Improving Exposure Models and Integrating Exposure and Risk Information for High-Throughput Chemical Screening (Prioritization) and Higher Tiered Assessments

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Thousands of chemicals require ecological and human health assessment; however, relatively few measured data required for these assessments exist. There are practical limitations to testing and measuring all these chemicals in the environment; therefore, predictive models are needed. Uncertainty in chemical exposure, hazard, and risk assessment exists whether the data are measured or predicted. This project improves models and data for chemical assessment to support the American Chemistry Council's Long-Range Research Initiative (ACC-LRI) goals to (i) advance scientific tools for chemical assessment (method development) and (ii) establish a basis for safe chemical use to enhance public confidence and decision-making (application, evaluation, testing or "ground-truthing" of methods).

We are advancing exposure science through the development and evaluation of chemical property databases and through the development, testing and improvement of predictive quantitative structure–activity relationship (QSAR) and mechanistic mass balance models for chemical fate and transport. We are integrating exposure and hazard information for risk estimation through the development and evaluation of new tools for linking the data (e.g., new data and models for biotransformation and degradation rates), and to improve chemical safety testing technologies (e.g., develop and apply *in vitro* models to better interpret *in vitro* bioassay data). We are evaluating models to (i) address uncertainty in the models and available measured data, (ii) further establish a scientific foundation for applying models for decision-making, (iii) foster public and regulatory confidence in their application, and (iv) prioritize future research needs. The specific components that comprise this project are as follows:

1. Evaluate chemical dermal permeation data and models used in regulatory assessments.
2. Develop and evaluate databases of *in vitro* biotransformation (metabolism) rates in humans and QSAR models to predict biotransformation (metabolism) rates from chemical structure.
3. Develop and improve "generic" physiologically-based pharmacokinetic (PBPK) models.
4. Evaluate and refine exposure and risk assessment models like RAIDAR, RAIDAR-ICE and PROTEX.
5. Develop and apply *in vitro* mass balance models to improve the interpretation and use of data from *in vitro* bioactivity assays.
6. Develop databases and QSARs for chemical partitioning and environmental degradation.
7. Refine and improve the Bioaccumulation Assessment Tool (BAT).
8. Critically evaluating bioaccumulation and toxicity criteria in common PBT assessment frameworks.

Implications: This research builds capacity to evaluate and better understand chemical hazard, exposure and potential risks to humans and the environment through the development and evaluation of measured datasets and predictive models.

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Peer-reviewed publications:

Arnot, J. A., Toose, L., and Armitage, J. M. A critical examination of bioaccumulation and toxicity criteria. *Manuscript in preparation.*

Arnot, J. A., Toose, L., Armitage, J. M., Embry, M., Foster, K. L., and Hughes, L. A quantitative weight-of-evidence framework for bioaccumulation assessment. *Manuscript in preparation.*

Arnot, J. A., Toose, L., Armitage, J. M., Sangion, A., Li, L., and Bonnell, M. A critical evaluation of ecological hazard and risk methods for chemical screening and prioritization. *Manuscript in preparation.*

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Sangion, A., Papa, E., Armitage, J. M., Toose, L., and Arnot, J. A. Screening chemicals for biomagnification potential in humans. *Manuscript in preparation.*

Other publication(s):

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Armitage, J. M., Arnot, J. A. (2017). Application of mass balance modeling to facilitate the interpretation and evaluation of in vitro toxicity data.

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