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Critical Review

REACH assessment of humans exposed to chemicals indirectly via the environment: screening modeling in EUSES versus state of the science

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Abstract

The assessment of humans indirectly exposed to chemicals via the environment (HvE) is an assessment element of the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) regulation. The European Union System for the Evaluation of Substances (EUSES) is the default screening tool, aimed at prioritizing chemicals for further refinement/higher tier assessment. This review summarizes the approach used in EUSES, evaluates the state of the science in human exposure modeling via the environment, and identifies areas for further research to strengthen the confidence and applicability of EUSES for assessing HvE. It confirms that EUSES v2.2 does serve as a conservative screening tool for identifying potential human risk due to HvE (via consumption of crops, meat and milk, fish, drinking water, and inhalation). However, certain submodels within EUSES have not been updated for at least two decades. For example, for highly soluble or highly hydrophobic or ionized organic substances, substance parameters are estimated based on outdated predictive models. We recommend to also update the REACH Technical Guidance to highlight possible refinements in HvE assessments as well as the integration of measured and (bio)monitoring data. Addressing limitations in the EUSES applicability domain, particularly for highly soluble and highly hydrophobic organic substances and ionized organics, would improve its applicability. We identified that some HvE submodels in EUSES could be readily updated to improve screening-level assessment in EUSES. In addition, updating the EUSES "food basket" using recent European Union food consumption data is crucial to accurately reflect recent dietary trends. Further research is required for prediction of leaf crop and drinking water exposure to better reflect the fate of chemicals in the environment. In particular for ionizable substances, research focused on QSAR (Quantitative Structure Acitivity Relationship) development and experimental measurement of fate properties is necessary to enhance the confidence of EUSES assessments.

Keywords: humans exposed via the environment, modeling, exposure assessment, EUSES, REACH

Introduction

Indirect and unintentional exposure of humans to chemicals via the environment (HvE) may occur via various pathways, including the consumption of food (meat, fish, crops, and dairy products) and drinking water when considering the oral route, and via inhalation of air. Under the REACH Regulation ([EC] No 1907/2006), the assessment of HvE is required in case a chemical presents systemic hazard for long-term effects and if the tonnage is $>1{,}000$ tonnes per year or if the tonnage is >100 tonnes per year and the substance is classified as single target organ toxicity repeated exposure category 1, as a carcinogen or mutagen (any category), or as toxic to reproduction (categories 1A or 1B; ECHA, 2016).

The HvE is calculated by considering intake via air, water, and food. The concentration of a substance in food is estimated from the concentration in water (surface water or groundwater), soil, and air considering the bioconcentration or bioaccumulation behavior of the substance (see Figure 1). In the context of REACH, the European Union System for the Evaluation of Substances (EUSES) is the default tool for assessing HvE (ECHA, 2016); EUSES is also available within the Chesar (CHEmical Safety Assessment and Reporting) Platform. The EUSES tool is generally considered to be applicable for the purposes of enabling a screening-level risk assessment, because model assumptions are intended to reflect a reasonable worst-case scenario. The objective is to

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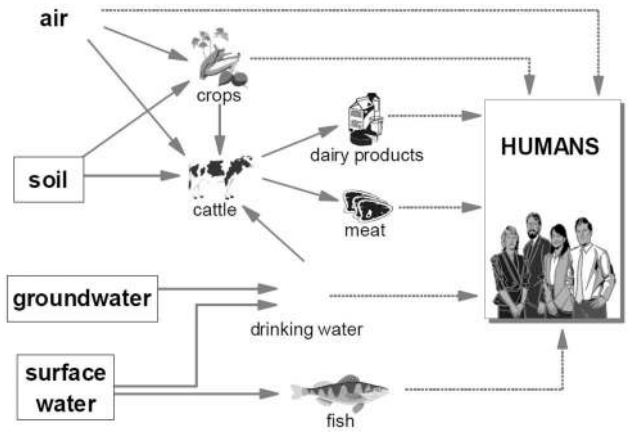

Figure 1. Indirect exposure routes for humans through the environment. Solid lines indicate (bio)transfer, broken lines indicate human intake (Source: European Chemicals Agency, http://echa.europa.eu/ [ECHA, 2016]).

eliminate large numbers of chemicals for which safe use can be demonstrated based on conservative assumptions.

Nevertheless, there are several HvE submodels in EUSES that have not been updated for many years, and more recent empirical data suggest that various model default values and assumptions may be inaccurate (Haug et al., 2017). Therefore, HvE in EUSES insufficiently represents the current state of the science. Moreover, the EUSES model is mainly applicable to neutral non-ionizable organics within only a narrow log K_{OW} (n-octanol/water partition coefficient) range (Franco et al., 2011a). There is thus an opportunity and need to consider adopting a number of updates to EUSES that would broaden the applicability domain and strengthen the tool in its ability to ensure that it is an appropriate screening tool for chemicals. Alternatively, there are currently a variety of screening and higher-tier models that may provide complementary support to EUSES, which include Risk Assessment, Identification, And Ranking (RAIDAR; Arnot & Mackay, 2008), PROduction-To-Exposure-High-Throughput (PROTEX-HT; Li et al., 2021), CalTOX (Mckone, 1993), ACC-HUMAN (Czub & McLachlan, 2004), and USETox (Rosenbaum et al., 2011). The European Chemicals Agency (ECHA) has identified improvement of the assessment of HvE as a key research area in its June 2024 Key Areas of Regulatory Challenge report (ECHA, 2024).

Given the advances in the area of environmental fate and exposure modeling over the last two decades, including the development and application of alternative modeling tools, the objectives of this review are first, to summarize and characterize the HvE modeling approach currently used within the EUSES version 2.2; and second, to reflect on the state of the science of HvE screening assessment, particularly applicability domain and the extent of predictivity/conservatism associated with the various tools and models. Finally, we identify research and regulatory update needs to strengthen overall confidence in the application of EUSES when assessing the risks of chemicals in the context of HvE. The submodels considered in this review are identified as the critical components of conducting a HvE assessment. Overall, the purpose of this review is to identify options for expanding the applicability domains, particularly for ionizable chemicals, and for improving the degree of realism of the predictions based on new scientific developments. Although some chemicals on the regulatory agenda may be covered by an expanded applicability domain, others may not.

Current screening HvE modeling in EUSES

This section discusses how chemical exposure in the context of HvE exposure is assessed under the REACH regulation. The HvE assessment in EUSES can be considered for both the local scale (representing the point source impact of a standardized industrial site or wide dispersive public use in an urban area) and the regional scale (representing the diffuse source impact of all uses of a substance over the entire life cycle, e.g., of a standardized environment like a small European Union [EU] member state). The three main steps required to conduct a realistic worst-case HvE assessment are (1) emission scenario and environmental release estimation, (2) environmental fate modeling; and (3) characterization and quantification of the accumulation of a chemical in the food web and subsequent human intake. Characterizing the environmental release of a chemical represents the first step in assessing environmental exposure under the REACH regulation, which is required for all hazardous substances manufactured or imported at an annual quantity of equal to or exceeding 10 tons. Emissions into the environment for HvE are expressed as release rates in kilograms per year and usually tonnage-based or consumption-based (e.g., per capita). The emission estimate is one of the main input parameters influencing the derivation of a predicted environmental concentration (PEC) in water, air, and soil, which thus subsequently influences the estimates of concentrations in food, drinking water, and outdoor air. Under REACH, a tiered approach is typically advocated starting with semiquantitative conservative default emission values (e.g., environmental release categories (ECHA, 2016), whereas more refined sector-specific estimations can be carried out using specific environmental release categories (Reihlen et al., 2015) or the Organisation for Economic Co-operation and Development emission scenario documents.

The derivation of concentrations in the various environmental media that might influence human exposure is based on the use of standardized environmental fate and human intake models, which are used to calculate environmental exposure and indirect exposure to humans. Exposure via inhalation, for instance, is based on estimates of the steady-state concentration in air, which is obtained from the environmental fate model used in EUSES. Exposure via drinking water, on the other hand, is derived from the worst-case concentration of a chemical in either groundwater or surface water. In EUSES, the groundwater concentration is influenced by the emission scenario, whereby groundwater has the potential to be contaminated as a result of emission to soils via sludge from a municipal sewage treatment plant to agricultural soil, or as a result of atmospheric deposition. There is a conservative assumption that leaching from the soil surface to groundwater is represented by the pore water concentration of the top soil layer. It does not include a further assessment of the fate of a chemical as it moves through various unsaturated soil layers to the saturated groundwater layer, typically found at greater soil depths. Surface water concentrations can be influenced either through direct emissions of the chemical into freshwater systems or indirectly, e.g., as a result of runoff from soils.

Assessing concentrations in food products, including fish, leaf crops (including cereals and fruit), root crops, meat, and dairy products, requires knowledge of the bioconcentration factor (BCF) or biotransfer factor (BTF). The BCF or BTF is defined as the external exposure (as a concentration or a dose) divided by the internal concentration in the organisms and imply a steady-state situation, in which the exposure period is assumed to be long enough to reach a steady state. Although BCF or BTF values can

be estimated, the use of reliable (and relevant) experimental BCFs/BTFs is typically preferred over estimated factors. In EUSES, a generic "food basket" is defined that describes the worst-case quantities of different food types that are consumed (ECHA, 2016). Additional conservatism is built in at the local scale, whereby populations are assumed to consume 100% of their food obtained from the immediate vicinity of a local point source. By contrast, the regional assessment represents an averaged exposure situation without direct impact of point sources.

Given the various conservative assumptions used to estimate exposure, mentioned above, the results of an HvE assessment should be seen as screening and helping to guide decision-making instead of being considered as an accurate characterization of human exposure in the EU. It is a first step in a tiered approach that is based on conservative and/or worst-case scenario assumptions, which should then gradually be refined, aimed at reducing uncertainty associated with the most sensitive input parameters at higher tiers. In practice, however, guidance is lacking on how to either refine EUSES calculations or when to consider the application of more advanced site-specific, time dependent, and/or higher-tier models (e.g., Haug et al., 2017). There is a need to extend the ECHA R.16 guidance (ECHA, 2016) to highlight the level of conservatism in an HvE assessment to clarify which refinements are needed for the purpose of risk assessment (in the context of REACH registration purposes) versus impact assessment (for nonthreshold substances in the context of REACH authorization [or restriction] processes). In addition, addressing uncertainty is, in practice, still insufficiently done (Verdonck et al., 2007) despite the availability of the specific ECHA guidance on uncertainty analysis (ECHA, 2012) and in contrast to the European Food Safety Authority (EFSA, 2018), which implemented its guidance on uncertainty analysis in general scientific areas from 2018 and regulated product areas to phase in over the following years. For risk assessment purposes in the REACH registration process, reasonable worst-case estimates are typically needed for the chemical safety report. For impact assessment in the REACH authorization or restriction process, more realistic (average) assessment is needed where required to demonstrate that the (average) social and economic benefits of continuing to use the substances outweighs the associated (average) impact to human health and the environment. Higher-tier tools such as MERLIN-EXPO (Ciffroy et al., 2016), INTEGRA (Sarigiannis et al., 2016), and SHEDS-HT (Isaacs et al., 2014) contain probabilistic assessment and account for both central tendency and worst-case exposure. Equally, screening tools like EUSES would benefit from such functionality to simulate an average as well as reasonable worst-case scenario.

State of the science of HvE assessment and tools

Since the development of EUSES 1.0 in 1996 and subsequent updates, there have been a variety of new tools and (sub)models that have been developed and applied to address aspects of HvE, both for screening and higher-tier purposes.

To conduct this review, a literature search was performed across multiple scientific databases, including PubMed, Scopus, and Web of Science, to identify relevant studies published between 1996 and 2023. Keywords and search terms included combinations of "human exposure modelling," "EUSES," "bioaccumulation," "bioconcentration," "Plant uptake," "TSCF," "Root uptake," and "ionisable organics." Additionally, references within the identified studies and tool manuals were cross-checked to capture any studies that may not have been retrieved through the initial database search. Inclusion criteria were defined to focus on peer-reviewed articles, reviews, and regulatory reports that specifically address the HvE modeling approach. Studies that evaluated the applicability, limitations, or updates required for EUSES submodels were prioritized.

Relevant data were extracted from each selected study, including information on model assumptions, default values, applicability domains, and predictive capabilities of HvE submodels. The data extraction process involved categorizing information based on different exposure pathways (e.g., air, water, food) and types of chemicals (e.g., neutral organics, ionizable substances). The extracted data were then synthesized to provide an overview of the current state of HvE assessment within EUSES, highlighting areas where updates and improvements are necessary (See online supplementary material Appendix).

Table 1 provides an overview of the exposure pathways that have been addressed and the screening and higher-tier tool models that are available. Specific examples include the screening level RAIDAR model (Arnot & Mackay, 2008), based on the fugacity concept and which estimates the fate and exposure of chemicals within the lipid and water fraction of each food, with considerations to also address partitioning to the nonlipid organic matter (such as proteins in animals and carbohydrates and cellulose in plants). The PROTEX-HT model is a time-variant, process-based (mechanistic), integrative model that includes the capability to assess the fate and exposure of a chemical from production to dose in the human body and represents a higher-tier version of the RAIDAR model (L. Li et al., 2021). Other examples of HvE models include USETox (Rosenbaum et al., 2011), MERLIN-Expo (Ciffroy et al., 2016), INTEGRA (Sarigiannis et al., 2016), CalTOX (Mckone, 1993), ACC-Human (Czub & McLachlan, 2004), and CSOIL (Bontje et al., 2005; Table 1). Typically, higher-tier tools introduce more granularity in the exposure pathways, such as in time and space, and include options to consider additional exposure pathways (CONCAWE, 2017; Shin et al., 2015).

The applicability domain of the various HvE models, including those in EUSES, for the different exposure pathways, along with considerations towards their relevance and reliability in the context of screening-level and higher-tier assessments, are discussed below. A split was made between (1) leafy (including cereals and fruit) and root crops, 2) meat and milk (including dairy) products, (3) fish, (4) air/inhalation, (5) drinking water, and (6) potential additional routes of exposure (see Table 1). Food consumption and use of monitoring data are discussed in two subsequent sections, respectively.

Exposure from crops

Conceptual approach

Plant products form a major fraction of the food products consumed by humans and livestock such as cattle. In EUSES, a distinction is made between root or tuberous plants and leaf crops (including cereals and fruit). In contrast, uptake in fruit and cereals is not considered separately from leaf crops in EUSES, which can lead to overestimation of the leaf crop intake, as the predicted environmental concentration (PEC) of chemicals in fruits would typically be lower than those estimated for leafy crops (Legind & Trapp, 2009). Consequently, it may be appropriate to consider a separate exposure pathway for fruit, cereals/grasses, and pulses/oilseeds as part of an improved approach.

The exposure of plants includes uptake from soil as well as uptake from air. Uptake from soil is, in general, a passive process governed by the transpiration stream of the plant (in the case of

Table 1. Overview of exposure pathways addressed in various screening and higher-tier HvE assessment models.

EUSES (European Union System for the Evaluation of Substances) (current)	**USETox**	**CSOIL**	**ACC-Human**	**CalTOX**	**RAIDAR (-ICE)/ PROTEX-HT**	**MERLIN-Expo**	**INTEGRA**	**(De Brouwere et al., 2022)**
Air	Air	Air (outdoor) Air (indoor)	Air	Air (outdoor) Air (indoor)	Air (outdoor) Air (indoor)	Air	Air (outdoor) Air (indoor)	Air
Leafy crops	Exposed produce	Leaf		Foliage vegetation	Foliage vegetation	Leafy vegetables Fruit	Leafy crops	Leafy vegetables Shoots Fruit Grain
Root crops	Unexposed produce	Root		Root vegetation	Root vegetation	Root vegetables Tuber vegetables	Root crops	Root vegetables Tuber vegetables Bulb vegetables
Fish (freshwater)	Fish			Fish and seafood	Fish	Fish	Fish	Fish
			Marine fish					Seafood
Meat	Meat		Beef Cattle	Meat	Poultry Beef Pork	Meat	Meat	Meat
				Eggs	Eggs			
Milk	Dairy		Milk cows	Milk animals Milk mother	Dairy milk Bulk dairy	Milk	Milk	Milk
Drinking water	Drinking water	Drinking water	Drinking water	Drinking water	Drinking water	Drinking water	Drinking water	Drinking water
		Soil and dust ingestion		Soil and dust	Dust	Soil and dust	Soil and dust ingestion	Soil and dust ingestion
		Dermal dust Showering		Dermal Shower, batch, swimming				
ECHA (2016)	Rosenbaum et al. (2011)	Bontje et al. (2005)	Czub & McLachlan (2004)	Mckone (1993)	Arnot and Mackay, (2008); Li et al. (2021)	Ciffroy et al. (2016)	Sarigiannis et al. (2016)	De Brouwere et al. (2022)

accumulation in leaves) or physical sorption (in the case of roots). Uptake into the leaves from the gaseous phase can also be viewed as a passive process, in which the leaf components (air, water, lipids) equilibrate with the air concentration. K_{OW} (the octanol water partition coefficient) and K_{AW} (the air-water partition coefficient) are used to assess distribution between the air and the plant phases.

Applicability domain and reliability

In general, the models currently applied in EUSES to estimate concentrations in leafy crops are best suited for neutral nonpolar organic chemicals. The tool selects the highest transpiration stream concentration factor (TSCF) based on the formulas of Briggs et al. (1982) and Hsu et al. (1990), which are calibrated for chemicals with partition coefficient ranges between log K_{OW} -0.57 and 4.6, and between log K_{OW} 0.96 and 5.3, respectively. For chemicals outside this applicability range, as well as for polar and ionizable organic chemicals, the relative confidence in leaf PECs needs to be acknowledged as being low. Ionized and/or inorganic substances are currently dependent on the availability of measured concentrations in food items to reliably determine BCF or biotransfer factor BTF. However, measured TSCF and BCF were also found to be highly variable between studies, depending on respective experimental setup and conditions (Legind et al., 2011; Krause et al., 2022; Lamshoeft et al., 2018; McKone & Maddalena, 2007). Therefore, there is a need to standardize methods, protocols, and quality criteria to improve the reliability of measured TSCF or BCF in different food items.

Prediction of concentrations in roots is currently based in EUSES on equilibrium partitioning, which has been found to provide good results in case of thin roots or less lipophilic compounds (log $K_{OW} < 2$; Bontje et al., 2005; Legind & Trapp, 2009; Trapp, 2002), but often overestimate the concentration of lipophilic compounds by several orders of magnitude in thicker roots, such as carrots (Hughes & Mackay, 2011; Prosser et al., 2014).

Finally, EUSES does not consider particle-bound transport, which could facilitate the atmospheric deposition of particles to various food crops and subsequent foliar uptake by plants or deposition on soil and subsequent resuspension (Trapp & Schwartz, 2000; Trapp & Matthies, 1995). However, primary examples of this in the literature are for legacy chemicals or chemicals that would already undergo restrictions or regulatory actions under REACH. The potential for an underestimation of the uptake of chemicals that are transported via sorption to soil is demonstrated, for instance, for PCB uptake by lettuce (Trapp et al., 1999; Li et al., 1994). Another example is where uptake occurs via particles in the air, such as for benzo[*a*]pyrene gas exchange and particle deposition (JECFA, 1991; Phillips, 1999) and for polychlorinated dibenzo-*p*-dioxins, where uptake from air has been shown to be the dominant uptake pathway (Schuhmacher et al., 2006). Collins et al. (2006) summarize studies that demonstrate the relative importance of dry deposition and uptake for polycyclic aromatic hydrocarbons and polychlorinated dibenzo-*p*-dioxins, substances with log $K_{OA} > 9$–11. Wet deposition is thought to be the dominant deposition mechanism for substances with log $K_{AW} < -6$ but is generally not considered as an important route for leaf uptake. Collins et al. (2006) further summarize additional potentially significant processes such as plant metabolism and photolytic degradation on plant surfaces. Volatilization from the foliage is also a possible pathway via which chemicals can be removed from the plant, mainly for substances with a high water solubility and vapor pressure.

State of the science

Since the last update of the Technical Guidance Document on risk assessment (European Commission, 2003) and EUSES, several notable advances in scientific understanding and model capability have been made. For instance, the current model of Trapp & Matthies (1995; which uses the formulas developed by Briggs and Hsu to calculate the TSCF, the highest of both being used to estimate the concentrations in leaves), used in EUSES to estimate leaf and root concentration, has been significantly refined, as detailed below. New regression models for the TSCF and adjustments to assumptions have been introduced. An overview of the major studies on plant uptake and distribution with reported information on reliability and applicability is provided in online supplementary material Appendix. Briefly, Dettenmaier et al. (2009) derived a relationship between TSCF and log K_{OW} based on measurements of organic chemicals with log K_{OW} from -0.8 to 5, thereby covering the full range of the current models of Briggs et al. (1982) and Hsu et al. (1990). Although none of the currently available models gives accurate results for hydrophobic compounds with log $K_{OW} > 5$, it should be noted that uptake via xylem and phloem for these hydrophobic chemicals is likely to be negligible and therefore may not represent a significant source of uncertainty in model results (Trapp et al., 2003). Deposition onto foliage, on the other hand, may be more important for this type of substances.

For roots, the dynamic flux approach developed by Trapp (2002) also takes into account growth dilution, resulting in a more accurate estimation of the concentration in the core of the root. In addition, biodegradation in plants, which is an important dissipation process of chemicals from plants, could be considered in a higher-tier approach (Hurtado et al., 2016).

Whereas the original models used in EUSES were parameterized based on an understanding of the environmental fate and behavior of predominantly neutral nonpolar organic chemicals, there have been some promising developments in the handling of polar and ionizable organic chemicals. Schriever and Lamshoeft (2020), for instance, have developed and applied a model that corrects K_{OW} based on the application of the Henderson-Hasselbach equation and results in the derivation of the pH-corrected log distribution coefficient or log D, thereby enabling capability to model the uptake of ionizable organic chemicals by plants. It would be valuable to consider and compare the model performance between organic acids and bases. Log D models are likely to demonstrate better performance for organic acids, but they may be less accurate for bases. The reason lies in the sorption interactions experienced by organic cationic chemicals, which are not addressed by nonspecific van der Waals interactions. In particular, cations will encounter additional electronic interactions due to the prevalence of negatively charged surfaces in the environment, whereas acids will predominantly be influenced by the nonspecific interactions described by K_{OW}. As a result, Log D is expected to work well for acids but may exhibit reduced accuracy for bases in exposure assessments.

Although plant models require input of plant-specific parameters and assumptions on the specific environmental compartment, generic, and often arbitrary values are used, which can have a major effect on the outcome of the model (Collins et al., 2006; European Commission, 2003). Apart from an evaluation of these default values for future improvement of the models, a higher-tier refinement option could be used to introduce opportunities for flexibility in input parameters and/or the adoption of specific algorithms where data are available and the respective

approach is identified as a relevant and reliable alternative. This would enable opportunities to account for plant-specific data, including soil particle resuspension and deposition from air, as relevant for hydrophobic organic chemicals (Trapp, 2015; Trapp & Schwartz, 2000), plant mass, differences in transpiration rates, surface area, etc. (Rein et al., 2011).

Overall, van de Meent et al. (2014) recommend including the model of Dettenmaier et al. (2009) for log K_{OW} -0.8 to 5 in EUSES as well as the dynamic root crop dilution model of Trapp (2002) and Legind and Trapp (2009) as discussed by Franco et al. (2011a). For ionizable compounds, the model of Schriever and Lamshoeft (2020) for leafy crops could be included. Further research to improve EUSES as a screening model should be oriented towards an improved leafy crop model for very lipophilic substances with log $K_{OW} > 5$ and a leafy crop model to consider aerial particle bound deposition of particles on crop cover and subsequent foliar uptake by plants or soil resuspension.

Meat, milk, and dairy product exposure

Conceptual approach

In EUSES, the BCF or BTF is used to characterize the uptake of chemicals from the environment to cattle. Cattle are exposed to chemicals via the ingestion of grass fodder, drinking water, soil particles deposited on grass, and via inhalation. Cattle are used as a surrogate for meat ingestion because other meat sources, such as pork and chicken, are not explicitly considered. All dairy products in EUSES are also combined in the "milk and dairy products" category. Milk, however, contains less fat than cheese and butter, and thus, the exposure in cheese and butter may be underestimated, largely because fat has the tendency to accumulate lipophilic compounds. Because the relative differences in fat content of milk, cheese, and butter are not captured in respective exposure calculations, these foodstuffs may not be well predicted, depending on the relative consumption of these food product categories. A future solution might be to consider the exposure to milk fat instead of exposure to milk and dairy (Bontje et al., 2005). This would better cover both lipophilic and water-soluble compounds.

Applicability domain and reliability

The transfer from feedstuff to meat and dairy products is obtained by means of the BCF or BTF factors, which are calculated in EUSES from K_{OW} as described by Travis and Arms (1988). The BTF calculation for meat is derived from data on 36 organic compounds, with a log K_{OW} range of 1.34–6.89. The BTF calculation for milk was derived from data on 28 organic compounds, with a log K_{OW} range of 2.81–6.5. For substances with higher values of log K_{OW}, the BTFs may be greatly overestimated, whereas for substances with relatively low log K_{OW} (< 1), BTFs may be underpredicted (Birak et al., 2001). In Arnot et al. (2010), RAIDAR cow/grass BTF factors are reported within one order of magnitude of the monitoring data for hexachlorobenzene (HCB) and PCB-153. EUSES BTFs are within one order of magnitude of the monitoring data for PCB-153, whereas HCB is underestimated by a factor of approximately 30.

State of the science

Despite concerns about the accuracy of the Travis & Arms (1988) regressions, a refined regression analysis did not lead to more accurate results (Birak et al., 2001; Legind & Trapp, 2009). Instead, Dowdy et al. (1996) developed a QSAR BTF model based on a molecular connectivity index, which improved the regression fit for milk (from $r^2 = 0.55$ to $r^2 = 0.89$) and for meat (from $r^2 = 0.66$ to $r^2 = 0.90$; Dowdy et al., 1996), whereas the range of the applicability domain remained the same as in Travis and Arms (1988). The BTF equations could also be replaced by a mechanistic steady-state model for bioaccumulation in cattle, such as the OSIRIS model by Franco et al. (2011a), which is based on McLachlan (1994). From this mechanistic model, concentrations in beef and milk are calculated with a default parameterization based on standard EUSES input. Metabolic transfer rates can optionally be used as input. The comparison of the EUSES and OSIRIS models yielded considerable differences in human exposure via meat and dairy products (Franco et al., 2011a). The differences were particularly large for (but by no means limited to) chemicals subject to biotransformation, which is considered by OSIRIS but not by EUSES. For example, considering cattle and persistent chemicals, fairly constant (and higher than EUSES) BTFs were predicted by OSIRIS in the log K_{OW} range of 3–6; with BTF values then dropping at higher K_{OW} (i.e., where EUSES BTFs are at maximum value). Indeed, the relationship between BTF and K_{OW} in the OSIRIS model is consistent with experimental observations for persistent chemicals, whereas the Travis and Arms model is not (Hendriks et al., 2007; McLachlan, 1994).

In summary, the more reliable model of Dowdy et al. (1996) could be easily implemented in EUSES to improve reliability of BTF predictions. As proposed by van de Meent et al. (2014), the bioaccumulation model for meat and milk would benefit from updates considering the findings of the OSIRIS project (Franco et al., 2011a). However, more research is needed to characterize the applicability domain of the suggested meat and milk BTF models from OSIRIS and the reliability outside the applicability domain, i.e., for hydrophilic (log $K_{OW} < 2.8$) and hydrophobic (log $K_{OW} > 6.5$) substances as well as for polar compounds and weak acids and electrolytes.

Fish exposure

Conceptual approach

Only freshwater fish consumption is considered in the default screening HvE assessment under REACH. Schwartz et al. (2000) suggested a distinction could be made between marine and freshwater fish, and also for highly fatty fish, such as eel. Considering that fish consumption can have a large contribution in the total human intake, consideration of marine fish could be justifiable in a higher-tier approach, because freshwater and marine concentrations can easily differ by minimum one order of magnitude (Bontje et al., 2005; De Brouwere et al., 2022; Arnot et al., 2010).

Fish concentration for human intake is calculated in EUSES by multiplying a BCF with the total PEC water without considering biotransformation. This approach does not consider some processes, such as biotransformation (i.e., loss process) and dietary fish uptake, and biomagnification along the food chain. The effect of the contribution of these processes will depend on the combined properties of the substance. For example, for substances that undergo fish metabolism, the BCF may be overestimated and thus overestimate concentration in fish. For substances that are very persistent and have very high K_{OW}, dietary uptake and biomagnification may also be relevant. For these types of substances, dietary uptake may represent an important mechanism by which hydrophobic organic chemicals accumulate in fish, as well as biomagnification along the fish food chain (i.e., accounting for the consumption of predatory fish; van de Meent et al., 2014).

Applicability domain and reliability

If measured BCF values are not available, the BCF is calculated by default in EUSES based on Veith et al. (1979) for log K_{OW} 1–6;

and a parabolic equation is used for log K_{OW} 6–10 (ECHA, 2016). The models are valid for chemicals with molecular weight below 700 g/mol, but overestimates BCF values for chemicals with molecular weight above 700 g/mol. Also, this model should not be used for surface active substances and inorganic compounds, for which use of measured BCF values is recommended (European Commission, 2003). Arnot et al. (2010) compared predicted BCFs in EUSES and bioaccumulation factors (BAFs) in RAIDAR for fish. The RAIDAR BAFs are greater than the EUSES BCFs when metabolic biotransformation rates are not included as a result of the RAIDAR model including biomagnification and using a greater lipid content parameterization; thus, these parameters could be explored further. It should be noted that this comparison does not include biotransformation and thus whether EUSES would underestimate BCF compared with RAIDAR when this process is included was not evaluated, and biotransformation represents an important process for substances that undergo metabolism. Although Arnot et al. (2010) found that EUSES BCFs underestimate measured field BAFs by more than one order of magnitude for hexachlorocyclohexane and HCB and by two orders of magnitude for PCB-153, these examples are for materials that are already restricted (e.g., Stockholm Convention on persistent organic pollutants [POPs]) or have very persistent, very bioaccumulative properties (ECHA, 2017), and this finding is not necessarily representative for the majority of the chemicals within the domain of EUSES.

State of the science

Since the last EUSES update, several alternative fish BCF QSARs have been developed. For example, Franco et al. (2011a) propose updated equations to estimate the BCF and biomagnification factor (BMF) for bioaccumulation of neutral organic chemicals in the aquatic food chain. Meylan et al. (1999) developed an algorithm that classifies a substance as either nonionic or ionic, the latter group including carboxylic acids, sulfonic acids and their salts, and quaternary N compounds. Log BCF for nonionics is estimated from K_{OW}, and a series of correction factors, if applicable, with different equations being applied for log K_{OW} 1.0 to 7.0 and log $K_{OW} > 7.0$. The correlation coefficient ($r^2 = 0.73$ for 694 chemicals) indicates that the new method is a significantly better fit to existing data than other methods. Fu et al. (2009) developed a BCF QSAR for ionizable compounds based on a database with BCFs of 73 acids and 65 bases collected from the literature. As another example, Petoumenou et al. (2015) reported a correlation coefficient r^2 of about 0.5 for a dataset of 148 measured and VEGA (Benfenati et al., 2013)/BCFBAF (USEPA, 2012)-predicted BCF values. By taking into account the applicability domain for the Virtual models for property Evaluation of chemicals within a Global Architecture (VEGA) QSARs, the r^2 markedly increased to > 0.77. Lunghini et al. (2019) developed a new BCF QSAR based on fragment descriptors that showed a similar performance to VEGA, BCFBAF, the Toxicity Estimation Software Tool (TEST; Martin et al., 2012), and Open (Quantitative) Structure-activity/property Relationship App (OPERA); Mansouri et al., 2018) for a validation set of 204 chemicals but had a much higher coverage of industrial chemicals (78%) and a broad log BCF range of -1 to 6 (compared to already existing QSAR models).

In summary, several alternative QSARs are available that are more reliable and cover other chemical groups outside current applicability domain of EUSES, especially for biomagnifying compounds. van de Meent et al. (2014) proposed to replace the equations in EUSES for bioaccumulation of neutral organic chemicals in the aquatic food chain with updated equations to estimate the BCF and BMF, based on, e.g., Franco et al. (2011a). Although many improved methods are available and discussed elsewhere (e.g., Arnot et al., 2010), additional consensus-seeking is needed to decide on the best overall approach. This is especially significant for strongly bioconcentrating/bioaccumulating chemicals (log $K_{OW} > 5$) where potential biotransformation can have a great impact on the predicted fish BCF and associated risks for human consumption.

Air/inhalation exposure

Conceptual approach

Air concentration in EUSES is estimated using a simplified operational model for priority substances at a 100-m distance from a central stack considering standard Dutch weather conditions (Vermeire et al., 1997). Fugitive emissions are not explicitly considered. In contrast to PROTEX/INTEGRA (Table 1), no differentiation in indoor and outdoor concentrations is made in EUSES for reasons of simplicity.

Applicability domain and reliability

There is limited information in the scientific literature. In Arnot et al. (2010), the human intake fractions calculated by RAIDAR and EUSES are compared considering four emission scenarios for selected POPs (hexachlorocyclohexane, hexachlorobenzene, and hexachlorobiphenyl) and petrochemicals. The greatest differences in calculations are for a scenario with emissions to air, with RAIDAR predicted human intake fractions being about 10–30 times higher. Indeed, RAIDAR predicts concentrations in air that are approximately five times greater than PECs in EUSES (Arnot et al., 2010). However, these examples are for materials that are already restricted because of their properties (e.g., Stockholm Convention on POPs), and thus may not be representative and outside the applicability domain for the majority of chemicals.

State of the science

Overall, little development occurred over the previous years in screening prediction models for concentration in local air. Franco et al. (2011b) developed a modified version of the multimedia activity model for ionics, including two-layered atmosphere, air–water interface partitioning, intermittent rainfall, and variable cloud coverage to simulate the atmospheric fate of ten low volatility or ionizable organic chemicals. They highlighted that atmospheric water determines the transport potential of low volatile organics, and that clouds can store and transport surface active chemicals (perfluorooctanoic acid). A Gaussian plume model can be used as a higher-tier model to generate more realistic predictions of local (point-source) air emissions ($C_{local\ air}$) compared to predictions by the EUSES model. Still, Gaussian plume models need additional input parameters on point sources (e.g., stack position, stack height and diameter, and temperature of gases at stack orifice).

Drinking water exposure

Conceptual approach

Drinking water exposure is by default obtained in EUSES as either the predicted groundwater concentration or the predicted surface water concentration, whichever is higher.

For surface water, the following challenges were identified. First, the derivation of the purification factor in EUSES (the factor to represent water purification procedures applied to surface water before it is used for drinking water) is based on a preliminary assessment of the removal percentage of organic chemicals by diverse treatment systems and has not been validated with new and more recent data (Bontje et al., 2005). Second, the worst-case scenario, which considers the most contaminated surface water

at the discharge point as the source for drinking water, can cause a great overestimation of the exposure through drinking water. Therefore, further research should improve the estimation of the purification factor, either through extending the underlying data set and checking for representativeness under REACH or by using drinking water treatment models to estimate the removal efficiency of a treatment process for a specific chemical. Additionally, modeling chemical transport in surface water to accurately quantify concentrations at realistic drinking water intake input locations rather than at discharge locations on rivers would also provide a more realistic representation of surface waters used for drinking water.

The groundwater concentration in EUSES is estimated as the pore water concentration of the top soil layer. The simplified modelling approach used in EUSES to derive the PEC in soil includes emissions from aerial deposition and sludge application, as well as considerations of various removal processes from soil, including degradation, volatilization, leaching, and other relevant processes. A key factor influencing the accumulation of a chemical in the soil compartment is the depth of the soil compartment, which has an influence on each of the loss processes. As the depth of the soil compartment increases or decreases, for instance, the relative importance of losses due to volatilization, leaching, and degradation can vary. Indeed, in an evaluation of EUSES, uncertainty in environmental parameters typically contributes more to overall output uncertainty than uncertainty in chemical-specific property data (Armitage et al., 2007). Nevertheless, a standard model environment is used to compare the relative environmental fate and exposure between different chemicals at a screening-level assessment: EUSES assumes a standard soil depth of 20 cm, with default values for volume fraction of solids in soil (0.6) and for fraction of air and moisture in soil (both 0.2). According to ECHA guidance (ECHA, 2016), the PEC in groundwater (PEC_{GW}) is derived by assuming equivalency to the soil pore water concentration in agricultural soil, with the bulk density of wet soil strongly influencing the PEC_{GW}. In reality, the groundwater compartment represents a saturated soil layer that is typically much greater than 20 cm in depth. Further, various environmental factors are known to influence the leaching of a chemical through the unsaturated soil zone prior to a chemical reaching groundwater, which could introduce a level of complexity inconsistent with a screening-level approach but may represent factors to be considered at a higher tier of evaluation (McKone & Bennett, 2003; Schwarzenbach et al., 2017). This is especially important given that drinking water is typically extracted from groundwater wells that are placed in aquifers that are deep below surface soils. Thus, using topsoil to represent groundwater concentrations is unrealistic as it does not consider chemical and fate transport (e.g., advection and dispersion) to realistic groundwater well locations that are well below the soil surface. Other refinements that affect ground water concentration, such as rates of sludge application to soil, could also be explored as parametrization updates.

Additionally, EUSES currently uses the maximum exposure from either groundwater or surface water, which does not consider the actual contribution of these two routes. Taking into account the amount of drinking water sourced from ground and surface water in the EU would provide more realistic estimates for exposure.

State of the science

For screening purposes, the method used in EUSES to derive drinking water concentration represents a conservative overestimate of exposure. A screening-level approach should ideally result in a higher number of false positives than of false negatives, which requires the adoption of a number of conservative but realistic assumptions. As long as a chemical fits within the applicability domain of the model parametrization, then the screening-level assessment should be sufficient to enable a reliable risk-based approach for prioritization of chemicals for higher-tier assessments. In this context, there is growing discussion regarding the potential for chemicals with high persistence and mobility as having a potential for exposure through drinking water. Refined modeling approaches are being used to improve the modeling of chemical fate into drinking water and these models are more predictive of drinking water exposure than screening based on a few physical properties alone (Zhang et al., 2023; Pawlowski et al., 2022; CEFIC LRI, 2023).

Other routes of exposure

In addition to the pathways provided by EUSES (as shown in Figure 1 and discussed above), various studies have reported additional exposure pathways in assessing HvE (See Table 1 for pathways covered in EUSES and higher-tier models). Depending on the tool and the tier, a higher granularity is foreseen for leafy crops, root crops, meat or milk, e.g., for meat, a distinction is made between poultry, beef, pork, and eggs. The incidental soil and dust exposure pathway, especially relevant for children, is currently not included in EUSES except for cattle. However, it is considered in other screening and higher-tier tools such as CalTOX, PROTEX-HT, MERLIN-Expo, and INTEGRA. Also, the CSOIL model includes indirect dermal exposure to dust and soil, dust inhalation, and showering (Bontje et al., 2005). The dermal showering exposure route is an indirect pathway via tap water (note that direct exposure to personal care products, such as soap, is considered in consumer exposure assessments). Models like CalTOX and INTEGRA account for dermal uptake from water, such as through swimming or bathing, which is identified as a key route for some substances, such as polycyclic aromatic hydrocarbons (CONCAWE, 2017).

Bontje et al. (2005) assessed the relevance of different exposure pathways by modeling 31 representative compounds with varying physico-chemical properties (high and low vapor pressure, K_{OW}, ionizable compounds). The most important pathways contributing to exposure across all simulated compounds were the following four routes (not in order, as this depends heavily on emission compartment and physical-chemical properties): air, root crops, drinking water, and fish, which are all included in EUSES. Roots, stems, and leaves, as well as meat and milk, were also important pathways, but less significant than the above four. In contrast, the exposure routes of soil ingestion, dust inhalation, and dermal exposure to dust were found to hardly contribute to the total exposure in this sample of 31 compounds. Direct soil contact was not very important for exposure to background concentrations, contrary to local contaminated soil scenarios. Also, Zhao et al. (2015) demonstrated that EUSES, RAIDAR, and ACC-HUMANsteady all have a good ability to identify key dietary exposure pathways, which can be used for screening purposes and an evaluative risk assessment.

Based on the findings of these studies, it can be concluded that, for many chemicals, additional exposure pathways may not be necessary in a screening level assessment, as the dominant exposure pathways are already included in EUSES. However, in cases where the screening risk characterization ratio for HvE is close to one, an assessment of additional exposure pathways may be required to ensure a comprehensive evaluation.

Food consumption

Conceptual approach

Once food item concentrations (expressed as mg/kg food) have been calculated, these are further multiplied by food consumption rates (expressed as kg food/day) to calculate human intake of substances (expressed as mg/kg body weight/day). In EUSES, a generic food basket is defined that describes the quantities for different food types that are consumed. The individual food types and consumption rates are derived from the highest country-average consumption rate observed across member states, consistent with a conservative exposure estimate of chemicals via the food basket (ECHA, 2016). Additional conservatism is built in at the local scale, whereby populations are assumed to consume 100% of their food obtained from the immediate vicinity of a local point source (e.g., entire fish consumption coming from locally caught fish at the discharge point).

Applicability domain and reliability

The impact of dietary preferences on human exposure pathways was demonstrated by Zhao et al. (2015) when comparing a default Western diet and a Chinese dietary scenario as modeled by three frequently used tools (EUSES, RAIDAR, and ACC-HUMANsteady), indicating that a relatively high consumption of vegetables and cereals can result in higher exposure via plant-based foodstuffs. In this context, it is notable that consumption rates of various food types are highly dynamic, with studies observing a shift in dietary patterns. For instance, guidelines published in many countries recommend consuming lean meat in moderation, with many recommending limiting the intake of red and processed meat (Cocking et al., 2020). Therefore, Haug et al. (2017) and ECHA (2018) have suggested that the generic food basket used in EUSES (ECHA, 2016) be updated to reflect a more realistic scenario, but that it should maintain a reasonable level of conservatism.

State of the science

Commonly used approaches to calculate human intake of substances adopt estimates based on distributions of consumption rates for various food categories, using the upper 95% probability distribution data, similar to approaches used by the World Health Organization (WHO, 2006) and the Scientific Committee on Consumer Safety (SCCS, 2023). Several relevant databases that contain food consumption data of EU member states are available: the European Food Safety Authority (EFSA) food consumption database (EFSA, 2022), the European Commission Joint Research Centre (JRC) ExpoFacts database (JRC ExpoFacts, n.d.; Zenié & Reina, 2007), and food consumption data in the PRIMo model (EFSA, 2019).

In addition, the relevance of the assumption that populations consume 100% of their food from the local vicinity is potentially insufficient to assess exposure to chemicals when considering the global import and export of food and beverages (Ng & von Goetz, 2017). The EUSES model currently assumes that the diet of humans living in the vicinity of a local industrial site completely originates from locally grown crops throughout the entire year, locally produced drinking water, locally grazing cattle, all in the immediate vicinity of the industrial site (or sewage treatment plant for widespread uses), and locally caught fish in the surface water at the discharge point of the local industrial site (ECHA, 2016). A more realistic worst-case representation would be to consider a mixed diet where during half of the year e.g., no local consumption is assumed as crops are typically harvested in particular seasons and food is bought from grocery stores or supermarkets (i.e., not locally produced), and for the remaining part of the year, locally produced food is consumed. This approach would be more aligned to the secondary poisoning assessment under REACH (ECHA, 2016) in which mixed diet from local and regional scale is proposed for top predators.

In conclusion, updating the EUSES food basket at both regional and local scales would be needed to reflect current dietary trends for screening and higher-tier assessments to accurately reflect current dietary trends. Further, food source at the local scale should be updated to better reflect a realistic worst-case scenario aligned with secondary poisoning assessment.

Use of monitoring data

In addition to modeling approaches, the state of the science increasingly recognizes the importance of utilizing monitoring data as an alternative to screening level or higher-tier assessment. As both modeling and monitoring data have their advantages and disadvantages, it is recommended to consider these assessments in parallel (ECHA, 2016). Monitoring data can be collected at three levels: (1) in environmental matrices (e.g., water, air, soil, groundwater, not further elaborated here), (2) in food items (crops, meat, milk, fish), or (3) in human matrices (e.g., blood, urine).

Food monitoring data

In the EU, EFSA receives data on the occurrence of chemicals in food items from various sources and reports the results of food analyses conducted for different purposes (e.g., surveillance or targeted analyses at hot spots) reporting threshold exceedances, although the quantification limits vary (Haug et al., 2017). Although less relevant for the EU, the HvE model SHEDS-HT (Isaacs et al., 2014) is another example of using large records on (food) monitoring data in the United States (Zartarian et al., 2008). The model equally emphasizes dietary and nondietary exposure (residential exposure), including exposure via hand-mouth contact, indoor air exposure, etc. As SHEDS-HT is intended for probabilistic use only, it cannot be readily simplified into a deterministic version. Additionally, SHEDS-HT can be coupled with models that estimate exposure via the environment, as shown in Csiszar et al. (2016). This again supports the consideration of multiple scenarios or a probabilistic approach in EUSES.

Biomonitoring

Use of human biomonitoring data can be considered the gold standard for integrated exposure assessment and can therefore be one of the highest tiers of an exposure and risk assessment for certain substances (Sexton et al., 2004). Alternatively, physiologically based pharmacokinetic modeling can be used to translate external dose into internal dose or to back-calculate external intakes based on human biomonitoring data (Haug et al., 2017). Human biomonitoring data reflect an integrated, internal exposure over time encompassing various sources and pathways. Such data have been published under the European Human Biomonitoring Initiative (HBM4EU) and are available at the Information Platform for Chemical Monitoring (IPCHEM, 2022). However, internal exposure does not align with the approach under REACH, where external exposure is compared to "external" derived no-effect levels. Additionally, adequate collection of biological specimens representing a given population can be resource intensive. Furthermore, human biomonitoring does not provide information on the relative importance of different routes and exposure pathways, which can be a significant limitation if distinguishing between consumer exposure and indirect HvE exposure is essential. Moreover, depending on the chemical

characteristics, biomonitoring data can have limitations with regard to analytical methods, sampling, metabolism, etc. Hence, if possible, both intake estimations and human biomonitoring should be considered in parallel to achieve a more comprehensive understanding. Examples of such combined use of biomonitoring and modeling can be found in Wittassek et al. (2011) and Koch et al. (2013).

Overall, integrating both modeling and monitoring data, including biomonitoring, contributes to a more robust and informed assessment of human exposure to chemicals via the environment.

Identification of chemical category research and regulatory HvE model update needs

Each submodule within EUSES represents an exposure pathway or food item, collectively estimating HvE. However, it is important to recognize that each submodule, along with its associated parameters, operates within its specific applicability domain and exhibits varying degrees of reliability. EUSES, as it stands, is predominantly suitable for assessing neutral nonionizable organics within a limited K_{OW} range. EUSES estimations for substances with K_{OW} values beyond this domain or belonging to other chemical groups require careful consideration, as they may introduce higher uncertainty and reduce the reliability of model predictions (Franco et al., 2011a). Consequently, when dealing with such substances, and especially in cases where the HvE risk characterization ratio is close to or above one, additional caution and potentially more refined modeling approaches may be necessary.

It has been suggested that no single approach will be able to address all exposure assessments for all types of chemicals, i.e., there is no "supermodel" (Trapp & Schwartz, 2000). Identifying a modular set of alternative "simple" submodels and developing guidance indicating when each approach is most justified would represent a potentially effective and efficient approach towards refining the exposure assessment of HvE. In the context of an HvE tiered process, a common approach is to focus refinement efforts on the exposure pathway(s) identified as being the most contributing (De Brouwere et al., 2022). The significance of the most contributing exposure pathways can vary based on two primary factors: (1) the physicochemical properties of the substance (such as K_{OW}, K_{OA}, vapor pressure, molecular weight, acid-base dissociation coefficient, pH, etc), and (2) the substance use patterns and exposure scenarios (e.g., emissions to air from an industrial site releasing dust or volatile compounds or emissions to water from an industrial site discharging into surface water). In the subsequent subsections, we explore how different chemical groups have been reported to interact with various emission scenarios and their impact on HvE exposure pathways using various HvE models such that regulatory and research update needs can be tailored to a chemical group and exposure pathway combination. Although dominant HvE exposure pathways are among those compared, they do not necessarily represent the overall dominant exposure pathway, as they do not include direct exposure pathways, e.g., exposure during product use (Jolliet et al., 2015; Csiszar et al., 2016). Additionally, they represent model results and thus chemical group and emission compartment combinations to further explore in terms of model updates and results.

Neutral (particularly volatile organics) and ionizable chemicals in emission to air scenario

Chemicals can be emitted to air due to volatilization, adsorption to dust and particulate matter, combustion or aerosolization. Volatilization is mainly driven by the vapor pressure, Henry's constant or the octanol air partition coefficient (K_{OA}). Franco et al. (2010) demonstrate that most ionizable compounds in the REACH chemical space are non- or semivolatile.

For most chemicals in emission to air scenarios in USEtox, inhalation and leafy crops are the important exposure pathways (Rosenbaum et al., 2011). The relative importance of ingestion and inhalation can be viewed as a function of K_{OA}: for log K_{OA} above 6, ingestion is the dominant route, but below this log K_{OA} value, substances have a higher inhalation intake fraction (Rosenbaum et al., 2011). Li et al. (2021) equally identified dietary ingestion and inhalation as important for solvents. Using sensitivity analysis on a EUSES-based model, Bontje et al. (2005) identified that (neutral) compounds with high vapor pressure and low solubility will be mainly present in the air, predominantly causing inhalation exposure (examples in Bontje et al. [2005] are methanol, tetrahydrothiophene, butylacetate, methyl *tert*-butyl ether, methyl ethyl ketone, ethylacetate, and cumene). Only when the concentrations in the air and surface water compartment are low is there the tendency that root exposure can be significant (Bontje et al., 2005). In particular, weak acids (within a certain K_{OW} range), such as many foliar applied systemic herbicides, tend to have the most favorable properties for leaf uptake, concentration in the phloem of the target plant and translocation to the roots (European Centre for Ecotoxicology and Toxicology of Chemicals; ECETOC, 2013). Kelly et al. (2007) showed that poorly metabolizable, moderately hydrophobic substances with a log K_{OW} between 2 and 5, which do not biomagnify in aquatic food webs, can biomagnify to a high degree in food webs containing air-breathing animals (including humans) because of their high K_{OA} and corresponding low rate of respiratory elimination to air. These low K_{OW} –high K_{OA} chemicals, representing a third of organic chemicals in commercial use, constitute an unidentified class of potentially bioaccumulative substances that are not covered by the existing models. This would suggest that also meat and milk could potentially be significant exposure pathways in emission to air scenario.

Regulatory updates in EUSES and research needs in an emission to air scenario should therefore focus on (1) an increased K_{OW} applicability domain for air/inhalation and leafy crop exposure pathways for neutral chemicals (and air-breathing animal biomagnification for particularly volatile organics) and (2) leaf uptake models for ionizable chemicals.

Neutral nonionizing hydrophilic organics (with low log K_{OW}) in emission to water scenario

Neutral nonionizing hydrophilic organics are water soluble and when emitted to the water compartment, partitioning to other compartments (e.g., air, soil) will not be a dominant removal process. As such, when using multimedia HvE fate models, drinking water is mostly reported as the resulting modeled dominant route for neutral nonionizing hydrophilic compounds, e.g., glyphosate, hydrochlorofluorocarbon-22 as described in Rosenbaum et al. (2011) for USEtox scenarios with emission to freshwater, or ethylene glycol, hexachlorobutadiene, ethyl acetoacetate, chlorocresol, and 4-chloro-*m*-cresol as described in Bontje et al. (2005). However, as discussed previously, these models could be updated to include, e.g., more realistic drinking water purification removal and fate processes that could substantially alter the results from these models.

The groundwater estimation approach used in EUSES (20 cm soil layer with 20% water content) may represent an appropriate level of conservatism. However, having a more reliable model could help to better implement a screening level risk-based

approach, as opposed to using a hazard-based screening approach for this exposure pathway as discussed in Zhang et al. (2023).

Further research for neutral nonionizing hydrophilic organics (with low log K_{OW}) in emission to water scenario should therefore be oriented towards modeling these compounds and accounting for their degradability and removal in drinking water treatment systems.

Neutral nonionizing hydrophobic organics (with high log K_{OW}) in emission to water scenario

Rosenbaum et al. (2011) found that, for USEtox scenarios with emission to freshwater, substance ingestion is strongly controlled by its n-octanol/water partition coefficient. At high K_{OW}, there is a set of chemicals for which the dominant ingestion pathway is dairy products or fish, due to consumption of water and substance bioconcentration by dairy cows or fish respectively (such as PCB-77 (3,3,4,4-tetrachloro-biphenyl), tetrachlorodibenzodioxin, and azocyclotin). Bontje et al. (2005) similarly concluded, based on model simulations, that a higher K_{OW} and lower solubility imply more substance exposure through fish, roots, meat, and milk (examples are dodecylbenzene, acrylaldehyde, and ivermectin). A combination of high K_{OW} and a higher molecular weight potentially leads to even higher soil concentrations, which means increased exposure through root, meat, and milk ingestion (Bontje et al., 2005; examples are chloro-alkanene, bis-pentabromophenylether, pentabromodiphenylether).

Further research for neutral nonionizing hydrophobic organics (with high log K_{OW}) in emission to water scenario should be oriented towards identified improvements above for fish, roots, meat, and milk and taking into account higher tier bioaccumulation models that incorporate metabolism and biotransformation to ensure more realistic scenarios.

Ionizable compounds

The usual pH in surface waters is between 6 and 8. Thus, a substance is considered as ionizable in the environment if it comprises an acid pKa <7 or a basic pKa >7 at a natural pH range (~6 to ~8), meaning it will at least be partly ionized in that pH range. The K_{OW} of the analyzed ionizable chemicals registered under REACH (Franco et al., 2010) varies over more than 10 orders of magnitude with the most frequent log K_{OW} values ranging between 0 and 4, and there is a high occurrence of hydrophilic chemicals. Examples include cationic triethanolamine, anionics cyclohexylamine, methacrylic acid, ibuprofen, and zwitterionic oxytetracycline. The substances that are mostly ionized at pH 7 are frequently polar in the neutral form, but lipophilic ionics occur as well. Long lipophilic structures with a polar ionizable head (e.g., surfactants) fall into this category.

ECETOC (2013) characterized the equilibrium chemical space for ionizable organic compounds using modeling and assessed how the partitioning behavior of chemicals might change as a function of pH, pK_a and their partition coefficients. The behavior of acids and bases differ from each other, with the suggestion that the sorption of ionized bases (i.e., cationics such as methylene dianiline) being significantly greater than that of the ionized acids (i.e., anionics such as methacrylic acid). They also suggested that cationic materials with relatively low log K_{OW} values may partition to a relatively significant extent, and thus sorption to solids can be an important fate process, whereas ionized acids even with relatively high log K_{OW} values may show limited partitioning to solids. It could also be derived that a higher pK_a (at high log K_{OW}) will lead to more sorption compared with lower pK_a.

The identification of the predominant pathways and their associated regulatory update and research needs are very similar to those of neutral organics as set out in the above three subsections with the main difference that the log K_{OW} cut-offs are different: Ionizing anionics are still hydrophilic at higher log K_{OW} and ionizing cationics are still hydrophobic at lower log K_{OW}. Further research for ionizable and inorganic substances should specifically be oriented towards QSAR development and/or protocols or quality criteria to measure TSCF or BCF for leafy crops, root crops, meat and milk.

Conclusion

This review highlights that EUSES serves as a HvE screening tool and a conservative first step in a tiered approach but requires refinement to reduce uncertainties at higher tiers. However, the HvE assessment in EUSES insufficiently represents the current state of the science and is mainly applicable to neutral nonionizable organic substances within only a narrow log K_{OW} range. Expanding the applicability domain of the EUSES HvE submodels and reliability of the existing exposure pathways can provide a tool that can be used to prioritize for higher-tier assessments not only for nonionized organic substances and within a limited K_{OW} range but also for some organic substances outside the original applicability domains and for ionized organics. Several new models, such as those for predicting concentrations in crops, fish, meat, milk, and dairy products, could be readily integrated to improve screening-level assessments in EUSES. However, updates should demonstrate the new models' enhancements to EUSES, especially for substances outside the applicability domain, and additional consensus seeking is necessary to determine the best overall approach.

Updating the EUSES food basket using recent EU food consumption data at both regional and local scales is crucial to accurately reflect recent dietary trends. Likewise, updating the food source at the local scale to represent a realistic worst-case scenario is critical, particularly for nonthreshold impact assessments under REACH.

Improvements to the ECHA guidance are recommended to better highlight the level of conservatism, the possible refinements in HvE assessments, including the possible integration of higher-tier data, such as chemical property data, monitored environmental concentrations, and (bio)monitoring data. Additionally, providing a comprehensive list of available screening and higher-tier HvE exposure models and their associated applicability domains and limitations, as part of a tiered HvE approach, is crucial for enhancing the HvE assessment process. Risk assessment in REACH registrations demands reasonable worst-case estimates, whereas impact assessment in REACH authorization and restriction requires more realistic evaluations, so the level of conservatism depends on the purpose of the assessment. Introducing a functionality to simulate average and reasonable worst-case predictions would enhance the utility of EUSES.

Other improvements identified in the scientific literature are not directly implementable in EUSES and require further research. This includes an improved leafy crop model for very lipophilic substances with log $K_{OW} > 5$. Also, leaf crop exposure (relevant for emission to air scenarios) needs to consider aerial deposition of particles on crop cover and subsequent foliar uptake by plants or soil resuspension. For drinking water, updates to models could focus on methods to estimate degradability and removal in drinking water treatment systems, accounting for

transport to drinking water intake locations, the assumptions in the soil pore water concentration calculations, accounting for transport to groundwater wells well below surface soils, and accounting for the relative amount of drinking water from both ground and surface water sources would help to better identify more realistic exposures.

Further research for ionizable substances should specifically be oriented towards QSAR development for chemical properties and/or protocols or quality criteria to measure TSCF or BCF for leafy crops, root crops, meat and milk.

Currently, workarounds are needed to deal with the shortcoming of the existing EUSES tool. Applying the workarounds and explaining them to stakeholders takes time. Hence, avoiding workarounds through an updated risk assessment guidance and tool will provide opportunities for a more efficient risk-based process of managing the use of chemicals.

The table in online supplementary material Appendix can be consulted to infer the impact of the proposed HvE updates on risk assessment outcomes. However, case studies to explore the impact of the proposed updates are beyond the scope of this work. The objective of this review was to identify options for expanding applicability domains and improving the degree of realism of HvE assessments, based on new scientific developments. Many of the suggestions for updating EUSES are aligned with this objective and aim to make the tool more reliable.

Supplementary material

Supplementary material is available online at *Integrated Environmental Assessment and Management*.

Data availability

All studies reviewed in this manuscript are available in the published literature. Any further details may be requested from the lead author (Johannes Tolls, johannes.tolls@henkel.com).

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Conflicts of interest

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Task Force members from industry are employed by companies producing a range of chemicals. The issues of assessment of human exposure via the environment impact substances of interest to these companies. The manuscript was subjected to the usual internal peer-review process required by the companies, and only few minor, mostly editorial changes were requested. The manuscript was also reviewed by the ECETOC Scientific Committee consisting of representatives of academia and industry (http://www.ecetoc.org/about-ecetoc/scientific-committee/). This review yielded relatively minor comments.

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References

Armitage, J. M., Cousins, I. T., Hauck, M., Harbers, J. V., & Huijbregts, M. A. J. (2007). Empirical evaluation of spatial and non-spatial European-scale multimedia fate models: Results and implications for chemical risk assessment. *Journal of Environmental Monitoring: JEM*, 9, 572–581. https://doi.org/10.1039/b700680b

Arnot, J. A., & Mackay, D. (2008). Policies for chemical hazard and risk priority setting: Can persistence, bioaccumulation, toxicity, and quantity information be combined? *Environmental Science & Technology*, 42, 4648–4654. https://doi.org/10.1021/es800106g

Arnot, J. A., Mackay, D., Sutcliffe, R., & Lo, B. (2010). Estimating far-field organic chemical exposures, intake rates and intake fractions to human age classes. *Environmental Modelling & Software*, 25, 1166–1175.

Benfenati, E., Manganaro, A., & Gini, G. (2013). VEGA-QSAR: AI inside a platform for predictive toxicology. In *Proceedings of the workshop "Popularize Artificial Intelligence 2013"* (Vol. 1107). Published in CEUR Workshop Proceedings. https://www.vegahub.eu/portfolio-item/vega-qsar/

Birak, P., Yurk, J., Adeshina, F., Lorber, M., Pollard, K., Choudhury, H., & Kroner, S. (2001). Travis and Arms revisited: A second look at a widely used bioconcentration algorithm. *Toxicology and Industrial Health*, 17, 163–175. https://doi.org/10.1191/0748233701th110oa

Bontje, D., Traas, T. P., & Mennes, W. (2005). A human exposure model to calculate harmonized risk limits. Model description and analysis. RIVM Report 601501022/2005.

Briggs, G. G., Bromilow, R. H., & Evans, A. A. (1982). Relationships between lipophilicity and root uptake and translocation of non-ionised chemicals by barley. *Pesticide Science*, 13, 495–504. https://doi.org/10.1002/ps.2780130506

CEFIC LRI. ECO54 (2023). Developing a tiered modelling framework in support of risk assessment of chemical substances associated with mobility concerns. https://cefic-lri.org/projects/eco-54-developing-a-tiered-modeling-framework-in-support-of-risk-assessment-of-chemical-substances-associated-with-mobility-concerns/.

Ciffroy, P., Alfonso, B., Altenpohl, A., Banjac, Z., Bierkens, J., Brochot, C., Critto, A., De Wilde, T., Fait, G., Fierens, T., Garratt, J.,

Giubilato, E., Grange, E., Johansson, E., Radomyski, A., Reschwann, K., Suciu, N., Tanaka, T., Tediosi, A., … Verdonck, F. (2016). Modelling the exposure to chemicals for risk assessment: a comprehensive library of multimedia and PBPK models for integration, prediction, uncertainty and sensitivity analysis—the MERLIN-Expo tool. *The Science of the Total Environment*, *568*, 770–784. https://doi.org/10.1016/j.scitotenv.2016.03.191

Cocking, C., Walton, J., Kehoe, L., Cashman, K. D., & Flynn, A. (2020). The role of meat in the European diet: Current state of knowledge on dietary recommendations, intakes and contribution to energy and nutrient intakes and status. *Nutrition Research Reviews*, *33*, 181–189. https://doi.org/10.1017/S0954422419000295

Collins, C., Fryer, M., & Grosso, A. (2006). Plant uptake of non-ionic organic chemicals. *Environmental Science & Technology*, *40*, 45–52. https://doi.org/10.1021/es0508166

CONCAWE (2017). CONCAWE workshop report "PAH integrated exposure modelling. *Report No 8/17. July 2017, Brussels*. Https://Www.Concawe.Eu/Wp-Content/Uploads/2017/07/Rpt_17-8.Pdf.

Csiszar, S. A., Ernstoff, A. S., Fantke, P., Meyer, D. E., & Jolliet, O. (2016). High-throughput exposure modeling to support prioritization of chemicals in personal care products. *Chemosphere*, *163*, 490–498. https://doi.org/10.1016/j.chemosphere.2016.07.065

Csiszar, S. A., Meyer, D. E., Dionisio, K. L., Egeghy, P., Isaacs, K. K., Price, P. S., Scanlon, K. A., Tan, Y. M., Thomas, K., Vallero, D., & Bare, J. C. (2016). Conceptual framework to extend life cycle assessment using near-field human exposure modeling and high-throughput tools for chemicals. *Environmental Science & Technology*, 50, 11922–11934. https://doi.org/10.1021/acs.est.6b02277

Czub, G., McLachan, M. S. (2004). A food chain model to predict the levels of lipophilic organic contaminants in humans. *Environmental Toxicology and Chemistry*, *23*, 2356–23366.

De Brouwere, K., Verdonck, F., Geerts, L., Navis, S., & Vanhamel, M. (2022). Assessment of human exposure to environmental sources of lead arising from the lead battery manufacturing and recycling sector in Europe: Demonstration of a tiered approach in a case study. *Journal of Exposure Science & Environmental Epidemiology*, 32, 418–426.

Dettenmaier, E. M., Doucette, W. J., & Bugbee, B. (2009). Chemical hydrophobicity and uptake by plant roots. *Environmental Science & Technology*, *43*, 324–329. https://doi.org/10.1021/es801751x

Dowdy, D., McKone, T., & Hsieh, D. (1996). Prediction of chemical biotransfer of organic chemicals from cattle diet into beef and milk using the molecular connectivity index. *Environmental Science & Technology*, *30*, 984–989.

ECETOC. (2013). Environmental exposure assessment of ionizable organic compounds. Technical Report No. 123. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium. https://www.ecetoc.org/wp-content/uploads/2021/10/ECETOC-TR-123-Environmental-risk-assessment-of-ionisable-compounds.pdf.

ECHA. (2012). European Chemicals Agency. Guidance on information requirements and chemical safety assessment. Chapter R.19: Uncertainty analysis. European Chemicals Agency, Report ECHA-12-G-25-EN, Helsinki, Finland

ECHA. (2016). Guidance on information requirements and chemical safety assessment. Chapter R.16: Environmental Exposure Estimation. Version 3.0, February 2016. European Chemicals Agency, Report ECHA-10-G-06-EN, 978-92-9247-775-2. Helsinki, Finland

ECHA. (2017). Guidance on information requirements and chemical safety assessment. Chapter R.11: PBT/vPvB assessment. European Chemicals Agency, Report ECHA-17-G-12-EN, Helsinki, Finland.

ECHA. (2018). Report from workshop on EUSES update needs. European Chemicals Agency, ECHA-18-R-13-EN. https://doi.org/10.2823/679687

ECHA. (2024). Key Areas of Regulatory Challenge. June 2024. European Chemicals Agency, Report ECHA-23-R-08-EN, 978-92-9468-381-6. Helsinki, Finland

EFSA. (2018). European Food Safety Authority. Guidance on uncertainty analysis in scientific assessments. *EFSA Journal*, *16*, 5123.

EFSA; Anastassiadou, M., Brancato, A., Carrasco Cabrera, L., Ferreira, L., Greco, L., Jarrah, S., Kazocina, A., Leuschner, R., Magrans, J. O., Miron, I., Pedersen, R., Raczyk, M., Reich, H., Ruocco, S., Sacchi, A., Santos, M., Stanek, A., Tarazona, J., Theobald, A., & Verani, A. (2019). Pesticide Residue Intake Model-EFSA PRIMo revision 3.1 (update of EFSA PRIMo revision 3). *EFSA Supporting Publications*, *16*, 15. https://doi.org/10.2903/sp.efsa.2019.EN-1605software available at. 2019; EN-1605. https://www.efsa.europa.eu/en/applications/pesticides/tools

EFSA. (2022). Food consumption data. European Food Safety Authority. Http://Www.Efsa.Europa.Eu/En/Food-Consumption/Comprehensive-Database. Date accessed December 9, 2022.

European Commission. (2003). Technical Guidance Document on Risk Assessment in support of Commission Directive 93/67/EEC on risk assessment for new notified substances, Commission Regulation (EC) No 1488/94 on risk assessment for existing substances, Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. Part III.

Franco, A., Ferranti, A., Davidsen, C., & Trapp, S. (2010). An unexpected challenge: Ionizable compounds in the REACH chemical space. *In International Journal of Life Cycle Assessment*, 15, 321–325. https://doi.org/10.1007/s11367-010-0165-6

Franco, A., *et al.* (2011a). Recommendations for adaptations of ECHA Guidance Documents (Report OSIRIS Deliverable D3.1.17), Technical University of Denmark.

Franco, A., Hauschild, M., Jolliet, O., & Trapp, S. (2011b). Atmospheric fate of non-volatile and ionizable compounds. *Chemosphere*, *85*, 1353–1359. https://doi.org/10.1016/j.chemosphere.2011.07.056

Fu, W., Franco, A., & Trapp, S. (2009). Environmental chemistry methods for estimating the bioconcentration factor of ionizable organic chemicals. *Environmental Toxicology and Chemistry*, *28*, 1372–1379. https://doi.org/10.1897/08-233.S1

Gredelj, A., Polesel, F., & Trapp, S. (2020). Model-based analysis of the uptake of perfluoroalkyl acids (PFAAs) from soil into plants. *Chemosphere*, *244*, 125534. https://doi.org/10.1016/j.chemosphere.2019.125534

Haug, L. S., Thomsen, C., & Sakhi, A. K. (2017). Report from a NEXPO workshop on human exposure to chemicals via the environment. Nordic Working Papers. http://dx.doi.org/10.6027/NA2017-922

Hendriks, A. J., Smítková, H., & Huijbregts, M. A. J. (2007). A new twist on an old regression: Transfer of chemicals to beef and milk in human and ecological risk assessment. *Chemosphere*, *70*, 46–56. https://doi.org/10.1016/j.chemosphere.2007.07.030

Hsu, F. C., Marxmiller, R. L., & Yang, A. Y. S. (1990). Study of root uptake and xylem translocation of cinmethylin and related compounds in detopped soybean roots using a pressure chamber technique. *Plant Physiology*, *93*, 1573–1578. https://doi.org/10.1104/pp.93.4.1573

Hughes, L., & Mackay, D. (2011). Model of the fate of chemicals in sludge-amended soils with uptake in vegetation and soil-dwelling organisms. *Soil and Sediment Contamination*, *20*, 938–960. https://doi.org/10.1080/15320383.2011.620046

Hurtado, C., Trapp, S., & Bayona, J. M. (2016). Inverse modeling of the biodegradation of emerging organic contaminants in the

soil-plant system. *Chemosphere*, *156*, 236–244. https://doi.org/10.1016/j.chemosphere.2016.04.134

Information Platform for Chemical Monitoring (IPCHEM). (2022). https://ipchem.jrc.ec.europa.eu/RDSIdiscovery/ipchem/index.html

Isaacs, K. K., Glen, W. G., Egeghy, P., Goldsmith, M. R., Smith, L., Vallero, D., Brooks, R., Grulke, C. M., & Özkaynak, H. (2014). SHEDS-HT: An integrated probabilistic exposure model for prioritizing exposures to chemicals with near-field and dietary sources. *Environmental Science & Technology*, *48*, 12750–12759. https://doi.org/10.1021/es502513w

JECFA. (1991). Benzo(a)pyrene. https://inchem.org/documents/jecfa/jecmono/v28je18.htm.

Jolliet, O., Ernstoff, A. S., Csiszar, S. A., & Fantke, P. (2015). Defining product intake fraction to quantify and compare exposure to consumer products. *Environmental Science & Technology*, *49*, 8924–8931. https://doi.org/10.1021/acs.est.5b01083

JRC ExpoFacts. (n.d.). JRC ExpoFacts database. Joint Research Centre data catalogue—ExpoFacts Database—European Commission. https://europa.eu. Date accessed 2022.

Kelly, B. C., Ikonomou, M. G., Blair, J. D., Morin, A. E., & Gobas, F. A. P. C. (2007). Food web-specific biomagnification of persistent organic pollutants. *Science*, *317*, 236–239. www.sciencemag.org

Koch, H. M., Lorber, M., Christensen, K. L. Y., Pälmke, C., Koslitz, S., & Brüning, T. (2013). Identifying sources of phthalate exposure with human biomonitoring: Results of a 48h fasting study with urine collection and personal activity patterns. *International Journal of Hygiene and Environmental Health*, *216*, 672–681. https://doi.org/10.1016/j.ijheh.2012.12.002

Krause, T., Moenning, J.-L., Lamp, J., Maul, R., Schenkel, H., Fürst, P., Pieper, R., & Numata, J. (2022). Transfer of polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs) and polychlorinated biphenyls (PCBs) from oral exposure into cow's milk—Part I: State of knowledge and uncertainties. *Nutrition Research Reviews*, *36*, 448–470. https://doi.org/10.1017/s0954422422000178

Lamshoeft, M., Gao, Z., Resseler, H., Schriever, C., Sur, R., Sweeney, P., Webb, S., Zillgens, B., & Reitz, M. U. (2018). Evaluation of a novel test design to determine uptake of chemicals by plant roots. *The Science of the Total Environment*, *613-614*, 10–19. https://doi.org/10.1016/j.scitotenv.2017.08.314

Legind, C. N., Kennedy, C. M., Rein, A., Snyder, N., & Trapp, S. (2011). Dynamic plant uptake model applied for drip irrigation of an insecticide to pepper fruit plants. *Pest Management Science*, *67*, 521–527. https://doi.org/10.1002/ps.2087

Legind, C. N., & Trapp, S. (2009). Modeling the exposure of children and adults via diet to chemicals in the environment with crop-specific models. *Environmental Pollution (Barking, Essex: 1987)*, *157*, 778–785. https://doi.org/10.1016/j.envpol.2008.11.021

Li, J. G., Gerzabek, M. H., & Muck, K. (1994). An experimental study on mass loading of soil particles on plant surfaces (No. OEFZS—4714). Oesterreichisches Forschungszentrum Seibersdorf GmbH (Austria)

Li, L., Sangion, A., Wania, F., Armitage, J. M., Toose, L., Hughes, L., & Arnot, J. A. (2021). Development and evaluation of a holistic and mechanistic modeling framework for chemical emissions, fate, exposure, and risk. *Environmental Health Perspectives*, *129*, 127006–127016. https://doi.org/10.1289/EHP9372

Lunghini, F., Marcou, G., Azam, P., Patoux, R., Enrici, M. H., Bonachera, F., Horvath, D., & Varnek, A. (2019). QSPR models for bioconcentration factor (BCF): Are they able to predict data of industrial interest? *SAR and QSAR in Environmental Research*, *30*, 507–524. https://doi.org/10.1080/1062936X.2019.1626278

Mansouri, K., Grulke, C. M., Judson, R. S., & Williams, A. J. (2018). OPERA models for predicting physicochemical properties and environmental fate endpoints. *Journal of Cheminformatics*, *10*, 10. https://doi.org/10.1186/s13321-018-0263-1; software available at https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-opera/opera

Martin, T., Harten, P., & Young, D. (2012). TEST (Toxicity Estimation Software Tool) V 4.1, US Environmental Protection Agency, software available at https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test.

McKone, T., & Bennett, D. (2003). Chemical-specific representation of air—Soil exchange and soil penetration in regional multimedia models. *Environmental Science & Technology*, *37*, 3123–3132.

Mckone, T. E. (1993). CalTOX, a multimedia total-exposure model for hazardous-wastes sites Part I: Executive summary. The Office of Scientific Affairs Department of Toxic Substances Control California Environmental Protection Agency Sacramento, California.

McKone, T. E., & Maddalena, R. L. (2007). Plant uptake of organic pollutants from soil: Bioconcentration estimates based on models and experiments. *Environmental Toxicology and Chemistry*, *26*, 2494–2504. https://doi.org/10.1897/06-269.1

McLachlan, M. S. (1994). Model of the fate of hydrophobic contaminants in cows. *Environmental Science & Technology*, *28*, 2407–2414. https://doi.org/10.1021/es00062a028

Meylan, W. M., Howard, P. H., Boethling, R. S., Aronson, D., Printup, H., & Gouchie, S. (1999). Improved method for estimating bioconcentration/bioaccumulation factor from octanol/water partition coefficient. *Environmental Toxicology and Chemistry*, *18*, 664–672. https://doi.org/10.1002/etc5620180412

Ng, C. A., & von Goetz, N. (2017). The global food system as a transport pathway for hazardous chemicals: The missing link between emissions and exposure. *Environmental Health Perspectives*, *125*, 1–7. https://doi.org/10.1289/EHP168

Pawlowski, S., Aicher, L., Berends, A., Curtis-Jackson, P., Häner, A., Hollender, J., Jene, B., Jenner, K., Redman, A., Sander, G., Vallotton, N., Wang, N., & Wheeler, J. R. (2022). Mobility in the context of exposure-based assessment of chemicals for drinking water resource protection. *Integrated Environmental Assessment and Management*. *Integrated Environmental Assessment and Management*, *19*, 775–791.

Petoumenou, M. I., Pizzo, F., Cester, J., Fernández, A., & Benfenati, E. (2015). Comparison between bioconcentration factor (BCF) data provided by industry to the European Chemicals Agency (ECHA) and data derived from QSAR models. *Environmental Research*, *142*, 529–534. https://doi.org/10.1016/j.envres.2015.08.008

Phillips, D. H. (1999). Polycyclic aromatic hydrocarbons in the diet. *Mutation Research*, *443*, 139–147. www.elsevier.comrlocatergentoxCommunityaddress:www.elsevier.comrlocatermutres

Prosser, R. S., Trapp, S., & Sibley, P. K. (2014). Modeling uptake of selected pharmaceuticals and personal care products into food crops from biosolids-amended soil. *Environmental Science & Technology*, *48*, 11397–11404. https://doi.org/10.1021/es503067v

Reihlen, A., Bahr, T., Bögi, C., Dobe, C., May, T., Verdonck, F., Wind, T., Zullo, L., & Tolls, J. (2015). SPERCS-a tool for environmental emission estimation. *Integrated Environmental Assessment and Management*, *12*, 772–781. https://doi.org/10.1002/ieam.1745

Rein, A., Legind, C. N., & Trapp, S. (2011). New concepts for dynamic plant uptake models. *SAR and QSAR in Environmental Research*, *22*, 191–215. https://doi.org/10.1080/1062936X.2010.548829

Rikken, M., Lijzen, J., & Cornelese, A. (2001). Evaluation for updating the most relevant exposure routes of CSOIL. National Institute for Public Health and the Environment (RIVM). Report no. 711701022.

Rosenbaum, R. K., Huijbregts, M. A. J., Henderson, A. D., Margni, M., McKone, T. E., Van De Meent, D., Hauschild, M. Z., Shaked, S., Li, D. S., Gold, L. S., & Jolliet, O. (2011). USEtox human exposure and toxicity factors for comparative assessment of toxic emissions in life cycle analysis: Sensitivity to key chemical properties. *The International Journal of Life Cycle Assessment*, *16*, 710–727. https://doi.org/10.1007/s11367-011-0316-4

Sarigiannis, D. A., Karakitsios, S. P., Gotti, A., Handakas, E., & Papadaki, K. (2016). The exposome and health impact assessment. *European Journal of Public Health*, *26*. https://academic.oup.com/eurpub/article/26/suppl_1/ckw172.048/2449034

SCCS. (2023). The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation-12th Revision-SCCS/1647/22. https://health.ec.europa.eu/publications/sccs-notes-guidance-testing-cosmetic-ingredients-and-their-safety-evaluation-12th-revision_en

Schriever, C., & Lamshoeft, M. (2020). Lipophilicity matters—A new look at experimental plant uptake data from literature. *The Science of the Total Environment*, *713*, 136667. https://doi.org/10.1016/j.scitotenv.2020.136667

Schuhmacher, M., Jones, K. C., & Domingo, J. L. (2006). Air-vegetation transfer of PCDD/PCDFs: An assessment of field data and implications for modeling. *Environmental Pollution*, *142*, 143–150. https://doi.org/10.1016/j.envpol.2005.09.017

Schwartz, S., Trapp, S., & Matthies, M. (2000). Validation of environmental exposure models and parameters: Part I. Institute for Environmental System Research, University Osnabruck. Report no. FKZ29667075. 164 pp.

Schwarzenbach, R., Gschwend, P., & Imboden, D. (2017). *Environmental Organic Chemistry* (3rd ed.). John Wiley & Sons, Inc.

Sexton, K., Needham, L. L., & Pirkle, J. L. (2004). Human biomonitoring of environmental chemicals measuring chemicals in human tissues is the 'gold standard' for assessing people's exposure to pollution. American Scientist. www.americanscientist.org

Shin, H.-M., Ernstoff, A., Arnot, J. A., Wetmore, B. A., Csiszar, S. A., Fantke, P., Zhang, X., McKone, T. E., Jolliet, O., & Bennett, D. H. (2015). Risk-based high-throughput chemical screening and prioritizationusing exposure models and in vitro bioactivity assays. *Environmental Science & Technology*, *49*, 6760–6771.

Trapp, S. (2002). Dynamic root uptake model for neutral lipophilic organics. *Environmental Toxicology and Chemistry*, *21*, 203–206. https://doi.org/10.1002/etc5620210128

Trapp, S. (2015). Calibration of a plant uptake model with plant- and site-specific data for uptake of chlorinated organic compounds into radish. *Environmental Science & Technology*, *49*, 395–402. https://doi.org/10.1021/es503437p

Trapp, S., Cammarano, A., Capri, E., Reichenberg, F., & Mayer, P. (2007). Diffusion of PAH in potato and carrot slices and application for a potato model. *Environmental Science & Technology*, *41*, 3103–3108. https://doi.org/10.1021/es062418o

Trapp, S., & Matthies, M. (1995). Generic one-compartment model for uptake of organic chemicals by foliar vegetation. *Environmental Science & Technology*, *29*, 2333–2338. https://doi.org/10.1021/es00009a027

Trapp, S., Matthies, M., & Reiter, B. (1999). *Überprüfung und Fortentwicklung der Bodenwerte für den Boden-Pflanze-Pfad: Teilbericht I: Transferfaktoren Boden-Pflanze*. Umweltbundesamt, UBA-FB.

Trapp, S., & Pussemier, L. (1991). Model calculations and measurements of uptake and translocation of carbamates by bean plants. *Chemosphere*, *22*, 327–339. https://doi.org/10.1016/0045-6535(91)90321-4

Trapp, S., Rasmussen, D., & Samsøe-Petersen, L. (2003). Fruit tree model for uptake of organic compounds from soil. *SAR and QSAR in Environmental Research*, *14*, 17–26. https://doi.org/10.1080/1062936021000058755

Trapp, S., & Schwartz, S. (2000). Proposals to overcome limitations in the EU chemical risk assessment scheme. *Chemosphere*, *41*, 965–971. https://doi.org/10.1016/S0045-6535(99)00532-9

Travis, C. C., & Arms, A. D. (1988). Bioconcentration of organics in beef, milk, and vegetation. *Environmental Science & Technology*, *22*, 271–274. https://doi.org/10.1021/es00168a005

United States Environmental Protection Agency (US EPA). (2012). Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11 or insert version used.

van de Meent, D., Quik, J., & Traas, T. (2014). Identification and preliminary analysis of update needs for EUSES. National Institute of Public Health and the Environment (RIVM).

Veith, G. D., Defoe, D. L., & Bergstedt, B. V. (1979). Measuring and estimating the bioconcentration factor of chemicals in fish. *Journal of the Fisheries Research Board of Canada*, *36*, 1040–1048.

Verdonck, F. A., Souren, A., van Asselt, M. B., van Sprang, P. A., & Vanrolleghem, P. A. (2007). Improving uncertainty analysis in European Union risk assessment of chemicals. *Integrated Environmental Assessment and Management*, *3*, 333–343. https://doi.org/10.1897/1551-3793(2007)3[333:IUAIEU]2.0.CO;2

Vermeire, T. G., Jager, D. T., Bussian, B., Devillers, J., Den Haan, K., Hansen, B., Lundberg, I., Niessen, H., Robertson, S., Tyle, H., & Van Der Zandt, P. T. J. (1997). European Union System for the Evaluation of Substances (EUSES). Principles and structure. *Chemosphere*, *34*, 1823–1836. https://doi.org/10.1016/S0045-6535(97)00017-9

WHO. (2006). Principles for evaluating health risks in children associated with exposure to chemicals. *Environmental Health Criteria*, *237*, 1–329.

Wittassek, M., Koch, H. M., Angerer, J., & Brüning, T. (2011). Assessing exposure to phthalates—The human biomonitoring approach. *Molecular Nutrition & Food Research*, *55*, 7–31. https://doi.org/10.1002/mnfr.201000121

Zartarian, V., Glen, G., Smith, L., & Xue, J. (2008). SHEDS-Multimedia Model Version 3 (a) Technical Manual; (b) User Guide; and (c) Executable File to Launch SAS Program and Install Model. U.S. Environmental Protection Agency, EPA/600/R-08/118, 2008.

Zenié, A., & Reina, V. (2007). ExpoFacts Database. European Commission, Joint Research Centre (JRC). http://data.europa.eu/89h/jrc-10114-10001.

Zhang, Z., Sangion, A., Wang, S., Gouin, T., Brown, T., Arnot, J. A., & Li, L. (2023). Hazard vs. exposure: Does it make a difference in identifying chemicals with persistence and mobility concerns? *Water Research*, *245*, 120610. https://doi.org/10.1016/j.watres.2023.120610

Zhao, S., Price, O., Liu, Z., Jones, K. C., & Sweetman, A. J. (2015). Applicability of western chemical dietary exposure models to the Chinese population. *Environmental Research*, *140*, 165–176. https://doi.org/10.1016/j.envres.2015.03.025

Integrated Environmental Assessment and Management, 2025, 21, 20–34
https://doi.org/10.1093/inteam/vjae016
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