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1. Introduction and objectives

Exposure assessment is essential for public and environmental health research, as correct characterization of exposure is required to accurately determine associations between environmental agents and health and disease-related outcomes. Exposure assessment together with hazard identification and characterization are the two fundamental regulatory pillars to perform risk assessment of chemicals. The current document describes the deliverable 6.1 in WP6 of the ONTOX project, the performance of exposure assessment. The work of identifying appropriate exposure assessment methods for oral, inhalation and dermal exposure is described in the systematic scoping review which is already published by Kalyva, Vist (1).

2. Results

2.1. Research statement

The objective of this deliverable is to find the most appropriate exposure assessment methods and performing exposure assessment using the most appropriate methods. Therefore, we conducted a systematic scoping review of existing human exposure methods and tools, where the method is properly described and/or freely available online in order to facilitate exposure assessments of environmental chemicals through oral, dermal and inhalation routes. The results from this scoping review will assist in the decision-making process regarding suitable exposure methods/tools to be used for environmental chemicals, supporting probabilistic risk assessments.

The deliverable fully supports the goal of the task 6.1 by providing the best methods for the probabilistic exposure assessment used in the probabilistic risk assessment in ONTOX. The deliverable provides methods for all exposure routes and aligns with the intention of providing exposure assessment for all exposure sources of a chemical.

To our knowledge, no systematic scoping review of methods for exposure assessment modeling is available and therefore it is of high value also outside the ONTOX project. In 2022 an inventory of exposure models used in Europe was reported, with a plan to foster a common

understanding of modelling-related methodology, terminology, and future research in Europe (2). However, this publication was not performed systematically, and only includes methods used in Europe.

2.2. Research and scientific evidence

The presented results can also be found in the published open access paper (1), with link [https://linkinghub.elsevier.com/retrieve/pii/S0269-7491\(24\)00823-6](https://linkinghub.elsevier.com/retrieve/pii/S0269-7491(24)00823-6).

The percent of each chemical class for each of the exposure routes studied in the included papers is presented in Fig. 1. We observe that the chemical classes of, mycotoxins, antimicrobial chemicals, food additives, PFASs, bisphenols, pesticides, and metals, have been studied the most using methods for the oral route of exposure. Nicotine, VOCs, disinfecting chemicals and environmental emissions have been studied mostly in methods for inhalation exposure. Pharmaceuticals, cosmetic ingredients, and non-persistent chemicals were mainly studied for dermal exposure route. Note that the number of papers for each chemical class varies widely with eighty-five included papers for pesticides, and only two for pharmaceuticals.

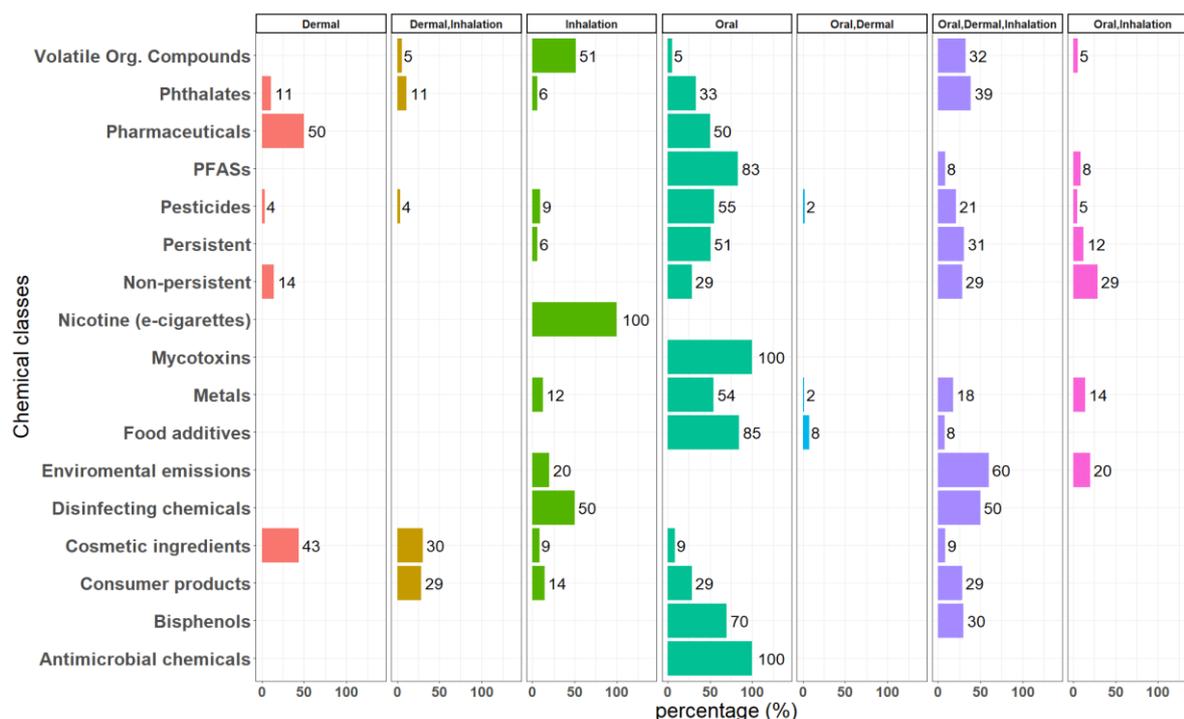


Fig. 1 Chemical classes versus exposure route described in the exposure methods of the included papers. Bar chart numbers are the percentage of each chemical class studied for each type of exposure route

We present the percent in a descending order of each chemical class for each of the estimation methodologies used to calculate/estimate the exposures found in Fig.2. We observe that mostly for the metals (51 %), phthalates (50 %), PFASs (42 %), persistent chemicals (41 %) and so forth, exposure was estimated using empirical equations. For the disinfecting chemicals (71 %), VOCs (59 %), cosmetic ingredients (52 %), mycotoxins (50 %) and the rest, the exposure was estimated by using a mathematical model. Finally, toolbox/software was used mostly to

calculate the exposure of non-persistent chemicals (43 %), consumer products (43 %), bisphenols (40 %), mycotoxins (33 %) and so forth.

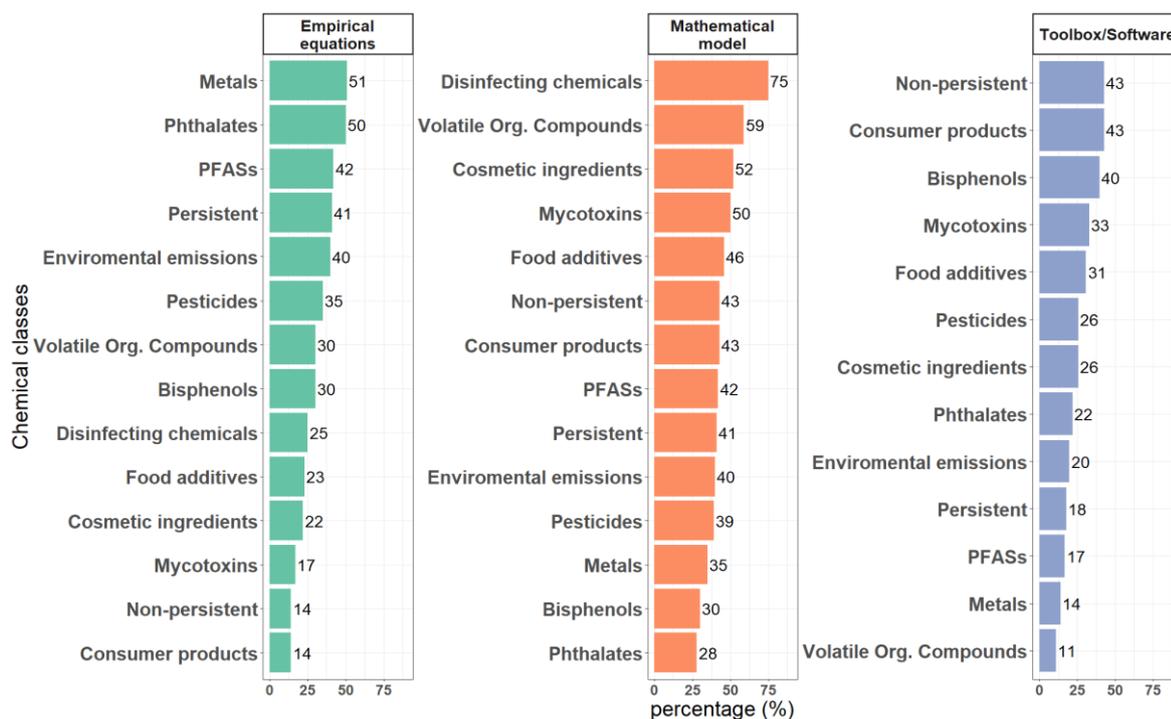


Fig. 2 Percentage of each chemical class for each of the estimation methodologies (descending order).

We have filtered out 12 of the mathematical models and toolboxes that have occurred 2 % (three times) or more, as most of them have occurred less than three times. This percentage is not reflecting the importance of the less occurring methods and tools, rather show how often these methods and tools are occurring by the included studies.

The percentage that each type of exposure route studied by each of these twelve mathematical models and toolboxes is presented in Fig. 3. The PRIMo model is used only for studying oral exposure and the MCRA tool has been mainly used (86 %) for oral exposure assessments. SHEDS-multimedia, USEtox, ConsExpo and PACEM models/tools are used to calculate human exposure for all the exposure routes in combinations and separately.

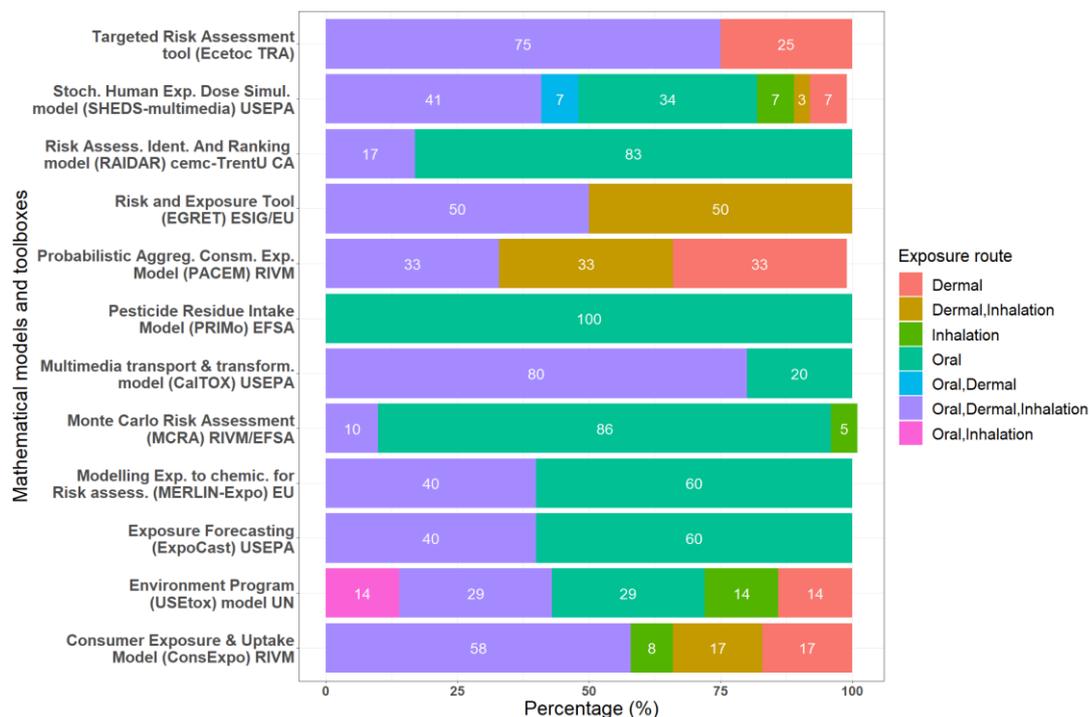


Fig. 3 Mathematical models and toolboxes most frequently used to estimate exposure in the included 299 papers versus exposure route.

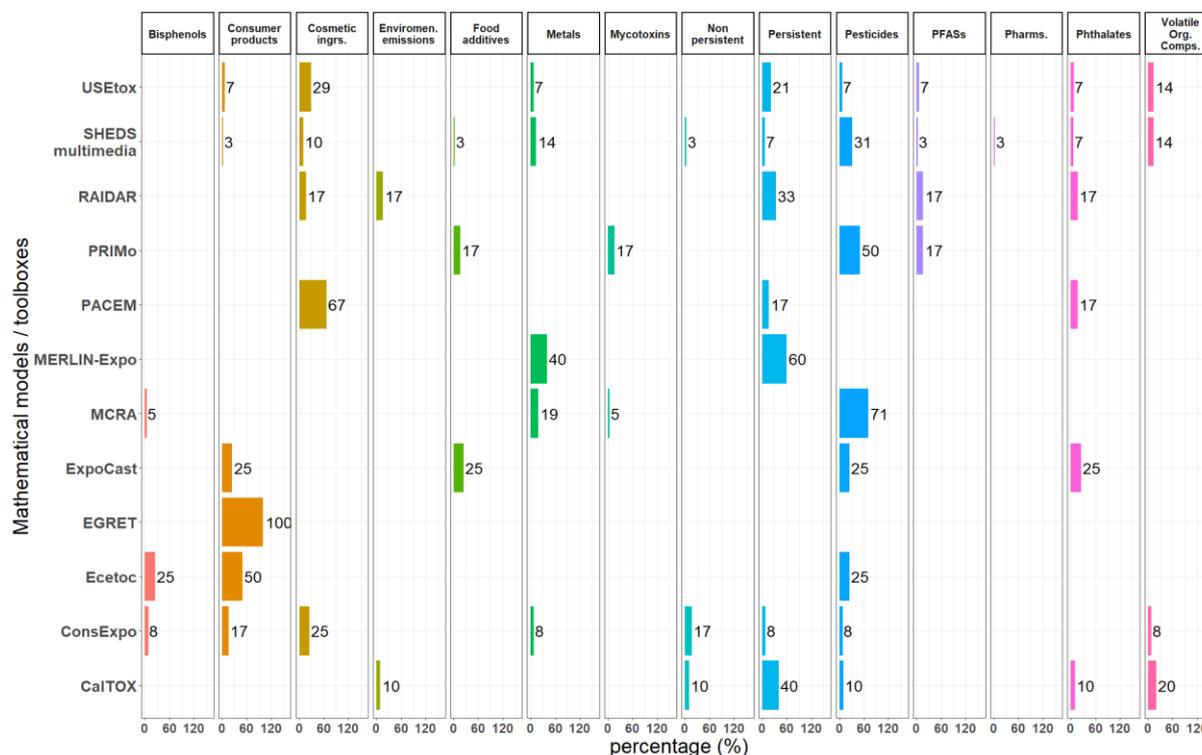
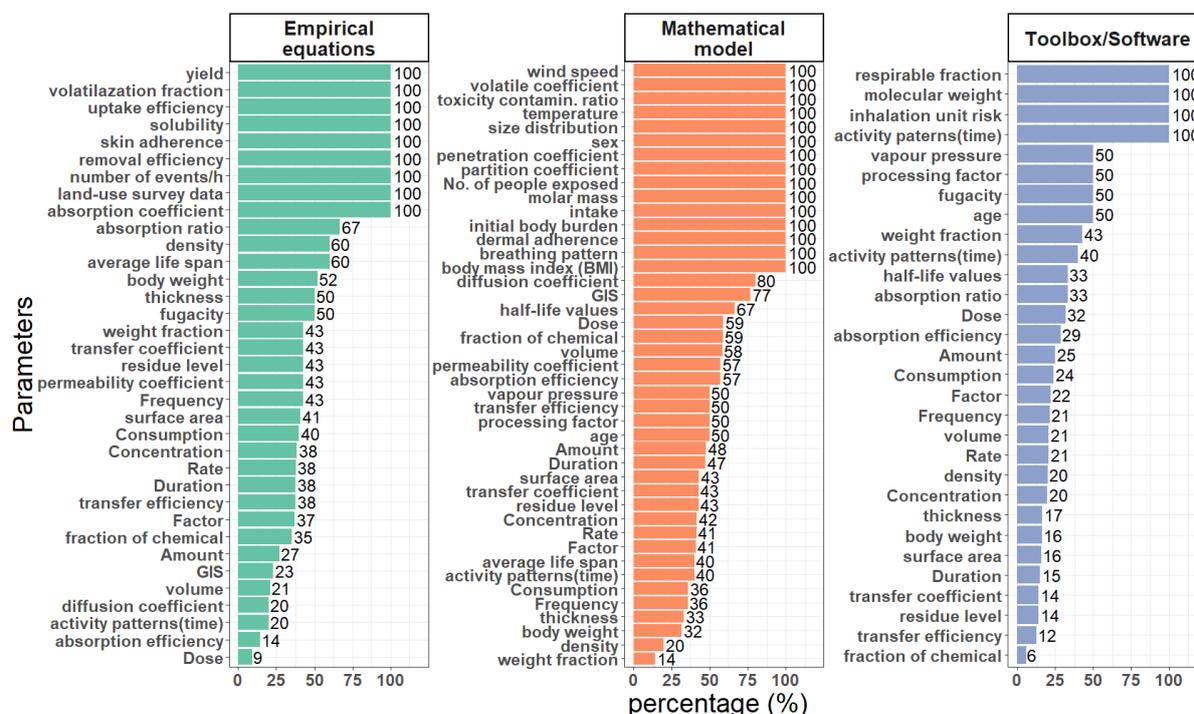


Fig. 4 Mathematical models and toolboxes are most frequently used to estimate exposure in the included 299 papers versus chemical classes.

The percentage of each chemical class that has been studied by each of the twelve mostly used exposure mathematical models and toolboxes are presented in Fig. 4. The most frequently used methods to estimate chemical exposure from food (e.g. MCRA and SHEDS), consumer products (e.g., EGRET, PACHEM, ConsExpo) and cosmetics (PACHEM). However, some methods such as SHEDS, can estimate exposure to environmental chemicals from multiple routes, including inhalation.

The percentage of the parameters reported to have been used as input values in the equations, models, and toolboxes to estimate human exposure for each of the estimation methodologies in the scoping review is presented in Fig. 5. We present which parameters have been used and how often each one of these parameters were used to estimate exposure. This gives an overview of what kind of parameters are needed to estimate exposure by the different methodologies. We observe that empirical equations used input parameters, such as, skin adherence, transfer efficiency, volatilization fraction that originate usually from self-reported experimental data that may be subject to bias. The input parameters in mathematical models and toolboxes, are identified to be processing factors, partition coefficients, inhalation unit risk values, half-life values, and more that can be found and retrieved from databases.



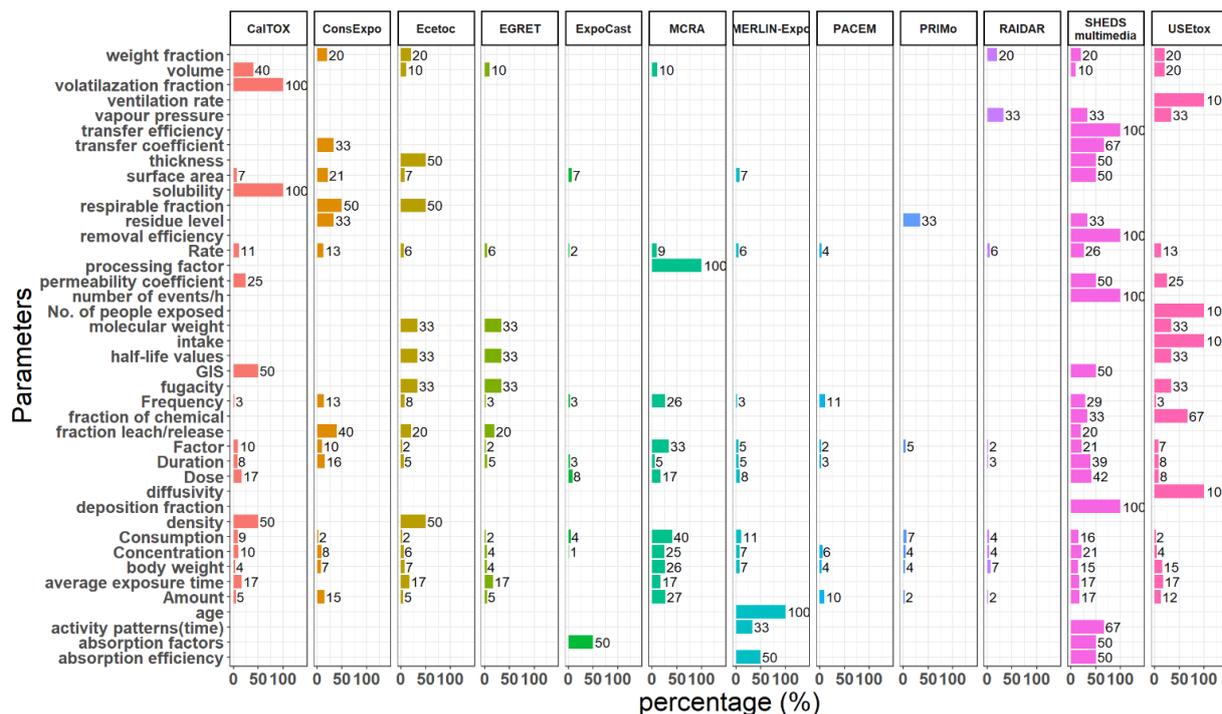


Fig. 6 Parameters (input data) used to estimate exposure versus most frequently occurred mathematical models and toolboxes.

2.3. Impact

To our knowledge, this is the first scoping review that increases knowledge and awareness about freely available human exposure methods and tools of environmental chemicals. Sixty-three mathematical models and toolboxes are identified in the scoping review with twelve of them occurring most frequently to calculate human exposure.

The work has been published open access in the journal *Environmental Pollution* in July 2024 (1). The work was presented on the Scientific day at the Department of Chemical Toxicology in August with the title “Ontology-driven and artificial intelligence-based repeated dose toxicity testing of chemicals for next generation risk assessment - (ONTOX)” and on the EuroTox conference in Copenhagen 8-11 September 2024 with the title “Probabilistic exposure assessment from food and cosmetics”. The work will also be a part of the planned case-study on probabilistic risk assessment of PFOA, where a protocol for the work has been published on the web page of NIPH ([Protocol for probabilistic risk assessment of perfluorooctanoic acid \(PFOA\) - FHI](#)).

3. Conclusions and follow-up

Exposure assessments methods were identified used for a broad range of environmental chemicals including pesticides, metals, persistent chemicals, volatile organic compounds, and other chemical classes. Our analysis by associating the frequently used mathematical models and toolboxes with exposure route, chemical classes, and input parameters (data) used, can guide researchers to select the appropriate mathematical model/toolbox to estimate exposure. Therefore, human exposure estimates calculations can be reproduced relatively easily for a

wide range of environmental chemical classes identified in this scoping review. Selected models will be used in the case-study on probabilistic risk assessment in the ONTOX project.

4. Delays, issues and contingency

No delays.

5. References

1. Kalyva ME, Vist GE, Diemar MG, Lopez-Soop G, Bozada TJ, Luechtefeld T, et al. Accessible methods and tools to estimate chemical exposure in humans to support risk assessment: A systematic scoping review. *Environ Pollut* 2024;352:124109. DOI: 10.1016/j.envpol.2024.124109
2. Schluter U, Meyer J, Ahrens A, Borghi F, Clerc F, Delmaar C, et al. Exposure modelling in Europe: how to pave the road for the future as part of the European Exposure Science Strategy 2020-2030. *J Expo Sci Environ Epidemiol* 2022;32(4):499-512. DOI: 10.1038/s41370-022-00455-4