Regulatory assessment and risk management of chemical mixtures: challenges and ways forward

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**Supplementary Material**

**Table S1:** Examples of relevant available exposure models and toxicokinetic models/platforms (part of the list are outputs from a JRC IPCHEM workshop)

| **Name / Tool** | **Description** | **Restricted to specific chemicals** | **Data type** | **Reference /links & Status** |
| --- | --- | --- | --- | --- |
| **Exposure** |  |  |  |  |
| US EPA Exposure tool box | EPA’s EXPOsure toolBOX (EPA ExpoBox) is a toolbox created to assist individuals from within government, industry, academia, and the general public with assessing exposure. It is a compendium of exposure assessment tools that links to guidance documents, databases, models, reference materials, and other related resources. EPA ExpoBox is organized according to the six tool sets. | Chemical Classes  Pesticides  Other Organics  Inorganics and Fibers  Nanomaterials | Use the advanced search interface to search an 700+ collection of tools for performing exposure assessments. The results will display a list of tools with a brief description | https://www.epa.gov/expobox  <https://cfpub.epa.gov/ncea/risk/expobox/efhToolSearch.cfm>  Continuously updated |
| USEtox | USEtox is a scientific consensus model endorsed by the UNEP/SETAC Life Cycle Initiative for characterizing human and ecotoxicological impacts of chemicals. Main output is a database of recommended and interim characterization factors including fate, exposure, and effect parameters. | Farfield exposure model (industrial releases) | Estimates the average amount of chemical that gets into the air, water, and soil; output: characterization factors including fate, exposure, and effect parameters | <http://www.usetox.org/>  Ongoing |
| ConsExpo  ConsExpo web | ConsExpo is a computer program that enables the estimation and assessment of exposure to substances from consumer products such as paint, cleaning agents and personal care products. The model is developed by the National Institute for Public Health and the Environment. | Substances from consumer products, e.g. paint, cleaning agents, personal care product | Estimation and assessment of exposure via inhalation, skin or oral intake | <https://www.rivm.nl/en/Topics/C/ConsExpo>  <https://www.rivm.nl/en/Documents_and_publications/Scientific/Reports/2016/december/ConsExpo_Web_Consumer_exposure_models_Model_documentation>  Active – several versions, continuous updates available from RIVM (NL) webpage |
| DustEx tool | DustEx is a model to assess exposure to semi-volatile substances from consumer products that are introduced into the indoor environment. | Semi-volatile organic compounds (SVOCs) released from solid material consumer products into indoor air | Assessment of exposure via inhalation of substance in gas phase or bound to airborne particles, dermal absorption from air, oral ingestion with dust | <http://www.rivm.nl/en/Topics/C/ConsExpo/Related_tools/DustEx_tool>  Ongoing |
| MCRA tool | MCRA stands for Monte Carlo Risk Assessment. MCRA is a web-based system for probabilistic exposure and risk assessment of chemicals in the diet. The MCRA system brings together statistical models, shared data and data uploaded by the user. MCRA 8 also provides Cumulative Exposure Assessment for chemicals grouped in a Cumulative Assessment Group for which a single health effect is considered relevant. | Food | Probabilistic exposure and risk assessment of chemicals in the diet, incl. chemicals grouped in a Cumulative Assessment Group for which a single health effect is considered relevant; exposure from other routes can be added in an Aggregate Exposure Assessment. | <https://mcra.rivm.nl>  Ongoing |
| Probabilistic Aggregate Consumer Exposure Model (PACEM) | Developed a person-oriented consumer exposure model, which was also used by Gosens et al. (2014) and Delmaar et al. (2014) to model aggregate exposure to parabens and diethyl phthalate, respectively. The performance of this higher tier tool was evaluated by comparison to the results obtained in a conventional lower tier assessment (see Section 1 of the Supplementary Information (SI)). The core of the developed model consists of a questionnaire database on biometric details and the C&PCP use data for 516 Dutch adults between 18 and 74 years old (Biesterbos et al., 2013). The product-use database contains a list of C&PCPs applied by each questionnaire respondent on a regular basis, the use amounts and frequencies for specified products, as well as the approximate time of day and body part of product application. | Consumer product ingredients | To take account of complex multi-route exposure scenarios | Gosens et al. (2014) and  Delmaar et al. (2014) |
| PROMISE© | PRObabilistic Methodology for Improving Solvent Exposure Assessment (PROMISE) | Solvents |  | Silken Inc.,( 2003)  Complete |
| Risk Assessment Identification And Ranking (RAIDAR) model | The Risk Assessment IDentification And Ranking (RAIDAR) Model is a screening level risk assessment model that brings together information on chemical partitioning, reactivity, environmental fate and transport, bioaccumulation, exposure, critical objective or effect levels and emission rates in a coherent system for assessing risk. | Farfield exposure model (industrial releases) | Estimates the average amount of chemical that gets into the air, water, and soil; brings together information on chemical partitioning, reactivity, environmental fate and transport, bioaccumulation, exposure, critical objective or effect levels and emission | <http://www.trentu.ca/academic/aminss/envmodel/models/RAIDAR100.html>  Ongoing |
| Stochastic Human Exposure and Dose Simulation (SHEDS) model | The SHEDS models are probabilistic models that can estimate exposures people face from chemicals encountered in everyday activities. The models are able to generate predictions of aggregate and cumulative exposures over time to inform risk assessments that protect human health. SHEDS can estimate the range of total chemical exposures in a population from different exposure pathways over different time periods given a set of demographic characteristics. SHEDS can also help identify critical exposure pathways, factors and uncertainties. | Nearfield exposure model (consumer products and in-home products) | Able to generate predictions of aggregate and cumulative exposures over time; from inhalation, skin contact, and dietary and non-dietary ingestion | <https://www.epa.gov/chemical-research/stochastic-human-exposure-and-dose-simulation-sheds-estimate-human-exposure>  Ongoing |
| Exposure Analysis Modeling System (EXAMS) | The Exposure Analysis Modeling System, first published in 1982 (EPA-600/3-82-023), provides interactive computer software for formulating aquatic ecosystem models and rapidly evaluating the fate, transport, and exposure concentrations of synthetic organic chemicals – pesticides, industrial materials, and leachates from disposal sites. EXAMS contains an integrated Database Management System (DBMS) specifically designed for storage and management of project databases required by the software. User interaction is provided by a full featured Command Line Interface (CLI), context-sensitive help menus, an on-line data dictionary and CLI users’ guide, and plotting capabilities for review of output data. EXAMS provides 20 output tables that document the input datasets and provide integrated results summaries for aid in ecological risk assessments. | Environmental pollutants | Interactive software application for formulating aquatic ecosystem models and rapidly evaluating the fate, transport, and exposure concentrations of synthetic organic chemicals | <https://www.epa.gov/exposure-assessment-models/exams-version-index>  Ongoing |
| Creme Food Safety | Creme Food Safety is a software service that can quantify total aggregate exposure from constituents and ingredients. | Food constituents and ingredients (pesticides, contaminants, additives, flavourings, packaging migratory compounds, microbial contaminants, heavy metals, crop treatment products, recipe ingredients) | Aggregate exposure to pesticides, contaminants, additives & other constituents; Europe, North/South America, Asia | <https://www.cremeglobal.com/products/creme-food-safety>  Ongoing |
| Creme Care & Cosmetics | Creme Care is a software tool for consumer analysis and safety assessment of personal care and cosmetic products. For each consumer, it reports what products are being used, when they are being used, and how often. With this powerful information, Creme Care allows you to test what impact the addition of cosmetic ingredients has on consumers. | Personal care and cosmetic products (e.g. body lotion, oral care, hydroalcoholics, shower products, cosmetics, air care products)  Colours  Flavours  Fragrances  Chemicals  Contaminants  Nanotechnology  Functional ingredients  Preservatives | Exposure from inhalation, dermal absorption, ingestion:  data from US and Europe | <https://www.cremeglobal.com/products/creme-care-cosmetics>  Ongoing |
| Creme RIFM | The Creme RIFM model provides a detailed aggregate systemic and dermal exposure assessment system for fragrance compounds. | Fragrance compounds | aggregate systemic and dermal exposure assessment system for fragrance compounds. The model has data to assess exposure for consumers across Europe and the USA | <https://www.cremeglobal.com/products/creme-rifm>  Ongoing |
| Creme Cumulative and Aggregate Risk Evaluation System Next Generation (CARES NG) | The Cumulative and Aggregate Risk Evaluation System Next Generation (CARES NG) CARES NG is a cloud-based probabilistic model that is built upon public data and used to estimate aggregate and cumulative exposure to pesticides | Pesticides | Is a cloud-based probabilistic software model facilitating multi-source, multi-route aggregate (for individual chemicals) and cumulative (for multiple chemicals) exposure | <https://www.cremeglobal.com/products/cares-ng>  Ongoing |
| BROWSE (Bystanders, Residents, Operators and Workers Exposure models for plant protection products) model | models currently used in the risk assessment of plant protection products (PPPs) to evaluate the exposure of operators, workers, residents and bystanders | Plant protection products | Calculates exposures for a range of pesticide applications  Models for key exposure scenarios covering different regions of the EU will be developed in order of priority based on consultation with stakeholders, implemented as user-friendly software, and tested with end-users. | <https://secure.fera.defra.gov.uk/browse/software>  Complete |
| Agricultural Operator Exposure Model (AOEM), BfR | Six validated models for typical scenarios of pesticide mixing/loading, and application outdoors including downwards and upwards spraying with vehicle-mounted/-trailed or hand-held equipment. As a major factor contributing to the exposure of operators, the amount of active substance used per day was identified. Other parameters such as formulation type, droplet size, presence of a cabin or density of the canopy were  selected as factors for particular sub-scenarios. | e.g. pesticides | Estimation of agricultural operator exposure | <https://mobil.bfr.bund.de/cm/350/joint-development-of-a-new-agricultural-operator-exposure-model.pdf>  Ongoing |
| HBM SIMULATOR | HBM Simulator is an easy-to-use software model that has been developed by Cefic LRI in collaboration with VITO, the Health & Safety Laboratory and the Summit Toxicology as part of the HBM4 project.  Runs on MATLAB Component Runtime 7.14 needs to be installed. | House hold, environmental chemicals | Human biomonitoring model “Understanding inter- and intra-individual variability in human biomonitoring spot samples“. | <http://cefic-lri.org/toolbox/hbm-simulator/>  Complete |
| MERLIN Expo | Large exposure modelling from source to human PBK models, MERLIN-Expo tool contains a set of models for simulating the fate of chemicals in the main environmental systems and in the human body | Environmental pollutants | Estimation of chemical release from source to target (human or animal) via several media (water, river, sea – land, farm – air) | <https://merlin-expo.eu/>  Active |
| ExpoCast | ExpoCast: Exposure Science for Prioritization and Toxicity Testing. Broadly and long-term, the ExpoCast program will foster novel exposure science research to (1) inform chemical prioritization, (2) understand implications of system response to chemical perturbations at the individual and population levels, (3) link information on potential toxicity of environmental contaminants to real-world health outcomes. | Environmental pollutants | ExpoCast will provide an overarching framework for science required to characterize biologically-relevant exposure in support of the Agency computational toxicology program. The overall goal of this program is to develop novel approaches and tools for evaluating and classifying chemicals, based on potential for biologically-relevant human exposure, to inform prioritization and toxicity testing | <https://cfpub.epa.gov/si/si_public_record_Report.cfm?dirEntryId=211811>  Ongoing |
| TERRACE, Terrestrial Runoff Modelling for Risk Assessment of Chemical Exposure | State-of-the-art tool for better prediction of concentrations of chemicals, such as pesticides and industrial pollutants, in waters entering river systems within a Geographical Information System (GIS). This system provided outputs of Predicted Environmental Concentrations (PECs) for use in risk assessment of chemical exposure. | Environmental pollutants | TERRACE consisted of three components: models which simulate hydrological runoff processes and associated pollutant transport; a database of parameters required for input to these models (e.g. information on topography, soils, geology, land-use etc), and mapping software. This mapping software acted as an interface between the models and the database, and as a medium for visualising model results. | <http://cefic-lri.org/toolbox/terrace/>  Complete - The TERRACE database is no longer compatible with current operating systems. |
| Estimation and Assessment of Substance Exposure (EASE) | The EASE model, which is a general model to predict workplace exposure to a wide range of substances hazardous to health, has been under development and in use since the early 1990s. EASE is a knowledge-based model used by regulators for assessing new and existing substances. | New and existing chemicals | The EASE model categorises occupational exposure with reference to historical data collected in the UK’s National Exposure Database (NEDB). | <http://www.hse.gov.uk/research/rrhtm/rr136.htm>  Ongoing |
| OECD Pov and LRTP Screening Tool | Software in a spreadsheet format containing multimedia chemical fate models. A tool for estimating overall persistence (POV) and long-range transport potential (LRTP) of organic chemicals at a screening level, A tool for comparative assessment of environmental hazard properties of different chemicals. Specifically designed to help identify potential POPs (Persistent Organic Pollutants) according to persistence and long-range transport metrics. | organic chemicals | Users can chose chemicals from a database installed in the Tool, or enter data for chemicals of interest, i.e. physical-chemical properties and degradation half-lives. It is possible to transport users’ own databases, and store them within the Tool. It is also possible to change model settings.  The result of model calculation is shown in both numerical and graphical outputs. | <http://www.oecd.org/env/ehs/risk-assessment/oecdpovandlrtpscreeningtool.htm>  complete |
| **Kinetics** |  |  |  |  |
| httk: High-Throughput Toxicokinetics | Functions and data tables for simulation and statistical analysis of chemical toxicokinetics (TK) using data obtained from relatively high throughput, in vitro studies. Both physiologically-based (PBTK) and empirical (e.g., one compartment) A Monte Carlo sampler is included for simulating biological variability and measurement limitations. | TK models can be parameterized for several hundred chemicals and multiple species. | Input Cl data, Fub and phisico chemical proprieties of the chemical.  These functions and data provide a set of tools for in vitro-in vivo extrapolation (IVIVE) of high throughput screening data (e.g., ToxCast) to real-world exposures via reverse dosimetry (also known as RTK).  Output time response curve in blood, other target organs and/or in urines. | John Wambaugh, Robert Pearce, Caroline Ring, Jimena Davis, Nisha Sipes, and R. Woodrow Setzer  <https://cran.r-project.org/web/packages/httk/index.html>  Active – several versions, continuous updates available |
| MEGen/Rvis | MEGen enables a user to describe physiology, biology and toxicology in order to output a set of mathematical equations that emulate the information supplied by the user and constitute a PBK model. | Any chemical for which data are available to parametrize the model | Several input parameter are needed to describe the chemical fate and the biochemistry and human/animal physiology.  Output time response curve in blood, other target organs and/or in urines. | <http://cefic-lri.org/toolbox/pbpkmegen/>  <http://xnet.hsl.gov.uk/megen/>.  Complete |
| Plethem | Freely available platform for rapid modeling across source to outcome using only in silico and in vitro data. – A generic 11 compartment diffusion limited PBPK model | Large library of chemicals and ability to import new chemicals  Drug  Environmental chemicals | High-throughput IVIVE model for extrapolating in-vitro measured point of departure to equivalent exposures.  In-vitro to In-vivo extrapolation model for extrapolating in-vitro measured metabolism values to predicted in-vivo values | <http://www.scitovation.com/plethem.html>  Ongoing by Scitovation |
| PKSIM | The Open Systems Pharmacology Suite contains different software tools and has been designed using a modular concept to allow efficient multi-scale modeling and simulation. The overall platform with its various software tools is implemented in a modular wa. The central software tools PK-Sim® and MoBi® make use of building blocks. While PK-Sim® is based on a whole-body concept, the focus of its counterpart, MoBi®, is at the molecular level. However, both tools extend to additional physiological scales | Drug | Building block concept: In PK-Sim, „Individual/Population“, „Compound”, “Administration Protocol”, "Formulation", and „Event“ are set up as separate and re-usable units. To create a simulation, building blocks are simply combined. In MoBi, these building blocks are defined in a way more usable for modelers: "Spatial Structure", "Molecules", "Reactions", "Observers", "Events", "Start Values" and "Passive Transport" | <http://www.systems-biology.com/products/pk-sim/>  available |
| PBK model for mixture review | A peer reviewed paper capturing all PBK models developed until December 15, 2016. Twenty two models were for binary mixtures, 5 for ternary mixtures, 3 for quaternary mixtures, and 5 for complex mixtures. | Drug  Environmental chemicals  mixtures |  | Desalegn et al., 2018, Computational Toxicology  Complete |
| SimCyp | It links in vitro data to in vivo ADME (absorption, distribution, metabolism, and excretion) and pharmacokinetic/pharmacodynamic (PK/PD) outcomes to help explore potential clinical complexities prior to human studies and support decision-making in drug development. | Drug | assisting in dose selection and informing product labeling | <https://www.certara.com/software/pbpk-modeling-and-simulation/?ap%5B0%5D=PBPK>  available with licence |
| Gastroplus  PBPKPlus  ADMET predictor | GastroPlus is a mechanistically based simulation software package that simulates intravenous, oral, oral cavity, ocular, inhalation, dermal/subcutaneous, and intramuscular absorption, pharmacokinetics, and pharmacodynamics in humans and animals | Drug | Integrate the data which has been collected and, within the context of a virtual animal or human model  Adult and paediatrics | <https://www.simulations-plus.com/software/gastroplus/>  available with licence |