



"Tissue Dose" Based Risk Assessments

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The Hamner Institutes for Health Sciences

Workshop on Health Risk Assessment of Essential Metals

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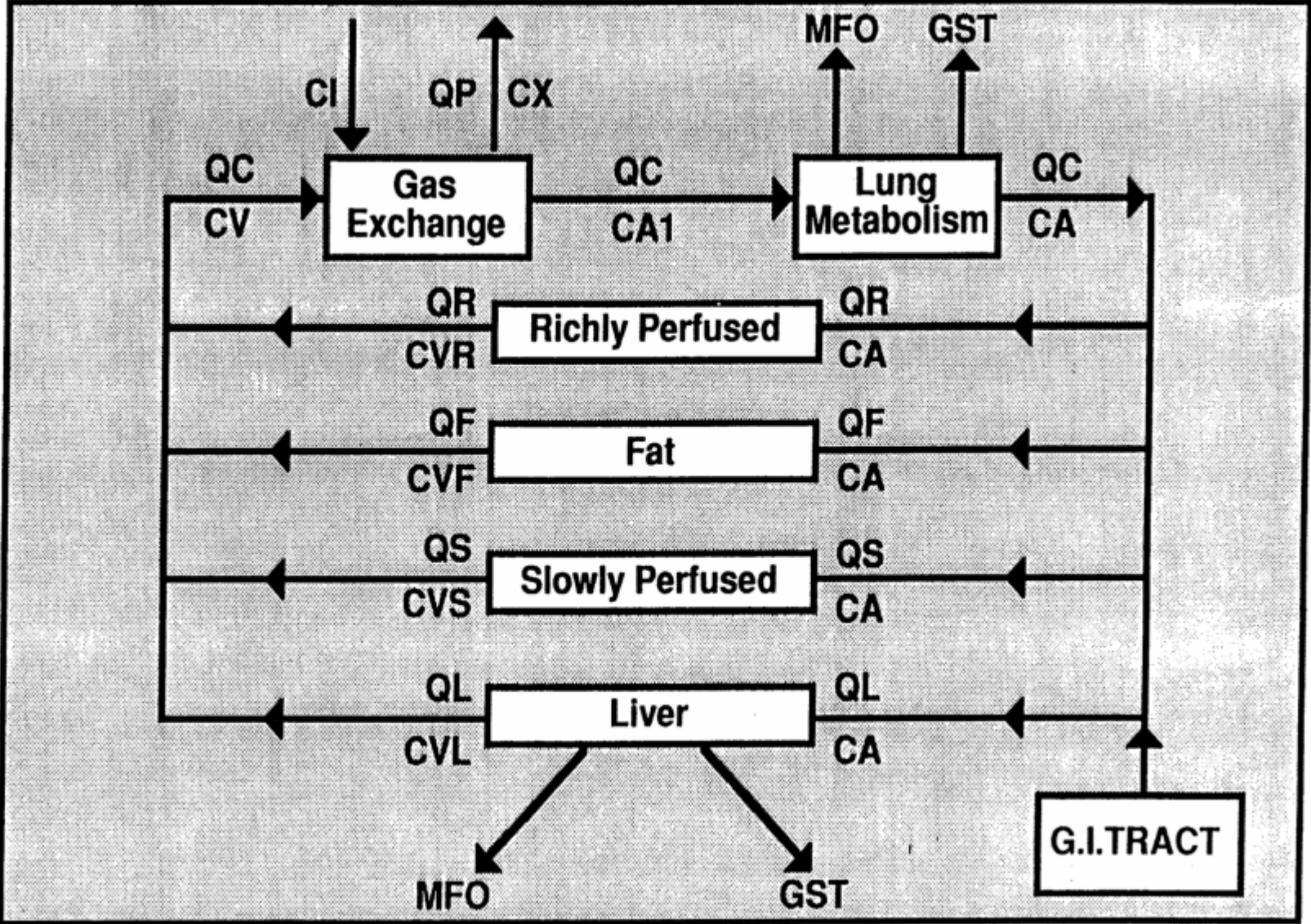
Outline

- PBPK modeling and the development of dosimetry based risk assessment approaches
- Differences in applying these approaches for 'xenobiotics' and for essential metals, e.g., 'normobiotics'
- Dosimetry modeling with manganese - status and plans
- Uses in risk assessments

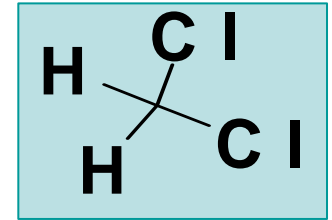
Dosimetry Models in Risk Assessment

- **Identify toxic effects** in animals or human populations
- **Evaluate available data** on time courses, tissue accumulation, route of exposure, etc.
- **Describe likely mode(s) of action**
- **Propose relationship** between tissue dose and response
- **Develop an appropriate dosimetry (PBPK) model**
- **Calculate tissue dose** during exposures causing toxicity
- **Estimate risk in humans** based on assumption of similar tissue response for equivalent target tissue dose

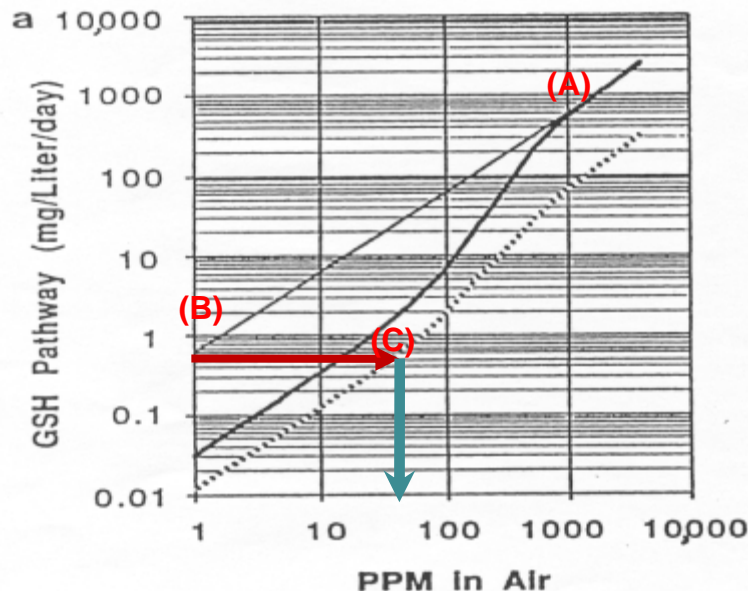
METHYLENE CHLORIDE - 1985



Glutathione Transferase Pathway - Tissue Dose



Liver Dose



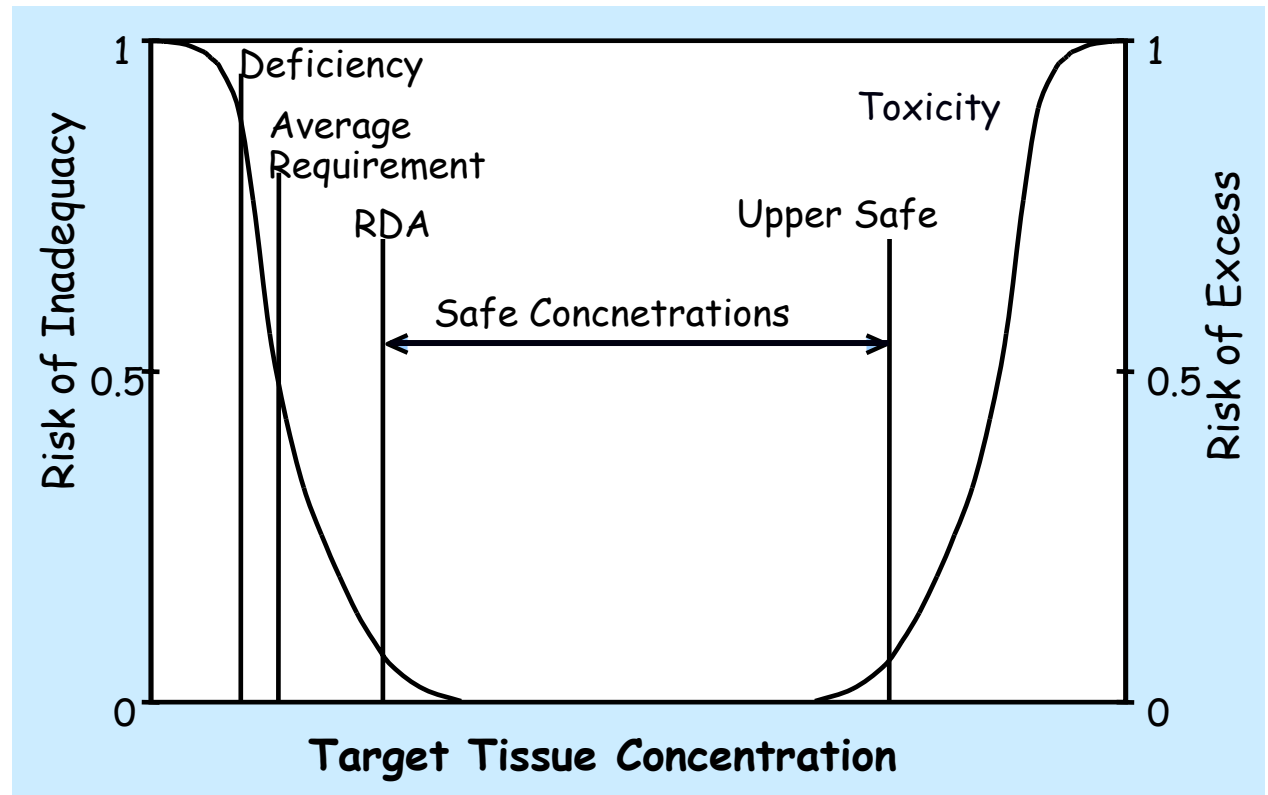
- At a toxic exposure, e.g., 1000 ppm, determine tissue dose (A) in test animals
- Extrapolate to lower level (divide by 1000 here) arrive at (B).
- Move from animal (solid straight line) to human (dashed line) curves relating tissue dose to concentration. Arrive at (C).
- Conduct reverse dosimetry to estimate safe human exposure, about 40 ppm in this example. Move along blue arrow.

Non-cancer Xenobiotic Risk Assessment

- Take the No-Observed-Adverse-Effect-Level (NOAEL) or BMD -**calculate tissue dose**
- **Uncertainty factors** applied for:

LOAEL to NOAEL	up to 10
short-duration to long	up to 10
animal to human	up to 10
human variability	up to 10
inadequate database	up to 10
- Apply UCFs to adjust tissue dose, use dosimetry model to **calculate acceptable exposures**

Adequacy and Excess- at the level of the tissues



- What **target tissue levels** are associated with normal function?
- What pharmacokinetic processes are responsible for maintaining manganese tissue concentrations in the body?
- In what manner do dose route and intake rates affect manganese concentrations in target tissues?

MANGANESE - Dr. Jekyll

- Essential nutrient with multiple adverse effects noted when levels in diet are inadequate, including
 - skeletal abnormalities
 - neonatal ataxia
 - impaired reproduction
 - defects in intermediary metabolism

MANGANESE - Mr. Hyde

- Toxicity associated with accumulation in specific portions of central nervous system
 - inhalation of dust (most frequent route)
 - drinking water/diet (infrequent)
 - complications of liver disease - humans
 - parenteral supplementation - humans

"Normal" Tissue Mn Concentrations

<u>TISSUE</u>	<u>[Manganese] ug/ g</u>
Bones (long)	3.3
Brain	0.34
Kidney	0.93
Liver	1.68
Ovaries	0.19
Pancreas	1.21
Testes	0.19
Muscle	0.09
Hair	0.80

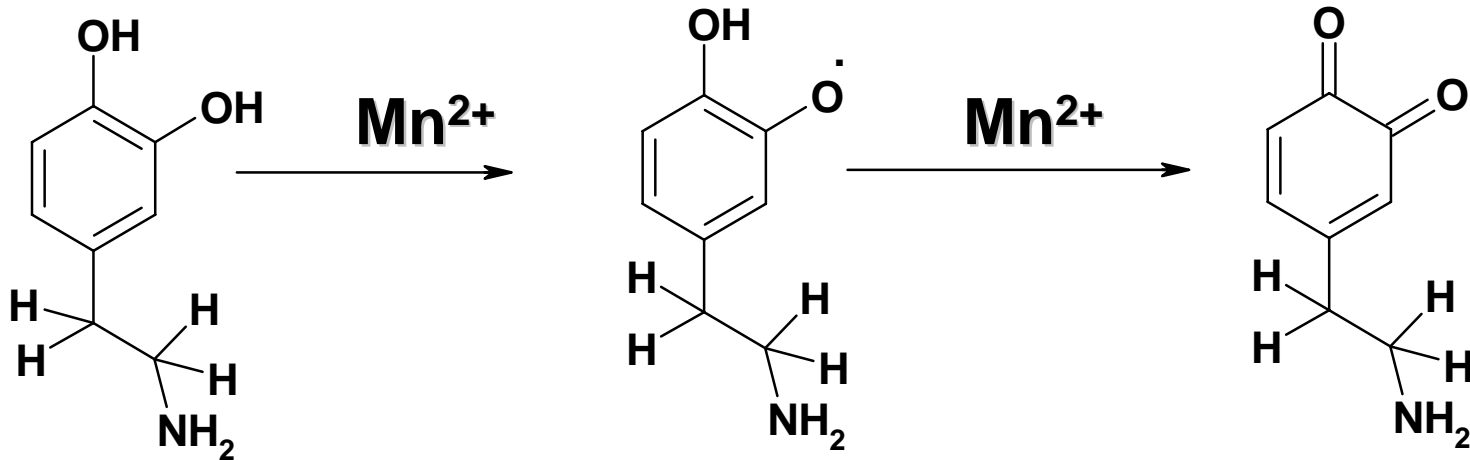
from Underwood, 1977

ORAL UPTAKE VARIES WITH DIET - DOSE-DEPENDENCE

Tissue	Dietary Mn level			
	4 ppm	75 ppm	300 ppm	1000 ppm
	% of dose/g of dry matter ^a			
Stomach	10.05 ± 3.24b	3.29 ± 1.62b	1.62 ± .31c	1.40 ± .41c
Duodenum	44.80 ± 18.28b	7.04 ± 2.05bc	1.62 ± .61c	1.62 ± .79c
Jejunum	10.30 ± 3.60b	3.68 ± .76bc	1.83 ± .64c	1.41 ± .46c
Ileum	4.62 ± 1.21b	5.43 ± .99b	4.68 ± 2.10b	6.90 ± 2.96c
Cecum	.81 ± .68b	1.12 ± .22b	1.21 ± .53b	.97 ± .59b
Colon	.22 ± .16b	1.39 ± 1.32b	.66 ± .27b	.98 ± .50b

Abrams et al., 1976

What do we mean by mode of action?

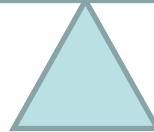


- Likely toxicity involves *free* (more loosely bound) manganese causing oxidative cycling, leading dopamine quinones
- After 'essential' sites are occupied, free (more loosely bound) Mn increases disproportionately

{ Preservation of
Tightly Bound Tissue
Stores of Mn }

{ Accumulation of
Excess Free, i.e.,
loosely bound Mn }

The Teeter will totter - both directions



Mn Intake
Loosely Bound Tissue Mn



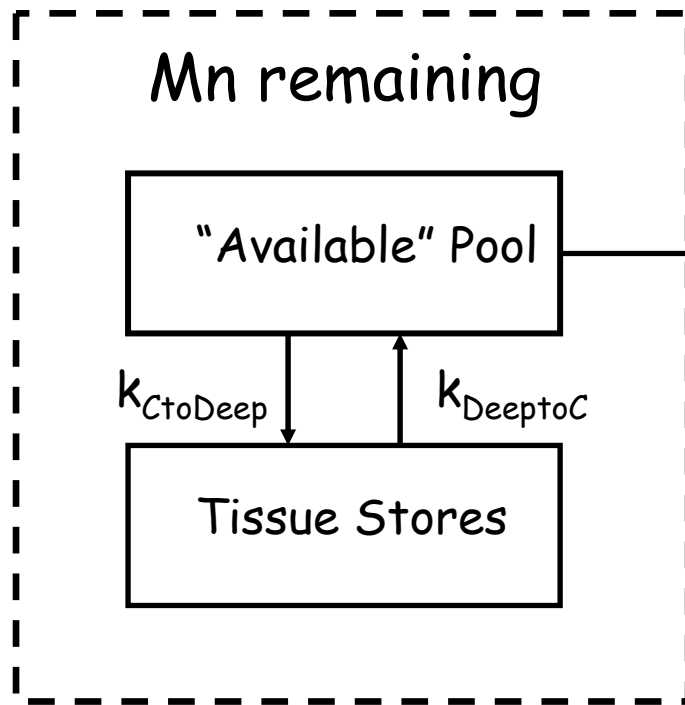
What needs to be considered in order to understand Mn disposition?

- Background tissue concentrations
- Multiple dose routes
- Different animal species - rats, monkeys, humans
- Dose dependent binding and tissue kinetics, to distinguish free and bound in tissues
- When do we expect significant increases in tissue free Mn

Why can we consider developing a dosimetry model for manganese?

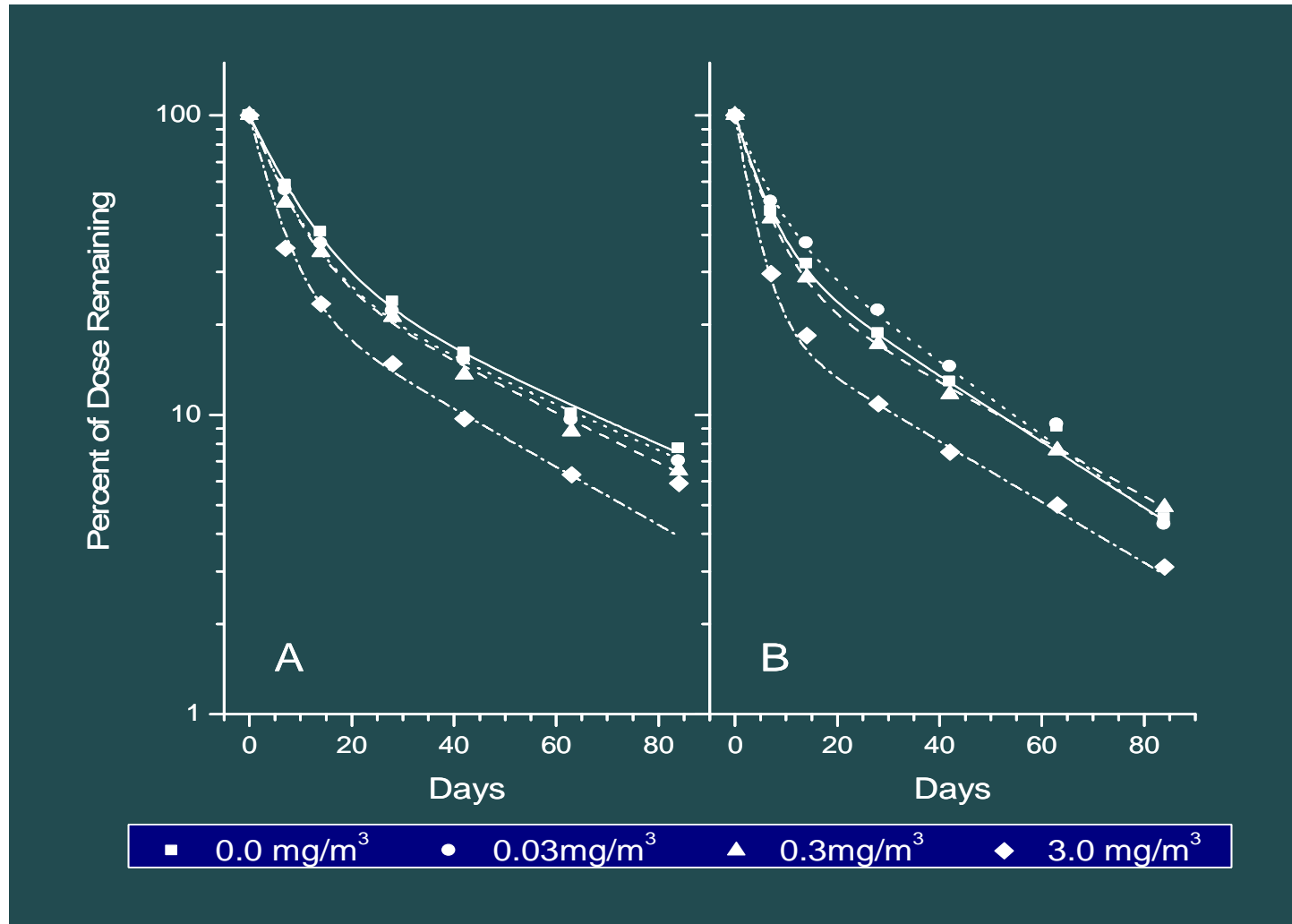
- Availability of high quality data sets with tissue time courses for Mn in rats and monkeys
- The dosimetry models do not create data; they serve to organize information and help understand relationships between varying dose rates and altered outcomes

Control of Mn Elimination with higher intake rates by diet and inhalation



A Simple PK Model was used to Evaluate Increasing Elimination Rate Constants with Increasing Exposures

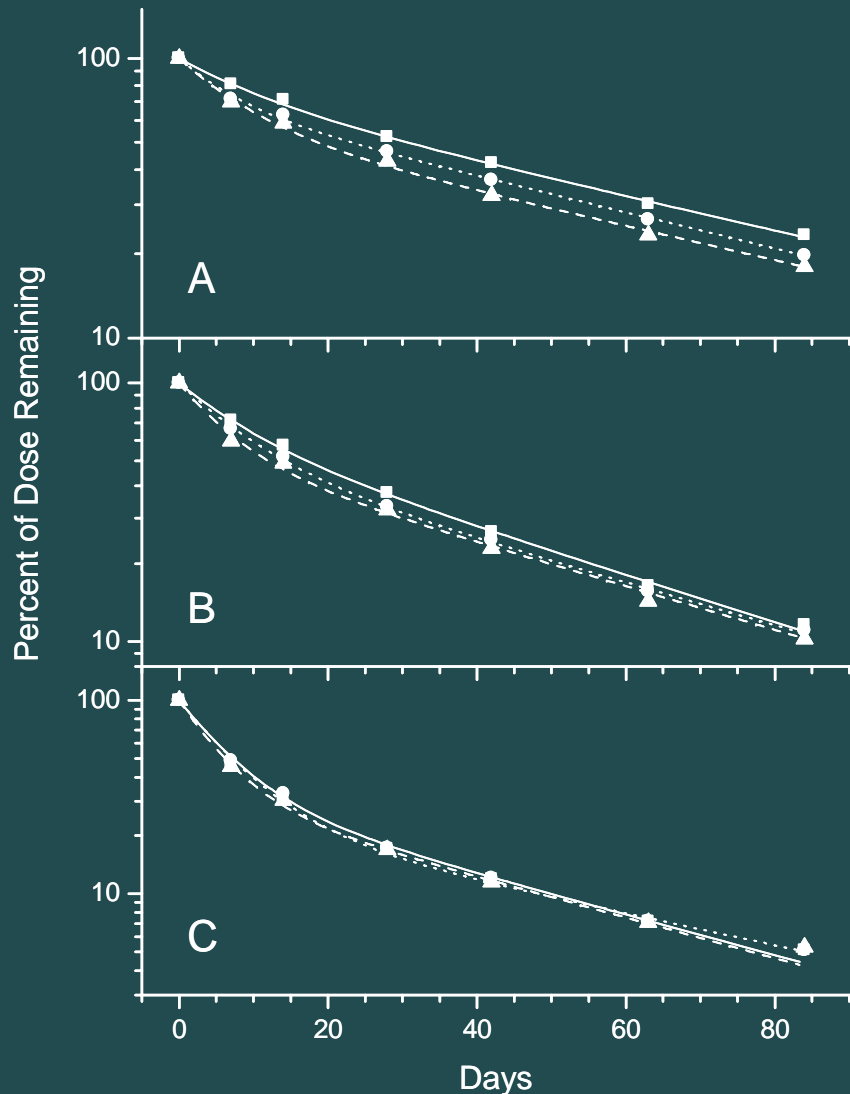
Elimination rate constant increased after exposures to high Mn for 2-weeks



Dorman *et al.* (2001a).

Dietary Mn also affected the elimination rate constant:

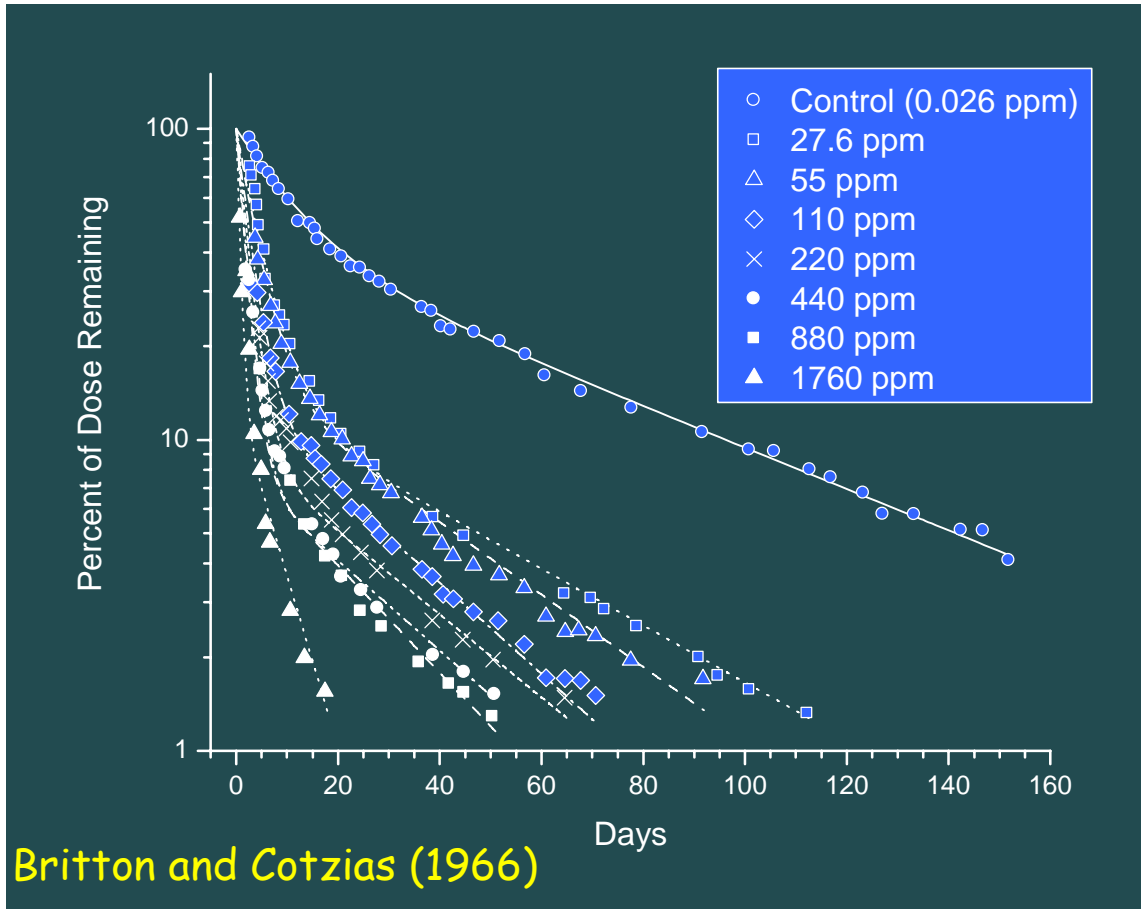
- (A) 2 ppm in diet
- (B) 10 ppm in diet
- (C) 100 ppm in diet



■ 0.0 mg/m³ ● 0.03 mg/m³ ▲ 0.3 mg/m³

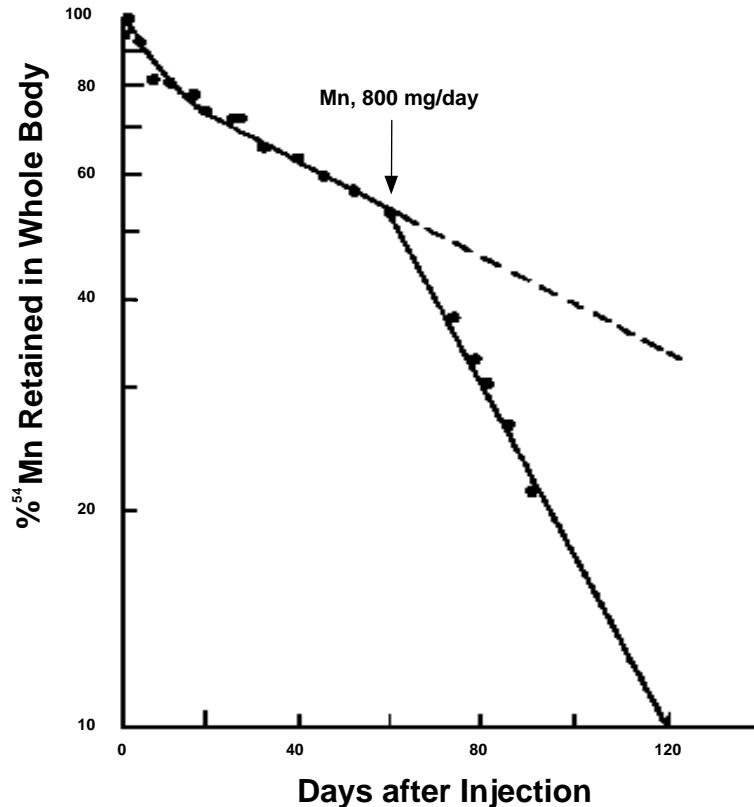
Dorman et al. (2001b)

Similar increases in elimination were observed in other species, including mice and



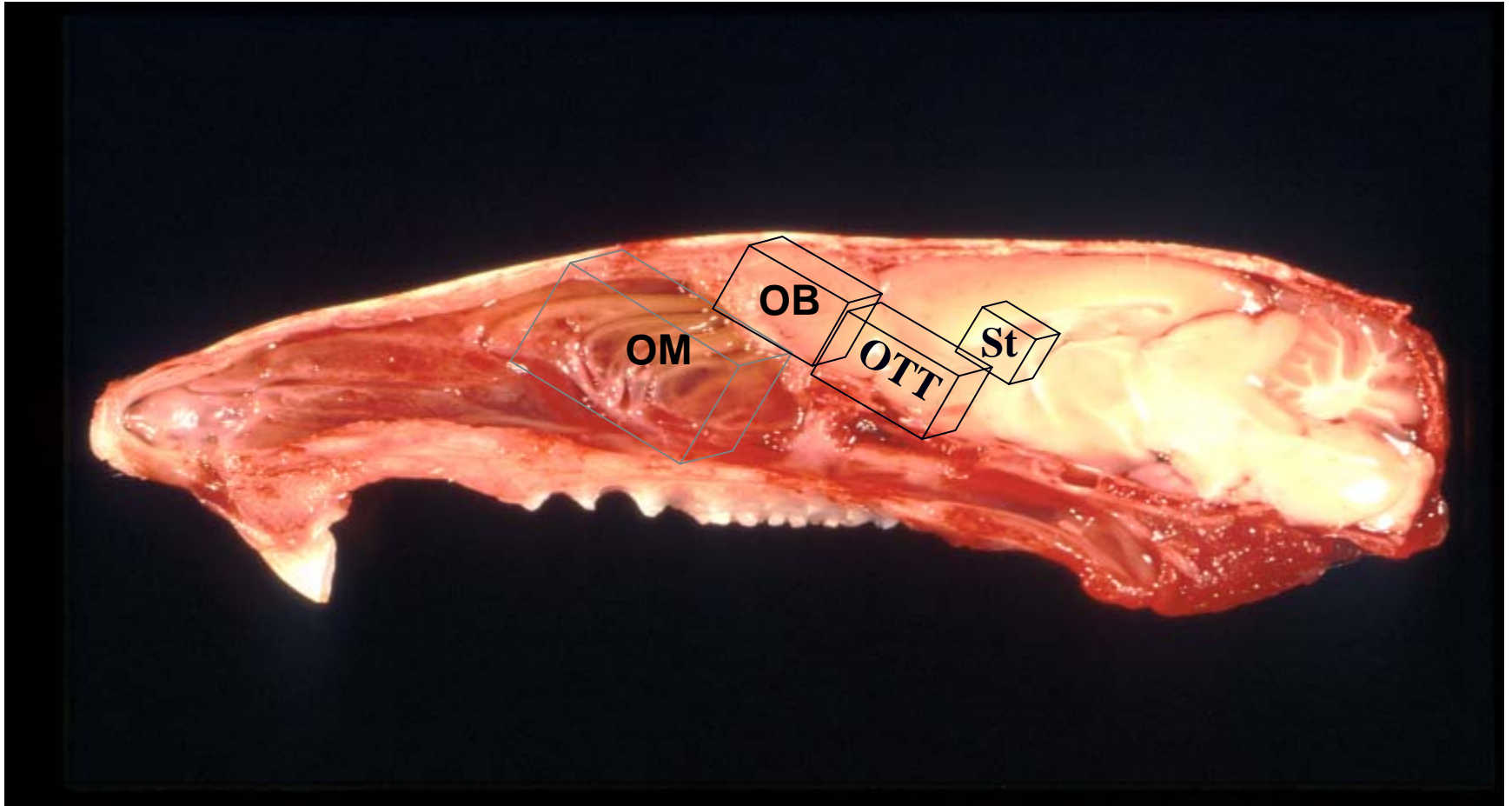
In all cases, the elimination rate constants changes, without changes in rate constants for movement between compartments.

in humans too



- 800 mg Mn/day beginning on day 60 after radiotracer injection
- Rate constants for exchange not very different from rodents
- Dose-dependent increases in kelim restrict accumulation in an otherwise linear model

Direct routes of uptake to CNS tissues



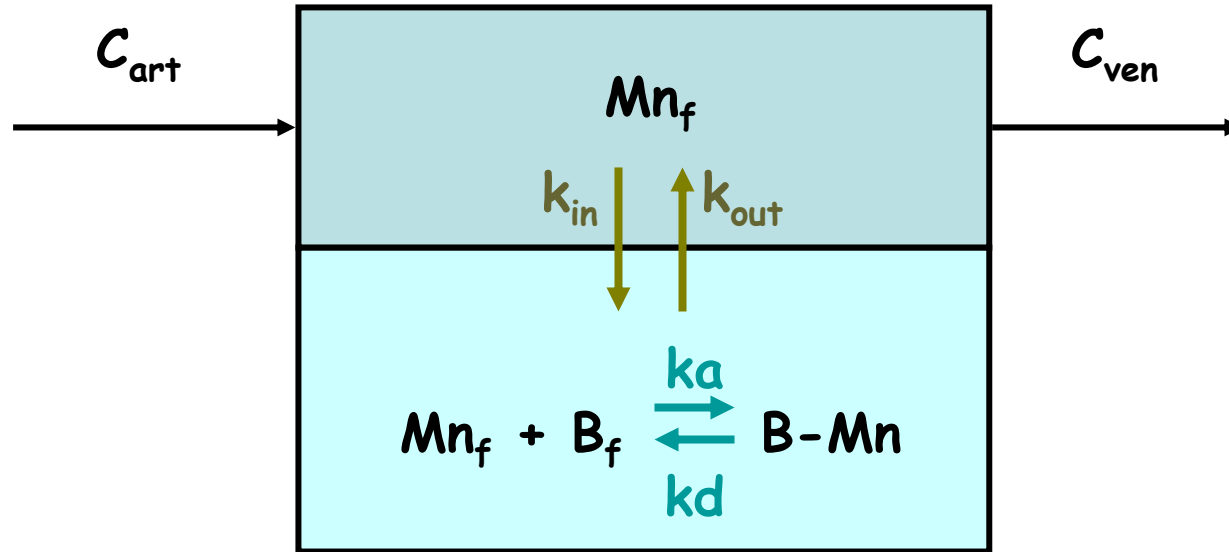
OM = olfactory mucosa

OTT = olfactory tract & tubercle

OB = olfactory bulb

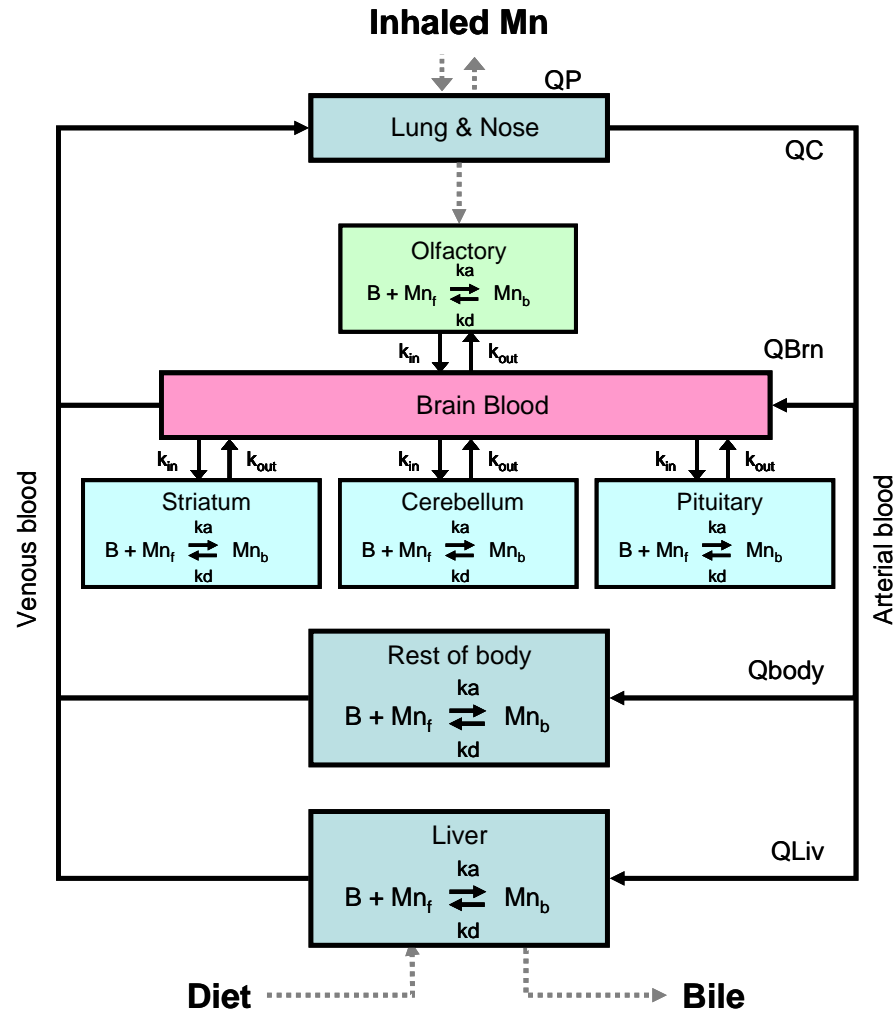
St = Striatum

Tissues - purposeful simplification

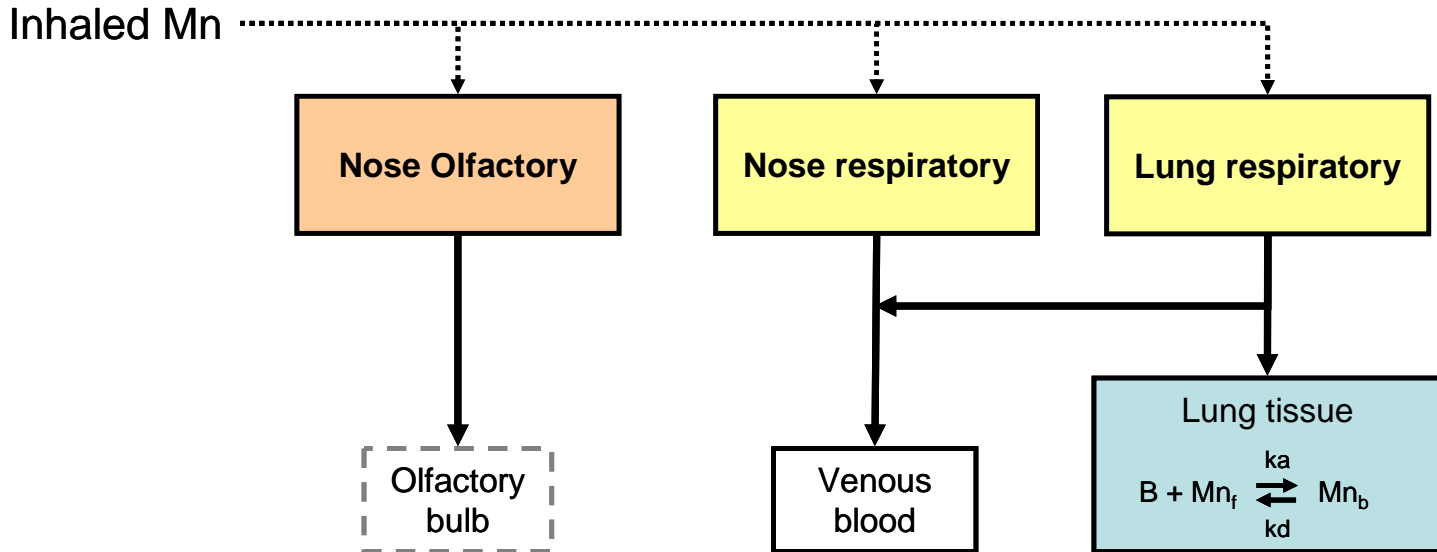


- B-Mn: Dr. Jekyll (too little, deficiency)
- Mn_f (loosely bound): Mr. Hyde (too much, toxicity)

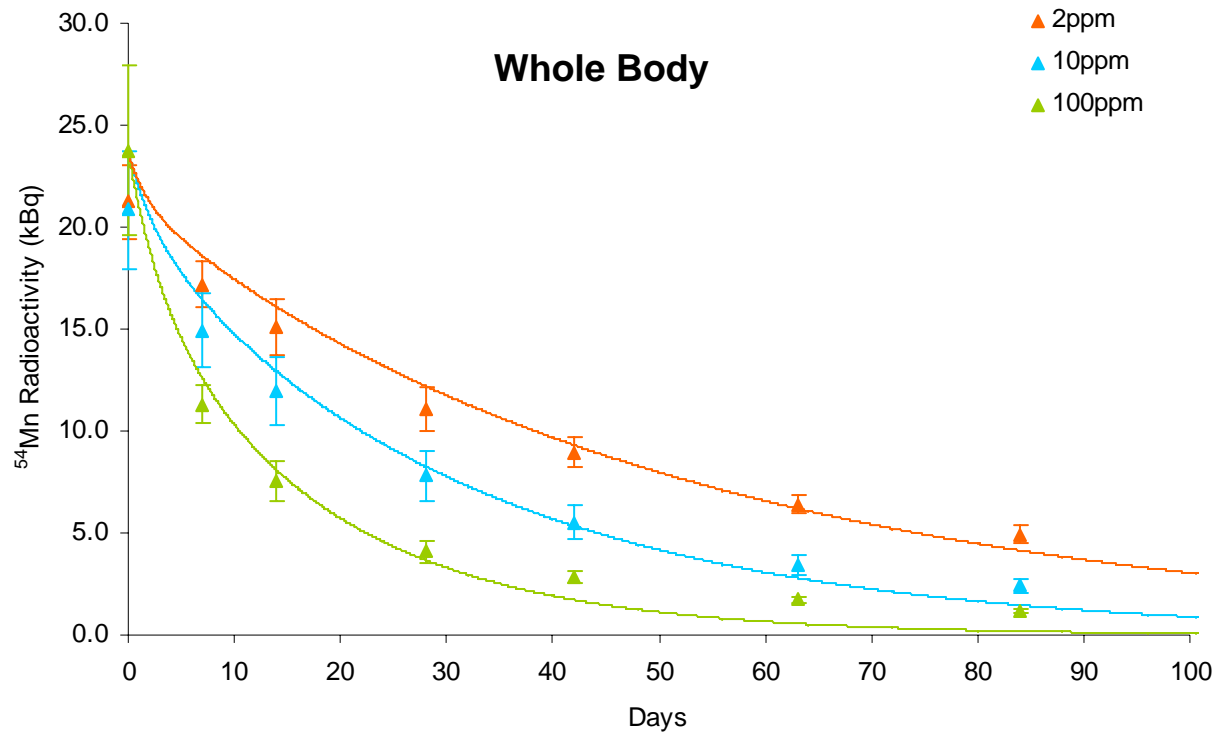
The Adult



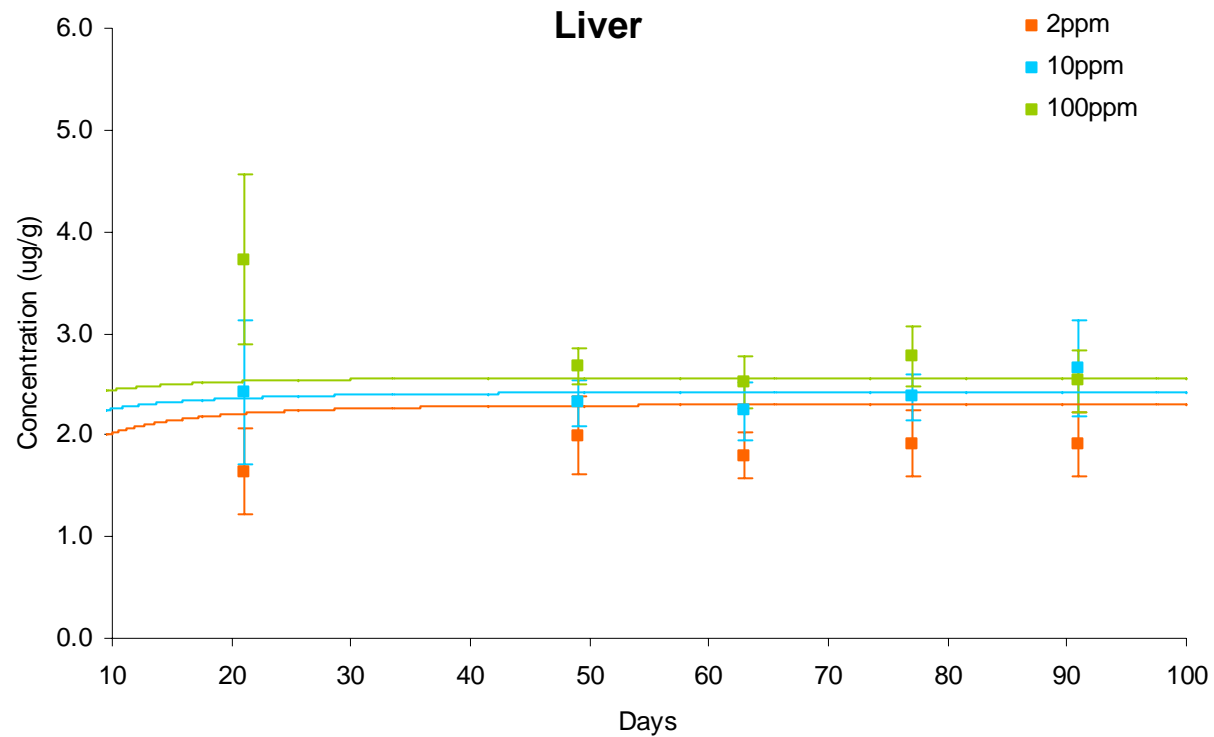
Respiratory and olfactory deposition depends on particle size



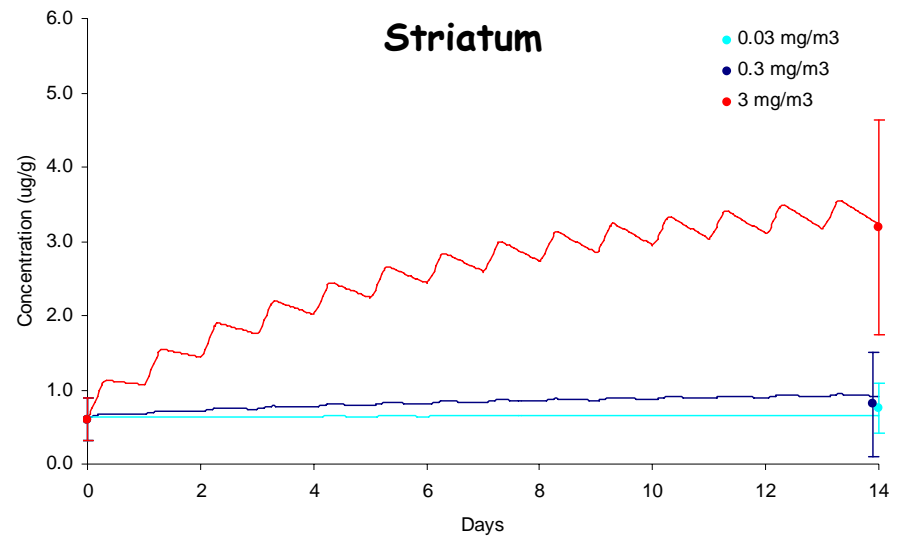
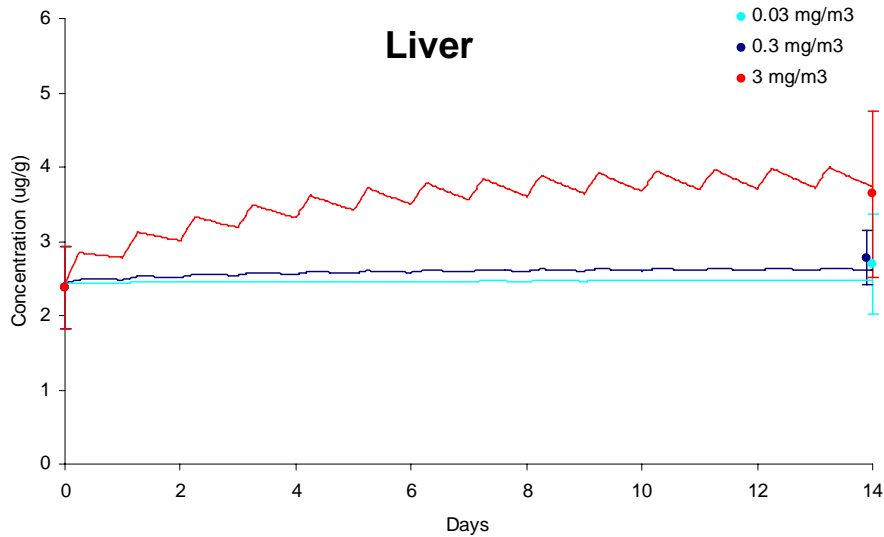
Diet affects biliary excretion of tracer



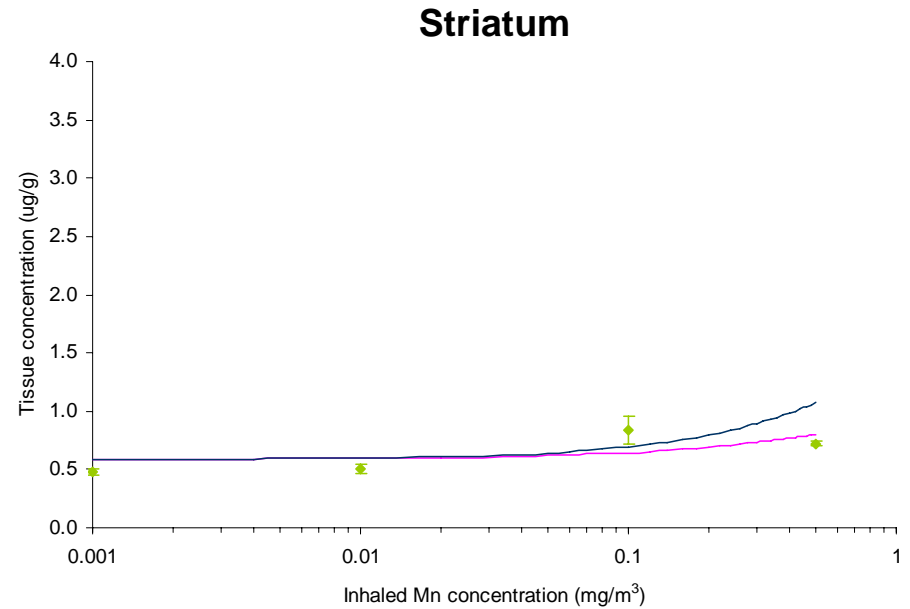
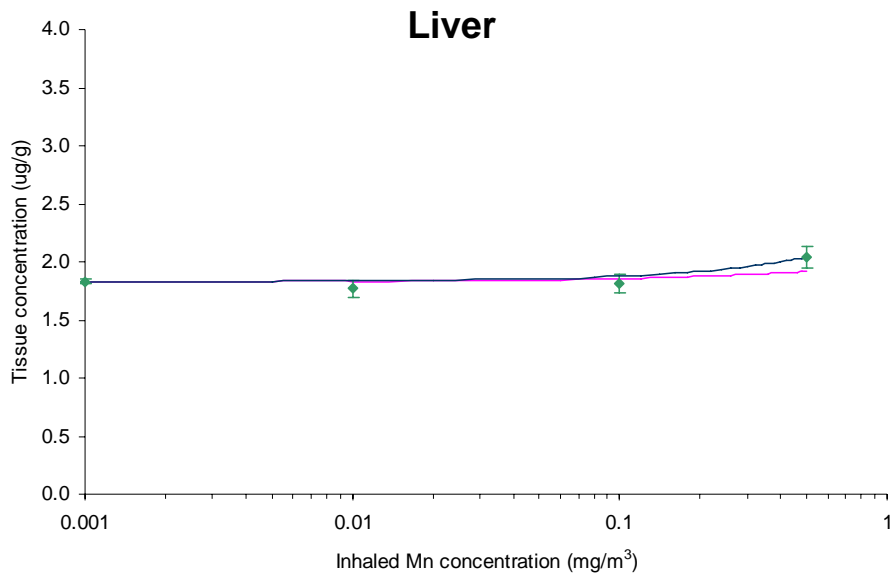
Maintain Tissue Steady States



Account for two-week exposures



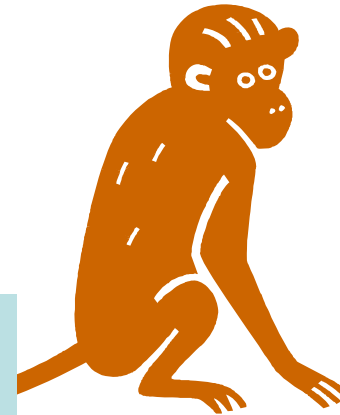
90-day exposure, not much difference



without and **with** increased biliary elimination of Mn
(Dorman et al 2004)

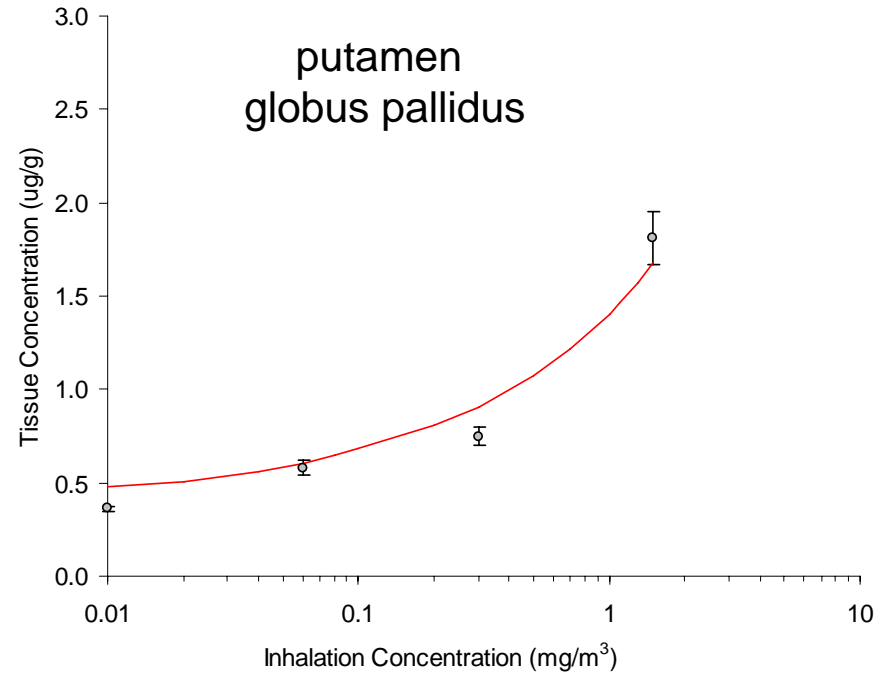
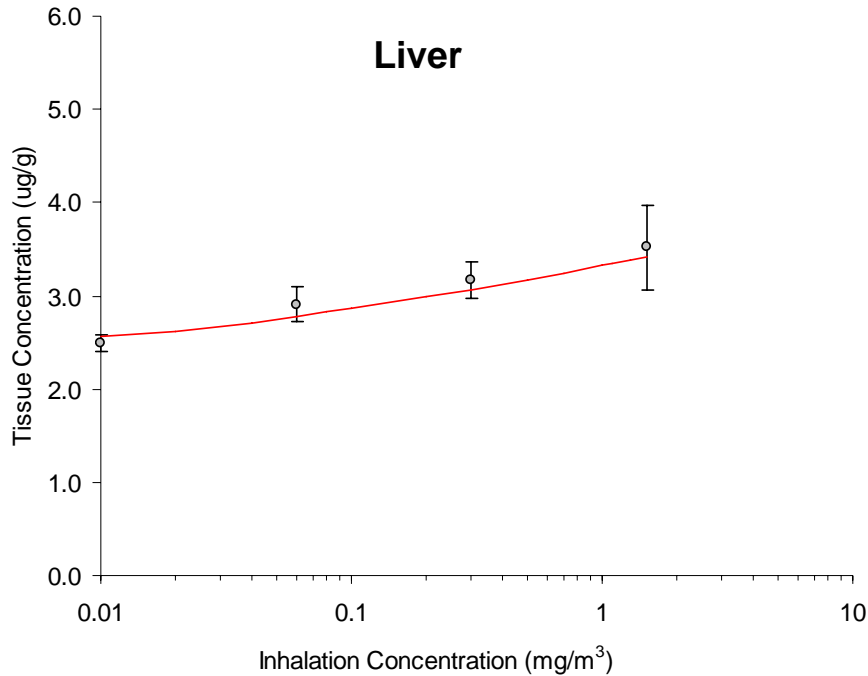
What do we need to add/change in the models to describe another animal species?

Extrapolation

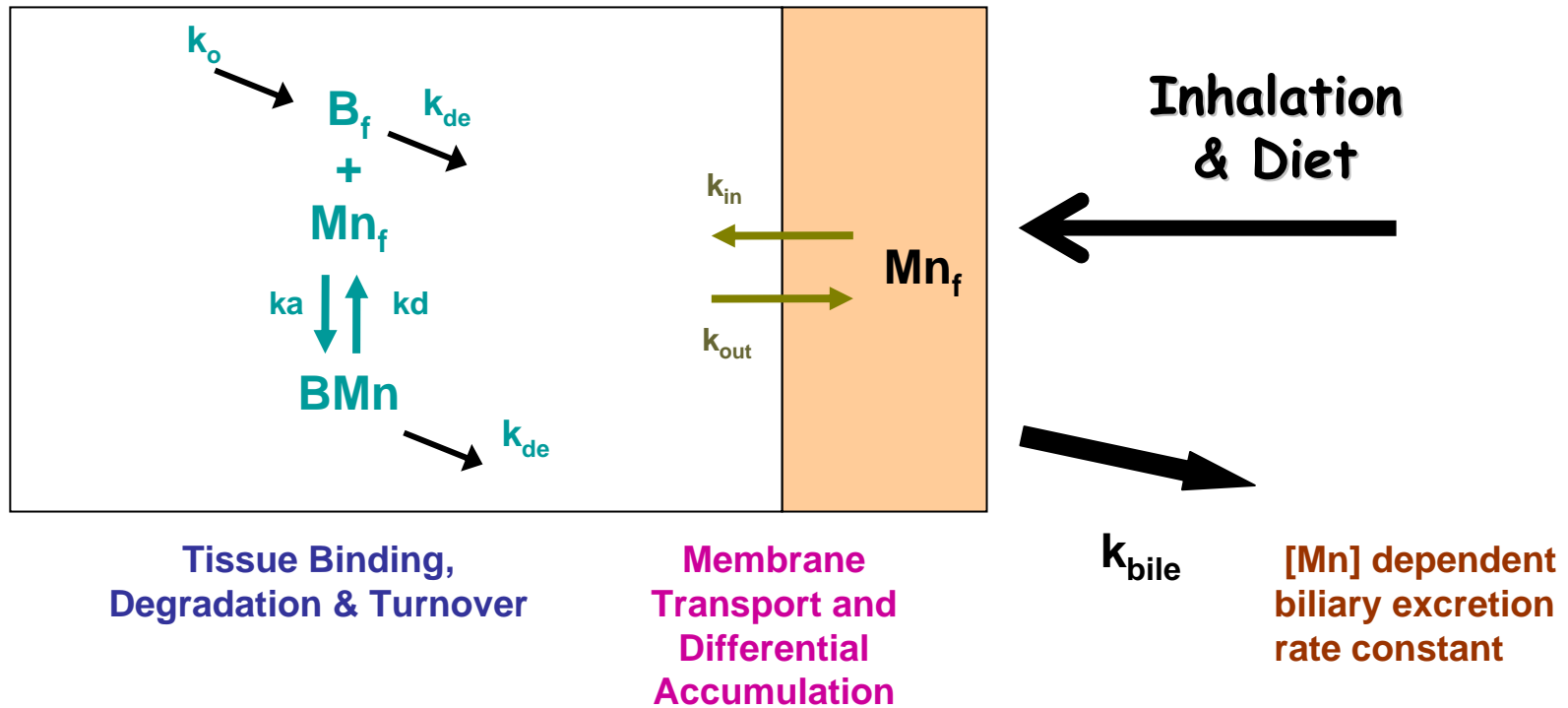


- Body weight
- Tissue volumes
- Blood flows
- Biliary excretion
- Scaled parameter

Manganese PK in Monkeys for 90-day exposures



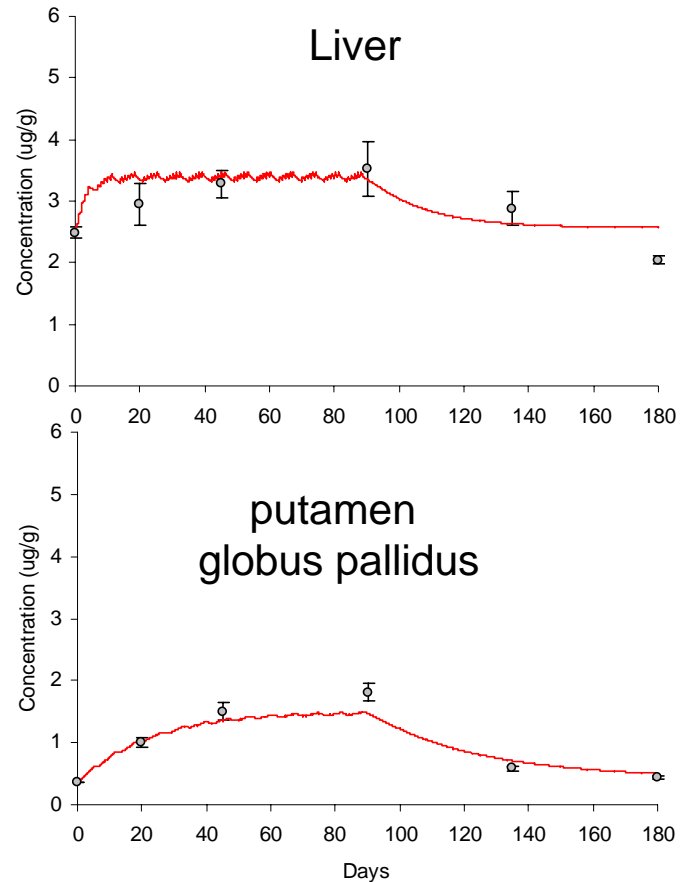
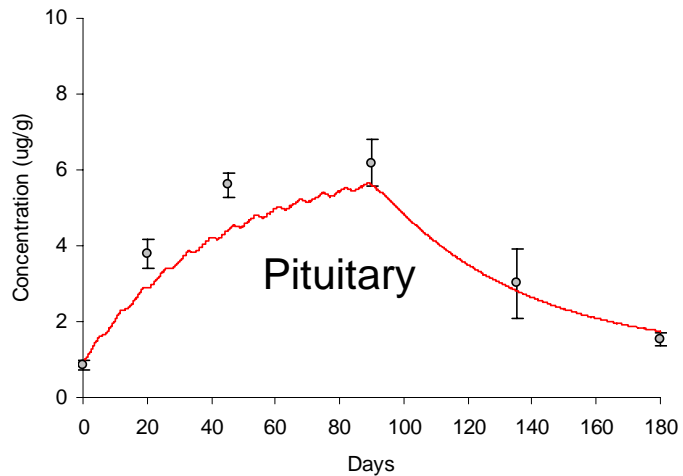
Determinants of Mn Distribution



Primary stores are tightly Bound - B-Mn

After saturation of binding enhanced elimination of free Mn

Time Course Changes in Monkeys



The lines represents the simulations of Mn tissue concentration and symbols are mean and standard error of measured concentrations (n=6-8).

PBPK Modeling in Chemical Risk Assessment

Exploratory - Calculate measures of tissue dose and correlate with toxic effects.

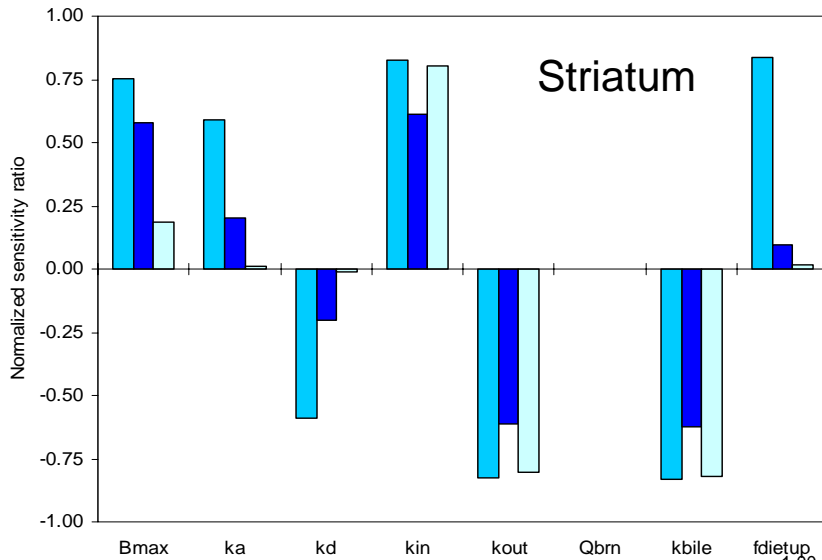
Mechanistic - Characterize relationships between dose measures and early biochemical responses and determine consistency with mode-of-action hypotheses.

Interpretive - Use 'validated' dose metric to determine relationship to response for evaluating acceptable exposure levels

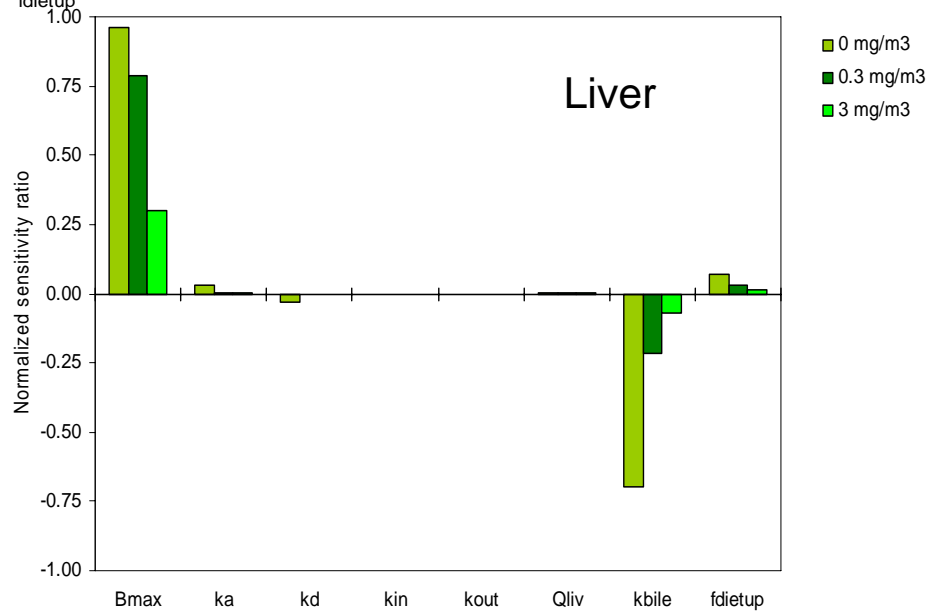
How Can Dosimetry Models Help Refine Mn Risk Assessments?

- Assess tissue dose in primates in relation to observed responses and develop a better understanding of the appropriate dose measure for risk assessment, i.e., the excursion in “free” Mn necessary for toxicity
- Show how changes in specific processes, e.g., dietary uptake, altered absorption, pre-existing liver disease, etc., are expected to alter “free” Mn in target tissues
- Assess “free” tissue Mn for different exposure situations

Sensitivity Coefficients:



Assessing factors important in controlling tissue Mn for different exposure situation.



How Can PBPK Models Help Refine Mn Risk Assessments?

- Dosimetry models and RfCs/RELS to consider:
 - route-to-route extrapolation
 - duration adjustments
 - interspecies extrapolation
 - intraspecies extrapolation
 - aggregate risk assessment

A more quantitative approach

develop a dosimetry based risk assessment for inhaled Mn taking into account Mn essentiality as well as Mn toxicity

based on variation in normal $[Mn_{\text{brain}}]$

Normal: $[Mn_{\text{brain}}] = Mn \pm \sigma [Mn_{\text{brain}}]$

Acceptable exposures would lead to an increase in $[Mn_{\text{brain}}]$ of no more than some fractional percentage, α , of the normal variability. Incremental increase = $\alpha \times \sigma$.

$$\alpha = 0.1 \text{ to } 0.50$$

How would we do this?

- Cannot directly measure the small incremental change in $[Mn_{\text{brain}}]$
- Use the PBPK model to calculate the exposure concentration that would give rise to this incremental increase in background $[Mn_{\text{brain}}]$.

ADVANTAGES OF SIMULATION MODELING IN PHYSIOLOGY & RISK ASSESSMENT

- Organize available information
- Expose contradictions
- Explore implications of beliefs about the chemical
- Expose data gaps
- Predict response under new or inaccessible conditions
- Identify what's important
- Suggest and prioritize new experiments

Yates, F.E. (1978). *Good manners in good modeling: mathematical models and computer simulation of physiological systems.* *Amer. J. Physiol.*, 234, R159-R160. 1978.

Andersen et al., *Applying simulation modeling to problems in toxicology and risk assessment: a short perspective.* *Toxicol. Appl. Pharmacol.*, 133, 181-187.

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