Evaluation of the IRIS draft PBPK modeling of RDX

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May, 2016

Canada

PBPK model of RDX

Rat model

- Basis of all the TK for RDX
- Calibrated against different doses and routes of exposure

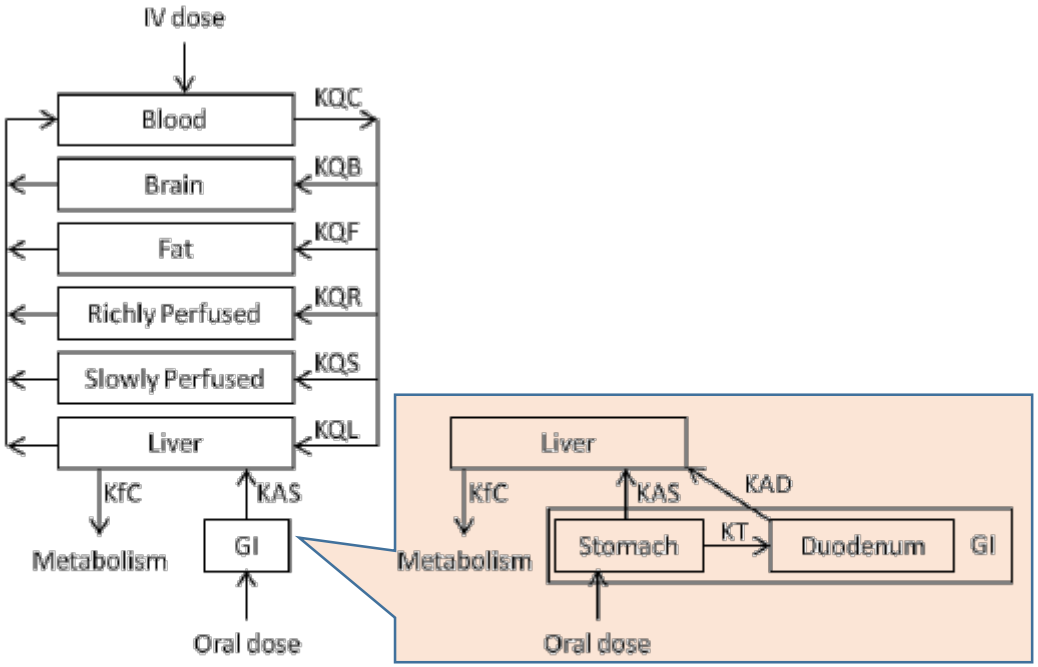
Human model

- Extrapolation of the rat model
- Calibrated against a few individuals
- Metabolic data to support the extrapolation between rat and human

Mice model

- Extrapolation of the rat model
- Calibrated against different oral doses

PBPK model of RDX



Exposure to RDX is by the i.v. or oral route, and clearance occurs by metabolism in the liver. See Table C-4 for definitions of parameter abbreviations. The GI tract is represented as one compartment in Krishnan et al. (2009) (on the left) and two compartments in Sweeney et al. (2012a) (on the right).

Figure C-1. PBPK model structure for RDX in rats and humans.

Dose metrics for noncancer endpoints

1. Neurotoxicity – systemic effect (tremors)
   - arterial blood concentration – average vs peak

2. Neurotoxicity – convulsion (acute)
   - Arterial blood concentration – peak

3. Neurotoxicity – seizures and long-term injury (chronic)
   - Arterial blood concentration – average
   - Area under the curve – average vs lifetime

4. Other tissues
   - Liver/kidney – tissue specific average blood concentration
   - Brain concentration – estimate based on blood brain barrier partition
   - Reproductive – average blood concentration

Mice Toxicokinetics and Model Assumptions

A case of "all models are wrong, but some are useful."

1. The mice PBPK model is well develop and calibrated based on available data
2. The model assumes linearity of the internal and external dose relationship based on rat TK
3. Specific metabolite data is not necessary since clearance from blood is enough to estimate parent form dose metrics
4. Low confidence of the model ability to describe the dosimetry of RDX
   A. Basis on a single TK study with some uncertainty in the analytical measurements
   B. Uncertainty of the metabolism between rat and mice (e.g. ethylbenzene)

Based on rat vs human extrapolation, can we accept the same linearity for rat vs mouse?

Potential solutions – mouse model

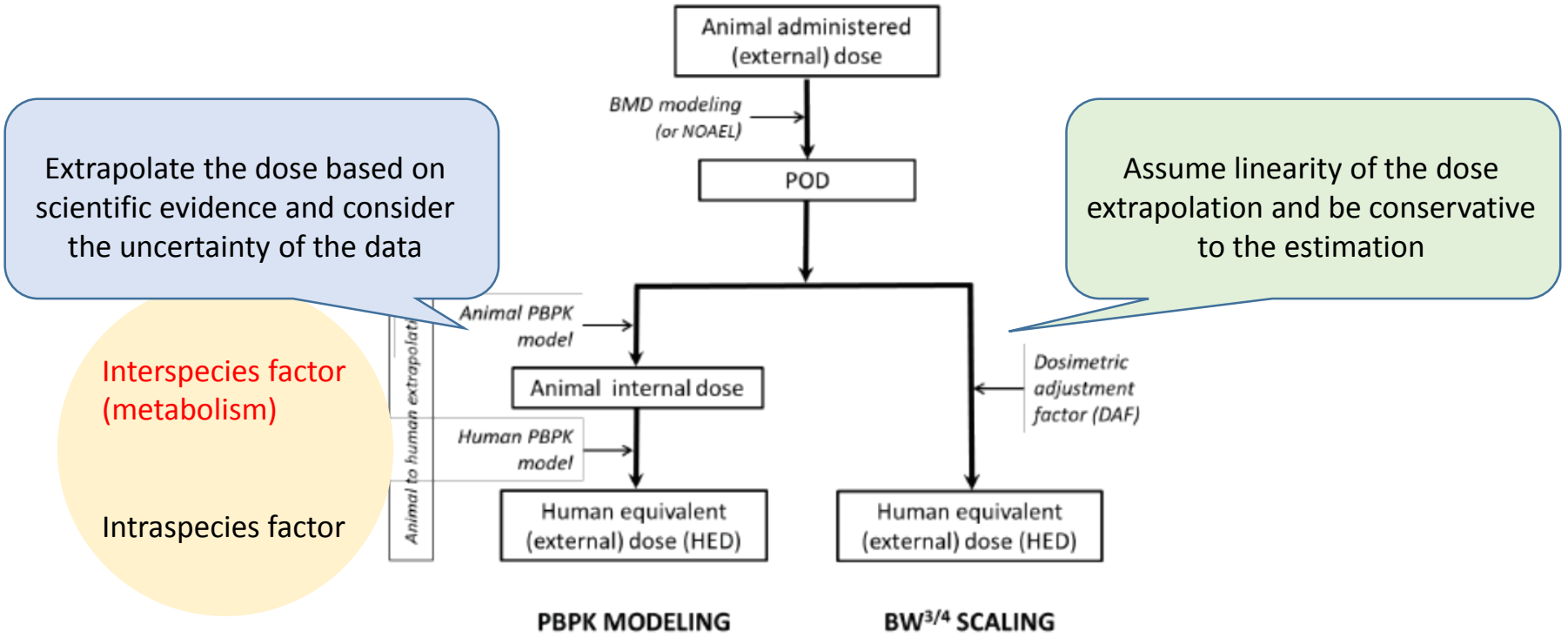


Figure 2-1. Conceptual approach to dose-response modeling for oral exposure.