Identifying pesticide cocktails at country-wide scale

General comments

This study presents an original and well-designed method to characterize the mixtures of currently used pesticides that wildlife may be exposed to in agrosystems. This approach was developed at country scale, based on available public data about sales of pesticides and cropping, and seems reliable to identify specific groups of pesticide mixtures, identify the spatial distribution of such groups, and identify both pesticides of broad use that are applied nationally and on different crops and "discriminating" compounds which are of specific use geographically and/or agronomically.

Within the current context of dramatic biodiversity loss in agricultural landscapes, providing knowledge to help understanding and predicting wildlife exposure to and unintentional impacts of pesticides on ecosystems is of crucial importance, making this manuscript of high scientific interest. The methods are scientifically sound, and the MS is well written.

As a consequence, I have a few minor remarks listed hereafter, but also I point out several drawbacks. The first one is about the recurrent use of the word "cocktail" even in cases where the related concepts and paradigms would justify using "mixture" instead. The second concern is about a validation of the approach, a way to corroborate the findings and interpretation, which is partly lacking. This may be achieved by considering further comparison with one of the references already cited, and by adding data and results from environmental surveys in France which report the mixtures actually found in environmental matrices (soil, air, water) and biota. The test of the temporal robustness should be refined by comparing the output from the "core" year 2017 to the output obtained from the dataset on the other years without including 2017. These issues are detailed in specific comments.

I thought in some cases within the manuscript that English language may be seen as of unequal quality. But I am not a native English speaker, I can neither perform a fully relevant review of English writing nor assert whether a review of English language is really needed or not.

Detailed comments

Title and throughout the manuscript – usually the word "cocktail" is used when dealing with (toxic) responses of organisms, since it refers to concepts and paradigms related to "cocktail effects" with underlying mechanisms and modelling of antagonism, additivity and synergy between compounds in inducing effects in organisms. Within the context of environmental chemistry and issues related to exposure, which is the case here in this study, the word "mixture" of pesticides or exposure/co-exposure to multiple compounds is used. This is the case in scientific literature as well as in regulatory context (see for instance (Beronius et al., 2020)). I recommend in the title and when relevant in the manuscript to use "mixture" instead of "cocktail", and keep the latest only when referring to toxicological issues.

Beronius, A., Zilliacus, J., Hanberg, A., Luijten, M., van der Voet, H., van Klaveren, J., 2020. Methodology for health risk assessment of combined exposures to multiple chemicals. Food Chem. Toxicol. 143, 111520. https://doi.org/10.1016/j.fct.2020.111520

Line 88. The reference of the database and/or URL must be added.

Line 93. “[…] a well-suited case country to try and identify pesticide […]” something weird in this sentence. “[…] a well-suited case country to try *identifying* pesticide […]”?

Line 96-101. The end of the introduction looks like a conclusion or summary rather than a classical end of introduction where expectations and hypotheses are usually described. I suggest to modify.

Line 106. The amount of what? Please provide details.

Lines 103-112. To make it clear for the readers, it would be necessary to explain the administrative and spatial meaning of postcode in France. (what is “township” versus “district”, the average size of township surfaces and their potential variability).

Lines 124-125. The probability that compounds are not used over the same postcode than bought is high looking at the organization of farms nowadays. It may be worth mentioning that however they are likely to be used closely, in the vicinity of the administrative location of the farmer, so in surrounding postcodes (which allow studying the spatial patterns at the national scale).

Lines 139-140. Is this related or similar to the “Registre parcellaire graphique (RPG)”? On official websites it is indicated that the annual RPG versions before 2013 (2010, 2011 et 2012) are available on the webpages of the “Agence de service et de paiement” while the most recent RPG versions since are available at “data.gouv.fr”. Since the data of pesticide sales in 2017 were studied, why not using the RPG data from 2017? The authors should explain why not using the RPG and what was the year of concern.

Lines 144-146. As far as I well understand, the total cropping area was summed up, thus merging both conventional and organic farming? Could this introduce a bias in further analyses and interpretation of the data since most of, if not all in the list studied, synthetic pesticides are not used in organic farming and the surfaces of organic farming might not be homogenously distributed in space at the township and/or the national scale. The plots cultivated under organic farming are available in the RPG.

Line 260. Please check the writing of “k”.

Line 301-312. It is a very good point that authors checked the reliability of the method over time. However, the fact that the data from the year 2017 are present in the two dataset is a flaw, since this of course artificially increases the probability of correlation, creates an absence of statistical independence between the measurements. It may be recommended to perform the same approach but comparing the output from 2017 to the output from the dataset ***2015-2018 without 2017***.

592 entirely surprising because of the presence of the 2017 data in both analyses.

Line 334. The end of the sentence in the Figure’ legend may be missing.

Figure 3. I get the point that authors focused on readability of the graph, choosing not to show the pesticide names, that is understandable. However, given the key issue of the study, i.e. “identify the number and composition of pesticide cocktails potentially occurring in French farmland” and provide lists of compounds that could of concern for regulation and for combined tests of toxicity, it would definitely be better to have the names of the pesticides at least in one principal figure of the manuscript. Moreover, large parts of the results / discussion mention pesticides that cannot be seen on information within the text but only as Supplementary Information. I recommend modifying the Figure, adding the names of the compounds in Figure 3 as it is done in Figure S8.

Lines 458-462. An interaction between the factors “type of crops” and “geographic location” is likely to be expected because plant pathogens and organisms considered as pests are heterogeneously distributed over space at the national scale due to climate and to distribution range. This means that for a given type of crops, the composition of pesticide mixture may be expected to vary between north/south and east/west for instance. While for a given geographic region the mixture of pesticides may be expected to differ between crops. Except for broad-spectrum pesticides that are not specific to one target plant protection issue only but may be used under various contexts. Another important issue is about the “spatially closer postcodes groups”: what is the extent, the spatial scale considered as “close”? Could we expect a role of farmer’s cooperatives, regulatory of administrative bodies (e.g. “chambre régionale d’agriculture”) and advisers/dealers of pesticides sellers on influencing the geographic patterns and thus the correlation between the geographic distance and active substance compositions of groups? If so, what is the spatial scale of correlation expected? Regional more than local or the other way round? How to disentangle from the effects of climate/spatial distribution of pests/spatial distribution of crops?

Line 501. Thiram… tebuconazole

Line 512. “substances are used with in the buying area”, with?

Line 531. “effects have already been studied. but mostly on pairs of substances”. Please check, the dot likely not should be there.

Line 533. A few recent studies under controlled conditions addressed broader mixtures, for instance using mixtures of herbicide/insecticide/fungicide or even larger using soils sampled in *natura*. See for instance:

Glinski, D.A., Purucker, S.T., Van Meter, R.J., Black, M.C., Henderson, W.M., 2019. Endogenous and exogenous biomarker analysis in terrestrial phase amphibians (Lithobates sphenocephala) following dermal exposure to pesticide mixtures. Environ. Chem. 16, 55–67. https://doi.org/10.1071/en18163

Panico, S.C., van Gestel, C.A.M., Verweij, R.A., Rault, M., Bertrand, C., Menacho Barriga, C.A., Coeurdassier, M., Fritsch, C., Gimbert, F., Pelosi, C., 2022. Field mixtures of currently used pesticides in agricultural soil pose a risk to soil invertebrates. Environ. Pollut. 305, 119290. https://doi.org/10.1016/j.envpol.2022.119290

Van Meter, R.J., Glinski, D.A., Purucker, S.T., Henderson, W.M., 2018. Influence of exposure to pesticide mixtures on the metabolomic profile in post-metamorphic green frogs (Lithobates clamitans). Sci. Total Environ. 624, 1348–1359. https://doi.org/10.1016/j.scitotenv.2017.12.175

Line 550. It would be necessary to address further comparisons with environmental surveys to check whether the core and discriminating substances identified in this study in group of postcodes have indeed been also detected in the environment or biota over the given postcodes. And also to check for the “crop effect” among other factors. The reference to the results of Silva et al (2019) is indeed relevant, and could be even more used to compare the results on the influence of crop type and geographical gradients (N-S, E-W). However, one might consider it of marginal significance to support the findings about the compounds characterizing the groups in the present French study and where they are used at national level. The fact that the compounds were indeed found (or not found) in field surveys in France could support the conclusions of the study about the relevance of the approach to identify mixtures of concern for environmental risks. The main trouble is of course to find data about current pesticide screening in soil, water, air or biota that could be used to compare with the data on purchase in France. Although incomplete in terms of selected screened compounds, year of sampling, location etc… some references/dataset may be useful for comparisons with the sales of pesticides presented here to ensure the reliance of the study. The authors may consider for instance the following:

https://data.eaufrance.fr/ - screenings of banned and currently used pesticides in surface water are performed regularly at the national level and the data are available.

https://www.atmo-france.org/article/phytatmo - in some years, measurements are performed in air samples using a multi-residue analytical menu screening many compounds and results are delivered by region or district.

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