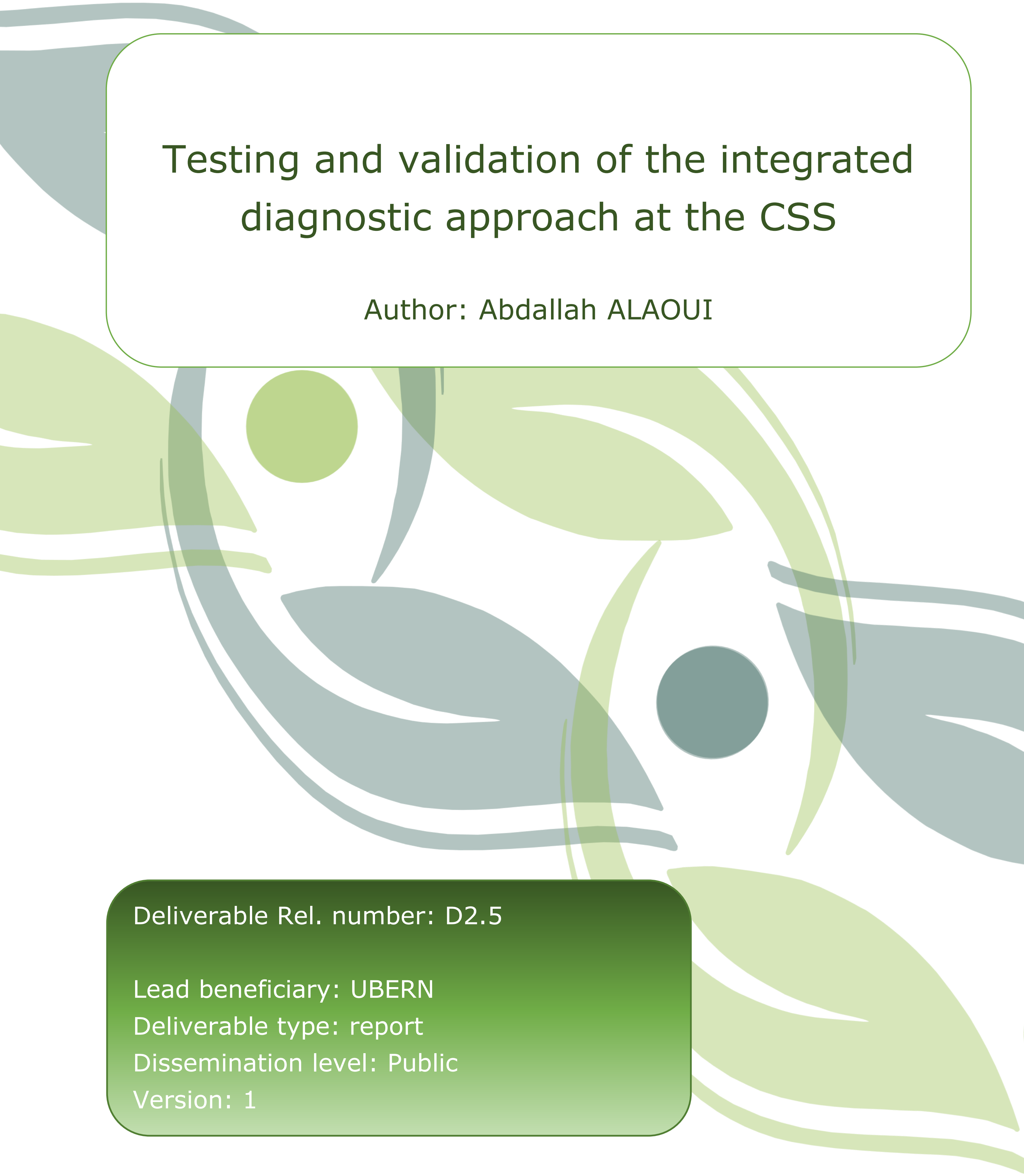

Testing and validation of the integrated diagnostic approach at the CSS

Author: Abdallah ALAOUI

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Overall Project coordinator	Prof. Dr. Violette GEISSEN violette.geissen@wur.nl
Scientific Coordinator	Prof. Dr. Paul SCHEEPERS paul.scheepers@radboudumc.nl
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Principle Author(s)	Dr. Abdallah Alaoui, Florian Christ, Dr. Anne Vested, Dr. Vera Silva, Dr. Vivi Schlünssen
Principle Author e-mail	abdallah.alaoui@unibe.ch, vs@ph.au.dk
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1. Introduction

The main aim of SPRINT is integrated risk assessment at the local, regional, national and European level, focusing on different PPP use patterns and detected residue mixtures in contrasting farming systems (conventional, integrated, organic). SPRINT consists of 9 interlinked work packages. **Figure 1** shows the main tasks and the workflow to achieve the goal of integration.

This deliverable aims to (i) summarize the steps involved in the CSS testing phase, (ii) show the usefulness of the approach in predicting pesticide distribution and effects, and (iii) provide a set of recommendations on how to use and improve the approach beyond the SPRINT project. More specifically, this protocol aims to (i) improve the predictability of the fate/distribution modelling compounds, and model chains, about specific PPP application patterns and PPP distribution ratios observed in CSS, or identification of predictors/correction factors based on how well the measured data are represented in the models; and to (ii) provide insights on how to refine and improve standard lab (eco)toxicological experimental setups, to better assess real, multi-endpoint, and multi-species pesticide effects.

D2.5 is essentially a protocol on the steps involved in the CSS testing phase (considering different pedoclimatic zones, soil type, and cropping systems), and on the usefulness of the approach in the validation of the predictions of pesticide distribution and effects (by comparison of D2.3/2.4 outcomes and results of the modeling and (eco)toxicological tests). D2.5 will also include a set of recommendations on how to use and improve the approach beyond the SPRINT project.

The reasoning involved in the testing phase was already published by Silva et al. (2021). The validation concept, linked to ongoing WP3 and WP4 activities, is still being developed. But the main goal is two-fold:

i. to improve the predictability of the fate/distribution modeling components, and model chains, by including, for example, specific PPP application patterns and PPP distribution ratios observed in CSS, or identification of predictors/correction factors based on how well the measured data are represented in the models.

ii. to refine and improve standard lab (eco)toxicological experimental setups, to better assess real, multi-endpoint, and multi-species pesticide effects. By linking PPP distribution with overall health assessment, and the application of quantitative methods (e.g. PNECs, hazard quotients), we can for example identify high priority PPPs and component-based mixture approaches, using a tiered approach in testing programs.

General recommendations will be provided to improve the overall approach taken, especially about the data set and related indicators, modeling, and laboratory testing to serve similar purposes.

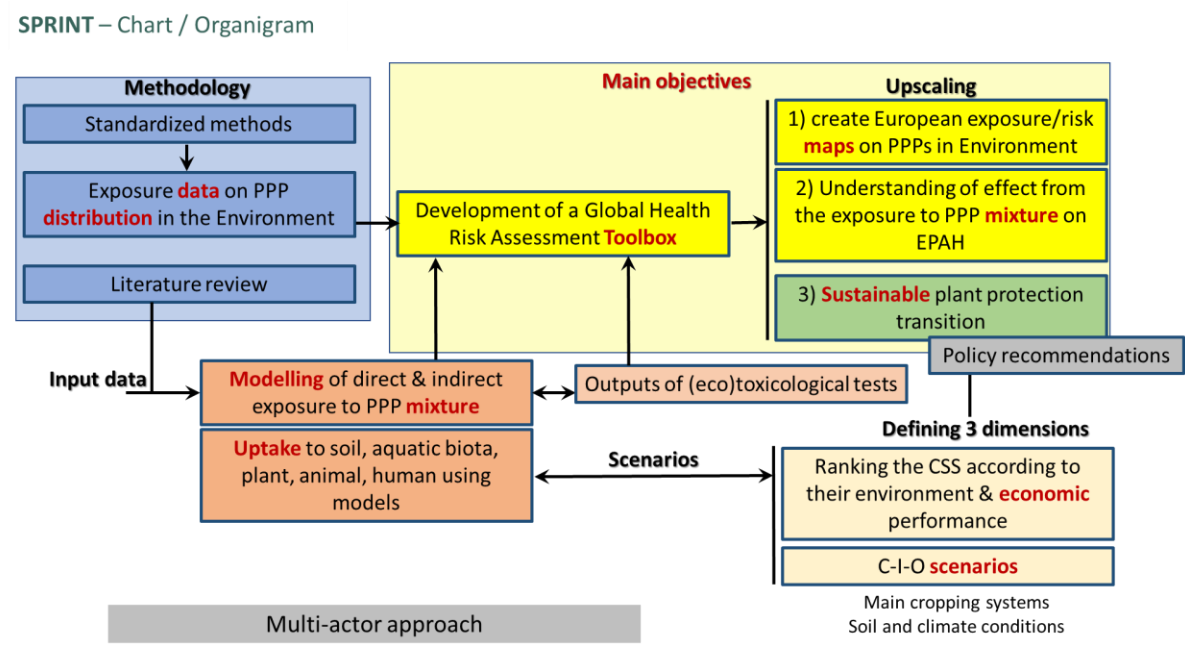


Figure 1. Main tasks to reach the overall goal of the SPRINT project; workflow is from the left to the right.

2. Exposure assessment – WP3

2.1. Short description of the WP3 tasks

Methodology (blue): The distribution and the impacts of PPP on EPAH health will be evaluated at 11 case study sites (CSS), ten located in diverse agricultural European landscapes, and one in Argentina (soy production for feed for EU market). WP2 developed a monitoring plan with standardized methods to be followed by the CSS leaders (**Fig. 1**). This enables us to compare the results of all sites. An inventory of EPAH health was assessed within this task supported by a literature review. The data generated within this WP are collected for modeling of exposure and environmental fate (for more details, refer to D2.4).

Modeling (dark orange): within this task, WP3 will deal with the development of exposure estimates for direct and indirect exposures to PPP mixtures relevant to EPAH health by integrating existing data with new data obtained from CSS and come up with innovative exposure assessment models (**Fig. 1**). The main task is to calculate the exposure of non-target species in ecosystems and uptake in crops using fate models.

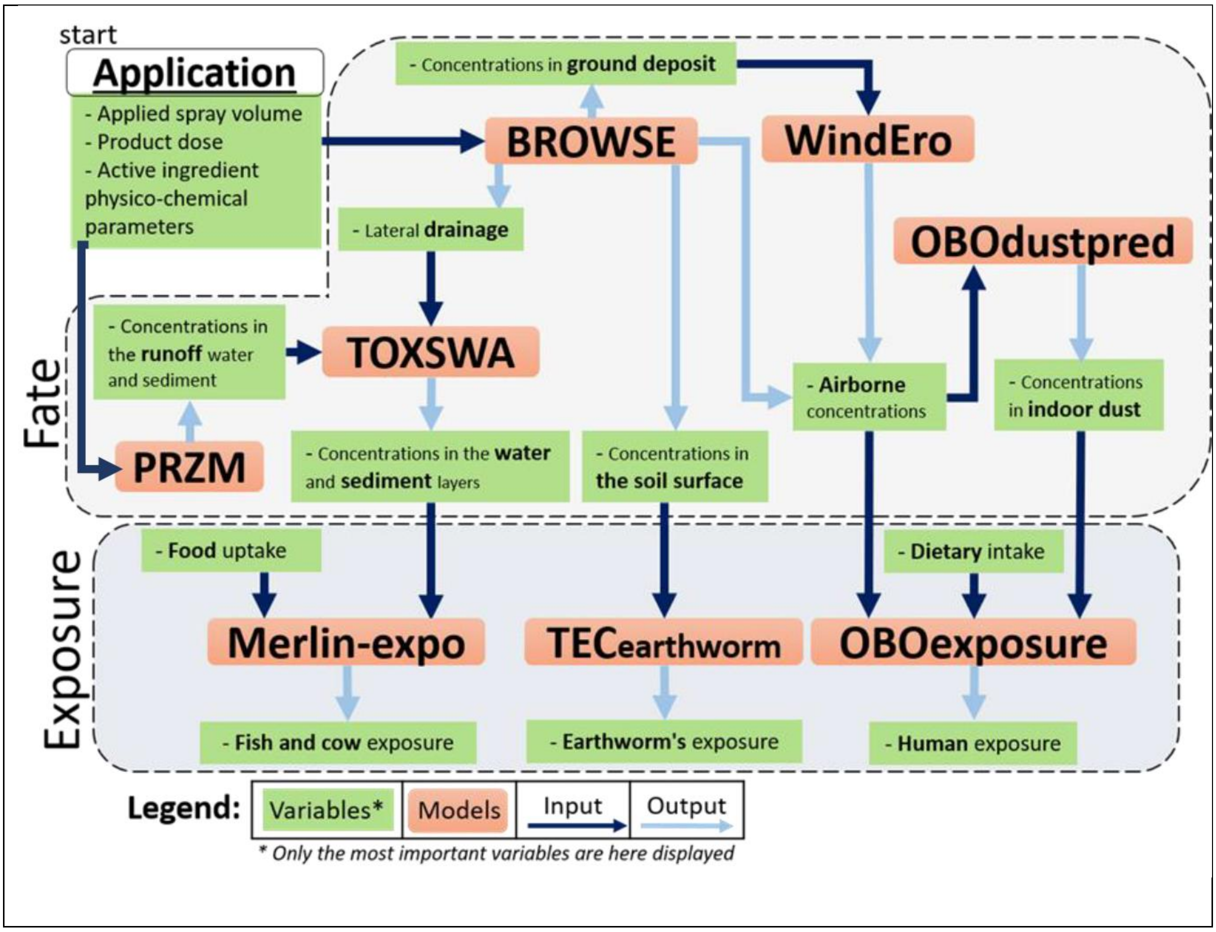


Figure 2. Model chain used in D3.2, connections, and most relevant inputs and outputs, as described in the Milestone 4. Note: "Start application" represents the input for both PRZM and BROWSE (from WP3).

Deliverable 3.2 – The FOCUS PRZM 4.3.1 (one-dimensional) model was used for calculating the runoff; FOCUS TOXSWA 5.5.3 (quasi-two-dimensional) model was used to calculate the predicted environmental concentration (PECsw); BROWSE-PEARL a dispersion model to determine vapor concentrations (**Fig. 2**). The data obtained from the FOCUS models were integrated into MERLIN-Expo in the "multi-river" scenario to evaluate the overall contribution of the different cultivated plots to the concentration of plant protection products in the main water body of the river basin; In the "multi-river" scenario in MERLIN-Expo, the "Atmosphere" model was also considered to facilitate the exchange between water-air matrices, in line with the approach of the FOCUS models, for more details, refer to Deliverable D3.2.

Deliverable 3.3 focuses on dietary and non-dietary exposure to PPPs across i) different species, namely humans, farm animals and cats (as non-target animal species); ii) different countries and iii) different sub-populations (e.g. farmer vs consumer). The authors also describe PPP co-occurrence (i.e. prevalent mixtures) and determinants of exposure. Finally, for a subset of PPPs, the task leaders will study the contribution of dietary and non-dietary routes to total exposure. For more details, refer to Figueiredo et al., 2023.

2.2. Main outcomes of D3.2

In this deliverable, D3.2, the authors studied the fate and transport of some of the pesticides used in three CSS, two reference CSS PT and NL, and DK, in soil, surface water, sediment, air and crops. Furthermore, the simulated concentrations were then used to assess the exposure of aquatic organisms, plankton, invertebrates and fish, and soil organisms, earthworms, to the pesticides selected. Finally, the simulated results were compared with the monitoring results to assess the appropriateness of the model calculation. The active substances (a.s.s) of the PPPs selected for the simulations are three: dimethomorph, metalaxyl-M and tebuconazole; all three fungicides widely used against grape downy mildew and powdery mildew.

2.3. Limitations

Although the encouraging results, some discrepancies between the model results and measurements of some orders of magnitude can be attributed to the limitations below.

- Short time-period considered in the simulation: the simulated results in PT CSS showed a very low exposure of water bodies with PECsw values lower than EQS, mainly due to the low rainfall in the post-application period resulting in low runoff and a distance of more than 30 meters between the water body and the application plots, which determines a mitigation of the drift of greater than 90% (surface water assessment, PT CSS).
- The modelling exercise allowed assessing the contribution of the different plots to the contamination of the main river in the catchment. However, several limitations of the application of Merlin-Expo were observed due to the limited information about the real river structure and miss of important processes in the model.
- No information about the use of the three fungicides in some fields located near the considered water bodies was available (surface water assessment, PT CSS).
- Inappropriate weather conditions shortly after the application of the pesticides; runoff only occurs when daily precipitation is higher than 20mm. Since no significant precipitations occurred the first days after the application of the two pesticides, runoff contribution is negligible (NL CSS).
- Few agricultural fields of the area under study were considered as contributing to the surface water, whereas other fields could have been treated and could be connected to the river (NL CSS).
- Lack of detailed measurements/background in soil to calibrate the model used; which results in discrepancies between simulated PEC_{soil} and the monitored values; degradation in soil was considered for PEC_{soil} without considering other losses, i.e., leaching.

- Exposure to certain substances was considered during one single event and at a given concentration (i.e., application of the pesticide on a given field) indicating low risk; however, when recalculating the exposure-toxicity (TER) to metalaxyl-M for example, with genotoxic effect as an outcome the values indicated that over a continuous exposure to metalaxyl-M DNA damage would likely occur.
- Large differences between modeled values and monitored values for the wind erosion model due to the large uncertainty surrounding some of the input data and also background values of particle-phase PPPs (i.e. other sources).
- In SPRINT, only one sampling time doesn't allow seasonal/temporal variations depriving of the assessment of the sensitivity analysis to evaluate model deviations; the concentrations of the three fungicides considered were estimated by considering as input data the experimental concentrations of the three fungicides, measured on June 14, 2020 (input from upstream river zone) which are only a snapshot depending on the actual conditions and are therefore not representative over a longer time.

2.4. Recommendations

Define the boundary conditions in the models:

In hydrological modeling, boundary conditions play a crucial role in defining how water flows into or out of the model domain due to external factors. The model domain corresponds to the catchment in hydrological modeling. These boundary conditions significantly influence the behavior of hydrological models, impacting water flow, transport, and storage within the system. Considering the exchange groundwater – rivers, and soil – rivers, is necessary since pesticides can move from one system to another system.

Define connectivity within the catchment:

The concept of hydrological connectivity is a useful frame for understanding spatial variations in runoff. The development of hydrological connections via overland and subsurface flows is a function of water volume (supplied by rainfall and irrigations, depleted by infiltration, evaporation, transpiration and transmission losses) and rate of transfer (a function of pathway, hillslope length and flow resistance). Considering the hydrological connectivity in the modeling will ensure to include the contribution of the different plots to the contamination of the main river within the boundary conditions of the catchment.

Long-time period for the simulation:

The modelling should take into account different events including different pesticide applications, and different weather conditions; this allows the assessment of the temporal variations that force the model over time and extreme variable values (e.g. high application rates, high PPP concentrations, high precipitations, high wind speed).

Calibration and validation of the models:

The models should be a priori calibrated with the measurements during one event. The validation should be made on other events.

Soil: A physically based model should be used to predict PPP concentrations. The model should be calibrated with soil properties and basic PPP concentrations before the application of the PPP on the field; different plots can be chosen to represent the Hydrological Response Units (HRU) (see for instance Alaoui et al., 2012).

Water: calibration of the model should be done by (i) defining the boundary conditions of the catchment, (ii) considering the topography and connectivity between the fields and channels, (iii) considering meteorological data, as rainfall events; and finally (iv) comparing the predicted total discharge with the measured total discharge at the final outlet of the catchment (validation).

Wind: The wind erosion model should be calibrated with measurements in a catchment area defined with hydrological boundary conditions and supported by PPP measurements using TIEM collectors. This assessment should be done during and shortly after application.

Crop: crop interception was predicted using FOCUS Soil Calculator; the partitioning between PPP in soil and crop interception should be based on consistent calibration using real crop interception and/or real PPP measurements in crop to assess model sensitivity. This calibration should allow realistic exposure assessments.

Inverse modeling:

Inverse modeling, on the other hand, aims to infer the unknown parameters or characteristics of the hydrological system based on observed data (such as streamflow measurements). Given observed streamflow data, inverse modeling works backward to estimate the basin characteristics (e.g., land-cover type, soil properties, etc.) that best explain the observed responses. It is particularly useful when basin characteristics are noisy or missing, impacting streamflow prediction. The goal is to obtain more explainable and trustworthy estimates from these models.

Probabilistic inverse model:

This model addresses: uncertainty estimation: quantifying the uncertainty associated with parameter estimates; robustness: Ensuring that the estimated basin characteristics are reliable even in the presence of noise or missing data.

In the case of SPRINT, we recommend using the inverse model since many data are missing and could be planned during the first phase of the project.

2.5. Main outcomes of D3.3

Duplicate Portion Analysis (DPA) - mixtures: Forty-three participants from seven countries collected portions of prepared food and beverages during a 24-h period. Each homogenized sample was analyzed for 204 PPP residues and piperonyl butoxide (synergist). The authors of D3.3 assessed the estimated dietary exposure for humans and estimated exposure from feed intake for animals. A mixture of four PPPs, namely tebuconazole, metalaxyl-M, propamocarb, pirimiphos-methyl and a co-formulant (piperonyl butoxide, a synergist), was found in almost all of the samples from participants' 24-hour portion in the DPA study. Estimate daily intake (using DPA data) vs acceptable daily intake enables exposure assessment.

Non-dietary exposure: Using wristbands to assess environmental exposure across various farm human and animals; this method has been shown previously to capture environmental exposure from inhalation and dermal uptake.

Integrated exposure assessment: environmental exposure can explain a small but significant part of the exposure for certain PPPs, along with dietary intake as the driver of exposures for most PPPs.

2.6. Limitations

The DPA dataset is based on a limited number of observations covering not all 10 countries where CSS data were collected.

The calculations of dermal exposure via skin contact required assumptions on the absorbed fraction and this is still quite an unknown.

Wristbands were used as a proxy for measuring environmental exposure across species. Cats and humans showed moderately strong correlation in wristband-measured concentrations, allowing extrapolation of exposure between species. Dietary exposure assessment, however, relies on questionnaire data, leading to some limitations in accuracy. The use of the EFSA 2020 database plus processing factors was also explored for dietary exposure assessment and tended to overestimate exposure when compared with the available DPA analysis data. When available, calculations can be redone using the EFSA 2021 database.

The assessment of estimated daily intake (using DPA data) vs acceptable daily intake needs information on the weight of the food composites which was not available for all CSS.

Exposure due to other sources such as inhalation, industrial, and household processes was not considered in detail in the assessment of exposure for humans, but rather as aggregated data obtained from wristband analysis which should not be considered as a direct measure of internal dose due to mismatches in mechanisms of uptake between silicon wristbands and humans.

Environmental exposure calculations (e.g. inhalation, dust ingestion, dermal contact, dermal from airborne PPPs) were based on assumptions using default values that do not vary per participant, such as percentage of dust that adheres to skin and fraction absorbed by the skin could result in large uncertainties.

For some farm animals, the number of samples was very limiting for some species (e.g. pigs, chickens).

2.7. Recommendations

- The DPA dataset should contain more observations by considering all 10 sites, which would allow a better understanding of the variability linked to various factors controlling exposure; It is also imperative to consider more varieties of animals. Animals' exposure from feed intake was quite variable across species, as it was also seen in wristbands. This is an indication that each species is likely exposed to a different set of PPPs and also at different concentration ranges.
- A survey should campaign the DPA for all participants, and the exercise should be made during a longer time to assess the various sources of exposure; indeed, the survey should explore all possible routes of exposure such as the use of veterinary drugs, type of function, work conditions, equipment factors, since pesticides residues detected may result from other uses than agriculture (see **D2.4**). The most common pesticide residues found in all of the samples from the participants' 24-hour portion in the DPA study are: tebuconazole (approved), metalaxyl-M (approved), and pirimiphos-methyl (approved) is used for agriculture and industrial and other issues, Propamocarb (approved) also used as pesticides in homes, gardens in addition to agricultural applications, and a co-formulant piperonyl butoxide (not approved) but still used in veterinary drugs. The survey should include information on the effectiveness of household processes, such as peeling, washing, and blanching in the reduction of PPPs residues.
- The DPA is not representative of the daily intake of the stakeholders investigated and does not reflect the consumption of food during the year; a reasonable extrapolation could be obtained from long-term data and the EFSA data; additional information on the diet of the stakeholders during a long time should be included in the survey. For this exercise, there is a need for a higher number of participants (>43) covering a wide range of diets and feeds representative of the diets of the year.
- Differentiation between stakeholders consuming organic and conventional food could provide more insights into the exposure routes; in addition, the origins of the countries exporting the food to be consumed in the country under consideration should be specified since a large difference in the use of pesticides exists and reported in the EFSA documents.
- For the animals, exposure was assessed with wristbands and feed, and the non-dietary exposure prediction was generally lower than predicted dietary exposure for PPPs.

However, inhalation due to the PPP distribution could significantly enhance the exposure of animals since they are exposed most of the time to air dust and the contamination of the grass of the pasture. This assessment could be taken from **D3.2** which considers the spatial distribution of the pesticide residues during and shortly after their application in the fields.

- The duration of the DPA should match the duration of the collection of the pesticides with the wristbands, which would make it possible to attribute the part due to digestion and the part due to inhalation and so on; in addition, the analysis of the urine should support the assessment since it will help to derive urinary excretion factors for the PPPs considered/assumed to be ingested.
- Special attention should be given to the comparison between the stakeholder groups (farmers, neighbors, and consumers), and a balance between the groups in terms of number should be ensured; a significant difference was observed between the different groups showing that farmers are the most exposed to pesticides (**D2.4**).
- Further investigations are needed to assess the uncertainty of input parameters for both dietary exposure and environmental exposure assessments which is part of D3.5 that will help feed in the risk assessment (WP4). As clinical and epidemiological studies support that air pollution and traffic noise are associated with a higher risk for cardiovascular disease and significantly contribute to overall mortality, it is imperative to consider the "exposome" that provides a comprehensive description of lifelong exposure history.
- Next step consists of studying the uncertainty of input parameters for both dietary exposure and environmental exposure assessments in deliverable 3.5. The output of D3.3, together with the other deliverables from WP3, form the basis to go from exposure at CSS to risk assessment in the following WPs (WP4 and WP5), as well as inform on which PPPs mixtures might be of interest across different matrixes and which routes should be given more focus in future studies. A proposition of the mixtures is provided in section 3.2.

3. (Eco)toxicological assessment

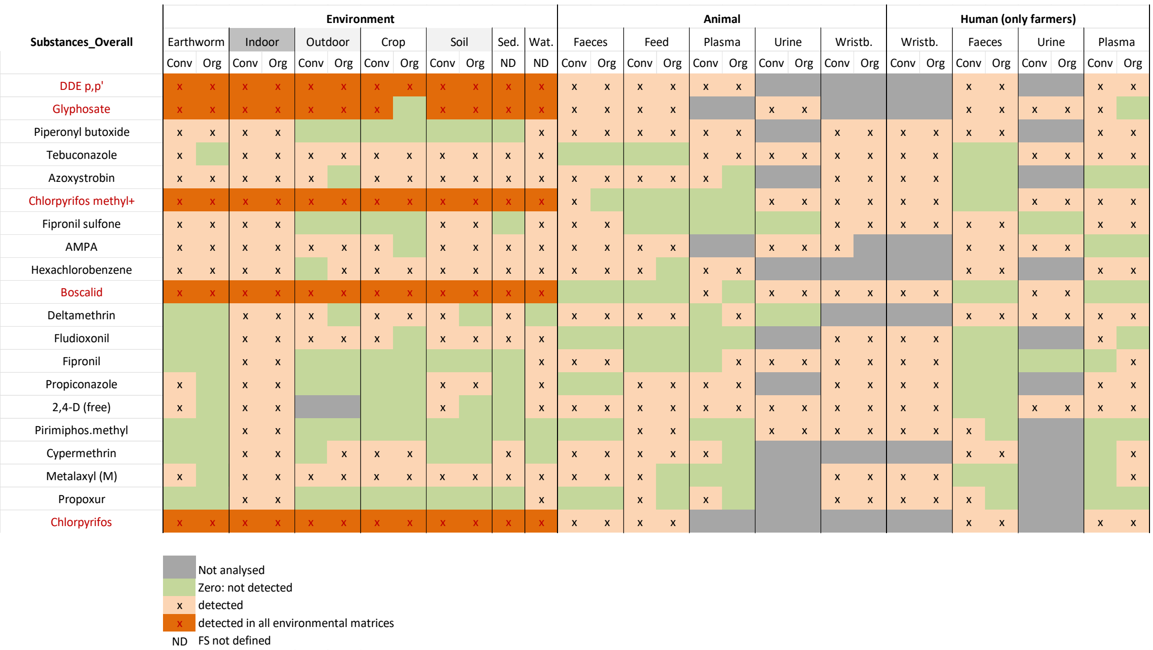
3.1. Short description of the WP4 tasks

The main objectives of WP4 are to assess i) the effects of PPPs' mixtures on terrestrial (TE) and aquatic (AE) ecosystems, using a stepwise approach, from single single-species tests with non-target organisms to multi-species microcosm, allowing also to assess the potential for trophic transfer, ii) the effects of PPPs' mixtures on animals (A) by exposing chickens directly (feed), or indirectly (inhalation, skin), to PPP residues and monitoring their health and gut microbiome composition, iii) the effects of PPPs' mixtures in animal models of mood disorders; and the associated changes in microbiota, immune and endocrine readouts, metabolomics markers and gut physiology, and iv) the effects of PPPs' mixtures on humans (H) using in vitro and in vivo experiments.

3.2. Recommendations

For Human, the risk assessment of mixtures to be carried out in WP4, **Table 1** provides a useful basis for selecting the pesticide residues to be considered in the investigation of mixtures, as it highlights the top-frequency substances across all matrices in all CSS (Alaoui et al., 2024). With so many substances omnipresent in the environment, it would be judicious to consider the mixtures of substances present in all matrices for the risk assessment planned in WP4 activities. This can be done per set of 3 or 4 compounds.

Table 1. Presence or absence in each matrix of each compartment of each of the twenty substances detected most frequently across all compartments and matrices (Alaoui et al. 2024, STOTEN, under review)



Substances_Overall	Environment												Animal										Human (only farmers)							
	Earthworm		Indoor		Outdoor		Crop		Soil		Sed.	Wat.	Faeces		Feed		Plasma		Urine		Wristb.		Wristb.		Faeces		Urine		Plasma	
	Conv	Org	Conv	Org	Conv	Org	Conv	Org	Conv	Org	ND	ND	Conv	Org	Conv	Org	Conv	Org	Conv	Org	Conv	Org	Conv	Org	Conv	Org	Conv	Org	Conv	Org
DDE p,p'	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	▨	▨	▨	▨	▨	▨	x	x	▨	▨	x	x
Glyphosate	x	x	x	x	x	x	x	🟩	x	x	x	x	x	x	x	x	▨	▨	x	x	▨	▨	▨	▨	x	x	x	x	x	🟩
Piperonyl butoxide	x	x	x	x	🟩	🟩	🟩	🟩	🟩	🟩	🟩	x	x	x	x	x	x	x	▨	▨	x	x	x	x	x	x	▨	▨	x	x
Tebuconazole	x	🟩	x	x	x	x	x	x	x	x	x	x	🟩	🟩	🟩	🟩	x	x	x	x	x	x	x	x	🟩	🟩	x	x	x	x
Azoxystrobin	x	x	x	x	x	🟩	x	x	x	x	x	x	x	x	x	x	x	🟩	▨	▨	x	x	x	x	🟩	🟩	▨	▨	🟩	🟩
Chlorpyrifos methyl+	x	x	x	x	x	x	x	x	x	x	x	x	x	🟩	🟩	🟩	🟩	🟩	x	x	x	x	x	x	🟩	🟩	x	x	x	x
Fipronil sulfone	x	x	x	x	🟩	🟩	🟩	🟩	x	x	🟩	x	x	x	🟩	🟩	🟩	🟩	🟩	🟩	x	x	x	x	x	x	🟩	🟩	x	x
AMPA	x	x	x	x	x	x	x	🟩	x	x	x	x	x	x	x	x	▨	▨	x	x	x	▨	▨	▨	x	x	x	x	🟩	🟩
Hexachlorobenzene	x	x	x	x	🟩	x	x	x	x	x	x	x	x	x	x	🟩	x	x	▨	▨	▨	▨	▨	▨	x	x	▨	▨	x	x
Boscalid	x	x	x	x	x	x	x	x	x	x	x	x	🟩	🟩	🟩	🟩	x	🟩	x	x	x	x	x	x	🟩	🟩	x	x	🟩	🟩
Deltamethrin	🟩	🟩	x	x	x	🟩	x	x	x	🟩	x	🟩	x	x	x	x	🟩	x	🟩	🟩	▨	▨	▨	▨	x	x	x	x	x	x
Fludioxonil	🟩	🟩	x	x	x	x	x	🟩	x	x	x	x	🟩	🟩	🟩	🟩	🟩	🟩	▨	▨	x	x	x	x	🟩	🟩	▨	▨	x	🟩
Fipronil	🟩	🟩	x	x	🟩	🟩	🟩	🟩	🟩	🟩	🟩	x	x	x	🟩	🟩	🟩	x	x	x	x	x	x	x	🟩	🟩	🟩	🟩	🟩	x
Propiconazole	x	🟩	x	x	🟩	🟩	🟩	🟩	x	x	🟩	x	🟩	🟩	x	x	x	x	▨	▨	x	x	x	x	🟩	🟩	▨	▨	x	x
2,4-D (free)	x	🟩	x	x	▨	▨	🟩	🟩	x	🟩	🟩	x	x	x	x	x	x	x	x	x	x	x	x	x	🟩	🟩	x	x	x	x
Pirimiphos.methyl	🟩	🟩	x	x	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	x	x	🟩	🟩	x	x	x	x	x	x	x	🟩	▨	▨	🟩	🟩
Cypermethrin	🟩	🟩	x	x	🟩	x	x	x	🟩	🟩	x	🟩	x	x	x	x	x	🟩	▨	▨	▨	▨	▨	▨	x	x	▨	▨	🟩	x
Metalaxyl (M)	x	🟩	x	x	x	x	x	x	x	x	x	x	x	x	x	🟩	🟩	🟩	▨	▨	x	x	x	x	🟩	🟩	▨	▨	🟩	x
Propoxur	🟩	🟩	x	x	🟩	🟩	🟩	🟩	🟩	🟩	🟩	x	🟩	🟩	x	🟩	x	🟩	▨	▨	x	x	x	x	x	🟩	▨	▨	🟩	🟩
Chlorpyrifos	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	▨	▨	▨	▨	▨	▨	▨	▨	x	x	▨	▨	x	x

▨ Not analysed
🟩 Zero: not detected
x detected
x detected in all environmental matrices
ND FS not defined

For the ecosystem, risk was calculated using the quotient ration (QR) in D2.4. When considering the medium to high risk, the substances were detected among the 20 most frequently detected in each matrix are presented in **Figure 2**.

Table 2. List of substances of moderate to high risks; this concerns the conventional fields only except in the case of lindane gamma (Alaoui et al., 2024, in prep.)

Substance	Soil	Crop	Water	Sed.	Type	Status	Found in x matrices
Diflufenican		50	100	50	Herbicide	App	3
Difenoconazole	67	8		100	Fungicide	App	2
Terbuthylazine		100	7	100	Herbicide	App	
Chlorpyrifos	70	44	100		Insecticide	**NA**	
Lambda cyhalothrin	70	8		100	Insecticide	App	
Permethrin		100	100		Insecticide	**NA**	
Acetamiprid	67	25			Insecticide	App	1
Deltamethrin	100	13			Insecticide	App	
Hexachlorobenzene		60			Fungicide	**NA**	
Atrazine	20	100			Herbicide	**NA**	
Lindane gamma*		50			Insecticide	**NA**	
Prosulfocarb	14	100			Insecticide	App	
Fludioxonil			100	8	Insecticide	App	
Spiroxamine			17	67	Fungicide	App	
Zoxamid			100		Fungicide	App	
Bifentrin		29	100		Insecticide	**NA**	
Terbutryn			63		Herbicide	**NA**	
Cypermethrin		30		50	Insecticide	App	
Folpet PHI				100	Fungicide (M)	App	

The compounds given in **Table 2** can be used for the mixture in **WP4** since the calculations of the risks and its frequency occurrence in ecosystem is calculated for individual compounds (**WP2**); it would be judicious to calculate the risk of their mixture 3 per 3 or 4 per 4 and compare the resulted risk with the individual risk.

Both Tables can be used as basis for the risk assessment of the mixtures if all CSS are considered.

4. General conclusions

4.1. Factors influencing exposure:

Exposure seems to be influenced by several factors.

- The seasons, with higher levels of pesticide exposure were documented during agricultural sprayings.
- Pesticide exposure is primarily associated with the geographical organisation of agricultural activities in a territory. Exposure studies should take into account spatial variables such as subject characteristics, occupant activities, and climatic and topological circumstances, as well as distance from the source of agricultural emissions (Teysseire et al., 2020).
- Spraying technologies and equipment, treated areas, and pesticide kinds that are authorised and employed vary by country; these factors may also change over time within a certain country.

- The physicochemical properties of the pesticide residues, the type of vegetation cover, and environmental factors such as meteorological and topological parameters have all been identified in the scientific literature as intervening in the spatial and temporal dispersion and transport of pesticides into the atmosphere (FOCUS, 2008).
- Farmworkers were clearly a significant contributor to pesticide exposure, mostly due to the take-home pesticide exposure pathway, as previous research has shown. Therefore, the primary matrix investigated in the observational exposure research was home dust.
- Another possible additional exposure source mentioned in epidemiological research is the subjects' temporal mobility. Certain epidemiological research took long-term residence mobility into account, retracing past exposures. Research on ambient air pollution has demonstrated that the individual exposure estimate may contain inaccuracies if nondomestic contexts are disregarded (Setton et al., 2019; Park and Kwan, 2017; Blanchard et al., 2019).

Finally, the characteristics of the populations living near agricultural areas can vary greatly depending on the period and the geographical area under consideration. Agricultural practices are constantly evolving, and active substances are regularly replaced in the market. Pesticides' exposure profiles can also vary over time. Thus, considering a long-time exposure in the modelling is recommended. Including these changes enables reliable risk assessment results.

4.2. Step forwards:

Further small-scale measurement studies at landscape scale, may enhance our knowledge of the pathways and factors influencing pesticide exposure, which is crucial for improving exposure assessments in epidemiological research or for proposing preventive measures for the population in environmental health regulations.

In order to understand spatial variations in the pesticide distribution by runoff and to determine the contribution of individual plots to the main river's contamination within the catchment's boundary conditions, it is necessary to define the catchment under consideration by establishing the spatial connectivity and hydrological boundaries. Without such investigations, the results obtained will reflect only a partial snapshot of a situation at a particular time. Appropriate and thorough monitoring that takes into account spatial and temporal indicators are needed for this purpose.

As the use of wristbands remain an indirect measure of exposure, which does not differentiate the various non-dietary exposure pathways, it should be completed by the measurements of urinary concentrations/biomarkers of pesticides to estimate the internal dose of exposure.

It is worth to mention that surveys or interviews are very useful to calculate surrogate exposure metrics, the most common being the historical exposures, and the amounts of pesticides applied or the surface area of crops around the dwelling.

Exposure in risk assessment studies was frequently obtained by modelling. The two main types of models reported in the literature are described below (Teysseire et al., 2020).

- Geographic Information Systems (GIS) generally used to define buffers around the residential location, assuming an isotropic distribution of the pesticide emissions into the atmosphere generally, without integrating meteorological data.
- Unlike GIS, dispersion models are deterministic models, based on atmospheric diffusion and reaction equations that can consider the anisotropic distribution of the aerial dispersion of pesticides.

Advantages: Using modelling, it could also be possible to isolate the contribution of local emissions sources from the background emitters. One further benefit of the modelling approach is its ability to forecast how management practices would affect exposure or to identify the mean factors driving the exposure (by e.g. sensitivity analysis). When paired with environmental monitoring, they could exploit their advantage, as has been done in the field of assessment exposures to outdoor ambient air pollutants. Indeed, dispersion/transport models have been widely used to monitor ambient air pollution and in most epidemiological studies to study its adverse health effects (Hoek, 2019)

Limitations: Certain models demand huge amount of input data (e.g., meteorological and topographical data, amounts of pesticides applied) and their computing capacity may restrict their use in epidemiological studies involving many subjects or assessing long-term exposure. They also need to be validated with monitoring data. Risk assessments are often based on numerous assumptions. The temporal and spatial evolution of pesticide concentrations in environmental compartments and the residents' exposure pathways should be considered in the modelling. This may be accomplished by conducting small-scale measurement investigations in residential areas (EFSA, 2014).

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