Using High-Throughput Methods to Conduct Risk-based Prioritization of Chemicals for the EDSP

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A major challenge for regulatory authorities is how to assess risk for the large universe of untested chemicals for which there is human or ecological exposure. This chemical universe has been estimated to be 30K-50K unique substances. In particular, the US EPA Endocrine Disruption Screening Program (EDSP) is required to test 5-10K chemicals due to pesticidal use or their potential to contaminate drinking water. The EPA Computational Toxicology program is developing methods and models to prioritize this large chemical universe for further testing based on estimation of risk. The prioritization framework includes consideration of hazard, exposure and dosimetry. Hazard estimation combines in vitro high-throughput screening (HTS) assays plus QSAR and docking models within an adverse outcome framework. The EPA's ToxCast program, together with the US Interagency Tox21 program, has generated data for over 8500 chemicals using a variety of HTS assays for endocrine activity (e.g., ER, AR, TR). Additionally, a large-scale multinational effort is developing and evaluating QSAR and docking models to use and extend the HTS data, initially for the estrogen receptor. Results of this modeling effort will in turn drive further in vitro testing. EPA's ExpoCast program is developing quantitative exposure prediction models based on chemical properties and use patterns. These models allow rapid estimates of exposure potential for thousands of chemicals. Finally, for dosimetry, we are using a combined in vitro and modeling approach (called RTK or Reverse Toxicokinetics) to provide quantitative estimates of dose-to-concentration scaling. By combining quantitative in vitro potency estimates from ToxCast, concentration-to-dose scaling from RTK, quantitative exposure values from ExpoCast, and estimates of uncertainty, we can provide quantitative risk metrics at the pathway level (estrogen, androgen, thyroid) for hundreds to thousands of chemicals. The first use of these estimates as part of a FIFRA based review for risk based prioritization of chemicals for inclusion in the EDSP Tier 1 assay battery. And to make this information publically available EPA has recently launched the iCSS Dashboard a web application to allow easier access to, and analysis of, endocrine related hazard information for thousands of chemicals. *This abstract does not necessarily reflect Agency policy.*