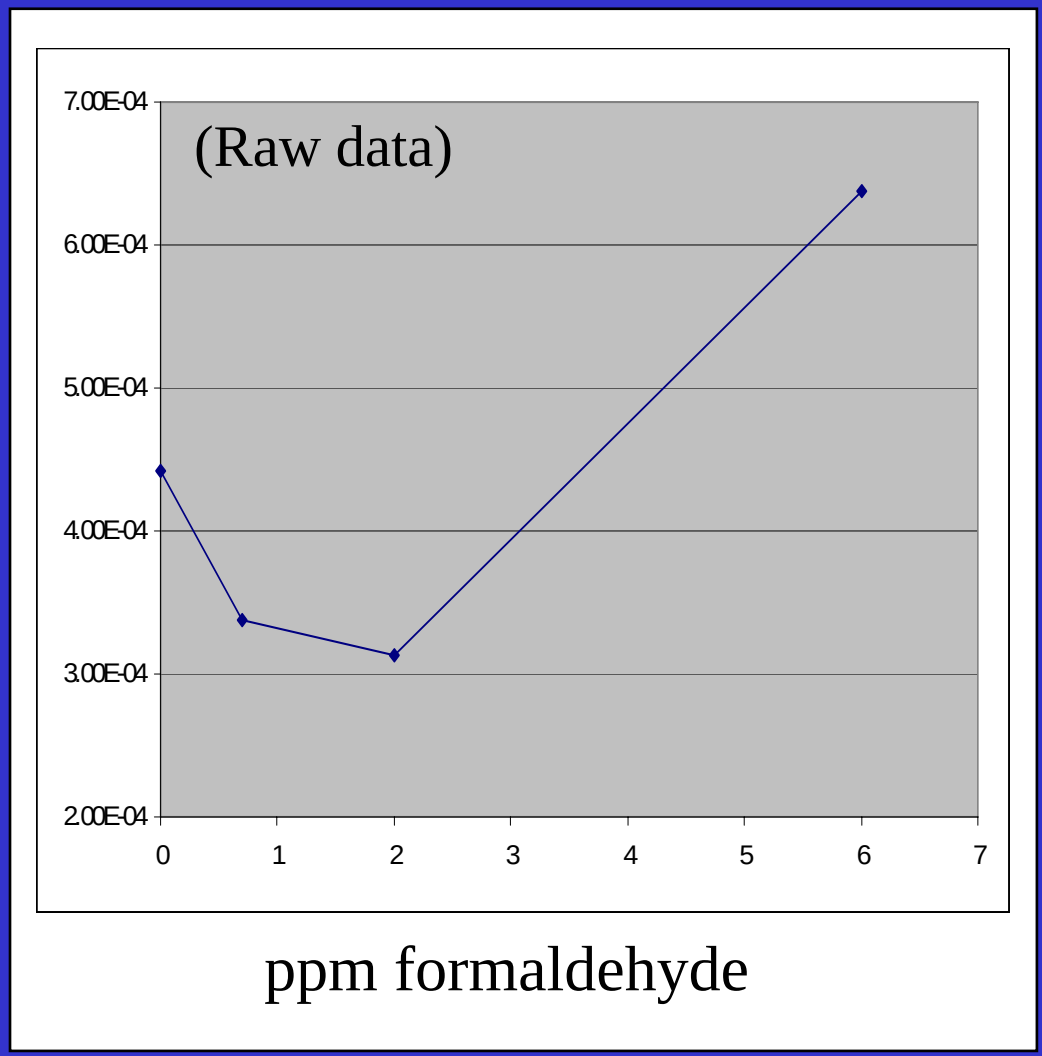
Normal respiratory epithelium in the rat nose



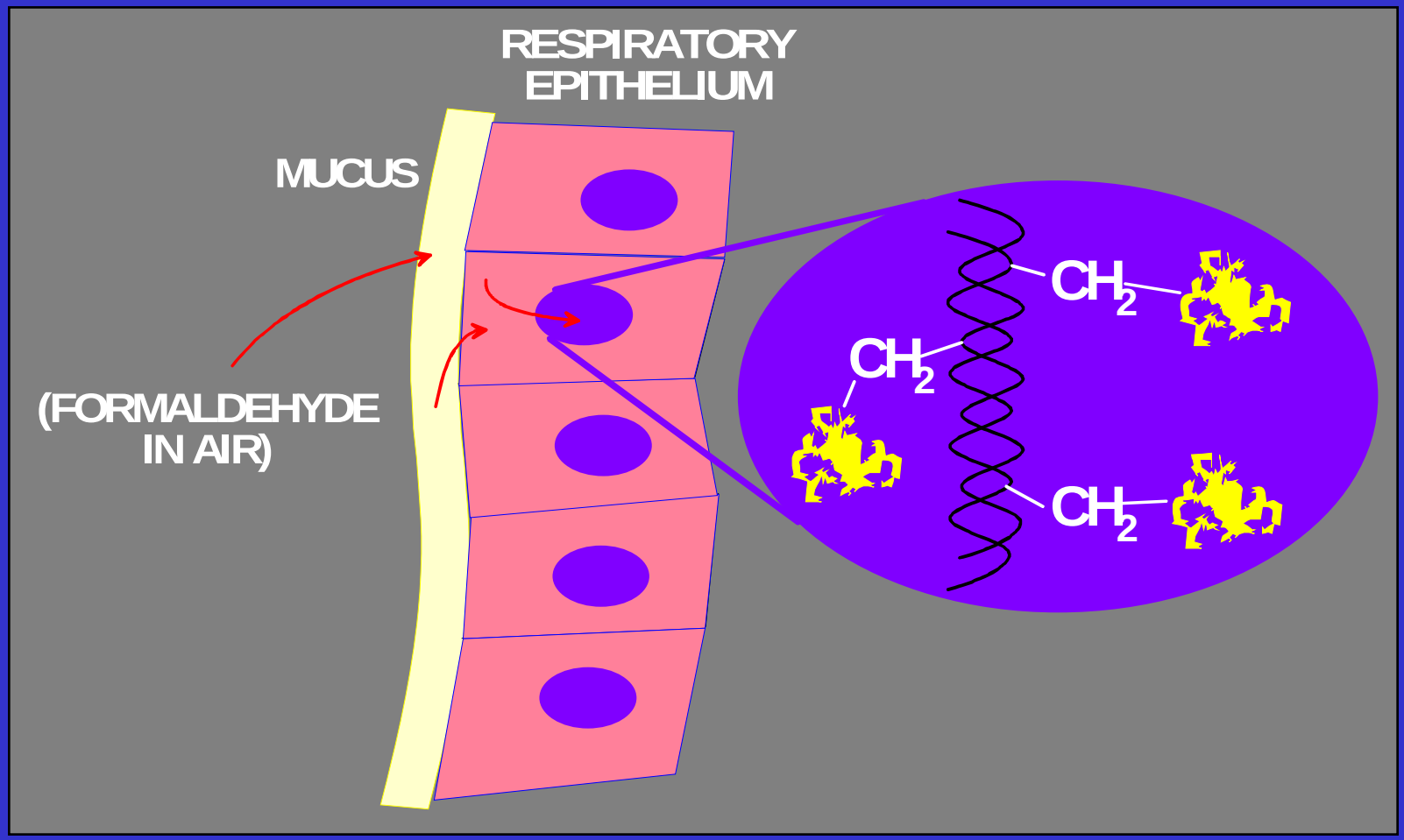
Formaldehyde-exposed respiratory epithelium in the rat nose (10+ ppm)



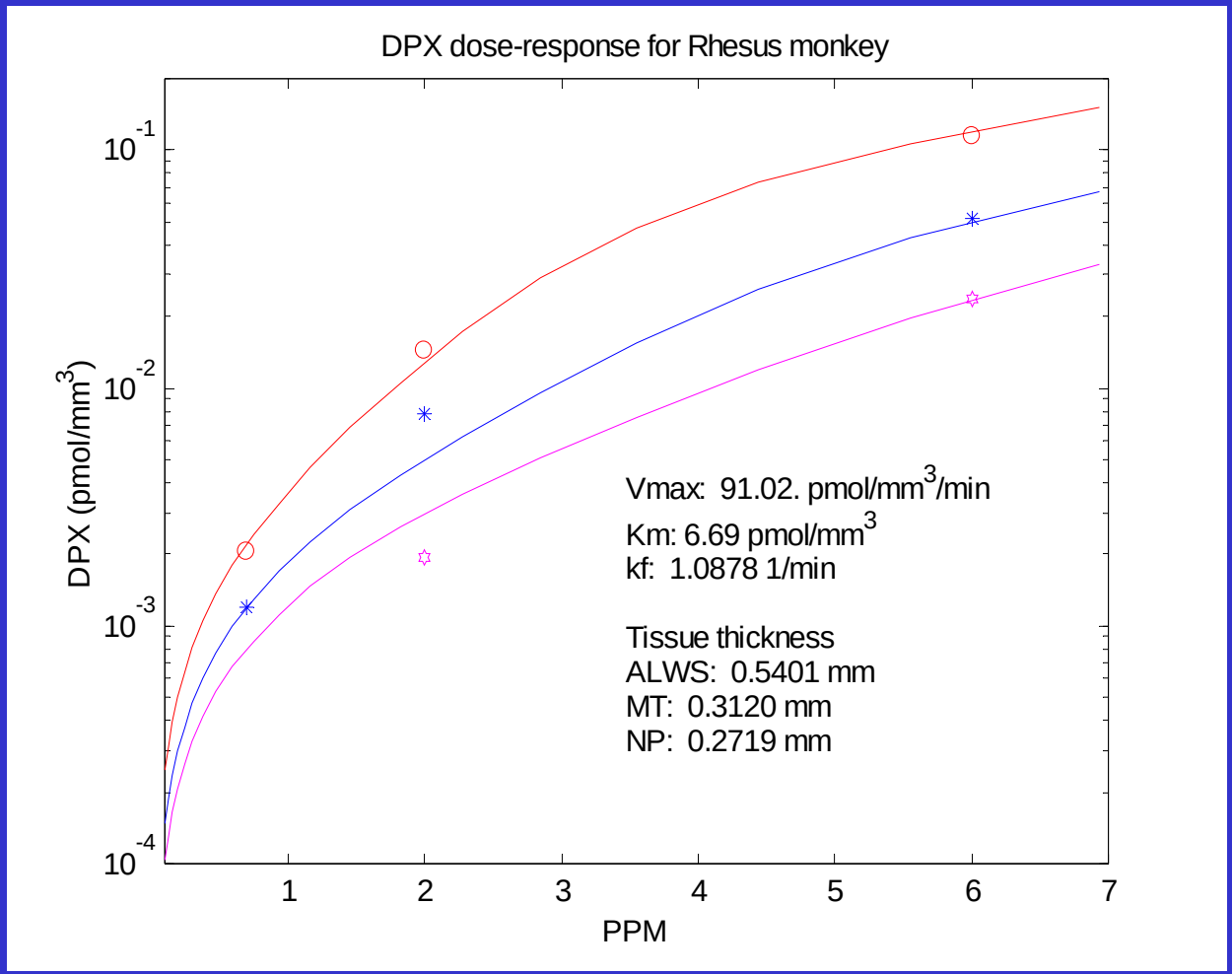
Dose-response for cell division rate



DPX


RESPIRATORY
EPITHELIUM
MUCUS
(FORMALDEHYDE
IN AIR)
CH2
CH2
CH2

DPX submodel – simulation of rhesus monkey data



DPX and direct mutation

- Direct mutation is assumed to be proportional to the amount of DPX:

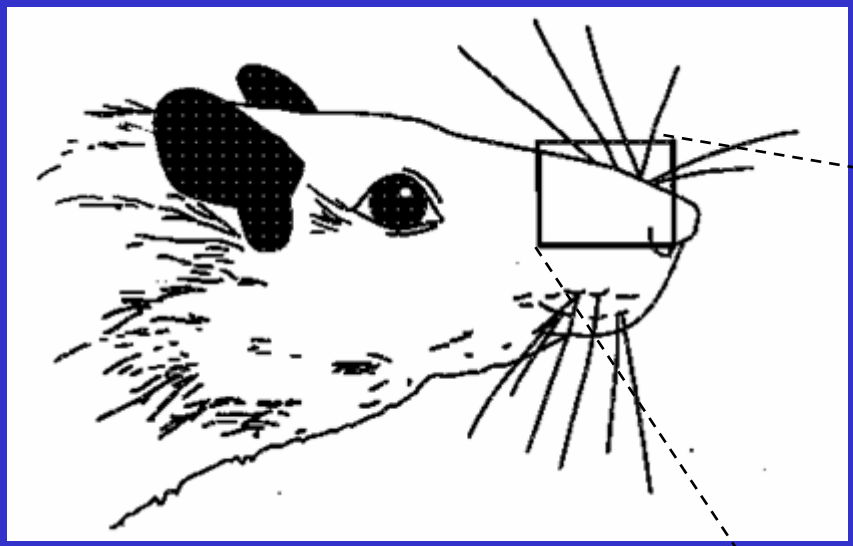
$$mutation = KMU \cdot DPX$$

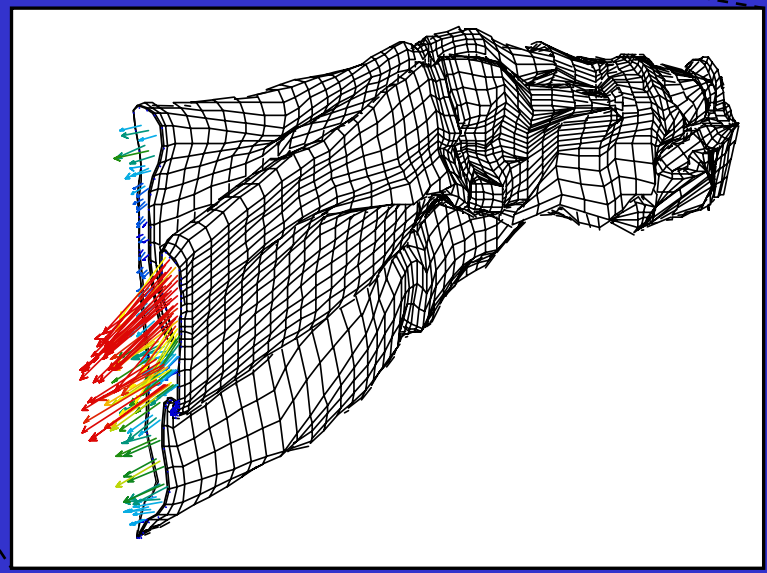
- Low-dose linear!
  - Is KMU big or small?

Summary of biomarker dose-response inputs to the clonal growth model

- Cell replication
  - J-shaped
- DPX
  - Low dose linear

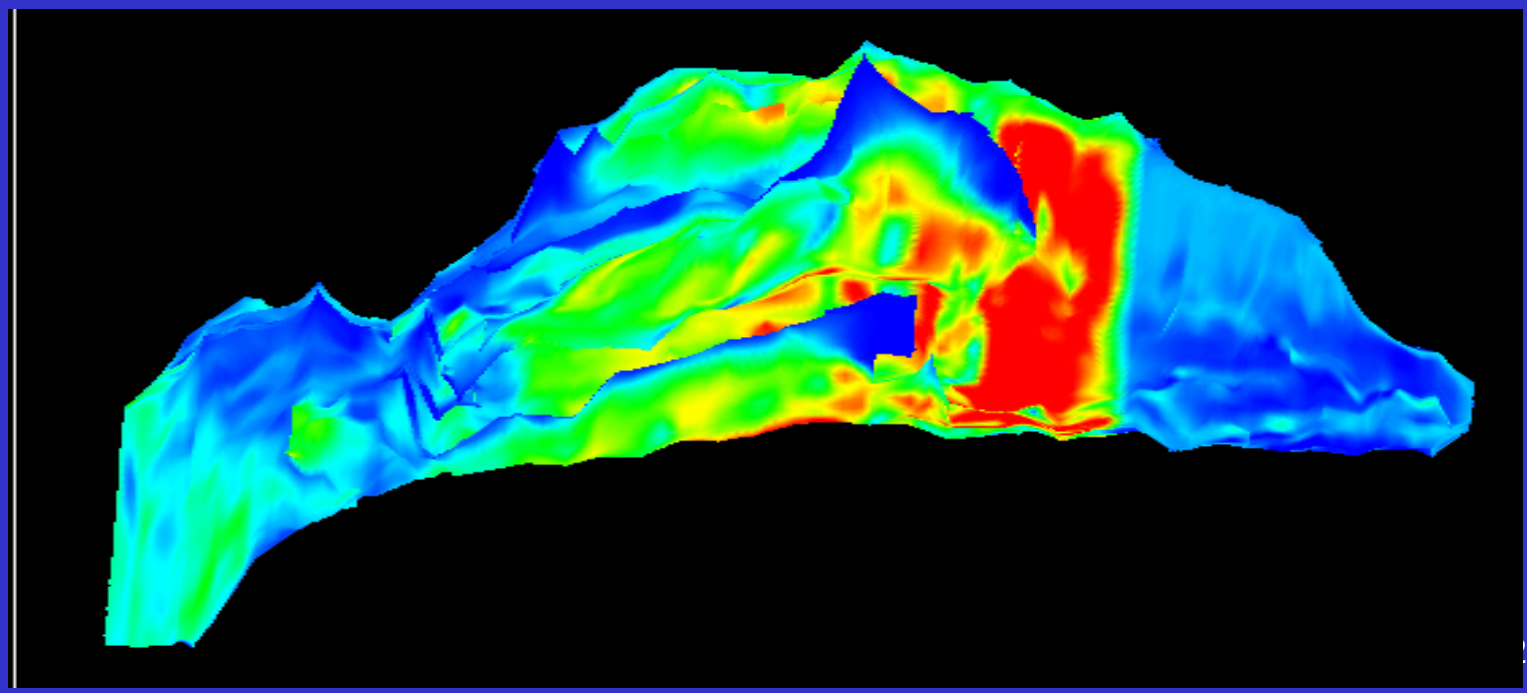
CFD Simulation of Nasal Airflow (Kimbell et. al)



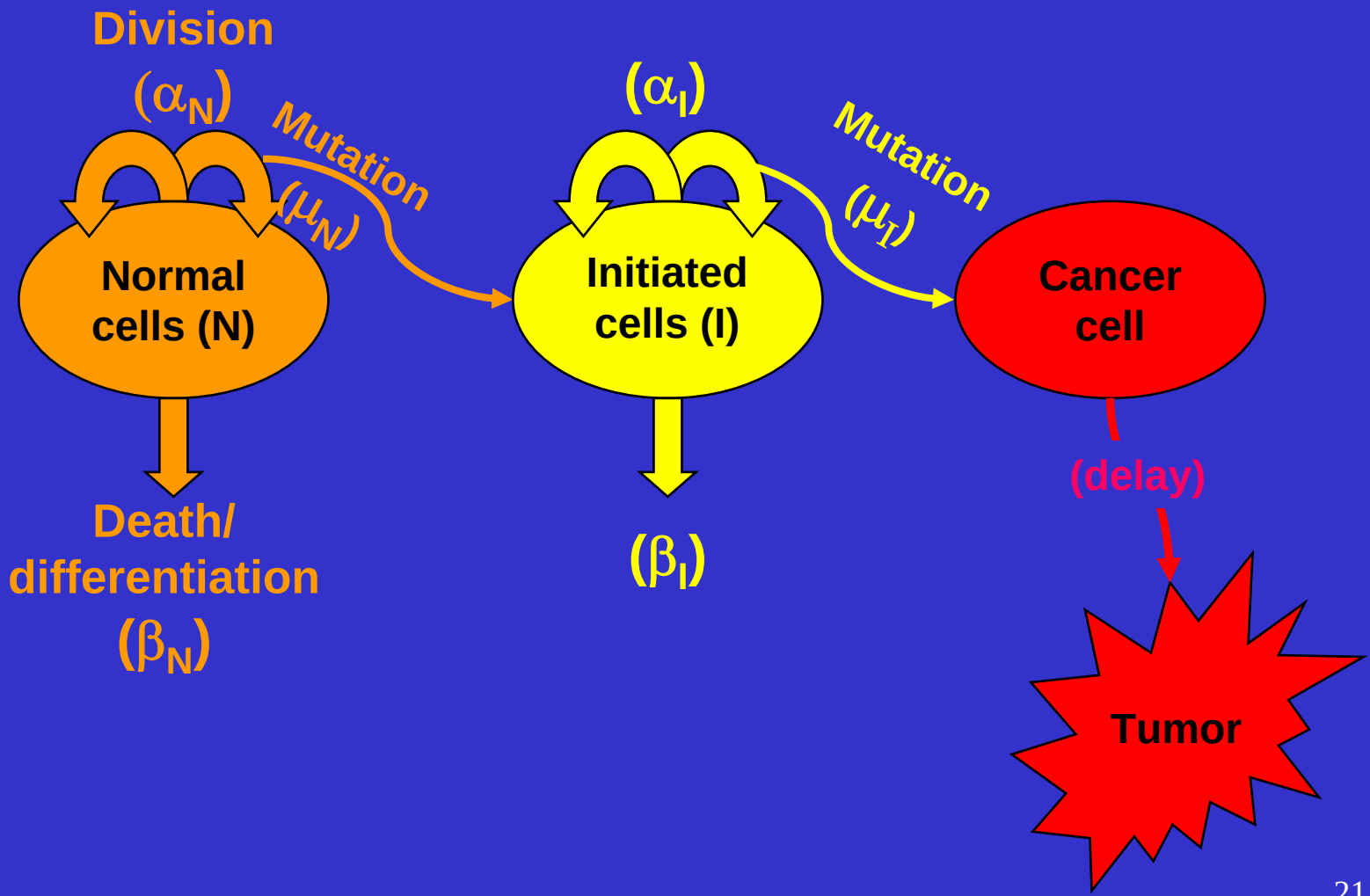


Flux bins

- Nasal surface area partitioned into 20 bins ranked according to flux of formaldehyde predicted by the CFD model



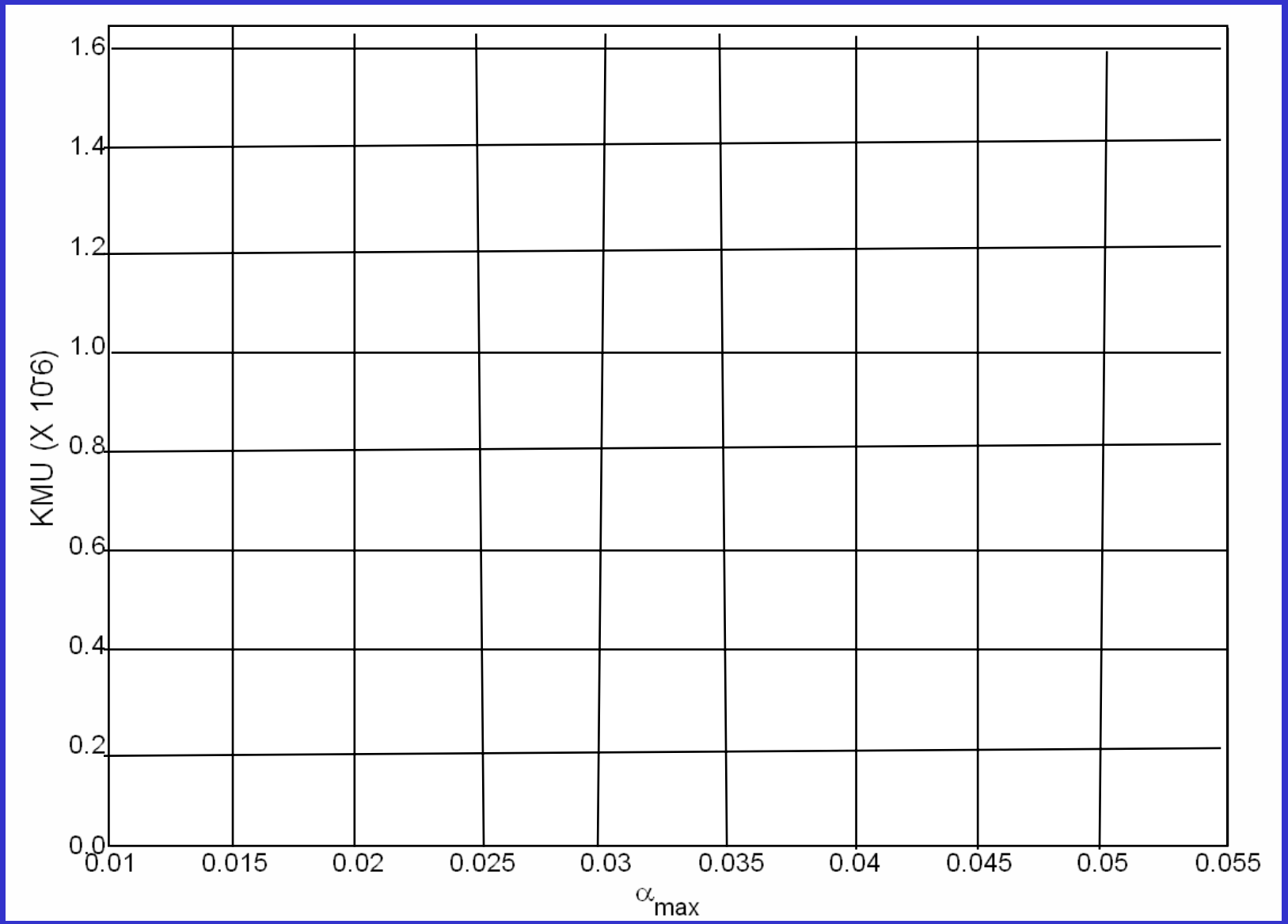
2-Stage clonal growth model (MVK model)



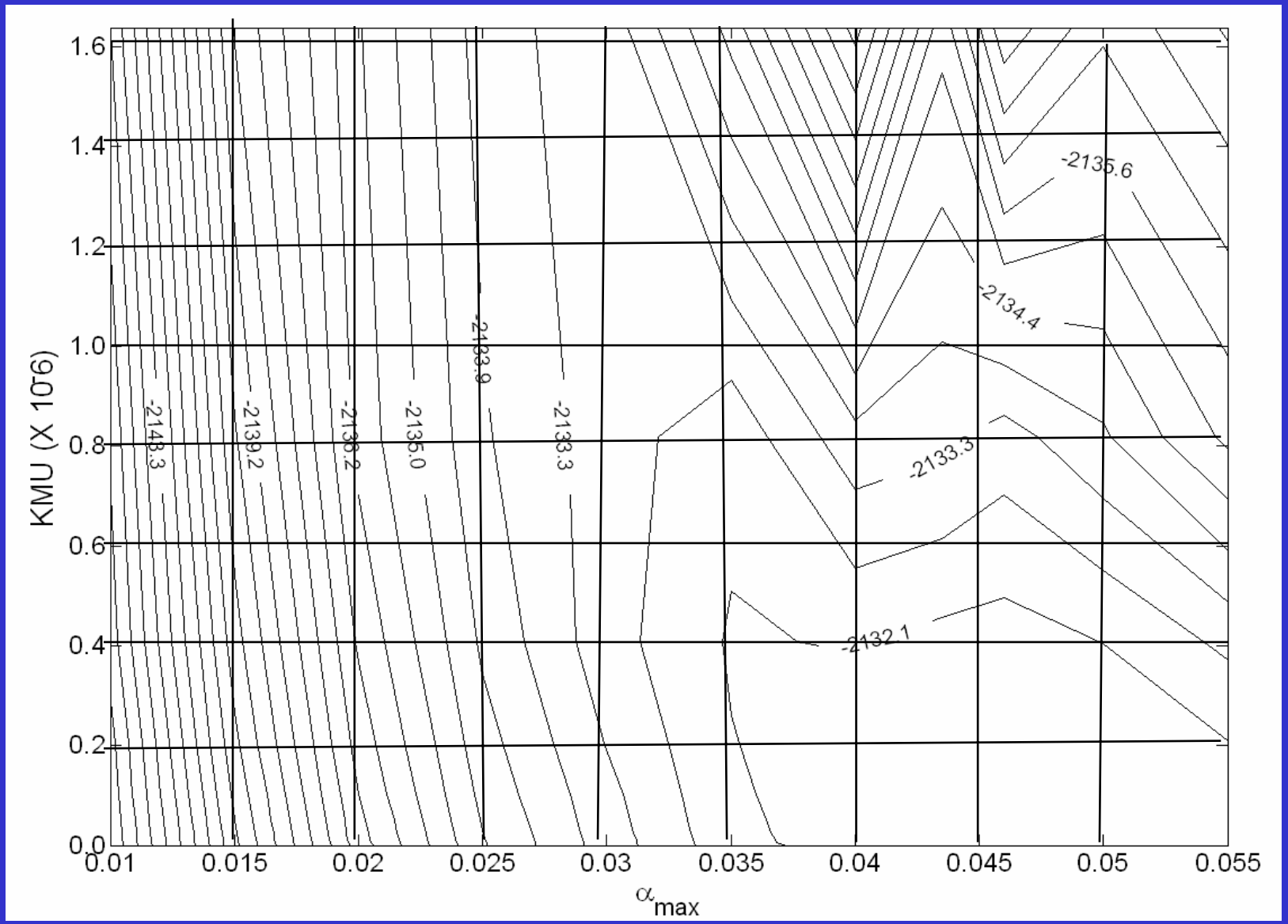
Calculation of the value of KMU

- Grid search
- Optimal value of KMU was zero
  - Modeling predicts that direct mutation is not a significant action of formaldehyde
- 95% upper confidence limit on KMU was estimated

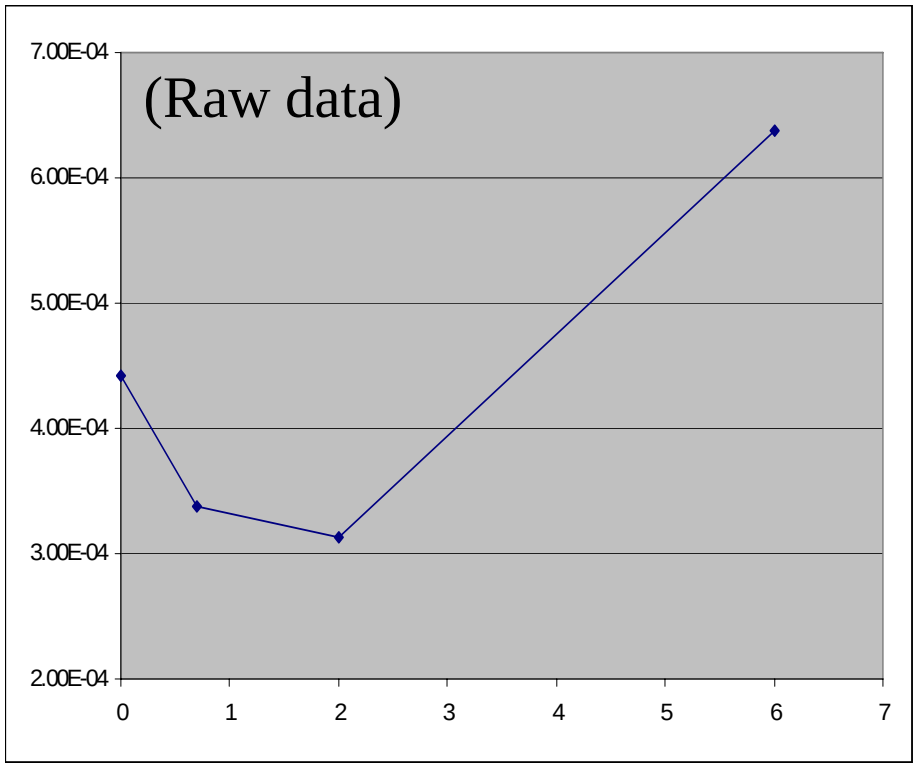
Maximum likelihood grid search



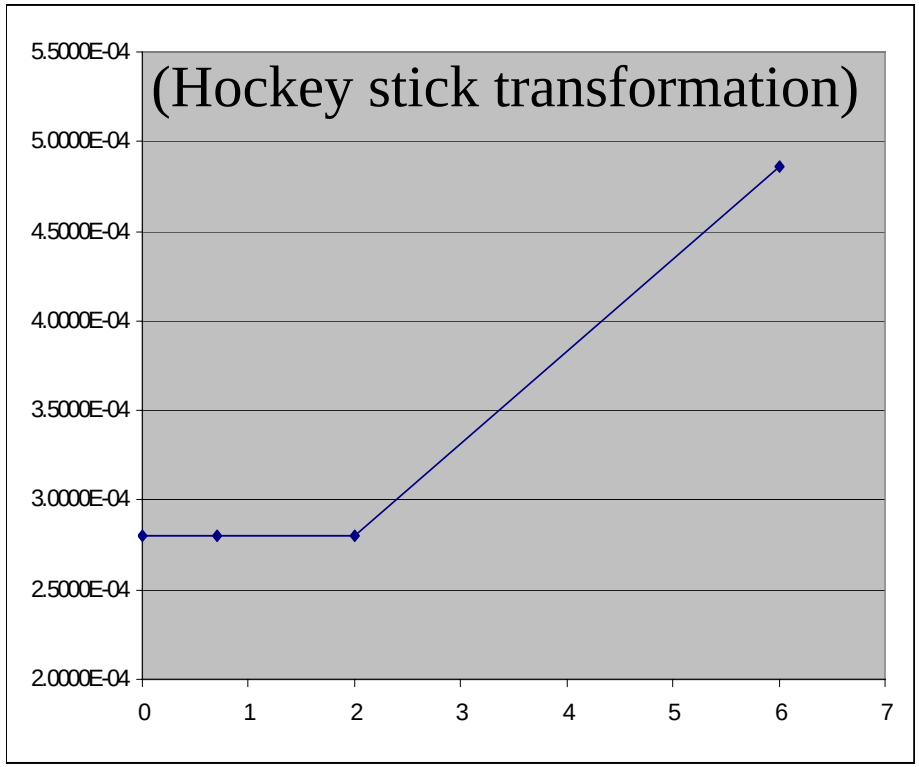
Optimal value of KMU is zero



Hockey stick model fit to raw data to cell division dose-response

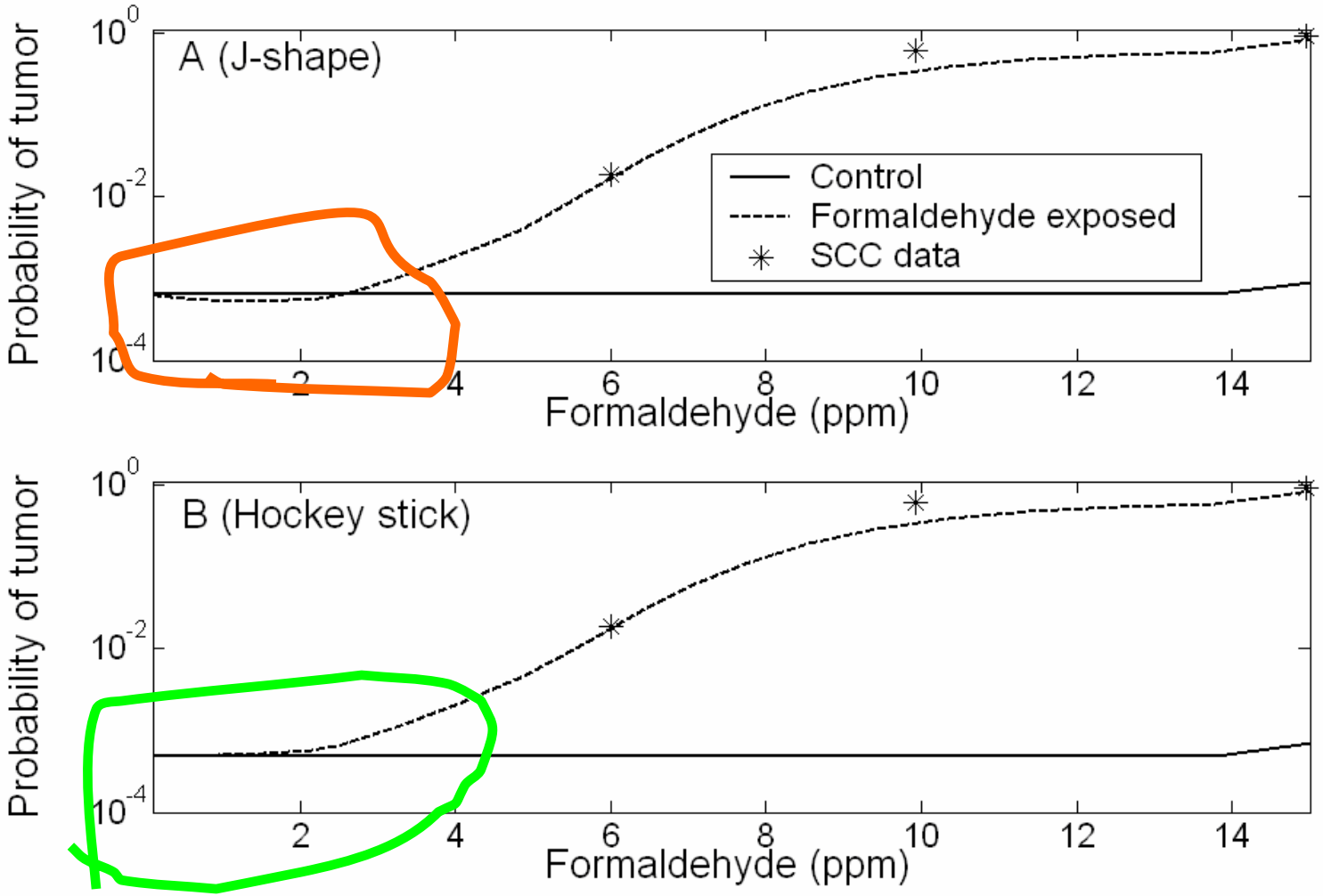


ppm formaldehyde



ppm formaldehyde

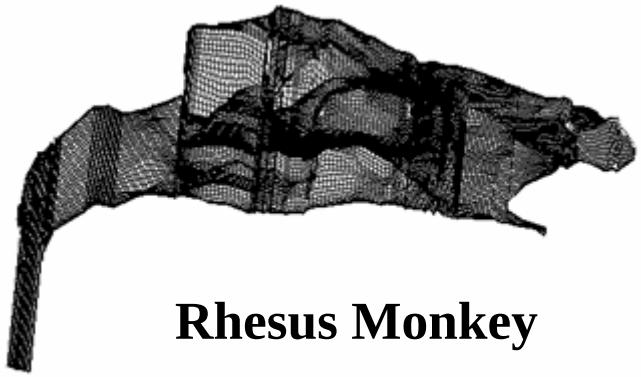
Simulation of tumor response in rats



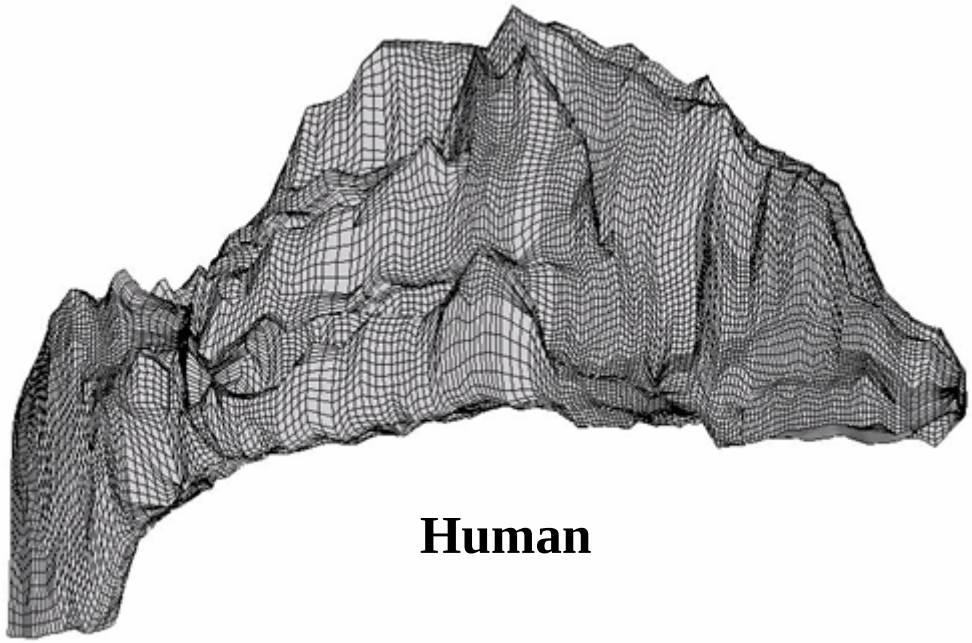
From rats to humans

Computational fluid dynamics models of the nasal airways

F344 Rat

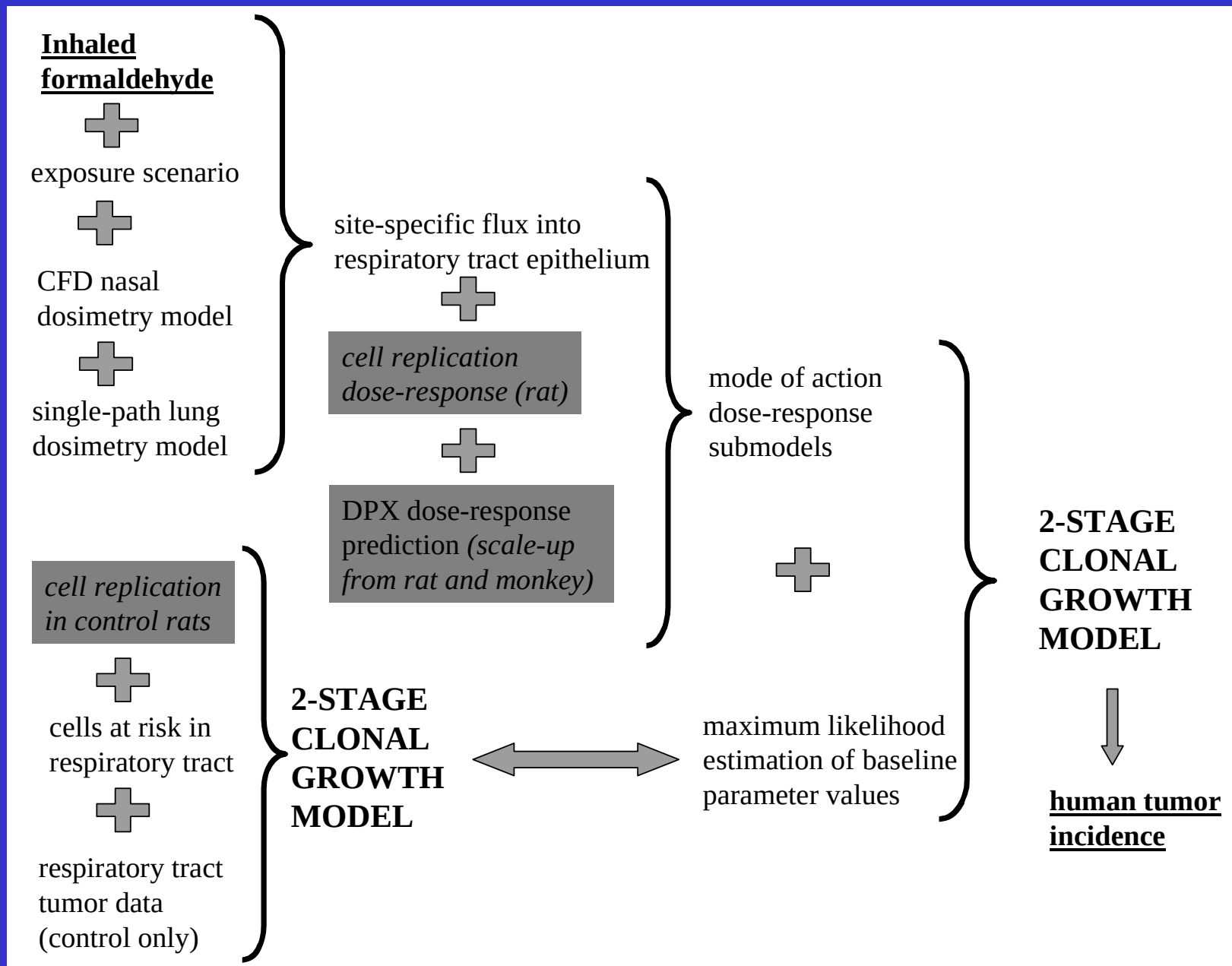


Rhesus Monkey

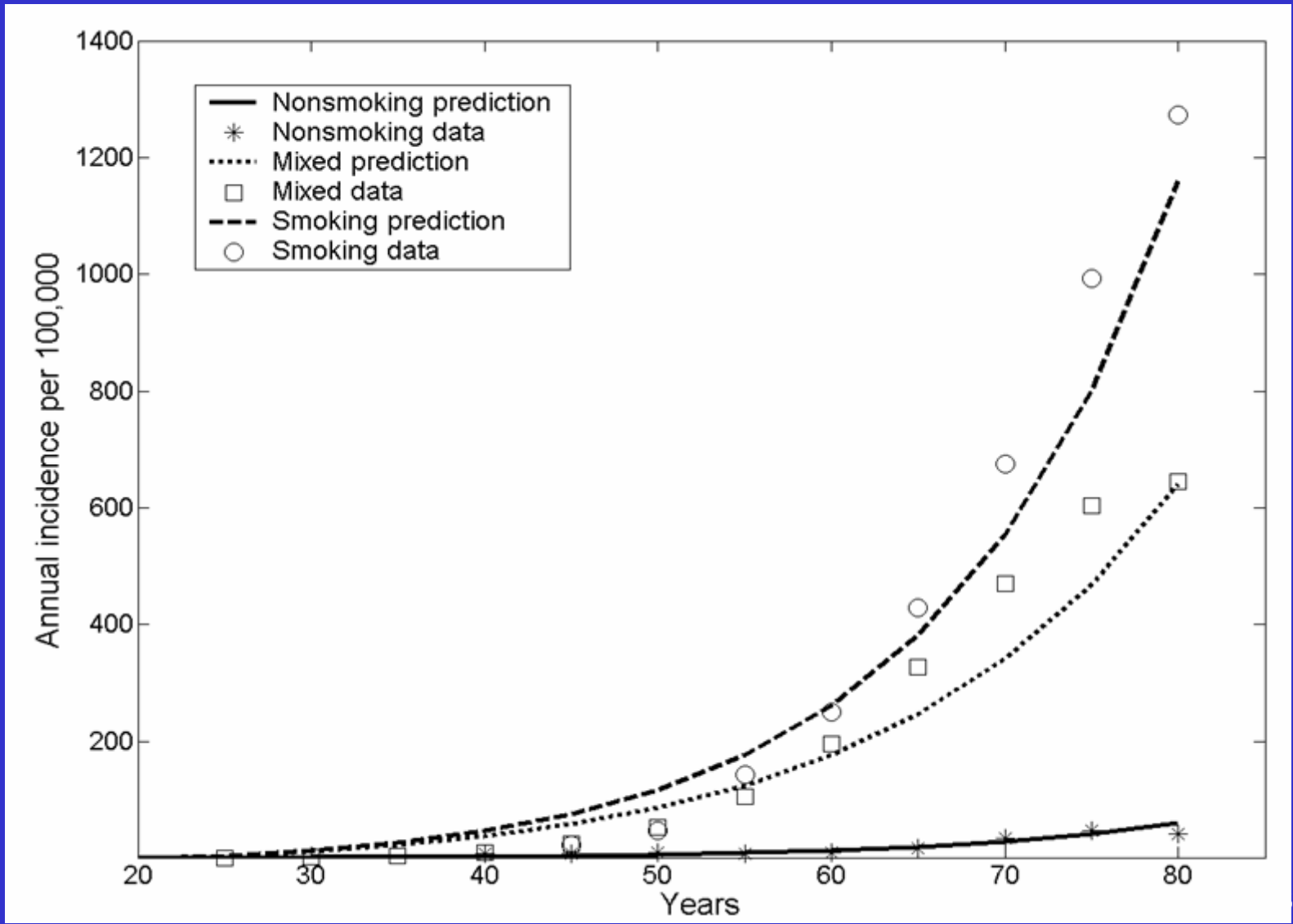


Human

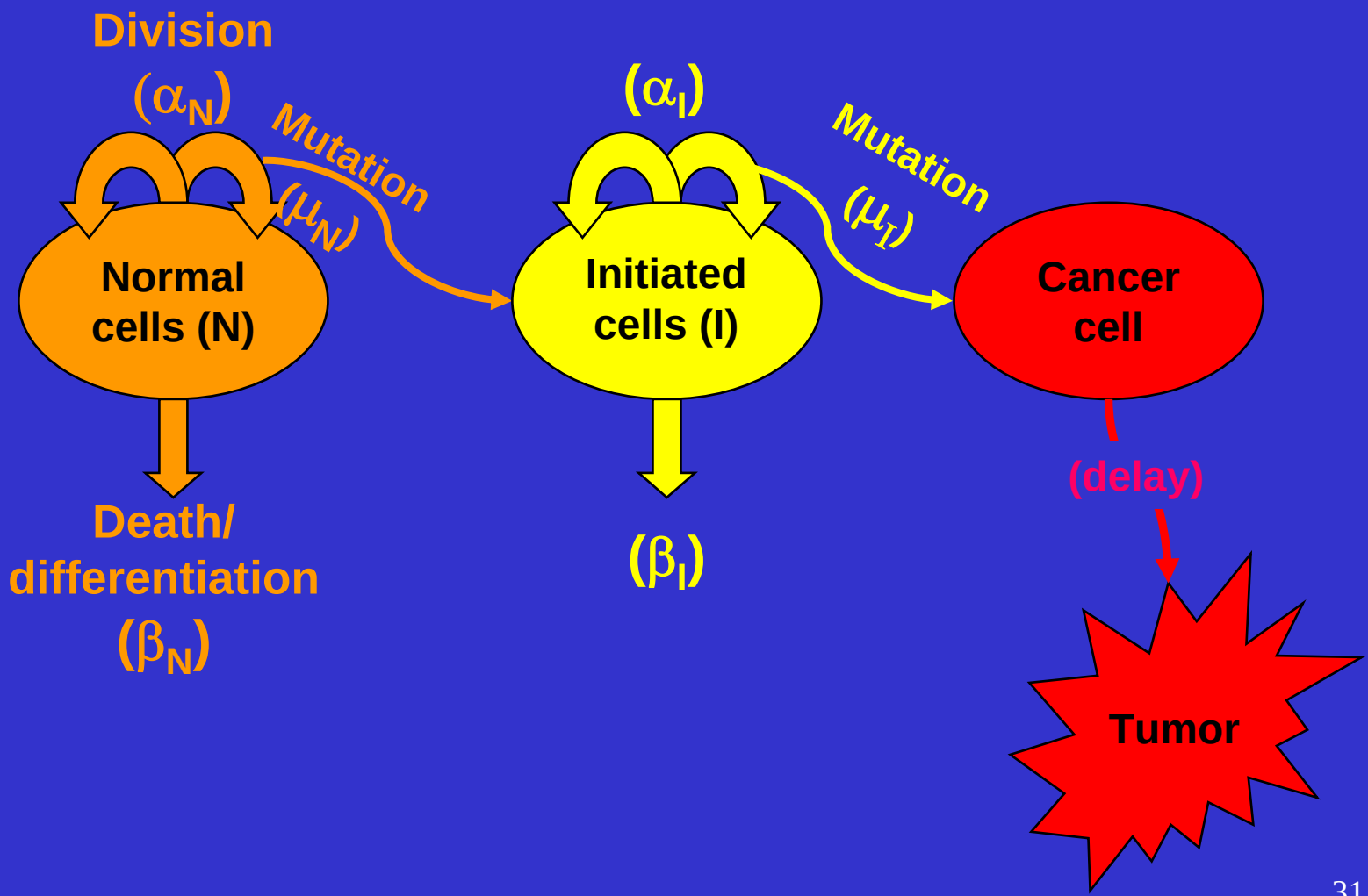
Human assessment



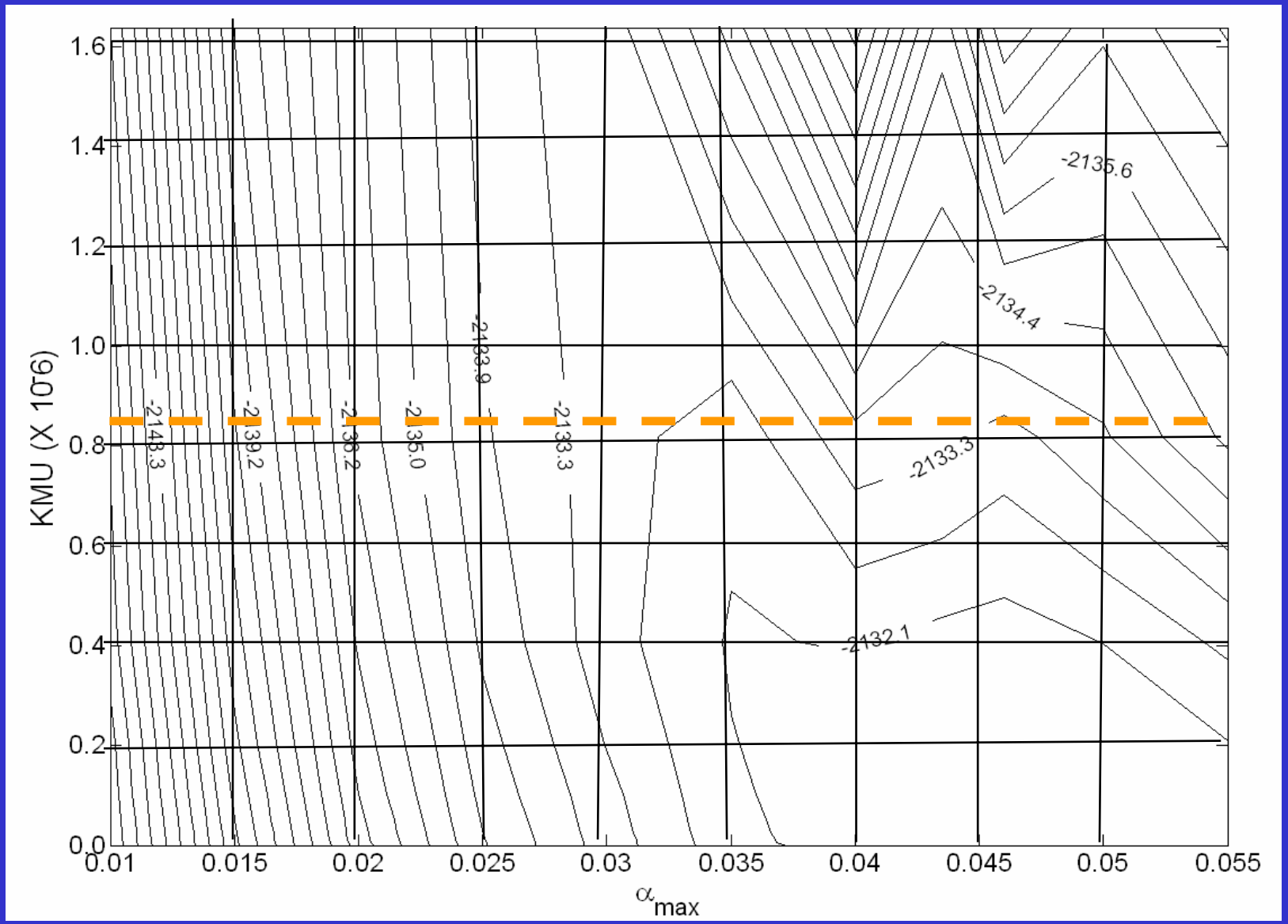
Baseline calibration against human lung cancer data



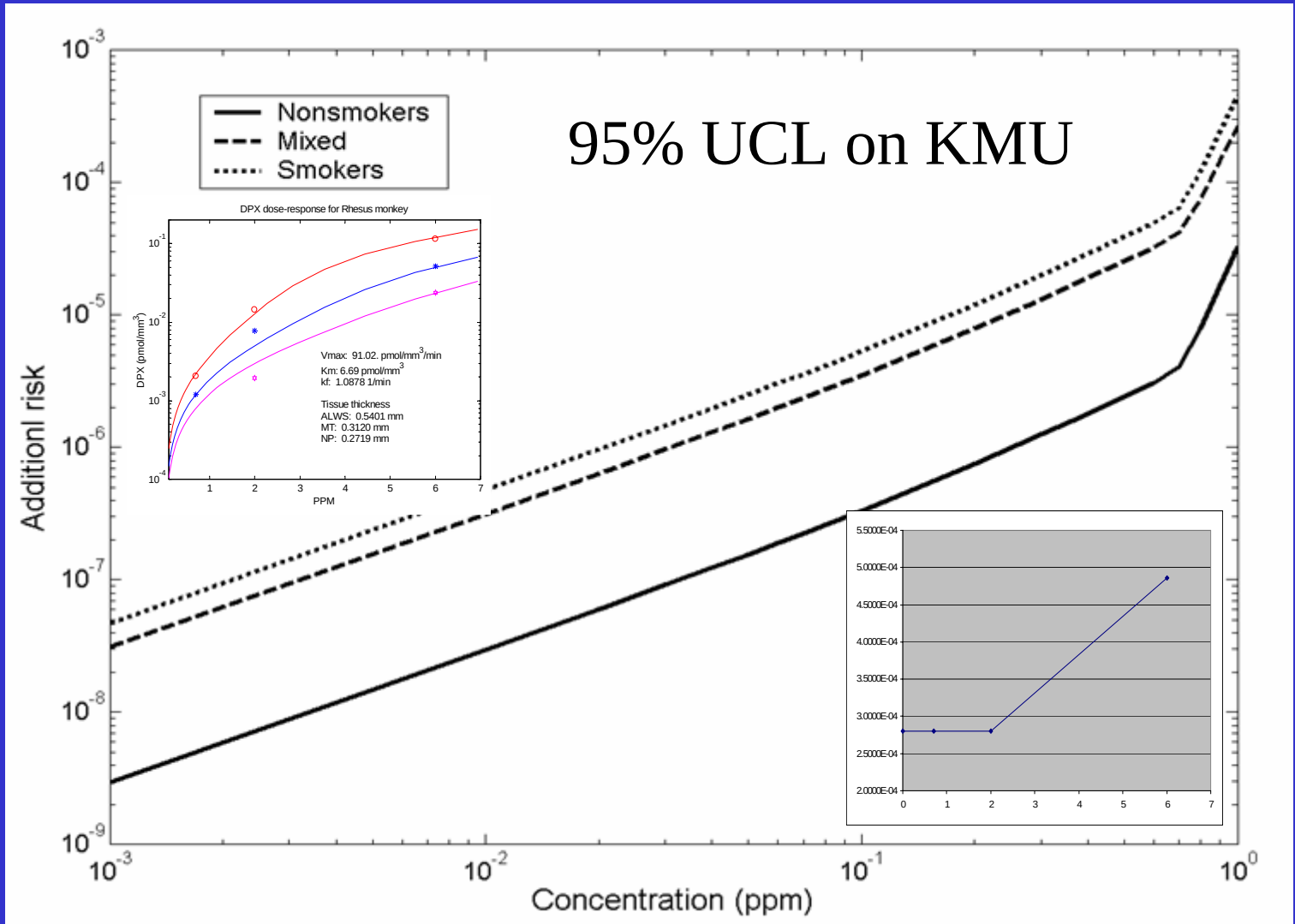
Human risk modeling



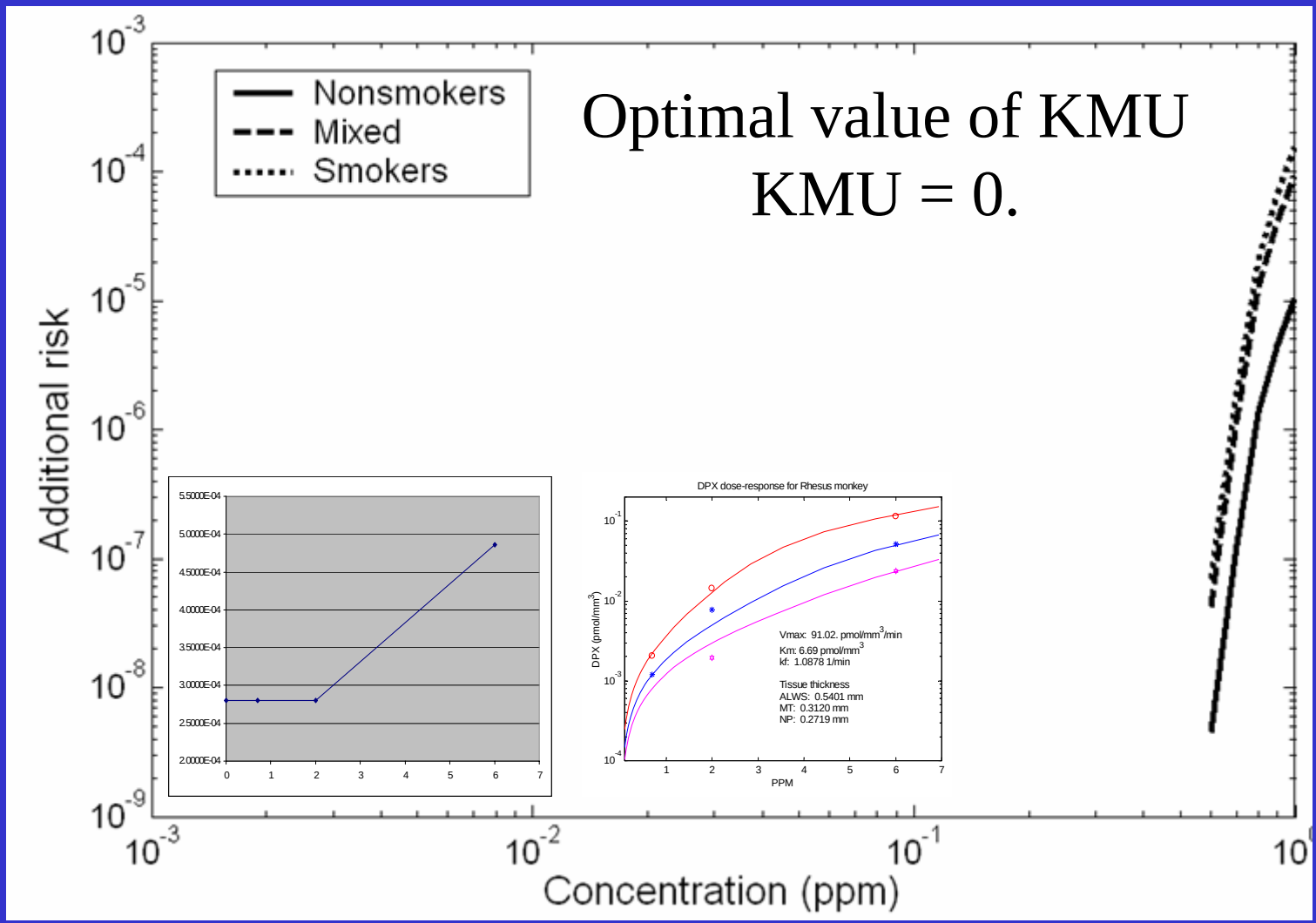
Upper bound on KMU



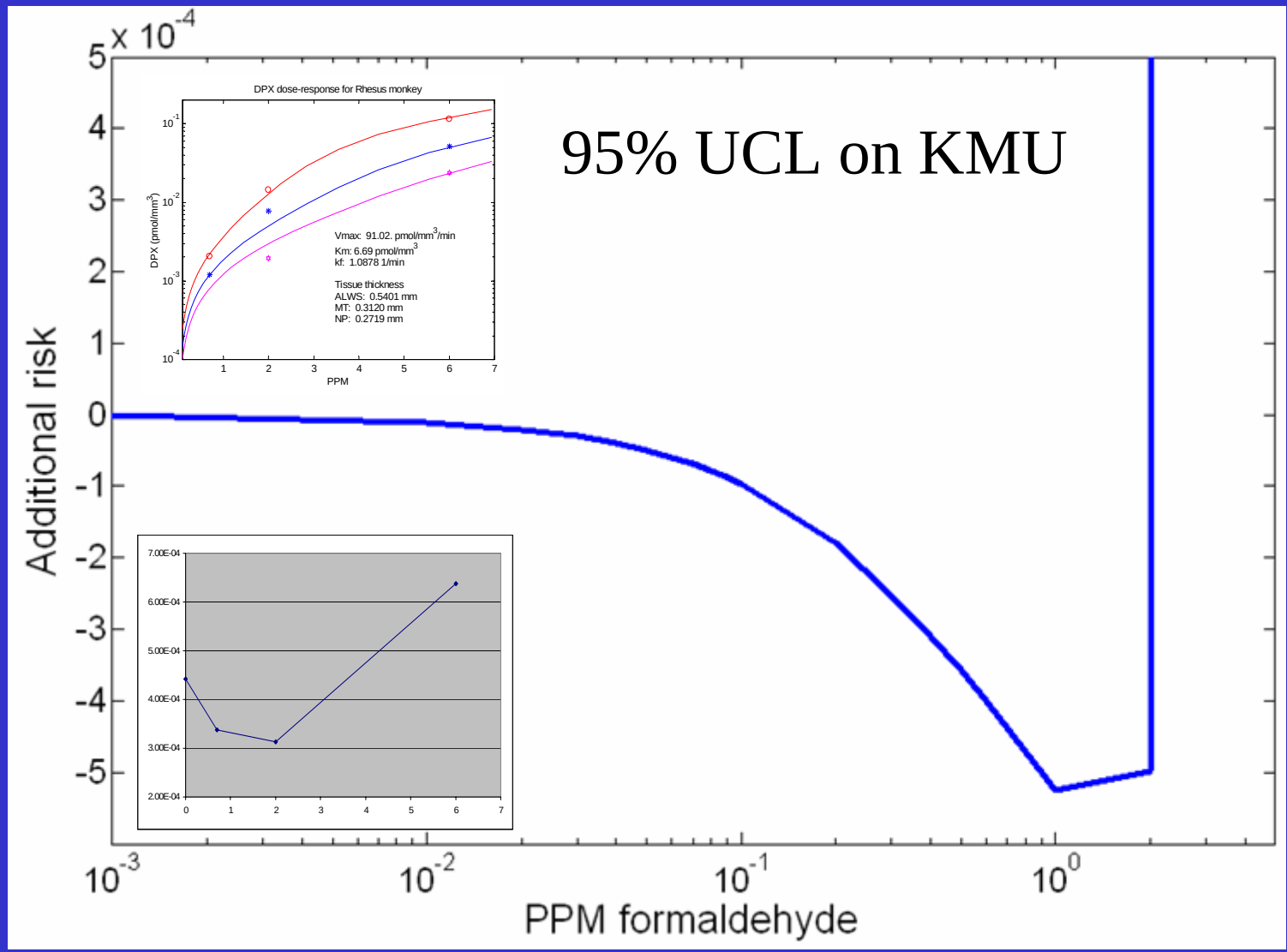
Final model: Hockey stick and 95% upper confidence limit on value of KMU



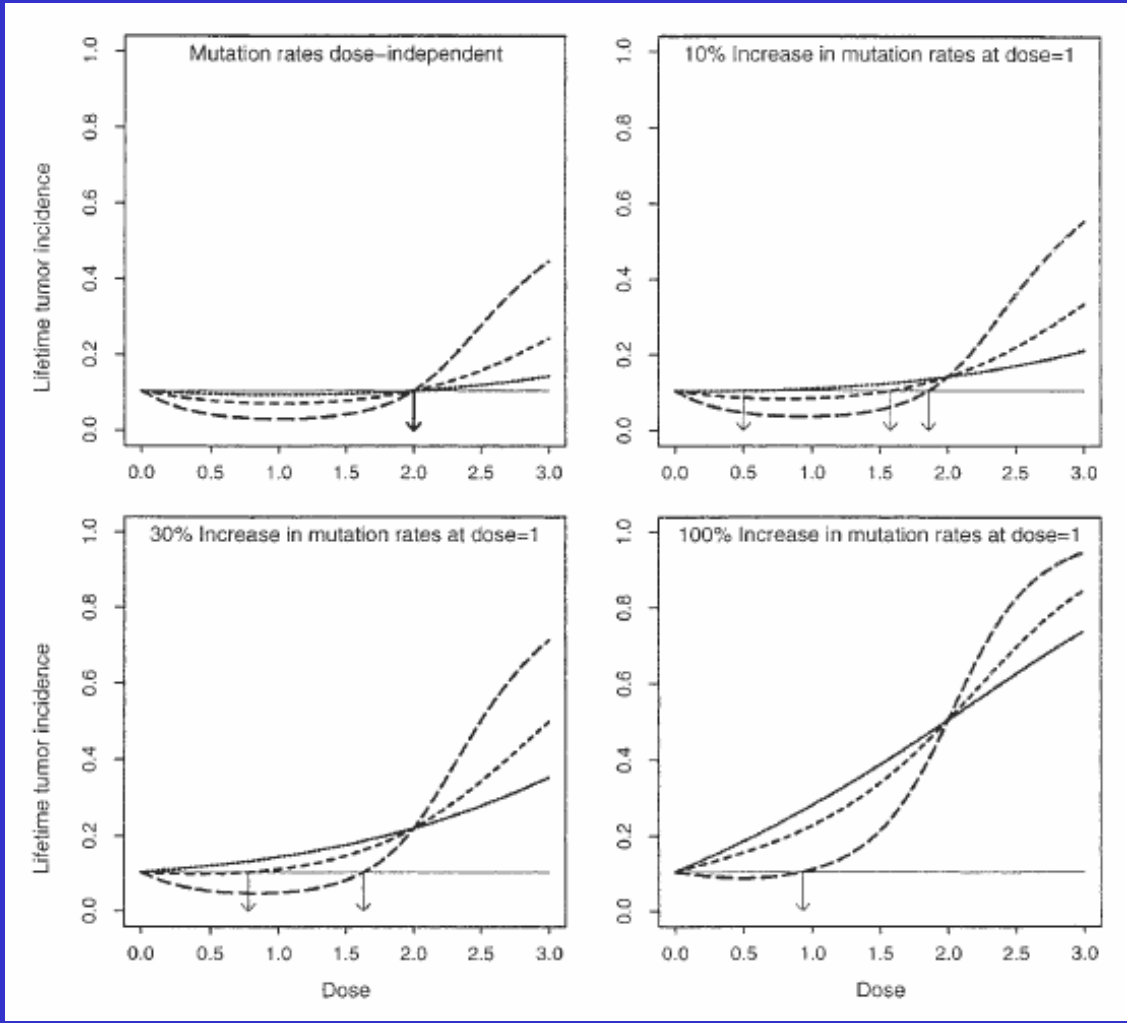
Predicted human cancer risks (hockey stick-shaped dose-response for cell replication; optimal value for KMU)



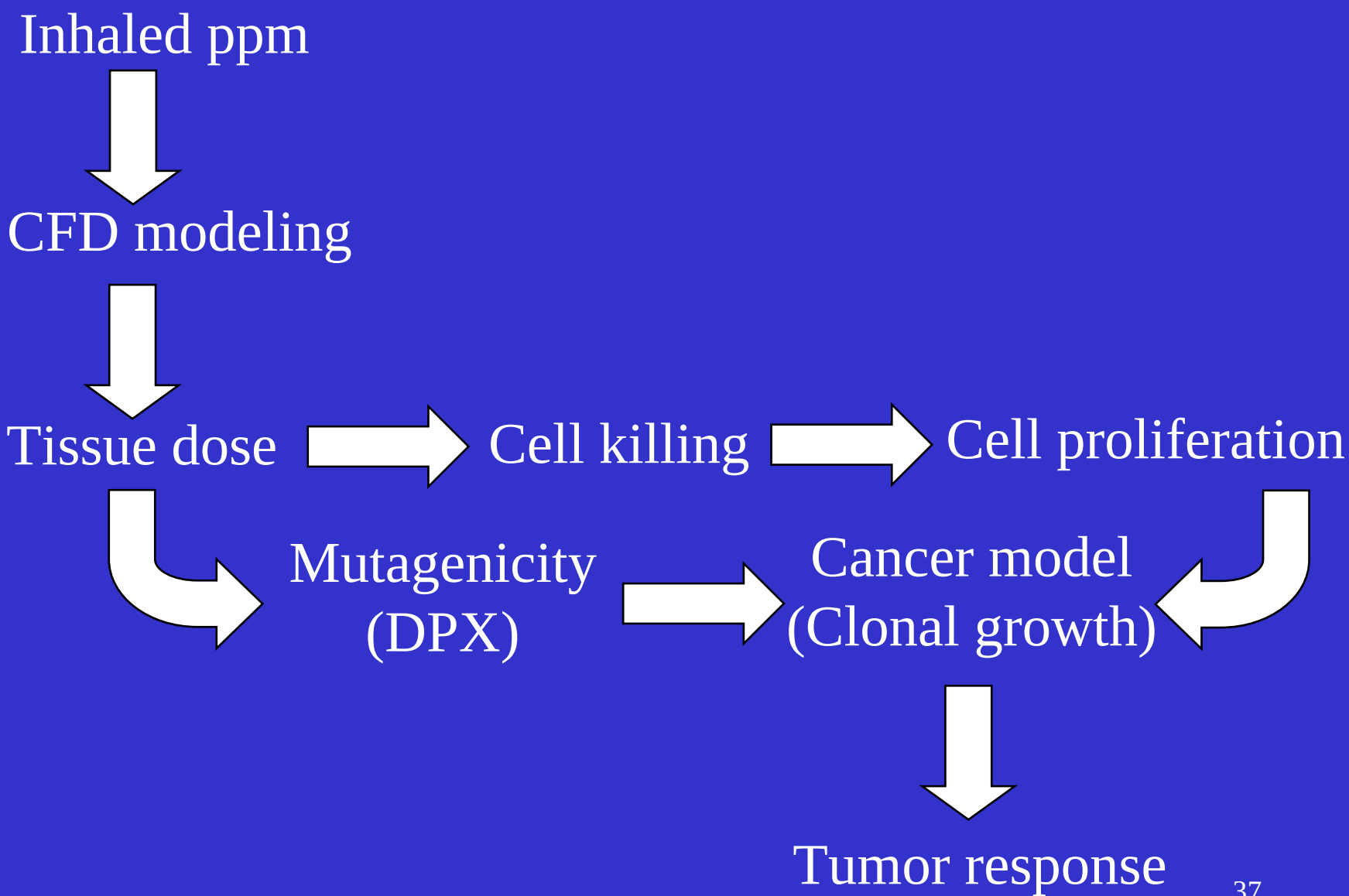
"Negative risk" using raw dose-response for cell replication



Lutz & Kopp-Schneider: Tumor incidence with J-shaped cell replication & linear mutation

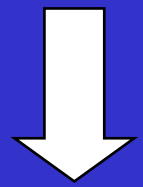


1999 - 2004 CIIT

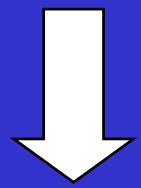


1987 U.S. EPA

Inhaled ppm

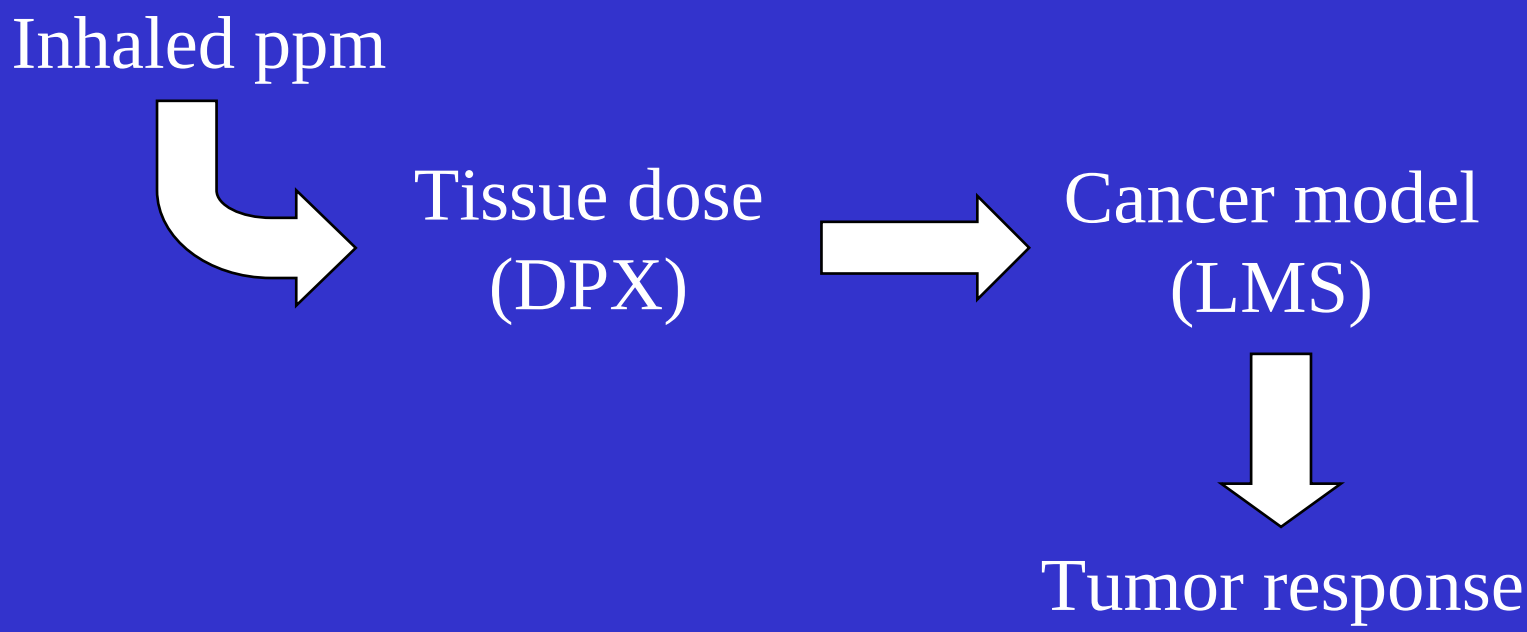


Cancer model
(LMS)



Tumor response

1991 U.S. EPA


Inhaled ppm
Tissue dose
(DPX)
Cancer model
(LMS)
Tumor response

Make conservative choices when faced with uncertainty

- Use hockey stick-shaped cell replication
- Use a 95% upper bound on the dose-response for the directly mutagenic mode of action
  - Statistically optimal model has 0 (zero) slope
- Risk model predicts low-dose linear risk.
- Optimal, data based model predicts negative risk at low doses

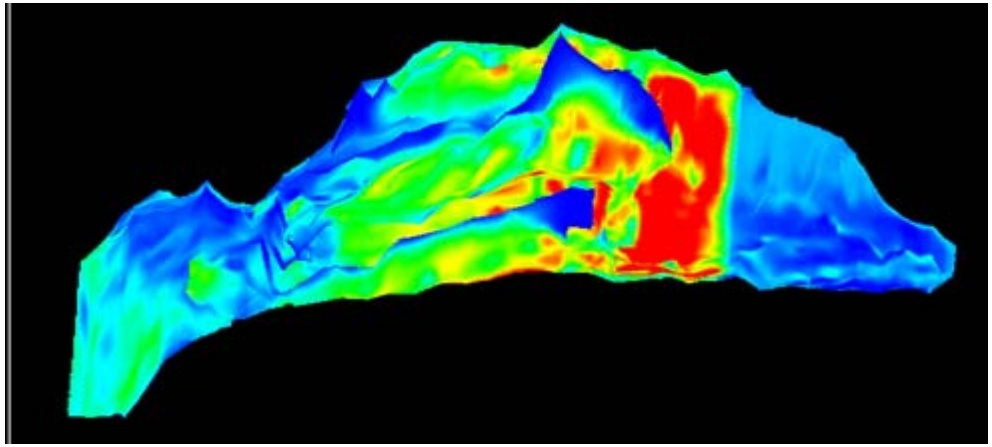
Summary: CIIT assessment of formaldehyde cancer risk

- Either no additional risk or a much smaller level of risk than previous assessments
- Consistent with mechanistic database
  - Direct mutagenicity
  - Cell replication

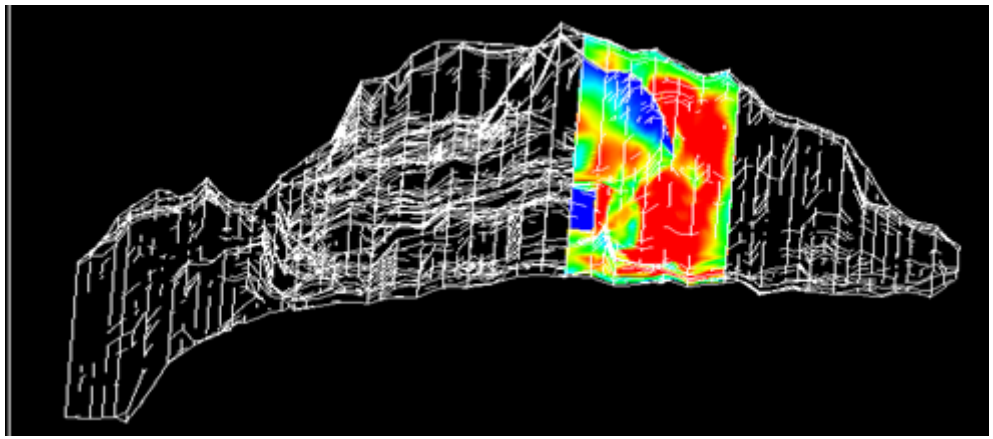
IARC 2004

- Classified 1A based on nasopharyngeal cancer
- Myeloid leukemia data suggestive but not sufficient
  - Concern about mechanism
  - British study negative
- Reclassification driven by epidemiology
- *In my opinion* inadequate consideration of regional dosimetry and mechanistic data from rat studies

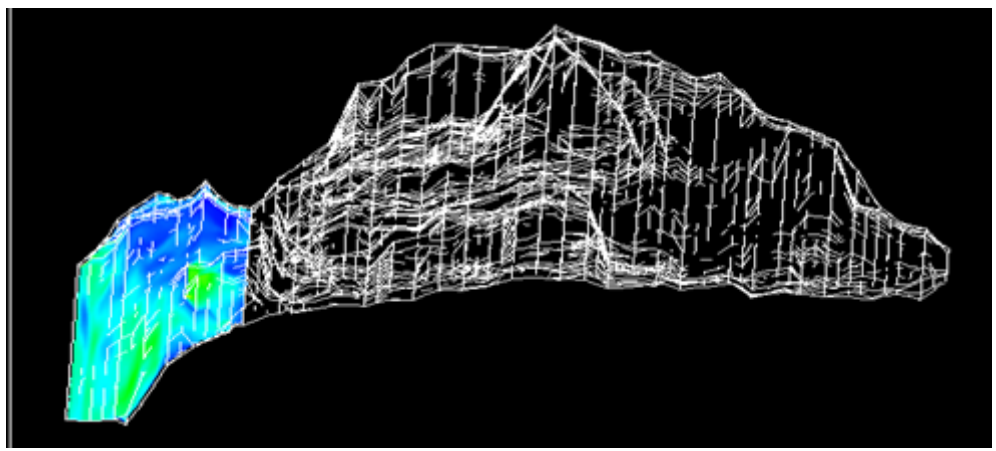
Whole nose



Anterior nose



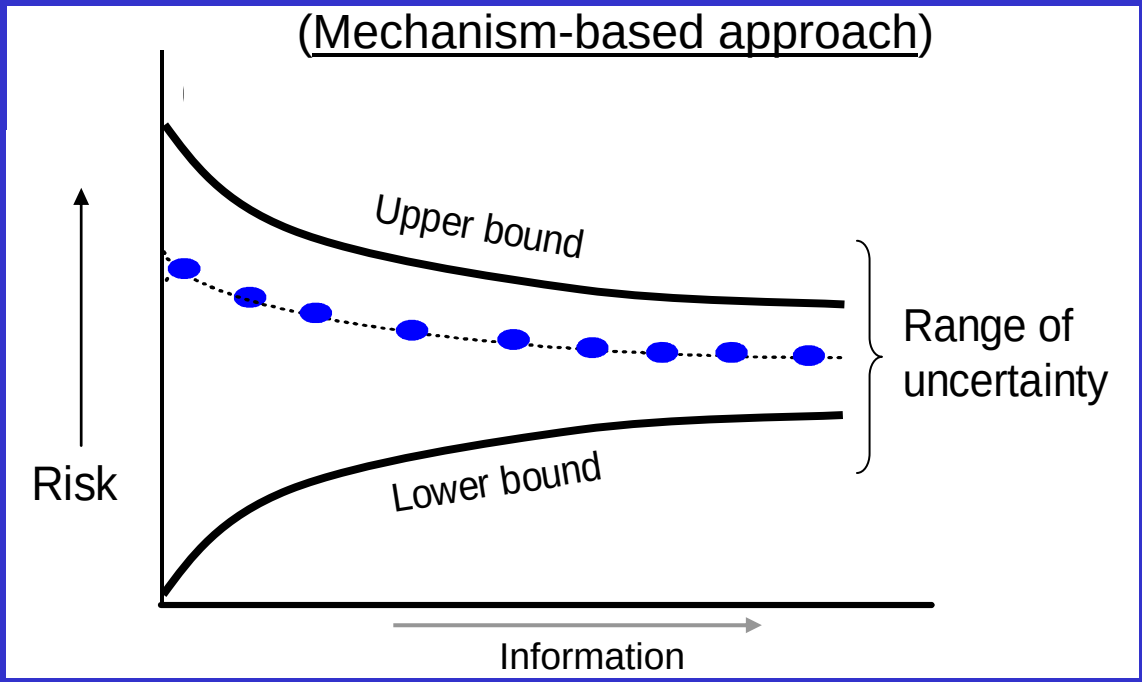
nasopharynx

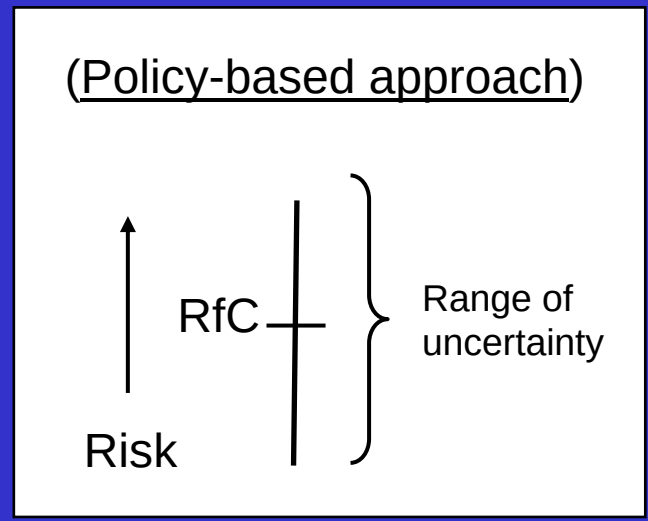


Formaldehyde summary

- Using mechanistic data to reduce uncertainty in risk assessment
- Formaldehyde nasal SCC in rats
- Mechanistic studies of the rat tumors
- Risk assessment driven by the data
- IARC

Reduction of uncertainty in risk assessment





Disclaimer

EPA has sponsored Dr. Conolly's attendance at this meeting. This presentation is not a statement of official policy of the United States Environmental Protection Agency.

Acknowledgements (I)

- Many, many investigators at CIIT (and elsewhere) who have studied formaldehyde.

Acknowledgements (II)

- Colleagues who worked on the clonal growth risk assessment
  - Fred Miller, Julian Preston, Paul Schlosser, Julie Kimbell, Betsy Gross, Suresh Moolgavkar, Georg Luebeck, Derek Janszen, Mercedes Casanova, Henry Heck, John Overton, Steve Seilkop

End