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Protocol for a systematic review and meta-analysis of human exposure to pesticide residues in honey and other bees' products

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ABSTRACT

Background: The presence of pesticides in honey and related products is an increasing concern for consumers and producers, although there is lack of data on the current burden of exposure of the general human population through these products. We present a protocol for a systematic review and meta-analysis of contamination to insecticides, herbicides and fungicides of products from honeybees, and an estimation of how much the consumption of these products contributes to the ADI (Acceptable Daily Intake) of selected substances.

Objectives: We aim to systematically review and meta-analyse studies on the contamination to plant protection products in honey, royal jelly, beeswax and propolis, applying the Navigation Guide and WHO-ILO systematic review methodology as an organizing framework.

Data sources: We will search electronic academic databases for potentially relevant records from PubMed, TOXNET and EMBASE. We will include quantitative studies analysing the contamination from insecticides, herbicides and fungicides in honey, propolis, royal jelly and beeswax. In particular, we will evaluate the presence of the following substances and classes of pesticides: Glyphosate, Chlorpyrifos, pyrethroid and neonicotinoid pesticides, fungicides and acaricides.

Study appraisal and synthesis methods: At least two authors will independently screen titles and abstracts at a first stage of review, and full texts at a second stage, of potentially eligible records against the eligibility criteria; data extraction of included studies will then be performed by at least two authors, in blind. At least two authors will assess risk of bias and the quality of evidence, using the most suited tools currently available. The data on prevalence of contaminated samples and concentration of pesticides in the products will be combined using meta-analysis: when more than three studies reporting the necessary measures to fit the models are available, meta-analysis will be performed separately by product and by exposure; otherwise, weighted descriptive analysis will be performed. We will report the results using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).

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1. Introduction

1.1. Rationale

It is well known that pollinators, in particular bees, play a fundamental role in the functioning of nearly all existing terrestrial ecosystems, including those that are agriculturally dominated: nearly 76% of the most important food crops, including seed crops, fruits and vegetables, are pollinated by animals (Klein et al., 2007; Pindar et al., 2017).

Extensive honeybee declines, particularly during the past few decades, have been recorded across the world (Neumann and Carreck, 2010). If bee losses continued at the pace registered so far, the supply of around 100 pollinated crop types could be threatened (Dötterl and Vereecken, 2010), equating to 35% of the global food production (Genersch et al., 2010), as well as natural biodiversity (Wisniewski, 2016).

The current decline of honeybees and other bee species has initiated significant research efforts in order to ascertain suitable explanations behind its occurrence, as well as calls for action from governments and international organizations. However, the reasons behind their decline are still not fully understood (Aston et al., 2009), as no single factor has been identified as being responsible for the simultaneous declines witnessed all over the world.

Plant Protection Products (PPPs) are believed to be one of the key drivers behind pollinator's decline (Cullen et al., 2019). One of the side effects of the use of agricultural pesticides is, indeed, the accidental poisoning of the surrounding environment, including the fauna: reports of accidental honeybee poisoning first appeared during the early 1870s. Modern insecticides and application procedures have been developed to directly affect target insects, and therefore to be safer for beneficial pollinators; fungicides and herbicides, though, are massively used in modern agriculture, and are usually applied in places where pollinators are active (Cullen et al., 2019; EUROSTAT, 2018). Consequently, a well-established body of evidence exists, reporting instances of contamination (Lundin et al., 2015; Pisa et al., 2017) of bees and their products from many types of pesticides, fungicides and herbicides, and their harmful effects on bees' health and survival. In particular, recent research has highlighted possible effects of fungicides on food consumption, metabolism and the immune response (Liao et al., 2017; Mao et al., 2017; Cizelj et al., 2016), and effects on bee navigation, learning and larval development (Mengoni Goñalons and Farina, 2018; Dai et al., 2018; Balbuena et al., 2015) of herbicides. Recently, the EFSA updated its risk assessments of three neonicotinoids (Clothianidin, Imidacloprid and Thiamethoxam), gathering all scientific evidence published since the previous evaluations: they concluded that most neonicotinoid pesticides represent a risk to honeybees (EFSA, 2018).

1.2. Objectives

We intend to systematically review, analyse and synthesise the available evidence on the proportion of contaminated samples out of total samples, and the concentration of pesticides in bees' products used for human consumption. In particular, we will concentrate on quantitative studies reporting the prevalence and/or a concentration of Glyphosate, Chlorpyrifos, pyrethroid pesticides, neonicotinoid pesticides, and/or fungicides, in samples of honey, beeswax, royal jelly and/or propolis.

Furthermore, we aim at estimating, for each exposure of interest, the contribution to the Acceptable Daily Intake that is assumed through the consumption of contaminated honey, so that we can provide valuable information on the share of the Acceptable Daily Intake (ADI) of pesticides assumed through these type of products for adults and children.

To our knowledge, this is the first systematic review that collects and organizes the existing evidence on the contamination of bees' products from pesticides, herbicides and fungicides, in order to quantify the amount of their intake from humans attributable to the consumption of honey, propolis and royal jelly. Our review is expected to provide results that can be used to estimate the burden of exposure to PPPs for humans derived from the consumption of honey, propolis and royal jelly.

2. Methods

Our methodology adheres to the guidelines for accurate and transparent health estimates reporting, such as the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA) (Moher et al., 2015; Shamseer et al., 2015; Beller et al., 2013Liberati et al., 2009), the Navigation Guide (Woodruff and Sutton, 2014; Koustas et al., 2014), the Cochrane Collaboration Higgins and Green, 2011(and the WHO/ILO joint methodology for systematic reviews (Mandrioli et al., 2018). In particular, we will apply the Navigation Guide methodology for systematic reviews in environmental and occupational health (Woodruff and Sutton, 2014; Koustas et al., 2014), as adapted by WHO-ILO, which developed the first guiding methodological framework specific for prevalence studies of exposure (Mandrioli et al., 2018). The Navigation Guide applies established systematic review methods from clinical medicine, including standard Cochrane Collaboration methods for systematic reviews of interventions, to the field of environmental health, to ensure systematic and rigorous evidence synthesis on environmental risk factors that reduces bias and maximizes transparency. Being this work focused on exposures only, the Navigation Guide will be adapted in several parts (Mandrioli et al., 2018).

We are contextually registering the present protocol in PROSPERO; any modification of the methods stated in the present protocol will be registered in PROSPERO and reported in the systematic review itself. This protocol adheres with the preferred reporting items for systematic review and meta-analysis protocols statement (PRISMA-P) (Moher et al., 2015; Shamseer et al., 2015).

2.1. Eligibility criteria

The "Population, Exposure, Comparator and Outcome" criteria (PECO Statement) (Woodruff and Sutton, 2014) for the systematic review are here briefly described. A complete overview of inclusion and exclusion criteria is given in Annex 1.

2.2. Types of population

We will include quantitative studies on products of honeybees that are usually intended for human consumption, namely honey, beeswax, royal jelly and propolis. These substances are not only consumed as food, but also used as natural medication, supplements or additives, or for the preparation of cosmetics and pharmaceuticals; for the scope of this review, nevertheless, we will focus on human consumption only.

2.3. Types of exposures

We will include quantitative studies that evaluated in the products of interest the presence of at least one of the following plant protection products, related metabolites or environmental degradation products:

- Glyphosate: glyphosate, aminomethylphosphonic acid (AMPA);
- Chlorpyrifos: chlorpyrifos, 3,5,6-trichloro-2-pyridinol (TCP);
- Pyrethroid pesticides: cyclopropane carboxylic acids (Cl2CA), phenoxybenzoic acids (m-PBA);
- Neonicotinoid pesticides: 6-chloronicotinic acid (6-CNA), imidacloprid;
- Fungicides: ethylenethiourea (ETU) thiazolidine-2-thione-4-carboxilic acid (TTCA).

The substances were chosen based on a study regarding sales of

several pesticides and residues in water from the Italian Institute for Environmental Protection and Research (ISPRA, 2016) and data on residues in food from EFSA (EFSA European Food Safety Authority, 2016). We also aimed to maintain coherence and comparability with other recent studies that investigated the contamination of pesticides of sample families, tracing their urine before and after a total organic diet (Hyland et al., 2019; Magnér et al., 2015).

2.4. Types of comparator

The theoretical minimum proportion of contaminated sample and theoretical minimum concentration of PPPs is zero, in the case they were extracted from a hive whose colony was never exposed to any insecticide, herbicide, fungicide or acaricides (some studies present samples extracted from wild hives located in forests, to have "blank samples" to base their comparisons on). Zero is probably more a theoretical than a realistic minimum proportion or level of contamination, given the widespread diffusion of PPPs. Furthermore, even if the methods to extract and quantify contamination in honey are improving in variety of detectable substances and in precision, there are always limits of quantification and detection, below which it is impossible to determine if, and to which extent, the products contain pesticides.

2.5. Types of outcomes

Being this work focused on exposures only, the proportion of contaminated samples, and the concentration of PPPs in bees' products for human consumption are the outcomes of interest.

2.6. Types of studies

We will include studies that quantitatively assess the proportion of contaminated samples and/or the concentration of the aforementioned pesticides, herbicides and fungicides in samples of the bees' products meant for human consumption.

We will exclude field and semi-field studies qualitative, modelling and case studies, studies that analyse samples in order to validate and test the performance of novel methods for extracting and quantifying residues, as well as non-original studies without quantitative data (e.g. reviews letters, commentaries and perspectives).

We will include objective measures of the concentration of PPPs, such as number of contaminated samples on total number of samples analysed, their mean concentration, and relative measure of variability (variance, S.D. or S.E.) for each PPPs. Subjective or partial measures (e.g., range of contamination, maximum level detected) will be excluded.

2.7. Years and language

Records published from 1980 to present, and in any language known by the reviewers (Dutch, Danish, English, Italian, French, Spanish, Portuguese, and Romanian) will be included.

The year 1980 was chosen as starting point for the systematic review based on the fact that different pesticides of interest were scarcely used or not even marketed before the '80s (e.g. neonicotinoids pesticides, glyphosate). On the other hand, choosing a starting point quite far in time allows for the possibility of observing the trend over time of the prevalence of contamination and the concentrations of PPPs in the products.

2.8. Information sources

We will search the following electronic academic databases for potentially eligible records:

- PubMed (1980–2020)
- EMBASE (1980–2020)
- TOXNET (1980–2020).

Furthermore, OpenGrey will be screened for grey literature, and the first 100 results obtained from Google and Google Scholar will be evaluated to check if any pertinent, non-duplicate result can be found. We will perform searches in electronic databases operated in English using a search strategy in English.

Before the publication of the final version of the systematic review, the search will be performed again, in order to update the set of studies and catch those that might be pertinent but will be published after the initial literature search.

2.9. Search strategy

Suitable systematic search strings will be prepared with the contribution of a librarian for each electronic database, including key-terms and database-specific terminology. We will modify the search strings based on the database. Strings will aim at being as inclusive as possible, so that no relevant publication should possibly be missed.

We report here the keywords that will be included in each search string that will be used in different databases:

- honey, beeswax, royal jelly, propolis, honeybee
- pesticide, insecticide, herbicide, fungicide.

2.10. Study records

2.10.1. Data management

Lists of all retrieved references will be exported from the electronic databases and stored in EndNote. The DistillerSR software from Evidence Partners will be used for title-and-abstract screening and for full-text screening EvidencePartner, 2017. Reasons for exclusion of articles at each stage will be documented in DistillerSR.

2.10.2. Selection process

After electronic and manual search and exclusion of duplicates, at least two review authors will independently screen the relevant literature. The first screening will be based on titles and abstracts; pertinent references will be screened again, basing the decision on full texts. Any conflict between the two authors will be resolved by a third author. Every step of the study selection will be documented in a flow chart, as per PRISMA guidelines. A complete list of all references retrieved and separate lists for the included and the excluded at each step, with the respective reason for exclusion, will be available as well.

2.10.3. Data collection process

A data extraction template in Excel format will be developed and piloted until convergence and agreement among data extractors is reached. At a minimum, two review authors will independently extract data from all literature resulted relevant after the screening process; a third author will be nominated to resolve conflicting extractions, if any.

In case any missing data is needed, we will send out a request to the principal study author by email or phone, using the contact details provided in the study record.

2.11. Data items

For each included study record, we will extract at minimum:

- information to identify the study (e.g., ID, title, authors, year of publication, journal, DOI …), the financial disclosures and funding sources of each author and their affiliated organization; information about the study design (type of study, country, place, year and period where it was performed, …);
- information about the methods of extraction and quantification of

exposure;
- information about the product examined and the exposure analysed;
- quantitative measures (proportion of contaminated samples, mean level of contamination of all substances identified, measure of dispersion).
- additional information about human exposure to PPPs (general population and/or occupational), if available.

2.12. Outcomes and prioritization

The outcomes of interest, for which information will be sought, in order to quantitatively summarise data, are the following:

- proportion of contaminated samples, meaning number of contaminated samples out of total samples analysed;
- quantification of the contamination, meaning the concentration of PPPs found in contaminated samples (samples where the level of PPPs could be quantified, > LOQ), and corresponding measures of variability, meaning the variance, Standard Error or Standard Deviation of the concentration of PPPs.

All the outcomes will be sought and extracted for all bees' products for human consumption, namely honey, propolis, royal jelly and beeswax, and for all plant protection products of interest (see paragraph Types of exposure).

2.13. Risk of bias in individual studies

We will use a modified version of the WHO/ILO joint methodology Risk of Bias tool, which has been developed specifically to assess prevalence studies of risk factors (see Annex 2). We will assess the risk of bias of the studies, separately evaluating five domains:

- selection bias;
- performance bias;
- misclassification bias;
- conflict of interest; and
- other possible biases.

Risk of bias can be judged as "low"; "probably low"; "probably high"; "high" or "not applicable". To evaluate the risk of bias in each domain, we will apply *a priori* instructions.

All risk of bias assessors will trial the tool until they synchronize their understanding and application of each risk of bias domain, considerations and criteria for ratings. At least two study authors will then independently judge the risk of bias for each study, and a third author will resolve any conflicting judgments.

To present the findings of the risk of bias assessment, we will report for each included study the assessment for each domain in a standard Risk of Bias table, as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* Higgins et al., 2011. Our risk of bias assessment will also be presented in a standard 'Risk of Bias summary' figure.

2.14. Data synthesis

Meta-analysis will be performed for the two main outcomes of interest extracted from the studies:

- the proportion of contaminated samples out of total samples analysed, and
- the concentration of pesticides in contaminated samples.

Each analysis will be performed separately by product and by exposure.

Quantitative synthesis of the results will be performed only on studies that analyse at least 10 samples for each bees' product; furthermore, meta-analysis will be conducted only on the PPPs that will be found in more than three studies per product.

We will produce summary measures and synthesise the evidence quantitatively (i.e., meta-analysis). The type of model to be used for meta-analysis will be chosen based on the evidence: meta-analysis will be likely performed using *random-effects models*, since we expect the sets of studies to be heterogeneous in their methods and in the characteristics of the included samples. For all models, the restricted maximum-likelihood estimator (REML) will be used to estimate the residual heterogeneity. For every analysis, forest plots will be reported; when analyses highlighted possible outliers and/or influential cases, these will be explored, using both sensitivity analysis and hypothesis tests. Consistency among the available data will be explored and tested using I^2.

The softwares StataIC version 15, RStudio (R Core Team, 2018), in particular the "metafor" package (Viechtbauer, 2010a,2010b), and ReviewManager version 5.3 will be used for quantitative synthesis of the evidence.

Information from all studies that will not be considered suitable for quantitative analysis will be collected in a separate table, so that a qualitative synthesis of their content is available.

Based on the results of the analysis of the proportion of contaminated samples, clusters that define the frequency of the contamination will be created. In particular, the contamination for each PPPs will be defined as:

- *rare*: the substance is present in < 1% of the samples;
- *relatively rare*: the substance is present in 1–5% of the samples;
- *relatively common*: the substance is present in 5–10% of the samples;
- *common:* the substance is present in > 10% of the samples.

Finally, the Average Daily Intake for each PPPs assumed through honey will be assessed**.** This estimate will be based on the summary measures obtained from random-effects models (or on the weighted mean, in case it was not possible to obtain a quantitative synthesis of the results).

There is no guideline for recommended daily intake of honey; however, it is a form of sugar, so intake should be moderate. The American Heart Association (AHA) recommends getting no more than 100 calories a day from added sugars; this is equal to a little over 6 teaspoons (around 25 g) (Johnson, 2009).

Regulatory agencies provide the measure of the Acceptable Daily Intake (ADI) for each plant protection product in this systematic review. All ADI will be taken from the European Pesticides Database, except for Coumaphos, whose use is forbidden in the EU; for this substance, the Reference Dose suggested from the RfD/Peer Review Committee on October 13th, 1994 will be adopted (US EPA, 1996).

Based on these quantities, we will estimate the percentage by weight of each pesticide's ADI assumed from honey samples considering:

1. Only samples of contaminated honey (and relative estimated levels of pesticides);
2. A consumption equivalent to the maximum recommended serving (25 g/day);
3. The intake of each substance that can be tolerated for an adult of 70 kg of weight.

It should be pointed out that, in case of children, the same daily intake of honey would lead to a higher percentage of each pesticide's ADI assumed from honey samples. This will be demonstrated repeating the same estimation, considering a child of 15 kg instead of an adult.

Based on the percentage the results will be clustered as follows:

- < 1%: the daily intake of the pesticide due to the consumption of

contaminated honey does not represent a significant fraction of the ADI;
- > 1%: the daily intake of the pesticide due to the consumption of contaminated honey does represent a significant fraction of the ADI.

2.15. Meta-biases

Selection bias will be evaluated in the risk of bias assessment of each individual study. If our systematic review will include ten or more studies, we will generate a funnel plot to judge concerns on publication bias. If it includes nine or fewer studies, we will judge the risk of publication bias qualitatively.

2.16. Confidence in cumulative evidence

We will assess quality for the entire body of evidence by product (honey, beeswax, royal jelly, and propolis). We will assess the quality of evidence using a modified version of the WHO/ILO joint methodology tool, which is based on the Navigation Guide quality of evidence assessment tool (Lam et al., 2016), and the GRADE approach, adapted specifically to systematic reviews in occupational and environmental health (Morgan et al., 2016) (see Annex 3). Should a more suitable method become available, we may switch to it.

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CRediT authorship contribution statement

Daria Sgargi: Conceptualization, Formal analysis, Methodology, Writing - original draft. **Balazs Adam:** Writing - review & editing. **Lygia T. Budnik:** Writing - review & editing. **Giovanni Dinelli:** Writing - review & editing. **Horatiu Remus Moldovan:** Writing - review & editing. **Melissa J. Perry:** Writing - review & editing. **Paul TJ. Scheepers:** Writing - review & editing. **Vivi Schlünssen:** Writing - review & editing. **João Paulo Teixeira:** Writing - review & editing. **Daniele Mandrioli:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Fiorella Belpoggi:** Writing - review & editing, Supervision.

Declaration of competing interest

All authors declare no financial conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.109470.

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