2026 SOT Annual Meeting & ToxExpo
Session: ADME/Toxicokinetics II
Abstract/Poster #: 4575/D349
Wednesday, March 25, 2026
1:45 PM – 4:15 PM

GRADIENT

Considerations for Appropriate Application of One-Compartment Toxicokinetic Models to Assess Per- and Polyfluoroalkyl Substances (PFAS) Exposures

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Background and Purpose: A one-compartment (OC) model is the simplest form of a toxicokinetic model where the entire body is considered a single, homogenous unit. This is unlike physiologically based (PB) models that characterize the movement of substances between different compartments within the body (*e.g.*, blood, bone, organs). A key advantage of OC models is the reduced data needs compared to PB models, allowing for broader applications. A good example of this is with per- and polyfluoroalkyl substances (PFAS) OC models, which have been developed to characterize PFAS exposures in impacted communities. These models have been useful for PFAS research and in public health contexts; however, their limitations can be overlooked, and such models can be used inappropriately. In this analysis, we review several OC models that have been used for risk assessment, compare the models' strengths and limitations, demonstrate how specific inputs can impact model results, and propose a list of considerations to inform whether use of the OC model is appropriate.

Methods: We identified OC PFAS models for inclusion based on the following considerations:

1) The model was developed for human exposure characterization;
2) The model was developed/updated in the last 15 years;
3) Data used in development and calibration were well described;
4) Model validation had been performed; and
5) The model had been applied in risk assessment.

We compared model features and evaluated how differences between them impact model outputs by running them with the same hypothetical exposure scenarios.

Results: We reviewed publications that developed or applied OC models, including models developed as part of the C8 Health Study, by the Minnesota Department of Health, and by the Agency for Toxic Substances and Disease Registry (ATSDR). All models include variables for intake dose, clearance rate (calculated based on half-life [t1/2]), and volume of distribution(Vd). The simplest OC models reflect steady-state conditions, while dynamic models include changes in parameters over time. Some models incorporate additional variables (*e.g.*, placental transfer, lactation, menstruation) while maintaining an OC structure. A few models incorporate background PFAS exposures in their calculations. The choice of values for input variables, such as Vd and t1/2, can have significant impacts on model outputs. For individuals, behavioral (*e.g.*, use of PFAS-containing consumer products) and physiological (*e.g.*, kidney function, lactation) factors can impact PFAS intake and clearance rates, and this information is often unavailable. Implementations of OC models rely on averages published in scientific literature for input values, which individually can vary by up to two-fold. We demonstrate that, together, these choices can have compounding (*i.e.*, four-fold or higher) impacts on model predictions..

Conclusions: While OC models all share a fundamental structure, the differences between models highlight the importance of careful planning when selecting which model to use. Key considerations include:

1) What is the study question that the user wants to address (*e.g.*, characterizing exposure for a particular community *vs.* establishing exposure limits)? Does the study question align with the original objectives driving model development?
2) What information is available about the target population being modeled? Does this population share characteristics (*e.g.*, age range, pregnancy history, degree of exposure) with the population that was used in model development?
3) How will the model be used to draw conclusions about exposure?

Given the simplicity of OC models, they are better suited to estimate a plausible range of values (*e.g.*, 5^{th}-95^{th} percentile) rather than a specific point estimate. If there are characteristics of the target population that deviate significantly from underlying model assumptions, then the model may not produce valid results. We identify here examples of invalid applications, such as using a model developed for a community impacted by drinking water contamination to characterize a different population where water concentrations are low compared to other sources; applying central tendency physiological parameters to individuals with very high or low values; and using a steady-state model when parameters are in flux over time. Careful consideration of model design and data needs is essential to obtaining outputs that are sufficiently accurate to address the study question.