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Overview of EPA's Quality Assurance Project Plan (QAPP) for Evaluating PBPK Models

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Why a QAPP?

EPA's Office of Research and Development (ORD) Policies and Procedure's Manual

- Chapter 13—Quality Assurance
- Section 13.9—Modeling Quality Assurance and Documentation
  - "Documentation of model development, evaluation, and application provides a basis for assessing the usability of model results."
  - QAPP suited for particular model or application
  - Distinct standards for "Regulatory" vs. "Research" models

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Why an "Umbrella"?

- Intended to **cover** most if not all particular PBPK (and PK) models to be evaluated
- Efficiency vs. developing separate QAPP for each model
  - Model-specific addenda can be created as needed
- Consistency in criteria for model acceptance

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Primary QAPP Features or Themes

- Chemical-specific ADME data:
  Know data landscape in which model operates

- Scientific (Qualitative), Criteria A:
  What you can tell from reading the paper or report

- Technical (Quantitative), Criteria B:
  Exactness and reproducibility of model code

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Chemical-specific ADME data

- Not all data are equal, some better than others
  - Analytic methods evolve
  - Assumptions?

    E.g., clearance constant estimated *assuming* a volume of distribution from a related chemical *and* that observed concentration is at steady state
- What is actually measured?

    E.g., tissue Mn = free + bound
- Recognize, hopefully understand discrepancies between data sets that no model could resolve

    E.g., clearance differences between rodent strains

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Scientific Criteria (Qualitative)

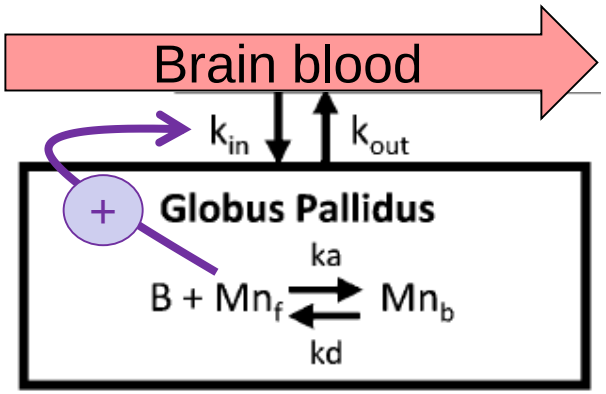
1) Biological basis for the model is accurate
   - Model equations are consistent with biochemical understanding and biological plausibility
   - Consistent with mechanisms that significantly impact dosimetry
   - Describes critical behavior, such as nonlinear kinetics in a relevant dose range
   - Predicts dose-metrics expected to be relevant and to be better correlated with toxicity or risk than applied doses
   - Applicable for relevant route(s) of exposure

Scientific Criteria, Example/Concern

- Model equations are consistent with biochemical understanding and biological plausibility
  - Mn uptake from brain blood to brain tissue
  - From Schroeter et al. (2011), Nong et al. (2009)

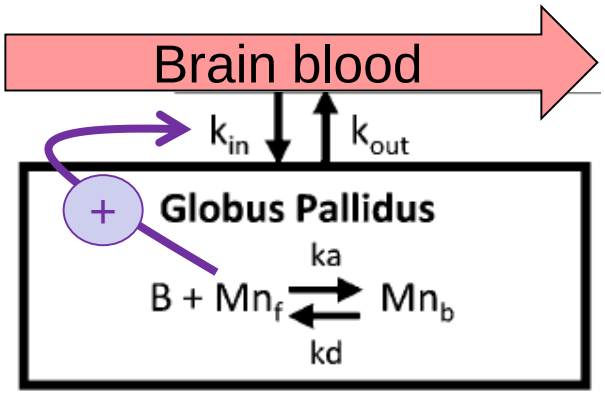
$$k_{in} = k_{in,0}\left(1 + \frac{k_{in,max}A_{free,t}}{A_{free,50} + A_{free,t}}\right)$$

  - As a picture:



Scientific Criteria, Example/Concern II

- This suggests that as (free) Mn builds up in the brain tissue, this signals to increase the activity of a transporter at the brain-blood interface to further increase (exacerbate) the accumulation
  - Contradicts premise of homeostasis
  - Is there a known mechanism for this signaling?
  - Opposite effect to saturable tissue binding on total tissue Mn



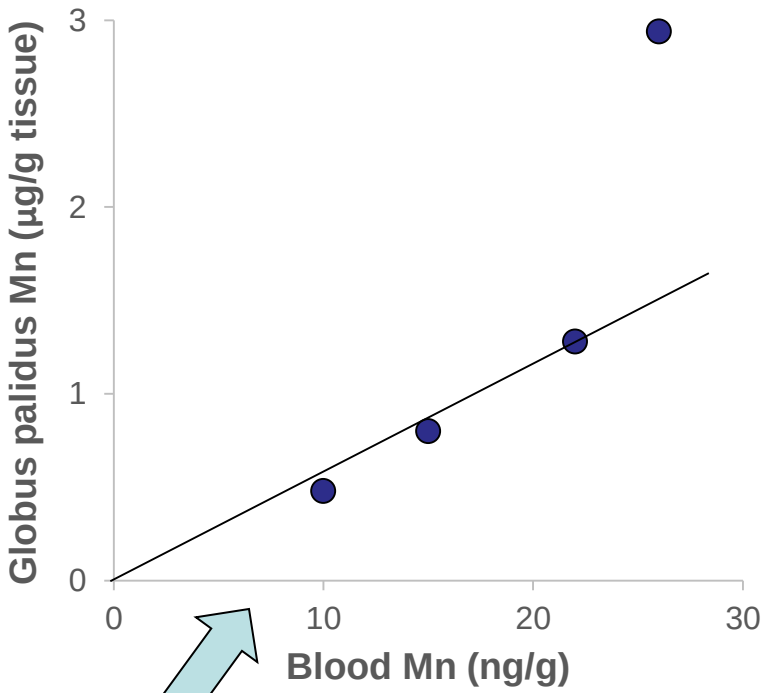
Scientific Criteria, Example/Concern III

- Data to indicate induction of blood-brain transport?
  - Monkey data, Dorman et al. (2006) (truncated)

Mean (± SEM) Tissue Manganese Concentrations (µg Mn/g tissue wet weight) in Young Monkeys Following Subchronic Exposure to Either Air or $MnSO_4$

	Nominal $MnSO_4$ concentration		
	Air	0.06	0.3
Olfactory epithelium[a]	0.42 ± 0.01	1.22 ± 0.15*	2.96 ± 0.46*
Olfactory bulb	0.31 ± 0.01	0.77 ± 0.04*	1.36 ± 0.15*
Olfactory tract	0.30 ± 0.06	0.43 ± 0.02	0.61 ± 0.05*
Olfactory cortex	0.19 ± 0.004	0.27 ± 0.02*	0.31 ± 0.01*
Globus pallidus[a]	0.48 ± 0.04	0.80 ± 0.04*	1.28 ± 0.15*
Blood	0.010 ± 0.001	0.015 ± 0.002	0.022 ± 0.003*
Group size (*n*)	6	6	4

- Data (total Mn) are nonlinear
  - But what mechanism?
  - Failure of defense mechanism?
  - Saturation of binding in blood?



Linear x axis!

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Scientific Criteria (continued)

2) Consistent with mechanisms that significantly impact dosimetry
   - Allows for parsimony, if mechanism is not significant
3) Describes critical behavior, such as nonlinear kinetics in a relevant dose range
   - Plot of model-predicted GP vs blood concentration, compared to Dorman data (linear x-axis)?
4) Predicts dose-metrics expected to be relevant ...
5) and to be better correlated with toxicity or risk than applied doses

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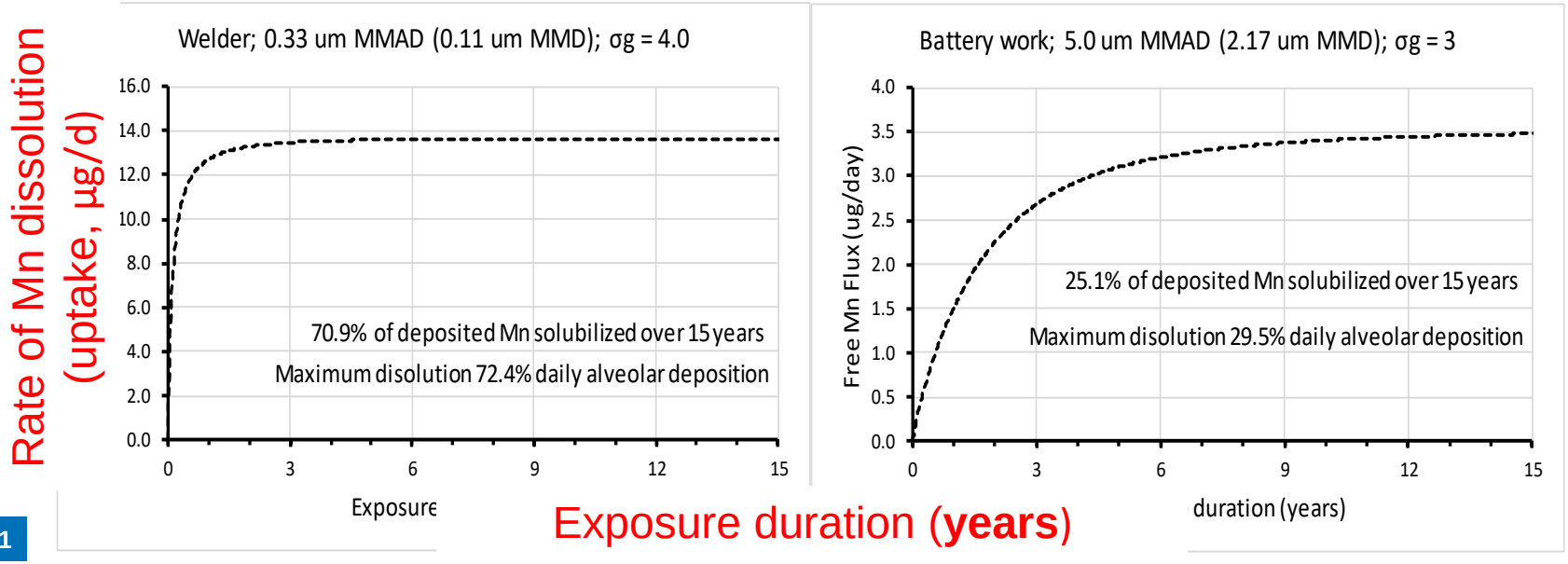
Scientific Criteria, 2nd Example/Concern

- ... mechanisms that significantly impact dosimetry

1) Less soluble particles have ~ same lung deposition as more soluble
2) Particles that deposit in the alveolar region, but don't dissolve immediately, can remain there for months-years (extremely slow clearance)
3) If particles dissolve at a rate of 1%/day, cumulative mass after a year of exposure is over 90x the 1-day deposition
4) So net rate of dissolution can ➔ rate of deposition
5) May not be evident in short-term PK data

Example simulations of Mn uptake

- Based on reasonable but un-reviewed assumptions for rate of particle dissolution (James Brown, NCEA)
- Alveolar deposition from MPPD (2016) model
- Clearance from alveolar region based on ICRP (1994)



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Technical Criteria (Quantitative)

- Well-documented model code
- Parameters are clearly identified, including origin and/or derivation
  - Track back to source, check calculations and units
- "Parameters do not vary unpredictably with dose (e.g., any dose-dependence in absorption constants is predictable across the dose ranges relevant for animal and human modeling)"
- Criteria for probabilistic models
- Sensitivity and uncertainty analysis

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Technical Criteria: Example/Concern

- Parameters do not vary unpredictably with dose....
- From Schroeter et al. (2011):

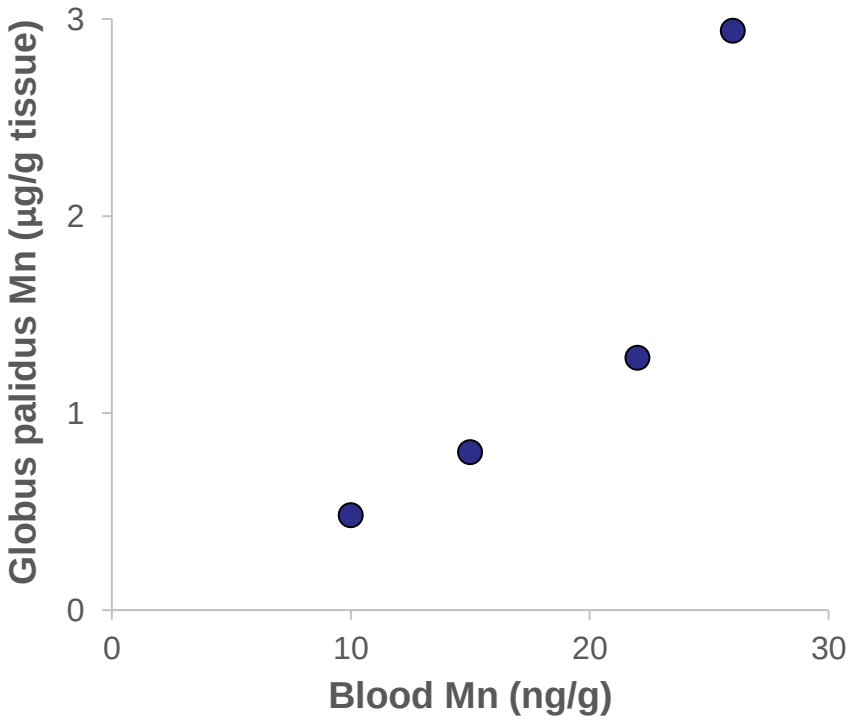
FIG. 5. Comparison of simulated whole-body retention of ^{54}Mn in human volunteers given supplemental Mn or Fe compared with the experimental data from Mahoney and Small (1968): (A) subject JM was on a reduced calorie diet and began to ingest 800 mg/day Mn on day 60 of the study; (B) subject WS was preloaded with 300 mg/day Mn 10 days prior to the start of the study; (C) subject SM had an iron deficiency and began to ingest 400 mg/day Fe on day 50. The condition of each subject was accommodated in the PBPK model by adjusting Mn dietary absorption (Fdietup). The curves represent model simulations and the symbols are retention data from individual subjects.

- Is this variation predictable?
- What value should be used for risk prediction?
- May indicate population variability

➔ Protect sensitive individuals

Technical Criteria: Parameter Derivation & Uncertainty

- Empirical brain tissue vs. blood curve ~ 3 parameters
- Model uses 7 parameters: k_{in} (function), k_{out} & binding
- Tissue binding term from Nong et al. (2008):
  - Empirical, fit to rat data
  - Mechanism not identified
  - ➔ Concave-down curve, doesn't match monkey data
  - Occam's Razor (parsimony): is binding term supported?



Summary

- QA criteria address:
  - ADME data (systematic evaluation)
  - Qualitative features (model structure)
  - Technical implementation of model (model code)
- Meant to assure that all aspects of a model are sound, self-consistent, and reproducible
- Can model predict data to which it's not been fitted?
- Some examples shown may not apply to new version
- But accumulation of less soluble particles in airways will impact long-term human dose predictions
  - This process is effectively "outside" the PBPK model
  - Issue of exposure vs. what happens after absorption