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EDITORIAL

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TKPlate 1.0: An Open-access platform for toxicokinetic and toxicodynamic modelling of chemicals to implement new approach methodologies in chemical risk assessment

EFSA along with several national agencies and academic partners have developed an open-access platform: 'TKPlate 1.0' that integrates a number of physiologically-based kinetic models and toxicokinetic-toxicodynamic models used in human health, animal health and ecological risk assessment. These models allow the derivation of quantitative metrics related to toxicokinetic (TK) processes (what the body does to the chemical) and toxicodynamic (TD) processes (what the chemical does to the body) for hazard and risk characterisation. Such in silico new approach methodologies (NAMs) support the integration of mechanism-based understanding of chemical toxicity and the reduction of animal testing in risk assessment. Among NAM-based approaches, biologically-based models are increasingly applied in chemical risk assessment.

This editorial describes EFSA's TKPlate platform and its suite of models for humans, test species (rat, mouse, rabbit, dog), farm animals (cattle, sheep, pig, chicken) and species of ecological relevance. TKPlate 1.0 consists of a workflow with seven modules: (1) input module to set the model, the chemical-specific data, exposure patterns and related time scales, (2) forward dosimetry module to predict kinetic parameters and concentrations in blood plasma and organs of interests, (3) reverse dosimetry module to back-calculate exposure from an internal dose profile using, for example, blood and urine biomonitoring data, (4) toxicodynamic module for benchmark dose modelling on an internal dose basis, (5) dynamic energy budget module to assess the impact of chemicals on the life cycle of individuals and populations of species of ecological relevance, (6) MIXTOX module for deterministic risk characterisation from exposure to multiple chemicals, (7) an automated report summarising inputs provided by the user and outputs, graphs and datasets. We conclude with perspectives on current and future development of TKPlate.

1 | BACKGROUND AND RECENT DEVELOPMENTS

Risk assessment (RA) is a scientific process that underpins the main part of EFSA's scientific advice to risk managers and decision makers on food and feed safety, animal health and welfare, plant health, nutrition and environmental issues (European Commission, 2002). RA steps include hazard identification, hazard characterisation, exposure assessment and risk characterisation (European Commission, 2002; WHO, 2009). In RA of chemicals, hazard identification and hazard characterisation aim to determine safe levels of exposure that ensure the protection of human health, animal health and the environment. Exposure assessment aims to derive exposure metrics for a given chemical and species through the integration of occurrence and, for example in the case of humans, food consumption data. Finally, risk characterisation aims to quantify risk while comparing hazard and exposure metrics (EFSA Scientific Committee et al., 2019).

Since the 1960s hazard metrics have been derived as reference points/points of departure using toxicological data from in vivo studies carried out in test species such as rats, mice, dogs, rabbits, fish and daphnia to predict the effect of chemicals on human health, animal health and the environment. Occasionally such data can be identified from epidemiological studies or intervention studies in humans. For each chemical, the derivation of these reference points requires a thorough assessment of the available toxicological evidence using a weight of evidence (WoE) approach. Such a WoE approach entails three steps, (a) assembling the evidence into lines of evidence, (b) weighing the evidence taking three considerations into account: reliability, relevance and consistency, and (c) integrating the evidence to derive a reference point while assessing uncertainties (EFSA Scientific Committee et al., 2017). For human health and animal health RA, common examples of reference points and points of departures include no-observed–adverse-effect-levels (NOAEL), benchmark dose limits (BMDLs) and no observed effect concentrations (NOECS) or no effect concentrations (NECs) for ecotoxicological effects. These references points are then divided by default uncertainty factors to derive reference values, as safe levels. Examples of reference values for human health RA include health-based guidance values such as acceptable daily intake (ADI) for chronic exposure to regulated products (e.g. food and feed additives, flavourings, pesticides, food contact materials), tolerable upper intake levels (UL) for vitamins and minerals and tolerable daily intake (TDI) for contaminants (EFSA NDA Panel, 2006; Ingenbleek et al., 2021). A repository of hazard data published by EFSA from its chemical risk assessments, since its creation in 2002, is available as an open-source

database, the OpenFoodTox repository. OpenFoodTox contains substance characterisation, physico-chemical properties, links to EFSA outputs, applicable legislation and a summary of hazard data including toxicokinetic data, reference points and reference values for over 5700 food and feed chemicals (Benfenati et al., 2022; Dorne et al., 2021). Evolving from the traditional toxicological assessment of chemicals using test species, reduction of animal testing has been explored since the 1980s as part of the 3Rs (Replacement, Reduction and Refinement) principle and has increasingly become a priority for the international scientific community with a major aspect being the derivation of safe levels using non-animal methods.

In 2007, the National Research Council (NRC) of the United States (U.S.) published a seminar report on 'Toxicity Testing in the 21st Century: a vision and a strategy' which led to the Tox21 and ToxCast collaborative programmes across a number of U.S. Federal Agencies including the Environmental Protection Agency of the United States (US-EPA)'s National Center for Computational Toxicology, the National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP), the National Human Genome Research Institute/National Institutes of Health Chemical Genomics Center and the Food and Drug Administration (FDA) (NRC, 2007). Both Tox-21 and ToxCast programmes have generated huge databases of in vitro toxicity results for hundreds of thousands of chemicals and these have been integrated within the US-EPA's CompTox Chemicals Dashboard[1] first released in August 2016. The CompTox Chemicals Dashboard now contains data for over 1.2 million chemicals together with chemical information, *in silico* tools and other resources (NRC, 2007; Williams et al., 2021). In parallel, the US-EPA released the high Throughput TK 'HTTK'[2] tool which allows users to integrate TK information of chemicals using generic kinetic and PBK models for (quantitative) *in vitro-in vivo* extrapolation, i.e. '(Q)IVIVE'. These models can be parameterised with *in vitro* data to provide *in silico* predictions for thousands of chemicals from the CompTox Chemicals Dashboard, multiple exposure routes and a range of test species while propagating parameter uncertainty (Pearce et al., 2017; Wambaugh et al., 2019; Wetmore et al., 2015; Williams et al., 2017). These tools can be used to convert *in vitro* chemical concentrations from high-throughput screening experiments from Tox21 and ToxCast assays to real-world *in vivo* exposures using (Q)IVIVE. These approaches have now been integrated into the NIEHS Integrated Chemical Environment (ICE) tool[3] (Daniel et al., 2022; Wetmore et al., 2015).

In a parallel and complimentary approach in the EU, EFSA's Scientific Committee endorsed a scientific report in 2014 'modern methodologies and tools for human hazard assessment of chemicals'. This report examined available modern hazard assessment methodologies for human health hazard assessment that investigate TK and TD processes focusing on mechanistic understanding of toxicity within the mode of action (MoA) and adverse outcome pathway (AOP) frameworks. It reviewed available *in vitro* systems, physiologically-based kinetic (PBK) and PBK-dynamic models, (Q)IVIVE models, *in silico* models such as (quantitative) structure activity relationship (Q)SARs, as well as OMICs technologies. Also, EFSA's identification of priorities regarding new risk assessment methodologies and recommendations for further work benefitted from consultations with EFSA's scientific panels and its Scientific Committee, the European Chemicals Agency (ECHA), the European Environment Agency (EEA), the European Medicines Agency (EMA) and the European Commission (including the Joint Research Centre [JRC]) as well as national and international scientific advisory bodies including the Organisation for Economic Co-operation and Development (OECD), US-EPA, FDA and Health Canada. Overall, the development of open-access databases, *in vitro* models, generic PBK models and other *in silico* models for a range of species of interest to food and feed safety were identified as key priorities (EFSA, 2014).

In April 2016, ECHA held a scientific workshop in Helsinki where the term 'New Approach Methodologies (NAMs)' was used for the first time for non-testing methods and their use in regulatory science were discussed with national and international stakeholders (ECHA, 2016). Currently, the term NAMs is collectively used to refer to non-animal-based testing approaches including *in vitro*, *in silico* and *in chemico* methods for hazard identification, hazard characterisation and risk characterisation of chemicals. However, there is currently no consensus definition of NAMs throughout the scientific community (Cattaneo et al., 2023; ECHA, 2016). Such NAMs are included in integrated approaches to testing and assessment (IATAs), defined approaches for data interpretation (DAs), and performance-based evaluation of test methods by the OECD.[4]

2 | EFSA'S DEVELOPMENT OF *IN SILICO* MODELS AND GENERIC PHYSIOLOGICALLY-BASED KINETIC MODELS

EFSA has developed several *in silico* models including (quantitative) structure activity relationships (Q)SARs) using the OpenFoodTox data to predict toxicity of chemicals for several test species (rats, fish, bees, frogs, collembola, earth worms etc.) (Benfenati et al., 2019; Carnesecchi et al., 2020; Dorne et al., 2021; Ghosh et al., 2020; Lavado et al., 2022; Toropov et al., 2022). All these models have been integrated in the open-source VEGA Hub[5] and the OECD QSAR toolbox. OpenFoodTox 2.0 is available for download from EFSA's Knowledge Junction[6] on Zenodo and can also be explored using an online dashboard.

[1] https://comptox.epa.gov/dashboard/
[2] https://github.com/USEPA/CompTox-ExpoCast-httk
[3] https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-ice/ice
[4] https://www.oecd.org/chemicalsafety/risk-assessment/iata/
[5] https://www.vegahub.eu/
[6] https://zenodo.org/records/8120114

Since 2015, EFSA has been developing kinetic, generic PBK, QIVIVE and TKTD models for species of relevance to its remit including humans, test species and species of ecological relevance through procurement and grants. Development of these models required collection of data on physiological parameters in relevant species, development of generic models as algorithms implemented in the freeware R, publication of physiological data and model codes on EFSA's Knowledge Junction and model evaluation using case studies comparing predictions with experimental data.[7] Overall, these generic kinetic, QIVIVE and PBK models have been developed for humans, test species (rat, mice, dog, rabbit), farm animals (pig, cattle, sheep, chicken) and fish species (rainbow trout, zebra fish, fathead minnow, European stickleback) (Bass et al., 2018; Dorne et al., 2021; Grech et al., 2019; Lautz, Dorne, et al., 2020; Lautz, Hoeks, et al., 2020; Lautz, Nebbia, et al., 2020; Testai et al., 2021). In addition, the standard dynamic energy budget model (DEB) has also been computed in R using available eco-physiological and life cycle trait data for over 2500 species from the open access Add-my-Pet database (Baas et al., 2018).

3 | TKPLATE 1.0: GENERAL WORKFLOW AND MODULES

3.1 | General workflow

To implement the generic PBK, Q(IVIVE) and DEB models described above, the TKPlate 1.0 platform was developed as an open-access tool coupled to a graphical interface (Bossier et al., 2020; Bossier, Chau, et al., 2023). TKPlate 1.0 focuses on toxicokinetic and toxicodynamic modelling of chemicals in species of relevance to food and feed safety. It is accessible online using a standard browser,[8] once the user has registered through the R4EU platform. In addition, the platform can be downloaded as a stand-alone application. The online version features an information module which describes the general features of TKPlate 1.0 to the user and additional publications provide further detailed information about the platform:

- External scientific reports describing the development of TKPlate 1.0 (Bossier et al., 2020; Bossier, Chau, et al., 2023).
- A technical report as a user guide providing detailed instructions on how to use the platform and case studies as supplementary material (Bossier, Cortiñas-Abrahantes, et al., 2023; Bossier, Spyropoulos, et al., 2023).
- All codes for models available within the TKPlate platform are also available on the EFSA Knowledge Junction (https://zenodo.org/record/7494936).

The general workflow of the platform is illustrated below in Figure 1 and is structured in the seven modules outlined above, namely, (1) Input, (2) Forward dosimetry, (3) Reverse dosimetry, (4) Toxicodynamic, (5) Dynamic energy budget, (6) MixTox, (7) Automated report. A detailed account of each module is provided in the following sections with a particular focus on their functionality and general applications.

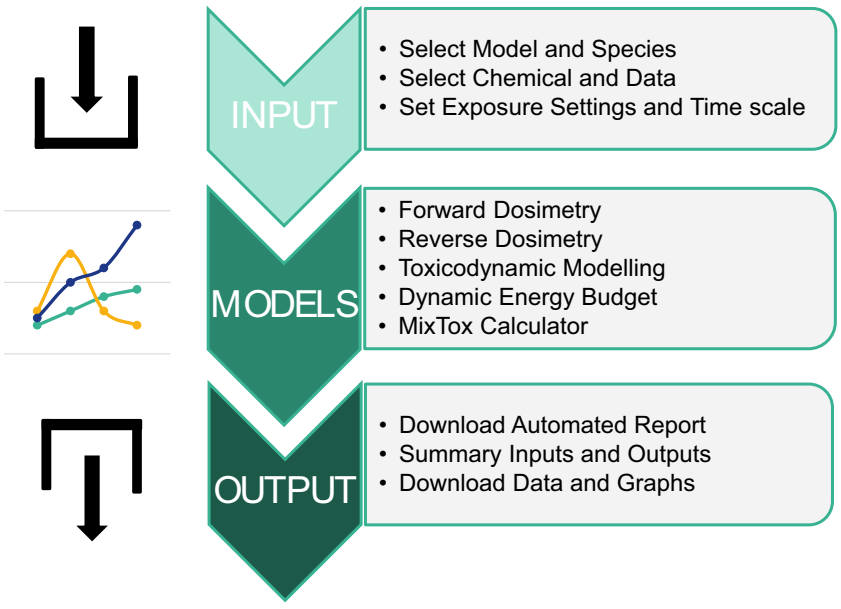

FIGURE 1 General Workflow of TKPlate 1.0.

[7] https://zenodo.org/record/7494936
[8] TKPlate: https://r4eu.efsa.europa.eu/app/tktd

3.2 | Modules

3.2.1 | Input module

This module allows the selection of model, species, chemical of interest and exposure settings. Available models include the generic *HTTK* one compartment model, generic PBK and QIVIVE models for humans (oral route and multiple routes), test species (rat, mouse, rabbit, dog) and farm animals (cattle, sheep, pig, chicken). This module is predominantly used as inputs for the forward dosimetry (external dose to internal dose), reverse dosimetry (internal dose to external dose) and toxicodynamic modules (internal benchmark dose modelling).

Once the user has selected the PBK or QIVIVE model and the species of interest, the chemical of interest needs to be selected and two options are available:

- A link to the US-EPA CompTox Chemicals Dashboard allows selection of chemicals for hundreds of thousands of chemicals from which properties are automatically filled as chemical-specific data (partition coefficients, etc.) with the exception of the hepatic clearance and absorption rate, which have to be entered by the user. The PBK model within the platform generates most parameters to allow simulations within the forward dosimetry module. For hepatic clearance, the user can either use *in vivo* values or *in vitro* metabolism to calculate absolute or relative clearance and perform QIVIVE to determine *in vivo* concentrations in the body fluids or organs of interest. Users can modify these parameters.
- A user-defined chemical for which the partition coefficient and kinetic parameters need to be input by the user and the model generates the remaining parameters allowing simulations within a defined exposure scenario.

In addition, the user has further options to define:

- Physiological and kinetic parameters from the PBK and QIVIVE models as fixed or random variables including population variability for the forward dosimetry simulations. Selection of random variables (≥2) allows the user to perform local or global sensitivity analysis to determine the impact of these variables on the model outcome as recommended in the OECD guidance document (OECD, 2021).
- Initial state values expressed as variables in body fluids or organs for reverse dosimetry simulations.

Finally, exposure settings are defined to allow model simulations for the chemical of interest:

- Dose unit (g, mg or µg) and time unit (days, hours, minutes, seconds),
- Exposure metrics expressed as absolute dose, dose adjusted to body weight or rate.
- Magnitude of each exposure input, time point of first exposure input and exposure time.
- Single or multiple doses.
- Time scale of the exposure in units of time.
- Duration of the simulations.

Once the input module has been filled in, the user can then perform simulations for the chemical of interest. Figure 2 illustrates TKPlate's input module.

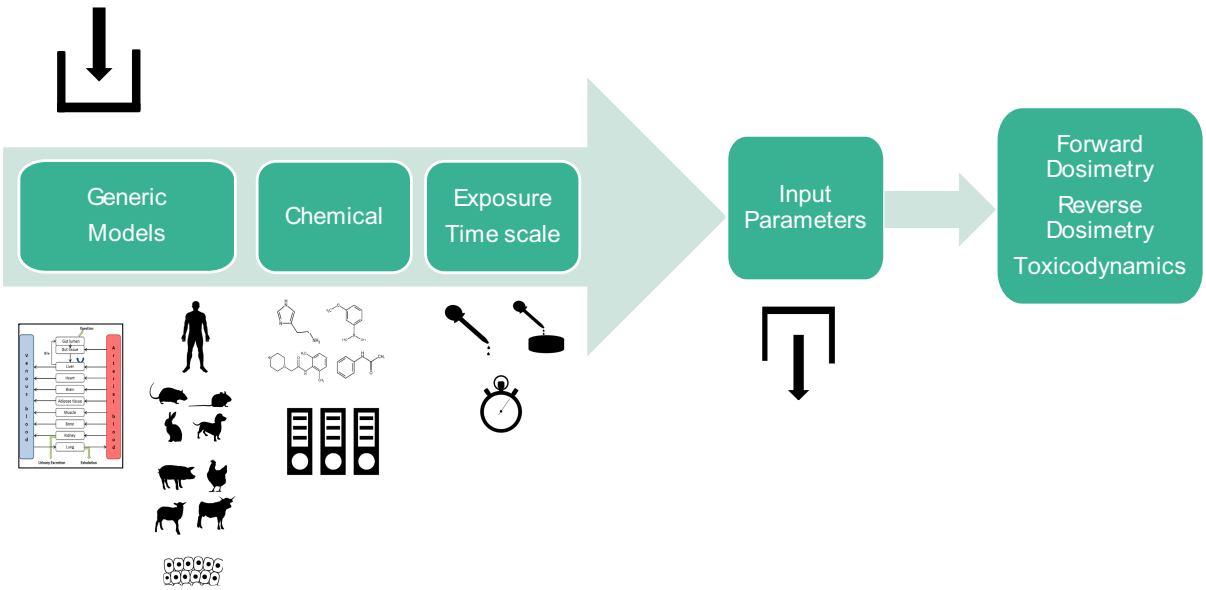

FIGURE 2 Input Module of TKPlate 1.0.

3.2.2 | Forward dosimetry module

The outputs of the forward dosimetry simulations are expressed as internal dose metrics including kinetic parameters reflecting acute exposure (maximum plasma concentration) or chronic exposure (clearance, half-life), concentrations in body fluids such as blood or urine and organs of interest (e.g. liver, kidney etc.), amount of the chemical metabolised and other parameters. The forward dosimetry is structured and accessible via different tabs illustrated in Figure 3:

- Simulate Model allows the simulation of internal dose metrics from available *in vivo* or *in vitro* chemical-specific data for species-specific PBK-QIVIVE models using chemical-specific parameters and exposure settings defined in the input module. The user simply needs to click on the 'calculate forward dosimetry' button after which outputs can be visualised and downloaded as a csv file through the download buttons 'simulated output' or Clearance (QIVIVE) data.
- Sensitivity analysis. Morris Screening, as local sensitivity analysis, can be performed for parameters that have been set as random variables in the input module through the 'Calculate Morris Parameters'. Similarly, global sensitivity analysis can be performed by clicking the 'Sobol Indices & Lowry Plots' button where both plots are generated as outputs as recommended in the OECD Guidance document (OECD, 2021).
- Model evaluation allows plotting model predictions against experimental data. Once the user has uploaded the experimental data from a csv file, these comparisons are available for both kinetic parameters and concentrations in compartments of interest.
- Compare different simulations allows visualising PBK or QIVIVE simulations for different species or populations once the user has uploaded individual csv files from simulated outputs.

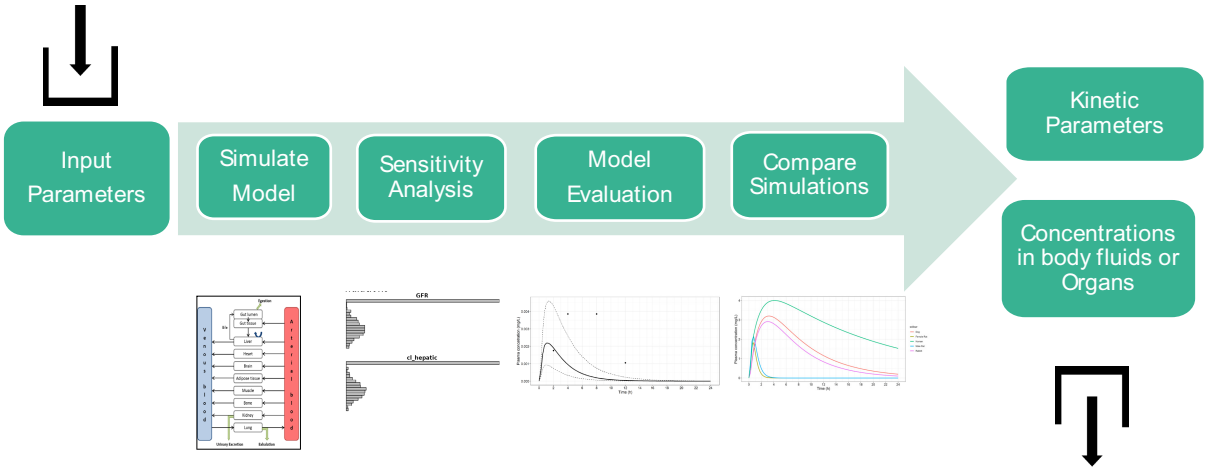

FIGURE 3 Forward Dosimetry module of TKPlate 1.0.

3.2.3 | Reverse dosimetry module

The reverse dosimetry module allows the reconstruction of the exposure distribution from internal dose using data from biomonitoring studies. In practice, Markov Chain Monte Carlo (MCMC) sampling algorithms recalculate the exposure distribution using a Bayesian method once the PBK model and chemical have been selected and time concentrations, as initial state values, have been uploaded in the input module. The initial state values provide a prior distribution defined under MCMC settings as truncated normal, lognormal, beta or uniform distributions. These prior distributions are then updated to a posterior exposure distribution using measured time concentration values and are provided as data and graphs as outputs (Figure 4).

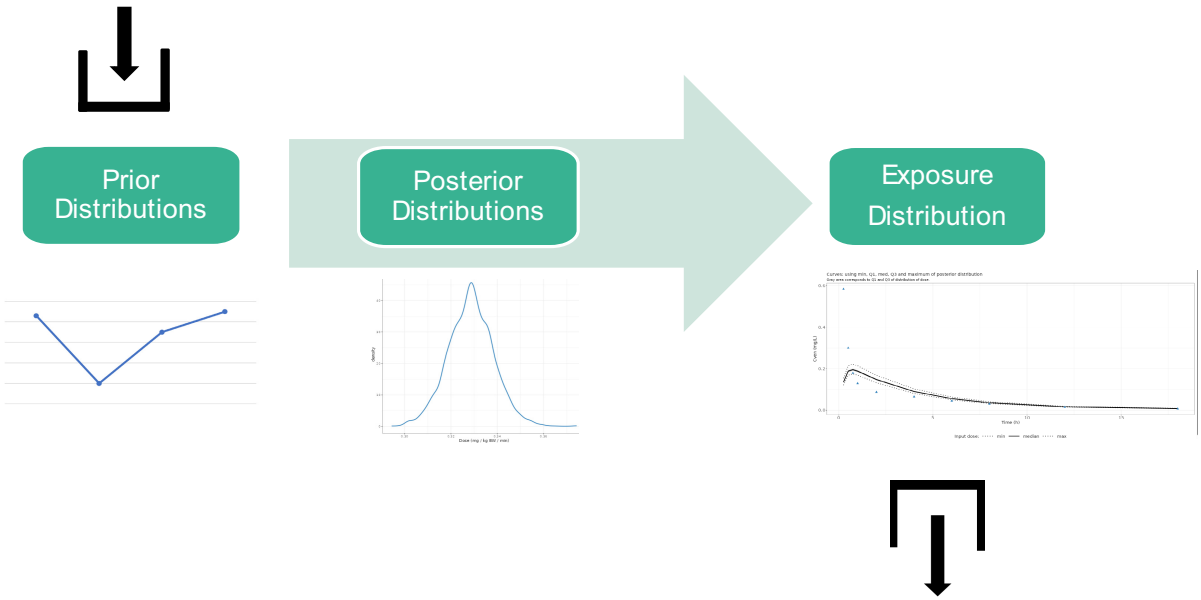

FIGURE 4 Reverse dosimetry module of TKPplate 1.0.

3.2.4 | Toxicodynamic module

The toxicodynamic module allows benchmark dose (BMD) modelling of dose–response data to derive BMD limits (BMDLs) on an internal dose basis using model averaging as described in the EFSA's Scientific Committee guidance document (EFSA, 2022). Hence, the results from forward dosimetry simulations generate internal dose metrics, such as kinetic parameters, blood or organ levels for the chemical of interest.

To model the internal BMD, the user needs to:

- Upload available dose response data for the chemical of interest;
- Tick the option to convert external doses to internal doses;
- Select the column containing the doses available and the time and target parameter (e.g blood levels) for which internal doses should be calculated through 'Convert doses!'.

The BMD modelling is automatically performed on an internal dose basis and generates an internal BMDL as well as BMD graphs and data outputs (Figure 5). Further details on the BMD tool are available in the manual provided within the application performing BMD on an external dose basis,[9] the source R code for which is also available.[10]

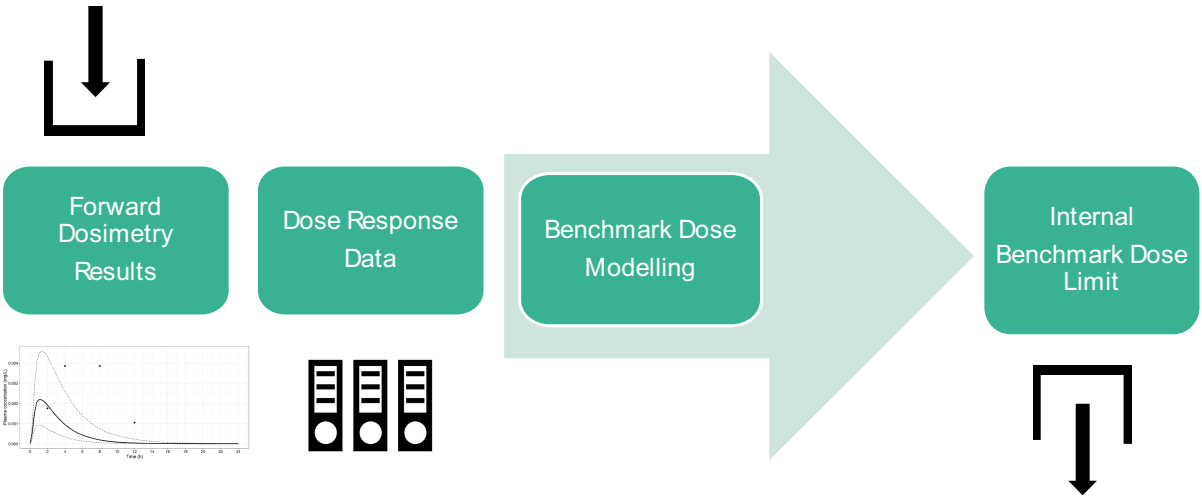

FIGURE 5 Benchmark Dose module of TKPplate 1.0.

[9] https://r4eu.efsa.europa.eu/app/bmd
[10] https://zenodo.org/record/3760370#.Y3eHdnbMJPY

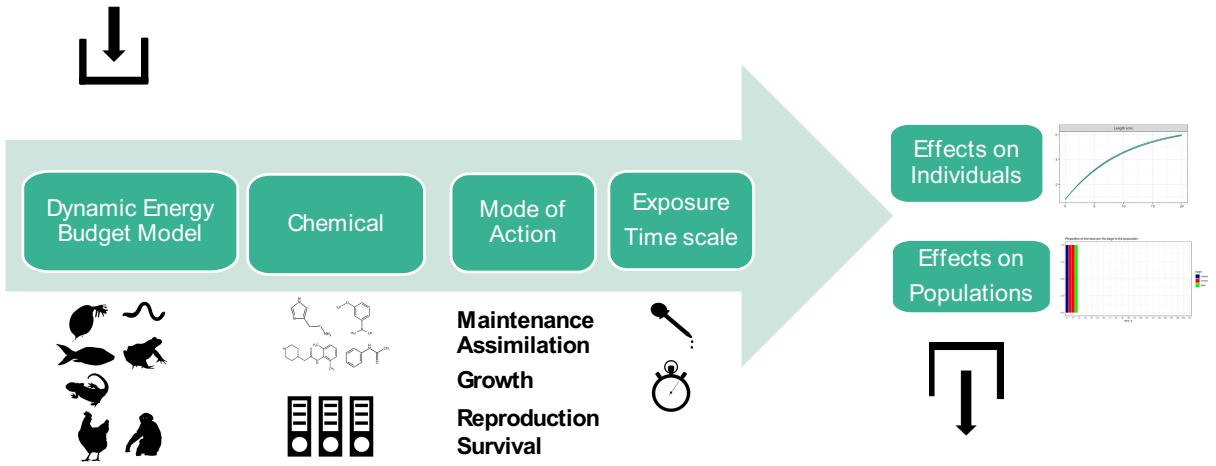

FIGURE 6 Dynamic Energy Budget module of TKPlate 1.0.

3.2.5 | Dynamic energy budget module

The dynamic energy budget (DEB) module in TKPlate has been implemented using the standard DEB model and available eco-physiological and life cycle trait data for over 2500 species from the open access Add-my-Pet database[11] as a stand-alone module (Baas et al., 2018). The module allows predictions of the impact of a chemical on the life cycle of a single species at the individual and population level. Such predictions can be performed for five DEB modes of action: (1) assimilation (A) or food uptake, (2) reproduction (R): impact of the compound on reproductive outputs, (3) maintenance (M): impact of the compound on both growth and reproduction, (4) growth (G): impact of the chemical on both growth and reproduction and (5) survival (S) from exposure to a compound.

In practice, the user selects:

- The species from the drop-down menu of the 'Add-my-Pet' database.
- Provides the name and concentration of the chemical, temperature (default temperature: 20°C) and number of days for the simulation (default value: 200 days).
- Fills in the required input datasets depending on whether the assessment is dealing with lethal or sub-lethal effects:

  - For sub-lethal effects which handle modes of action 1 to 4 (A, R, M and G), the user sets three parameters:
    1. The No Effect Concentration (NEC) as a toxicological threshold below which no effects occur (expressed as Co in mg/kg for terrestrial species);
    2. The tolerance concentration of effect (Ct) (expressed in mg/kg);
    3. The elimination rate (Ke) as a kinetic parameter describing how fast the equilibrium between the external and internal concentrations is achieved (expressed in 1/days).

  - For lethal effects (Survival S), the user sets the NEC, the killing rate (b) as a measure of the toxic potency after the NEC is exceeded and Ke.

In addition, the user can upload experimental data to the output, as follows:

- Input data with columns 'value', 'time' (measured in days), 'label' and 'cohort'.
- Values in the 'label' can include: 'Length (cm)', 'Wet Weight (g)', 'Cumulative Reproduction' and/or 'Survival Probability' (exact spelling required). The cohort for a given species should either be at the 'Individual' or 'Population' level depending on the available dataset.

The outputs of the DEB module assessments include graphs and datasets representing the impact of the chemical on the given species for the selected DEB modes of action at the individual and population level (Figure 6).

3.2.6 | MIXTOX module

The MIXTOX module performs deterministic risk characterisation for combined exposure to multiple chemicals using a component-based approach and the default dose addition assumption as described in the EFSA guidance on harmonised

[11] https://www.bio.vu.nl/thb/deb/deblab/add_my_pet/

methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2019). The methods that have been implemented in the tool include hazard index, risk index, reference point index, sum of margins of exposure and the sum of toxic units. In this context, the user is only required to provide exposure and hazard metrics for each chemical within a given assessment group and the tool is linked to the OpenFoodTox 2.0 database. The user is referred to the open Monte Carlo Risk Assessment (MRCA) tool for full probabilistic risk assessment in the context of combined exposure to multiple chemicals.[12]

3.2.7 | Automated report module

The automated report module exports an EFSA technical report word file with tables, graphs and associated datasets in Excel summarising the input and output data defined by the user for modules 1 to 6. For the DEB module, the TRACE report is provided as a separate file and as a transparent assessment of the DEB model itself.

4 | CURRENT AND FUTURE DEVELOPMENTS

Current TKPlate developments include data collection of physiological, metabolism and TK data as well as development of further refined generic PBK and dynamic models in subgroups of the human population and farm animal species.[13] A consortium of EU institutions and agencies published the 'Development of a Roadmap for Action on NAMs' which helped EFSA to prioritise further developments needed to integrate NAMs into regulatory hazard and risk characterisation of chemicals in food and feed (EFSA et al., 2022; Escher et al., 2022). In this NAMs roadmap, TK assessment was highlighted as a priority particularly with regards to PBK modelling using *in vitro* and *in vivo* TK data for model development, variability and uncertainty assessment. Consequently, EFSA launched the 'ADME4NGRA project: implementing the EFSA NAMs Roadmap through Advancing Toxicokinetic Knowledge in Chemical Risk Assessment'.[14] The project aims to: (a) use advanced *in vitro* systems to compare intestinal, liver, kidney and microbiome metabolism of chemicals in humans and rats; (b) develop open-access databases and *in silico* ADME (absorption, distribution, metabolism and excretion) models and databases; (c) refine generic human and rat PBK models using refined metabolism information for next generation risk assessment (NGRA) and validation using illustrative case studies. In this context, to further enhance the regulatory implementation of such models, attention is needed on the comparison of prediction accuracy between chemical specific PBK models and generic models. In addition, EFSA's PPR Panel has highlighted the need to provide strategies and guidance to highlight practical steps to integrate PBK and IVIVE approaches in the food and feed safety area (EFSA PPR Panel et al., 2021).

With regards to chemical mixtures, further developments of PBK and TK-TD models are also ongoing for farm animals and species of ecological relevance. These include the application of multidisciplinary approaches for the development of biological-based and *in silico* models addressing mixture toxicity as well as multiple stressor modelling such as chemicals and emerging pathogens in farm animals and species of ecological relevance.[15] The expectation is that such models will prove useful to address the complex challenge of risk assessment of multiple stressors in humans, animals and the environment and allow the integration of data at different levels of biological organisation (molecular, individual, species, population, ecosystem) (Astuto et al., 2022).

Last but not least, a key aspect to support regulatory uptake of such models is the need for specialised and fit for purpose training for the risk assessment community in regulatory agencies as well as for independent experts. Such training should particularly focus on illustrating, through practical case studies, the use of tools such as TKplate for the risk assessment of regulated products and contaminants.

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[12] https://mcra.rivm.nl/mcra/#/

[13] https://etendering.ted.europa.eu/cft/cft-display.html?cftId=6548

[14] https://etendering.ted.europa.eu/cft/cft-display.html?cftId=11405

[15] https://etendering.ted.europa.eu/cft/cft-display.html?cftId=8859; https://etendering.ted.europa.eu/cft/cft-display.html?cftId=8861

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CONFLICT OF INTEREST

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