Integrated exposure model to estimate exposure of animals and human for C-I-O farming scenarios using models calibrated with data from the CSS

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Table of Contents – short version D3.3

1. Introduction

Plant protection products (PPPs) are extensively utilized in agriculture, industry, and homes to protect plants from pests, fungi, and weeds. Regulatory authorities have implemented international policies and regulations to minimize the risks associated with PPP use (e.g. Vizena et al. 2021). However, the potential threat of exposure to these via the environment, food, and water remains a topic of debate (Conolly & Koch 2023). Measuring actual exposures is challenging, as surrogate indicators like self-reported PPP use do not provide precise information about true exposure. While there is no definitive "gold standard" for exposure assessment, improving exposure estimates is crucial to differentiate between low and high exposed and which PPP mixtures are of greater concern.

PPPs and their derivatives can enter the body through dermal absorption, inhalation or oral ingestion. Increased likelihood of uptake occurs in the occupational setting, due to exposure and contact with items treated with PPPs (e.g., cut flowers), plant cultivation infrastructure, and contaminated materials. Environmental exposure to PPPs can occur through contaminated water, soil, dust or air resulting from PPP applications in domestic or agricultural settings. In the general population, residential PPP use, contact with contaminated household surfaces or dust, and notably, dietary intake has been identified as significant pathways of PPPs exposure (Melnyk et al. 2014). Short-term and cumulative exposure to various PPPs have been recognized as public health concerns, in particular regarding possible effects on neurodevelopment and neurodegeneration (Justyna et al. 2023). To safeguard public health, screening for PPPs in food and feed, as well as monitoring human exposure, play critical roles.

Not only humans are exposed to PPPs via the environment and diet. Animals, namely farm animals and companion animals, are also often exposed to these chemicals (Vicini et al. 2019, Avila et al. 2023). Moreover, animals and humans share a myriad of diseases that have been related to PPP exposure (Nicolopoulou-Stamati et al., 2016), such as different types of cancer (Norouzi et al. 2023, Sasikala et al. 2023), reproductive disorders (Yan et al. 2023), and hormonal imbalance (due to endocrine disruption) (Wieczorek et al. 2022). Hence, an integrated exposure assessment including both humans and animals should be performed. This allows to answer various questions such as: "Are humans exposed to similar PPP mixtures as animals?"; "What are the main determinants of human exposure and animal exposure?" and ultimately "Which PPPs are of greater concern and for which species?".

In this deliverable, D3.3, we focus 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). We also describe PPP co-occurrence (i.e. prevalent mixtures) and determinants of exposure. Finally, for a subset of PPPs, we study the contribution of dietary and non-dietary routes to total exposure. In Table 1 the deliverable main aims are listed, together with a summarized explanation of how we address them.

Table 1. Summary of D3.3 aims and how they are assessed.

Aims	How is it assessed? [highlights]
A) Better understanding of dietary exposure, specifically a) predominant PPP mixtures via food/feed intake and b) which amounts	1. In a subset of CSS participants, we collected duplicate portions of their food. 2. Portions were analysed in the lab (DPA) for the same group of PPPs defined in the SPRINT PPP selection (see Deliverable 2.1). 3. To assess generalisability, we linked DPA participants' consumed food to the EFSA PPP residuals on raw food stuffs database to derive individual dietary exposure estimates. We then compared estimates with DPA lab results. 4. The above exercise was performed for predominant PPP mixtures (excl. samples with few detects) 5. Dietary exposure of CSS participants was calculated by studying self-reported food intake similarities between DPA participants and CSS participants. 6. For animals, feed data was analysed and exposure from feed intake was calculated for each species, in line with the DPA for humans.
B) Better understanding of non-dietary exposure, specifically a) predominant PPP mixtures, b) variability between species, countries and farming system	1. CSS participants used silicon wristbands as passive samplers for a week during the spraying season (wristbands capture environmental exposure relevant for inhalation and dermal exposure). 2. Farm animals, namely cow, goat, sheep and chicken, also wore silicon bands for a fixed period during spraying season. 3. Co-occurrence of PPPs and variability between and within species, as well as between EU countries and comparisons with Argentina, was assessed. Comparison between farming systems (organic vs. conventional) was also assessed.
C) Study determinants of environmental human exposure for CSS participants	1. Determinants of environmental PPP exposure (captured by wristbands) were assessed using multivariable generalized least squares (GLS) models, including questionnaire data as predictors (e.g. use of PPPs indoors or having pets).
D) Study non-dietary exposure of animals species	1. We modelled environmental PPP concentrations for animals using the Merlin-expo model (see also D3.2). For mammals this was however not feasible. 2. In an exploratory approach, we assessed mammals exposure via inhalation (breathing) of PPP concentrations in air.
E) Combined exposure comparison at group levels	1. We combined results of aim (A) and (B) to evaluate how dietary and non-dietary contributions compare at different subgroup levels (e.g. farmer, neighbour, consumer, and by gender). 2. We analyse exposure contributions by comparing dietary intake and wristbands levels to measured urinary concentrations.

2. Summary of main findings

The main findings of this deliverable are presented in the BOX below (Box 1).

Box 1. Summary of main findings from SPRINT deliverable 3.3.

Dietary exposure

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 analysed for 204 PPP residues and piperonyl butoxide (synergist).
- 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. (See Figure 1).
- Based on DPA findings, dietary exposure was similar in magnitude between individuals but different in terms of mixture profiles. This implies that subsets of populations may have similar concentration ranges, but individuals could be exposed to different mixtures due to various factors like diet, food origin, and food processing factors.
- Estimated daily intake (EDI) calculated for all DPA-participants turned out to be well below the acceptable daily intake (ADI), with the highest hazard quotient (ADI/EDI*100%) of 24%.

Estimated dietary Exposure – humans:

- Exposure from dietary intake was quite variable between CSS participants.
- Dietary exposure, for almost all PPPs, is very similar between sexes.

Estimated exposure from feed intake – animals:

- Feed intake exposure was highly variable between species. Between countries, exposure variability was less pronounced, with exception for a few PPPs in Argentina where concentrations measured in feed were significantly higher than in EU countries.
- Glyphosate and folpet-PHI were the most frequently co-occurring PPPs across all feed samples.

Non-dietary exposure

Wristbands as Efficient Proxies: Using wristbands to assess environmental exposure across various farm animals is a novel approach. Wristbands have been previously used for PPPs but no for so many species in the same study. This method has been shown previously to capture environmental exposure from inhalation and dermal uptake.

Wristbands-Humans:

- Measured PPP concentrations are consistent with findings from previous studies. Concentrations in wristbands worn by farmers were overall higher than those measured in neighbors and consumers. PPP concentrations in wristbands worn by study participants living close to conventional farms were higher compared to study participants living close to organic farms.

Box 1. CONTINUATION of summary of main findings from SPRINT deliverable 3.3

- When examining the factors affecting concentration variability for the biocide use of fipronil and fipronil sulfone, a clear influence of having pets is observed. This is probably linked to biocide-impregnated collar or flea repellent treatments. For other PPPs, reported spraying PPPs or people working in the agricultural sector come out as main predictors.

Wristbands-Animals: Overall, there are no statistically significant differences between measured concentrations across different animal species. However, for certain PPPs, such as thiamethoxam and pendimethalin, concentrations were significantly higher in chicken and cows, respectively (See Figure 2).

Estimated environmental exposure-humans: Estimated environmental exposure of CSS participants was generally lower than predicted dietary exposure. Independently, exposure via dust ingestion and skin contact tends to be higher for CSS participants living close to conventional farming in comparison to organic farming (route comparison example, see Figure 3).

Environmental Exposure-animals: Environmental exposure of mammals is generally lower than predicted dietary exposure. Currently, environmental exposure is not considered in risk assessments for farm animals. Some PPPs or metabolites detected in urine were not detected in animal wristbands, suggesting that dietary uptake is the main exposure route.

Correlation with matrices

Spearman Correlation Matrix: Based on the different Spearman correlation matrices, there is no apparent clustering across different PPPs, except within functional application groups (i.e. fungicides correlate higher with fungicides) and between parent compounds and their metabolites.

Integrated exposure assessment

Integrated exposure – humans: For several PPPs, dietary exposure was associated with an increase in urinary concentrations. For some PPPs, environmental exposure was a statistically significant predictor for variability in urinary excretion values, which indicates that environmental exposure can explain a significant part of the exposure for certain PPPs, along with dietary intake. For some findings, environmental exposure is explained by biocide applications (e.g. fipronil and pyrethroid-based products).

Integrated exposure – animals: For few PPPs, dietary exposure was associated with an increase in urinary concentrations (although not significant if values below LOD were considered by statistical imputation).

Next steps and limitations

Next Steps: In the subsequent stage (deliverable 3.5), we will study the uncertainty of input parameters for both dietary exposure and environmental exposure assessments. Additionally, we will determine which parameters have a greater impact on the estimated exposure. We aim to link these deliverables with WP5, specifically in transiting from exposure to risk for both humans and farm animals. Moreover, the influence of physicochemical properties of the PPPs is outside the scope of D3.3 and will be assessed in detail in deliverable 3.5.

Box 1. CONTINUATION of summary of main findings from SPRINT deliverable 3.3

Extrapolation and Limitations: Wristbands are a good 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 comparing with the DPA analysis data. When available, calculations can be redone using the EFSA 2021 database.

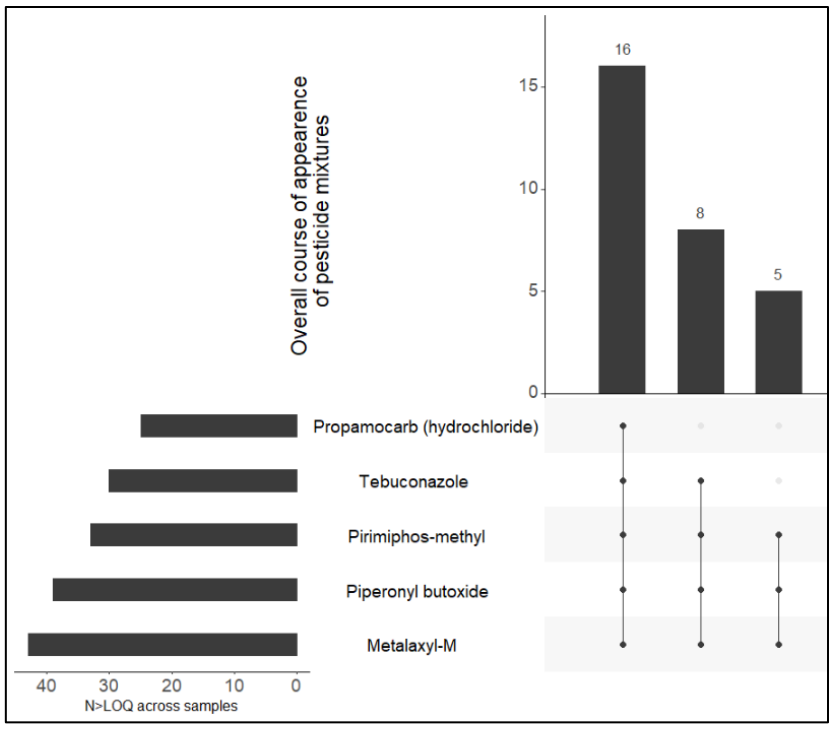

Fig 1. Upset plot for co-occurrence of PPPs across the DPA samples. Top 3 mixtures are presented.

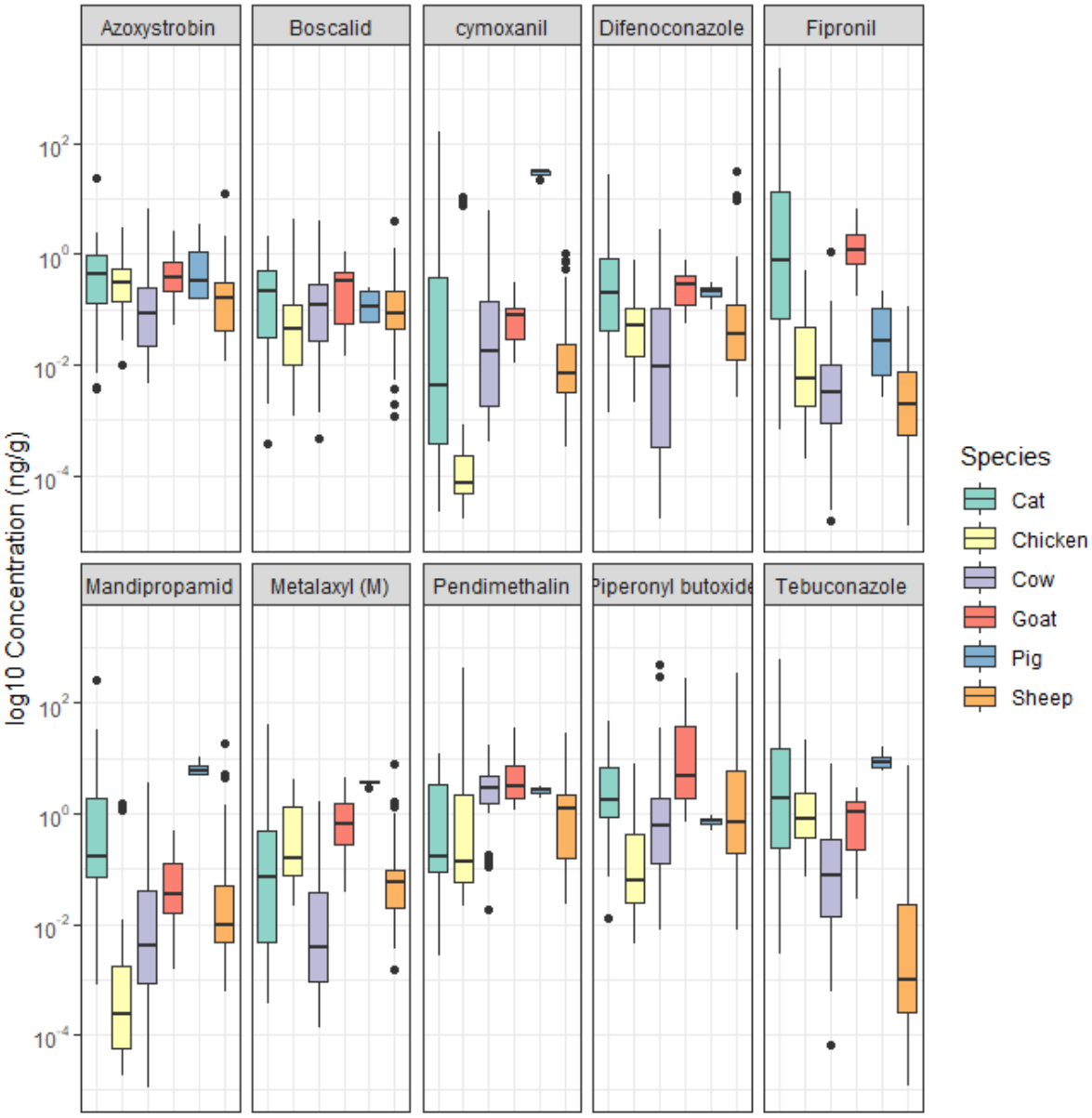

Figure 2. Measured concentrations for the top-10 most detected PPPs in wristbands. Boxplots grouped by animal type. Summary statistics in boxplots (min, max, 1st and 3rd quartile and median). In the y-axis the log10 of concentration is presented in ng/gram wristband.

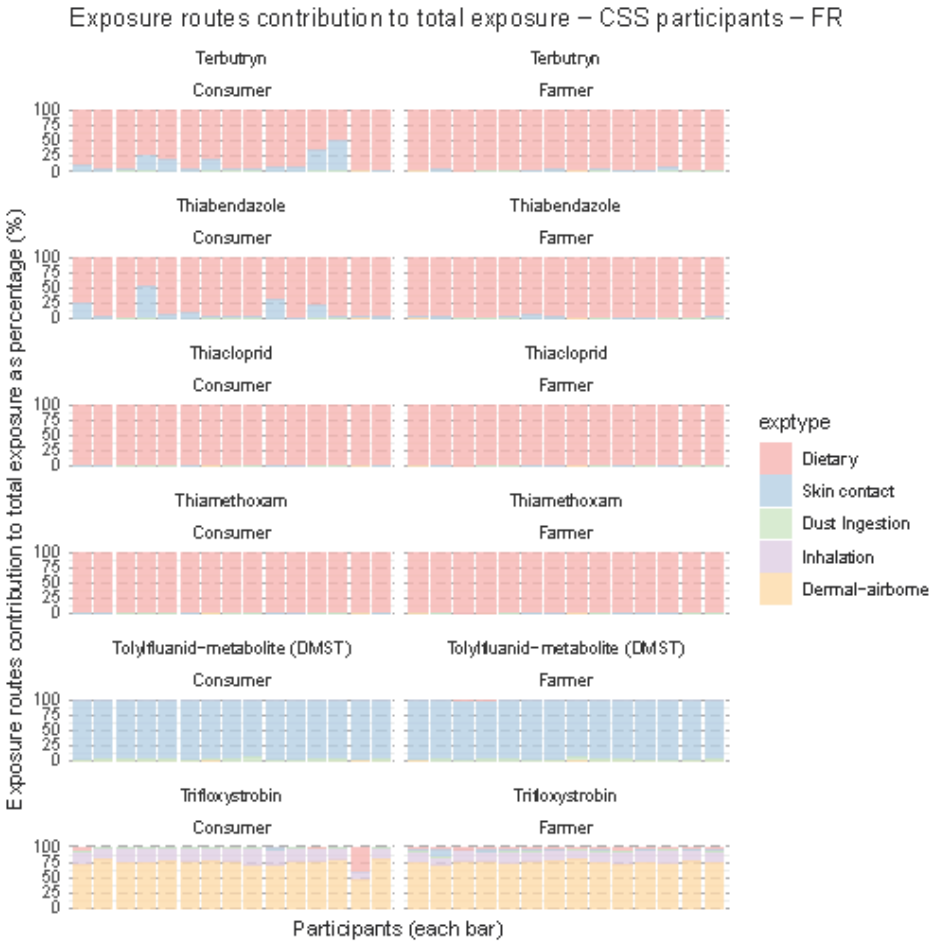

Figure 3. Percentage contribution of different routes, grouped by farmer and neighbor for France (FR) for some PPPs. On the x-axis each individual participant is shown in a separate bar and on the y-axis the percentage route contribution to total exposure is shown (0-100%, with 100% as the total exposure in that individual). Exptype=exposure type.

3. Strengths and limitations

Strengths

For food intake we could rely on data from the duplicate portion analysis that provides more complete assessment than using a market basket approach, e.g., the size of portions, the contribution of food processing and the contribution of food items from home-grown origin. For exposure we used data of PPP analysed in silicone wrist bands from large numbers of human subjects in 10 EU countries and from different subgroups reflecting contact with PPPs from different environmental sources on participant level to be used as approximations (proxies) for different exposure routes (inhalation, dermal, ingestion).

Limitations

The DPA dataset is based on a limited number of observations covering not all 10 countries where CSS data were collected. DPA data were available from a single 24 h sample per person. The wristband data for PPPs to be analysed by GC-MS/MS are not yet available and could not yet be included in the analysis. The distributions of PPPs in wristbands are left censored, although for some PPPs it was possible to apply imputations for data below the LOQ.

For some farm-animals the number of samples was very limiting. For this species, such as pigs and chickens, more studies are needed to understand variability in exposure and co-occurrence of PPPs.

There are still uncertainties regarding the limited experience with silicone wristbands and how well they reflect the complexity of individual exposures for humans and animals that depend on substance properties and also on activity and behavioural patterns of the wearer.

Finally, the calculations of dermal exposure via skin contact required assumptions on the absorbed fraction and this is still quite an unknown as there is little literature on pesticides and values for absorbed fraction.

4. Connection with other deliverables

Previous deliverables

This deliverable had several dependencies from previous deliverables, namely those from WP2 and also D3.1 and D3.2. The merlin-expo model used in D3.2 was used in an exploratory approach to environmental exposure of mammals in section 4.2.2.2. Moreover, data collected in WP2 and WP3, such as PPPs concentrations measured in dust wristbands and urine were used in this deliverable. In WP3 additional dust samples were also collected to study temporal variability in exposure and active air sampling measurements were performed in NL and PT to inform the inhalation and dermal route estimates.

Future deliverables

This deliverable has several connections to forthcoming work. Primarily, and the biggest connections are within WP3. Information from this deliverable on the weight of different routes for different PPs will inform D3.4 on selection of certain PPPs for volunteer studies, where environmental exposure plays a bigger role. Moreover, in D3.4 PBPK models will be developed for a set of compounds, this can be further linked to exposure estimates in order to assess distribution and metabolism for different PPPs. Finally, D3.4 will output urinary excretion factors for certain PPPs (based on volunteer study), which can be used to calculate, via reverse dosimetry, the total exposure. This output will be used in D3.5 to verify exposure estimates presented here vs the urinary concentrations measured.

The clear link with D3.5 is on the study of uncertainty across the integrated exposure assessment present in D3.3. As discussed in some sections, some input parameters are quite uncertain or unknown, so in D3.5 distributions will replace fixed input in order to study variability on exposure estimates due to variability in predictors. This will be done for both dietary and non-dietary exposure routes.

Skin contact takes into account a fixed dermal absorption factor by skin, but does not include the full pharmacokinetics (e.g. distribution, metabolism). This can be explored in Deliverable 3.4.

D3.3 methodology and output on dietary exposure will also serve as input for the risk assessment framework developed in WP5. The aim in WP5 being to estimate dietary exposure across EU for a set of selected PPPs and food items. From the results of WP4, in toxicology and eco-toxicology, if enough data is created to derive dose-response curve than this can also be used in WP5 together with exposure estimates from this deliverable. This would give a straight forward connection, from field measurements to risk assessment (from WP2 to WP5).

Finally, the output of this deliverable will inform following deliverables when it comes to PPP selection and decision-making regarding cost-benefit analyses (e.g. WP6).

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