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Abstract

A wide diversity of plant protection products (PPP) is used for crop protection leading to the contamination of soil, water, and air, which can have ecotoxicological impacts on living organisms. It is inconceivable to study the effects of each compound on each species from each compartment, experimental studies being time consuming and cost prohibitive, and animal testing having to be avoided. Therefore, numerous models are developed to assess PPP ecotoxicological effects. Our objective was to provide an overview of the modelling approaches enabling the assessment of PPP effects (including biopesticides) on the biota. Six categories of models were inventoried: QSAR, DR and TKTD, population, multi-species, landscape, and mixture models. They were developed for various species (terrestrial and aquatic vertebrates and invertebrates, primary producers, micro-organisms) belonging to diverse environmental compartments, and address different goals (e.g., species sensitivity or PPP bioaccumulation assessment, ecosystem services protection). Among them, mechanistic models are increasingly recognized by EFSA for PPP regulatory risk assessment but, to date, remain not considered in notified guidance documents. The strengths and limits of the reviewed models are discussed together with improvement avenues (multi-generational effects, multiple biotic and abiotic stressors...). This review also underlines a lack of model testing by means of field data and of sensitivity and uncertainty analyses. Accurate and robust modelling of PPP effects and other stressors on living organisms, from their application in the field to their functional consequences on the ecosystems at different scales of time and space, would help going towards a more sustainable management of the environment.

Keywords: Ecotoxicological models, ecological models, risk assessment, environment, ecotoxicity, multi-stressors, European regulation

Graphical abstract

Contents

1 Abbreviations

EC_x	x% Effective Concentration
HC_p	p% Hazard Concentration
LC_x	x% Lethal Concentration
LD_{50}	50% Lethal Dose
R^2_{adj}	Adjusted correlation coefficient
R^2	correlation coefficient
t_{95}	95% depuration time
AA-EQS	Annual Average-EQS
ABM	Agent Based Model
ACF	Atom Centered Fragments
AD	Applicability Domain
ADI	Applicability Domain Index
AF	Assessment Factor
AFT	Accelerated Failure Time
AMBIT	chemical substance database
ANN	Artificial Neural Networks
AOP	Adverse Outcome Pathway
BCF	Bio-Concentration Factor
BMC	Bayesian Matbugs Calculator
BMF	Bio-Magnification Factors
BN	Bayesian Networks
BSAF	Biota-Sediment Accumulation Factors
CA model	Concentration Addition model
CADDIS	Causal Analysis/Diagnosis Decision Information System
CCC	Concordance Correlation Coefficient
CDF	Cumulative Distribution Function
CI	Combination Index
DaLaM	Daphnia Lake Model
DEB	Dynamic Energy Budget
DEBtox	DEB applied to ecotoxicology
DR model	Dose-Response model
DT	Decision Tree
EA model	Effect Addition model
EFSA	European Food Safety Authority
ETO-RAC	Ecological Threshold Option - RAC
EcoRR	Ecological Risk Ratio
EQS	Environmental Quality Standard
ERA	Ecological Risk Assessment
ERO-RAC	Ecological Recovery Option - RAC
ETR	Exposure Toxicity Ratio
f-SSD	Field-SSD
GIS	Geographical Information System
GMDH	Group Method of Data Handling
GUTS	General Unified Thresholds model of Survival
GUTS-RED	GUTS reduced model
IA model	Independent Action model
IBC	Individual-Based plant Community

IBM	Individual Based Model
ICE	Inter-species Correlation Estimation
k-NN	k-Neural Network
LM	Levenberg–Marquardt
LOEC	Lowest Effect Concentrations
LOF	Lack Of Fit
LOO	Leave-One-Out
MCMC	Monte-Carlo Markov Chain
MDR	Model Deviation Ratio
MechoA	Mechanism of action
MIE	Molecular Initiating Event
MLP	Multi-Layer Perceptron
MLR	Multiple Linear Regression
MoA	Mode of action
MOSAIC_{SSD}	MOdelling and Statistical Analyses for ecotoxICology
MSM	Multiplicative Survival Model
msPAF	Multiple-Substance PAF
MTI	Mixture Toxicity Index
NOEC	No Observed Effect Concentrations
ODE	Ordinary Differential Equation
OPP	Office of Pesticide Programs
PAF	Potentially Affected Fraction
PBPK	Physiologically-Based pharmacokinetic
PBTK	Physiologically-Based TK
PBTKTD	Physiologically-Based TKTD
PEC	Predicted Exposure Concentration
PLS	Partial Least Squares
PNEC	Predicted No Effect Concentration
PPDB	Pesticide Properties DataBase
PPP	Plant Protection Product
QAAR	Quantitative Activity - Activity Relationship
QMRF	(Q)SAR Model Reporting Formats
(Q)SAR	(Quantitative) Structure - Activity Relationship
QSAAR	Quantitative Structure - Activity - Activity Relationship
QSPR	Quantitative Structure - Property Relationship model
QSTR	Quantitative Structure - Toxicity Relationship
RA model	Response Addition model
RAC	Regulatory Accepted Concentration
RF	Random Forest
RMSE	Root Mean Square Error
RQ	Risk Quotient
RS	Reference Species
S-SDM	Stacked Species Distribution Modeling
SAM	Stress Addition Model
SD	Stochastic Death
SFI	Safety Factor Index
SI	Supplementary Information
SI model	Simple Interaction model
SPG	Specific Protection Goal
SSD	Species Sensitivity Distribution

SVM	Support-Vector Machine
TCM	Time–Concentration–Mortality
TER	Toxicity Exposure Ratio
TK	ToxicoKinetics
TKTD	ToxicoKinetics-ToxicoDynamics
TU	Toxic Unit
UP	Uniform Principles
WFD	Water Framework Directive
WoS	Web of Science

2 Introduction

The European Plant Protection Product (PPP) Regulation (EC) No 1107/2009 (European Commission, 2009) requires the PPP ecotoxicological properties (among others) to be fully characterized before to be placed on the market. Active substances should only be included in PPP where it has been demonstrated that they are not expected to have any harmful effect on human or animal health or any unacceptable effects on the environment (European Commission, 2009). Breakdown products (from environmental degradation or metabolic transformations) of substances have also to be identified and evaluated (Casalegno et al., 2006; European Commission, 2009). Considering the total number of PPP and the number of related breakdown products, such task is susceptible to lead to many ecotoxicological tests though animal testing has to be avoided. Thus, modelling approaches constitute an interesting support.

Models aim at delivering insights and possible solutions to real-world problems, but also at supporting regulators for risk assessment. Regarding PPP, they (i) allow the derivation of critical effect concentrations and environmental protective thresholds from animal and plant testing; (ii) could help to fill in data gap and thus save time, money, and reduce the number of animals used for experimental testing purposes (Basant et al. 2016; Casalegno et al. 2006); (iii) improve mechanistic understanding. For regulation, decision makers have to select the most appropriate models for the problem at hand (extrapolation from experimental data, extrapolation to other species, higher level of biological organization, other environmental conditions...), and to get evidence that a model works, having demonstration that it is realistic while based on reliable data inputs and key assumptions. Consequently, there is a crucial need for a clear communication of models and of their context (Grimm et al., 2020). To fulfill that need, EFSA has published several recommendations to support the development of models compatible with PPP regulation (EFSA PPR Panel, 2014).

In this context, the objective of this work was to review effect modelling approaches enabling ecological risk assessment of PPP (including biopesticides) for organisms, biodiversity and ecosystem functions/services. The review

starts with the presentation of the bibliometric methodology that led to the definition of the bibliographic corpus, and with the analysis of this corpus (Section 3). Then, the whole reviewed models, which belong to six main model categories (QSAR, DR and TKTD, population, multi-species, landscape, and mixture models) are presented (Section 4). In particular, sub-section 4.1 gives full details on each type of model including the main (standard or not) outputs they provide, while sub-section 4.2 further explains what are the main model usages. Section 5 points out the strengths and limits of the different model categories, including genericity and transversality, uncertainty quantification and reproducibility. In parallel with the corpus analysis, the Section 6 explores the recommendations in terms of usage of modelling approaches in the context of the European PPP regulation. Potential contributions and prospects of current and future modelling tools to Environmental Risk Assessment (ERA) are discussed (Section 7). ERA of PPP assesses the impact that the use of PPP has on non-target organisms, and on soil, water, and air (European Commission, 2009). ERA can be done as a prospective assessment for registration of substances before products enter the market, or as a retrospective assessment for potentially harmful substances that are already in use (Forbes and Calow, 2002). Finally, the review ends with some perspectives to be considered to improve ecological risk assessment (ERA) to preserve biodiversity.

3 Bibliographic corpus

Six main model categories were *a priori* defined to structure the bibliographic query: QSAR, DR and TKTD, population, multi-species, landscape, and mixture models (see Section 4):

- **(Q)SAR** category refers to the mathematical models to predict the ecotoxicity of compounds via statistical correlation of molecular descriptors with the biological activity of interest.
- **Dose-Response (DR) and ToxicoKinetics-ToxicoDynamic (TKTD)** category refers to static dose-response models (DR) and dynamic TK and TKTD models.
- **Population** category refers to the population dynamic models, including all degree of detail and disaggregation (stock, matrix, life cycle, individual-based models...).
- **Multi-species** category refers to the models considering several species, namely species sensitivity distribution (SSD) and food-chain models assuming they include both food-web models (with only trophic relationships) and community models (also considering other kinds of inter-species interactions). In case, food-chain models account for the dynamics of abiotic factors they can also be classified as "ecosystem models".
- **Landscape** category refers to the models considering the landscape structure (*e.g.*, spatial and temporal variability) to predict the exposure of organisms to a chemical compound, the associated toxicity or the population effects in non-target species.

- The category of **mixtures** refers to the models used to analyse the interaction of several chemicals; these models can also be used to assess the effects of combined stressors (e.g. PPP and ecological factors).

3.1 Methodology

Scientific articles and international proceedings screening was conducted with the Web of Science (WoS), the world's leading scientific citation search and analytical information platform (Clarivate Web of Science © Copyright Clarivate 2020). The final paper collection from WoS was achieved in December 2020, then manually completed over time until April 2021 from complementary bibliographic databases, such as PubMed (McEntyre and Ostell, 2002), Google Scholar (Lopez-Cozar et al., 2019), Scopus (Baas et al., 2020), publications within authors' own databases, even grey literature (*e.g.*, regulatory documents). This paper collection covers the period 2000-2020 chosen as contiguous with the existence of the WoS itself.

On a general point of view, the bibliographic query was performed according to the following steps:

- Definition of a first query over the limited period 2018-2020 (see Section 3.2).
- First analysis on the basis of titles and abstracts of papers to identify points of improvement of the query.
- Update of the query by adding and removing some terms.
- Running the final query over the period 2000-2017, over 2018-2020 again, and combination of both periods.
- Final analysis of the results with Orbit Intellixir bibliometric software (Copyright © Questel 2021, all rights reserved).

Besides the query terms, we limited our paper collection to only include research and review papers written in English, as well as scientific articles published in peer-reviewed journals. The paper collection, any reference being duplicated, was imported into Intellixir and analyzed to quantify, for example, the scientific production per year, country, organization, and annual evolution of publication rates. Collaboration networks between countries, public institutions and/or private companies, as well as the main research concepts, were graphically represented using the most relevant formats available in Intellixir. In particular, papers were analyzed to point out the main trends in research related to the use of models in ERA for PPP, as well as to highlight their strengths and limitations, leading to the identification of future key topics for research.

Some papers were manually added or removed from the final collection before performing the analysis. The Supplementary Information (SI) is available at https://doi.org/10.5281/zenodo.5775038 (Larras et al., 2021), where the full list of keywords is provided, as well as both source files with all references and their DOI in `.csv` format: the list of references in the initial corpus,

and the list of additional references. Reasons for which some papers were added are the following:

- Some scientific research areas were missing although corresponding keywords were in the final query, such as sensitivity analysis, uncertainty, calibration, validation and prediction. So, some papers were added accordingly.
- Very recently published papers, not published yet (such as papers in bioRxiv for example), were also added by hand.
- Some general methodological references were clearly missing as they do not specifically concerned PPP.
- All references focused on human health risk assessment were removed as we exclusively focused on ERA.

3.2 Details on the bibliographic query

The bibliographic query was composed of seven items, each of them encompassed within three global items and associated with a sub-query (Table 2). List of keywords used in the different sub-queries were established *a priori* from the authors' expertise (see SI at https://doi.org/10.5281/zenodo.5775038, Larras et al. 2021).

Item nbr	Specific item	Global item	Nbr of references
1	(Q)SAR model		427
2	DR and TKTD	Pesticides	143
3	Population	General	392
4	Multi-species	Modelling	79
5	Landscape	Ecotoxicology	202
6	Mixture		398
7	Regulation		399

Table 2 Combination of the keyword lists composing the first bibliographic query. Columns were joined together with the logical operator `AND`. All keyword lists are available in Supplementary Information at https://doi.org/10.5281/zenodo.5775038 (Larras et al., 2021).

Running the first bibliographic query over the limited period 2018-2020 led to 380 references. This short list was quickly analysed from titles and abstracts to improve the different items and their associated sub-queries. Of these 380 references, only 130 were kept (35%).

The updated sub-queries we obtained were run over the period 2000-2017, then again on the period 2018-2020. The combination of both finally provided the final paper collection we in-depth analysed. This collection was composed of a total of 1259 papers. From this total, relevant papers for the review were checked one-by-one finally leading to a paper collection of 376 references ($\sim$ 30%) that were analysed by Intellixir.

3.3 Simple bibliometric measurements

As first results, we provide here simple bibliometric measurements giving a factual description of the paper collection ($n = 376$).

The time course of the selected references (Figure 1) clearly shows an increase in work integrating modelling tools over the last twenty years, together with a strong inequality between contributing countries. The countries with the highest number of contributions in our bibliographic corpus could be explained by the nationality of the main producing and R&D companies (BASIC, 2021), which are in the main contributing institutions (see below), and/or by the leading countries in natural sciences research (Nature Index, 2020).

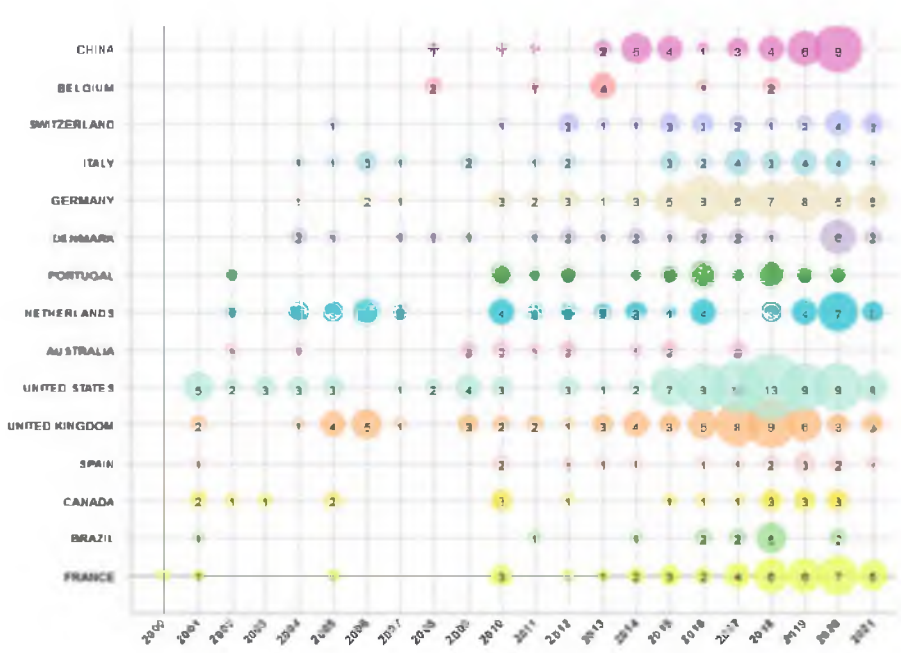

Fig. 1 Cross-view of the origin country of the first author with the time course of the paper collection. Numbers correspond to the number of papers.

Looking at the main research topics, that is words found in titles and abstracts, as automatically extracted by Intellixir, makes emerge the main keywords. The three main keywords are `Model` (in 98.5% of the papers), `Pesticide` (69.0%), and `Exposure`(66.4%). `Aquatic` (31.3%) is the first living environment found (10^{th} position) and the first PPP usages found are `Insecticide` (24.8%) and `Herbicide`(19.6%).

Figure 2 below describes the main collaborations between host institutions of all co-authors who contributed to each paper. These main collaborations are defined as at least one reference authored by each institution plus at

least four co-publications between institution pairs. The ten main contributing institutions (accounting for multiple affiliations) represent 42% of the total contributing ones, among which the top-five is composed of `SYNGENTA JEALOTTS GROUP` (6.8%), `UNIV WAGENINGEN IMARES` (NL, 6.6%), `BAYER` (DE, 3.9%) and `CNRS` (FR, 3.9%). All affiliations of the first authors have been taken into account, and for example, `ALTERRA WAGENINGEN` and `UNIV WAGENINGEN IMARES` are used for a same author in 90% of the articles.

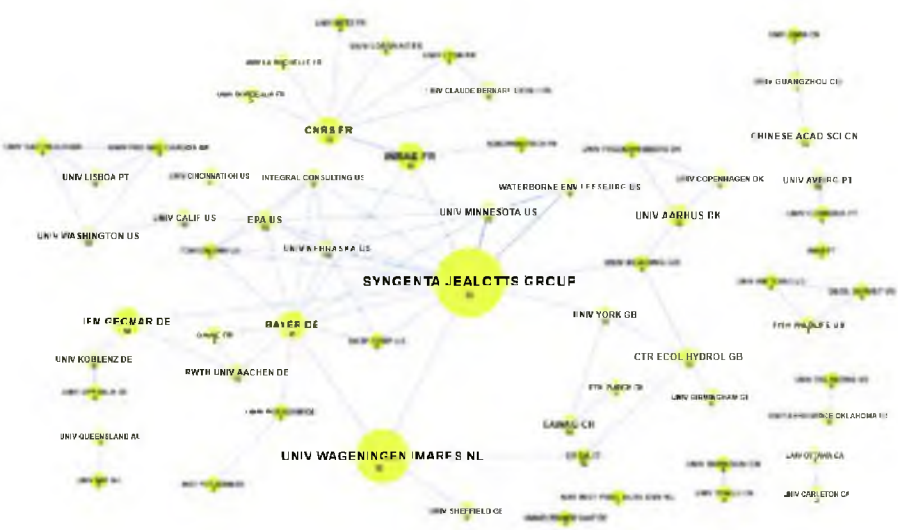

Fig. 2 Network between host institutions of first authors.The institutions represented have published at least three papers and three co-publications with other institutions.

3.4 Advanced bibliometric measurements

In order to refine the previous bibliometric description, we went further into the analysis of the main concepts appearing within the paper collection. Figure 3 shows all words appearing at least 35 times within the references. We notice that some words form well identified groups, four in total, distinguished by different colors and corresponding to the semantic proximity of words. The `Model` group is strongly related to the `Pesticide` group of words, while relationships with more general terms, such as `Environment risk assessment` (left side of Figure 3), are tinier. Nevertheless, single word `Risk` and pair `Risk assessment` are within the big `Pesticide` group, the `Risk` word appearing almost at the same frequency than the `Pesticide` word (267 versus 223 occurrences). It is particularly interesting to note that the `Regulatory` word belong to the `Model` group.

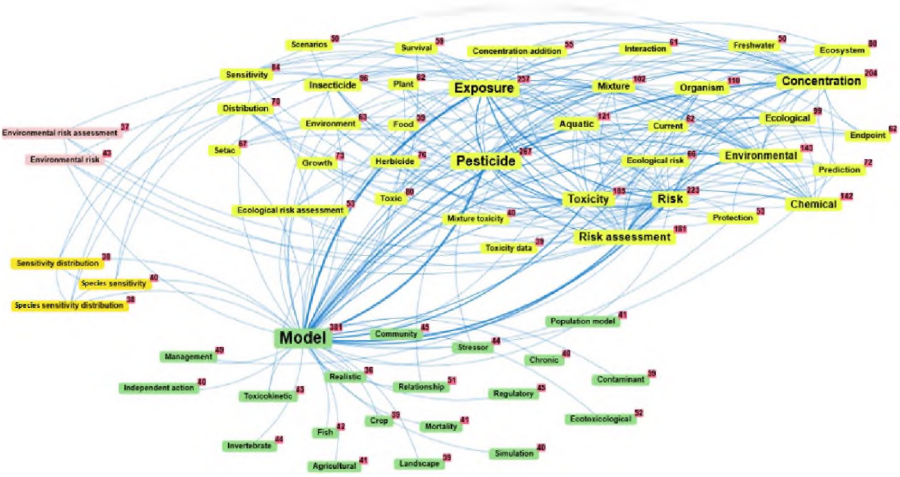

Fig. 3 Main concepts appearing at least 35 times within the paper collection; the different colors correspond to the semantic proximity of words.

Coming back to the time course of the references, and refining the analysis by model types, leads to Figure 4. To this aim, all the models used in each paper was noted, and thus, a same article could be counted in different model categories. It is worth noting that models diversify over time, with an increase in the use of TKTD models, especially since 2018, the year at which the Scientific Opinion on the state-of-the-art of TKTD models was published by EFSA (EFSA PPR Panel, 2018a). We also notice that mixture models are widely used all along the period 2000-2020 with a regular increase for almost 15 years. Regarding (Q)SAR models, if used a few in the past, there is an upsurge in PPP references involving these models since 2017. The bibliometric evolution of the use of population models within our corpus focused on PPP literature is interesting to analyse further, as it can be compared to the general evolution of population modelling practices in applied ecology. We used as a reference the review of Accolla et al. (2021), who gathered a corpus of 450 population models used for risk assessment in ecology, including conservation science studies. The rate of publication related to the use of population models for PPP ERA has experienced a strong growth since 2010 (1.5 articles per year over the period 2000-2010, 4 per year over 2011-2015 and 9 per year over 2016-2020). This dynamic is specific to the field of PPP ERA, as we do not observe the same inflation in the corpus of Accolla et al. (2021): 50% increase in the rate of publications in 2011-2014 compared to 2004-2010, while PPP studies exerted a 100% increase on the similar periods. We can also note a recent amplification of population modelling applications to PPP impacts in pollinators, 30% of the population studies since 2017, against 10% before this date in our corpus. The dynamics recorded from 2010 onwards correlates with the structuring of a community of European and North American

researchers, both academic and industrial, on ecological modeling for regulatory chemical risk assessments (LEMTOX workshop 2007 Forbes et al. 2009, US-EPA Risk Assessment Forum Technical Workshop on Population-Level ERA 2008, Roskilde Workshop on Integrating Population Modeling into ERA 2009, MODELINK workshop 2012-2013, 7^{th} Framework European Program CREAM 2009-2013, SETAC interest group on Effect Modeling). For instance, the European CREAM project (https://cream-itn.eu/) was responsible for a strong increase in papers on TKTD and population models in PPP effect modelling in this period. The agrochemical industry has invested heavily in this dynamics, signing nearly 40% of the publications on PPP population models since 2011, whereas before this date it was practically absent from the authorship (less than 10%). This rising interest of PPP ERA community in population models is explained by the fact that the protection goal in revised PPP registration procedures for most species is either the population or the community (Hanson and Stark, 2012; Dohmen et al., 2016; EFSA Scientific Committee, 2016). Moreover, the use of higher Tier risk assessment, which aims at integrating fine ecological realism, allows overcoming the conservatism inherent in risk assessment based on the application of safety factors to lower Tier assessment outputs (Maund et al., 2001; Dalkvist et al., 2009; Brain et al., 2015). In this context, population and landscape models are mobilized particularly to assess (i) the relative importance of PPP toxic stress compared with natural stochastic fluctuations (Topping and Odderskær, 2004), (ii) the influence of biological and environmental factors conditioning population state and sensitivity to PPP (Dalkvist et al., 2009; Forbes et al., 2015; Thorbek et al., 2017; Schmolke et al., 2019; Abi-Akar et al., 2020), especially possible compensatory effects due to the interplay between PPP demographic effects and the natural density control of populations (Wang and Grimm, 2010; Mintram et al., 2018), (iii) the ability to recovery related to demographic resumption after short term exposure or recolonization processes from refuge areas that could make PPP impacts ecologically acceptable at larger time or spatial scales (Galic et al., 2012; Hanson and Stark, 2012; Focks et al., 2014; Dohmen et al., 2016).

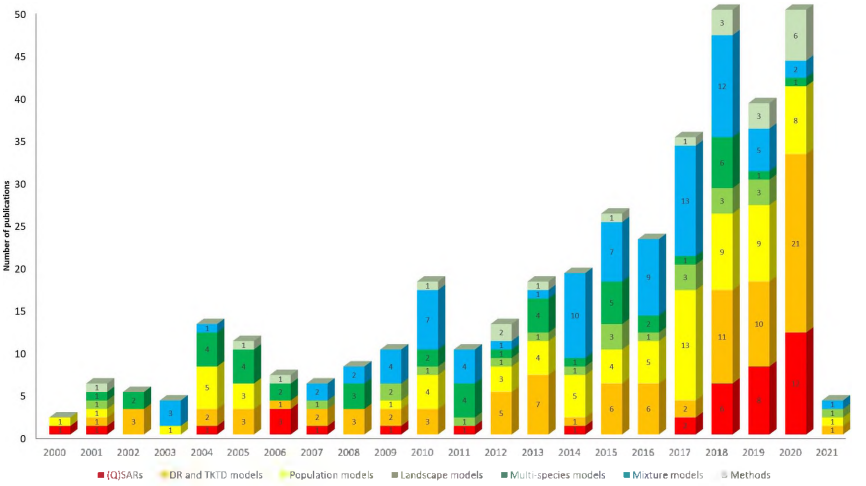

Fig. 4 Time course of references sub-divided by model categories. Model classes were defined according to the keyword lists presented in Table 1. `Methods` refers to general methodological papers not necessarily related to PPP.

We crossed the analysis of categories of biological group with the model types (Figure 5). Articles were classified following these different groups of taxa: micro-organisms (e.g. single species bacteria from water or soil media), aquatic microbial communities (e.g. biofilm), aquatic primary producers (microalgae and macrophytes), aquatic invertebrates, various aquatic groups (studies gathering more than one aquatic biological group, such as food-web studies), teleost fish, amphibians, reptiles, terrestrial invertebrates (including bees), terrestrial primary producers, mammals and birds. A large majority of papers concerned aquatic invertebrates (29.5%), all categories of models having been employed. At the second and third positions, with close number of occurrences, are terrestrial invertebrates (17.3%) and fish (13.3%).

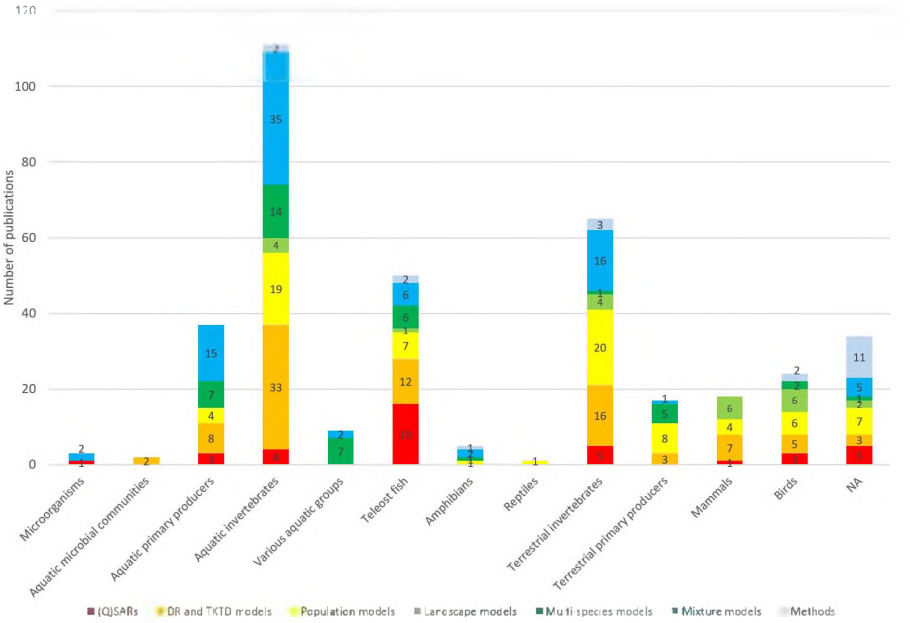

Fig. 5 Distribution of models by biological groups, each category being sub-divided according to the model categories. The `Methods` word refers to general papers and/or those including several model categories. Abbreviation `NA` means *Not Available*.

In addition to the previous cross-analysis on biological group categories, Figure 6 provides an overview of the level of biological organization at which the models were built, sub-divided by the type of living environment where the studied species in the papers referred to. As expected, almost half of the papers deal with the individual level (49.5%), followed by a quarter of the papers at the population level (25.8%). Community level models are less numerous (11.2%). A rather important part of the papers (10.9%) do not refer to a specific level of biological organization. Several reasons may explain this fact: for example no model was employed; landscape or ecosystem was concerned as a whole (so that several levels may be concerned); or several levels were concerned without one more important than the others (so that they could not be classified into one specific category). Combining this information with the living environment of the studied organisms provides information rather redundant with those extracted from Figure 5. Indeed, whatever the model category or almost, freshwater species have been the most studied, then the terrestrial ones, equivalently followed by the other types of species living environment. Saltwater species are less represented because saltwater ecosystems are not considered in the European regulation.

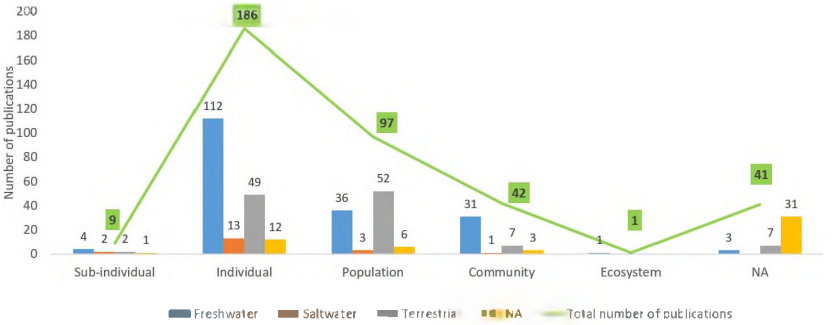

Fig. 6 Overview of the level of biological organization accounted for in the models for each type of species living environment. Abbreviation NA means *Not Available.*

4 ERA modelling for PPP effect on organisms, populations, communities and ecosystems

4.1 Description and classification of existing models

Based on our literature review, we identified six categories of models that fulfill all or a part of the above requirements. They are described below.

4.1.1 (Q)SAR models

The knowledge about systematic relationships between the structure and activities of the chemicals dates back to the prime infancy of the modern pharmacology and toxicology (Devillers, 2001). Since the pioneering work of Corwin Hansch in the 60's, the development and utilization of structure-activity relationships have become increasingly more important over the past years for industrial and regulatory applications (Mombelli and Ringeissen, 2009). In particular, a large number of models have been developed recently for the PPP: 38 papers from 2000 and 2020, including 28 on the last five years, in our bibliographic corpus.

Current structure - activity relationship usage in PPP safety assessment can be divided into rule based expert systems (SAR models) and statistical systems ((Q)SAR models). The notation (Q)SAR includes both types of models.

Expert systems (SAR) use rule-based methods to qualitatively predict specific endpoints by matching identified molecular (sub) structures or fragments of the compound to similar structures (known as structural alerts) with known adverse effects (*e.g.*, liver toxicity, skin irritation, mutagenicity) (Herrmann et al., 2020).

Statistical systems ((Q)SAR systems) use mathematical models to predict the toxicity of compounds via statistical correlation of molecular descriptors with the biological activity of interest. (Q)SAR model is composed by three

elements: (i) data on the biological properties to be predicted, (ii) data on molecular descriptors which translate chemical structures into numbers, and (iii) a modelling algorithm that is able to identify the relationship between molecular descriptors and biological activity. The basic assumption of these models is that similar chemicals (biological, chemical, and/or physical properties) induce similar effects (from a qualitative and quantitative point of view) in living beings (Lo Piparo et al., 2006). Some authors had therefore proposed specific sub-names for (Q)SAR models to stress these differences, *e.g.*, Quantitative Structure - Property Relationship (QSPR) models (Basant et al., 2016), Quantitative Structure - Toxicity Relationship (QSTR) models (Lo Piparo et al., 2006), Quantitative Activity - Activity Relationship (QAAR) models (Furuhama et al., 2019) or Quantitative Structure - Activity - Activity Relationship (QSAAR) models (Furuhama et al., 2019).

(Q)SAR models could also be classified according to a trade-off between their accuracy and genericity. Depending on the intended purpose and on the underlying data set of the model, (Q)SAR models are used to predict the properties of con-generic compounds (local (Q)SAR) or of more diverse compounds (global (Q)SAR) (Furuhama et al., 2019; Herrmann et al., 2020; Jia et al., 2020). These authors proposed that depending on the respective requirements of sensitivity (correct positive) and specificity (correct negative), appropriate models (global/local), accounting for the chemical space of query structures, have to be selected.

Basant et al. (2015a) proposed a figure clearly describing the (Q)SAR modelling procedure (Figure 7). This procedure follows the OECD principles for (Q)SAR models (OECD, 2014). These five principles were proposed to facilitate the consideration of a (Q)SAR model for regulatory purposes (explained in Mombelli and Ringeissen 2009):

1. a defined endpoint.
2. an unambiguous algorithm.
3. a defined domain of applicability (AD).
4. appropriate measures of goodness-of–fit, robustness and predictivity.
5. a mechanistic interpretation, if possible.

The computation of internal and external validation metrics (on the species included in the training set or on other species) and the definition of the domain of applicability appear as important steps, as proposed by the OECD principles. The domain of applicability is defined as "the physico-chemical, structural, or biological space, knowledge or information on which the training set of the model has been developed, and for which it is applicable to make predictions for new compounds [...]. Ideally, the (Q)SAR should only be used to make predictions within that domain by interpolation not extrapolation" (Carnesecchi et al., 2020; Eriksson et al., 2003). It is important to note that the Figure 7 does not explicitly include the "data curation" step (included in OECD principle 1, "a defined endpoint") described as essential by other

authors: data curation contributes to define unambiguously an endpoint (*e.g.*, identical exposure time for EC_{50})(Khan et al., 2019; Villaverde et al., 2020).

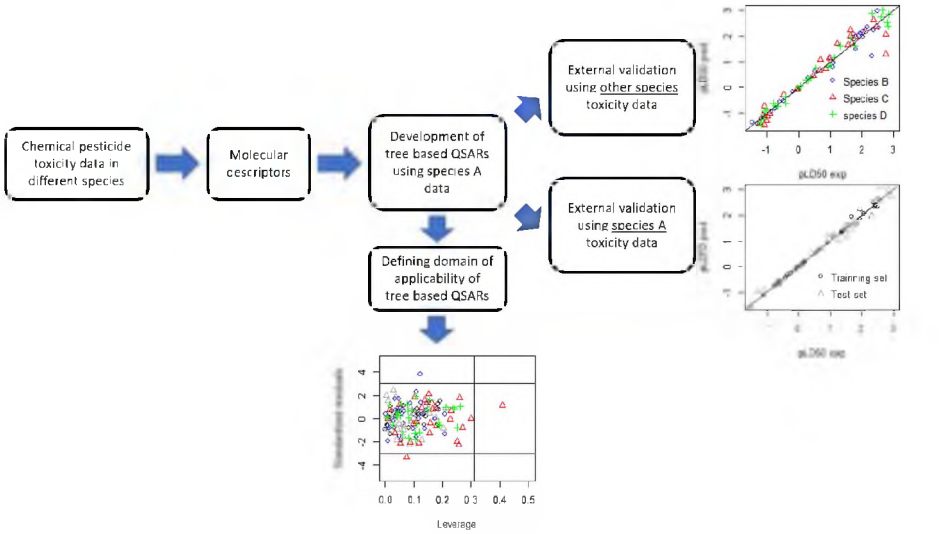

Fig. 7 Flow chart adapted from Basant et al. (2015b) showing the (Q)SAR modeling procedure. `pLD50` is effective concentration data converted to a molar basis and logarithmically transformed. `exp` and `pred` are experimental and predicted data, respectively.

Indeed, the (Q)SAR models can only be as reliable as the experimental data that are used for their calibration, and therefore, the standardisation procedures to obtain each data and to curate the data set of compounds should be considered with care (Villaverde et al., 2020).

As reported by Villaverde et al. (2020), there are several easily accessible databases that can be used to develop (Q)SAR models (*e.g.*, ACToR, BindingDB, CCRIS...). In the bibliographic corpus analysed, other databases were frequently used to develop (Q)SAR: EFSA's chemical hazards database "OpenFoodTox", US-EPA ECOTOXicology knowledge-base (ECOTOX), Pesticide Properties DataBase (PPDB), OECD (Q)SAR toolbox, Office of Pesticide Programs (OPP), Pesticides Ecotoxicity Database (produced by the International Center for Pesticides and Health Risk Prevention), AMBIT (developed by Cefic-LRI, current version 2.0 at https://apps.ideaconsult.net/data/ui), and BBA (Biologische Bundesanstalt – Federal Biological Research Center for Agriculture and Forestry).

Nevertheless, ideally, databases for model calibration should be developed in a single laboratory and by means of a single protocol to enhance the signal to noise ratio. However, these conditions are not met in most of the (Q)SAR models that are developed today, and much less in those developed from

databases in which the information is deposited by numerous contributors (Khan et al., 2019; Villaverde et al., 2020). Consequently, (Q)SAR modellers should always subject to curation the systematic and random errors present in all databases by special and well-established protocols and tools (Khan et al., 2019; Villaverde et al., 2020).

A large diversity of chemical descriptors (experimental measurements or theoretical molecular descriptors) is used to develop (Q)SAR models specific to the PPP. The most common descriptor is the octanol–water partition coefficient K_{ow} (Devillers, 2001). However, the rapidly falling price of computing power has stimulated the use of more sophisticated statistical methods for increasing the domain of application of the (Q)SAR models (Devillers, 2001). Hence, the spatial dimension of the chemical descriptors (one, two, three or four dimensions) have been used to distinguish different (Q)SAR models on the descriptor basis. In the literature, over 6000 descriptors have been proposed and the number is still growing (Hamadache et al., 2018). Considering the large number of calculated descriptors, it was necessary to use approaches of variable reduction, which consists in the selection of a subset of variables able to preserve the essential information contained in the whole data set but eliminating redundancy (Carnesecchi et al., 2020; Hamadache et al., 2018). Hence, severe selection steps using a range of methods were applied to reduce the number of descriptors. Classically, all highly correlated descriptors (pairwise correlation coefficient above 0.9) and those with low variance ($s^2 < 0.3$) or the semi-constant descriptors (more than 80% of the data with the same value) were excluded (Venko et al., 2018; Yang et al., 2020). To this goal, after centring and scaling the descriptors, Carnesecchi et al. (2020) used the following methods: Decision Trees (DT), k-nearest neighbours (k-NN), Multiple Linear Regression (MLR), Partial Least Squares (PLS) regression (based on Genetic algorithm), and Random Forest (RF). Additionally, the Norm index concept was proposed by Jia et al. (2020), and a series of normed descriptors based on molecular structure were defined and used to develop (Q)SAR models with satisfactory prediction results for the aquatic acute toxicity of various PPP (Jia et al., 2018, 2020). (Q)SAR models for PPP could also be based on descriptors computed by other *in silico* methods, using a combination of fingerprint, structure-based pharmacophore approaches, homology modelling, molecular-docking and molecular dynamics simulation (Chaudhuri et al., 2020; Marimuthu et al., 2019).

Globally, and in the PPP bibliographic corpus, the most common techniques for establishing (Q)SAR models are based on regression-based approaches, and the methods of MLR (Furuhama et al., 2019; Yang et al., 2020; Yang et al., 2020) and PLS (Jackson et al., 2009; Khan et al., 2019; Marimuthu et al., 2019) are classical approaches to regression problems in (Q)SAR models. In PPP (Q)SAR, genetic algorithms are often used to fit MLR (Furuhama et al., 2019; Yang et al., 2020; Yang et al., 2020) or PLS models (Jackson et al., 2009; Khan et al., 2019). For these techniques, a postulate is

made that only linear relationships exist between the variables involved in the modelling process while it is generally not true (Devillers and Flatin, 2000). The Artificial Neural Networks (ANN) have shown their usefulness for deriving complex structure-activity relationships possibly non-linear (Devillers and Flatin, 2000; Hamadache et al., 2018). Several different neural networks were used to develop (Q)SAR models for PPP: Multilayer perceptron (MLP) (Devillers and Flatin, 2000; Hamadache et al., 2018), Counter-propagation ANN (Drgan et al., 2016; Venko et al., 2018), and GMDH neural networks (Lo Piparo et al., 2006). Diverse methods of linear classifications were also used in the field of PPP ecotoxicity. Mazzatorta et al. (2004) provided an overview of the classification techniques and conclude that no general rule exists to define the best approach to a specific classification problem. Recent research in Machine Learning and Statistics resulted in several efficient approaches to perform a linear or a non-linear classification: Support-Vector Machines (SVM) (Mazzatorta et al., 2006), quantile support vector machine regression (QSVMR) (Villain et al., 2014), DT and RF (Basant et al., 2015b, 2016; Carnesecchi et al., 2020)

In our literature analysis on (Q)SAR for PPP, a large majority of the (Q)SAR models were developed to predict the acute toxicity on aquatic animals: mainly fish and crustaceans (55% of the (Q)SAR models reviewed; Table 3). Insects (*i.e.*, 100% of the terrestrial invertebrates) represent the third group of non-target species for which (Q)SAR models have been developed (half of them concerns honeybees). Despite the extent of the harmful effects of PPP on bees, studies specifically devoted to (Q)SAR models for the prediction of PPP toxicity on this pollinator (six articles from 2000 to 2020) remain rather limited (Hamadache et al., 2018).

Taxa	% of reviewed (Q)SAR papers ($n = 39$)
Fish	33%
Aquatic invertebrates	22%
Terrestrial invertebrates	16%
Birds	10%
Algae	10%
Mammals	6%
Plants	4%

Table 3 Percentage of (Q)SAR models by taxa (39 papers were analysed; one paper can be counted for different biological models).

Although the majority of the (Q)SAR models were developed for aquatic species, these models are available for a broad range of chemicals but predict toxicity to only a few standard test organisms and do not address the broader range of taxa within aquatic communities (Raimondo and Barron, 2020). Basant et al. (2016) have proposed that, for a comprehensive safety evaluation of chemicals by means of (Q)SAR models development, toxicity data in multiple test species of different trophic levels and complexities are needed. Therefore, if new ecotoxicological data are produced, (Q)SAR models with a single species

toxicity analysis could replace and/or be enhanced by multi-species models (Basant et al., 2016; Furuhama et al., 2019).

As noted by other authors on (Q)SAR non-specific of the PPP toxicity and confirmed by our analysis of (Q)SAR for PPP, there are few applicable (Q)SAR models for algal toxicity due to the lack of a consistent data set with experimental algal test results and because of the variability of the results (Villain et al., 2014; Douziech et al., 2020).

4.1.2 DR and TKTD models

In total, 58 papers were selected to embrace various types of dose-response (DR) and toxicokinetic-toxicodynamic (TKTD) models. DR models are less represented (18.9%) compared to TKTD models (72.4%, see Table 4 for details). DR and TKTD models make the link between chemical concentrations to which living organisms are exposed to and the potential effects on their life-history traits (survival, growth rates, reproduction features). The main difference between DR and TKTD approaches is that time is taken into account or not. On an ERA point of view, only DR models are used today at Tier-1 assessment in support of the daily work of regulators (see Section 6). Nevertheless, in order to better address risks of time-variable exposures, a situation that often occurs with PPP, the Tier-2 assessment may be refined by the use of TKTD models (EFSA PPR Panel, 2013) (namely to conduct a Tier-2C assessment). In addition, based on a recent Scientific Opinion on the state of the art of TKTD effect models for regulatory risk assessment of PPP for aquatic organisms (EFSA PPR Panel, 2018a), EFSA emphasized the added-value of TKTD models for the Tier-2C assessment, even considering the General Unified Threshold models of Survival (namely, GUTS models, Jager et al. (2011); Jager and Ashauer (2018)) as ready-to-use for ERA in their two reduced versions (GUTS-RED models), when analysing standard toxicity test data for survival (see Section 6). A full application case study of GUTS models for ERA at Tier-2C has been published by Brock et al. (2021).

In addition to GUTS models already recommended as they are to handle survival data, others TKTD models allow considering sublethal effects such as growth for plants, or both reproduction and growth for ectotherms with DEBtox models. Note that DEB stands for Dynamic Energy Budget with 'tox' extension referring to additional stress functions that can be applied on some DEB parameters to account for different modes of action of potentially toxic chemical substances (Jager, 2020). Among plant models, the *Lemna* model is also considered ready to be used in ERA (Schmitt et al., 2013; EFSA Scientific Committee, 2018). Regarding DEBtox models, EFSA only considers their current state limited to research applications, mainly because they still lack enough documented and evaluated case studies (EFSA Scientific Committee, 2018). An explanation may come from the diversity of DEB models themselves for which a unifying framework seems difficult to establish regarding the diversity of biological species fitness they are able to describe (Add-my Pet, 2021).

It is worth to note that TKTD models, even if recommended today at Tier-2C assessment (EFSA PPR Panel, 2013), could also be used at Tier-1 assessment (Charles et al., 2021). Indeed, TKTD models translate the chemical exposure (even if time-variable) into expected effects on the life-history traits of living organisms. TKTD models explicitly describe the chemical dynamic within organisms and the related damages (namely the TK part) together with the dynamic of the effects (namely the TD part). In doing so, TKTD models allow to connect the external exposure concentration dynamics to the prediction of effects over time. Consequently, TKTD models allow to calculate any x% effect at any time t, thus providing $EC_{x,t}$ or $LC_{x,t}$ (Baudrot and Charles, 2019), in particular EC_{50} or LC_{50} values at final time as requested for ERA at Tier-1.

Focusing only on the toxicokinetics, we face with a wide diversity of models that are all compartment first-order kinetic models. These so-called TK models either consider an organism as a whole, thus written with only one compartment (Charles et al., 2021; Ratier et al., 2021; Rubach et al., 2010), or consider several compartments that may represent internal entities such as the digestive system or a set of organs, or even defining compartments as organs or physiological fluids to finely decipher chemical fluxes between compartments (see Grech et al. (2017) for a review). These latest category of refined TK models are called Physiologically-Based TK (PBTK) models. They are equivalent to physiologically-based pharmaco-kinetic (PBPK) models in their writing, the way they are rather called when vertebrate or mammal species are concerned (Berntssen et al., 2020; Li et al., 2018; Maclachlan, 2009, 2010; Mavroudis et al., 2018). Except work by Weijs et al. (2013) who implemented a Bayesian approach to infer their model parameters, PBPK models are mainly used to perform simulations, parameters being valued from the scientific literature. These simulations typically serve to extrapolate between species or from mammals species towards humans. It is worth noting that Berntssen et al. (2020) proposed to account for the seasonal fluctuations in their PBTK model. Today, only few PBTK models are developed for ecotoxicological purpose (42 models published until 2019 as reviewed in Grech et al. 2017; Gestin et al. 2021), and, to our knowledge, very few PBTK models exist for PPP (Abbas and Hayton, 1997; Pery et al., 2014; Mit et al., 2021; Grech et al., 2019).

Model type	% of reviewed DR and TKTD papers ($n = 58$)
DR models	18.9% ($n = 11$)
DEBtox	6.9% ($n = 4$)
GUTS	20.7% ($n = 12$)
PBPK	8.6% ($n = 5$)
TK models (bioaccumulation)	27.6% ($n = 16$)
TKTD	8.6% ($n = 5$)
Others$^{(*)}$	8.6% ($n = 5$)

$^{(*)}$ Others refer to two ordinary differential equation (ODE) models (Booton et al., 2018; Pisani et al., 2008) and one model based on stepwise behavioural responses combined with a Self-Organizing Map (Ren et al., 2013).

Table 4 Quantitative overview of dose-response (DR) and toxicokinetic-toxicodynamic (TKTD) models ($n = 58$).

4.1.3 Population models

Aiming at an ecologically-relevant assessment of PPP hazard for ecosystems, the scaling-up of toxicological effects usually assessed at the organism level now benefits from the development of population models. Mechanistic population models can also be employed to analyse demographic responses in experimental model ecosystems or in the field. They have long been developed in species conservation science as tools for projecting the viability of populations and the long-term outcomes of management actions or biological resource exploitation (Forbes et al., 2016). These models are increasingly recognized as important tools in PPP risk assessment (Forbes et al., 2009; Stark, 2012; Forbes et al., 2015, 2016; Schmolke et al., 2017, 2018). We identified 87 papers related to population models and PPP (2000-2021). This includes 55 case studies specific to the impacts of PPP on non-target species: 25% in aquatic invertebrates - with only 2 marine studies (Lindsay et al., 2010; Thursby et al., 2018) -, 25% in terrestrial invertebrates (two thirds of which on pollinators), 30% in vertebrates (half in mammals and one third in birds), and 20% of the studies in primary producers (algae and plants equally).

Using the classification established in previous reviews of population model implementation in ERA (Forbes et al., 2016; Accolla et al., 2021), three main categories of models can be identified regarding the way in which they describe populations: unstructured, structured and Agent-Based Models (ABMs). In unstructured population models (*e.g.*, scalar models, ordinary differential equation...), a unique state variable (population size or total biomass) is considered. The population is viewed as a random mixture of individuals, particularly with respect to their exposure and sensitivity to the contaminant. Unstructured models represent only 15% of PPP population modeling case studies in our corpus, with a strong bias towards taxonomic groups: they concern the totality of the studies on unicellular algae and half of the plant population studies (*e.g.*, Weber et al. 2012; Schmitt et al. 2013; Hommen et al. 2016) against less than 5% of the animal studies (only one study in rodents, Wang et al. 2001, and one in birds, Millot et al. 2015). Structured

models (matrix models, Leslie, Lefkovitch, metapopulation models, differential equation systems, compartment models...) take into account a structure within populations (*e.g.*, age classes, sex, developmental stages, spatial distribution) to model their response to toxic stress based on the alterations of life history traits under PPP exposure. A very underdeveloped option in this category is compartment models relative to the healthy, contaminated or affected status of individuals (very used in epidemiology) with only one example of a bee colony model exposed to a neonicotinoid insecticide (Bryden et al., 2013). Structured models represent one third of the case studies identified in our corpus, covering a large taxonomic spectrum: aquatic invertebrates, terrestrial invertebrates, birds, fish and plants. ABMs (50% of the 55 case studies), often also called Individual Based Models (IBMs) in the case of population models, cover all taxa as well. ABMs have been proposed for a wide variety of ecosystem organization scales, ranging from social relationships within pollinator hives (Crall et al., 2019), or population dynamics of earthworms in contaminated soil columns (Johnston et al., 2014; Forbes et al., 2021), up to the occupancy of river networks by aquatic invertebrate populations at the watershed scale (Focks et al., 2014). This demonstrates the high generic value of the population modeling framework to studying the unintended effects of PPP in ecosystems. In ABMs, each individual is represented and can differ from all other individuals, depending on biological or state attributes or location. This formalism explains that the sub-individual effects of PPP (behavior modification, food limitation...) or other abiotic influences and biotic interactions (competition, predation...) are directly integrated in ABMs (*e.g.*, Topping and Odderskær 2004). For structured and unstructured models, sub-individual effects and environmental influences are treated by means of external "submodels" (*e.g.*, Lopes et al. 2005; Topping et al. 2005) that link them to the modification of life history traits (*e.g.*, survival, growth, fecundity) or directly to population criteria (*e.g.*, carrying capacity) (see Accolla et al. 2021, for the review of methodological aspects).

The population endpoints supplied by these models can be of different natures. Under certain stability assumptions of environmental condition regime during population exposure scenarios (constancy, periodicity, even stochasticity), the unstructured and structured models can be analytically studied to provide demographic indicators (population growth rate, equilibrium densities, stable structure, perturbation analysis...), which guarantee robustness and genericity of the results obtained by these so-called projection methods (Caswell, 2001). ABMs proceed by simulation to provide population outcomes with respect to different tested scenarios (*e.g.*, evolution of population size). Nevertheless, we observe that a large proportion of structured population models dedicated to PPP abandons the analytical approach and proceeds by numerical simulations as well, in particular when describing transient dynamics of response to pulse exposure to PPP (see below recovery aspects) or to formalize population viability analysis via the empirical calculation of population extinction probabilities. Furthermore, the vision that opposes generic

structured models with low environmental realism versus complex hyper-parameterized ABMs specific to each case study seems to be vanished by the literature, as both types of formalism can implement all key determinisms and processes of population dynamics (density-dependence, spatialization, influences of environmental conditions, phenology) (Topping et al., 2005; Wang and Grimm, 2010; Forbes et al., 2016; Accolla et al., 2021). On the other hand, several publications propose decision guides for the development of population models in PPP ERA (Schmolke et al., 2017; Awkerman et al., 2020; Raimondo et al., 2021), stressing on the importance of selecting the processes encompassed in the population model consistently with the question that the modelling approach must answer. This point should always drive the trade-offs to be made between ERA genericity, realism, and precision in each case, rather than the type of adopted formalism.

There is an unbalanced tendency to use ABMs in the assessment of the unintended population effects of PPP: ABMs represent half of the 56 population models in our corpus compared with only 15% in the 450 studies implementing population models in applied ecology reviewed by Accolla et al. (2021). At the same time, structured models are less represented (33% of PPP studies compared to 75% of the studies in ERA in general). The habits and background of the modeler communities -with a strong contribution of the European CREAM project (https://cream-itn.eu/) to this development-, but above all the choice of questions specifically addressed in the majority of these studies (recovery, spatialization...) and the suitability of ABMs to treat these aspects, seem to explain this bias. However, we will see further (Section 5.2.3), how some authors propose to mobilize the different types of population models to broaden the scope of questions to be addressed when evaluating the effects of PPP on non-target species (Raimondo and McKenney Jr, 2005; Topping et al., 2005; Forbes et al., 2015; Rico et al., 2016; Hayashi et al., 2016; Thursby et al., 2018; Rueda-Cediel et al., 2019).

4.1.4 Multi-species models

In this section, we will present both static descriptive statistical approaches like species sensitivity distributions (SSD, first sub-section), together with dynamic models inspired from population models (second sub-section).

Species Sensitivity Distributions (SSD)

Within the original corpus, 29 papers mentioned the use of Species Sensitivity Distributions (SSD), or related ones, to study PPP effects on sets of several species under various environment types. If works by Van Straalen and Denneman (1989), Aldenberg and Jaworska (2000), Solomon et al. (2001) and Sanchez-Bayo et al. (2002) can be seen as precursors of the SSD as known today, Van Straalen and Denneman (1989) already used the idea of the p% Hazard Concentration (HC_p), the book from Posthuma et al. (2002) posing all the bases of this concept. SSD is assumed to reduce the uncertainty related to differences in sensitivity of standard test species and those expected to be

exposed in field from the inter-specific variability in sensitivities to contaminants in order to predict effects at the community level (Maltby et al., 2005; Van Den Brink et al., 2006). More broadly, SSD may allow quantifying relationships between species richness and single environmental factors, thus helping in better understanding and predicting biodiversity patterns, identifying environmental management options and setting Environmental Quality Standards (EQS) (Schipper et al., 2014).

On a theoretical point of view, the SSD approach is defined as a Cumulative Distribution Function (CDF) of the toxicity of a single compound or mixture to a set of species that is considered as an assemblage or a community. A small cut-off value in the left tail of the distribution is used to estimate a concentration below which a certain fraction of species exposed above their toxicity threshold level is considered acceptable. Usually a cut-off value of 5 or 10% is chosen and their corresponding concentrations are named HC_5 and HC_{10} (Hazardous Concentration to 5 or 10% of the species). The use of the SSD concept in ERA relies on several hypotheses, among the following ones:

1. The species sample on which the SSD is fitted is a random and representative selection of the community of interest.
2. Interactions among species do not influence the sensitivity probability distribution.
3. Because functional endpoints are usually not incorporated in the SSD, the community diversity is the target of concern.
4. The laboratory sensitivity of a species approximates its field sensitivity.
5. The protection of the prescribed percentile of species ensures a sufficient protection of field ecosystems.

Note that HC_p estimates based on laboratory toxicity tests do not provide information neither on the recovery potential of sensitive endpoints nor on indirect effects, which may be important for regulatory decision-making (Brock et al., 2004).

Within a community, some species are very intolerant while others are more tolerant. Consequently, the CDF is expected to exhibit a sigmoidal increasing shape, and a low exposure concentration is expected to affect only a small proportion of the species. The derivation of this trigger value (namely the HC_p as mentioned above) thus requires to fit a presupposed probability distribution (usually a log-normal or a log-logistic probability distribution) to the toxicity values of all the sampled species. Even if some authors are still using No Observed Effect Concentrations (NOEC) or Lowest Effect Concentrations (LOEC) entries for SSD analyses (Brock et al., 2004; De Zwart, 2005; Iwasaki et al., 2015; Cederlund, 2017), the toxicity values used as SSD inputs usually come today from DR models (thus being LC_x or EC_x values, with usually $x = 50\%$), more rarely from TKTD model (*e.g.*, the No Effect Concentration, Kon Kam King et al. 2015). Then, the SSD is performed in two steps:

1. The choice of a probability distribution, suited to the data set to be analysed: parametric distributions or non-parametric methods are possible

choices. Parametric distributions are more reasonable with small data sets, while log-normal and log-logistic distributions are the customary choices among parametric ones.

2. Using a parametric distribution, all the parameters need to be estimated. In this perspective, several methods exist (Belanger and Carr, 2019):

   - Moment matching as in the ETX free software (current version is 2.3), an Excel spreadsheet with embedded Visual Basic macro-driven calculation tools to calculate HC_p and Potentially Affected Factions (PAF) from normally distributed toxicity data (Van Vlaardingen et al., 2004); ETX is one of the most used software (Brock et al., 2004; Van Den Brink et al., 2006; Daam et al., 2010; Silva et al., 2015; Van Den Brink et al., 2019).
   - Least-square regression on the empirical CDF as in the Excel spreadsheet with the built-in macro SSD generator (current version V1) developed from the Causal Analysis/Diagnosis Decision Information System (CADDIS) of the US Environmental Protection Agency based on the US EPA's 2000 Stressor Identification Guidance document (US EPA, 2000, 2018). Mensah et al. (2013) used the US EPA SSD generator to deal with indigenous aquatic biota in South Africa, while Giddings et al. (2019) used it to derive a combined SSD for acute toxicity of nine pyrethroids to aquatic animals.
   - Maximizing the likelihood, *i.e.*, selecting parameters for which the probability of observing the data is the highest, as *e.g.*, in the software Burrlioz (current version 2.0) used as the standard software to derive water quality guideline values for toxic compounds in Australia and New Zealand (Campbell et al., 2000; Barry and Henderson, 2014): Burrlioz uses a log-logistic distribution for data sets that comprise less than eight toxicity values and a Burr Type III distribution for data sets of eight or more toxicity values (Anzecc, 2000). Regarding PPP, Burrlioz has been used by Chen et al. (2015); Li and You (2015).
   - Maximizing the likelihood, accounting for interval-censored values and providing 95% bootstrap confidence intervals on HC_p estimates (particularly robust with small-size samples) in the MOSAIC$_{SSD}$ web tool (Kon Kam King et al., 2014) used for PPP by Kon Kam King et al. (2015); Brock et al. (2018); Gabsi et al. (2018); Charles et al. (2021).
   - An amalgam of the above algorithms (maximum likelihood, moment estimators, linearization and the Metropolis-Hastings algorithm), also handling censored data to support fitting and visualization of simple SSD according to the choice of a distribution among six possibilities, in the SSD Toolbox from the US EPA (Etterson, 2020).

All above software are based on a frequenstist inference method, while other authors attempted to use Bayesian approaches: Jesenska et al. (2013) fitted SSD in the R software (R Core Team, 2021) with the winBUGS language; He et al. (2014) developed a novel platform, named the Bayesian Matbugs Calculator (BMC), in order to select the best SSD fit to assess ecological risk

at high-, mid- and low-levels of the 95% credible interval and to set the priority of toxic substances.

Food web and Community models

The food web and community models represented 21 papers within the final bibliometric corpus. They encompass a wide diversity of models, from simple ones involving only two species in competition (Damgaard et al., 2008; Joncour and Nelson, 2021), to the most complex ones considering as many as possible species for field studies, the one of Galic et al. (2019), further developed by Bartell et al. (2020), the CASM model, being maybe the most complete, addressing even ecosystem services within a lake. Most of the models are specific to particular situations which makes it difficult to present a short overview and to identify common denominator as there are so many different mathematical formalisms that have been used, as well as species-contaminant combinations that have been studied.

Nevertheless, we can distinguish food-web models from those accounting for other types of ecological interactions such as competition for example. The simplest food-web model we identified is the one of De Hoop et al. (2013) only involving two species whose dynamics is described by the Rosenzweig-MacArthur equation (namely a two-dimensional ODE system). Pioneer works with food-web models were done by Rose et al. (1988), calibrating a multi-species phytoplankton-zooplankton simulation model from laboratory data, Hommen et al. (1993), predicting pollutant effects on freshwater plankton communities, or Hanratty and Liber (1996), modelling the effects of diflubenzuron within a littoral ecosystem. Some years later, Traas et al. (2004) proposed a food-web model to analyse a microcosm experiment studying the combined effects of nutrients and insecticides for their impact on recovery of a model freshwater ecosystem; the final aim was to link eutrophisation and contamination. De Laender et al. (2011) also focused on microcosms to study the effect of linuron, a PPP also studied by Viaene et al. (2013) with the use of diversity indices; while Nfon et al. (2011) developed a dynamical combined fate- and food-web model to estimate the food-web transfers of chemicals in small aquatic ecosystems. Their innovation lies in the fact that aquatic macrophytes were included in the fate model and also as a food item in the food-web model. Based on simulation, Nfon et al. (2011) were able to determine the influence of macrophytes on fate and bioaccumulation of several hypothetical PPP showing in particular that macrophytes have a significant effect on the fate and food-web transfer of highly hydrophobic compounds. More recently, Bartell et al. (2018) proposed two integrated bio-energetics-based and habitat quality models to describe the daily biomass values of selected producer and consumer populations both in ponds and wetlands within farms.

The bee biological species has been used in two models to deal with the community level of biological organization. Becher et al. (2018) capitalized on the already existing BEEHAVE model (Becher et al., 2014) to simulate the colony, population and community dynamics of up to six UK bumblebee species living in any mapped landscape, based on an agent-based spatially-explicit model.

This kind of modelling approach has also been used for example by Reeg et al. (2017), Reeg et al. (2018) and Reeg et al. (2018) to extrapolate individual-level effects to the population and community level of non-target plant communities (the individual-based plant community or IBC-grass model). It has also been used to extrapolate from laboratory to field information in order to highlight herbicide effects with direct and indirect effects on population level. The herbicide effect extent depends not only on the distance to the field, but also on the specific plant community, its disturbance regime and the resource level. Strauss et al. (2017) successfully merged an individual-based population model for *Daphnia magna* with a dynamic ecosystem lake model, utilising the accuracy of the former and the dynamic environment of the latter to simulate realistic field populations. They thus created the DaLaM model (Daphnia Lake Model) to simultaneously predict population dynamics of *D. magna* and phytoplankton within a simplified daphnid-dominated food web under relevant variable field environmental conditions, such as underwater light climate, water temperature, turbulence and nutrient availability. As a main result, their hybrid modelling approach is capable of extrapolating single-species data from the laboratory to the field level as well as of decreasing the model uncertainty by including an appropriate level of complexity. Regarding lake ecosystems, two other types of models have been proposed: (1) Ren et al. (2017) applied a fugacity-based dynamic bioaccumulation model (namely mass-balanced equations) to study short food chains in high-altitude alpine lakes, that was specifically adapted to the fish species living in the Central Tibetan Plateau; (2) Galic et al. (2019) used the existing AQUATOX framework (Park et al., 2008) to quantify insecticide-induced impacts on ecosystem services provided by a lake from toxicity data for organism-level endpoints. The AQUATOX framework allows to integrate environmental fate of chemicals and their impacts on food webs in aquatic environments. Galic et al. (2019) highlighted that complex response of fishing services are mainly due to non-linear feed-backs in the lake food web, and that the water clarity increased with reduced insecticide use being mostly driven by changes in food web dynamics. The AQUATOX framework was also used by Scholz-Starke et al. (2018) to simulate the dynamics of trophic guilds of aquatic organisms, hydrodynamics and nutrients including the dynamics of the exposure substance and its metabolites. They found that there were several interconnected trophic levels and a significant biomagnification of metabolites.

As Strauss et al. (2017) with their DaLaM (Daphnia Lake) model, Kattwinkel et al. (2016) took advantage of ecotoxicological mesocosm data to develop a mechanistic food-web model that they specifically called Streambugs, in order to investigate the dynamics of the macro-invertebrate community exposed to pulses of the insecticide thiacloprid. They used Bayesian inference to estimate parameters (in particular their uncertainty) then investigated vital rates (such as the emergence process and sub-lethal effects) and limiting environmental factors in the model. They thus yielded insights into recovery

dynamics and supported the use of more accurate modeling approaches in general. A statistical model based on multiple linear regressions was specifically used for biofilms (Bhowmick et al., 2021) to better understand the influence of diuron, chlorophyll a concentrations and photosynthetic efficiency on changes in the river biofilm community structure and growth pattern of lotic ecosystems.

Even if of strong interest (Crocker, 2005), birds and mammals are probably the less studied category of animals. Let's cite the recent proposal by Dittrich et al. (2019) who assessed the potential effects of chlorpyrifos on bird communities based on a multi-year and multi-site monitoring program that was carried out in treated cider orchards (in the UK) and in treated citrus orchards (in Spain). The authors used N-mixture models fitted to the number of trapped birds (capture data) using the p-count function of Royle (2004). They come to the conclusion that the abundance of most bird species was strongly and significantly affected by seasonality, while no species showed any tendency of reduction in their population size over the years.

4.1.5 Landscape models

At the frontier with population models, our literature searches identified a corpus of 24 studies that introduce a spatial representation to implement integrated modeling approaches at the scale of agricultural landscapes assessing unintended ecological impacts of PPP. Seventy-five percent of them concern terrestrial species (more than half in mammals or birds). Population endpoints related to the maintenance of non-target species inhabiting the landscape constitute the outputs of the model in two thirds of the studies. The other ones predict contamination levels in non-target species (*e.g.*, in hare Kleinmann and Wang 2017; Mayer et al. 2020) or the exceeding of toxicity thresholds at the individual level (*e.g.*, in a warbler, Moore et al. 2018, or an owl, Engelman et al. 2012) as a function of habitat occupancy, spatial or dietary behaviors, or landscape structure. Two thirds of the 24 landscape studies consider a spatially explicit representation of the transfer and fate of PPP, 85% the spatialization of species life cycle (in particular for the use of trophic resources or habitats). Surprisingly, only less than 50% of them consider the contamination history of individuals with regard to the realization of the whole life cycle in heterogeneous landscape conditions. ABMs are again very much used (90% of the studies) for the integration of spatial and temporal dynamics of life cycles, and they are recommended for tracing the complex histories of individual exposures in landscape contexts (EFSA PPR Panel, 2018b). Contrary to our expectations, the spatialization of population dynamics (metapopulation, sink-source relationships, migration, colonization...) is of interest to only two-thirds of the PPP landscape-scale studies. Landscape models thus gather a set of rather heterogeneous objects with different objectives, where landscape spatio-temporal dynamics can be taken into account either in the environmental fate of the PPP, or/and in the realization of the life cycle of the individuals, or/and in the demographic response of the populations, depending on the objectives of each

study or risk evaluation to be carried out. The spatio-temporal dimension of the chain "PPP application - transport and fate - exposure -toxicological effect - ecological impact" is a major aspect of the understanding and the management of untargeted effects of PPP on biodiversity in agricultural ecosystems. For this reason, we chose to gather in a specific category all the mechanistic modeling studies, when any element of which falls within a landscape framework. Our literature searches also revealed the existence of a few PPP studies at the landscape level that are based on spatial statistical approaches (species distribution models, Szabo et al. 2009; Richardson et al. 2019, pressure-impact relationships, Kattwinkel et al. 2011). These studies, while not based on dynamic mechanistic models, do incorporate various elements of spatially explicit modeling related to PPP uses and environmental fate, or ecological determinisms of non-target population exposure.

4.1.6 Mixture models

More and more studies are reporting the occurrence of various PPP in a variety of environmental compartments such as water, soil, or air, meaning that aquatic, terrestrial and aerial biodiversity is often exposed to cocktails of PPP and contaminants from different sources (*e.g.*, Pelosi et al. 2021). In the early 20^{th} century, several mathematical models have been developed to assess and support the prediction of joint effects caused by mixtures of chemicals (Jonker et al., 2005; Schell et al., 2018) (Figure 8).

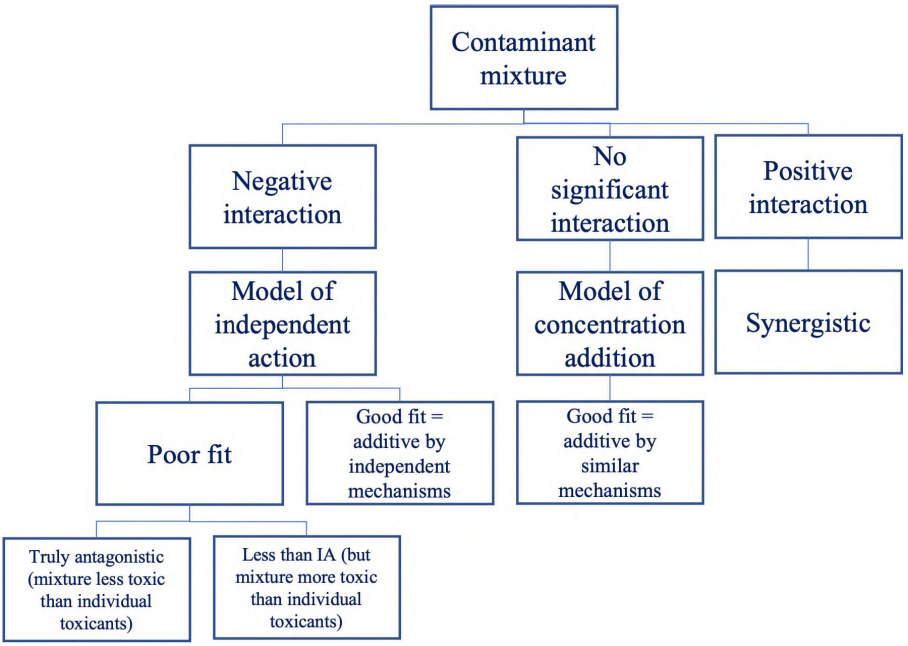

Fig. 8 Tier-2 approach to analyze the mixtures of contaminants, tested for interactions (regressions). The interactions are then characterized by a qualitative comparison of the mixing data with concentration addition (CA) and independent action (IA) models (from Hoffmann et al. 2016).

1. The Concentration Addition (CA) model assumes that all components of a mixture share a common Mode of Action (MoA) (Claudio Cacciatore et al., 2018). The CA model is also known as "toxic unit summation" since one chemical can be replaced by an equal fraction of an equi-effective concentration of another, without changing the overall effect (Qiu et al., 2017).
2. The Independent Action (IA) model, also called RA (Response Addition) or Multiplicative Survival Model (MSM), addresses mixtures of chemicals with dissimilar MoA (Garcia-Gomez et al., 2019; Englert et al., 2017) as it considers that the probability of the effect of one chemical is independent of the probability of the effect of the other chemicals in the sample.
3. The Simple Interaction (SI) model assumes that one substance in the mixture, at a non-toxic concentration, is able to influence the toxicity of other substance through an indirect mechanism. These interactions between chemicals can be due to chemical and physico-chemical interactions with the constituents of the matrix (*e.g.*, soil), toxicokinetic interactions affecting uptake and elimination (*e.g.*, Roesch et al. (2017) or toxicodynamic interactions affecting compound metabolism or associations at the target site (Gomez-Eyles et al., 2009).

Both CA and IA models assume no interaction among mixture components (Schell et al., 2018) while, in some mixtures, interactions between chemicals can result in stronger (synergistic) or weaker (antagonistic) effects than those expected of the toxicity of single components. CA and IA models thus fail to predict cases where interactions occur (*e.g.*, Olmstead and Leblanc 2003). Moreover, there are some limitations in the application of CA and IA models to predict the impacts of more complex multi-chemical (*e.g.*, ternary or more) mixtures (Jonker et al., 2005), and the exact modes of action are often unknown for the majority of compounds (Ginebreda et al., 2014; Wilkinson et al., 2015). Considering the broad range of PPP applied on agricultural fields, it is likely that PPP mixtures in streams are composed of compounds with both similar and dissimilar MoA. Moreover, there is a growing awareness that the MoA of a PPP may vary among organisms. In addition, if the MoA of PPP is known for the target organisms, it remains largely unknown for the non-target species (Verro et al., 2009).

Although interactions of chemicals cannot be tested directly from the CA and IA models, they can be detected from the deviations between predicted and actually observed values (Qiu et al., 2017; Filimonova et al., 2018; Tao et al., 2020). Deviations from the CA and IA models are referred to as antagonism (when the toxicity of the mixture is less than that predicted by each model) and synergism (when the toxicity of the mixture is greater than that predicted by each model, Phyu et al. 2011). The reported inability of the CA and IA models to consistently model mixture toxicity led Jonker et al. (2005) to propose three additional functions that may be added to the basic CA and IA models to describe the three types of biologically relevant deviations from additivity: antagonistic deviation, dose level–dependent deviation, and dose ratio–dependent deviation.

To explore the joint action of chemical mixtures, the isobologram model (Combination Index (CI)-isobologram equation) is a commonly used and powerful graphical approach (Tagun and Boxall, 2018). By comparing the isoboles based on the CA and IA predictions and experimental mixture data, conclusions can be drawn on the type(s) of interaction occurring (Cedergreen, 2014). Moreover, Dupraz et al. (2019) described the Hewlett and Vølund models that are extensions of the CA model. Other methods relying on the same approaches (CA/IA models) have been proposed such as the Computational Approach to the Toxicity Assessment of Mixtures (Schmidt et al., 2017), the Accelerated Failure Time (AFT) model (Qiu et al., 2017), the CI method (Yang et al., 2017), the calculation of Mixture Toxicity Index (MTI) or Safety Factor Index (SFI) (Toumi et al., 2018). Another commonly used tool is the MIXTOX model (*e.g.*, Maloney et al. 2017; Mansano et al. 2017; Robinson et al. 2017; Raby et al. 2019; Rocha et al. 2018), a regression-based, dose-response mixture analysis modeling framework. This tool fits ecotoxicity data to the conceptual models (CA or IA) and then evaluates if there are any deviations for synergism/antagonism or dose level or ratio dependencies (*i.e.*, depending on low or high doses, or dependent on the ratio of the chemicals in the mixture,

respectively). In the same way, the Model Deviation Ratio (MDR) technique is used to determine the biological significance and reproducibility of observed mixture effects (*e.g.*, Belden et al. 2007; Lopez Aca et al. 2018; De Perre et al. 2017; Belden and Brain 2018; Lanteigne et al. 2015) by comparing predicted and observed results of mixture toxicity. If the MDR values are < 5, then the CA model applies since the additive MoA can be assumed. If the MDR values are > 5, there is a potential that synergistic MoA dominates (Chen et al., 2020). When the MDR value is > 2.5, high levels of uncertainty exist, and this decreases the applicability of the model to risk assessments (Belden and Lydy, 2006). In addition, an MDR value > 2 could result from test variability or could be a result of the analytical quantification techniques (Lanteigne et al., 2015).

In risk assessment of mixtures, the mathematical model used should be protective for complex, environmentally relevant mixtures which do not show synergistic interactions (Cedergreen, 2014). Based on its more conservative approach, CA is often suggested as a default model for risk assessment of chemical mixtures (Schell et al., 2018). Another advantage of CA is that frequently reported EC_x are sufficient for the calculation, whereas IA requires information about the whole concentration response function, which is rarely reported or available (Verro et al., 2009). Finally, the assumptions on the MoA in the IA model are unlikely to be met in environmental mixtures (Svendsen et al., 2010).

Some authors reported the IA model to underestimate the mixture effects, as Hasenbein et al. (2017) who studied the combined effect of diuron and hexazinone on the growth of the green algae *Pseudokirchneriella subcapitata* and on *Daphnia magna.* In order to be adequately protective of sensitive aquatic insect species, these authors proposed to consider a prediction window that incorporates both reference models when interpreting cumulative effects, accounting for any potential greater-than-additive effects that may occur resulting from mixture exposure. Ginebreda et al. (2014) reported that CA tended to overestimate toxicity in controlled experiments as compared to IA, and some other authors found that the CA model slightly underestimated mixture effects, indicating potential synergistic interactions (Knezevic et al., 2016; Liess et al., 2016). Belden and Brain (2018) explained that if the empirical data deviates from the CA model by a factor of greater than 5, then synergy is considered likely and the ERA is based on the empirical data. Otherwise, the ERA may use CA to calculate Risk Quotients (RQ) or be based on the most toxic active ingredient. Another approach proposed by Ginebreda et al. (2014) can be used to describe how a compound ecotoxicity is statistically distributed rather than to predict the exact ecotoxicity value of the mixture (where a major part is unknown). They define a procedure whereby the compounds identified in a sample are ranked in descending order according to their toxic load expressed in terms of toxic units, and then the shape of the distribution is characterized. This compound prioritization, depending on the sampling site, is important from a management point of view.

4.2 What are the model usages?

4.2.1 Prediction of PPP ecotoxicological properties based on their chemical characteristics using (Q)SAR models

Our literature analysis, specific to the PPP, identified some (Q)SAR models predicting toxicokinetic parameters (mainly bioconcentration factor, BCF) and numerous articles describing (Q)SAR models predicting acute toxicodynamic parameters. In addition, some (Q)SAR models were developed to deal with substance classification.

Toxicokinetic outputs

For the toxicokinetic parameters, the most commonly used (Q)SAR models are based on the established correlation between BCF and the hydrophobicity ($\log_{10}(K_{ow})$) of organic chemicals (Pavan et al., 2008). There is general agreement that these linear correlations give a fair approximation of the BCF for non-ionic, non-metabolised substances with $\log_{10}(K_{ow})$ in the range of 1 to 6 (Pavan et al., 2008). Numerous (Q)SAR studies have attempted to predict the BCF accurately for more hydrophobic substances as well as for the substances that are metabolised to an appreciable extent in the exposed organism, for example by including additional descriptors in the equation and using more complex non-linear approaches (reviewed in Pavan et al. 2008 and Miller et al. 2019). During the last twenty years, a large number of global (Q)SAR models (diverse substances, Tables 1-5 in Pavan et al. 2008) were developed for predicting the BCF but, to the best of our knowledge, few new (Q)SAR models were developed to predict specifically the BCF of PPP (Jackson et al., 2009; Miller et al., 2019; Nendza and Herbst, 2011).

Toxicodynamic outputs

Most of the (Q)SAR models identified in our bibliographic analysis predict the dose that gives the toxic effect in 50% of the organisms, and therefore predict only acute toxicity of the substances. For instance, oral LD_{50} (the Lethal Dose for 50% of the tested organisms) is used for birds (Basant et al., 2015b; Mazzatorta et al., 2006), contact LD_{50} is reported in μg/bee for honeybees (Hamadache et al., 2018) and, for aquatic animals, the LC_{50}, the lethal water concentration likely to kill 50% of the organisms is used (Devillers, 2001; Khan et al., 2019). Finally, the EC_{50} inhibiting the algae biomass growth rate (Villain et al., 2014; Xiao et al., 2019), even if the endpoint is not at an organism level, can be assimilated to the acute toxic endpoints.

Another toxicodynamic endpoint well investigated by the (Q)SAR models is the mutagen properties of the substances, frequently based on the result of the bacterial reverse mutation test often referred to the Ames test or OECD test guideline No. 471.12 (Benigni et al., 2020; Herrmann et al., 2020). For the *Ames* test, all (Q)SAR models generated statistically significant predictions, comparable with the experimental variability of the test. The reliability of

the models for other assays/endpoints appears to be still far from optimality (Benigni et al., 2020).

Very few (Q)SAR models were developed for ecologically relevant endpoints able to predict potential chronic effects of substances, and at biological level convenient to manage the risk (population, community or ecosystem). Among the reviewed papers, only one really recent study addresses these sorts of endpoints. Finizio et al. (2020) developed successfully two simple (Q)SAR models to predict the effect of narcotic compounds on aquatic communities (HC_5, concentration at which 5% of the species exhibit an effect). To fill this gap, Inter-species Correlation Estimation (ICE) - (Q)SAR models could also be used to determine HC_p without the need for additional *in vivo* testing to help prioritise which chemicals with no or few ecotoxicity data require more thorough assessment (Mombelli and Pery, 2011; Douziech et al., 2020).

Classification and modes/mechanisms of action

Even if, for ecotoxicity assessment, most of the (Q)SAR models are regressions referring to the dose that gives the toxic effect in 50% of the organisms, some authors proposed to work with classification (Mazzatorta et al., 2004). Classification is the process of dividing a data set into mutually exclusive groups so that the members of each group are as "close" as possible to one another, and different groups are as "far" as possible from each other, where distance is measured with respect to specific variable(s) involved in the prediction (Mazzatorta et al., 2004). For example, Venko et al. (2018) proposed to classified compounds according to the thresholds as defined in PPDB: lowly toxic (LD_{50} more than 100 μg/bee), moderately toxic (LD_{50} between 1 and 100 μg/bee) and highly toxic (LD_{50} less than 1 μg/bee). These authors argue that classification offers two main advantages in ecotoxicology: (i) the regulatory values are indicated as toxicity classes and (ii) classification can allow better management of data which are often noisy (Mazzatorta et al., 2004).

Among the models developed to classify the substances, some were developed to determine the mode of action (MoA) or mechanism of action (MechoA) of the substances including PPP (Bauer et al., 2018b,a; Kienzler et al., 2017; Martin et al., 2013). MechoA differs from MoA because it refers to the molecular interaction that a molecule will undergo, leading to a biological outcome, which can be the key starting point of the Adverse Outcome Pathway (AOP) for this substance, *i.e.*, the Molecular Initiating Event (MIE) Boone and Di Toro (2019). MoA is not so clearly defined, often referring to the pathological effects that can be seen at the whole organism level in terms of behaviour or death *i.e.*, at the other end of the AOP (Russom et al., 1997). The idea behind these works is that a good understanding of MoA or MechoA, and appropriate methods to determine them, is crucial for the efficient prediction of toxicity using local (Q)SAR models and AOP framework (Boone and Di Toro, 2019; Carnesecchi et al., 2020). To this goal, various structure-based classification schemes have been developed to categorize chemicals based on the MoA or

MechoA (Bauer et al., 2018b; Kienzler et al., 2017). In addition, several predictive methods were developed with narrow applicability domains, and recently new methods were proposed to predict the MoA/MechoA only from the chemical structure to a wide range of organic chemicals including PPP (Raimondo and Barron, 2020).

4.2.2 Quantification of biological time-dose responses to PPP exposure using DR and TKTD models

As recommended since decades in most of the OECD guidance documents to study the ecotoxicity of chemical substances for a range of species under standard protocols, DR analyses are employed to directly link constant exposure concentrations to endpoints of interest (such as survival, reproduction, growth...) at the end of the experiment (see for example Felten et al. 2020). DR models are mainly used to calculate standard outputs such as EC_x or LC_x on which the Tier-1 assessment is based to make decisions regarding approval of active substance (Brock et al., 2018; Charles et al., 2021). Let us mention here the original work of Nian et al. (2015) who tried to take into account the temporal dimension of the effects in a classical DR model by an approach known as time concentration mortality (TCM) modelling. Note that TCM models originate from Complementary log–log (CLL) models describing the relationship between time, dose, and the cumulative probability of mortality (Preisler and Robertson, 1989; Nowierski et al., 1996).

In essence, DR models do not allow any consideration of the time dimension of the effects. They also do not include exposure modelling, so that they are purely descriptive and unusable to perform predictions under time-variable exposure scenarios, more environmentally realistic. However, recent work has attempted to include pulsed exposures (Copin et al., 2015; Copin and Chevre, 2015; Copin et al., 2016; Copin and Chevre, 2018). Other work has extended the use of DR models for example to take into account the seasonal and the gender variability on EC_{50} values (Dalhoff et al., 2018), to account for hormesis (Jager et al., 2013; Tyne et al., 2015), or to make a link with biological traits (Rubach et al., 2012). More interestingly, Monti et al. (2015) addressed the thorny issue of systematically considering a normal distribution of toxicity data, while it is well-known that such an assumption may be wrong for binary or count data for example (Forfait-Dubuc et al., 2012; Delignette-Muller et al., 2014; OECD, 2016). Monti et al. (2015) proposed an alternative approach to deal with proportion data while the initial number of individuals remains unknown; their innovation lies in the use of the Beta probability distribution, without classical optimization techniques but the use of the log-ratio. Finally, cite work from Baillard et al. (2020) who proposed including ecological interactions in ERA, by studying how inter-specific competition affects plant species response to herbicides and more specifically how it may modify DR curves and the resulting toxicity indices.

Regarding TK models, our literature review reveals two clusters of papers. The first cluster encompasses classical TK models. TK models are mainly used for calculating bioaccumulation metrics such as bioconcentration, biota-sediment accumulation or biomagnification factors. The type of factor depends on whether the exposure is via water, sediment or food, respectively, providing the so-called BCF, $BSAF$ and BMF values, respectively, as required by regulators for ERA. The most used is clearly the BCF, originally developed to analyse bioaccumulation in fish according to the OECD guideline 305 (OECD, 2012). Regarding PPP, we have unearthed two old publications in which the bioaccumulation model is not formalised as it is today by ordinary differential equations describing the dynamics of the different compartments that are considered (Elliott et al., 2005; Satyanarayan and Ramakant, 2004). The other papers on TK models applied to PPP divide in work providing BCF (Brox et al., 2016; El-Amrani et al., 2012; Loureiro et al., 2002) or BMF values (Carafa et al., 2009; Lazartigues et al., 2013; Fraser et al., 2002).

In the second cluster, with more elaborated TK models, three studies emphasize the importance of considering biotransformation, that is the possible degradation of the parent compound into metabolites, that may be even more toxic (Firdaus et al., 2018; Gao et al., 2013; Wu and Zhu, 2019), the work by Wu and Zhu (2019) having the particularity to concern plants. One study has accounted for time-variable exposure (Rubach et al., 2010) going so far as to propose the 95% depuration time (t_{95}) as a complement to the BCF. The depuration time is important as it defines the minimum length of the interval between repeated exposure events required for the organisms to recover. Consequently, it could be particularly useful in ERA when evaluating effects due to pulsed exposure. Last but not least, Roesch et al. (2017) propose a TK model to deal with binary mixtures, focusing on the synergistic potential of azole fungicides from the CA hypothesis (see Section 4.1.6).

In essence, TKTD models are of course best able to quantify the dynamics of chemical effects on life-history traits of exposed organisms, whatever the type of effects they account for (lethal or sub-lethal). See section 4.1.2 were they are presented.

4.2.3 Extrapolation of effects of a tested exposure pattern to others, untested, exposure patterns

At the individual level, only TKTD models really enable to extrapolate effects under a tested exposure pattern to other untested ones (EFSA PPR Panel, 2018a). As already stated above, TKTD models finely describe the internal dynamic of the damages due to a (time-variable) chemical exposure, leading to effective or lethal changes on living organisms. TKTD models actually bring together several types of models depending on the biological traits that are observed (see Table 4 and Figure 1 in EFSA PPR Panel 2018a).

Regarding our literature review on PPP, GUTS models appear as the most used. As described in the founding article (Jager et al., 2011), and later in

more details (Jager and Ashauer, 2018), GUTS models specifically describe the survival probability as a function of time and exposure concentration, this latter may vary over time. Note that the GUTS name dates from 2011 (Jager et al., 2011); before that, a large number of very different TKTD approaches for survival existed in the literature with just as many different names. For clarity reasons, the GUTS name is used hereafter, whatever the TKTD model for survival is mentioned.

Mostly used for research purposes, initially at constant exposure concentrations (Jager and Kooijman, 2005; Hesketh et al., 2016; Kretschmann et al., 2012), GUTS is today more and more employed to account for time-variable exposure (Ducrot et al., 2010; Focks et al., 2018; Nyman et al., 2012; Gabsi et al., 2018). GUTS models are also used for ERA, for example at Tier-2C assessment in combination with Tier-2B assessment based on SSD approaches (see Brock et al. 2021, and Figure 6 in EFSA PPR Panel 2018a). Extensions of GUTS models have recently been published to deal with chemical mixtures (Arlos et al., 2020; Bart et al., 2021), in combination with a shortage of food resources (Nyman et al., 2013), while Dalhoff et al. (2020) have proposed to relate GUTS models with morphological and physiological traits.

For explaining effects on sub-lethal individual life-history traits (such as growth and reproduction endpoints), DEBtox models are today the leading TKTD models (Jager, 2020). EFSA even recognizes the great potential of DEBtox models for future use in prospective ERA for PPP, although the DEBtox modelling approach is currently limited to research applications (EFSA PPR Panel, 2018a). Regarding the use of DEBtox models for PPP, we only found few relevant papers. Pieters et al. (2006) exposed daphnids to PPP pulses with either low or high food availability, leading them to conclude that effect of PPP application on field populations of daphnids will depend not only on the trophic state of the receiving water body, but also on the reproductive state and size of the animals. Jager et al. (2007) exposed *Folsomia* to chlorpyriphos via food, simultaneously modelling survival (this part being similar to a GUTS model in its Stochastic Death (SD) version), growth and reproduction, then making the link to the population dynamics via the Euler-Lotka equation. Zimmer et al. (2018) proposed a model for the effects of time-variable exposure to the β-cyfluthrin pyrethroid on rainbow trout early life stages. And very recently, Vignardi et al. (2020) proposed a DEBtox-like modelling approach to study how aquatic species respond to incidental exposure to Cu-based nano-engineered PPP, pointing out that future efforts should focus on toxicity studies and TKTD model development for nano-pesticides to make advance in ERA. Jager (2020) also proposed some directions that could improve ERA, like including a starvation module in DEBtox models to account for time-variable exposure profiles in particular, and performing more experiments under time-variable exposure in order to support the validation of DEBtox models for ERA.

In terms of innovation with TK models, the combined TK-IBM framework proposed by Liu et al. (2014) revealed particularly interesting to better assess the PPP risk on wood mouse when the temporal pattern of feeding and time spent in exposed area by individuals is accounted for. Also, works of Chaumet et al. (2019)a and Chaumet et al. (2019)b on biofilms is worth mentioning, as well as work of Roeben et al. (2020) including both time and space explicitly as explanatory variables in addition to the exposure concentration. Those studies then employed an explicitly spatialized TKTD model combined with a trait-based approach and a population dynamic model in a modular approach that revealed particular efficient. Last but not least, Mit et al. (2021) are the first to illustrate how PBTKTD models (that is considering several compartments for the TK part) may be used to better characterize and understand the interactions of chemical compounds within a binary mixture.

Coupled with TKTD models, population models - whether they are unstructured, structured or ABMs - allow understanding the ecological consequences of complex exposure scenarios, especially time-varying patterns particularly relevant in the case of PPP, *e.g.*, Galic et al. (2014); Thursby et al. (2018); Weber et al. (2019); Ashauer et al. (2020); Schmolke et al. (2021). These integrated mechanistic models are most often used to theoretically extrapolate the consequences of PPP use scenarios to other exposure patterns, other ecosystems, or new climate conditions, *e.g.*, Dohmen et al. (2016); Hommen et al. (2016). When coupled with fate models in the frame of landscape models, these models can act as a toolbox in which a range of PPP exposure scenarios can be simulated. This allows to better inform the possible effects of these substances in realistic landscapes and realistic agricultural application patterns (Dalkvist et al., 2009; Focks et al., 2014; EFSA PPR Panel, 2018b). Various studies in both terrestrial and aquatic environments illustrate how this approach makes it possible to identify the influence of agricultural practices on the ecological risk for non-target species (Topping et al., 2016), the effect of land use change, for example in an owl (Engelman et al., 2012) or the woodpigeon (Kulakowska et al., 2014), or the benefit of mitigation actions such as the establishment of buffer zones, *e.g.*, in rodents (Dalkvist et al., 2013), carabid beetles (Topping et al., 2015), aquatic invertebrates (Dohmen et al., 2016), or fish (Schmolke et al., 2021).

Natural and chemical stressors occur simultaneously in the different compartments of the environment (De Coninck et al., 2013). Population or community models can be used to assess effects of a PPP in different environmental settings including stressors ignored in the lab tests (e.g. increased temperature, reduced soil moisture, resource limitation, predation pressure). Moreover, mathematical models used for joint effects caused by mixtures of chemicals can be used to assess the effects of combined stressors, *e.g.*, soil moisture in Morgado et al. (2016); ultraviolet-B radiation in Yu et al. (2015); food limitation in Shahid et al. (2019); bacterial parasite in De Coninck et al.

(2013); predation in Pestana et al. (2010); predation threat, parasitism and carbaryl in Coors and De Meester (2008). Thus, current efforts aim at including the additional risk of PPP mixtures and environmental stressors into the environmental risk assessment of PPP. Generally, the IA model, used to study combined effects of dissimilarly acting stressors, is chosen to assess the effects of combined stressors (De Coninck et al., 2013). Liess et al. (2016) developed the Stress Addition Model (SAM) that assumes that each individual has a general stress capacity towards all types of specific stress that should not be exhausted. This model relies on three principal assumptions that provide a mechanistic understanding of the combined impact of independent stressors, in this case a chemical in combination with one environmental stressor: (i) each individual has a certain tolerance towards all types of stress, its general stress capacity; (ii) every specific unit of a given stressor (*e.g.*, $\mu g/L$ for chemicals, ^oC for temperature) can be transferred into a general stress level ranging from 0 to 1 as a "common currency" for all stressors (the main challenge); (iii) general stress levels of independent stressors are additive, with the sum determining the total stress exerted on a population. This model was used by Shahid et al. (2019) who compared it to CA and Effect Addition (EA) in order to assess the combined effects of food limitation and of a pyrethroid insecticide or an azole fungicide. The combined effects of PPP and food stress was best predicted with the SAM that showed the lowest mean deviation between effect observation and prediction.

4.2.4 Assessment of the relevance of PPP effects observed on individuals for the population level

Some works emphasize that linking TKTD models to population dynamic models would be a further step toward a more effective risk assessment (Horig et al., 2015; Kretschmann et al., 2012). More concretely, Vignardi et al. (2020) enlightened potential population-level effects of exposure to very low-levels of nano-pesticides from their TKTD modelling outputs. Based on an integrated multi-faceted modelling approach, Roeben et al. (2020) were able to make the link between PPP exposure, ecology and toxicological effects on earthworms.

The most basic aim of using population models for the ERA of PPP is to establish the demographic outcome of the repetition of organism-level toxic events during the development of successive generations, through either simulation or projection exercises (Forbes et al., 2016). In connection with the cyclic repetition of agricultural treatments, they thus consider the cumulative outcome of mortality events (Topping et al., 2015), reductions of reproductive capacities (*e.g.*, insecticides in pollinators Cresswell 2017 and seabirds Goutte et al. 2018) or disturbances of all the phases of the life cycle (Chandler et al., 2004). But the first great value recognized in these models is that they simultaneously integrate all the toxic effects of PPP exposure (survival, reproduction, growth, behavior, etc.), taking into account the characteristics

of the life cycle of the species of concern when predicting the PPP consequences on population persistence (Stark and Banks, 2003; Topping et al., 2005; Forbes et al., 2016). Some authors establish dose-response relationships at the population level using as output different indicators of population size, population growth capacity or extinction risk calculated by these models (Stark et al., 2004; Lopes et al., 2005; Preuss et al., 2010; Hanson and Stark, 2012; Stark, 2012; Goutte et al., 2018). Although highly conditioned by the choice of processes and conditions considered in each model, these studies propose to define protective concentration thresholds for the population by confronting these outputs with theoretical thresholds of maintenance or good demographic state of the populations.

In a cognitive mode of use, population models and sensitivity-elasticity analyses (Caswell, 2001) - frequently used in species conservation management - allowed to understand the crucial role that life history traits plays in the demographic impacts of PPP. Numerous modeling studies have emphasized the importance of species life cycle characteristics in the demographic impact of PPP on animals or plants (Stark and Banks, 2003; Stark et al., 2004; Raimondo and McKenney Jr, 2005; Lindsay et al., 2010; Stark et al., 2015; Schmolke et al., 2017, 2018; Thursby et al., 2018; Banks et al., 2019). Structured population models are widely used in this framework of ERA (Forbes et al., 2016; Accolla et al., 2021), which is also found for PPP in our corpus of case studies: 50% of structured models versus only 15% for ABMs address the issue of differential demographic sensitivities between life cycle stages. Another major point relating to life cycle characteristics in PPP ecological models is the phenology and timing of exposure in relation to cultural practices that influence the risk of population exposure, the capacities of demographic compensation, or the recovery after short-term exposure. These temporal aspects, which have been extensively studied in pest management and biocontrol (Stark et al., 2004; Tonnang et al., 2017; Tang et al., 2019), are now being emphasized as determining factors in the vulnerability of non-target species, and in the relative severity of impacts of PPP treatment practices: reproductive phenology in bird species (Etterson and Bennett, 2013; Etterson et al., 2017; Moore et al., 2018; Crocker and Lawrence, 2018), annual development cycle in pollinators (Thompson et al., 2005), in aquatic invertebrates (Galic et al., 2012; Sorensen et al., 2020) or in plants exposed to herbicides (Schmitt et al., 2013). The other overarching element considered is the spatial dimension in the processes of exposure or in population dynamics response (Topping and Odderskær, 2004; Dalkvist et al., 2009; Forbes et al., 2016; Schmolke et al., 2017; Accolla et al., 2021). PPP population and landscape models thus make it possible to retrace (i) the complex ecology of certain species (amphibians in EFSA PPR Panel 2018b; endangered mammals in Nogeire et al. 2015; or fish in Schmolke et al. 2021), (ii) the spatial heterogeneity of resources (soil invertebrates in Johnston et al. 2014; birds in Topping and Odderskær 2004; bees in Becher et al. 2014; Thorbek et al. 2017; Gegear

et al. 2021; More et al. 2021), (iii) the migratory links between habitats or throughout the population distribution area (Galic et al., 2012; Focks et al., 2014), which can compensate for local PPP effects or on the contrary export the demographic impacts to non-contaminated areas (Chaumot et al., 2003; Schaefer et al., 2017). Various studies have thus highlighted the influence of landscape structure on the impacts of various agricultural PPP practices on non-target populations (*e.g.*, in vole, Wang and Grimm 2010; Dalkvist et al. 2013; hare, Topping et al. 2016) and identified specific areas of the landscape that are particularly at risk for species of conservation concern (Engelman et al., 2012) or important for ecosystem functioning (Kattwinkel et al., 2011).

The demographic framework also led some studies to emphasize the possibility of compensation between PPP-induced mortality or reduced fecundity and the release of natural density-dependent controls (*e.g.*, competition) that buffer PPP population impacts (Stark and Banks, 2003; Stark, 2012). These processes have been investigated in wild rodents (Wang et al., 2001; Wang and Grimm, 2010), in relation to territorial behavior in fish (Mintram et al., 2018) or hare (Kleinmann and Wang, 2017), in soil invertebrates (Reed et al., 2016), in pollinators (Bryden et al., 2013), and in plants (Schmolke et al., 2018). This effect of density level led some authors to point out the specificity of the demographic response of rare or endangered species to PPP exposure (Topping et al., 2005). Taking into account density-dependence phenomena can complicate the mathematical analysis of structured models, as well as the degree of knowledge required for the parameterization of simulation models. Similarly to the habits in generic ERA (Accolla et al., 2021), our PPP case studies show that 80% of ABMs include density-dependence against only 40% of structured models. One of the great advantages of ABMs is to make these density-dependence phenomena emerge from individual behaviors and thus mechanistically include the effects of PPP at the heart of these processes, as illustrated by the interplay of the demographic effect of neonicotinoids and the size of bumblebee colonies (Crall et al., 2019).

One current perspective for increasing the ecological relevance of population models is the consideration of PPP multigenerational effects in ERA. As illustrated by pioneer studies on the transgenerational effects of fungicides acting as endocrine disruptors in wild rodent populations (Dalkvist et al., 2009, 2013), ABMs are particularly well suited to take into account the exposure history according to the pedigree of individuals and the transfer of effects between generations. Moreover, while population genetic models have been integrated in the study of PPP resistance for several years (Onstad and Meinke, 2010), the micro-evolutionary aspects possibly leading to adaptation and associated fitness costs are up to now totally absent from PPP population modeling for non-target species. But here again, ABMs seem particularly promising for integrating this type of long-term effects once they are better documented in the

ecotoxicological literature, following the example of quantitative genetics modeling practices used in pest resistance management (Ives et al., 2017; Slater et al., 2017).

4.2.5 Integration of recovery processes, from individual to population level recovery

Population models place the assessment of PPP effects at larger spatial and temporal scales than the evaluation solely focused on toxicological individual responses (Forbes et al., 2009). Agricultural treatments cause toxic stresses that may be episodic and punctual (pulse exposure) or localized in the habitat space of non-target populations. Various population studies have thus focused on the capacity for population recovery after exposure to PPP (Wang et al., 2001; Hanson and Stark, 2012; Wang, 2013; Mintram et al., 2018), implying the capacity for recolonization from uncontaminated refuge areas on small spatial scales (Van Den Brink et al., 2007; Galic et al., 2012, 2014) or at larger distances, *e.g.*, river network (Focks et al., 2014). This issue is very predominant in the literature on the use of ecological models for PPP ERA: 60% of the case studies of population models in our corpus fit into such a framework of pulse exposure, as well as 40% of the landscape studies. These developments are partly driven by the proposal to use population models to apply an ecological recovery option in PPP ERA, where legislation explicitly allows limited adverse effects of PPP if recovery of exposed populations can be achieved within a given time period (Hanson and Stark, 2012; Focks et al., 2014; Galic et al., 2014). The literature offers different definitions and a multitude of recovery indicators, which refer to a return to a pre-exposure state, or a state simulated in a control scenario. This population state can be of different natures, based on the abundance or on the level of occupancy of the different patches of the population distribution area (Topping et al., 2015). PPP impacts and their acceptability are defined in terms of recovery capacity, recovery time, response amplitude, probability of extinction, or duration of low-level density period, *e.g.*, Wang et al. (2001); Hanson and Stark (2012); Hayashi et al. (2016); Thursby et al. (2018). Population models can be used to identify the determinants of recovery capacity, in particular to distinguish between autogenic (local demographic recovery) and allogenic (recolonization) capacity, *e.g.*, Van Den Brink et al. (2007); EFSA PPR Panel (2018b); Schaefer et al. (2017). From an applied point of view, highlighting the importance of migratory processes in population recovery within agricultural landscapes justifies the preservation of spatial connectivity and the importance of refuge zones (Galic et al., 2012, 2014; Focks et al., 2014). Modeling can also allow the evaluation of sustainable levels of treatment frequency for populations (Focks et al., 2014) following similar methodologies developed in biocontrol and for the pest management (Stark et al., 2004; Tonnang et al., 2017; Tang et al., 2019).

4.2.6 Assessment of PPP impacts at the community level

Statistical extrapolation using SSD approaches

There are two main types of standard outputs when performing SSD analyses. When SSD is used in a prospective risk assessment, the final aim is to derive Predicted No-effect Concentrations (PNEC) and the derived Toxicity Exposure Ratios (TER). The PNEC is a prospective level of environmental safety corresponding to the concentration below which adverse effects are not expected to occur (European Commission, 2003). The TER is defined as the ratio of the measure of the effects (*e.g.*, LD_{50}, LC_{50}, $NOEL$) to the estimated exposure. It is the reciprocal of a risk quotient (RQ) or a hazard quotient (HQ, Stephenson et al. (2006)). In a retrospective assessment of the level of environmental safety, EQS are preferred, especially in the context of the Water Framework Directive (WFD, Technical Guidance Document (2011), Lepper (2002)). Within the WFD, a distinction is even made between the annual average EQS (AA-EQS) and the maximum allowable concentration EQS (MAC-EQS) values (Brock et al., 2006).

For both types of apical criteria (namely, final decision criteria that will be used by regulators), the main standard output derived from SSD is the HC_p statistically corresponding to the p^{th} percentile of the probability distribution that is fitted to toxicity input values. As stated by Posthuma et al. (2002), the HC_p is the exposure concentration assumed to be protective for $(1-p)\%$ of the species within the considered ecosystem. Most of the time, the HC_5 is calculated, at least for PPP (Brock et al., 2004; Van Den Brink et al., 2006; Daam et al., 2010; Mensah et al., 2013; Ramo et al., 2018; Iwasaki et al., 2015; Van Den Brink et al., 2019; Baillard et al., 2020). Almost all tools associate uncertainty limits around the mean or the median of the delivered HC_p estimates. The PNEC can be calculated from the HC_5 (Tier-2 PNEC), accounting for uncertainty by dividing the HC_5 by a certain coefficient. According to authors, the relationship between the HC_5 and the PNEC may differ: it can be assumed equal to the median HC_5 (Brock et al., 2006), to its lower-limit (Daam et al., 2010), to the ratio of the HC_5 by an uncertainty factor (Mentzel et al., 2021); in the regulatory context, either to the ratio of the HC_5 by an appropriate Assessment Factor (AF, European Commission 2003) or also equal to the median HC_5 estimate (*e.g.*, EFSA PPR Panel (2015b)). Note that ratios based on SSD outputs are now preferred: for example the Tier-1 Regulatory Acceptable Concentration (RAC) is an EC_{50}/AF, while the Tier-2B RAC is an HC_5/AF as usually preferred in aquatic risk assessment (EFSA PPR Panel, 2013). Note that in EFSA PPR Panel (2013), the TER is rather denoted as ETR (standing for exposure–toxicity ratio), defined as the Predicted Environmental Concentration (PEC) over the RAC. A value of ETR $<$ 1 (that is PEC $<$ RAC) indicates an acceptable risk. Other calculations from single or very few toxicity indices for isolated species are more related to the REACH terminology, such as for example the RQ equal to the PEC over the PNEC (Iwasaki et al., 2015; Sorgog and Kamo, 2019).

The application of SSD in a retrospective risk assessment of chemicals consists in predicting a fraction of the community which is likely to be impacted by a specific concentration of a given substance. Then, the standard output is the Potentially Affected Fraction (PAF) (De Zwart, 2005).

Regarding mixtures studied via SSD, most analyses aim at calculating multiple-substance PAF or $msPAF$. Such outputs come from a combination of SSD for each individual compound with CA or RA models (Jesenska et al., 2013). In particular, Jesenska et al. (2013) evaluated the impact of different data validation approaches (such as removal of duplicate values and outliers, testing of different exposure durations and purity levels of studied herbicides, using different sets of input data, namely NOEC vs. EC_{50}, and considering different taxonomic groups) in a retrospective model case study. Interestingly, they conclude that the use of rough non-validated data seems to provide robust results, especially when few ecotoxicity values are available for certain compound(s).

Analysis and prediction of possible indirect PPP effects within communities

Even if the SSD method does not account for any species interaction, comparing the SSD method used at Tier-2 to food-chain models at Tier-3 of ERA, Brock et al. (2004) stated that a protection level based on direct effects (such as reflected by the HC_5 estimate) could also protect against indirect effects. Nevertheless, while unavoidable within community experiments, indirect effects are not very often directly studied and accounted for in models at the community level, in general. Only Clemow et al. (2018) used an SSD-based approach to highlight both direct and indirect effects for fish and aquatic invertebrates exposed to malathion. Compared to the SSD concept and food-chain models, the PERPEST model was proposed to account for more information on ecological risks when a common toxicological MoA is evaluated (Van Den Brink et al., 2002, 2006); indeed the PERPEST model considers both recovery and indirect effects. In brief, the PERPEST simultaneously predicts the probability of classes of effects (no, slight, or clear effects, plus an optional indication of recovery) on various grouped endpoints of a particular concentration of a PPP on community endpoints (*e.g.*, community metabolism, phytoplankton, and macro-invertebrates). It is entirely based on literature data gathered in a database to perform prediction where no effects on a semi-field scale have been published. The PERPEST model was specifically emplopyed to address direct and indirect effects in Van Den Brink et al. (2006) and successfully applied to PPP (Daam et al., 2010; Ramo et al., 2018). Reeg et al. (2017) studied direct and indirect effects of herbicides on non-target grassland communities.

In fact, food-web models are more appropriate to deal with indirect effects. For example, Traas et al. (2004) studied indirect effects of PPP on biomass and recovery within a microcosm. With very simple models, De Hoop et al. (2013) concluded to the existence of food mediated indirect effects of atrazine on zoobenthos populations, while Joncour and Nelson (2021) demonstrated the direct and indirect impact of spinosad on insect life-histories.

PPP bioaccumulation and biomagnification within food chains / food webs

Within our bibliographic corpus, only the paper by Scholz-Starke et al. (2018) appeared as addressing the issue of biomagnification. Indeed, they employed the AQUATOX framework to simulate aquatic trophic guild dynamic accounting for hydrodynamics and nutrients together with the dynamics of the exposure substance and its metabolites: they showed a significant biomagnification of metabolites. However, the issue of bioaccumulation is mentioned several times within food-web studies (Nfon et al., 2011; Ren et al., 2017), while it has been far more basically addressed by Sanchez-Bayo et al. (2002) via the use of the Ecological Risk Ratio (EcoRR) approach.

Development of tools that integrate both exposure and effects

From a particular case study on bees, Crenna et al. (2020) underlined how important it is to consider both exposure and effects across all applied PPP, instead of focusing only on PPP with high ecotoxicity potentials or modes of action specifically targeting insects. Nevertheless, combined studies that looked at both exposure and effects are rather rare within our corpus. At the community level, a first attempt was made by Sanchez-Bayo et al. (2002) with its EcoRR approach, while a deeper integration of both aspects came later with Nfon et al. (2011) who combined fate and food-web models to estimate the food-web transfer of chemicals in small aquatic ecosystems. Then, thanks to the AQUATOX models, improvements in integrating both exposure and effect modelling was undertaken either for trophic guilds of aquatic organisms (Scholz-Starke et al., 2018) or lake ecosystems (Galic et al., 2019).

The SYNOPS-WEB model (Strassemeyer et al., 2017) allows quantitative assessment of the potential risk of PPP for the environment (leaching to groundwater) and for various Reference Species (RS) in soil (RS: earthworms), surface water (RS: algae, Lemna sp., Daphnia sp., Chironomus sp. and fish) and field margins (RS: bees). The acute and chronic risk indices are calculated as exposure toxicity ratio (ETR) where the PEC (in soil, surface water or field margin) is related to a toxicity value of the considered RS. For multiple application events and multiple active ingredients, the acute risk of a full application strategy is considered as the maximum risk posed by all application events and all active ingredients applied within one vegetative period. The chronic risk values are aggregated additively for each RS according to the concept of CA. The chronic risk aggregation of an application pattern is carried out in two steps: first, the chronic risk values are calculated for each applied active ingredient and added on a daily basis to derive curves of ETR sums; second, the maximum of these ETR-sum-curves is derived thus constituting the chronic risk of the full application strategy. It was demonstrated that SYNOPS-WEB reliably modelled the PPP exposure of aquatic organisms. The model could be improved with the integration of more mitigation measures such as strip till techniques, mulch seeding, creation of buffer strips or multi-functional field margins (Strassemeyer et al., 2017).

Among models accounting for both exposure and effects, there is also the work by Baudrot et al. (2020) who developed a heuristic non-spatialized model including montane water voles, specialist vole predators and the red fox as a generalist predator consuming voles, mustelids and other preys. Thanks to a broad-range sensitivity analysis on poorly informed toxicological parameters, they investigated the impact of five farmer functional responses (that is varying amounts of anticoagulant rodenticide spread according to different thresholds in vole densities) on predator–prey relationships, anticoagulant rodenticide transfer across the trophic chain and population effects.

At last, Baudrot et al. (2021) made a step further developing a spatially-explicit exposure-hazard model considering both the dynamics of pollen dispersal obtained by convolving genetically modified plants emission with a dispersal kernel and a TKTD model accounting for the impact of toxin ingestion on individual survival of on non-target Lepidoptera. This exposure-effect combined modelling approach allowed authors to better assess the ecological risk of Bt-maize at the landscape scale.

5 Strengths and limitations of the employment of the different model categories in PPP ERA

5.1 Genericity and transversality

5.1.1 Applicability of population models: from general to local case-study specific ERA

There is a consensus in the literature on the complementarity between simple generic population models addressing large scale questions for ERA of PPP (*e.g.*, identification of species at risk at a national level with respect to a certain type of PPP use) and more precise and specific modeling at local scales (*e.g.*, influence of landscape elements, or specific agricultural practices on a species locally at risk) (Topping et al., 2005; Forbes et al., 2015). Decision guides for the choice of population models now make it possible to identify the trade-offs to be made between genericity, realism and precision of an ERA according to its objectives (Raimondo et al., 2021). One of the strong aspects of population model frameworks is their portability between species, as already illustrated for birds (Etterson et al., 2017), pollinators (Becher et al., 2018), earthworms (Forbes et al., 2021), and plants (Schmolke et al., 2018). This rapid cross-species transposition of population models (especially structured models) benefits from the recent constitution of large ecological databases of demographic traits in conservation science (*e.g.*, in birds, fish, mammals, plants). It allows the rapid parameterization of population models on a large number of species and it could help in the relative ranking of species vulnerabilities to the different uses of PPP (Forbes et al., 2015; Etterson et al., 2017; Rueda-Cediel et al., 2019). On the other hand, mechanistic population models can also be adapted to local or population-specific conditions by incorporating the influence of environmental parameters on individual biological input variables and

species phenology (50% of the case studies in our corpus integrate such influence). The assessment of PPP population impacts is then refined, for example, according to temperature conditions in chironomids (Diepens et al., 2016) or in aquatic plants (Schmitt et al., 2013), according to trophic and dietary conditions, such as in daphnids (Preuss et al., 2010), bee (Abi-Akar et al., 2020), partridge (Millot et al., 2015), or in function of different landscape structures (Focks et al., 2014; Topping et al., 2016). This also enables the projection of scenarios of climate change or land use evolution (Nogeire-McRae et al., 2019) as can be done in the field of pest control (Donatelli et al., 2017). These environmental factors may constitute stressors additional to PPP, and population models are mobilized to compare PPP relative impacts in multi-stress contexts (hypoxia and insecticides in salmon, Landis et al. 2020, insecticides and parasitism in pollinators in Becher et al. 2014; Schmolke et al. 2019, flooding regime and herbicides in a threatened plant in Schmolke et al. 2017).

5.1.2 Limitation and applicability of mixture models to environmental case studies

Regarding environmental monitoring and risks, mixture models have been used for many years to assess the risks estimated from monitoring data on environmental concentrations (George et al., 2003; Schuler and Rand, 2008; Vaj et al., 2011; Chen et al., 2020). Cruzeiro et al. (2016) measured 56 priority PPP belonging to distinct categories (insecticides, herbicides and fungicides) in 42 surface water samples. Based on the CA and IA models, they used a two-tiered approach to assess the hazard of the PPP mixture, at the maximum concentration found, reflecting a potential risk. In the same way, Kuzmanovic et al. (2016) assessed ecotoxicological risks of chemical pollution in four Iberian river basins and its relationship with the aquatic macro-invertebrate community status using a data set including more than 200 emerging and priority compounds measured at 77 sampling sites along four river basins. The Toxic Units (TU) approach was used to assess the risk of individual compounds and the CA model to assess the site-specific risk. A difficulty highlighted by Perez et al. (2011) is that shifts for synergism and/or antagonism might occur depending on the dominant chemical present. However, Verro et al. (2009) exposed several considerations that support the suitability of the CA model for assessing risk for ecologically relevant PPP mixtures. These authors said that a few chemicals are responsible for $> 80\%$ of the toxicity, rendering differences between CA and IA predictions very small. Moreover, the most toxic components of the mixtures often have the same MoA. A geo-referenced representation of results allows analyzing the spatial pattern of toxic mixture assemblage in order to prioritize the locations at risk and to detect the group of compounds causing the greatest risk at different scales (Faggiano et al., 2010). However, predicting the effect from mixture assumes that the compounds will co-occur spatially and temporally which is not always the case (Faggiano et al., 2010).

Moreover, evaluation of effects on organisms at stimulatory doses of chemicals, known as hormesis, lacks a common statistical approach for mixtures

(Belz and Duke, 2018). Prediction of effective hormetic doses can be facilitated by using joint action models but to date there is no mechanistic models to predict the hormetic magnitude in mixtures. The IA model assumes a dissimilar MoA and multiplicity of effects up to a maximum response of 100% (Streibig et al., 2000), which is inappropriate to model hormetic doses leading to a response of > 100 (Belz and Duke, 2018). Nevertheless, some promising attempts were made to predict the hormetic magnitude. The selection of a reference model like CA can be used to describe mixtures of dissimilarly and similarly acting compounds (Belz and Duke, 2018). If the observed mixture data deviates synergistically or antagonistically from a reference model, the predefined curved isobole models of Hewlett or Vølund are available to model observed deviation patterns (Sorensen et al., 2007).

5.2 Uncertainty and modelling practices

In the guidance on how to characterize, document and explain uncertainties in risk assessment recently published by EFSA (EFSA Scientific Committee, 2018), uncertainty analyses are the process of identifying limitations in scientific knowledge and evaluating their implications for scientific conclusions. ERA relies on a very general definition of the uncertainty, that is referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question. Focusing on the modelling cycle, it is strongly recommended, if not mandatory, to quantify the parameter uncertainty (for example with 95% confidence or credibility intervals), but also to include a sensitivity analysis, an uncertainty analysis and the comparison of predictions with observed data when setting up the model (EFSA PPR Panel, 2014). In particular, if the model is eventually to be used to extrapolate from one situation to another, the resulting effect on the level of uncertainty should be clearly stated.

In support of the above general statement, note that within the guidance document on tiered risk assessment of PPP for aquatic organisms in edge-of-field surface waters (EFSA PPR Panel, 2013), it is clearly recommended that:

- A qualitative evaluation of the uncertainties affecting refined RA should be provided based on a tabular approach. In case of multiple lines of evidence, uncertainties affecting each line should be evaluated separately.
- If the qualitative evaluation of uncertainty reveals not sufficient to determine whether an unacceptable level of impact may occur, it is required to either (i) make an effort to get additional data to reduce the uncertainty, or (ii) use deterministic or probabilistic methods to refine uncertainty quantification.

5.2.1 (Q)SAR models

In general, the uncertainty of the (Q)SAR models is well characterized due to the conformation of the models to the OECD (Q)SAR validation principles (see Section 4.1.1). First, the recent (Q)SAR models were always developed using

a training and a validation data set (80% - 20% of the data set generally) and could also be evaluated on another external data set (Figure 7). In addition, several traditional validation metrics are applied to assess the accuracy, the stability/robustness and the reliability of the (Q)SAR models (reviewed in Gramatica and Sangion 2016):

- **Goodness-of-fit**: Root Mean Square Error (RMSE), determination coefficient (R^2), determination coefficient adjusted (R^2_{adj}), and Lack Of Fit (LOF) which was defined as being proportional to the least-squares error corrected by the number of descriptors and the number of training data (Furuhama et al., 2019).
- **Robustness**: cross-validation correlation coefficient, *i.e.*, Q^2 LOO (Leave-One-Out) which shows the predictive ability for internal validation of the model (based on the training set compounds), and leave-one out cross-validated $RMSE$, and R^2_{adj} (*i.e.*, $RMSE_{cv}$ and Q^2_{adj}). The absence of correlation could be checked by low values of R^2 calculated on scrambled response (Galimberti et al., 2020).
- **Reliability**: Q^2 metrics (predictive performance or R^2 Prediction) measures the reliability of a model, which will not be enough to define the model performance when new molecules are engaged (see application domain). Q^2 can be calculated using different formulae (referred as F_1, F_2 or F_3). Q^2 and the Concordance Correlation Coefficient (CCC) are the typical statistical metrics used for the external validation of the developed model Pandey et al. (2020).

Elsewhere, numerous quantitative and graphical quality indicators for classification models can be applied (Venko et al., 2018). In binary classifications, such as toxic (positive) or non-toxic (negative), several metrics were computed to assess the model qualities: accuracy (proportion of any substances correctly classified), sensitivity (proportion of true positives correctly classified), specificity (proportion of true negatives correctly classified), and efficacy (proportion of de-prioritization candidates) (Benigni et al., 2020; Herrmann et al., 2020).

The reliability of the (Q)SAR model predictions is also due to their domain of applicability. Leverage is one of the standard methods for the analysis of the domain of applicability of the model. The leverage value h_i for the i^{th} PPP is calculated from the descriptor matrix and compared to their critical leverage value (h^*) depending on the number of variables used in the model and on the number of training compounds (Basant et al., 2015b). The value of $h_i > h^*$ indicates that the structure of the compound substantially differs from those used for the calibration. Therefore, the compound is located outside the optimum prediction space. Frequently, the Williams plot is considered for representing the domain of applicability of the (Q)SAR models. This graph represents the standardized residual value according to the leverage value (Figure 7) (Basant et al., 2015b). Some software, such as the open source platform VEGA-HUB, assess the reliability of the prediction using the

Applicability Domain Index (ADI) . This index is an aggregated result taking into account several aspects: (i) similar molecules with known experimental value and their accuracy (or average error) in their prediction, (ii) concordance among the target and similar molecules for the experimental data, (iii) Atom Centered Fragments (ACF) similarity check, (iv) descriptors noise sensitivity analysis, and (v) model descriptors range check (Carnesecchi et al., 2020).

Finally, accuracy, stability/robustness and reliability of most of the (Q)SAR models were generally checked during the last fifty years on PPP toxicity (Basant et al., 2015a, 2016; Carnesecchi et al., 2020; Hamadache et al., 2018; Venko et al., 2018). In addition, some of the papers published before have been re-assessed for their consistency with these principles (Pavan et al., 2008). Moreover, according to the OECD guidance document (OECD, 2014), the consensus approach can be applied when several complementary models are available. Thus, the newly developed models would contribute to more reliable predictions of toxicity of PPP (Venko et al., 2018). Concordance with all these principles guarantees rigorous and independent validation of (Q)SAR models which is an essential step toward their regulatory acceptance (Eriksson et al., 2003).

5.2.2 DR and TKTD models

Most probably due to old habits in ERA, but maybe also due to a lack of computer resources some decades ago, uncertainties associated with the use of DR models are still rarely fully reported, meaning not systematically, usually only summarized by rough standard deviations. On the contrary, among works based on TKTD models, there is an increasing number of contributions providing information on uncertainties, in various forms depending on the inference method used. Baudrot and Charles (2019) even proposed some useful recommendations to address uncertainties in ERA using TKTD models. Fraser et al. (2002) discussed of uncertainty in biomagnification factors and half-lives of metabolites, while Weijs et al. (2013) used a Morris sensitivity analysis followed by the eFAST test to quantitatively test the influence of the most sensitive parameters on their model output. We also noticed an increasing use of probabilistic methods, such as Bayesian inference (Weijs et al., 2013) or Bayesian Networks (BN) (Kaikkonen et al., 2020; Mentzel et al., 2021), which have proven their efficiency in quantifying uncertainties. And to go in the same direction, Rubach et al. (2010) have even illustrated that a complementary use of least-squares fitting with the Levenberg–Marquardt (LM) algorithm and Monte Carlo Markov Chain (MCMC) methods is much more useful than the use of LM alone.

5.2.3 Population and landscape models

The uncertainty associated with the outputs of population or landscape models is very often addressed by these up-scaling tools, which methodologically

rely on different sensitivity or elasticity analyses (50% of the models in the corpus) or which integrate environmental stochasticity into the scenarios tested (60% of the studies). The outputs of these models are thus most often expressed in the form of distributions of values or probabilities of demographic effects. However, the fact that an uncertainty is almost systematically expressed in the outputs of these models should not make us forget the reductionist aspect of these modelling approaches which, by definition, can only focus on a limited number of processes. Also, this issue is of high relevance considering that the use of population and landscape models is proposed in the literature to contribute to higher Tier assessment of PPP (refinement for population-level endpoints) (Forbes et al., 2009; EFSA PPR Panel, 2018b). These models are indeed sometimes seen as surrogate cost-effective methods of achieving higher levels of ecological relevance when higher Tier data (mesocosms, field studies) are lacking (Hanson and Stark, 2012). However, like any bottom-up approach, it only accounts for the toxic effects and environmental variables that are considered in the modelling processes. It is therefore important for risk assessors to bear in mind this reductionist aspect of the up-scaling approach, which is often falsely erased in view of the integrative and population-level dimension of the outputs of these models. Hence, the efforts to propose sound decision guides, *e.g.*, Schmolke et al. (2017); Raimondo et al. (2021), which explicitly state the hypotheses taken into account in the modelling process and the scope of the questions addressed for the ERA, become very important for this issue. As a warning illustration, we were able to document in our corpus some adverse effects of PPP that are mostly ignored despite their importance for population effects, and the suitability of ecological models to integrate these effects. Models, particularly ABMs, are for instance very adapted to take into account individual behaviors in the emergence of population dynamics (Accolla et al., 2021), especially spatial behaviors. However, it appears from our case studies data set that direct behavioral disruption by PPP is actually considered in only 15% of population models for animal species while more than half of these models deliver an impact assessment in a spatial frame, and less than 10% in landscape-scale studies. Another finding from our analysis of population case studies is that less than 50% of them consider sub-lethal effects (75% for structured models but 40% for ABMs). This also illustrates the gap that may exist between the integrative possibilities offered by the population-modelling framework and the reductionism of the proposed assessment. This gap is mainly explained by a problem of experimental data availability on PPP sublethal effects in environmental species (effects on reproduction, individual growth, development, behaviour) but also in some cases to deliberate choices in modeling assumptions. Indeed, studies that integrate only mortality for animals or population growth inhibition phenomena in algae and plants represent 50% of the studies between 2000 and 2010, 70% between 2011 and 2015 and again 50% from 2016 to 2020. This is partly related to the strong development of population recovery studies that only consider the acute lethal toxic effects

of PPP during short peaks of exposure and ignore the delayed or long-term effects of environmental impregnation by PPP.

5.2.4 Multi-species models

SSD approaches On a general point of view, SSD analyses are expected to provide smaller uncertainties on apical risk assessment indices in comparison with the approach using AF that is applied for a limited number of toxicity values (Borges et al., 2017; Jesenska et al., 2013). Such indices are for example the RAC as defined in the guidance document on tiered risk assessment for PPP for aquatic organisms in edge-of-field surface waters (EFSA PPR Panel, 2013). In addition to the EU PPP regulation, water bodies are also regulated by the WFD Technical Guidance Document (2011); European Commission (2002a) which provides a framework to evaluate the chemical and ecological quality of the water bodies in the EU from EQS. Short-term (Maximal Acceptable Concentrations, MAC-EQS) and long-term (Annual Average, AA-EQS) EQS are based on EC_{50} and EC_{10} values, respectively, or SSD calculations.

Even if not systematically provided when delivering HC_p estimates, the uncertainty is nevertheless sometimes taken into consideration (Daam et al., 2010; Van Den Brink et al., 2006). Van Dam et al. (2004) tried to identify possible uncertainty sources in using SSD. First, they noted that small sample sizes when characterizing SSD added substantial uncertainty to the assessment. Another factor contributing to uncertainty is the unknown ability of the considered species to recover following exposure to the compounds under study. They also established that uncertainty may surround the exposure characterization. Van Dam et al. (2004) concluded that, although the uncertainty can be quantified using the confidence limits around the fitted probability distributions, which in some cases spanned an order of magnitude of the reported HP_p values, the data variability is usually high, a part never explained by the models. Very interestingly, Kon Kam King et al. (2015) innovated with a hierarchical approach of the SSD exploiting its founding basis that all tested species represent a random sample from a theoretical community so that their responses follow a distribution; this means that parameters describing the DR of each species within the sample follow a probability distribution themselves. In this approach, species for which the response is characterized with large uncertainty on the parameters of the DR, or where data are missing, contribute less to final fitted SSD. Kon Kam King et al. (2015) were finally able to provide HC_5 estimates accounting for the uncertainty of the original raw data. At last, even if identified a long time ago (Aldenberg and Jaworska, 2000; Verdonck et al., 2000; Forbes et al., 2001; Forbes and Calow, 2002), great progress and improvements have only been made recently to account for uncertainties in SSD approaches. For example, to overcome some theoretical criticisms of the SSD, Bayesian inference may be used to fit SSD (He et al., 2014). Also Grist et al. (2006) demonstrated that it could reduce the uncertainty. More generally, Bayesian inference and MCMC

methods gradually become popular in the field of environmental science like with water quality models and hydrological models (Jeremiah et al., 2012) as it allows considering multiple issues and system components as well as handling missing data and uncertainty easily. Bayesian inference is now also successfully used in the field to environmental risk assessment (see for example Chen and Pollino 2012; Baudrot and Charles 2019; Charles et al. 2021).

Community models

Usually involving a large number of parameters, community models inevitably exhibit a higher parameter uncertainty (Strauss et al., 2017), compared to simpler models such as DR or even TKTD models. This is indeed a matter of fact that having more parameters to estimate (what in essence characterizes community models), if the sample size of input data sets is limited, then parameter estimates will be less precise. This can be due to difficulties in making converge the optimizing algorithm in particular. The use of Bayesian inference to estimate the parameters of the mechanistic food-web model Streambugs (Kattwinkel et al., 2016) perfectly illustrates how to adequately handle uncertainties, and how it is particularly helpful to identify potential improvements in the model structure and in the experimental design.

5.2.5 Mixture models

In mixture models, uncertainties will be generally larger than in assessments of single chemical substances as there are more sources of uncertainties. As for other models, it is important to consider the uncertainties when interpreting the results. Thus, uncertainties have to be identified in each stage of the mixture model framework and an overall uncertainty analysis has to be integrated in the risk characterisation. The EFSA guidance on risk assessment of multiple chemicals (EFSA Scientific Committee, 2019) lists the most important aspects of uncertainty analysis for each step of the risk assessment of combined exposure to multiple chemical substances.

5.3 Reproducibility of model outputs

The issue of reproducibility is more generally related to scientific integrity, an issue reviewed by Mebane et al. (2019) for applied environmental sciences, with a particular emphasis on ecotoxicology. Reproducibility is only one of the prerequisites for a credible research (Wilkinson et al., 2016) and differently concerns materials, especially data (*e.g.*, Rubach et al. (2010); Reeg et al. (2018); EFSA PPR Panel (2017)), methods and results (*e.g.*, Tyne et al. 2015) as described in papers. Focusing on model outputs, only few authors gave enough information for full reproducibility, given that some results cannot of course be exactly reproduced due to stochastic processes in the modelling approach (Carr and Belanger, 2019; Schneckener et al., 2020; Charles et al., 2021; Charles et al., 2021).

6 Modelling approaches in the European PPP regulation

6.1 Regulatory context

In the European Union, the approval of an active substance and the placing of a PPP on the market require, among others, to assess their ecotoxicological effects and the corresponding risks. The soil, water (including sediments) and air compartments are considered. The overall objective is to approve only the compounds which do not have any harmful effect on human or animal health or any unacceptable effects on the environment (European Commission, 2009) (see Section 2). Therefore, the regulation holds on strict approval and exclusion criteria for active substances (European Commission, 2020). In this context, prospective risk assessment based on modelling approaches is of great interest.The ecotoxicological risk assessment phase is detailed in the regulation and in the guidance documents notified at the European level (*i.e.*, approved by the different member states), leading to a harmonized procedure between member states. In the light of the diversity of organisms potentially exposed *in situ* to the different PPP and their active substances, the assessment has to be done for several biological groups which are related to a wide range of environmental media: birds, aquatic organisms, arthropods, earthworms, soil non-target microorganisms, and other non-target organisms (flora and fauna) believed to be at risk. Each biological group is associated to specific protection goals, which will drive the choice of the methods to use (*e.g.*, kind of tests and models) for risk assessment.

6.2 Risk assessment in PPP regulation

Whatever the investigated biological group, the risk assessment follows a tiered-approach which is since decades widely used within the scientific community. The tiered-approach consists of structuring the risk assessment process along a gradient of environmental representativeness, and complexity of experimental system, leading to a refinement of the risk (Figure 9). The risk is usually assessed by comparing effect (hazard identification and characterization) and exposure.

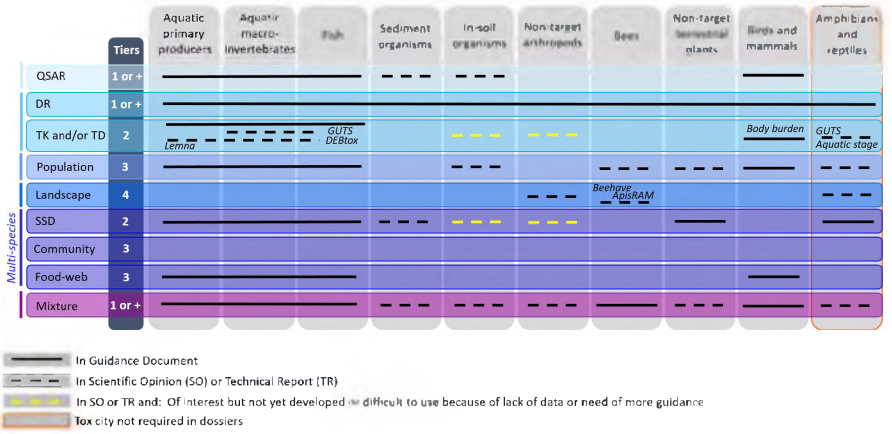

Fig. 9 Tiered approach illustrated across the six categories of models (in rows) and the different biological groups (in columns) considered for registration dossiers, according to EFSA documents related to PPP regulation (Guidance Documents, Scientific Opinions and Technical Reports). In Tiers, `n.c.` means not classified.

The first Tier (Tier-1) is intended to be simple and protective. It mostly relies on the use of normalized or standardized tests (*e.g.*, DR exposure design) performed in laboratory and including one taxa (*e.g.*, one micro-algal species) exposed to one compound under controlled conditions. As such tests are relatively easy to reproduce and to perform, they neglect the effects of various other factors such as the biotic interactions into stress organism responses. The following tiers rely on approaches characterized by a higher degree of environmental representativeness. This kind of approach aims at refining the risk assessment and at producing more realistic thresholds. In the different guidance documents, going from Tier-1 to higher tiers means, for example, to integrate more realistic exposure concentrations into the risk assessment, to consider organisms susceptible to be particularly exposed (*e.g.*, according to their habitat, feeding habits, life-cycle), to integrate additional sensitivity data or to use more sophisticated models or experimental devices such as mesocosms (EFSA PPR Panel, 2013).

6.3 Current use of modeling in PPP regulation

Currently, most of the notified guidance document recommendations are linked to the type of tests to perform (*e.g.*, organism, exposure duration) and to the methods to assess and to refine the risk assessment. Nevertheless, the use of various kinds of model is already recommended in several cases (EFSA PPR Panel, 2013; EFSA, 2009).

First, DR models are widely used for dossier constitution as it supports the derivation of a sensitivity value (*e.g.*, EC_x) which can be later used to derive for example an HC_p as well as to assess the risk (*e.g.*, TER). This type of model can be applied at every Tier as long as it fits modelling good practice (*e.g.*,

enough tested concentrations) but is especially of great importance in Tier-1 studies to model the required organism responses (*e.g.*, mortality, growth, reproduction) to an increasing gradient of stress (here, chemical concentration). For example, the normalized tests performed on aquatic organisms, as well as on birds or mammals, rely on such models. However, DR model can also be recommended in the context of higher Tier experiments, as it can potentially support the development of more sophisticated models.

Second, notified guidance documents also recommend for Tier-2 approaches the use of SSD models. In the regulatory context, the SSD models present the advantage to induce less uncertainty compared to Tier-1 approaches, as they are based on the sensitivity values of various taxa (five to eight are at least requested depending on the biological group). For example, the use of SSD models is recommended for aquatic organisms, non-target plants and soil organisms but, in this last case, a methodological guidance for this kind of organisms is still required. However, SSD are not suitable models for all of the biological groups involved in the PPP regulation (*e.g.*, EFSA PPR Panel (2015a)).

Within the multi-species category, community models are also of great interest for regulatory purposes, especially for higher tier studies dedicated to refine risk assessment. However, working at such an ecological level could constrain their use by regulators because these community models are all case-study dependent.

Finally, notified guidance documents also recommend the use of (Q)SAR models to estimate sensitivity values, to reduce the number of tests on the biota, and to explore PPP metabolites (*e.g.*, potential to bioaccumulate).

Over the above-cited modeling approaches, the notified guidance documents also deal with other models to develop or to validate (if those models already exist but are not enough tested for a use in the regulatory context). For example, in 2013, the notified guidance document for the aquatic organisms (EFSA PPR Panel, 2013) highlighted that mechanistic models such as TKTD, population or food-web models have a great potential for effect and risk assessment. But the insufficient insights regarding those models have so far prevent their use in the regulatory context. It has to be underlined that, since 2013, EFSA have published several documents to promote the development of models for PPP regulatory purpose, and to give to the assessors enough elements to understand and assess these models. These documents are detailed in the following section.

6.4 Towards the implementation of more models in the regulatory context

The findings drawn from the guidance documents currently notified is that only few models are approved in the context of PPP regulation, and can be used routinely for ecotoxicological risk assessment. If the documents make authority and are the references for the decision-makers to state if a dossier is admissible or not, the other publications of the EFSA journal (*e.g.*, Scientific Opinion,

Technical Report) draw the perspectives and provide new lines of thinking for the next guidance documents. Figure 10 shows, in a chronological, order the publications of the guidance documents (dark blue) for the different biological groups, and the other publications such as " Scientific Opinion" and "Technical reports" (grey) which are directly or indirectly related to the use of modeling in PPP regulation. As indicated above, several documents have been published in the EFSA journal since 2013 highlighting the increasing interest of EFSA for the use of modeling in this context. Those publications can be specific to one biological group or addressed to several groups.

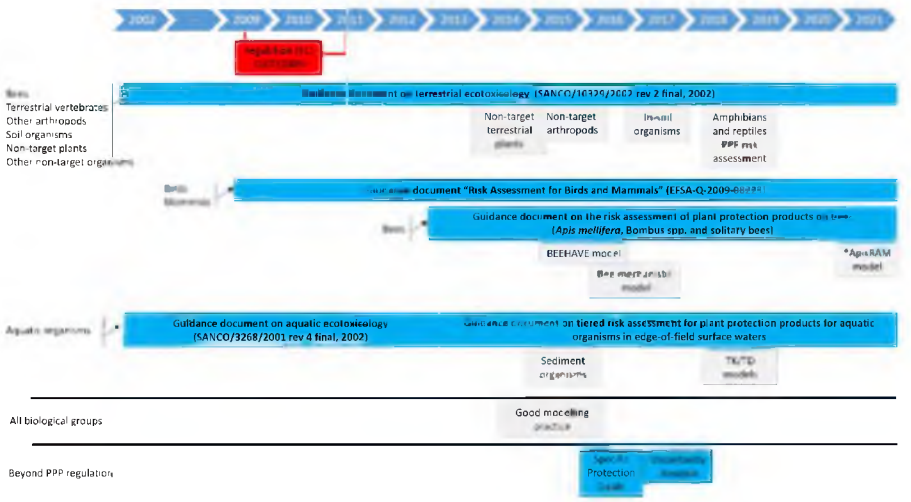

Fig. 10 Publication timeline of the Guidance documents (blue), the Scientific Opinions, and the Technical Reports (grey) dealing with modelling and directly or indirectly related to PPP regulation. *ApisRAM is a model under development to be released in 2025 (More et al., 2021).

In 2014, the Scientific Opinion dealing with the good modeling practice in the context of mechanistic effect models for risk assessment of PPP (EFSA PPR Panel, 2014) showed EFSA encourages the use of mechanistic models in regulation, and the need of an harmonized procedure at the EU level for the development and the validation of new models. The crucial role of modeling and its application at the different levels of the tiered-approach is illustrated in Figure 9. The EFSA Scientific Opinion highlights the relevance of effect models but deplore the rejection of several models used in dossiers because of: (i) the lack of harmonization in their development, (ii) the lack of quality control, and (iii) disagreement between the member states. Moreover, this Scientific Opinion highlights various points to consider during the development of a model that will be used under the regulatory context and notes that there is still a room for improvement regarding modeling development or

validation. Currently, the models of interest for PPP regulation are mechanistic models such as organism level effect (TKTD) models, population models (*e.g.*, Individual-Based Modelling), community models (*e.g.*, food web model) or those combining several of them.

The lack of data constitutes one of the major limiting factors to develop new models and/or to validate the existing ones. Except the DR models and the (Q)SAR models which are already used and accepted in the dossiers, it appears from the EFSA documents that there is a real need to use the SSD models on more biological groups (limits explained in the above section), as well as the TKTD, population and food web models (Figure 9). However, models like SSD, QSARs or TKTD which require testings are of course not compatible with the animal welfare consideration. Thus, the choice of the models depends on the biological group and on the bio-ecological characteristics (*e.g.*, ability to move and at what scale, stages of life, physiology) of the organisms targeted by each document.

TKTD models are of high interest for the dossiers (EFSA PPR Panel, 2018a; EFSA, 2009). For example, DEBtox models based on energetic budgets deal with sublethal effects and thus present a great potential for various organisms. Also, the GUTS model, based on survival data, is of high potential for fishes, benthic macro-invertebrates and aquatic stages of amphibians. Regarding primary producers, for which the sensitivity to a PPP is mostly characterized using growth as endpoint, a TD model developed for microalgae (Weber et al., 2012) and a TKTD model developed for the macrophyte Lemna (Schmitt et al., 2013) have been reported. TKTD models can also be used for the reptiles and amphibians but the lack of data for those groups have prevented any progress (EFSA PPR Panel, 2018b).

Population models also present a high potential for most of biological groups involved in PPP regulation. Based on their bio-ecological characteristics, the population models at the landscape scale would be the most suitable ones to characterize the risk induced by the PPP for non-target arthropods, and for reptiles and amphibians. For example, the reptiles and the amphibians can be associated to different media depending on their stages of life, and they are able to move at the landscape scale. For this group, it is recommended to use population models such as ALMaSS (Animal, Landscape and Man Simulation System, Topping et al. 2003) which takes into consideration these different variables. Finally, the birds and mammals group may benefit from population models but the notified guidance document of 2013 deplore the lack of methodology and guidance for their use.

The Figure 10 also demonstrates that bees received a specific attention during the last years with the setting in 2013 of a dedicated guidance document (EFSA, 2013). However, as this document was not accepted at the European scale, the SANCO document from 2002 is still the official guidance

document (European Commission, 2002b). In 2015, the BEEHAVE model was also in the heart of a Scientific Opinion for its use in the regulatory context (EFSA PPR Panel, 2015d). This model aims at estimating the decrease of a colony after PPP exposure. Its assessment by EFSA experts revealed its reliability for bees but not for wild bees because of the lack of experimental data. More recently, an editorial document has announced the development of the ApisRAM model (More et al., 2021) dealing with data directly obtained from hives, and deriving the risk assessment of chemical factors alone or combined at large spatial and temporal scales, among others. In both cases, BEEHAVE and ApisRAM are based on population models.

Finally, food-web models are of high interest for sediment organisms (EFSA PPR Panel, 2015c). The sediment compartment can play the role of sink for persistent substances and/or hydrophobic ones ($\log_{10} K_{ow} > 3$), and can change the exposure of the organisms living in the sediment. In this case, the use of such model could support the consideration of biomagnification into PPP ERA. Guidances are expected (EFSA PPR Panel, 2015c).

Beyond all of the above-cited models, those dealing with PPP mixture toxicity prediction should also be considered in the regulatory framework (European Commission, 2020; EFSA, 2013; EFSA PPR Panel, 2013). Recently, the Court of Justice of the European Union confirmed the need to consider the join toxicity of all of the components (e.g., active substance, safener, synergist, co-formulant) before the placing on the market of a PPP (CJEU, 1st oct. 2019, C-616/17, pt 75). Also, mixtures are integrated to the regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures. Two models are frequently used in the scientific community: the CA and the IA models. The first one is mainly recommended by the guidance documents as it tends to be more conservative (EFSA PPR Panel, 2013).

At the end, the use of modelling approaches in registration dossiers will mostly rely on the targeted biological group, on the required level of risk refinement (*e.g.*, Tier-2 or more), and on the available data to parameterize the models. However, among the different models which are recommended in EFSA documents, one can suspect a temporal evolution in the category of used models. For example, "simple" ones like SSD have a long history in PPP regulation as they were already recommended in 2002 for non-target plants (European Commission, 2002b), while more developed ones still required guidance for users and assessors. This calls for a comprehensive analysis of the dossiers to characterize the real usage of modelling approaches in PPP regulation.

7 Potential contributions and prospects of current and future modelling tools

7.1 (Q)SAR models

(Q)SAR models have the potential to provide rapid, *in silico* estimates of ecotoxicological endpoints. In addition, they can be an important tool for environmental risk assessment of the degradation products, metabolites and impurities, when it cannot be performed experimentally.

The potential for application in PPP regulation seems there as (Q)SAR approaches properly used can be a valuable tool for providing predictions on chemical toxicity (Villaverde et al., 2020; Mombelli and Pandard, 2021). In addition, several available tools already exist and, for a given substance, may fall into the applicability domain of a multitude of *in silico* models, raising the question of which model(s) and/or tool(s) to apply (Herrmann et al., 2020). Nevertheless, there are several areas for improvement to facilitate the work of decision-makers. It is necessary to allow them to establish with a maximum of certainty if: (i) the (Q)SAR model is scientifically valid, (ii) the predicted effect is of regulatory utility, and (iii) the model is applicable to the substance of interest.

As far as scientific validity is concerned, (Q)SAR models can provide predictions in case of unknown MoA, but a prerequisite is the availability of appropriate training data for model development (Herrmann et al., 2020) and appropriate supporting information such as (Q)SAR Model Reporting Formats (QMRF) (*e.g.*, JRC QSAR model Database). Overall, it appears that, if properly used and evaluated, (Q)SAR approaches can be a valuable tool for providing fit-for-purpose predictions in the framework of regulations on chemical toxicity (Mombelli and Pandard, 2021). For example, Mombelli and Pandard (2021) highlighted the regulatory relevance and robustness of (Q)SAR predictions for acute fish toxicity and demonstrated a level of reliability of the prediction comparable to the experimental data. This kind of validation exercises conducted by third parties can also contribute to enhance knowledge about models and their intrinsic limitations so that informed decision-making can take places (Mombelli and Pandard, 2021).

For a ready regulatory applicability usefulness, focusing the development of (Q)SAR models as a function of endpoints of regulatory interest formalized by OECD guidelines would render their application straightforwardly relevant. Always from a regulatory point of view, it would be very useful to extensively cover the different trophic levels and biological organization levels since, for instance, only a minority of work on (Q)SAR provided models for algae or for long term risk at the population or community level. (Q)SAR approaches are constrained by the experimental data availability and quality, so the data sets are one of the most important (Q)SAR elements. Consequently, to improve their ecological relevance, the scientific community has to work on the lack of ecotoxicological data for PPP covering the whole biodiversity and investigating sub-lethal and chronic effects.

To overcome this limitation, the development of the quantitative form of AOP (qAOP) (see for example, Conolly et al. (2017))and their association with (Q)SAR models seems very promising. Indeed, MechoA approach in (Q)SAR aiming at predicting the Molecular Initiating Event (MIE) sounds convenient to provide input to qAOP, which are able to translate subtle functional deficits within individuals into population-level effects under different ecological and environmental scenario.

For the applicability to a given substance, the framework proposed by VEGA hub (Benfenati et al., 2013) seems very promising (ADI), and uncertainty associated to the model prediction should be more systematically communicated. However, an identified limitation of the (Q)SAR model comes from the difficulty to explain data from complex MoA using relatively simple models, and therefore the causal toxicological mechanisms generally stay unknown even if the physico-chemical determinants can be accurately described (Villaverde et al., 2020). Lastly, even if tools are available, an expert judgment should as often as possible be consulted. For example, a (Q)SAR prediction can be compared with a read-across prediction based on the closest structural analogues to have an idea of the relevance of the prediction. To improve applicability, different studies have explored strategies for combining predictions from multiple (Q)SAR tools to improve the prediction of several endpoints. These consensus models show better overall predictive capacity than individual (Q)SAR tools and sound promising (Villaverde et al., 2020).

The integration of TKTD and (Q)SAR modelling represents an interesting and promising field of research. In such an integrated scheme, (Q)SAR models provide interpolation for toxicological responses and toxicokinetic parameters. Indeed, this synergy between the two modelling approaches can greatly reduce the need for animal testing while optimizing in cost-efficient ways toxicological resources (Mombelli and Pandard, 2021). Finally, the promotion of capacity building in governmental agencies aiming at increasing awareness about *in silico* tools would rapidly result into an enhanced and informed use of *in silico* approaches during decision-making.

7.2 TKTD models

Below are some possible directions that can be learned from the analysis of the literature on TKTD models in terms of prospects for the future, both from a purely research point of view, and to improve ERA:

- For regulatory purposes and for use by non-experts, TKTD models need to be as simple (*i.e.*, simple enough to be used on - somewhat extended - standard toxicity test data) and transparent as possible (Jager, 2020).
- TKTD models should be as representative as possible of the widest diversity of PPP, both in their bioavailability and MoA (Crenna et al., 2020).
- TKTD models should be both calibrated and validated on data collected under time-variable exposure, agreeing that this type of scenario is more realistic from an environmental point of view (Van Den Brink et al., 2019);

in other words they should include the exposure history of organisms (Jager and Kooijman, 2005).
- Tested species should be relevantly chosen regarding their representativeness of field conditions, rather than being selected for their accessibility in laboratories (Arlos et al., 2020; Roeben et al., 2020; Bart et al., 2021).
- TKTD models could be improved by considering ecologically relevant biological traits, such as the movement behaviour (Roeben et al., 2020), the actual size (Dalhoff et al., 2018) or the membrane permeability (Crenna et al., 2020), to name but a few examples.
- TK models should consider several routes of exposure as well as the possible presence of metabolites in order to also quantify their bioaccumulation; indeed, sometimes metabolites can be more toxic than the parent compound to which they derive. In addition there is no longer technical reasons to limit ourselves to simplistic TK models since ready-to-use tools exist to perform relevant TK modelling analyses in all-in-one facilities (Ratier et al., 2021).
- Field studies are still too rare, while they would be really useful to test the predictive power of model outputs.

Of course, such improvements for a better use of TKTD models should not make us forget that in recent years, there has been a widespread drive to have more relevant testing strategies, accounting for the animal welfare and including the 3R principles European Commission (2009). Already a current practice in REACH (Lilienblum et al., 2008), but first introduced few decades ago (Russel, W. M. S. and Burch, 1959) and still debated (Goldberg, 2009; Balls, 2020), the 3R principles refers to the principle of reduction, replacement, and refinement of animal studies. The objective of reduction is to decrease the number of animals used for research and regulatory purposes. The replacement approach includes *in vitro* or *in silico* methods. Refinement involves reducing, eliminating, or relieving animals' pain or distress, and thereby improving their well-being (Tan et al., 2021). Additionally, there is a need to change the classical, animal testing-based approach towards more modern tools that are more predictive for humans. This has been particularly explored for TK and TKTD models (Heringa et al., 2013; Terry et al., 2014).

7.3 Population and landscape models

Various authors suggest, in the reviewed papers, that ecological models are very little applied in regulatory PPP ERA (Hommen et al., 2016; Accolla et al., 2021; Raimondo et al., 2021). A specific analysis of PPP registration dossiers actually submitted to regulation agencies should be conducted to confirm this statement. This probable underuse of population models in regulatory ERA is surprising when compared to the wide use of similar population models in species conservation or fisheries resource management. Nevertheless, there is a strong consensus among stakeholders on the potential contribution of ecological models to PPP ERA. One possible explanation emerging from our literature review in using population and landscape models in ERA is an obvious lack of

easy running tools for people not advertised in modelling in general, in these type of models in particular. Filling this gap could be a new challenge in a near future.

Firstly, models could inform the ecological criteria to be taken into account at all tiers of prospective ERA (Forbes et al., 2015), *e.g.*, choice of test species and life stages fixed by regulators for lower Tier assessments, definition of ecological scenarios to be tested in higher Tier assessments with a worst-case scenario approach (Rico et al., 2016). Secondly, they allow the uncertainty sources attached to the evaluation criteria to be tested *in silico*. They should make it possible to reexamine the arbitrary safety factors applied in ERA to guaranty ecosystem protection when extrapolating to the multitude of contexts of PPP use (Focks et al., 2014). But while ignoring the fact that most of these mechanistic models are rather cognitive tools to inform on the ecological complexities in PPP impacts (Forbes et al., 2009), the debate for their use in ERA is most often unfortunately confined to the sole question of validating their predictive capacity as stated by Wang (2013), the models then being only considered as mere forecasting tools in the same way as meteorological models for weather prediction. Yet, as pointed 30 years ago by Barnthouse (1992), the real issue in determining whether models can contribute to regulatory risk assessment should be credibility rather than validity.

In addition to prospective ERA, population and landscape models can contribute to understand field ecological impacts of PPP by providing information on their relative contribution to degradation of biodiversity, particularly for non-target species of patrimonial value or keystone species for ecosystem functioning (*e.g.*, Topping and Odderskær 2004; Abi-Akar et al. 2020; Landis et al. 2020). Similarly, they can be used to evaluate future population trajectories under different scenarios of climatic, agricultural or landscape evolution (as in Nogeire-McRae et al. 2019).

The informative value of model outputs regarding population and ecosystem threat in agricultural landscapes is crucial for their acceptance in environmental risk management. Some works already illustrates how ecological models can be used to establish the relevance of traditional risk assessment endpoints with respect to the recovery capacities of populations (Hayashi et al., 2016). They may also inform the choices of evaluation endpoints regarding their relationship with key ecosystem services (Croft et al., 2018). However, the endpoints derived from population projection models or the indicators quantifying population extinction risk in simulation approaches currently lack any reference grid for their interpretation in terms of impact severity and possible population collapse. Conservation science (*e.g.*, for the definition of species conservation status by the International Union for Conservation of Nature), but also the widely-accepted use of models in fisheries management or in epidemic forecasting, may well inspire the evolution of future PPP ERA practices (Thursby et al., 2018). The harmonization and the common definition of reference thresholds of population vulnerability to be applied to these endpoints could indeed operationalize the use of ecological models in the management

of PPP risk for non-target species and better inform decision-making in PPP environmental management. This could present a high value for ERA since Specific Protection Goals (SPG) are in most cases defined on the population level. Thus, the use of ecological models offers a promising avenue to link typical test results on the organism level and the SPG of PPP ERA.

7.4 Multi-species models

SSD models

Ecological interactions are rarely taken into account in ERA, while it is important to consider both direct and indirect effects of chemical exposure (*e.g.*, Brock et al. 2004). Nevertheless, SSD approaches currently have large implications in legislation and risk management, so that they are discussed a lot (Posthuma et al., 2002). Critical issues are both fundamental (*e.g.*, its statistical rather than its ecological basis) and technical (*e.g.*, the necessary number of input data). Also, it is not confirmed to what extent classical outputs, such as PAF (for substance alone) and msPAF (for mixtures) could be considered predictors in a retrospective perspective of mixture impacts on field communities (Posthuma and De Zwart, 2006); this motivated a lot of model confirmation studies that were mainly focused on the 5^{th} percentile of the fitted SSD namely the HC_5 (see Posthuma et al. 2002). Recently, the SSD method was scrutinized in detail for its potentiality to support ERA within the framework of the European WFD which suggests using models to assess the likelihood that chemicals affect water quality for management prioritization. Deriving SSD analyses for more than 12000 chemicals, Posthuma et al. (2019) concluded that SSD is a versatile and comprehensive approach to prevent, assess, and manage chemical pollution problems.

Recently, Fox et al. (2020) published a summary of the current status of SSD approaches, and elaborated on several recent developments for SSD methods, specifically, model averaging, multi-modality and software development. Identifying several technical issues to urgently deal with for SSD improvements, Fox et al. (2020) also proposed some future directions with respect to the use of SSD, ultimately aiming at facilitating wider international collaboration and, further, a possible harmonization of SSD methods. Regarding technical issues, to name but a few, Fox et al. (2020) mention the choice of a parametric or a non-parametric (*i.e.*, distribution-free) modelling, the choice of frequentist versus Bayesian inference, the tricky question of the sample size (also stated by Carr and Belanger 2019), the expected shape of the distribution, the representativeness of species sample possibly leading to bi-modality when there are clearly two groups of species sensitivities or because of a very specific MoA of chemical compound.

SSD methods have also been used in combination with complementary approaches in order to account for additional influencing phenomena on species sensitivities. Nagai and Taya (2015) showed that considering the MoA of compounds improved the accuracy of estimating SSD markedly. The PERPEST model is also an approcha allowing to include the consideration of MoA (Van

Den Brink et al., 2002, 2006). Based on the fact that SSD is a probabilistic risk assessment model, Giddings et al. (2000) evaluated potential toxic effects of diazinon in the Sacramento–San Joaquin system, based on data sets collected from laboratory toxicity tests for 63 species. Qu et al. (2011) illustrated the improvement in the RQ method expressing the ecological risk as the degree of overlap between the distribution of environmental exposure concentrations and the distribution of toxicity values. A step further was made in the study of mixtures effects using SSD (Cedergreen et al., 2004; Jesenska et al., 2013; Li and You, 2015; Silva et al., 2015), some authors also accounting for the effects of environmental factors (Rico et al., 2011, 2018). Clemow et al. (2018) proposed a refinement of the SSD including exposure simulation aiming at identifying direct and indirect effects of malathion on amphibians. Nevertheless, Clemow et al. (2018) agree that their approach does not allow for representing the daily fluctuations of malathion over the course of multiple applications. However, taking into account a time-variable exposure was early identified as a crucial issue (Cedergreen et al., 2004; Van Dam et al., 2004); so the combination of SSD with TKTD models could be the next step further in improving Tier-2 ERA based on SSD, especially for PPP (Van Den Brink et al., 2019).

Last but not least, field study data have been highlighted for their added-value in SSD analyses to better characterize the exposure, as for example De Zwart (2005) who used a Geographic Information System (GIS) map to predict aquatic exposure to PPP in field ditches; Van Dam et al. (2004) who fitted a break-point regression model to field monitoring data, providing a time-dependent estimate of exposure to tebuthiuron; or Li and You (2015) who combined effect data with the probability distributions of environmental exposures of contaminants. But field study data have also been highlighted to benefit from field ecotoxicity information issued from microcosm or mesocosm studies. For example, Brock et al. (2004) concluded that the SSD approach cannot be seen as a complete alternative to semi-field experiments, even if a protection level based on direct effects (*e.g.*, the HC_5) will also protect against indirect effects. Van Den Brink et al. (2006) then proposed the concept of $NOEC_{ecosystem}$ (defined as the highest test concentration causing no observed effects in microcosm or mesocosm experiments) to be used to extrapolate from laboratory to field data. Today, $NOEC_{ecosystem}$ is not used anymore, replaced by the concept of effect classes and the derivation of Ecological Threshold Option (ETO)- and Ecological Recovery Option (ERO)-RAC from mesocosm studies (EFSA PPR Panel, 2013). Schipper et al. (2014) presented a different approach from the previous ones, based on the Stacked Species Distribution Modeling (S-SDM). Establishing an S-SDM for several species to describe their probability of occurrence in relation to multiple environmental factors, they were able to study the variation of this probability of occurrence along the gradient of each environmental factor with the remaining ones fixed. Hence, Schipper et al. (2014) investigated how field-based SSD (f-SSD) for a given environmental factor changed under confounding influences, such as low, medium or high environmental disturbance.

Community and food web models

What is particularly striking about the community models in terms of gaps is different according to the type of models. ABM/IBM-type models, together with BN models, account for a lot of refined biological processes combined with stochastic links, thus making it difficult to keep a critical eye on the relevancy of model outputs at the community level: do they really emerge from the modelling itself? Are they only artifactual, due to specific initial condition in simulations, for example? These models also rarely quantify uncertainties on outputs while they include both uncertainty and variability as input by essence.

Food-web models, also rarely accounting for uncertainties, reveal a noticeable gradient from the simplest ones (Damgaard et al., 2008) to the most complex ones (Nfon et al., 2011) giving rise to the question of the best compromise to find. There is a real challenge to be realistic enough from a biological point of view (enough species and ecological processes to account for) but simple enough from a modeling point of view (based on the parsimony principle) so that the model appears finally sound. However, to find the best compromise may strongly be related to the available experimental data, obviously not manipulable afterwards. Hence, simple food-web models will usually be employed with microcosm data (Traas et al., 2004), while more complex ones will be suitable for mesocosm data (Bartell et al., 2018; David et al., 2019). Some food-web models also seldom proved helpful because strictly dependent on a particular species (*e.g.*, bumble bees with bumble-BEEHAVE Becher et al., 2018 or ApisRAM More et al. 2021).

A probabilistic RQ is a more informative alternative to the traditional single-value RQ, which is often interpreted as a binary outcome. Indeed, it can be useful useful for ranking of different scenarios as well as prioritizing among alternative risk scenarios (in Campbell et al. (2000), cited in Mentzel et al. (2021)). Among probabilistic approaches, the Bayesian Network (BN) models are increasingly being used to model environmental systems, in order to: integrate multiple issues and system components; utilise information from different sources; and handle missing data and uncertainty (Chen and Pollino, 2012). As illustrated by Mentzel et al. (2021), a BN has been developed and parameterised for three PPP based on monitoring data from a catchment located in South-East Norway. The authors used toxic effects data for several freshwater species representing various taxonomic groups (namely, *NOEC* values for growth and reproduction).

7.5 Mixture models

Mixture models should include the assessment of dose-level dependent deviation as it was suggested that concentrations of chemicals can influence interactions between PPP (Lopez Aca et al., 2018; Sanches et al., 2018; Kristofco et al., 2015). For instance, in Chen et al. (2014), it is reported that CA had severe limitations when the dose–response curves of the individual chemicals were not identical at low effect concentrations. Similarly, Ritz et al.

(2021) found that fixed-ratio designs (PPP and their mixture are used at increasing doses) should be preferred as they allow validation of the assumed dose–response relationship and, consequently, provide much stronger claims about antagonistic and synergistic effects than factorial designs (lots of PPP are only available at a single dose level and a mixture simply combines these doses). For this reason, Marques et al. (2012) or Pestana et al. (2010) underlined the need for higher number of testing combinations and concentrations of each stressor to improve model calibration.

Moreover, mixture models should include the status of test species at different time points (time-to-event), as suggested by Qiu et al. (2017) who used the AFT model, that assesses the relationships between the time-to-event and treatments. The AFT model, which predictive power and accuracy can be improved by setting more observation time points in experimental design, provides a simple and valuable method to quantify the interactions and to evaluate the outcomes of exposure to a mixture of chemicals. This is in accordance with Broerse and Van Gestel (2010) who explained that analyzing mixture toxicity at successive time points may be a good way to explain observed mixture effects. Indeed, this allows the application of process-based models (time–toxicity relationships, DEBtox) that estimate time-independent parameters (uptake and elimination rate constants) besides only time-dependent toxicity estimates (LC_x or EC_x), which may enable extrapolations beyond the standard exposure time.

Finally, Carnesecchi et al. (2019), working on bees, proposed the following perspectives for mixture and other models:

- Development of *in silico* tools such as (Q)SAR models to predict combined toxicity of mixtures.
- Characterization of the synergistic potential of chemicals including TK interactions either through inhibition or induction of metabolism or through direct TD interactions. The CA and IA models provide a validated initial risk assessment approach to predict mixture toxicity, but they are mechanistically uninformative (Lister et al., 2011). Accounting for chemical uptake and elimination in mixtures is an essential requirement for mechanistic understanding of chemical interactions. Svendsen et al. (2010) explained that where interactions occurred between the five tested PPP, these could be explained by information on the potential mechanisms of compound toxicokinetics. These authors concluded that detailed analysis of toxicokinetics and toxicodynamics can aid in further understanding of interactions in mixtures. A need exists for a better understanding of the dynamics of the effects of mixtures, underlining the need for measurements with intermediate time points (Baas et al., 2007). To select CA or IA as the most appropriate model for any given mixture, knowledge about the MoA of chemicals included is required. This mechanistic classification is achieved using knowledge of the toxicodynamics rather than, for example, the toxicokinetics of the chemical.

- For multiple species or the whole ecosystem, SSD can be applied to estimate HC_x (hazardous concentration for $\leqslant x\%$ of the species) for multiple chemicals of concern with the aim to identify whether the estimated exposure exceeds the HC_x, as the median for $x\%$ species affected in the SSD (EFSA Scientific Committee, 2019).

In brief, to better understand mixture effects of PPP, efforts must be done on:

- Understanding the mechanisms (uptake and elimination, effects)
- Predicting time series of exposure.
- Using more concentrations in tests with mixtures.
- Coupling mixture models to other modelling approaches; for instance, Bart et al. (2021) combined both CA and IA models to GUTS models to account for both mixtures and the time course of processes leading to toxicity.

8 Conclusion and perspectives

The basic expectation from the use of computational prediction models in PPP ERA is to avoid testing all the PPP and metabolites. Hence, they can be used to link chemical structure or concentrations of PPP with activity and toxicity on organisms. Models also have the potential to assess PPP effects on sets of several species under various environment types, to extrapolate adverse effects across levels of biological organization, to decipher their underlying mechanisms, and to support the prediction of joint effects caused by mixtures of chemicals. This review led thus to the conclusion that (Q)SAR, DR, TKTD, population, landscape, and community models are increasingly recognized for the risk assessment of PPP, notably under the impetus of regulatory authorities having encouraged the development of good modeling practice guides, harmonization and reference modeling procedures. In the framework of the prospective ERA, (Q)SAR models are already used to supply *in silico* ecotoxicological endpoints filling in the toxicity data gaps for the multitude of PPP and species diversity, and reducing the breadth of the experimental task. While the value of ecological models addressing population, landscape and community scales is undisputed for PPP ERA, their possible place is still ambiguous in assessment schemes, oscillating between strict simulating tools of ecological outcomes used as endpoints for risk assessment, versus cognitive tools informing on species vulnerabilities and critical environmental factors in PPP-exposed ecosystems to be considered in assessment procedures. These tools still suffer from unfriendliness to be routinely used in ERA.

The vision of models as surrogate cost-effective methods for ecotoxicological assessment offering cross species/substances extrapolation facilities, between climatic or geographical conditions extrapolation, and up-scaling integration of multiple PPP effects should not hide the still major weakness of available experimental data informing on chronic and non-lethal effects of PPP among

ecological communities. This point is still a major limitation for a sound application of models as predictive tools of PPP ecological impacts. At the same time, although more information is needed to better depict and predict the effects of PPP on living organisms at different scales, models should be parsimonious, meaning that they must accomplish the desired level of explanation or prediction with as few predictor variables and parameters as possible. Decision guides are increasingly proposed to help modelers to select relevant modelling options adapted to each specific risk assessment questioning. With a too large number of input parameters, models exhibit a higher uncertainty which has to be characterized. Moreover, the parameters which drives the model should be estimated as accurately as possible to decrease the uncertainty. Thus, to be relevant, prediction models should include a sensitivity analysis, an uncertainty analysis and the comparison of predictions with observed data. In that, Bayesian inference is a relevant and promising approach to estimate the parameters, to handle uncertainties, and to identify potential improvements in the model structure and experimental designs.

Some future developments of models also emerged from this review such as the consideration of PPP multigenerational effects or the study of "multiple stressors". These terms generally refer to the combination of natural stressors (abiotic and biotic) and chemical exposure, thus including "cocktail effects" due to chemicals mixture. Effect modelling can help to gain knowledge on interactions between multiple stressors and their joint effects. Moreover, in order to address the "things that matter" in protecting the environment, *i.e.*, keystone species and ecosystem services, ecotoxicological models describing effects on organisms could be coupled with ecological models informing on interactions between organisms and the functions they fulfill. Thus, modelling the effects of PPP and other stressors on living organisms, from their application in the field (exposure) to their functional consequences on the ecosystems at different scales of time and space would help going towards a more sustainable management of natural resources. However, a lot of data and knowledge remain to be acquired, whether on ecological or ecotoxicological part. For instance, food web and community models at scales relevant for ecological processes are still not enough developed. Also, modelling approaches based on emerging methods such as the so-called "omics" are still lacking despite their great potential for ERA (*e.g.*, detect early effects, improve mechanistic understanding). In addition, the consideration of the different reviewed modeling facets is still poorly developed in the framework of retrospective ERA of PPP, while their use for the interpretation of ecological monitoring data in view of PPP use practices, and a dialog with the domains of species conservation and wildlife exploitation management which routinely use models, could constitute wealthy avenues to facilitate the use of models in ecotoxicology, and improve the knowledge and the prediction of PPP effects on biodiversity.

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