WHITE PAPER

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The European Chemicals Agency Develops Comprehensive Toxicokinetics Database

Powerful Data to Support Chemical Safety and Causation Analyses

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The new mammalian toxicokinetics database MamTKDB 1.0, covering 4,013 entries on 1,407 unique chemicals, was created by the Norwegian Institute of Public Health (NIPH) and the European Chemicals Agency (ECHA). Published this month (Hofer et al. 2021a), MamTKDB 1.0 contains 3,927 elimination half-lives that are attributed to different administration regimens and doses, routes, vehicles, and study durations in a dozen different animal species and humans, making it one of the most comprehensive kinetics databases available today. NIPH and ECHA curated, analyzed, and combined existing compilations of kinetics data and also extracted previously sequestered information from a variety of sources, including the following:

- The European Food Safety Authority's EU Draft Assessment Reports
- European biocide dossier study summaries
- Registration dossiers under the European regulation Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)
- The REACH Candidate List
- European Public Maximum Residue Limit Assessment Reports by the European Medicines Agency
- Published scientific studies (e.g., Arnot et al. 2014).

The main substance groups in this database are pesticides, pharmaceuticals, and persistent environmental contaminants, including 113 entries on per- and polyfluoroalkyl substances (PFAS) and 208 entries on polychlorinated biphenyls (PCBs). The compiled data offer powerful information for assessing the safety or risk associated with chemical exposures. Conversely, it can also introduce scientific pitfalls if used with insensitivity to principles of applied kinetics or their underlying scientific foundations. In well-considered anticipation thereof, the authors of MamTKDB 1.0 published an article leading up to the official release of this database (Hofer et al. 2021b) that not only describes the scope of the data and its comprehensiveness, but also alerts the knowledgeable reader to data limitations that necessitate nuanced expert interpretation.

The importance of kinetics in risk assessment

Kinetics describes the disposition of a chemical in the body over time: its absorption, distribution, metabolism, and excretion. Kinetics is the rate-determining step for the manifestation of toxicity if a chemical's elimination half-life is longer than its toxicodynamic half-life (i.e., physiological recovery from toxic insult) (Rozman and Doull 2000). Understanding and using the power of kinetics in the context of toxicodynamics enables risk assessors to determine the likelihood of causality of an effect from a specific chemical exposure. The breadth and granularity of MamTKDB 1.0 make it valuable in aiding in the assessment of bioaccumulation, as well as in reducing uncertainty in risk assessment.

How kinetics can be used to answer critical questions regarding time and causality

Toxicologists employ kinetics in a multitude of applications, from therapeutic uses to environmental exposures to poisonings, across acute, chronic, or intermittent exposures via ingestion, inhalation, dermal contact, or other routes. Application of kinetics can allow toxicologists to precisely calculate systemic concentrations or body burden of a chemical at any given time during or after exposure. It allows the back-calculation of previous blood levels at time points of interest, and it allows the prediction of residence time of a chemical in the body after cessation of exposure.

Example

Hours after an accidental occupational exposure, a worker's measured blood level of a toxicant can be used—in combination with the chemical's elimination half-life and other kinetics parameters—to back-calculate the original exposure dose.

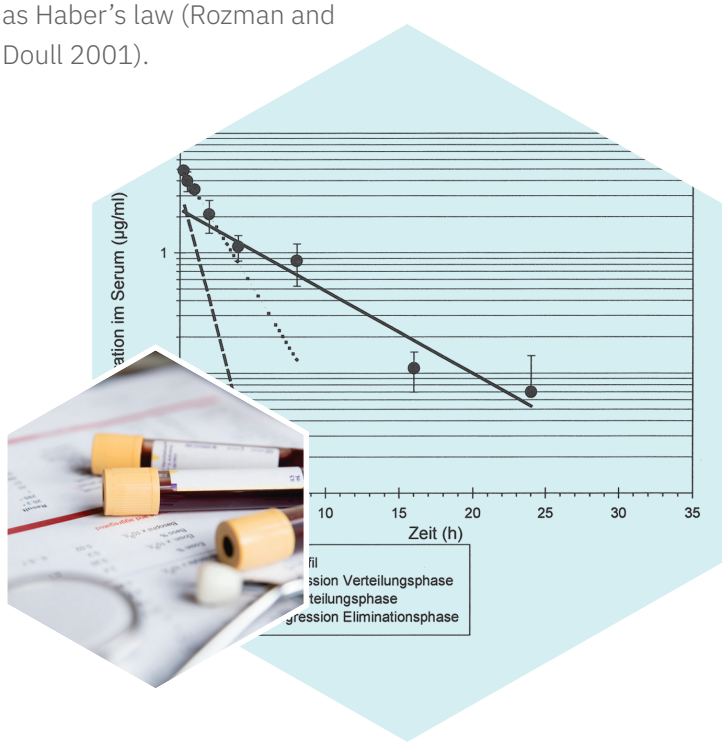
Kinetics provides the basis for the quantitation of bioaccumulation and the precise calculation of maximum achievable steady-state levels during continuous exposure, as well as how long it takes to reach steady-state conditions.

Example

The presence of a persistent contaminant in a regularly used consumer product can lead to detectable concentrations of the contaminant in the consumer's bloodstream. Knowledge of the elimination half-life of that contaminant can be used to calculate anticipated blood levels for the affected consumers. The comparison of calculated values with clinical measurements can be used to understand the potential of additional exposure pathways. Furthermore, a comparison of blood concentrations between affected consumers and animal data enables risk assessors to evaluate the potential for adverse effects.

Using kinetics in regulatory context

Understanding species differences in the disposition of chemicals in the body allows for the quantitative comparison of animal and human data. When the required kinetics data are available, uncertainty factors can be reduced or eliminated altogether. Furthermore, knowledge of kinetics and exposure enables toxicologists to assess the use of auxiliary risk assessment tools such as Haber's law (Rozman and Doull 2001).



Example

The U.S. Environmental Protection Agency (USEPA) Reference Dose/Reference Concentration (RfD/RfC) Technical Panel (USEPA 2002) suggested the inclusion of kinetic information early in the process of developing safe lifetime exposure levels. It established "pharmacokinetic differences among the species" as a decision-making factor in choosing appropriate uncertainty factors. USEPA also identified the applicability of Haber's law under continuous exposure—which leads to kinetic steady state, depending on the exposure duration and the compound's elimination half-life.

Safety assessments or regulatory dossiers often necessitate the use of toxicological data from structural analogues to address data gaps that exist for a chemical of interest—especially if the generation of new animal data is disapproved. Demonstrating similarities in kinetics between parent compound and analogue is a key step in the justification of read-across.

Example

ECHA lists information on the toxicokinetic properties of the parent compound and its read-across substance as supporting evidence for read-across. ECHA's Read-Across Assessment Framework also emphasizes the importance of understanding toxicokinetic interactions among components of mixtures for read-across cases involving multi-constituent substances (ECHA 2017). MamTKDB 1.0 contains data from structural analogues and congeners that were previously widely dispersed across individual regulatory documents. They can now be readily extracted for comparisons and analyses as demonstrated by the authors (Hofer et al. 2021b).

Application of kinetics at Integral Consulting Inc.

Integral risk assessors apply toxicokinetic information to questions of exposure and causality. For example, we use toxicokinetics to assess whether an unintentional chemical exposure is likely responsible for health effects. A straightforward kinetics assessment can illuminate whether the onset of symptoms is temporally consistent with body burdens at the time when symptoms are recorded.

Conclusions

MamTKDB 1.0 provides risk assessors with easy-to-find kinetics data that can be used for initial estimates as well as for deep-dive analyses. The consideration of kinetics in addition to dynamics and exposure enables risk assessors to estimate uncertainty, justify read-across, ascertain causality, and develop a holistic assessment. In addition, the completeness of this approach also supports simple risk communication.

Dr. Kristian Fried holds doctoral degrees in both chemistry and toxicology. He is certified by the American Board of Toxicology and by the European Register of Toxicologists. Dr. Fried has extensive experience in the chemical and consumer product safety and stewardship sectors and has been appointed Adjunct Assistant Professor for his teaching of human risk assessment at Rutgers University. With specific expertise in human health sciences, environmental toxicology and fate, as well as applied regulatory toxicology, Dr. Fried's professional practice extends from occupational safety to consumer exposure to cleaning and fabric care products, cosmetics, and therapeutic applications. In his previous leadership roles in corporate toxicology, Dr. Fried developed strong analytical and strategy skills in the management of consortia work regarding scientific fundamentals as well as ingredient defenses.

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