Integration of time-related factors in dose-response analysis and exposure assessment

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ECETOC Chronos & Kairos: Understanding time in biology – time for next-generation risk assessment

Disclaimer

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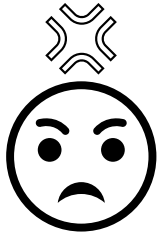
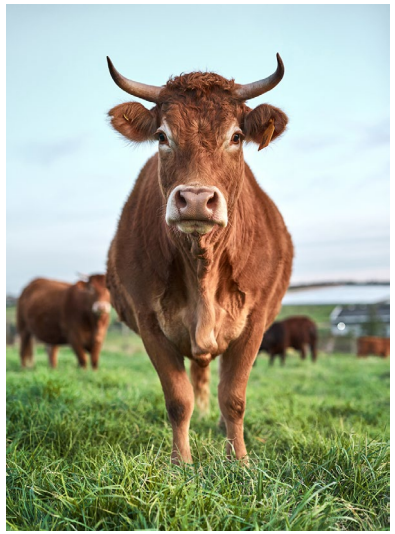
A common medium of exchange or comparison

The primary limitation of a barter system is the lack of a standardized measure of value

Jack



Jack's mom



Magic beans??

- Money is a generally accepted medium of exchange to facilitate trade by factoring in, for example, supply and demand, perceptions of value, forms (e.g., coins, paper notes, digital currency), inflation/deflation, and economic and political stability
- Time is a common medium of space comparison by factoring in, for example, distance, velocity, form of transportation (e.g., air, car, walk), and weather

“Dose” (or concentration) is the common medium of comparison in risk assessment

Risk estimate is a function of hazard and exposure

Hazard

- Dose reflects “responses” or “lack of responses”
  - Lowest Observed Adverse Effect Level (LOAEL) is the lowest dose at which an adverse effect is observed
- Dose also reflects “time”
  - LD_{50} (LD stands for Lethal Dose) is the dose, given all at once, which causes the death of 50% of a group of test animals
  - Reference Dose (RfD) is a maximum dose a person can be exposed to on a daily basis without an appreciable risk of adverse health effects

“Dose” (or concentration) is the common medium of comparison in risk assessment

Exposure

- Exposure dose is a function of available residues and personal behaviors (such as food & water consumption, use patterns, activities), which are represented using “time” (duration, frequency)

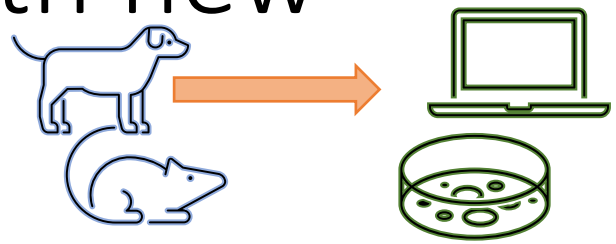
Risk

- Risk can be quantified as a margin of exposure (MOE), for instance, the ratio of the RfD to the exposure estimate.

Risk assessment is a pragmatic approach

- Animal toxicity studies are conducted for varying durations, e.g., acute, 14–28-day, subchronic (90-day), one-generation, two-generation, and chronic (1.5-2-year) studies
- Human exposures can vary widely in durations and frequencies
- Chemical risk assessment is a pragmatic approach that does not derive a RfD or an exposure estimate for every conceivable “Chronos & Kairos” scenario
- Both RfD and exposure estimates are designed with a degree of conservatism to account for variability and uncertainty of various factors, including “time”

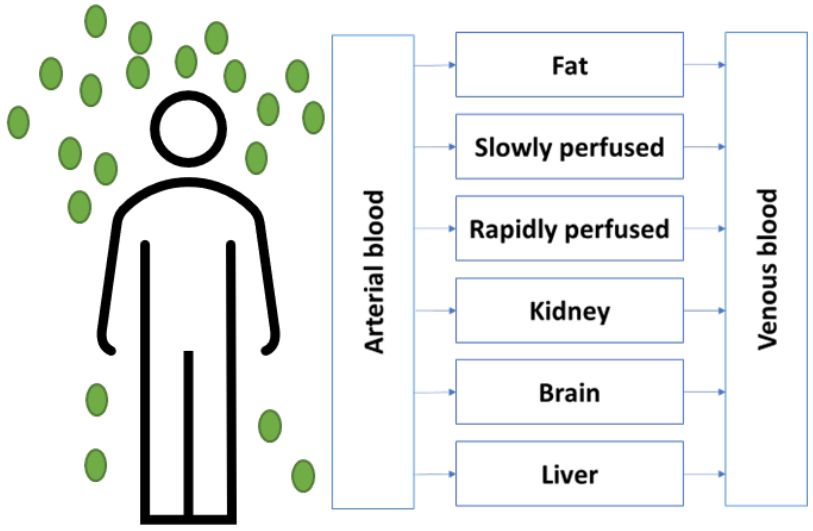
Replacing *in vivo* toxicity studies with new approach methods (NAMs)

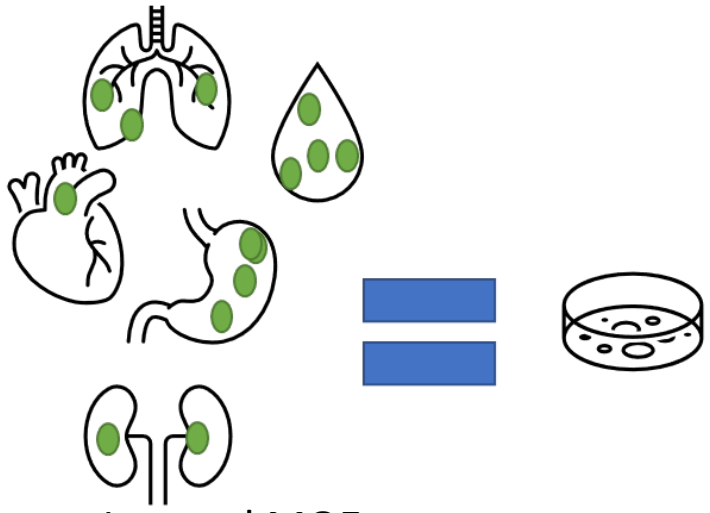


- Some questions proposed for this workshop
  - How to interpret the influence of time window, exposure duration and frequency, and effect development in *in vitro* assay battery?
  - What is the biological transition over time in an adverse outcome pathway (AOP)?
- To address these questions, several key principles in *in vivo*-based risk assessment apply
  - Risk can be quantified as an MOE (hazard vs. exposure)
  - Exposure assessment is conducted separately from hazard assessment
  - Risk assessment does not require estimating MOEs for all possible time scenarios, because conservatism is incorporated in hazard/exposure estimates
  - Dose is the common metric for comparison

Which dose?

Unlike *in vivo* studies, where a point of departure (POD) is based on an external dose, an *in vitro* POD is typically equivalent to an internal dose





External MOE = $\frac{converting\ in\ vitro\ POD\ to\ external\ conc}{exposure\ estimate}$

Internal MOE = $\frac{in\ vitro\ POD}{converting\ exposure\ estimate\ to\ internal\ conc}$

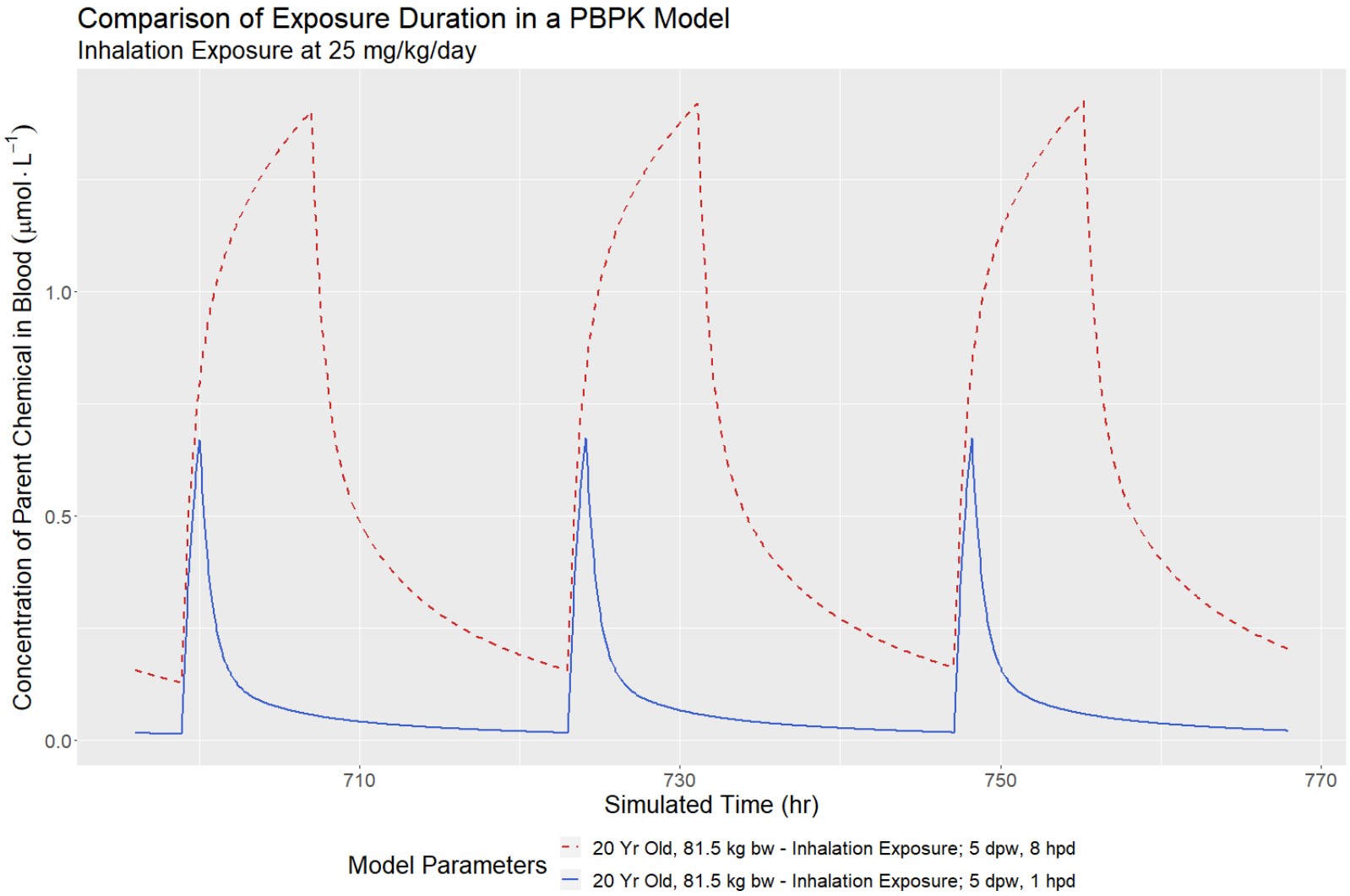
Converting between external and internal dose: physiologically based kinetic (PBK) modeling

PBK modeling

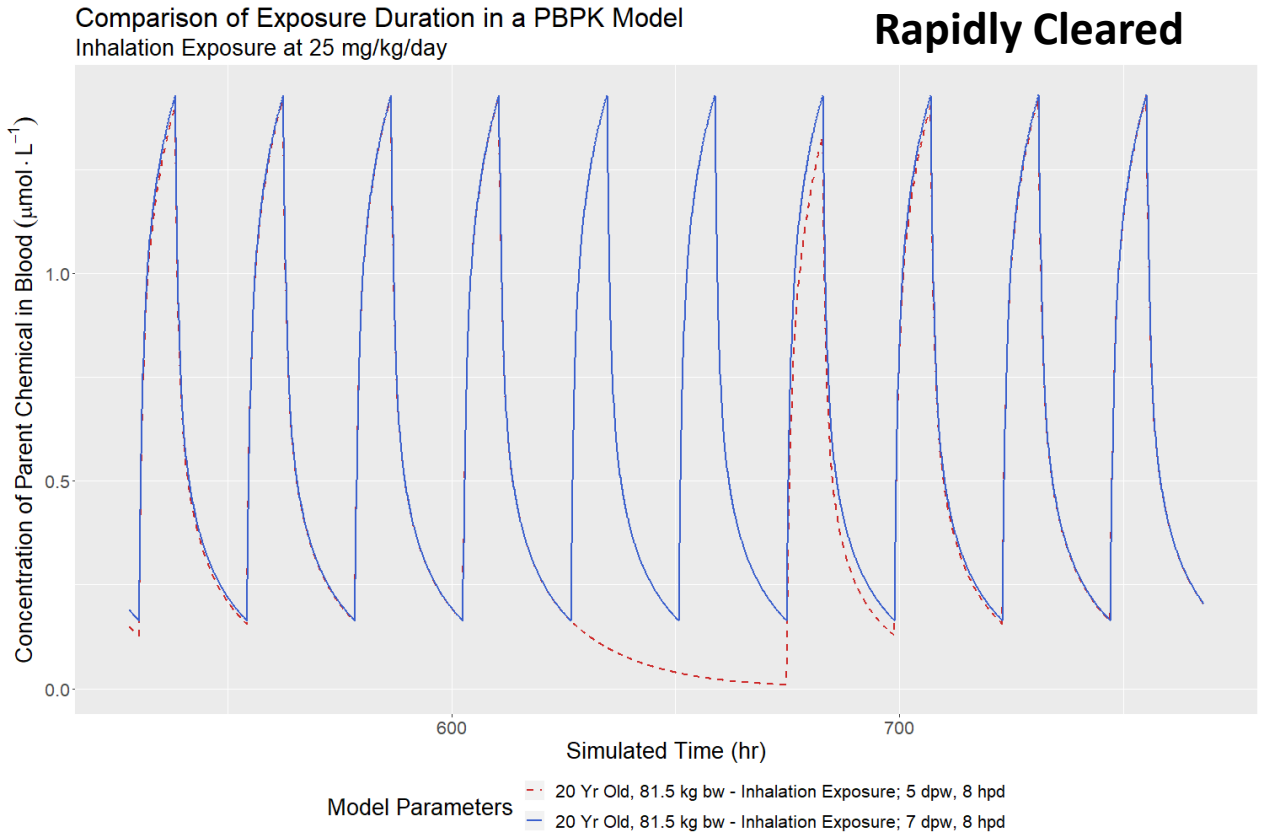
- A PBK model is a mathematical representation of the absorption, distribution, metabolism, and excretion processes

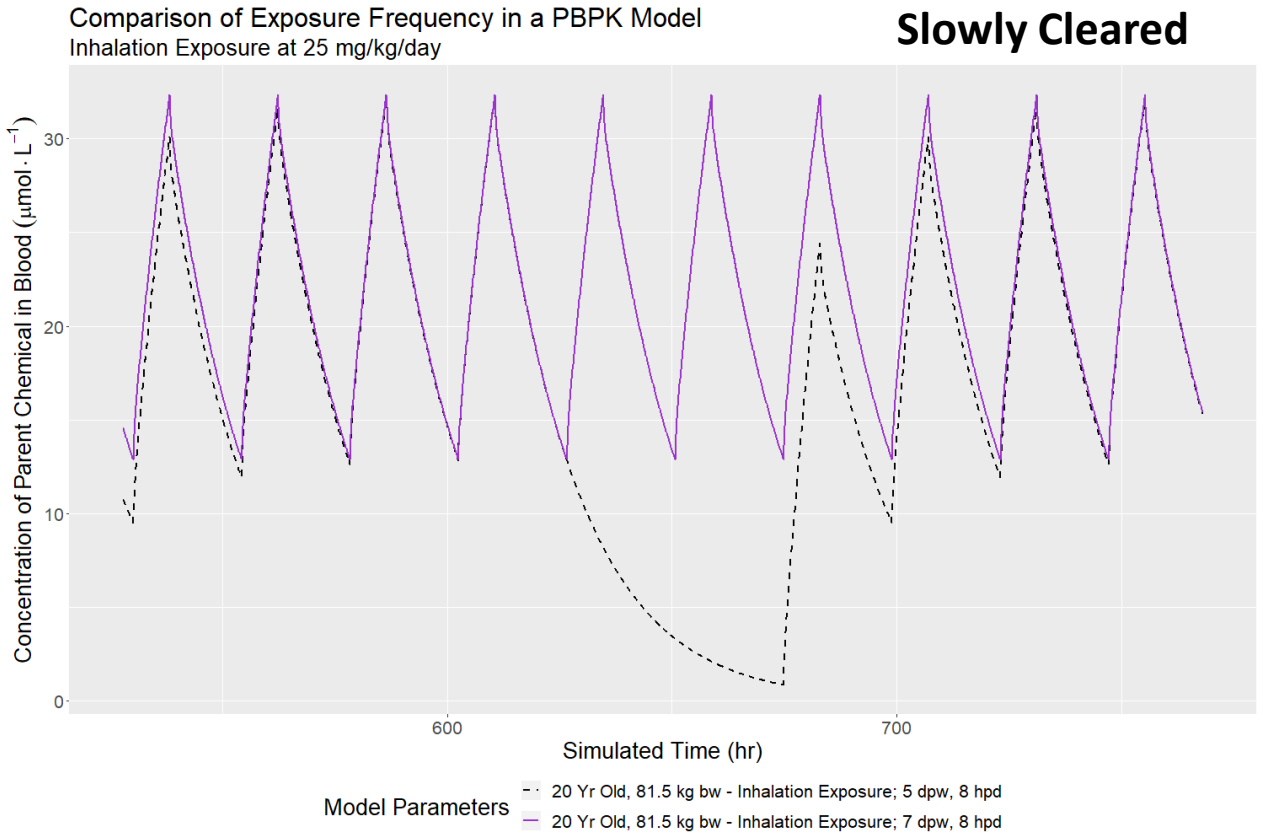
- Given an external dose, a PBK model predicts plasma/tissue concentrations based on
  - Physiologic and anatomic characteristics, including specific time window
  - Physiochemical properties of a chemical and biochemical processes
  - Exposure scenarios (routes, duration, frequency)

PBK models incorporate exposure duration



PBPK models incorporate exposure frequency





Considering a pragmatic approach

- It is acknowledged that the currently available *in vitro* models have a series of limitations, such as the lack of *in vivo*-like functionality, uncertainty related to adverse vs. adaptive responses to chemical exposure, and the time between exposure and response can differ between *in vitro* and *in vivo* situations
- Uncertainty concerning “time” issues might not significantly affect the risk estimate when an adequate level of “conservatism” is expected to be integrated into the selection of an *in vitro* system
  - *in vitro* testing does not account for the self-repair ability of cells
  - Even if a chemical demonstrates activity *in vitro*, it may not be toxic to the whole organ because other cells in the organ may compensate the imbalance
  - A battery of *in vitro* assays that cover a sufficient number of biochemical and cellular biomarkers could gauge the degree of perturbation in a toxicity pathway, without considering adaptative responses

Roggen 2011 (PMC3112250); Zhang 2018 (PMC6141783);Madorran 2020 (PMC7202182)