Environmental and human health at risk – scenarios to achieve the EU’s 50% pesticide reduction goals.

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Abstract

The recently released Farm to Fork Strategy sets, for the first time ever, pesticide reduction goals at the EU level: 50% reduction in overall use and risk of chemical pesticides and 50% use reduction of more hazardous pesticides. However, little guidance is provided to achieve these targets. In this study, we compiled the characteristics and recommended application rates of 230 EU approved, synthetic, open-field use active substances and explored the potential of eight pesticide reduction scenarios (defined based on application rates, pesticide type, persistence, and hazard) to achieve the reduction goals. Our approach revealed that all 230 substances are potentially harmful to humans or ecosystems, and that only severe pesticide use restrictions such as full conversion to organic farming or allowing only low hazard substances will result in 50% reductions. Our results emphasize the need of an EC action plan on how to achieve and maintain the aimed reduction levels.

Introduction

Pesticides are used in agriculture to reduce crop losses due to pests, weeds and/or pathogens\(^1\). Farming systems have been facing an increasing pressure to produce more food as a result of the rapidly growing population and of more caloric diets observed over the last decades\(^2\). Currently, global pesticide use exceeds 4 million tonnes per year. Europe is responsible for almost 400,000 tonnes\(^3\). The long-term and intensive use of pesticides raises major health and environmental concerns since several pesticide active substances (a.s.) and/or their metabolites are persistent\(^4,5\), bio-accumulative\(^6,7\), and/or toxic to non-target-species\(^8\)–\(^10\). The awareness of undesired pesticide effects has triggered biotechnological developments\(^11,12\) and multiple efforts to minimize pesticide use and negative impacts\(^13,14\). The recently published EC Farm to Fork Strategy\(^15\), part of the European Green Deal, sets the first pesticide reduction targets at the EU level: a 50% reduction in overall use and risk of chemical pesticides by 2030, and a 50% reduction in use of more hazardous pesticides by 2030 also (i.e., pesticides containing a.s. identified as candidates for substitution). In line with EC terminology, in this study the term pesticide(s) is used to refer to the commercial product, and a.s. to the active ingredient of the pesticide. Despite the clear targets, the Farm to Fork Strategy provides little guidance on how to achieve these goals; and priority a.s., types or classes of pesticides, crops or EU regions are not indicated.

Significant pesticide use reductions at the farm level are usually the result of the adoption of a new farming strategy with lower and more regulated pesticide use\(^16\), and pesticide risk reductions are generally the result of restrictions on the use of hazardous pesticides (e.g., neonicotinoids ban after proved risk to honeybees\(^17\)). Integrated pest management (IPM) and organic farming, with respectively reduced and no synthetic pesticides input, are felt to be adequate strategies towards achieving sustainable food production\(^18\). IPM is compulsory in the EU since 2014\(^19\), and organic production highly encouraged, and expected to represent at least 25% of EU’s agricultural land by 2030\(^15\). Nevertheless, even IPM and organically managed areas can be affected by pesticides, due to current and/or past use of pesticides, or due to off-site contamination\(^20\)–\(^22\). Environmental and bio-monitoring data on pesticide residues are essential to quantify exposure and potential risks of pesticides, including the risk reductions along increasingly regulated pesticide use gradients, yet such monitoring data are scarce and fragmented. Given these limitations, and the uncertainties associated to exposure estimates, the intrinsic, hazardous properties of a pesticide residues, i.e. its potential to do harm, can be a good predictor for risk (risk = hazard * exposure\(^23\)). Achieving risk reductions also requires addressing pesticide use and toxicity data fragilities. FAOSTAT and EUROSTAT, the reference databases for pesticide statistics, provide use and sales data.
on groups of a.s. only\textsuperscript{24}, which are not suitable for such assessments. Other pesticide use data sources also have limitations: i) the world pesticide use review\textsuperscript{1} does not indicate the applied amount per a.s. either; ii) the PESTCHEMGRID\textsuperscript{SD} dataset\textsuperscript{25} has use estimates for only some of the a.s. allowed in the EU; and iii) the JRC estimates on EU pesticide use revealed data availability and accessibility issues and heterogeneity on the use data collected among Member States\textsuperscript{26}. The existing monitoring data in soils\textsuperscript{5,27}, water\textsuperscript{28} and air\textsuperscript{29} indicate that mixtures of pesticide residues are the rule rather than the exception, yet (eco)toxicity data on complex mixtures are rarely available, especially for observed concentrations in the environment, realistic mixture ratios, and other than standard toxicity endpoints\textsuperscript{30}.

While designing ways to address the Farm to Fork pesticide reductions targets, an important aspect must be considered: pesticide use varies across regions and specially across crop types\textsuperscript{1} (pesticide use is highly consistent between years for the same location\textsuperscript{31}). Given the already mentioned pesticide use data limitations, which are expected to be exacerbated by additional spatial and crop specification requests, a.s. representative uses can be a reasonable pesticide use proxy to explore the impacts of Farm to Fork driven measures on different farms, and to assess the feasibility of the pesticide use and risk/hazard targets in the first place, using scenario analyses. These a.s. representative uses are good agricultural practices for the use of the a.s., and include the recommended number of applications per year and the recommended application rates per treatment, crop and EU region. Representative uses are available in the EU dossiers of the individual a.s., i.e., EFSA conclusion reports on the peer review of the pesticide risk assessment, draft assessment reports (DAR), and if applicable renewal assessment reports (RAR). In line with the above described challenges, this study has two main objectives: i) establish a pesticide use and hazard baseline, via compilation of the representative uses and (eco) toxicity data of 230 approved a.s. − 91 herbicides, 87 fungicides, 50 insecticides, 2 multi-action substances; and ii) quantify pesticide use and hazard reductions of different pesticides scenarios compared to a Business As Usual scenario (derived from the use and hazard baseline).

**Results**

**Pesticide use and hazard baseline**

This study focuses on the overall use and hazard of 230 EU-approved, synthetic and open-field use fungicides/herbicides/insecticides (see Fig. 1, an methods on selection criteria). These 230 a.s. constitute the primary group of interest for this study and were used to characterise the Business As Usual (BAU) reference scenario. The 230 selected a.s. present a great variability in physicochemical properties, environmental persistence and (eco-) toxicological profile. Herbicides (HB) and fungicides (FU) dominate the EU pesticide market, representing 40% and 38% of the selected a.s. respectively. The 230 selected a.s. cover 99 chemical groups and 64 modes of action. The most represented chemical groups are the sulfonylureas, carbamates, triazoles and pyrethroids, and the most frequent modes of action are inhibition of plant amino acid synthesis, inhibition of ergosterol/sterol biosynthesis and inhibition of succinate dehydrogenase (Supplementary Table 6). In general, the selected a.s. present low volatility, low solubility in water, and low leachability (90%, 57%, 55% of a.s., respectively). Around half of the 230 a.s. are expected to be moderately-persistent to very persistent in soil (51–55%, lab-field data) or in water-sediment medium (47%). Approximately half of the 230 a.s. present high bioconcentration potential (51%), a characteristic especially common in moderately persistent and persistent compounds. The 230 selected a.s. have 414 known metabolites, 243 of which with maximum formation fractions
above 10% and biological relevance (i.e., target activity comparable to the parent substance, comparable or higher risk to organisms than the parent substance or severe toxicological properties\textsuperscript{13}, Supplementary Fig. 1). Finally, 49 out of the 230 selected a.s. are in EC as candidates for substitution list. 45 of those 49 a.s. are in this list because i) they meet two of the PBT criteria - Persistent, Bio-accumulative or Toxic substance (n = 33, 67%); ii) they have a low ADI - Acceptable Daily Intake, low ARfD - Acute Reference Dose, or low AOEL - Acceptable Operator Exposure Level (n = 9, 18%); or because iii) they are toxic for reproduction category 1A or 1B (n = 3, 6%; see\textsuperscript{32} for further details on these categories). The remaining 4 a.s. meet two or three cut-off conditions: low ADI/ARfD/AOEL + two PBT criteria (haloxyfop-P and lambda-cyhalothrin, 4%); two PBT criteria + toxic for reproduction 1A/1B + endocrine disrupting properties (epoxiconazole, 2%); two PBT criteria + low ADI/ARfD/AOEL + endocrine disrupting properties (dimoxystrobin, 2%).

Nearly half (49%) of the 230 a.s are specific for one of our crop classes while the other half can be applied to two, three, four, or to all the eight classes (31, 16, 3 and 1%, respectively). The highest number of a.s. is expected to be used in cereals (51–88 a.s. approved/region), however, the highest total a.s. use is expected in dry pulses-vegetables-flowers, grapes, and root crops (Table 1). These are the crops where the soil sterilant metam, the a.s. with the highest application rates is allowed. Total a.s. use differs substantially across EU regions, being in general the highest in SEU. This because SEU has more approved a.s. than the other EU regions, and because most of the a.s. with different region rates have their highest recommend application rates in SEU (Supplementary Table 5). Annual application rates are highly variable across a.s., with a couple a.s. being allowed at extremely high levels (Fig. 2). Metam and dazomet have maximum inputs of 1,020 and 500 kg/ha/year, respectively, i.e. inputs 2–3 orders of magnitude higher than most of the other pesticides in the market (Fig. 3). Paraffin oils, tolclofos-methyl, dodemorph, folpet, captan and fosetyl have also very high recommended rates (> 10–100 kg/ha/year). The controversial glyphosate and other 46 compounds have maximum inputs between 1 and 10 kg/ha/year; and the remaining 174 a.s. (76% of the selected a.s.) have maximum inputs lower than 1 kg/ha/year.

Most of 230 a.s. are expected to present low or moderate toxicity to the different ecotoxicological endpoints, except for mammals, if exposed short-term via diet (Table 2). However, there are hazard data gaps in all 20 ecotoxicological endpoints, ranging from 2 to 97% of the a.s. The largest data gaps occur on long-term endpoints and soil macro-organisms, arthropods, and sediment dwelling organisms (Table 2). Acute and long-term endpoints result often in different levels of toxicity that are organism and pesticide dependent. Mammals, birds and earthworms, for instance, appear to be highly resistant to acute pesticide exposures, with ≥ 90% of selected a.s. showing low or moderate toxicity to them. However, when long-term endpoints are considered, only birds remain highly resistant, with 79% of a.s. showing low or moderate toxicity. Mammals appear highly vulnerable to pesticides, with at least 50% of a.s showing high long-term toxicity, and earthworms resistance becomes highly questionable, with long-term toxicity data missing for 46% of the a.s. The attribution of risk scores to the severity of effect, allow comparison of a.s. based on overall hazard (see methods section on details on the score system used). The a.s. with highest ecosystem, cumulative hazard scores are chlorpyrifos, bifenthrin, beta-cyfluthrin, dimethoate, gamma-cyhalothrin, alpha-cypermethrin and esfenvalerate (Fig. 4), of which bifenthrin, dimethoate and esfenvalerate are candidates for substitution. There were no a.s. with cumulative hazard score 0. Chlorpyrifos, known to affect twelve of the twenty ecotoxicological endpoints considered (twelve was the maximum number of endpoints known to be affected by a selected a.s.) was banned at the end of 2019. Bifenthrin is known to affect 11 endpoints, beta-cyfluthrin, alpha-cypermethrin and esfenvalerate are known to
affect 9 of the endpoints, gamma-cyhalothrin affect 8 and dimethoate 7 endpoints. Most of other a.s. are known to affect 1 or 2 ecotoxicological endpoints (36% and 15% of a.s.; Supplementary Fig. 2).

The 230 selected pesticides are also associated with several human health issues, being the most common eye, skin or respiratory tract irritations (37%, 25% and 22% of a.s.), skin allergies (21%), and reproductive/development toxicity (24%; Table 3). Over a third of the 230 selected a.s. are possibly carcinogenic, and nearly a fifth possible endocrine disruptors. Just as ecotoxicological data, human health endpoints present data gaps. The biggest gaps are on phototoxicity, skin sensitivity, endocrine disruptions and mutagenicity character of a.s. (82%, 56%, 54% and 47%, respectively). The a.s. with the highest human, cumulative hazard scores are fenoxycarb, pendimethalin, ziram, chlorothalonil and gamma-cyhalothrin, of which only pendimethalin and ziram are candidates for substitution (Fig. 5). Chlorothalonil is known to affect six of the eleven human endpoints considered (six is the maximum number of endpoints known to be affected by a single a.s.), gamma-cyhalothrin and pendimethalin are known to affect five of the endpoints, and ziram and fenoxycarb four. Most of a.s. are known to affect 1, 2 or 3 human endpoints (29%, 23%, and 16% of a.s., respectively; Supplementary Fig. 3). The only a.s. proved to not affect any of the 11 human endpoints is fluoxastrobin.

The a.s. with highest application rates are often not the most hazardous for ecosystem or humans (Fig. 6). In fact, only 7 a.s. are amongst the top use a.s. (i.e. the 56 a.s. with maximum annual application rates > 1 kg/ha/ha - excluded from the LDP scenario), top hazard ecosystem (i.e. the 65 a.s. with cumulative hazard scores ≥ 31, Fig. 4) and top hazard human (i.e. the 50 a.s. with cumulative hazard scores ≥ 15; Fig. 5): captan, chlorothalonil, ethoprophos, fluazinam, malathion, oxamyl, ziram. Thirty-four a.s. are in two of these three top positions - i) in top use and top hazard for ecosystem: aclonifen, dithianon, fenpropidin, fenpropimorph, fenpyrazamine, isofetamid, metamitron, metribuzin, oxyfluorfen and pyrimethanil; ii) in top use and top hazard for humans: 8-hydroxyquinoline, dazomet, dimethachlor, dodemorph, folpet, fosetyl, metam, pendimethalin, prosulfocarb, thiophanate-methyl; and iii) in top hazard for ecosystem and top hazard for humans: alpha-cypermethrin, bifenthrin, cyprodinil, desmedipham, gamma-cyhalothrin, lambda-cyhalothrin, methomyl, nicosulfuron, phosmet, pirimicarb, tefluthrin, terbuthylazine, triadimenol and zeta-cypermethrin. 124 out of the 230 selected a.s. are in one of these top use or top hazard positions.
Table 1 – Number of active substances (a.s.) allowed under the Business As Usual (BAU) scenario, maximum recommended annual application rate among allowed a.s., and total a.s. use per crop- EU region combination. Annual application rates were calculated as the product of the (maximum) number of recommended treatments per year and the (maximum) recommended application rate per treatment in respective EC approved, a.s. representative use (retrieved from individual a.s. EU dossiers). Total a.s. use was calculated as the sum of the highest annual application rate of all the a.s. allowed per crop- EU region combination. The average of total a.s. use in NEU, CEU and SEU was used in the European characterization (the last column of the table). Maximum annual application rates among allowed a.s. are presented in kg ha⁻¹ year⁻¹, with zero or two decimal places (if above or below 100 kg ha⁻¹ year⁻¹, respectively). Total a.s. use is also presented in kg ha⁻¹ year⁻¹, with zero decimal places. NEU - Northern Europe, CEU - Central Europe, SEU - Southern Europe. DPVF = dry pulses, vegetables, flowers; NPIC = non-permanent industrial crops; Perm. = permanent; Max. = maximum.

| Crop         | Parameter                        | NEU     | CEU     | SEU     | EUROPE |
|--------------|----------------------------------|---------|---------|---------|--------|
| Cereals      | Number of a.s. allowed           | 77      | 51      | 88      | 98     |
|              | Max. recommend annual rate/a.s.  | 4.00    | 2.16    | 4.00    | 4.00   |
|              | Total a.s. use                   | 31      | 18      | 31      | 27     |
| DPVF         | Number of a.s. allowed           | 49      | 30      | 68      | 72     |
|              | Max. recommend annual rate/a.s.  | 612     | 612     | 612     | 612    |
|              | Total a.s. use                   | 1,210   | 713     | 1,196   | 1,039  |
| Grapes       | Number of a.s. allowed           | 40      | 19      | 56      | 56     |
|              | Max. recommend annual rate/a.s.  | 15.00   | 1,020   | 1,020   | 1,020  |
|              | Total a.s. use                   | 54      | 1,046   | 1,088   | 729    |
| Grassland    | Number of a.s. allowed           | 8       | 7       | 8       | 11     |
|              | Max. recommend annual rate/a.s.  | 1.44    | 1.80    | 1.44    | 1.80   |
|              | Total a.s. use                   | 4       | 6       | 4       | 5      |
| Maize        | Number of a.s. allowed           | 21      | 18      | 23      | 24     |
|              | Max. recommend annual rate/a.s.  | 2.16    | 2.16    | 2.16    | 2.16   |
|              | Total a.s. use                   | 8       | 7       | 9       | 8      |
| NPIC         | Number of a.s. allowed           | 28      | 18      | 32      | 39     |
|              | Max. recommend annual rate/a.s.  | 3.00    | 2.40    | 2.40    | 3.00   |
|              | Total a.s. use                   | 18      | 11      | 19      | 16     |
| Perm. crops  | Number of a.s. allowed           | 29      | 9       | 39      | 40     |
|              | Max. recommend annual rate/a.s.  | 12.50   | 16.38   | 94.80   | 94.80  |
|              | Total a.s. use                   | 60      | 45      | 157     | 87     |
| Root crops   | Number of a.s. allowed           | 58      | 30      | 64      | 67     |
|              | Max. recommend annual rate/a.s.  | 153     | 153     | 153     | 153    |
|              | Total a.s. use                   | 198     | 178     | 280     | 219    |
Pesticide reduction scenarios

Our pesticide reduction scenarios represent a decrease from 21 to 100% in the number of a.s. allowed in the EU market (from the least to the most restrictive scenario: CFSE > LDP > NH > LHP > FDP > LET > SHH > TPB; Fig. 7, Supplementary Tables 7–13). Only aclonifen was not covered in any reduction scenario; the other 239 a.s. were covered in one, two, three, four, five, six or seven reduction scenarios (5, 22, 57, 73, 47, 20 and 5 a.s., respectively; Supplementary Table 3). The number of a.s. allowed per crop type vary greatly across pesticide reduction

Table 3 – Human health problems associated with the use of the 230 selected active substances according to PPDB\textsuperscript{13}. The numbers in the table indicate the number of active substances known to cause the problem, known to not cause the problem, with status not identified or no data available. Grey highlighted cells show the most represented class per endpoint. Blue cells indicate the average number of a.s. considered per hazard score (the 11 human endpoints considered).

Table 2 – Ecotoxicological profile of selected active substances (a.s., n=230) according to PPDB: Pesticide Properties Database\textsuperscript{13}. The numbers in the table indicate the number of a.s. known to have low, unknown, moderate or high toxicity to a respective organism-endpoint. PPDB toxicity thresholds are defined according to EU guidelines or EU regulatory values. Detailed timescale was provided whenever this information was available. LC – lethal concentration; EC – effect concentration; NOEC – highest no observed effect concentration. Grey highlighted cells show the most represented toxicity class per ecotoxicological endpoint. Blue cells indicate the average number of a.s. considered per hazard score (for the 18 ecosystem endpoints or the 2 microbial endpoints considered).

| Hazard score | 0 | 1 | 2 | 3 |
|--------------|---|---|---|---|
| **Effect?**  | No (known to not cause a problem) | Unknown (No data available) | Possibly (status not identified) | Yes (known to cause a problem) |
| **Endpoint** | **126 (53%)** | **11 (5%)** | **81 (35%)** | **12 (5%)** |
| 1. Carcinogen | | | | |
| 2. Mutagen | 106 (46%) | 108 (47%) | 13 (6%) | 3 (1%) |
| 3. Endocrine disruptor | 55 (24%) | 125 (54%) | 42 (18%) | 8 (4%) |
| 4. Reproduction/development effects | 47 (20%) | 20 (9%) | 107 (47%) | 56 (24%) |
| 5. Acetyl cholinesterase inhibitor | 194 (85%) | 19 (8%) | 7 (3%) | 10 (4%) |
| 6. Neurotoxicant | 147 (64%) | 37 (16%) | 30 (13%) | 16 (7%) |
| 7. Respiratory tract irritant | 76 (33%) | 86 (38%) | 17 (7%) | 51 (22%) |
| 8. Skin irritant | 133 (58%) | 10 (4%) | 29 (13%) | 38 (15%) |
| 9. Skin sensitizer | 32 (14%) | 128 (56%) | 21 (9%) | 49 (21%) |
| 10. Eye irritant | 110 (48%) | 10 (4%) | 25 (11%) | 85 (37%) |
| 11. Phototoxicant | 36 (16%) | 189 (82%) | 4 (2%) | 1 (<1%) |
| **Average number of a.s. per score** | 97 (42%) | 68 (29%) | 34 (15%) | 32 (14%) |
scenarios but, and similar to BAU, the highest number of a.s. is expected in cereals, and in SEU. The reductions in
the number of a.s. allowed per crop-region-scenario are not necessarily translated in similar reduction of annual
application rates. In fact, and as somehow expected from the large variance in a.s. annual application rates
(Fig. 3), the reductions in total a.s. use are sometimes much bigger or much lower than those in the number of
allowed a.s. in the corresponding crop-region (Supplementary Table 14). The 24% reduction in number of a.s. of
LDP leads to a 77% reduction in total a.s. use, but the FDP 54% reduction in the number of a.s. leads only to a
28% reduction in total a.s. use. NH, SHH and LET presented similar reductions in number of a.s. and total a.s. use
(reductions in number of a.s. were ± 7% reductions in total a.s. use). Total a.s. use in reduction scenarios was 28–
100% lower than in BAU (from lowest to highest reduction: FDP > CFSE > NH > LHP > LET > LDP > SHH > TPB;
Fig. 7). Five out of the 8 pesticide reduction scenario lead to an overall input reduction of ≥ 50%. Except for LHP,
the highest total a.s. use is expected in dry pulses-vegetables-flowers, grapes or permanent crops, and in SEU. In
LHP, root crops and CEU have some of the highest a.s. uses.

All pesticide reduction scenarios led to reductions in the number of a.s. with high or moderate toxicity to non-
target organisms; the percentage of the reduction was endpoint and scenario dependent (Supplementary
Tables 14–21, 30). NH performed worse than the other scenarios with 0% hazard reductions in 9 endpoints
(mammals – acute, birds – acute and short-term, sediment dwelling organisms, honeybees – contact and oral
acute, earthworms – acute and chronic, and other soil macro-invertebrates - acute). Besides NH, only LDP had
situations of no hazard reduction; LDP had 0% reductions on earthworms – chronic, and on other soil macro-
invertebrates – acute exposure. Overall ecosystem hazard reductions ranged from 22–80% (from lowest to
highest reduction: LDP > NH > CFSE > FDP > LHP > TPB > SHH = LET; Fig. 7). Five out of the 8 pesticide reduction
scenarios lead to a hazard reduction of ≥ 50% (LDP, NH, CFSE, FDP, LHP).

Similar to ecosystem results, the number of a.s. known to cause or possibly causing human effects was reduced
in almost all endpoints after pesticide scenarios restrictions; the exceptions were: i) mutagen in NH and FDP; ii)
endocrine disrupter in LDP; iii) acetyl cholinesterase inhibitor in NH, and iv) phototoxicant in LDP, NH, TPB, CFSE
and LHP (Supplementary Tables 23–30). These 0% hazard reduction situations were observed at the four
endpoints with less a.s. in BAU. For instance, as only 1 out of the 230 selected a.s. is known to be a phototoxin,
and this a.s. is a persistent fungicide, both NH and TPB (where fungicides/insecticides and very persistent a.s.
are allowed, respectively) present no hazard reductions (Supplementary Table 31). Overall human hazard
reductions ranged from 27–88% (from lowest to highest reduction: CFSE > NH > LDP > FDP > LHP > TPB > LET >
SHH; Fig. 7). Five out of the 8 pesticide reduction scenarios lead to a hazard reduction of ≥ 50% (same scenarios
as in ecosystem).

Discussion

BAU, the reference scenario to assess pesticide use and hazard reductions, assumes that all a.s. allowed per crop-
EU region are applied, and at their maximum recommended annual application rates (retrieved from EC approved
representative uses). We recognize that it is unlikely that all a.s. allowed per crop-EU region are applied on single
fields or on each field, and indeed interviews to EU conventional farmers indicate a smaller pool of a.s. and lower
pesticide input than predicted here. Geissen et al. reported a maximum of 11, 22, 18 and 44 a.s. applied per
field/year in Spanish orchards, Spanish vegetables fields, Portuguese vineyards and Dutch potato fields,
respectively – for these crop-regions BAU considers 39, 68, 56 and 58 a.s., respectively. On the other hand, these
interviews also revealed that the number of recommended applications and the recommended application rates
are sometimes exceeded in the field, when pest pressure is severe. Geissen et al. reported a total a.s. use of 38
kg/ha/year in Portuguese vineyards, 49 kg/ha/year in Dutch potato fields, and 86 kg/ha/year in Spanish vegetables fields (application rates were not available for Spanish orchards). Real a.s. inputs in these fields were actually higher as indicated by the farmers confidentially. BAU estimates 1,088 kg/ha/year, 198 kg/ha/year and 1,196 kg/ha/year for these areas, respectively. If the soil sterilant metam and soil fumigant dazomet, with extremely high and very high recommended application rates, are not considered in the predictions (both substances were not reported to be applied in the interviews), total a.s. use estimates drop to 68 kg/ha/year, 45 kg/ha/year, 84 kg/ha/year, respectively - values very close to those reported to be used in these EU farms. FAOSTAT\textsuperscript{34} reports a lower pesticide use in EU croplands, with maximum pesticide use oscillating between 8.79 and 13.76 kg/ha/year (this for the years between 1990–2018). FAOSTAT data suggest that metam, dazomet and other few approved a.s. with high recommended application rates are not being applied in most EU fields, but individual a.s. use data would be necessary to corroborate this hypothesis. One could think that the pesticide use reduction targets would be easily achieved by restricting the use of only these a.s. however, since these and other high placation rates substances are low persistence compounds and of intermediate hazard to humans and ecosystem, such measure would be misleading and would not guarantee the coupled 50% risk reduction target. Phase-out a.s. should be selected via an integrated use and hazard approach. Finally, the fact that Geissen et al.\textsuperscript{21} reported higher values than those of FAOSTAT raise concerns on the quality of reference pesticide statistics data and/or need of clarification or improvement of reference pesticide indicators.

According to recent EC data\textsuperscript{35}, 61% of 2018 approved a.s. are intermediate hazard a.s., 37% low hazard a.s., and the other 2% high hazard. a.s. How this overall hazard classification per a.s. is determined is unfortunately not completely clear, neither are the hazard thresholds. Our review revealed a different picture, with all 230 selected a.s. having the potential to cause adverse effects on human or non-target organisms; 124 of them had a high cumulative hazard score to human and/or ecosystem (Fig. 4, 5). Furthermore, our review exposed major gaps in the hazard knowledge of many of the a.s. in the market, raising serious concerns on the protection level of current pesticide policies. Our ecosystem and human-effects review was performed based on PPDB data; different percentages of adverse effects, and of not (public) available data, are expected if other data sources are considered (EU Pesticides Database/EU dossier reports, EFSA OpenFoodTox database, US-EPA ECOTOX database, PubChem database, eChemPortal), or if more or other non-target organisms are considered\textsuperscript{36,37}. The same applies if metabolites or pesticide adjuvants were also considered. Remember that the 230 selected a.s. have 414 known soil metabolites, which sometimes are more persistent and more toxic than their parent compounds\textsuperscript{38,39}. Some adjuvants (i.e. additives added to pesticide formulations to enhance the function or application of the a.s.) can also be toxic to non-target species, consider for instance POEA and organosilicon surfactants used in in some glyphosate-based herbicides or some neonicotinoid insecticides, respectively\textsuperscript{40}. An especially concerning aspect of this review relates to the fact that we could not find any data on mixtures toxicity in PPDB nor in EU dossiers, even if the a.s addressed in the dossiers are known components of mixed application (tank-mixing) or environmental mixtures. One could think that the EFSA framework for combined exposure to multiple chemicals\textsuperscript{41} could be used to characterize the risks of such mixtures, however, the framework approach requires co-occurrence, concentration and toxicity data of pesticides which, as exposed above, might not be available for all a.s. in the mixture, even less so for whole mixtures. Furthermore, the framework does not consider different mixture compositions over time, which are very likely to occur under field conditions with sequential application of pesticides, and different degradation rates of pesticide residues. More research and legislative efforts should focus on the combined effects of pesticides (including with recently or long term banned but still detected pesticide residues) on human and ecosystem health.
Eight pesticide reduction scenarios were explored in this study to provide the EC with options for change: LDP, NH, FDP, TPB, CFSE, LHP, SHH and LET. Their representativity and implications are explored below. It is important to stress that the estimated reductions are not about absolute data but on the relative expected reductions of the scenarios. We considered maximum recommended rates of individual a.s. in BAU and in the different pesticide reduction scenarios, but if we would have used a different (lower) application rate per a.s., the differences between BAU and the scenarios use results (our approach to estimate potential use reductions) would show the same pattern. Furthermore, although recognized that pesticides hazard is not directly translated into risk (the exposure data available was considered too limited to explore this transition properly), our approach allows the identification of priority a.s. for risk assessments and risk reductions strategies, which was ultimately the objective of this study.

NH and TPB are linked to existing farming strategies, IPM and organic farming, respectively. The NH scenario is particularly relevant for farms with (or planning to convert to) an herbicide-free production. In these farms weeds are often controlled by tillage applications, although precision farming techniques such as robotic weed control are gaining more popularity over the years. Several EU farms are expected to present a BAU-NH intermediate situation, using chemical and mechanical weed control methods. Indeed, at least for orchards and vineyards it is common to apply herbicides only in the within-rows of trees and plough soil every other year, in alternate interrows. The NH scenario one of the more easy scenarios to be implemented at both EC and farm level, and relevant due to the health concerns raised over the last years on glyphosate-based herbicides, is close to the 50% use reduction goal but leads to rather low hazard reductions as the highly toxic a.s. in the market seem to be mostly insecticides and fungicides. The TPB scenario is particularly relevant for areas recently converted or in-conversion to organic farming. The EU has one of the biggest shares of organic agricultural land globally, with 12.8 million hectares – 65% of which is fully converted to organic and 19% in conversion. These 12.8 million hectares correspond to 8% of EU’s agricultural land, a value that, as mentioned before, is targeted to increase to at least 25% by 2030. TPB meets use and hazard reduction goals, yet, all EU farmland area would have to be converted to organic, which seems unlikely in the near future unless organic farmers receive financial support to compensate for the lower yields and in first instance higher production costs.

CFSE that excludes the a.s. in the EC list of the candidates for substitution subject to comparative assessments and gradual substitution, represents therefore a predictive scenario for planned EC efforts. CFSE results stress the need of an additional action from the EC to meet the Farm to Fork goals; even if all candidates of substitution are removed from the market before 2030, their sole removal result in use and hazard reductions far below the 50%. The right selection of a.s. to remove is essential as shown by FDP and LDP results. The FDP scenario considers pesticide persistence in soil as the only criterion to cut-off pesticides from the market. Soil half-life times are available for all the selected a.s. making this scenario in principle easy to implement by the EC. Less persistent pesticides result in shorter exposure to pesticides, but not necessarily in lower inputs or toxicity. In fact, although more than half of the 230 initial a.s. were excluded in the FDP scenario, it performs only borderline to hazard and poorly for use. A similar situation happens with LDP. The LDP scenario, also defined on a practical excluding criterion (annual application rates ≥ 1 kg/ha/year), leads to a marked reduction on pesticide use (after removal of metam, dazomet and a few other high use a.s.) but to rather low hazard reductions.

The remaining hazard based scenarios LHP, SHH and LET, are the ones leading to use and hazard reductions > 50%, indicating hazard as the best criterion for pesticide restrictions. LHP is a promising scenario as it has bigger
differences between the reductions in number of a.s. and the reductions in hazard compared to SHH and LET. However, the SHH and LET scenarios outperform the others on protecting human and ecosystem health, and are most likely the ones attracting most attention from the general public for possible implementation. These scenarios could be refined further by considering a different weight to the different endpoints (namely carcinogenic, mutagenic and toxic for reproduction), and indirect exposure and risks of (mixtures of) pesticides. LHP, SHH and LET, aiming to medium and high human and ecosystem protection, are probably the scenarios with higher impact and benefit for humans and/or ecosystems as they are defined based on (eco-) toxicological observations, and related endpoints considered in EFSA documents and EC decision making.

According to our results, and assuming no major changes in land use in Europe in the coming years, the 50% pesticide use and risk reduction goals of the Farm to Fork Strategy will only be met if the pool of a.s in the EU market reduces significantly and/or their uses severely restricted. Within this process, particular attention is required to the 124 a.s. with higher hazard scores to human and/or ecosystems, in line with the LHP scenario included in this study. The hazard gaps detected in many human and ecosystem endpoints required more and better attention in the future. The same applies for the role of metabolites and mixtures in overall pesticide risks. It is evident, that the development of transition pathways away from reliance on pesticides must be driven by an integrative, global health perspective. An active role of the EC is required for achieving the Farm to Fork goals by implementing legally binding instruments, e.g. current revision of the Sustainable Use of pesticides Directive – SUD, a requirement for implementing one or a combination of pesticide reduction scenarios. Although our pesticide reduction scenarios were inspired on the Farm to Fork Strategy pesticide reduction goals, our results are relevant for other EC environmental and sustainable development goals, namely those of the Mission Board for Soil Health and Food, the Biodiversity Strategy, the Zero Pollution Action Plan, and the Chemicals Strategy.

METHODS

The pesticides in the EU market – selection and characterization

On 05 February 2019 (starting date of this study) there were 484 approved a.s. under the EC Regulation 1107/2009 concerning the placing of Plant Protection Products on the EU market. From these, we selected the 365 fungicides (FU), herbicides (HB) and/or insecticides (IN) – the groups with the highest sales, and therefore of high relevance for pesticide reduction approaches. These 365 a.s. included 91 HB, 87 FU, 50 IN, and 2 multi-action a.s. (FU + HB, FU + HB + IN). The other 119 a.s. in the market were acaricides, attractants, bactericides, elicitors, molluscicides, nematicides, plant activators, plant growth regulators, repellents, rodenticides, or did not have a specific category. The EU dossiers of these 365 FU/HB/IN a.s. were gathered and two types of data were retrieved from them: predicted environmental concentrations in soil (PECs) and soil degradation data (i.e., degradation kinetics, kinetics parameters and representative half-life times, to allow PECs calculation). This step was required to i) establish a pesticide baseline in soils, a matrix where pesticide distribution data is particularly fragmented (results presented in Silva et al., in prep), and ii) select the a.s. used in open-fields, and therefore likely to pose a risk to ecosystems and humans (including not pesticide operators). Note that PECs and degradation studies are not required for greenhouse and indoor uses. PECs and/or soil degradation data were found for 249 FU/HB/IN a.s. The remaining 116 FU/HB/IN a.s. were approved only to greenhouse or indoor uses, were not expected to be released to the surrounding environments (e.g., solid passive retrievable dispenser), were microbial substances, had no soil degradation data (data gap identified), or were not expected to present degradation (i.e.
copper compounds). From these 249 FU/HB/IN a.s., 230 were synthetic substances, and 19 were natural or inorganic substances (Fig. 1; Supplementary Table 1). These 230 synthetic FU/HB/IN a.s. constitute the primary group of interest for this study and were used to characterise the Business As Usual scenario.

General information, environmental fate data, and (eco)toxicological data of the selected 230 a.s. were extracted from the Pesticide Properties DataBase – PPDB\textsuperscript{33} due to its practicality and the existence of qualitative classes for (eco)toxicity data. These qualitative classes are consistent with EU or EFSA guidance documents, with EU regulatory values, or with common use literature-based classification systems. PPDB is a reputable database, regularly updated, with a vast number of primary data sources including EU pesticide regulatory and evaluation data from RAR, DAR & EFSA Conclusion dossiers. Twenty ecotoxicological endpoints (covering acute and chronic effects on mammals, birds, fish, aquatic invertebrates, aquatic plants, algae, sediment dwelling organisms, honeybees, earthworms, other macro- and meso fauna, and soil micro-organisms), and eleven specific human health issues (carcinogen, mutagen, endocrine disruptor, reproduction/development effects, acetyl cholinesterase inhibitor, neurotoxicant, respiratory tract irritant, skin irritant, skin sensitiser, eye irritant, phototoxicant) were considered in this study. These are standard toxicity endpoints, and are in line with the endpoints considered in EC and EFSA assessments\textsuperscript{57} (see endpoints correspondence in Supplementary Table 2).

**The pesticide scenarios**

Nine pesticide scenarios were defined in this study (Fig. 1; Supplementary Table 3): a reference, Business As Usual scenario and eight pesticide reduction scenarios inspired by the Farm to Fork Strategy pesticide reduction goals:

1. Business As Usual - BAU: a scenario with no pesticide use restrictions. BAU covers the 230 selected a.s. (FU/HB/IN), and assumes all EU farms have current recommended pesticide input. BAU is assumed to be the initial condition to the following reduction scenarios.
2. Low Dose Pesticides only - LDP: a scenario where only the 174 a.s. with application rates < 1 kg/ha/year are allowed. LDP assumes all EU farms will only use low dose pesticides.
3. No Herbicides - NH: a scenario where herbicides are not allowed. NH covers the 139 FU/IN or multi-action a.s., and assumes all EU farms will use non-chemical alternatives to control weeds.
4. Fast Degradable Pesticides only - FDP: a scenario where only the 106 FU/IN/HB with DT\textsubscript{50} (50% degradation rates) in soil lower than 100 days are allowed. FDP assumes all EU farms will only use fast degradable pesticides.
5. Total Pesticides Ban - TPB: a scenario where all the 230 synthetic a.s. are no longer allowed. TPB assumes all EU farms will be converted to organic production. In hazard reduction assessments, PBT covers the 60 FU/IN/HB that are still likely to be found in the environment after pesticide use stops (i.e., a.s. with DT\textsubscript{90} > 365 days), and possible posing risks to humans and ecosystem.
6. Candidates For Substitution Excluded - CFSE: a scenario where the 49 a.s. identified by the EC as candidates for substitution are no longer allowed. CFSE covers the other 181 FU/IN/HB not included in the candidates for substitution list. CFSE links the two Farm to Fork pesticide reduction goals, i.e. reduction of overall pesticides and the more hazardous pesticides.
7. Low Hazard Pesticides only – LHP: a scenario where the a.s. with the hazard scores \(\geq 15\) for humans or hazard scores \(\geq 31\) for ecosystem are not allowed. The a.s. hazard scores were estimated based on severity of effects on standard (eco-)toxicity endpoints - see methods for details. The 15 and 31 thresholds were
established based on BAU hazard scores histograms. LHP covers 136 a.s. with low hazard scores, and assumes all EU farms will only use these lower hazard pesticides.

8. Safe Human Health - SHH: a scenario where only the 49 a.s. known to not cause appreciable human health problems are allowed. These a.s. are known not to be carcinogenic nor mutagenic, and most likely not (i.e. known not to be + no data available) an endocrine disrupter, neurotoxin or a causing agent of reproduction/development adverse effects. SHH assumes all EU have will only use SHH pesticides.

9. Low Ecosystem Toxicity - LET: a scenario where only the 57 a.s. with low or moderate toxicity to ecosystem are allowed. These a.s. are known to have low or moderate toxicity on mammals (acute), birds, fish, aquatic invertebrates, aquatic plants, algae, honeybees, earthworms (acute), and no significant adverse effects on soil micro-organisms. LET assumes all EU farmers have only access to LET pesticides.

Although inspired by the Farm to Fork Strategy 50% pesticide use and risk reduction goals\(^\text{15}\), the scenarios were defined based on practical a.s. cut-off criteria and not on a reversed 50% goal reasoning. All reduction scenarios were defined as potentially applicable policy alternatives. The scenarios differ on the type and number of a.s. allowed, while the annual application rates of individual a.s. (derived from the EC approved, a.s. representative uses) remain the same across scenarios to guarantee efficient pest control.

**Pesticide-crop profiles**

As mentioned above, each a.s. in the EU market is approved by the EC to specific representative uses; when the representative uses of all substances approved per pesticide scenario are compiled and re-organized by crop type, a list of allowed a.s. per crop arises (a pesticide-crop profile). In order to explore a reasonable yet relevant number of pesticide-crop profiles, the specific crops from the representative uses were aggregated into eight crop classes: cereals, dry pulses-vegetables-flowers, grapes, (temporary) grassland, maize, non-permanent industrial crops, permanent crops, and root crops. The attribution of the specific crops in the a.s. representatives use into our crop classes followed the LUCAS 2018 classification\(^\text{58}\) (Supplementary Table 4). Maize and grapes were not merged into broader classes due to their particularly high frequency in representative use records. Pesticide-crop profiles take into account the different a.s. and their application rates across the three EU regulatory zones\(^\text{13}\): Northern Europe (NEU), Central Europe (CEU) and Southern Europe (SEU; Supplementary Table 5).

**Use and hazard of a.s.**

Total a.s use per combination of crop class-EU region-scenario was estimated using a conservative approach based on a.s. current representative uses; it is assumed that all the a.s. allowed per crop class-EU region-scenario were applied at the recommended application scheme leading to their highest annual application rate. Annual application rates were calculated as the product of the (highest) number of recommended applications per year and the (maximum) recommended application rate per treatment in the respective representative use. When an a.s had the same annual application rate for different representative uses, we selected the representative use leading to the highest predicted concentration in soil right after pesticide application (highest PECs 0; values extracted from the a.s. EU dossiers), to account for the worst-case scenario.

Hazard predictions involved a slightly more complex approach, with the attribution of hazard scores to the PPDB qualitative classes in order to allow comparison of a.s.. The hazard scores were attributed to these qualitative classes as follows: a) human endpoints: known to have no effect = 0, no data available = 1, possible effect
(status not identified) = 2, known effect = 3; b) other terrestrial and aquatic non-target species’ endpoints: low toxicity = 0, no data available = 1, moderate toxicity = 2, high toxicity = 3; c) soil micro-organisms’ endpoints: no significant adverse effect = 0, no data available = 1, EC/NOEC value or chronic effect = 3. The score 0 was attributed to ‘low toxicity’ because while aiming for a similar score system for human and ecosystem endpoints the ‘low toxicity’ class seemed the closest to ‘no effect’, or to a possibly acceptable effect; remember that in order to be market approved by the European Commission, an a.s. must not have any harmful effect on animal and human health nor any unacceptable effect on plants and environment\textsuperscript{13}. A slightly higher score was attributed to ‘no data available’ class to account for possible toxicity situations hidden by data confidentiality. The main reason why (eco)toxicity data might be missing in PPDB relates to fact that it has not been made available for the public domain and so PPDB does not have it or do not have permission to use it. Different a.s. were compared based on their cumulative hazard scores to ecosystem or human, obtained from the sum of the hazard scores of the a.s. in the different ecosystem or human endpoints, respectively. The same weight was attributed to all endpoints; add a second layer to the score system based on our interpretation of endpoints severity could lead to a biased LHP scenario. Hazard reductions were calculated based on the difference in the number of a.s. per qualitative class-endpoint-scenario compared to respective BAU figures. Overall hazard reductions are the average of the reductions in high or moderate ecotoxicity endpoints, or of the reductions in known or possible human effects. As in use predictions, it was assumed that all a.s. allowed per scenario (or covered in the case of TPB) were applied.

Declarations

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AUTHOR CONTRIBUTIONS

VS: Conceptualization, data collection and data analysis, writing original and final draft. VG and CR: Conceptualization, resources, funding acquisition, review and editing of the original and final draft. XY and LF: Conceptualization, review and editing of the original draft.

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Figures
Figure 1

Diagram used in the selection of the pesticides considered in this study, including the different pesticide reduction scenarios. BAU = Business As Usual, LDP = Low Dose Pesticides only, NH = No Herbicides, FDP = Fast Degradable Pesticides only, TPB = Total Pesticides Ban, CFSE = Candidates For Substitution Excluded, LHP = Low Hazard Pesticides only, SHH = Safe Human Health pesticides only, LET = Low Ecosystem Toxicity pesticides only. For the list of active substances excluded per criterion, see Supplementary Table 1. For the list of substances allowed per pesticide scenario, see Supplementary Table 3. N = number of active substances.
Figure 2

Histograms for the maximum recommend annual application rates of the 230 selected active substances (in kg/ha/year; a), and cumulative hazard scores for ecosystem and human (b and c, respectively). Twenty ecotoxicological endpoints and eleven human toxicity endpoints were used to characterize a.s. hazard to ecosystem and humans, respectively. 0-3 hazard scores were used to assess the degree of effect in each endpoint. For details on score system see methods section. The a.s. with ecosystem-cumulative hazard scores ≥31 and/or human-cumulative hazard scores ≥15 were considered highly hazardous a.s, and therefore excluded in the LHP scenario.
Figure 3

Maximum recommend annual application rate of the 230 selected a.s., according to their EU representative uses. The dot colour indicates the crop at which the maximum recommended annual application rate per a.s. is expected. Given the high variability of maximum annual application rates across a.s., data is presented in four panels according to input ranges: >100 kg/ha/year, 10-100 kg/ha/year, 1-10 kg/ha/year, <1 kg/ha/year. The a.s. with maximum annual application rates >1 kg/ha/year were considered of top use a.s, and were therefore excluded in the Low Dose Pesticides only (LDP) scenario. For readability purposes only the name of the 20 top use a.s. were added to the graph; for the full list of a.s. excluded/covered in LDP scenario see Table S3. When the maximum annual application rate of an a.s. was common to more than one crop, a lower case letter was added. Letters correspondence (the first crop mentioned is the one presented in the figure) - a: Perm. crops/grapes, b: root crops/cereals, c: root crops/DPVF, d: cereals/DPVF/grassland, e: cereals/DPVF/root crops, f: NPIC/maize, g:maize/DPVF, h: grapes/DPVF, i: root crops/grapes, j: maize/root crops/NPIC, k: NPIC/DPVF, l: maize/cereals, m: root crops/NPIC, n: DPVF/cereals, o: root crops/Perm. crops, p: DPVF/NPIC/root crops, q: DPVF/Perm.
Figure 4

Cumulative hazard scores of the selected 230 a.s. to ecosystem. Hazard scores were attributed to the severity of effect per in the endpoint as follows: low toxicity=0, no data found=1, moderate toxicity=2, high toxicity=3. For soil carbon and nitrogen mineralisation: no significant adverse effect=0, no data available=1, EC/NOEC value or chronic effect=3. The scores in the different endpoints were summed up to obtain the cumulative score per a.s. For complete a.s. hazard profiles see Supplementary Fig. 2. The a.s. with cumulative scores $\geq 31$ were considered of top hazard for ecosystem, and were therefore excluded in the LHP scenario.
Figure 5

Cumulative hazard scores of the selected 230 a.s. to humans. Hazard scores were attributed to the severity of effect in the endpoints as follows: no effect=0, unknown effect=1, possible effect=2, known adverse effect=3. The scores in the different endpoints were summed up to obtain the cumulative score per a.s. For complete a.s. hazard profiles see Supplementary Fig. 3. The a.s. with cumulative scores $\geq 15$ were considered top hazard for humans and therefore excluded in the LHP scenario.

Figure 6
Scatter plot of human and ecosystem cumulative hazard scores of the 230 selected a.s. Different colours were attributed to different classes of maximum recommended annual application rates, and increasing symbol sizes were attributed to highest input levels, to allow the visualization of a.s. with same human-ecosystem scores but different input classes.

Figure 7

Reductions in the number of a.s. allowed, total a.s. use, and on overall hazard to ecosystem and human in the different pesticide reduction scenarios. Overall use reductions are the average values of all crop-EU region reductions in respective scenario. Overall hazard reductions are the average values of all ecotoxicological or human endpoints reductions in respective scenario. Reductions were calculated using Business As Usual (BAU) scenario values as reference. LDP = Low Dose Pesticides only, NH = No Herbicides, FDP = Fast Degradable Pesticides only, TPB = Total Pesticides Ban, CFSE = Candidates For Substitution Excluded, LHP = Low Hazard Pesticides only, SHH = Safe Human Health, LET = Low Ecosystem Toxicity. For crop-EU regions use reductions see Supplementary Table 14. For (eco)toxicological endpoints hazard reductions see Supplementary Table 31.

Supplementary Files

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