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Identifying pesticides of high concern for ecosystem, plant, animal, and human health: A comprehensive field study across Europe and Argentina

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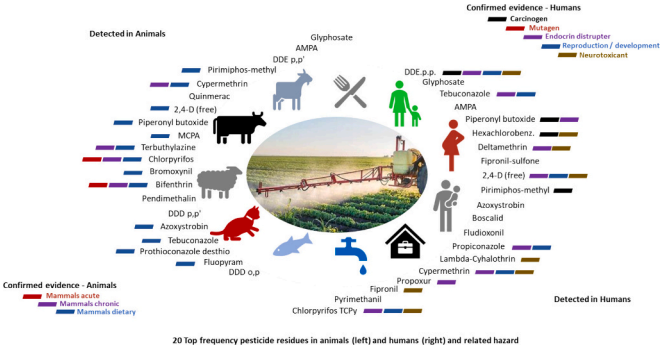
HIGHLIGHTS

- Multiple pesticide residues were tested in environmental and biological matrices.
- Pesticides are detected at lower frequencies and levels in organic fields.
- Not-approved pesticides, of high hazard, were frequently detected in samples.
- Common hazardous substances of dual use were detected in all matrices.
- A holistic approach is needed to assess pesticide impacts and chart transition paths.

GRAPHICAL ABSTRACT



20 Top frequency pesticide residues in animals (left) and humans (right) and related hazard

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ABSTRACT

The widespread and excessive use of pesticides in modern agricultural practices has caused pesticide contamination of the environment, animals, and humans, with confirmed serious health consequences. This study aimed to identify the 20 most critical substances based on an analysis of detection frequency (DF) and median concentrations (MC) across environmental and biological matrices. A sampling campaign was conducted across 10 case study sites in Europe and 1 in Argentina, each encompassing conventional and organic farming systems. We analysed 209 active substances in a total of 4609 samples. All substances ranked among the 20 most critical were detected in silicon wristbands worn by humans and animals and indoor dust from both farming systems. Five of them were detected in all environmental matrices. Overall, higher values of DF and MC, including in the blood plasma of animals and humans, were recorded in samples of conventional compared to organic farms. The differences between farming systems were greater in the environmental samples and less in animal and human samples. Ten substances were detected in animal blood plasma from conventional farms and eight in animal blood plasma from organic farms. Two of those, detected in both farming systems, are classified as hazardous for mammals (acute). Five substances detected in animal blood plasma from organic farms and seven detected in animal blood plasma from conventional farms are classified as hazardous for mammals (dietary). Three substances detected in human blood plasma are classified as carcinogens. Seven of the substances detected in human blood plasma are classified as endocrine disruptors. Six substances, of which five were detected in human blood plasma, are hazardous for reproduction/development. Efforts are needed to elucidate the unknown effects of mixtures, and it is crucial that such research also considers biocides and banned substances, which constitute a baseline of contamination that adds to the effect of substances used in agriculture.

1. Introduction

Among the substances used in agriculture, the most harmful to non-target species are pesticides, and human activities have greatly increased the usage of these chemicals to kill undesirable species including fungi, weeds, rodents, and insects. Approximately 1.4 million metric tons of herbicides were used globally in 2020, compared to 606 and 471 thousand metric tons, respectively, of fungicides and bactericides (statistica, 2023). Approximately 355,175 tons of pesticides were sold in the EU in 2021 (Eurostat, 2021) and 440 substances are approved in the EU market. According to McGinley et al. (2023), fungicides and herbicides were the most common pesticides used in the EU from 2011 to 2020, accounting for 40–44 % and 30–36 % of total pesticide sales, respectively. Insecticides accounted for 9–16 % of pesticides applied, with the rest consisting of plant growth regulators, anti-sprouting chemicals, and molluscicides (McGinley et al., 2023). The usage of pesticides has grown during the last 10 years, from 35 kt in 2011 to 64 kt in 2020. This rise can be attributed to economic expansion, the emergence of new pests and diseases, and increased pesticide resistance (Sparks et al., 2020).

Pesticides have been crucial to the success of contemporary crop production (Malik et al., 2021) and have contributed significantly to increased agricultural yields. However, they are considered a major cause of environmental contamination, and because of their extensive usage in agriculture, they pose potential threats to the environment, animals, and humans (Giglio and Vommaro, 2022; Richardson et al., 2019). It is known that only 10 % of applied pesticides reach their intended targets (Bose et al., 2021; Oliveira-Silva et al., 2001; Satish et al., 2017); the rest enters and contaminates various environmental matrices, such as soil, dust, water, and crops (Singh et al., 2020).

Pesticide residues are widely present in the environment, as evidenced by their frequent detection in soil, water, and air (Kruse-Plaß et al., 2021; Dulsat-Masvidal et al., 2023; Silva et al., 2019) and in non-target plants (Zioga et al., 2023; Qi et al., 2020; Duffner et al., 2020). The widespread presence of pesticides in different environmental compartments may cause adverse effects on non-target species (Beketov et al., 2013; Stehle and Schulz, 2015), potentially leading to disruptions in ecosystem function and services that regulate soil respiration, pollination, natural pest control, nutrient cycling, and other functions (Chagnon et al., 2015; Köhler and Triebskorn, 2013). For instance, pesticides detected in urban streams have been identified as the primary cause of aquatic organism deaths, including fish and invertebrates (Aktar et al., 2009; Kamble et al., 2016). Under some circumstances, even pesticides with a short half-life may persist in soil for several years, posing a risk to soil invertebrates (Bonmatin et al., 2015).

Original research papers and systematic reviews show that basically all people are exposed to pesticides (Kim et al., 2017). In population-based studies, pesticide exposure has been shown to be associated with an increased risk of chronic diseases such as different types of cancers (Burns and Juberg, 2021; Girard et al., 2020), neurodegenerative disorders like Parkinson (Ohlander et al., 2022; Allen and Levy, 2013; Hernández et al., 2016; Tangamornsuksan et al., 2019), diabetes (Miranda et al., 2023; Brugel et al., 2022; Djekkoun et al., 2021), Alzheimer's (Mostafalou and Abdollahi, 2013; Hernández et al., 2016), amyotrophic lateral sclerosis (ALS) (Sánchez-Santed et al., 2016; Re et al., 2022), birth defects (Rivera-González et al., 2021), and reproductive and developmental disorders (Miranda et al., 2023; Basso et al., 2022). Furthermore, there is circumstantial evidence linking exposure of pesticides to several other chronic ailments, such as respiratory disease (Wani et al., 2014; Hernández et al., 2013), particularly asthma and chronic obstructive pulmonary disease (COPD) (Buralli et al., 2020; Hansen et al., 2021; Hoppin et al., 2008; Ratanachina et al., 2020), cardiovascular diseases, such as atherosclerosis and coronary artery disease (Huang et al., 2022a; Wells, 2019), autoimmune diseases (Woo et al., 2022), and kidney diseases (Valcke et al., 2017) such as chronic nephropathies (Arcoverde Fechine Brito et al., 2021; Vervaet et al., 2020).

Action has been taken by various authorities at the national and European levels. Governments, regulatory agencies, and regulatory instruments such as Regulation (EU) 2019/6 on veterinary medicines, Regulation (EU) No 528/2012 on biocidal products, Regulation (EC) No 1107/2009 on plant protection products, and the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation applying to a wide range of chemicals (Regulation (EC) No 1907/2006) enforce safety standards for consumers, the environment, and people's health in Europe. Thus, recent data from the European Commission (EC, 2023) showed a decreasing trend in the use of chemical pesticides (by 33 % in 2021 compared to the baseline period of 2015–2017) and in the use of the more hazardous pesticides qualified as candidates for substitution (by 21 % over the same period).

The European Commission defined two pesticide reduction targets set as part of its Farm to Fork strategy: a 50 % reduction in chemical pesticide use and risk by 2030, as well as a 50 % reduction in the use of more hazardous pesticides by 2030, compared to the baseline period of 2015–2017 (EC, 2020). However, no specific plans of action are in place to guarantee that the Farm to Fork pesticide targets are fulfilled. Such

plans of action could take the form of general recommendations catered to specific crop systems, more substantial changes such as adopting organic farming, or stricter regulations on the pesticides that can be purchased (Gauthier, 2020; Silva et al., 2022).

While EU has a pre-market entry risk assessment process for pesticides, pesticide-related benchmarks and post-market monitoring programs are limited to drinking water and food (EFSA, 2022a, b; EC, 1998; EC, 2000; EC, 2005; EFSA, 2013; EU, 2008). Environmental and biomonitoring data on pesticide residues are crucial in fully quantifying and evaluating the load and risks of pesticides (Damalas and Eleftherohorinos, 2011). In addition to the limited and fragmented data (ECA, 2020; Peris et al., 2022; Zaller et al., 2022), there are significant obstacles to this goal:

1. Due to many diverse coding systems, there is a lack of large-scale, systematic, and harmonized exposure assessment needed for coordinated occupational health research (Maitre et al., 2023; Peters et al., 2022). In addition, despite the availability of many large occupational exposure databases, lacking adherence to the FAIR (findable, accessible, interoperable, reuseable) principles has restricted the use of these databases in population-based research (Peters et al., 2020). According to 't Mannetje and Kromhout (2003), a high-quality exposure assessment is needed to identify and characterize relevant exposure–disease relationships.
2. There is a lack of studies on the possible risk that mixtures pose to ecosystem, animal, and human health. Standardized and comprehensive monitoring data on (mixtures of) pesticide residues are urgently needed. Their long-term persistence in various ecosystem matrices and the use of recent mixtures increase pest resistance, endanger numerous environmental functions globally, and have an impact on food safety (Beketov et al., 2013; Stehle and Schulz, 2015). The effect of the cocktails of multiple active compounds on soil, for example, has not yet been assessed.
3. Over time, many active substances are banned due to knowledge gained a posteriori on their high persistence and/or toxicity to non-target species (EASAC, 2023; OJL, 2023). the risk related to their interaction effect is not considered in mixture studies, which often only include pesticides currently used in agriculture.

The above considerations add a great deal of complexity to assessments of pesticides on public health. To shed light on this complexity, it is necessary to identify the sources of the pesticide residues, their distribution, and the possible hazards they pose to the environment, animals, and humans. Furthermore, complete, large-scale data are needed to inform legislators and civil society and empower them to take action. This study was carried out as part of the SPRINT project, which aims to advance knowledge of the association between exposure to pesticides and environmental, animal, and human health effects, leading to proposals for sustainable alternatives that can help reduce reliance on pesticides.

This study aimed (1) to identify the 20 substances of higher concern for ecosystem, animal and human health based on detection frequency (*DF*) and median concentrations (*MC*); (2) to compare results from conventional and organic farming systems (FS); and (3) to provide indicative information on the identified substances' potential hazard to health.

2. Material and methods

During an extensive sampling campaign spanning Europe and Argentina, we examined a total of 209 active substances in a total of 4609 samples, comprising 153 approved and 56 not approved substances (approval status refer to 2022). Of these substances, 75 are fungicides (of which 60 are approved in the EU), 64 are herbicides (53 approved), and 70 are insecticides (32 approved).

2.1. Samples and compounds covered within the SPRINT field campaign

This study relates to the SPRINT sampling campaign, performed in the growing season of 2021, in 11 case study sites, ten covering the main European crops, and one in Argentina, the main exporter of soy for animal feed in Europe, where the following matrices were analysed for multiple pesticide residues:

- Environment: Soil, sediment, water, outdoor dust, indoor dust, plant (crops), and earthworms.
- Animal: Blood plasma, urine, stool, milk, feed, and wristbands.
- Human: Blood plasma, urine, stool, and wristbands.

The list of analytes was designed to include plant protection products known or expected to be applied in the SPRINT case study sites, based on pre-screening results and the literature (Silva et al., 2021). Due to analytical limitations, it was not possible to test all active substances in all matrices.

Each case study site included an average of 10 fields under conventional/integrated pest management and 10 organic fields. Crop types and livestock production are shown in Table 1. The selected farms were representative of farms in the case study site regions (in terms of size, soil type, topography, socioeconomic conditions, etc.). Organic fields/farms were only considered where the transition had occurred at least 5 years ago.

2.2. Selection of ecosystem, plant, animal, and human samples

The 742 participants involved in this study were (1) 243 farmers; (2) 238 neighbors; and (3) 261 consumers. Neighbors were defined as people living near the farm/field under consideration, who might in one way or another be exposed to pesticides applied to the fields. Consumers were defined as people living in the region where the farms were located, but not necessarily close to the farmland. For the human sampling, the total number of involved actors allowed us to analyze 731 blood samples, 736 urine samples, 724 stool samples, and 712 wristbands. For the environmental matrices, a total of 890 samples were analysed as follows: 215 for soil, 64 for water, 38 for sediment, 20 for outdoor dust/air, 130 for indoor dust, 223 for crops, and 200 for earthworms. The farm animals considered were goats, pigs, chickens, cats, dairy cows, and sheep. Blood, urine, and stool were sampled from a total of 36 animals. One milk and feed sample were collected per farm. A total of 172 wristbands were collected.

2.3. Methods used in the laboratory analysis

The crop samples were thawed, homogenized and split into two parts: one for the determination of glyphosate and its major metabolite aminomethylphosphonic acid (AMPA) and one for multi-residue

Table 1
Cropping system and animal types of SPRINT Case Study Sites (CSS).

CSS (region, country)	Crops	Animals
1. Spain	Vegetables	Goat
2. Portugal	Wine grapes	Pig and chicken
3. France	Wine grapes	Pig, chicken
4. Switzerland	Fruits[a]	Darry cows
5. Italy	Vegetables	No Livestock
6. Croatia	Olives	Sheep
7. Slovenia	Maize	Dairy cows and cattle
8. Czech Republic	Oil plants[b]	Dairy cows, chicken
9. Netherlands	Potatoes	Dairy cows
10. Denmark	Cereals[c]	Dairy cows
11. Argentina	Cereals	Dairy cows cattle

[a] Apple, pears, strawberries.
[b] Rapeseed, sunflower, mustard seed, poppy seed.
[c] Spring barley, winter barley, winter rye, winter wheat, and oats.

analysis. The former part of 5 g (2 g in case of wet samples), the latter of 10 g (2 g in case of wet samples). Glyphosate and AMPA were determined using the modified method described by Yang et al. (2015), Goscinny et al. (2012) and Kaczyński and Łozowicka (2015) which involves isotope-labelled standards, 0.1 % formic acid and dichloromethane-based extraction, and a FMOC-Cl based derivatization step. The other pesticide residues were extracted using an adaptation of the QuEChERS approach, as described by Silva et al. (2019). Acetonitrile was used as extraction solvent, and dispersive sorbents for the extra clean-up step before the GC analyses.

Each **indoor dust** sample was analysed by three methods: (I) determination of multi-residue analysis of pesticides, (II) glyphosate and AMPA, and (III) organochlorinated pesticides. Multi-residues were analysed via the QuEChERS approach, which involved labelled standards, acetonitrile containing 1 % of acetic acid as extraction solvent, and dSPE cleaning of the GC extract, followed by a solvent change to isooctane. Glyphosate and AMPA were analysed as described in Mendez et al. (2017), also using labelled standards and $KH_2PO_4/Na_2B_4O_7$ as extraction solvent, and a FMOC-Cl based derivatization. Finally, organochlorinated pesticides were measured as described in De la Torre et al. (2020). Here the extraction was done with a hexane: acetone solution (3:1), and extract purification by a 1 g florisil column eluted with 16 mL of hexane.

Air Outdoor – Extraction of the TIEM-PUF disks was carried out with dichloromethane in a Soxhlet extractor. Samples were extracted for 24 h using at least 16 extraction cycles. After concentrating the extract to 1 mL under a stream of nitrogen, the extract was analysed by LC–MS/MS and GC–MS/MS. Glyphosate and AMPA were extracted from the PEF materials with 0.125 N hydrochloric acid and derivatized with FMOC. The analysis was conducted by LC–MS/MS.

Earthworm subsamples were spiked with the labelled standards and extracted with water containing 0.1 % formic acid. Derivatization was carried out following Yang et al. (2015). The remaining pesticide residues were extracted using the QuEChERS approach, as described by Silva et al. (2019), Svobodová et al. (2018), and Lehotay et al. (2005). Earthworm subsamples were spiked with D6-tebuconazole and mixed with Millipore water and acetonitrile. After agitation, a mixture of $MgSO_4$, NaCl, NaCitrate, disodium citrate was added. The tube was then vortexed and centrifuged, and the supernatant collected, and one part analysed using LC-MS/MS with electrospray ionization (ESI) and one part analysed using GC–MS/MS.

Soil – Soil was vortexed and centrifuged (5 min, 3500 rpm) and the supernatant was collected: part to be analysed using LC-MS/MS, with electrospray ionization (ESI) in positive and negative mode, and part to be analysed using GC–MS/MS. For the LC-MS/MS analysis, 100 μL of the supernatant and 100 μL of Millipore water (0.1 % formic acid) were added directly into a LC filter vial to be analysed. For the GC-HRMS analysis, there was an extra clean-up step: 1 mL of the supernatant were transferred into an Eppendorf tube containing 25 mg of primary secondary amine (PSA), 3.5 mg of Graphitized Carbon Blacks (GCB) and 150 mg of magnesium sulfate. The Eppendorf was then centrifuged (15 min, 13,000 rpm) and 100 μL of the cleaned supernatant and 10 μL of 13C-PCB-162 1 μg/mL (used as injection standard in the GC-HRMS analysis) was added into a conical glass vial to be analysed.

The **sediment** samples were analysed almost exactly as the soil samples, with two minor adaptations. Sample preparation involved a centrifugation step (at 3500 rpm for 5 min; decanting and discarding the water fraction), and the aliquot for determination of glyphosate and AMPA, and the aliquot for screening of multi-residues both had 2 g. The methods used were those described by Bento et al. (2016) and Yang et al. (2015), and Silva et al. (2019).

The **water** samples were thawed, filtered, and analysed by three methods, for determination of multi-residue analysis of pesticides, glyphosate and AMPA, and organochlorinated pesticides. Multi-residue analysis was carried out by solid-phase extraction (SPE) using Oasis HLB cartridges conditioned with methanol and ultrapure water. The extract was evaporated under a stream of nitrogen and divided into two aliquots, for GC and HPLC- MS/MS analyses. Glyphosate and AMPA were extracted with KH_2PO_4 and $Na_2B_4O_7$ (0.1 M, pH = 9) and derivatized with FMOC-Cl (1 mg/mL) in darkness at room temperature, followed by SPE. The organochlorinated pesticides were liquid-liquid extracted with dichloromethane and analysed by HRGC-HRMS.

Feed – Similar methods for multi and glyphosate and AMPA assessments in feed were used as in feces.

Blood plasma – The sample preparation method for plasma PPP analysis was based on an adapted QuEChERS extraction method as described in AOAC (2007). In short, 1 mL of plasma is added to an extraction tube together with 3 mL of 0.1 % formic acid in acetonitrile.

After vortexing, 1.5 g of QuEChERS salts were added (1.3 g magnesium sulfate, 0.3 g sodium acetate) and vortexed. Samples are centrifuged for 5 min at 3200 RCF and the supernatant is collected and divided in 2 times 1 mL in separate sample concentration tubes (1 mL for LC analysis and 1 mL for GC analysis). Ten μl of dimethyl sulfoxide (DMSO) was added to the 1 mL LC-MS/MS fraction prior to evaporation under a stream of nitrogen at 40 °C. Samples were evaporated till dryness and subsequently reconstituted into 5 mM ammonium formate (NH_4HCO_2) 50:50 (*v*/v) Ultrapure water: methanol (CH_3OH) solution. An aliquot of 1 mL GC–MS fraction was inserted into a DisQue QuEChERS tube (150 mg $MgSO_4$: 25 mg primary secondary amine (PSA): 25 mg C18) vortexed and centrifuged for 5 min at 21000 RCF. From this an aliquot of 500 μL was taken and placed in an Eppendorf tube for further GC–MS pretreatment and analysis at Limoges CHU.

Feces Before handling, the samples were allowed to reach room temperature. Then, 2 g of sample were weighted in an extraction tube followed by the addition of 4 mL of water. Next, 4 mL of acetonitrile containing 1 % of acetic acid were added. The tubes were shaken for 30 min followed by addition of 1.6 g of magnesium sulphate and 0.4 g of sodium acetate. The tubes were once again shaken for 10 min followed by centrifugation. For LC-MS/MS measurements, 250 μL of extract were diluted in vial with 250 μL of methanol containing 0.1 % acetic acid. For GC–MS/MS measurements, a clean-up procedure was applied. For this, 1 mL of acetonitrile was added to a tube containing 150 mg $MgSO_4$, 25 mg C18 and 250 mg PSA followed by addition of 1 mL of the initial acetonitril extract. The tubes were shaken, centrifuged, and 200 μL of extract were transferred to an insert vial for analysis.

Urine – Urine was analysed using a multi-method involving enzymatic deconjugation, QuEChERS extraction, and LC-MS/MS analysis. While FMOC-CI derivatization and LC-MS/MS method-2 were used for the glyphosate and AMPA-analysis.

Procedure for AMPA: To a 200 μL sample portion, 10 μL of the isotopically labelled internal standard of 20 ng/mL was added. 100 μL borate buffer 5 % was added followed by 100 μL 6.5 mM FMOC-Cl. The tubes were gently homogenized and allowed to stand for 30 min for derivatization. Following, the derivatization reaction was stopped by addition of 10 μL of formic acid. The samples were shaken and placed in autosampler vials for analysis.

*Procedure for glyphosate:*To a 1 mL sample portion, 10 μL of the isotopically labelled internal standard at 100 ng/mL was added. After homogenization, the samples were loaded to the SPE 21 cartridges (Strata SAX, 200 mg) previously conditioned with 1 mL of acetonitrile followed by 1 mL of water. The cartridges were washed with 2 mL of water followed by 2 mL of acetonitrile, and dried under vacuum. The samples were eluted with 1 mL of 200 mM NaCl in 0.1 M HCl into a polypropylene reaction tube and 20 μL 5 M NaOH was added.

The derivatization procedure was performed by adding 500 μL of borate buffer 5 % followed by 500 μL 6.5 mM FMOC-Cl. The tubes were gently homogenized and allowed to stand for 30 min for derivatization. The derivatization reaction was stopped by adding 50 μL formic acid. The samples were shaken and placed in autosampler vials for analysis. The LOQ for glyphosate was 8 μg/kg and for AMPA 25 μg/kg feces.

Wristband – Pesticides collected in wristbands were analysed on an Agilent 6890 N GC with dual 7683 injectors, dual columns, DB-XLB and

DB-17MS columns (Agilent), and dual microelectron capture detectors (μ-ECD) (Donald et al., 2016).

3. Data analyses

3.1. Quality control

Chemical determinations and quality control of analytical data were carried out following EU guidance documents SANTE/2020/12830 and SANTE/11312/2021. Several sets of multi-pesticide calibration standards were prepared for LC-MS/MS-based multi-method, GC–MS/MS, GC-HRMS-based multi-method and glyphosate/AMPA analysis, respectively. Each set of calibration standards was prepared from a mixed solution that combined the reference standards of all compounds that were going to be analysed by the respective analytical method. The calibration standards for LC-MS/MS analysis were prepared in solvent (multi-method: ACN 1 % HAc + Millipore water; glyphosate/AMPA: Millipore water) while the calibration standards for GC-HRMS analysis were matrix-matched. For initial validation, the response's linearity was determined by solvent calibration standards. Selectivity was assessed by analysis of two blank samples. Recovery and repeatability were established by analysis of spiked samples (see SM1) at different levels. The LOQ was defined as the lowest level meeting the criteria for recovery (default 70–120 %) and precision (RSD $\leq$20 %). The LOD was defined as the concentration corresponding to an S/N = 3 for both quantifier and qualifier and was estimated based on the data obtained for the lowest spike level. For quality control during analysis of the samples, the linearity was re-assessed by analysis of a set of solvent-based set of standards. If linearity criteria were met (back-calculated concentrations not deviating >20 %), then the 1-point calibration used for sample quantification was justified in the range of the standards. Each of the analytes was identified according to (i) the retention time and peak shape of the respective reference standard (or of the isotopically labelled internal standard, in the case of glyphosate and AMPA) and (ii) the ion ratio, with ratios between the quantification and confirmation transitions within ±30 % of the average ion ratio of the calibration standards. The response of the GC-HRMS analytes was normalized according to the response of PCB-198, and the glyphosate and AMPA response was normalized according to the response of the isotopically labelled analogues.

In the case of LC-MS/MS analysis, a calibration curve was done with calibration standards (multi-method: 0.1 to 2000 μg/mL, 2 to 43 points depending on the matrix) was injected at the start, middle and end of each sample sequence (SM1). For GC–MS/MS analysis, the calibration curve was done with calibration standards of 0.125 to 50 μg/kg, 2 to 9 points injected at the start and the end of each sequence depending on the matrix considered. For GC-HRMS, a calibration curve of calibration standards (multi-method: 1, 10, and 50 μg/mL for indoor dust samples; 5, 10, and 100 ng/kg to 2000 μg/mL for water samples) was injected at the start and the end of each sequence. For GC–MS analysis, a calibration curve (2, 20 μg/mL for crop; 5, 10, and 100 ng for water, and 1, and 5 μg/kg for wristbands) was injected at the start and the end of each sequence. For blood analysis using LC-MS/MS and GC–MS/MS, the calibration standards are 0.125, 1, and 10 ng/mL.

3.2. Statistical analysis

The correlation analysis as well as the median and frequency distribution of all pesticide data were performed using the R package version 4.2.2. Statistical analyses were carried out by means of the software SPSS 14.0 and Statgraphics Centurion XVII·I for Windows. Pearson correlations were applied to check associations between PPPs in environmental matrices and biological matrices.

3.3. Ranking of the substances

A first ranking was done to select the 20 most frequently detected substances considering DF of each compound in (1) all compartments and all matrices, and (2) all matrices of each compartment. We listed the 20 most frequently detected substances for the following cases: across all matrices, all compartments, and all fields; and across all matrices within each of the three compartments (environment, animals, and humans). A second ranking was done within this list using a prioritization indicator (PI). The PI considers the DF and the MC of each substance, first for one matrix and then for all matrices of the compartment under consideration (environment, animal, and human).

For this purpose, and based on a careful examination of the data, a weighting factor was assigned to each matrix to distinguish it from the others in terms of its ability to reflect exposure to the various substances (Eqs. (1)–(4)). The matrices considered for the environment are: earthworm, indoor air, outdoor dust, crop, soil, sediment, and water; the ones for animals are: wristbands, feces, urine, and blood plasma. The ones for humans are: wristbands, feces, urine, and blood plasma. Earthworms were considered in the environmental compartment because they are highly susceptible to pesticides in soil (Miglani and Bisht, 2019; Liu et al., 2020). For the environment, we have assigned a weighting factor of 2 to the crop and earthworms since they reflect accumulation, while the weighting factor for indoor and outdoor dust, and soil remains 1 as they are primary sources. For the animal and human compartments, we assume that urine reflects the past 6–24 h (Huang et al., 2022b), feces reflect the past 24 h to some days (Rached et al., 2023), and reflect actual internal exposure, whereas wristbands reflect external exposure. Blood is known to act as a target and carrier of pesticides (accumulation) (Doroudian et al., 2022). Therefore, to differentiate between the various exposition and accumulation modes, on one hand and between internal and external exposure on the other hand, we attributed different weighting factors to the DF x MC value of each product in each matrix: 2 for blood plasma, 1 for urine and feces, and 0.5 for wristbands.

Thus, we established the following approach to calculate the *PI* for each compartment.

$$PI_C = \left(\sum_{i}^{n} PI_{C,x}\right)\Big/ n \tag{1}$$

PI_C is the prioritization indicator of the compartment considered (*H* for human, *A* for animal, and *E* for environmental); $PI_{C,x}$ is the prioritization indicator of the matrix *x* of the compartment under consideration, and *n* is the number of the matrices for which the substance was measured; $n = 5$ if the substance is measured in all environmental (indoor dust, outdoor dust, crop, earthworms, and soil) or animal matrices (feces, feed, plasma, urine, and wristbands) and $n = 4$ if the substance is measured in all human matrices (feces, plasma, urine, and wristband).

With

$$PI_{E,x} = (DF_I.MC_I) + (DF_O.MC_O) + (DF_S.MC_S) + (DF_E.Med_E).2 + (DF_C.MC_C).2 \tag{2}$$

$$PI_{A,x} = (DF_F.MC_F) + (DF_U.MC_U) + (DF_P.Med_P).2 + \frac{(DF_f.MC_f)}{2} + \frac{(DF_W.MC_W)}{2} \tag{3}$$

$$PI_{H,x} = (DF_F.MC_F) + (DF_U.MC_U) + (DF_P.MC_P).2 + \frac{(DF_W.MC_W)}{2} \tag{4}$$

DF and the MC of the substance measured, respectively. The subscripts used for DF and MC represent the different matrices (*F* for feces, *U* for urine, *P* for plasma, *W* for wristband, *f* for animal feed, *I* for indoor dust, *O* for outdoor dust, *S* for soil, *E* for earthworms, and *C* for crop/plant).

3.4. Prioritization of the potentially hazardous substances

Once the substances had been ranked according to their PI, we matched their potential effects on the environment (toxicity class) and the health of animals and humans (level of evidence). This evaluation was mostly based on the Pesticide Properties DataBase data (PPDB, see Lewis et al., 2016). The toxicological descriptors, and the endpoints covered in the database, are in line with those required by the European Food Security Agency (EFSA). The data are mostly verified data used for regulatory purposes, and the thresholds considered are consistent with EU regulatory thresholds (PPDB, 2023). Based on the PPDB, 2023, two distinct types of classification were assigned depending on the matrix considered: (1) qualitative class of hazard (low/moderate/high/no data), based on thresholds applied to LC/EC_{50} or NOEC values, and (2) the evidence level for human health endpoints. In this manuscript, we refer to substances as hazardous in the case of confirmed evidence. We compiled qualitative data for the specific compartment-related health issues presented in the PPDB and updated them with the latest scientific literature (SM2). For the environment, we considered earthworms (acute and chronic effects), honeybees (acute and chronic effects), and effects on beneficial insects. For the animal compartment, we considered acute, dietary, and chronic effects in mammals. For the human compartment, we considered carcinogenic, endocrine-disrupting, reproduction/development toxicological, and neurotoxicological effects. For each one of these hazard categories, the PPDB provides one of the following classifications: “yes, known to cause a problem”, “possible, status not identified”, “no, known to not cause a problem”, or “no data”.

Based on this procedure, the substances ranked highest in our analysis (high DF and high MC) and which have a high hazard class or have been linked to human health issue are assumed to be more likely to represent a health hazard.

4. Results

4.1. Analysis of detection frequencies

4.1.1. Detection frequency of substances within each compartment

The 20 substances with the highest DF across all matrices are listed in Table 2. Of the 20 substances listed, nine are not approved in the EU market. There are nine insecticides, including four metabolites; three herbicides; and seven fungicides, including one metabolite. Piperonil butoxide, defined as a biocide, is ranked third.

Six of the substances ranked in Table 2 are also among the 20 most frequently detected substances in each of the three compartments (environment, animals, and humans). These are: DDE p,p’, glyphosate, piperonyl butoxide, tebuconazole, AMPA, and azoxystrobin. Eight substances are among the top 20 in the human and environmental compartments, namely DDE p,p’, hexachlorobenzene, glyphosate, AMPA, tebuconazole, azoxystrobin, boscalid, and piperonyl butoxide (Tables 3, 5), and nine substances are among the top 20 in the human and animal compartments, namely glyphosate, AMPA, DDE p,p’, piperonyl butoxide, cypermethrin, pirimiphos methyl/pirimiphos-methyl DAENPY, tebuconazole, 2,4-D, and azoxystrobin (Tables 4, 5).

4.1.2. Detection frequency of substances across all matrices and compartments

Fig. 1 shows that all of the 20 top frequency substances were detected in indoor dust from both conventional and organic FS. Four substances – DDE p,p’, chlorpyrifos methyl TCPy, boscalid, and chlorpyrifos – were detected in all environmental matrices of both FS. Thirteen substances were detected in soil from both organic and conventional FS, namely DDE p,p’, glyphosate, tebuconazole, azoxystrobin, chlorpyrifos methyl TCPy, fipronil sulfone, AMPA, hexachlorobenzene, boscalid, fludioxonil, propiconazole, metalaxyl (M), and chlorpyrifos. 2,4-D was detected only in soil from conventional FS. In water, all top frequency substances were detected except three: deltamethrin, pirimiphos-methyl, and chlorpyrifos. Thirteen substances were detected in sediments (DDE p,p’, glyphosate, tebuconazole, azoxystrobin, chlorpyrifos methyl TCPy, AMPA, hexachlorobenzene, boscalid, deltamethrin, fludioxonil, cypermethrin, metalaxyl (M), and chlorpyrifos). The substances detected in earthworms from both FS are: DDE p,p’, glyphosate, piperonyl butoxide, azoxystrobin, chlorpyrifos methyl TCPy, fipronil sulfone, AMPA, hexachlorobenzene, boscalid, and chlorpyrifos; four were detected only in earthworms from conventional FS: tebuconazole, propiconazole, 2,4-D, and Metalaxyl (M). Nine substances were detected in crops from both FS: DDE p,p’, tebuconazole, azoxystrobin, chlorpyrifos methyl TCPy, hexachlorobenzene, boscalid, deltamethrin, cypermethrin, metalaxyl (M), and chlorpyrifos. Three were detected only in conventional farms' crops: glyphosate, AMPA, and fludioxonil. Nine substances were detected in outdoor dust from both FS (DDE p,p’, glyphosate, tebuconazole, chlorpyrifos methyl TCPy, AMPA, boscalid, fludioxonil, metalaxyl (M), chlorpyrifos); azoxystrobin and deltamethrin were detected only in

Table 2
Substances detected most frequently across all compartments and matrices, and their detection frequencies. A total of 4609 samples were considered. Compounds are sorted based on percentage of detection.

Substance	Detected overall		Concentration (μg/kg)		MC (μg/kg)		Type & status	
	Number	%	Min	Max	Conv.	Org.	Type	Status
DDE p,p’	1335	48	9.86E-06	4.34E+03	1.1	1.3	Insecticide (M)	NA
Glyphosate	1382	47	2.39E-03	4.95E+04	33.5	33.5	Herbicide	App
Piperonyl butoxide	1056	29	2.35E-04	1.39E+04	9.6	7.9	Other	NA
Tebuconazole	1093	24	1.16E-03	1.73E+03	4.0	1.7	Fungicide	App
Azoxystrobin	837	23	2.88E-03	6.71E+03	11.3	3.1	Fungicide	App
Chlorpyrifos methyl TCPy	1024	23	1.41E-02	3.89E+02	1.2	0.7	Insecticide (M)	NA
Fipronil sulfone	938	21	6.58E-04	5.70E+02	0.5	0.6	Insecticide (M)	NA
AMPA	562	19	1.21E-03	9.79E+03	54.5	3.1	Herbicide	App
Hexachlorobenzene	534	19	4.04E-05	8.55E+01	0.4	0.4	Fungicide	NA
Boscalid	852	19	9.00E-04	6.33E+03	5.1	1.6	Fungicide	App
Deltamethrin	624	17	1.24E-02	1.31E+03	3.1	2.4	Insecticide	App
Fludioxonil	625	17	5.58E-03	1.45E+03	3.6	1.3	Fungicide	App
Fipronil	722	16	4.24E-03	5.18E+03	1.2	1.6	Insecticide	NA
2,4-D	660	15	5.00E-03	5.04E+03	2.3	0.8	Herbicide	App
Propiconazole	536	15	2.46E-03	4.13E+02	3.7	3.7	Fungicide	NA
Pirimiphos methyl	556	13	9.90E-03	8.44E+01	3.3	1.5	Insecticide (M)	App
Cypermethrin	352	13	2.39E-02	1.29E+05	9.4	2.9	Insecticide	App
Metalaxyl (M)	450	12	7.82E-04	3.14E+03	3.7	2.4	Fungicide (M)	App
Propoxur	435	12	5.33E-03	1.41E+04	0.8	0.7	Insecticide	NA
Chlorpyrifos	295	12	1.06E-03	7.14E+03	5.1	1.3	Insecticide	NA

NA: not approved; App: approved; M: metabolite; MC: median concentration; in this Table, undefined FS is not considered in the MC analysis.

Table 3
Substances detected most frequently in the environmental compartment and their detection frequencies, and median concentrations; a total of 890 samples were considered.

Substance	Detected		Detected (%)		Concentration (μg/kg)		MC (μg/kg)		Type & status	
	N	%	Conv.	Org.	Min	Max	Conv.	Org.	Type	Status
DDE p,p'	470	56	25	22	9.86E-06	4.34E+03	7.43	6.90	Insecticide (M)	NA
Hexachlorobenzene	297	36	15	13	4.04E-05	8.55E+01	0.59	0.70	Fungicide	NA
Glyphosate	278	34	16	7	2.39E-03	4.95E+04	723.50	198.42	Herbicide	App
Lindane gamma	201	30	11	9	9.58E-05	1.60E+03	2.16	1.59	Insecticide	NA
AMPA	233	29	14	5	1.21E-03	9.79E+03	345.99	43.16	Herbicide	App
Dieldrin	239	29	11	9	1.48E-05	3.20E+03	0.91	0.71	Insecticide	NA
Azoxystrobin	237	28	17	8	2.88E-03	6.71E+03	20.26	6.67	Fungicide	App
Tebuconazole	225	27	16	8	1.16E-03	1.18E+03	22.95	11.06	Fungicide	App
DDD p,p'	213	26	10	8	1.52E-05	1.15E+03	3.45	4.33	Insecticide (M)	NA
Fluopyram	203	24	13	8	1.99E-03	7.76E+02	6.21	2.56	Fungicide	App
Metalaxyl (M)	201	24	14	8	7.82E-04	3.14E+03	8.98	3.10	Fungicide	App
Imidacloprid	199	24	14	10	2.73E-01	6.93E+03	32.28	23.31	Insecticide	App
Difenoconazole	192	23	15	7	3.36E-03	1.08E+04	11.15	4.24	Fungicide	App
Acetamiprid	189	23	15	7	1.25E-02	8.20E+03	15.13	1.59	Insecticide	App
Boscalid	189	23	14	7	1.84E-02	6.33E+03	29.10	12.62	Fungicide	App
Dimethomorph	180	22	12	7	3.32E-03	5.89E+03	15.88	2.89	Fungicide	App
Permethrin	141	21	12	8	1.95E-03	2.06E+05	521.24	424.73	Insecticide	NA
Chlorpyrifos	173	21	13	7	1.06E-03	7.14E+03	7.86	3.02	Insecticide	NA
Dicamba	48	21	12	9	8.11E-01	7.77E+02	15.98	19.70	Herbicide	App
Piperonyl butoxide	166	20	9	8	2.35E-04	1.39E+04	161.06	142.84	Other	NA

NA: not approved; App: approved; M: metabolite; MC: median concentration.

Table 4
Substances detected most frequently in the animal compartment, their detection frequencies, and median concentrations; a total of 816 samples were considered.

Substance	Detected		Detected (%)		Concentration (μg/kg)		MC (μg/kg)		Type & status	
	N	%	Conv.	Org.	Min	Max	Conv.	Org.	Type	Status
Glyphosate	276	67	47	21	8.97E-02	2.37E+03	30.18	9.03	Herbicide	App
AMPA	131	32	26	6	1.33E-01	7.30E+02	8.24	0.39	Herbicide (M)	App
DDE p,p'	148	29	17	12	3.00E-02	5.34E+01	0.23	0.19	Insecticide (M)	NA
Quinmerac	30	23	11	12	6.56E-01	4.96E+01	2.69	6.15	Herbicide	App
Piperonyl butoxide	144	21	14	7	5.94E-02	3.01E+03	3.87	2.41	Other	NA
Pendimethalin	127	18	13	6	5.00E-02	4.39E+02	3.09	2.51	Herbicide	App
Chlorpyrifos	49	17	11	6	1.21E-01	3.59E+01	0.97	0.32	Insecticide	NA
Cypermethrin	86	17	11	6	2.91E-01	8.06E+02	3.03	2.14	Insecticide	App
Bifenthrin	43	15	10	6	1.60E-01	4.03E+01	0.58	0.64	Insecticide	NA
Pirimiphos methyl	122	15	11	4	1.31E-01	2.35E+02	3.93	1.49	Insecticide	App
Tebuconazole	115	14	9	5	1.10E-02	6.21E+02	1.22	0.86	Fungicide	App
2,4-D	115	14	9	5	1.53E-01	8.19E+01	2.45	2.00	Herbicide	App
DDD p,p'	38	14	6	7	1.25E-01	2.41E+00	0.29	0.28	Insecticide (M)	NA
MCPA	98	12	8	4	7.60E-03	6.94E+02	1.80	0.63	Herbicide	App
Bromoxynil	88	11	6	5	5.00E-03	3.19E+01	2.06	2.82	Herbicide	NA
Terbuthylazine	68	10	7	3	2.10E-01	8.11E+00	1.22	0.58	Herbicide	App
Prothioconazole desthio	59	10	5	4	1.09E+00	1.66E+01	2.61	1.92	Fungicide (M)	App
Fluopyram	64	9	6	3	6.21E-02	1.41E+01	0.67	0.52	Fungicide	App
DDD o,p'	26	9	4	6	1.04E-01	2.18E+00	0.22	0.22	Insecticide (M)	NA
Azoxystrobin	63	9	6	3	3.76E-02	2.66E+01	1.07	1.48	Fungicide	App

NA: not approved; App: approved; M: metabolite; MC: median concentration.

samples from conventional FS, while hexachlorobenzene and cypermethrin were detected only in samples from organic FS. More details on the frequency per substance and per matrix are given in SM3.

In the animal compartment, the substances detected in different matrices are: DDE p,p' was detected in feces, feed, and blood plasma from both conventional and organic FS. Glyphosate was detected in feces, feed, and urine from both FS. Piperonyl butoxide was detected in feces, feed, blood plasma, and wristbands from both FS. Tebuconazole was detected in plasma and wristbands from both FS. Azoxystrobin was detected in feces, feed, and wristbands from both FS. Chlorpyrifos methyl TCPy was detected in urine and wristbands from both FS and in feces from conventional farms. Fipronil sulfone was detected in feces and wristbands from both FS. AMPA was detected in feces, feed, and urine from both FS and in wristbands from conventional farms. Hexachlorobenzene was detected in feces and plasma from both FS and in feed from conventional farms. Boscalid was detected in urine and wristbands from both FS and in plasma from conventional farms. Deltamethrin was detected in feces and feed from both FS and in plasma from organic farms. Fludioxonil was detected in wristbands from both FS. Fipronil was detected in feces, urine, and wristbands from both FS and in plasma from organic farms. Propiconazole was detected in feed, plasma, and wristbands from both FS. 2,4-D was detected in all animal matrices from both FS. Pirimiphos-methyl was detected in feed, urine, and wristbands from both FS. Cypermethrin was detected in feces and feed from both FS and in plasma from conventional farms. Metalaxyl (M) was detected in feces and wristbands from both FS and in feed from conventional farms. Propoxur was detected in wristbands from both FS and in feed and plasma from conventional FS. Chlorpyrifos was detected in feces and feed from both FS.

In the human compartment, looking at farmers, thirteen substances from the list of 20 were detected in the wristbands of both conventional and organic farmers: piperonyl butoxide, tebuconazole, azoxystrobin, chlorpyrifos-methyl TCPy, fipronil sulfone, boscalid, fludioxonil, fipronil, propiconazole, 2,4-D, pirimiphos-methyl, metalaxyl (M), propoxur,

Table 5
Substances detected most frequently in the human compartment and their detection frequencies, and median concentrations; a total of 2903 samples were considered.

Substance	Detected		Detected (%)		Concentration (µg/kg)		MC (µg/kg)		Type & status	
	N	%	Conv.	Org.	Min	Max	Conv.	Org.	Type	Status
DDE p,p'	717	50	9	9	2.00E-02	1.16E+01	0.54	0.42	Insecticide (M)	NA
Glyphosate	828	49	9	7	5.24E-02	2.06E+03	12.32	14.23	Herbicide	App
Piperonyl butoxide	746	35	6	6	9.00E-04	7.86E+02	4.56	3.05	Other	NA
Chlorpyrifos-methyl TCPy	849	29	5	5	1.41E-02	1.96E+01	0.83	0.59	Insecticide (M)	NA
Fipronil sulfone	760	26	4	5	5.90E-03	8.47E+01	0.26	0.37	Insecticide (M)	NA
Tebuconazole	753	26	6	5	4.40E-03	1.73E+03	1.98	1.04	Fungicide	App
Azoxystrobin	537	25	5	4	5.00E-01	3.97E+02	8.47	2.13	Fungicide	App
Deltamethrin	468	21	4	3	5.23E-02	5.00E+01	0.98	0.87	Insecticide	App
Fludioxonil	451	21	4	3	3.54E-02	3.41E+02	2.47	0.74	Fungicide	App
Boscalid	595	21	4	3	9.50E-03	3.15E+03	1.81	0.73	Fungicide	App
Fipronil	540	19	3	3	5.00E-02	6.78E+02	0.52	0.62	Insecticide	NA
Propiconazole	372	17	3	4	1.58E-02	3.15E+02	1.79	1.99	Fungicide	NA
Pirimiphos-methyl DAEMPY	459	16	3	3	8.37E-02	8.44E+01	0.88	1.75	Insecticide (M)	App
2,4-D	457	16	3	3	5.00E-03	3.67E+02	0.43	0.31	Herbicide	App
Hexachlorobenzene	225	16	3	4	5.00E-02	6.98E+00	0.24	0.25	Fungicide	NA
Propoxur	291	14	3	2	2.12E-02	1.81E+03	0.30	0.39	Insecticide	NA
Cypermethrin	186	13	2	3	5.00E-02	5.78E+01	1.56	1.94	Insecticide	App
AMPA	198	12	2	2	1.05E-01	1.71E+02	0.45	0.38	Herbicide	App
Lambda-cyhalothrin	167	12	2	2	5.00E-02	1.00E+02	0.97	1.26	Insecticide	App
Pyrimethanil	239	11	2	2	7.70E-03	1.17E+03	1.23	0.81	Fungicide	App

NA: not approved; App: approved; M: metabolite; MC: median concentration.

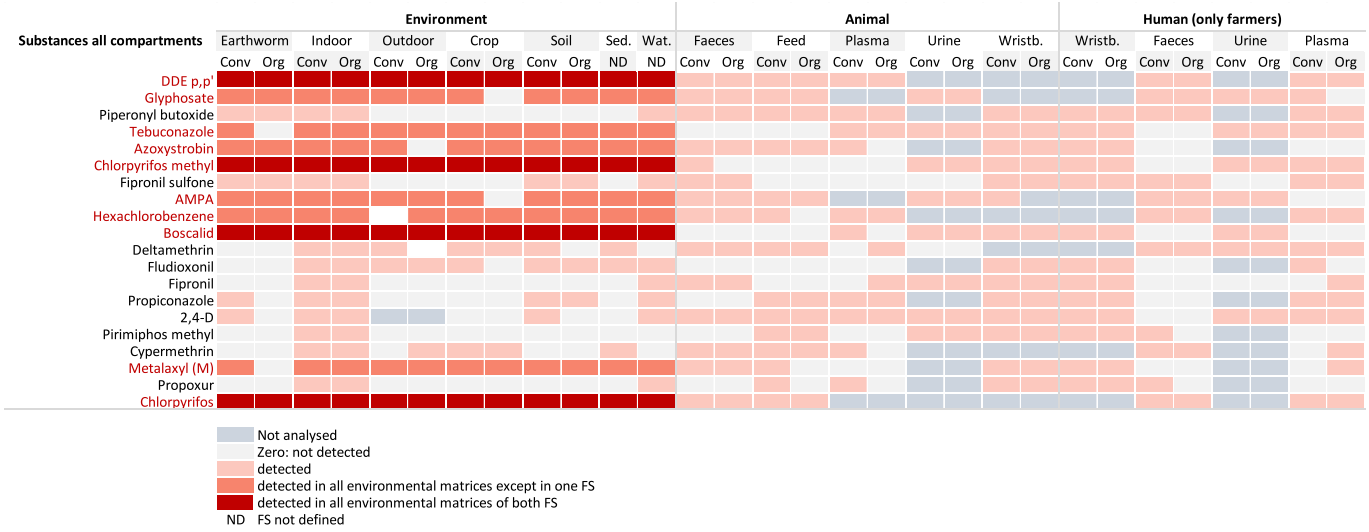

Fig. 1. Presence or absence in each matrix of each compartment of each of the twenty substances detected most frequently across all compartments and matrices (see Table 2).

and difenoconazole. The other substances were not analysed in wristbands. Nine substances were also detected in feces from both farmer groups: DDE p,p', glyphosate, piperonyl butoxide, fipronil sulfone, AMPA, hexachlorobenzene, deltamethrin, cypermethrin, and chlorpyrifos. Pirimiphos-methyl and propoxur were detected only in conventional farmers' feces. The other substances were not detected in farmers' feces (which were analysed for all substances). Seven substances were detected in urine from both farmer groups: glyphosate, tebuconazole, chlorpyrifos-methyl TCPy, AMPA, boscalid, deltamethrin, and 2,4-D. Fipronil and fipronil sulfone were not detected in farmers' urine. Urine was not analysed for the rest of the substances.

Ten substances were detected in blood plasma from both farmer groups: DDE p,p', piperonyl butoxide, tebuconazole, chlorpyrifos-methyl TCPy, fipronil sulfone, hexachlorobenzene, deltamethrin, propiconazole, 2,4-D, and chlorpyrifos. Glyphosate and fludioxonil were detected only in plasma from conventional farmers, whereas fipronil, cypermethrin, and metalaxyl (M) were detected only in plasma from organic farmers.

4.1.3. Comparison between detection frequencies on conventional and organic farms

A comparative analysis of DF on conventional and organic farms was carried out for each compartment, considering the top 20 substances (Fig. 2–4).

Regarding the environmental compartment, we observed that all substances had a much higher DF in conventional FS compared to in organic FS. Environmental matrices whose farming system was not defined exhibited relatively high DF for certain substances, such as glyphosate, lindane gamma, AMPA, DDE p,p', hexachlorobenzene, and dieldrin (Fig. 2).

In the animal compartment, DF were generally higher on conventional farms than on organic farms, with the exception of Quinmerac (Fig. 3). Conversely, larger shares of samples from conventional farms were free of the substances, whereas organic farms had smaller shares of clean samples.

In the human compartment, 11 substances had a higher DF on conventional farms than on organic farms (Fig. 4). The DF of DDE p,p' and

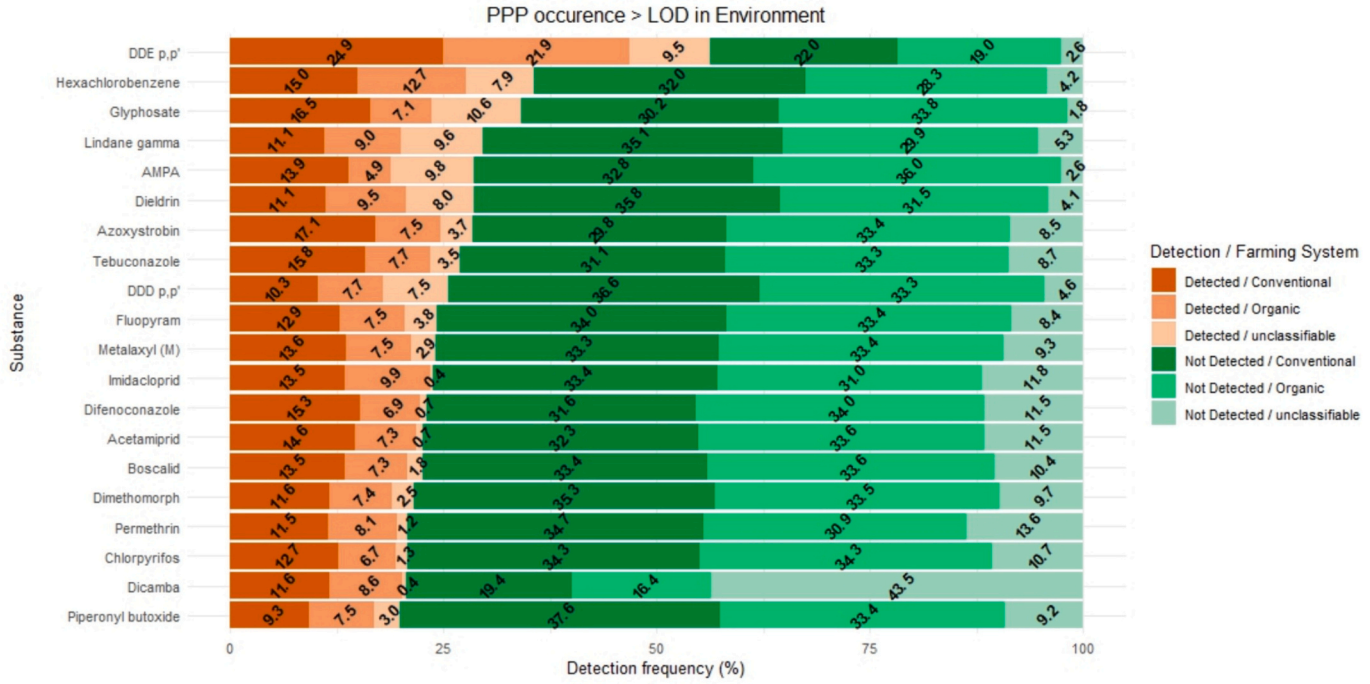

Fig. 2. Detection frequencies in percent across all matrices of the 20 substances most frequently detected in the environmental compartment. PPP, plant protection product; LOD, level of detection; FS, farming system.

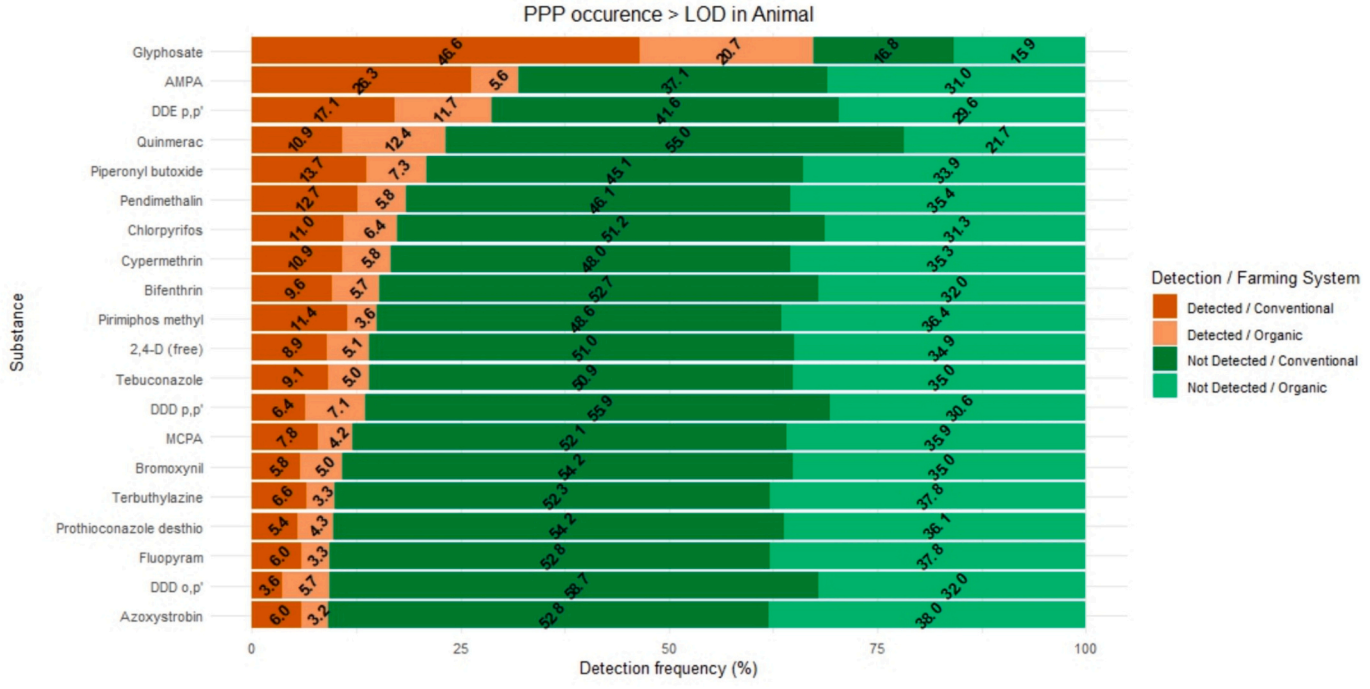

Fig. 3. Detection frequencies in percent across all matrices of the 20 substances most frequently detected in the animal compartment. PPP, plant protection product; LOD, level of detection; FS, farming system.

AMPA were the same in both FS. Piperonyl butoxide, fipronil sulphone, fipronil, propiconazole, hexachlorobenzene, cypermethrin, and lambda-cyhalothrin were detected more frequently on organic farms than on conventional farms. Relatively high DF were recorded in unclassified FS (neighbors and consumers). Between 35 and 60 % of the samples from unclassified FS were free of the various substances.

4.2. Analysis of median concentrations

In the environmental compartment, 17 out of the top 20 substances have a higher MC in conventional FS than in organic FS (Fig. 5). For eleven of these substances, the difference was significant, namely for glyphosate, AMPA, azoxystrobin, tebuconazole, fluopyram, metalaxyl-M, difenoconazole, acetamiprid, boscalid, dimethomorph, and

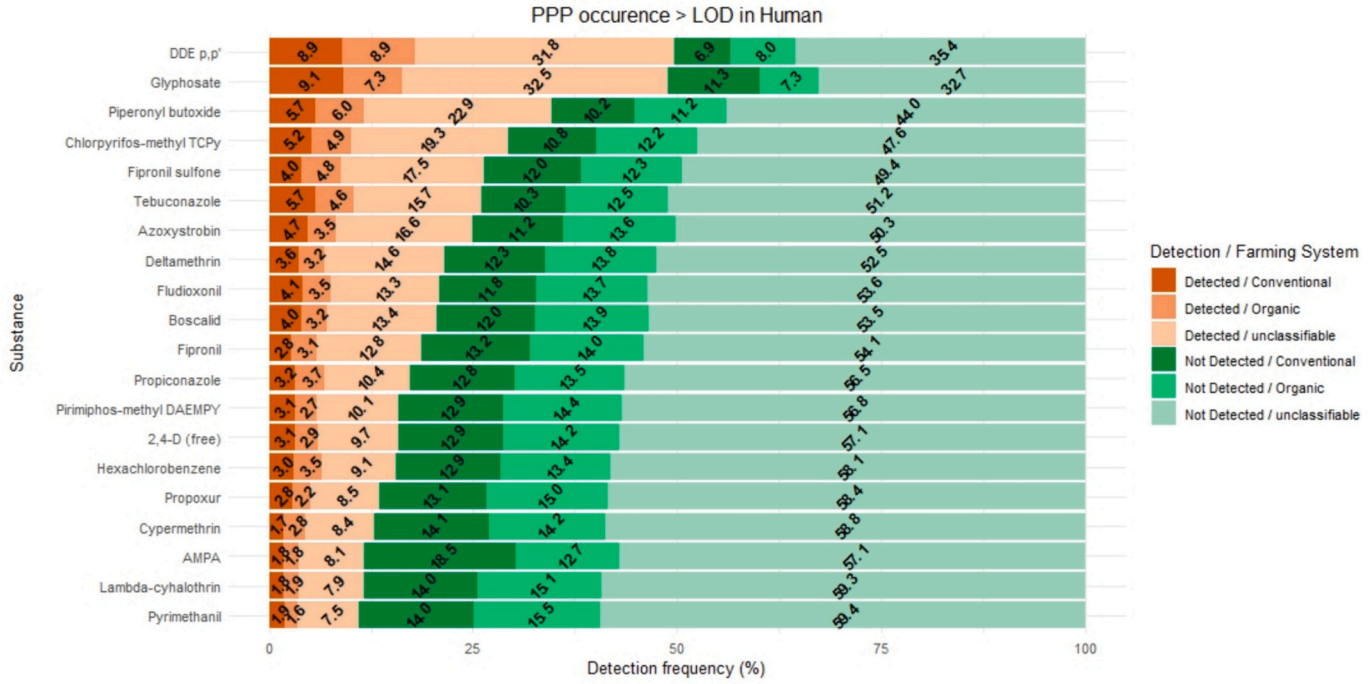

Fig. 4. Detection frequencies in percent across all matrices of the 20 substances most frequently detected in the human compartment. PPP, plant protection product; LOD, level of detection; FS, farming system.

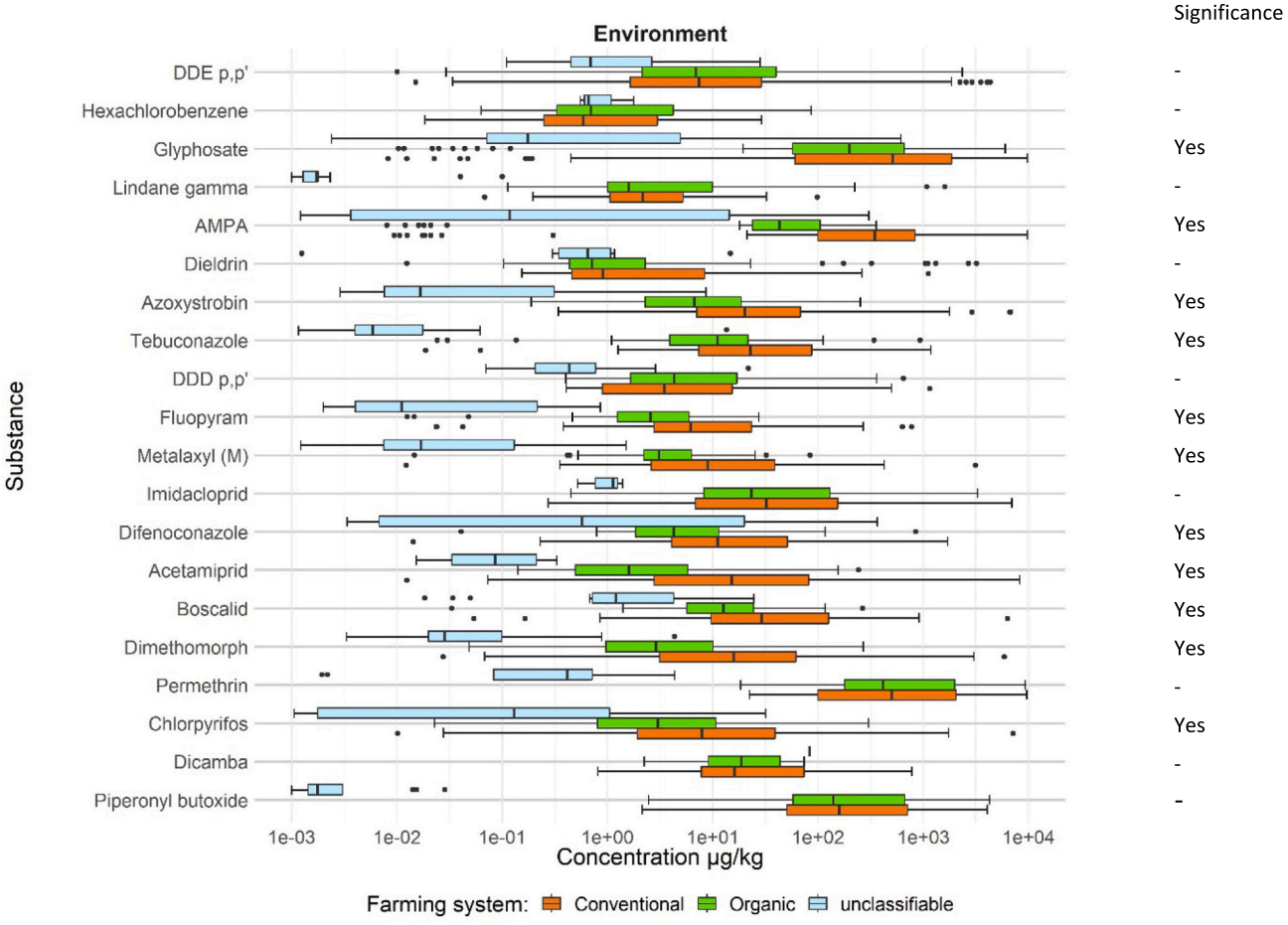

Fig. 5. Comparison between farming systems of the median concentrations of the 20 substances most frequently detected across all matrices of the environmental compartment. The farming system was left undefined for water and sediment samples.

chlorpyrifos. SM4 provides the concentration of each substance calculated per matrix and compartment.

In the animal compartment, sixteen out of 20 substances have a higher MC in conventional FS than in organic FS (Fig. 6). Among these, the difference was significant for the following seven substances: glyphosate, pendimethalin, pirimiphos methyl, tebuconazole, MCPA, terbuthylazine, and prothioconazole desthio.

In the human compartment, ten substances had a higher MC in conventional FS than in organic FS (Fig. 7). Among these, MC of six substances measured in samples from conventional farmers significantly exceeded that of organic farmers: chlorpyrifos-methyl TCPy, tebuconazole, azoxystrobin, fludioxonil, boscalid, and 2,4-D. By contrast, in the case of pirimiphos-methyl DAEMPY and propoxur, the MC measured in samples from organic farmers significantly exceeded that of conventional farmers.

Overall, we observe that the cases where there is a significant difference between conventional and organic FS follow the pattern environmental > animal > human. In the case of tebuconazole, the MC in conventional FS significantly exceeded that in organic FS in all three compartments.

4.3. Hazard profile of the detected residues

4.3.1. Hazard to environment species

In the environmental compartment, in conventional FS, the 20 most frequently detected and highly ranked substances are: glyphosate, AMPA, boscalid, permethrin, tebuconazole, piperonyl butoxide, acetamiprid, dieldrin, difenoconazole, azoxystrobin, imidacloprid, dimethomorph, DDE p,p', fluopyram, metalaxyl (M), chlorpyrifos, lindane, DDD p,p', dicamba, and hexachlorobenzene (Fig. 8A). Acetamiprid is highly hazardous for earthworms (acute) and chlorpyrifos for earthworms (chronic), honeybees (acute, oral acute, chronic), and for beneficial insects. Three substances are hazardous for honeybees (acute). Nine other substances are hazardous for beneficial insects (glyphosate, boscalid, azoxystrobin, acetamiprid, difenoconazole, fluopyram, dicamba, chlorpyrifos, and dimethomorph).

In organic FS, among the highly ranked substances, eight are detected in all matrices: dieldrin, boscalid, DDE p,p', difenoconazole, fluopyram, chlorpyrifos, dimethomorph, and hexachlorobenzene (Fig. 8B). Of the nine most hazardous substances for beneficial insects, five of them are detected in all matrices (boscalid, difenoconazole, dimethomorph, fluopyram, acetamiprid, and chlorpyrifos).

4.3.2. Hazard to animals

In the animal compartment, looking at conventional FS, the 20 most frequently detected and highly ranked substances are: glyphosate, AMPA, DDE p,p', pirimiphos methyl, cypermethrin, quinmerac, 2,4-D, piperonyl butoxide, MCPA, terbuthylazine, chlorpyrifos, bromoxynil, bifenthrin, pendimethalin, DDD p,p', azoxystrobin, tebuconazole, prothioconazole desthio, fluopyram, and DDD o,p'. Nine of them were detected in animal blood plasma: piperonyl butoxide, cypermethrin, 2,4-D, pendimethalin, MCPA, bromoxynil, tebuconazole, DDE p,p', and fluopyram (Fig. 9A). MCPA was detected in all matrices, including blood plasma. Five substances were detected in three matrices, with two of them present in blood plasma; and nine substances were detected in two matrices, with two of them present in blood plasma. Among the 20 substances, two are hazardous for mammals (acute); thirteen are hazardous for mammals (dietary), with seven of these detected in blood

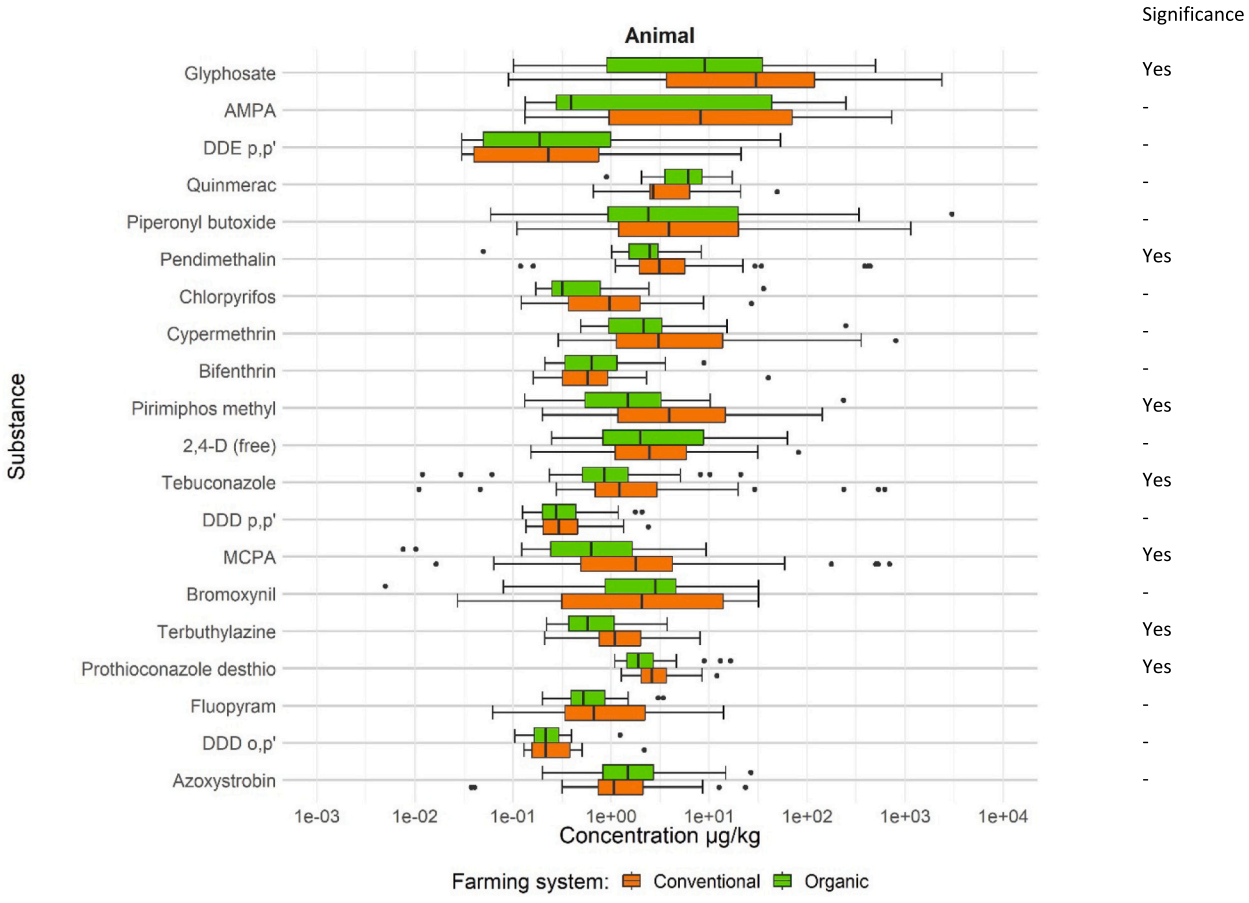

Fig. 6. Comparison between farming systems of the median concentrations of the 20 substances most frequently detected across all matrices of the animal compartment. The farming system was left undefined for water and sediment samples.

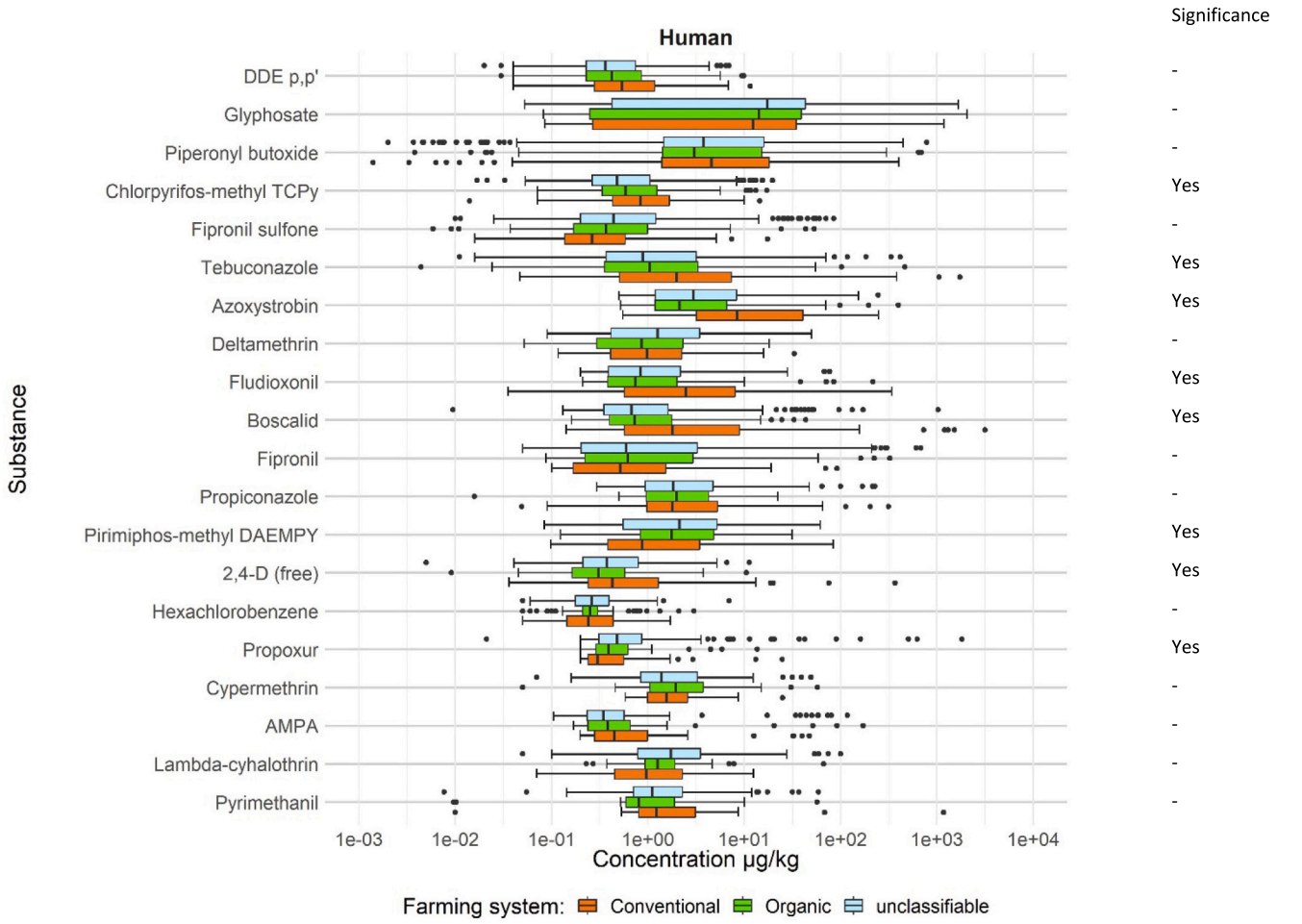

Fig. 7. Comparison between farming systems of the median concentrations of the 20 substances most frequently detected across all matrices of the human compartment. The farming system was left undefined for water and sediment samples.

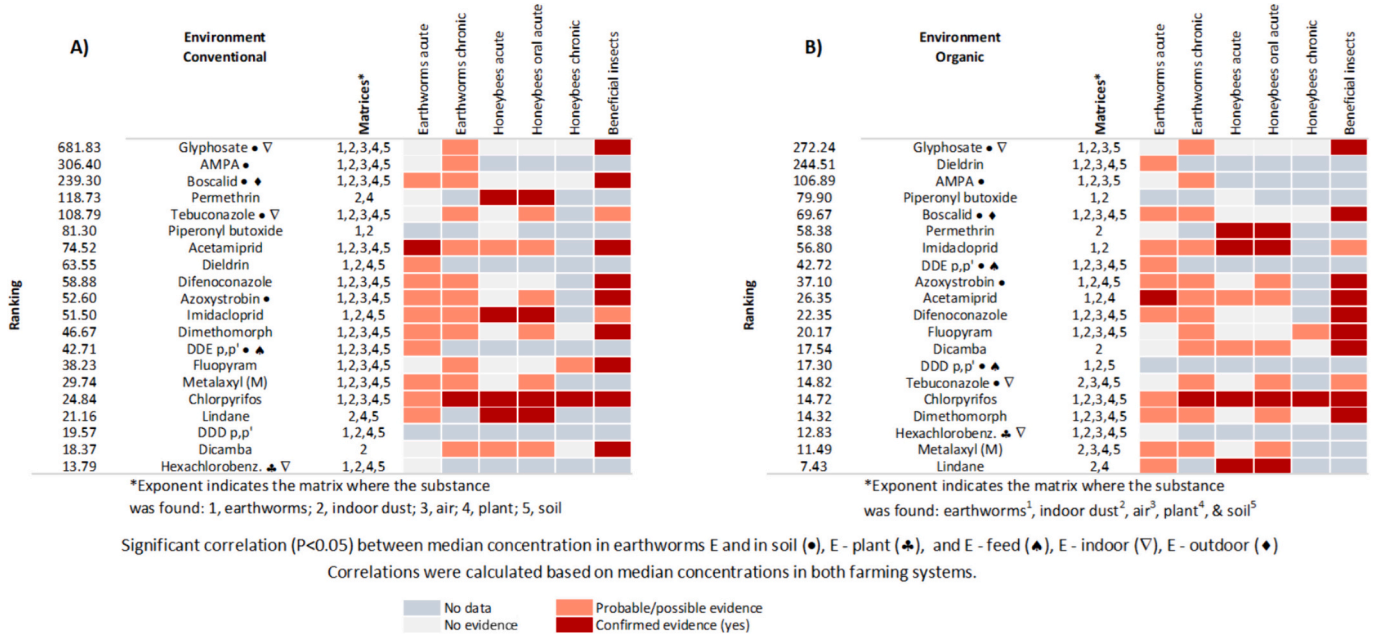

Fig. 8. The 20 substances most frequently detected in the environmental compartment, by farming system: (A) conventional, (B) organic. The figures given in the ranking column represent DF x MC. Cell colors represent the level of evidence according to the PPDB: red, confirmed evidence (yes); orange, possible evidence; green, no evidence; grey, no data available.

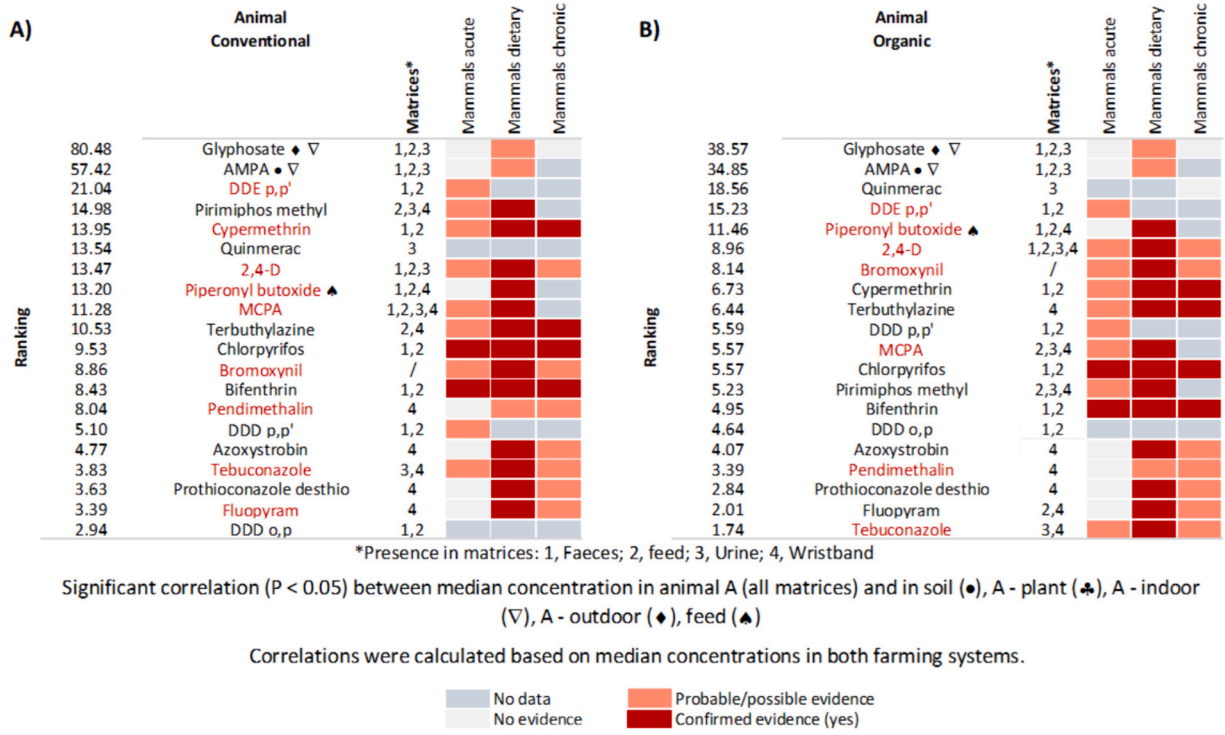

Fig. 9. The 20 substances most frequently detected in the animal compartment, by farming system: (A) conventional, (B) organic. Substances shown in red were detected in animal blood plasma. The figures given in the ranking column represent DF x MC. Cell colors represent the level of evidence according to the PPDB: red, confirmed evidence (yes); orange, possible evidence; green, no evidence; grey, no data available; bromoxynil was detected only in blood plasma.

plasma; and 4 are hazardous for mammals (chronic).

In organic FS, seven of the 20 most frequently detected and highly ranked substances were detected in blood plasma: DDE p,p', piperonyl butoxide, 2,4-D, bromoxynil, MCPA, pendimethalin, and tebuconazole. 2,4-D was detected in all matrices. Five substances were detected in three matrices, with two of them present in plasma (deltamethrin,

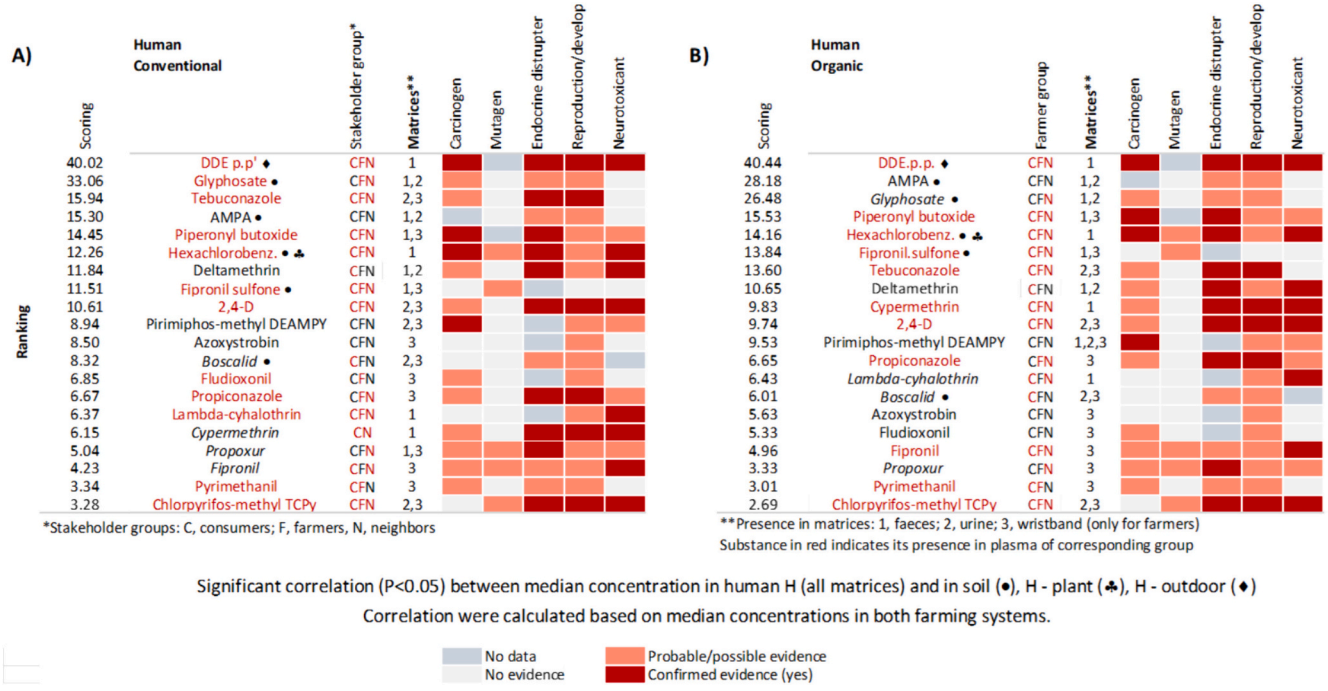

Fig. 10. The 20 substances most frequently detected in the human compartment, by farming system: (A) conventional, (B) organic. Substances shown in red were detected in the respective groups' blood plasma; those shown in black italic were detected in the blood plasma only of consumers and/or neighbors. The figures given in the ranking column represent DF x MC. Cell colors represent the level of evidence according to the PPDB: red, confirmed evidence (yes); orange, possible evidence; green, no evidence; grey, no data available.

tebuconazole). Bromoxynil was not detected in any other matrices apart from blood plasma in either FS. Among the 20 substances, two are hazardous for mammals (acute). Five of those detected in animal blood plasma in organic FS (against seven in animal blood plasma in conventional FS) are hazardous for mammals (dietary), namely piperonyl butoxide, 2,4-D, bromoxynil, MCPA, and tebuconazole; and no data exists for DDD o,p' (Fig. 9B).

4.3.3. Hazard to humans

In the human compartment, in conventional FS, the 20 most frequently detected and highly ranked substances are: DDE p,p', glyphosate, tebuconazole, AMPA, piperonyl butoxide, hexachlorobenzene, deltamethrin, fipronil sulfone, 2,4-D, pirimiphos-methyl, azoxystrobin, boscalid, fludioxonil, propiconazole, lambda-cyhalothrin, cypermethrin, propoxur, fipronil, pyrimethanil, and chlorpyrifos-methyl TCPy (Fig. 10A). Twelve of them are present in conventional farmers' blood plasma, namely DDE p,p', glyphosate, tebuconazole, piperonyl butoxide, hexachlorobenzene, fipronil sulfone, 2,4-D, fludioxonil, propiconazole, lambda-cyhalothrin, pyrimethanil, and chlorpyrifos-methyl TCPy, while five – deltamethrin, boscalid, cypermethrin, propoxur, and fipronil – are present only in the blood plasma of the other stakeholder groups, that is, neighbors and/or consumers. Among the 20 substances, four are hazardous with regard to cancer: DDE p,p' piperonil butoxide, hexachlorobenzene, and pirimiphos methyl, and ten are classed as probably carcinogen (glyphosate, tebuconazole, deltamethrin, 2.4-D, fludioxonil, propiconazole, cypermethrin, propoxur, fipronil, and pyrimethanil); ten – DDE p,p, tebuconazole, piperonyl butoxide, hexachlorobenzene, deltamethrin, 2,4-D, propiconazole, cypermethrin, propoxur, and chlorpyrifos methyl TCPy – are hazardous in terms of endocrine disruption; six – DDE p,p', tebuconazole, 2,4-D, Propiconazole, cypermethrin, and chlorpyrifos metabolite TCPy – are hazardous regarding reproduction/development; and eight are neurotoxicants, namely DDE p,p', hexachlorobenzene, deltamethrin, 2,4-D, lambda-cyhalothrin, cypermethrin, fipronil, and chlorpyrifos metabolite TCPy.

In organic FS, eleven substances were detected in farmers' blood plasma: DDE p,p', Piperonyl butoxide, Hexachlorobenzene, fipronil sulfone, tebuconazole, cypermethrin, 2,4-D, Propiconazole, fipronil, Pyrimethanil, and chlorpyrifos-methyl TCPy (Fig. 10B). Fludioxonil, lambda-cyhalothrin, and glyphosate, were detected in the blood plasma of conventional farmers, but not in the blood plasma of organic farmers. Conversely, fipronil and cypermethrin were detected only in the blood plasma of organic farmers.

4.4. Correlations between expected linked matrices

AMPA and glyphosate concentrations show the highest number of significant correlations ($P < 0.05$) between matrices. The other significant correlations may indicate that the correlated matrices have commons sources of pollution having high DF. A significant correlation ($P < 0.05$) between concentrations in soil and earthworms was observed for 7 substances: DDE p,p', glyphosate, tebuconazole, azoxystrobin, fipronil sulfone, AMPA, and boscalid. Concentrations in plants are significantly correlated with those in animal blood plasma for azoxystrobin, and with those in earthworms for hexachlorobenzene. Feed concentrations are significantly correlated with those in animal feces for piperonil butoxide. Indoor dust concentrations are significantly correlated with those in earthworms for tebuconazole and hexachlorobenzene, and those in animal blood plasma for hexachlorobenzene, attesting to a probable common source of pollution. The results of the analysis of statistical correlations between concentrations in environmental and animal matrices are shown in SM5-A.

The correlation between environment and human highlights the main findings below. A significant correlation was observed between the concentration of DDE p,p' in outdoor dust and farmer feces (see also Fig. 10). Additionally, significant correlations were observed between the concentrations of several substances detected in soil and in human matrices. While this correlation does not likely indicate that soil is the source of uptake for humans, it may indicate that the concentrations in these matrices might have common sources to which they are exposed via the same pathways. The substances are: fipronil sulfone (soil – farmer feces, $P < 0.05$); AMPA (soil – farmer feces, $P < 0.1$; soil – farmer urine, $P < 0.05$; and soil – neighbor urine, $P < 0.05$), hexachlorobenzene (soil – farmer feces, $P < 0.1$; soil – neighbor feces, $P < 0.05$); boscalid (soil – neighbor urine, $P < 0.05$). In only one case – hexachlorobenzene – plant concentrations were significantly correlated with those in neighbors' feces ($P < 0.05$). This probably reflects its persistence and occurrence in many matrices subject to a common source. The different numbers of analytes and sampling schemes across matrices – i.e. that some substances were measured for some matrices but not for others – hamper further statistical analyses. SM5-B shows the correlations between concentrations in environmental and human matrices.

5. Discussion

5.1. Occurrence of pesticide residues per FS

This study shows that the difference between conventional and organic FS is significant in terms of DF and MC in the environmental compartment and, to some extent, in the animal and human compartments. The ranking of substances according to the indicator established for this purpose shows that on average, organic farmers had a slightly lower number of substances found in their blood plasma (11 out of 20 substances) than conventional farmers (12 out of 20 substances). This difference in favor of organic FS is contrasted by another fact. If we look closely at the hazard ranking of substances in the two systems (Fig. 10), eleven substances have a higher ranking (higher PI) in conventional FS than in organic FS (glyphosate, tebuconazole, deltamethrin, 2,4-D, azoxystrobin, boscalid, fludioxonil, propiconazole, propoxur, pyrimethanil, and chlorpyrifos-methyl TCPy) and conversely, nine substances rank higher in organic FS than in conventional FS (DDE p,p', AMPA, piperonyl butoxide, hexachlorobenzene, fipronil sulfone, cypermethrin, pirimiphos-methyl DAEMPY, lambda-cyhalothrin, and fipronil). The high PI of the substances detected in humans associated with organic FS compared to humans associated with conventional FS can be explained by the following observations.

- DDE p,p' had a slightly higher DF in farmer plasma from organic FS (51 μg/kg) than from conventional FS (49 μg/kg).
- Cypermethrin and fipronil were detected only in human blood plasma from organic FS.
- Lambda-cyhalothrin, although only detected in human blood plasma from conventional FS, has a higher ranking in organic FS due to its high value in human feces from organic FS.
- Fipronil sulfone had a higher DF and MC in human blood plasma from organic FS (11.2 % and 0.28 μg/kg) than in that from conventional FS (9.54 % and 0.15 μg/kg).
- Pirimiphos-methyl DEAMPY, in addition to its presence in human urine in comparable amounts in both FS, was detected only in human feces from organic FS (5.2 μg/kg).
- Hexachlorobenzene has a higher DF in human blood plasma from organic FS (6.2 μg/kg) than in that from conventional FS (5.8 μg/kg).

It is worth noting that glyphosate, fludioxonil, and lambda-cyhalothrin were detected only in human blood plasma from conventional FS, while cypermethrin and fipronil were detected only in blood plasma from organic FS. Apart from the fact that piperonyl butoxide has a higher PI in organic than in conventional FS, its occurrence is not only related to agriculture. It has a very wide range of uses in humans, animals, birds, and plants, as well as in food storage, in addition to its classical use in household and industrial pest control (Tozzi, 1999).

More specifically, when looking at the MD of glyphosate and AMPA,

their values in the environmental compartment are 4 and 8 times higher on conventional farms than on organic farms, respectively (735.5 vs. 198.4 μg/kg for glyphosate and 346 vs. 43 μg/kg for AMPA) (Table 3). However, in the human compartment, this difference is significantly reduced or reversed. The MC of glyphosate is 12.3 μg/kg on conventional farms and 14.2 μg/kg on organic farms. The MC of AMPA is 0.45 μg/kg on conventional farms and 0.38 μg/kg on organic farms (see Table 5). These results are surprising considering that the MD of indoor dust is roughly 9 and 3 times higher on conventional than organic farms for glyphosate (2450 vs. 275 μg/kg) and AMPA (349 vs. 129 μg/kg), respectively (data not shown).

The above considerations attest to a wide range of sources of contamination in addition to agriculture, such as conservation of industrial goods, road and railroad maintenance, private gardening, forestry, or human and veterinary medicine (e.g. Schleiffer and Speiser, 2022).

In fact, among the 20 substances ranked for humans in our study, the eight substances not approved for agricultural use are used for different other purposes: five (DDE p,p', piperonil butoxide, chlorpyrifos-methyl TCPy, fipronil sulphone, and propoxur) are used to manufacture medicines, while the three others (fipronil, propiconazole, and hexachlorobenzene) are used for a variety of purposes, such as manufacturing construction materials, therapeutic purposes (in the case of fipronil), or to kill or inhibit the growth of fungi on wood, plastics, and in swimming pools (propiconazole and hexachlorobenzene). Concerning the twelve approved substances, in addition to glyphosate and its key metabolite AMPA, which are still extensively used in agriculture, ten are used for other purposes besides agriculture: azoxystrobin as a fungicide on golf courses; fludioxonil, boscalid, and cypermethrin in drugs and medications; tebuconazole, pirimiphos-methyl, and pyrimethanil in industrial processes; and 2,4-D and lambda-cyhalothrin in-home use products and other commercial products (National Library of Medicine, PucChem). More details on the use of the pesticide residues per compartment are given in SM4).

5.2. Widespread contamination and its consequences

Most of the correlations observed between matrices concern the most frequently detected substances (SM5). For example, a correlation between concentrations in soil and earthworms concerns 7 substances (with the exception of fipronil sulphone) that are detected in practically all environmental matrices (Fig. 1). A significant correlation between soil and human matrices was observed for fipronil sulfone, AMPA, hexachlorobenzene, and boscalid. Although this association is not obvious because of the lack of detailed investigations, a link between soil and crops was demonstrated in some studies (Wang et al., 2021), and others addressed the risk these crops may pose to humans if their uptake exceeds the threshold values (EFSA, 2022a, b). Wang et al., 2021 showed that all tested pesticides found in soil were taken up by maize, with accumulation amounts of 27.73, 17.75, 18.96, 12.56, 10.66, and 2.13 μg for imidacloprid, acetamiprid, tricyclazole, azoxystrobin, tebuconazole, and difenoconazole after 14 d, respectively. They determined that uptake, accumulation, and translocation of pesticides in soil by maize are governed by their physicochemical properties (Wang et al., 2021).

The wide occurrence of pesticides in the environment is demonstrated by their DF in different environmental matrices such as soil, water, and air (Kruse-Plaß et al., 2021; Mohaupt et al., 2020; Silva et al., 2019) and the occurrence of pesticides in non-target plants (Duffner et al., 2020; Qi et al., 2020; Zioga et al., 2023). As shown in this study, all substances ranked in the list of the 20 most frequently detected ones were found in indoor dust from both conventional and organic FS, and among them, five were detected in all matrices. It also appears that outdoor dust can play a certain role in contaminating the environmental, animal, and human compartments, as evidenced by the significant correlations between the concentrations of boscalid in outdoor dust and earthworms, between the concentrations of AMPA and glyphosate in outdoor dust and animal urine, and between the concentrations of DDE p,p' in outdoor dust and farmer feces.

The most hazardous substances for the environmental matrices (earthworms, honeybees, and beneficial insects) are listed in Table 8. Nine substances among the top 20 have harmful effects on insects; in the first place is glyphosate. Because of its persistence and spread in many habitats, glyphosate can impact plants' interactions with its biotic environment (Hoagland and Duke, 1982). It can, directly and indirectly, impact non-target organisms since its induced changes in plant phenotype can have cascade consequences on non-target organisms with whom they interact (Fuchs et al., 2021). We have listed four of the top 20 substances with established effects on honeybee health (permethrin, imidacloprid, chlorpyrifos, and lindane). The harmful effect on bees has been reported in previous studies (Nekoei et al., 2023; Raine and Rundlöf, 2024; Shannon et al., 2023). Bee populations have been declining in recent years, mostly due to rising pressure from factors such as pathogen spillover and chemical exposure (Hristov et al., 2021; Olynyk et al., 2021; Wood et al., 2020; Graystock et al., 2016). It has been found that the period of larval development and pupation of a bee is a fragile yet critical life stage of all bee species, hastening their decline (James, 2011; Mullin et al., 2010). As a result, brood diseases in such species can directly lower the number of reproductive individuals available for future generations, decreasing solitary bee populations and diminishing the pollination services they provide (Evison and Jensen, 2018). Further research is needed to assess bee brood diseases and their interactions with common stressors, particularly in wild bee species. Honeydew is the sugar-rich excretion of phloem-feeding hemipteran insects and can serve as a primary glucose source for beneficial insects in some ecosystems. Contaminated honeydew by pesticides, in turn, can be hazardous to beneficial insects (Calvo-Agudo et al., 2022). Because honeydew is a possible cause of insect decline in environments where honeydew is an important carbohydrate source for insects, we propose that this route of exposure be included in future environmental risk assessments.

We listed sixteen substances among the top 20 having established or possible effects on earthworms. Studies revealed that earthworms are highly susceptible to insecticides, which cause immobility and rigidity. Insecticides also have a significant effect on biomass reduction, growth, and reproduction by disrupting various physiological activities, resulting in the loss of earthworm population and soil biodiversity (Miglani and Bisht, 2019). Since earthworms play a functional role in soil by enhancing aeration, organic matter turnover, and having an overall positive impact on soil fertility (Roeben et al., 2020), there is an urgent need to estimate the bioaccumulation of organic chemicals by earthworms, which is critical for improving the accuracy of the risk assessment of pesticides.

Among the top 20 substances detected in animals and humans, thirteen have an established effect on health (Fig. 10), including twelve detected in human blood. Glyphosate, pirimiphos-methyl, tebuconazole, chlorpyrifos methyl TCPy and deltamethrin were among the highly detected pesticide residues in monitoring programs since 1999 (Sevim et al., 2024). The risk of exposure to these pesticides has been identified in several monitoring studies worldwide (Government, 2021; EFSA, 2023; Sevim et al., 2024). Al-Nakhle et al. (2024) conducted a thorough assessment of the hepatotoxicity induced by pirimiphos-methyl (detected in all compartments of our study), using multiple evaluation levels, including histological analysis, liver enzyme measurements, and real-time polymerase chain reaction (PCR) to detect changes in hepatic miRNA-target gene expressions. The authors reported that the administration of pirimiphos-methyl and bifenthrin caused detectable hepatic damage in rats, as shown by substantial changes in serum aspartate transaminase (AST) and alanine transaminase (ALT) levels. Kugathas et al. (2016) assessed the ability of pesticides most commonly used in the European Union to suppress prostaglandin D2 (PGD2) synthesis. The pesticides boscalid, cypermethrin, fludioxonil, pyrimethanil, and

tebuconazole (all detected in humans and/or animals of our study) suppressed PGD2 production which could increase the risk of congenital malformations. From use as an insecticide, both dichlorodiphenyltrichloroethane (DDT) and its breakdown product dichlorodiphenyldichloroethylene (DDE) remain widely present in human adipose tissue [Darbre, 2017] and are endocrine disrupters (Darbre, 2017).

In addition to the substances cited above, the ones not listed in the top 20 (Fig. 9 and 10) and detected in the bodies of animals and humans constitute a potential health risk. To regulate such exposure, legislation has been developed based on evidence from trials involving a single chemical exposure. However, such an approach underestimates the possible synergy, potentiation, or inhibition that might result from exposure to a variety of substances (as occurs in real life). For this reason, the real-life risk simulation scenario was established to investigate the possible effect of long-term exposure to mixtures of pesticide residues under actual circumstances of modern life (Sevim et al., 2024; Tsatsakis et al., 2016; Tsatsakis et al., 2017; Dinca et al., 2023).

Scientific evidence shows that pesticides have already entered the food chain (EFSA, 2022a, b) and are increasingly contaminating animals and humans. The world's consumption in 2015 resulted in 2 Gt-bw of pesticide footprints and >90 % of pesticide footprints imported by some European countries originated from active substances that were banned for use in those importing countries (Tang et al., 2022). Our study shows that a large share of the ranked substances are not approved for agricultural use in Europe. When considering all matrices and compartments (Table 2), nine active substances out of 20 are not approved; eight out of 20 are not approved when considering the environmental (Table 3) and human (Table 5) compartments, and six out of 20 are not approved when considering the animal compartment (Table 4). This widespread contamination has also affected the organic products available to markets, as reflected by the quantities of pesticide residues measured. For example, 6 % of organic products in the EU contain pesticide residues (EFSA, 2018); in southern Germany, residues were found in up to 28 % of organic food products (Schleiffer and Speiser, 2022), and in the Swiss market, residues were found in 9 % of organic food products (Schleiffer et al., 2021).

Of all matrices tested, indoor dust contained (i) all active substances (ii) the highest frequency, and (iii) the highest median concentration. Although inhalation seems to represent a relatively small contribution to pesticide exposure, the children's vulnerability to pesticides is of concern for some reasons. (i) Children have a larger body surface area/weight ratio, which leads to increased dermal absorption, skin perfusion, and hydration; and (ii) young children's enhanced respiratory rate and minute ventilation account for their higher chemical absorption by inhalation (Pascale and Laborde, 2020). Pesticide exposure and consequences can occur at any period, from preconception and prenatal stages to infancy, but diseases associated with them can manifest in infancy, adolescence, or adulthood (CEH, 2012; WHO, 2008; Pascale and Laborde, 2017). All these aspects enhance the exposure and risk of health consequences at the time of diagnosis. These results underline the need to consider the timing and nature of exposure relative to each disease developed by the farmer and his family.

5.3. Strength and limitations

The study examines prominent crops in both conventional and organic agricultural systems in various climate zones throughout Europe. Standard operating procedures were developed to standardize sample collecting, storage, and shipment techniques. The whole study protocol was published prior to the start of fieldwork (Alaoui et al., 2021; Silva et al., 2021). The project is particularly unique in that it aims to analyze a large number of pesticide residues in a wide range of matrices using standardized methods for treatment and analysis by experienced and reference laboratories. On the other hand, its large-scale and multi-matrix nature imposed several constraints.

Some substances were excluded from the lists of 20 despite their high DF, namely Folpet PHI, 3-PBA, and DCCA. Folpet PHI is not solely the product of a single substance (Folpet), but can have different origins, and could also have interfered with chemical agents during analysis. 3-PBA (3-phenoxybenzoic acid), detected only in the urine of animals (21 %) and humans (93 %), could have resulted from multiple pyrethroids such as permethrin, cypermethrin, deltamethrin, and cyhalothrin. This is also the case for DCCA (3–2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylic acid, which was detected in animal and human urine. Its derivatives DCCA trans and DCCA cis were detected with a frequency of 83 and 52 % in animal urine, respectively, and with a frequency of 21 and 5 % in human urine, respectively. DCCA can also originate from multiple pyrethroids such as permethrin, cypermethrin, and cyfluthrin. This makes it difficult to assess their risk to animal and human health.

Because the crops differed from site to site, the comparison between FS is based on DF and MC in different matrices without considering differences in the crops or the doses applied. However, the occurrence of products in different matrices is more closely linked to the pesticides used for the entire crop rotation, which better reflect the agricultural practices of a FS than a single crop. In addition to data heterogeneity, it was not always possible to compare different matrices in terms of DF and MC because not all substances were tested in all matrices. Some matrices, such as water bodies and sediments, are often not directly linked to the fields under consideration, neither to a FS. The same is true of neighbors and consumers. It is important to note that the estimates are based on average values for each matrix. This was done to avoid biases from individual values resulting from the above limitations.

In addition to single-pathway pesticide exposure addressed in this study, global studies have shown that cumulative pesticide exposure via multiple pathways can significantly increase the amount of pesticides entering the human body (Beamer et al., 2012; Mekonen et al., 2016; Son et al., 2018). On the other hand, internal exposure assessment, focuses on the quantity of a chemical biotransferred in human organs and tissues, that deals with the chemical's distribution and dissipation kinetics within the body (Li, 2022). Assessing external and internal exposure to pesticides is challenging due to the complexity and resource limitations, and a holistic approach is required to identify effective mechanisms involved and the complex exposure pattern. Physiological-based kinetic (PBK) models are widely used to simulate the fate and transport of chemicals in organs and tissues (Dyck et al., 2018; Li, 2019; Li and Wania, 2017; Tan et al., 2020; Li, 2022; Li and Xiong, 2023). Based on the intake estimate of a chemical obtained through the external exposure assessment, the internal exposure assessment can provide information about the amount of chemicals in organs and tissues after they enter the body, which is critical for characterising the health risks (Katsikantami et al., 2019). This information can be gained by analysing pesticide concentrations directly in adipose tissue, known to be the preferential reservoir for pesticide accumulation in the human body and the most appropriate tissue for assessing long-term exposure (e.g., Quintana et al., 2004; Ellsworth et al., 2018). Factors, such as living habitat, occupation, health status, physical activity, and genetic expression, may result in a significant variability in the chronic internal exposure dosage of the chemical. Assessing such information using biomonitoring data and detailed surveys could overcome the lack of a quantitative relationship between risk and simulated biotransfer factor, BTF (Li and Xiong, 2023). Future studies should focus on the interconnection between external and internal exposure to assess the health risks of pesticides.

We listed the 20 most frequently detected substances for each of the 3 compartments and classified them using their *DF* and *MC* values to identify substances of potentially high concern regarding risks to the environmental, animal, and human compartments. The second ranking of substances based on the PI takes into account both DF and MC, averaged for each matrix. A weighting factor was used to distinguish between matrices reflecting exposure (internal and external) and those reflecting accumulation. Use of the PI does not change the list of

substances previously established using their DF; it only changes the order of the substances within the list, reorganizing them based on both their DF and their MC. We opted to use PPDB as our main source of pesticide hazard information. We have updated the PPDB information with recent results where appropriate based on the primary data sources used to populate the database (e.g., ECHA, EPA, PubChem) (Silva et al., 2023). In the case of human endpoints, we compared PPDB information with the EFSA documents where higher criticism exists. Differences between PPDB and EFSA classifications, or between both databases and recent scientific publications, are (i) mainly linked to the time lag between the publication of scientific findings and the updating of the databases or (ii) due to the different evaluation criteria used for the classification. The case of glyphosate is a good illustration of this. According to EFSA, "the assessment of the impact of glyphosate on the health of humans, animals, and the environment did not identify critical areas of concern" (EFSA, 2023a, b). Meanwhile, various authors assessed all in vivo, ex vivo, and in vitro mechanistic studies of humans and experimental animals (mammals) that compared exposure to glyphosate with low/no exposure counterparts for evidence of ten newly described key characteristics (Rana et al., 2023). They confirmed the conclusion of the International Agency for Research on Cancer (IARC, 2015) that glyphosate was "probably carcinogenic to humans". Increasing evidence shows that glyphosate and glyphosate-based herbicides "exhibit cytotoxic and genotoxic effects, increase oxidative stress, disrupt the estrogen pathway, impair some cerebral functions, and likely correlate with some cancers" (Peillex and Pelletier, 2020). Based on our assessment of different databases and their sources, we verified the hazard categories against recent literature when available. This exercise reminded us that rigorous studies are needed to establish the causal link between exposure and health effect. However, hazard assessment, i.e., verifying the hazard categories was not the main aim of this study. The hazard information should be regarded as indicative because it was based on (i) detection (>LOD) rather than levels, and on (ii) a conservative approach (hazard was considered when it was reported in a given source). For more in-depth information, readers should refer to the sources cited in SM3. Despite the considerable effort put into sampling, further investigations are still needed to assess the risk based on advanced epidemiological studies and to include the effect of mixtures of substances on health, and to assess the relationship between external and internal exposure.

6. Conclusions

In this study, we showed that most of the pesticide residues detected in soil, water, indoor dust, outdoor air, sediment, and crop samples are hazardous for non-target organisms, including animals and humans. We have also shown that humans are mainly exposed to substances from the environment and, to a certain extent, to dual-use substances, evidenced by the presence of a set of common pesticide residues across all matrices suggesting exposure to mixtures of multiple pesticides. The toxic effect of such exposure is unknown, especially over a longer period. This study provides a useful basis for selecting the pesticide residues to be considered for this purpose. With so many substances omnipresent in the environment, it would be judicious to consider biocides and banned substances, which constitute a baseline of contamination found in different human matrices and adds to the effect of substances used in agriculture. The association between exposure to certain pesticides and their hazardous effects has been thoroughly proven and cannot be ignored. Furthermore, some members of the population are more exposed to pesticides and are therefore more vulnerable than others, such as farmers and their families, and particularly children living in contamination hotspots. Following the precautionary principle, premarket risk assessment practices should be revised, considering all relevant external and internal exposure pathways and mechanisms. A risk assessment is required to test the real risk to environmental, animal, and human health based on our findings. Given that the negative effects of health hazards on humans depend on both the individual and the wider environmental context, it is imperative to take a comprehensive approach and use integrative and interdisciplinary methods.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.174671.

Abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AOAC	Association of Official Analytical Collaboration
ALT	Alanine transaminase
AST	Aspartate transaminase
BTF	Biotransfer factor
CEH	Council of Environmental Health
DCCA	(3–2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylic acid
DDD	Dichlorodiphenyldichloroethane
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DF	Detection frequency (%)
EASAC	European Academies Science Advisory Council
EC	European Commission
ECA	European Court of Auditors
ECHA	Europe Chemical Agency
EFSA	European Food Security Agency
EPA	Environmental Protection Agency
ESI	Electrospray ionization
EU	European Union
FAIR	Findable, Accessible, Interoperable, Reuseable
FMOC-Cl	Fluorenylmethyloxycarbonyl chloride
FS	Farming system
GCB	Graphitized Carbon Blacks
GC-HRMS	Gas Chromatography-high Resolution Mass Spectrometry
GC–MS	Gas chromatography–mass spectrometry
GC–MS/MS	Gas chromatography–mass spectrometry
HLOQ	higher limit of quantification
LC-MS/MS	Liquid chromatography–mass spectrometry
LLOQ	lower limit of quantification
LOD	Limit of detection
LOQ	Limit of quantification
MC	Median concentration (ug/kg)
MCPA	(4-Chloro-2-methylphenoxy)acetic acid
NOEC	No observed effect concentration
OJL	Official Journal of the European Union
PBK	Physiological-based kinetic
PCR	Polymerase chain reaction
PI	Prioritization indicator
PPDB	Pesticide Properties DataBase data
PSA	Primary secondary amine
PubChem	*Open chemistry database, National Institutes of Health*
QuEChERS	Quick Easy Cheap Effective Rugged Safe
REACH	Registration, Evaluation, Authorization, and Restriction of Chemicals
RSDr	Relative standard deviation intraday repeatability
RSDwr	Relative standard deviation within laboratory reproducibility
2,4-D	2,4-Dichlorophenoxyacetic acid
TIEM-PUF	TIEM (Integrated Environmental Monitoring)-Polyurethane foam
WHO	World Health Organisation

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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