CEFIC-LRI ECO30

Executive Summary

Expanding the applicability domain of the chemical activity approach for hazard and risk assessment

The chemical activity approach has been proposed for applications in chemical hazard, exposure and risk assessment. The approach is considered complementary to other methods for interpreting and applying monitoring, modelling and testing data for chemical assessments; all of which have merits and limitations. Recognized merits of the chemical activity approach are that it has a strong theoretical foundation and physical-chemical basis and that it allows exposure and toxicity (effects) data to be presented in a common currency potentially fostering the communication of information used to make regulatory decisions.

The general objective of this project was to further evaluate the merits and limitations of the chemical activity approach for different chemical evaluation contexts. An extensive array of bioassay datasets were compiled, critically evaluated and examined as case studies using the chemical activity approach. Bioassay datasets in the project include in vivo tests with microorganisms, algae, invertebrates, and fish and in vitro cell-based assays for mammals. Physical-chemical property databases were collected and evaluated and new models for estimating chemical properties necessary for applying the chemical activity approach were developed. Mass balance models for in vitro and in vivo systems were developed and applied to better understand chemical fate and activity in these systems.

Some of the key outcomes of the project include (i) an expanded evaluation of the chemical activity hypothesis to various datasets, (ii) further evidence that chemical activity for baseline toxicity remains relatively constant across a range of species and test systems, exposure scenarios and life stages (La50 or Ea50 = 0.01 – 1), (iii) evidence that chemicals that can exert an additional specific or reactive mode of action exhibit a wider range of chemical activities corresponding to the response but can overlap with the baseline toxicity range, especially for more hydrophobic compounds, (iv) recognition of the limitations of the chemical activity approach for mode of action classification (similar issues with concentration based methods are also acknowledged), (v) further support that chemical activities corresponding to lethality or other adverse effects remain directly amenable to risk assessment activities, (vi) further support to propose an effective chemical activity threshold of 0.001 as an initial guideline for screeninglevel risk assessment of neutral organic chemicals that exert only baseline toxicity, (vii) iii improved and corroborated models for simulating chemical distribution in in vitro bioassays,(viii) recognition and characterization of the uncertainty in chemical property data for chemical activity calculations, (ix) recognition of the challenges in applying the chemical activity approach to certain chemicals, i.e., ionizable organic chemicals.

The utility of the chemical activity approach for hazard assessment depends on the objective of the exercise. The analyses conducted during the LRI-ECO30 project indicate that the approach can readily be applied to identify chemicals that exert excess toxicity, defined here as La50 or Ea50 < 0.001. For neutral organic chemicals with low to moderate hydrophobicity (log KOW < 4), the chemical activity approach may also be useful for identifying and/or confirming chemicals that exhibit specific or reactive Modes of Action (MOA). However, as noted above, lethal chemical activities in the baseline toxicity range were observed for hydrophobic chemicals assumed to operate via specific and reactive MOA in several LRI-ECO30 data sets. In

practical terms, identification of chemicals that exert excess toxicity is likely sufficient in the hazard assessment context. The results of the LRI-ECO30 project provide additional support for the use of the chemical activity approach for risk assessment, whereby as noted above, exposure and toxicity (effects) data can be presented in a common currency across multiple abiotic compartments (water, sediments, soil) and biota. Application of the chemical activity approach to high throughput in vitro bioassay data (e.g., ToxCASTTM) for hazard and risk assessment also appears to be feasible, but is currently subject to limitations related to characterization of test system parameters and low specificity for the assays considered at this time.

The project has directly led to five new publications in the scientific literature and contributed to the preparation, execution and completion of an ECETOC workshop and report on chemical activity. Several more manuscripts are in preparation as an outcome of the project including a critical review that will summarize merits and limitations of the chemical activity approach using case studies and provide interim guidance for selecting reference state chemical property information for estimating chemical activity.