CEFIC Long-range Research Initiative
Request for Proposals (RfP)

Title and Code Number

Human Exposure Assessment Framework for Complex Substances – **LRI-B22**

Background

Existing human exposure models were mainly developed and calibrated with data for mono-constituent substances[1]. In many situations, however, humans may come into contact with multiple chemicals simultaneously, as in the case of use of a formulated product containing multiple substances or upon the contact with a complex substance[2] (e.g. essential oils), which by definition is comprised of multiple individual constituents. The fact that these constituents may have different physicochemical properties makes complex substance exposure assessments particularly challenging.

This project aims to investigate the mechanisms and processes influencing **inhalation and dermal external exposure to multiple chemicals originating from a common source** (terminology aligned with WHO/IPCS framework, Meek et al., 2011) like a liquid complex substance. In this scenario, the interactions between the individual constituents of a complex substance may impact their exposure potential/bioaccessibility by governing the factors needed to predict the associated diffusion and mass transfer kinetics of inhalation and dermal exposures during and post-application, e.g. air-liquid and dermal-liquid partitioning equilibria. Appropriate solution thermodynamics models may be capable of offering a reasonable scientific explanation of the constituents' interactions effect to accurately predict the true nature of human external (co-)exposure and enable a "whole substance" approach to exposure assessment of complex substances.

An example of a simple solution thermodynamics model is the Raoult's law that can be applied when the constituents of interest are assumed to behave as if they were in an "ideal" liquid. The deviation from ideality, however, will increase with increasing differences between the molecular environments of the pure solute compared to that of the solvent. For such "non-ideal" liquids (e.g. solvent and solute has a large difference in polarity; non-hydrocarbon constituents are structurally diverse) it may be more appropriate to estimate air-liquid and dermal-liquid partitioning equilibria of substance constituents using other methods, e.g. UNIFAC[3].

UNIFAC is a mechanistic equation-of-state model that uses the functional groups present on the molecules in a solution to calculate the activity coefficients characterizing inter-

[1] A mono-constituent substance is a substance made up of at least 80% of one main constituent and the impurities count for less than 20% of the composition of the substance.

[2] Here, the term complex substance denotes a substance of unknown or variable composition, complex reaction products or of biological materials (UVCB).

[3] UNIFAC – UNIversal Functional-group Activity Coefficients (see the link to the UNIFAC consortium for more details http://unifac.ddbst.de/).

molecular interactions[4]. These activity coefficients can be determined experimentally or computationally (Fredenslund et al, 1975). The information is then used to predict the equilibrium partitioning behavior of the molecules in the model system. More recently, attempts have been made to explore the utility of the UNIFAC method for advancing *in silico* dermal absorption models (Miller and Kasting, 2015) and for predicting phthalates emissions from polymer mixtures (Addington et al., 2018). In addition, the Advanced REACH Tool (van Tongeren et al., 2011) for worker exposure modeling already integrates the UNIFAC-based rules (Fransman et al., 2010, Gmehling et al., 2002), although, their predictive power has never been tested with measured data.

Objectives

The project is expected to increase current understanding of key mechanisms impacting inhalation and dermal external exposure of complex substances to allow derivation of realistic and representative exposure estimates. The results of this study should facilitate tiered approach to human exposure assessment of complex substances by determining circumstances, under which the interactions between complex substance constituents overrule the effect of other exposure determinants.

Furthermore, the findings may also lay groundwork for future development of improved computational tools to predict bio-accessibility of additives from polymer mixtures and elastomers for the purpose of human health exposure assessment and hazard classification.

Deliverables

The envisaged LRI research project is looking to compare external exposure assessment outcomes for constituents of complex substances using both the existing exposure models designed for mono-constituent substances and more refined tools capable to accurately account for interactions between multiple constituents in a complex substance.

The deliverables should include:

1. A knowledge base of how complex substance constituents (thermodynamically) interact with each other, how these interactions impact external exposure, and what general rules can be developed to describe these interactions;
2. A list of rules (i.e. a rule base) with a set of clear examples for different types of substances and exposure scenarios, for a mass-balance modeling approach to predict the quantity of a complex substance leading to potential inhalation and/or dermal exposure. Should a new model/tool be designed as an outcome of this project, it must be made publicly available along with supporting documentation (e.g. open code, manual guidance, etc.);

[4] Mean the non-ideal thermodynamic interactions between organic functional groups of chemical species at the exposure-contact media interface. They differ from toxicological interactions (which are out of scope of this project) that may lead to combined adverse effect (e.g. synergistic or antagonistic).

3. A prototype of a tiered human exposure assessment framework integrating basic and advanced human exposure models capable to predict external exposure to complex substances.
4. A final report containing an executive summary (2 pages max), a main part (max. 50 pages) and a detailed bibliography. It is expected that the project findings will be published in at least one peer reviewed journal, following by poster(s) and presentation(s) at suitable scientific conference(s). At least one publication shall be open-access.

Scope

It is advised that this project is structured in a manner that ensures regular delivery of the work products and timely review of the project deliverables by the LRI monitoring team.

The following activities are proposed to be included:

1. Gap assessment:
   - Literature review on the factors and mechanisms governing inhalation and dermal exposure to complex substances;
   - Identification of available measured exposure datasets (e.g. volatilization rates or partitioning coefficients) and/or recommendations to generate new data suitable for comparison with predicted exposure;
2. Identification of complex substances to focus on, covering potentially constituents of regulatory concern and/or of wide range of chemistries/properties. This should be done by the researchers in consultation with the LRI monitoring team based on a systematic analysis of relevant information.

NOTE: it is considered to be more feasible/practical to start investigating synthesized complex substances of pre-defined composition, assuming that the complex substances and formulated mixtures behave similarly in terms of the resulted external exposure. In the absence of good tools to assess the pre-mixed products, it is unreasonable to initiate the project with non-pre-mixed naturally occurring complex substances/UVCBs, where another layer of complexity of analytical characterization of the composition is introduced;

3. Scenario-based exposure modeling to selected complex substances for key worker and consumer exposure scenarios (to be identified by the researchers in consultation with LRI monitoring team) using:
   - Existing human exposure models (e.g. TRA, ART, ConsExpo, SkinPerm, Petrorisk, Product Intake Fraction).
   - Refined models (based on Raoultian and non-Raoultian solution thermodynamics models, or more complex quantum chemistry-based equilibrium thermodynamics models like COSMO-RS).

4. Series of dedicated scenario-based exposure experiments (where necessary) to generate evaluation datasets.
5. Evaluation of exposure predictions with measured data to conclude on the fit-for-purpose of the identified human exposure models and their practical implementation for the key exposure scenarios considered.

This project is expected to complement and leverage other LRI activities in this area (e.g. B13, ECO42, and B19). The successful research group is advised to take into account the findings and outcomes of such other work. Exploring possibility to use the deliverables in a regulatory context (e.g. REACH, BPR) is strongly encouraged.

Out of scope

Environmentally mediated exposure, oral exposure, assessment of systemic exposure (e.g. route-specific systemic absorption rates, PBPK), systemic bioavailability testing, mixture hazard characterization, biological/biomolecular interactions, combined risk assessment, chemical reactions between complex substance constituents, which lead to formation of new constituents.

Cost and Timing

Start in 2020, duration 18-24 months
Budget in the order of €300K

Partnering/Co-funding

Applicants should provide an indication of additional partners and funding opportunities that can be appropriately leveraged as part of their proposal. Partners can include, but are not limited to industry, government/regulatory organizations, research institutes, etc. Statements from potential partners should be included in the proposal package.

Fit with LRI objectives/Possible regulatory and policy impact involvements/ Dissemination

Applicants should provide information on the fit of their proposal with LRI objectives and an indication on how and where they could play a role in the regulatory and policy areas. Dissemination plans should also be laid down.

References

- Addington, C., 2018. ISES-ISEE 2018 annual meeting, 29.08.2018, Ottawa. Prediction of Composition and Emission Characteristics of Articles in Support of Exposure Assessment Cody Addington, Oak Ridge Institute for Science and Education, United States.
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1.5.12110.3/doc/ART%20Mechanistic%20model%20report_v1_5_20130118.pdf (last accessed on 01.02.2019).

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- Meek, M.E., Boobis, A.R., Crofton, K.M., Heinemeyer, G., van Raaij, M., Vickers, C., 2011. Risk assessment of combined exposure to multiple chemcials: a WHO/IPCS framework. Regulatory toxicology and pharmacology, 60, S1-S14.
- Miller, M.A., Kasting, G., 2015. A spreadsheet-based method for simultaneously estimating the disposition of multiple ingredients applied to skin. Pharmaceutics, Drug Delivery and Pharmaceutical Technology. DOI 10.1002/jps.24450.
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DEADLINE FOR SUBMISSIONS: September 1st, 2019

Please see www.cefic-lri.org/funding-opportunities/apply-for-a-grant/ for general LRI objectives information, project proposal form and further guidance for grant applications.