Development of ultra-high-throughput IVIVE for Tier 0 prioritization


Use of new approach methodologies for chemical safety decisions depends on appropriate translation between internal dose and an exposure context relevant to human exposure. Information on chemical absorption, distribution, metabolism, and excretion—termed in vitro to in vivo extrapolation (IVIVE)—is essential to this approach. While the conceptual framework for IVIVE is rapidly developing, there are significant gaps in the metabolism data required to implement the approach. As such, IVIVE is applicable for a small fraction of compounds currently in commerce, driving a need for tools to computationally predict the required parameters. One of the most critical—and difficult to measure—parameters is intrinsic clearance, which describes the rate at which a compound is biotransformed. Existing tools for de novo clearance prediction suffer from several limitations resulting from the fact that these tools are developed to predict structures for drug-like compounds that fall into a much narrower chemical space than environmental chemicals. To facilitate the development of our own clearance models we have created a MySQL database containing clearance information, chemical identifiers, chemical structures, physiochemical properties, etc. We have used this data to develop preliminary models using machine learning and quantitative structure-activity relationship (QSAR) based analysis.

Implications:
ACC-LRI funded efforts to develop a high-throughput (HT)-IVIVE methodology substantially improved the utility of high-throughput in vitro assays for chemical prioritization and Tier 1 evaluation by allowing rapid estimation of oral equivalent doses for comparison with estimated exposure. This work has culminated in inclusion in the Office of Chemical Safety and Pollution Prevention’s draft Strategic Plan for implementation of alternative test methods. However, the approach is hindered by the need to generate in vitro clearance data.

There is currently no reliable approach for incorporating dosimetry considerations into Tier 0 (i.e., ab initio) prioritization. As such, the use of dosimetry models such as high-throughput in vitro to in vivo extrapolation is limited by generation of experimentally derived kinetic data. To keep pace with the Tier 0 computational approaches for estimating hazard, the field needs a methodology that can provide reasonable estimates of chemical clearance without requiring analytical chemistry. While prediction algorithms exist for intrinsic clearance, our experience using existing tools for Case Studies 1, 2, and 3 revealed significant shortcomings in current metabolism prediction tools.

Collaborations: EPA NCCT, EPA NERL

Key words: IVIVE, metabolism, QSAR, machine learning

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