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Assessment of combined risk to pesticide residues through dietary exposure

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Abstract

Plant protection products (PPPs) are preparations intended to protect plants and their products including one or more active substances. The use of PPPs may cause direct or indirect risks. Residues that can remain in or on food might pose a danger to human health through consumption and acute or/and chronic exposure. Authorisation of active substances and PPPs are decided at European and national level, respectively. Risk assessment of dietary exposure to residues of PPPs is regulated by a very extensive legal framework, ensuring consumer safety. The review and evaluation of the residue section of active substance monographs and the dossiers for PPP authorisations within the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) helped gain hands-on experience on food risk assessment, as previewed in the framework of the European Food Risk Assessment Fellowship Programme (EU-FORA). The programme also focused on the cumulative effects of acute exposure to pesticides in food on the human nervous system using probabilistic methodology and it was in continuation of the work carried out by ANSES and the regulated products department residue unit. Using the European Database for processing factors for pesticides in food was one of the main challenges in order to approach a more realistic scenario of exposure. The probabilistic methodology followed was used in accordance with the European Food Safety Authority harmonised guidance.

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Keywords: plant protection products, pesticide residues, dietary risk assessment, combined dietary risk assessment, processing factors

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1. Introduction

The overall objective of the European Food Risk Assessment Fellowship Programme (EU-FORA) offered by the European Food Safety Authority (EFSA) is to give an opportunity to young and mid-career researchers to gain hands-on experience and skills on risk assessment in a food safety framework. This specific programme focused firstly on risk assessment of dietary exposure to residues of plant protection products (PPPs) on a regulatory basis and secondly, on combined dietary risk assessment of multiple pesticide residues.

The work was performed at the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) in the Residues and Food Safety Unit (URSA) within the Department of Regulated Products. URSA is responsible for the activities related to assessment of risks to human health via dietary exposure in the area of plant protection active substances and products, non-indigenous macro-organisms considered beneficial to plants and introduced into the environment, biocidal active substances and products, fertilisers, growing media and similar products. It is also responsible for assessing marketing authorisation application dossiers in the area of PPPs in the framework of the regulations in force.

This report will start with general background information on regulations concerning PPPs. The framework for PPPs authorisation in relation to their respective maximum residue levels (MRLs) will be briefly described focusing on the dietary exposure and risk assessment of residues. Finally, the issue of dietary exposure to multiple pesticides will be presented, summarising the available methodologies in the framework of regulatory science on European level. The need of refining the risk to be assessed towards more realistic approaches will also be discussed alongside with the surrounding uncertainties.

1.1. Regulation of plant protection products

Plant protection products are preparations intended to protect plants and their products. Herbicides, insecticides, fungicides, plant growth regulators and biocontrol are all grouped under pesticides, a group which also includes biocides.

Preparations consist of one or more active substances responsible for the action and use of the PPP. The risk assessment process is undertaken at two stages. Firstly, according to Regulation (EC) No 1107/2009¹ concerning the placing of PPPs on the market, prior to the authorisation of PPPs, active substances should be approved by the European Commission. In parallel, food and/or feed cannot be placed on the market without setting MRLs for the requested specific substance. Therefore, according to Regulation (EC) No 396/2005 on MRLs of pesticides in or on food and feed of plant and animal origin, MRLs for each combination of active substance and food should be set a priori using a harmonised approach in the European Union. The MRLs set assure that the remaining residues after the most critical agricultural practice pose no unacceptable risk for the consumers. Finally, as long as the active substance of the preparation is approved, the risk assessment associated with the specific and requested use of the PPPs is performed within different European geographical zones. At the end, the relevant Member states decide their authorisation at national level. France although typically belongs to the Southern zone, data of both northern and southern geographical zones are required to evaluate consumer exposure.

The Member States, the EFSA and the European Commission all have an active role in the procedure for approving active substances, setting MRLs and placing PPPs in the market.

1.2. Dietary risk assessment of pesticide residues

The use of PPPs may cause direct or indirect risks. Residues that can remain in or on food might pose a risk to human health through consumption and acute or/and chronic exposure.

For the authorisation of an active substance, the applicant needs to submit the dossier to a Rapporteur Member State (RMS), which will peer review the application and upon completion will discuss it with other member States and EFSA. At the end, EFSA will publish a conclusion to support risk managers and the final decision at European level. The PPPs risk assessment is similar, but the respective authorisation is decided on a national level upon geographical zonal requirements and recommendations.

¹ Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.

A very extensive legal framework regulates the risk assessment of active substances, PPPs and their respective residues in food and the environment. The data requirement to evaluate the risk because of PPP residues include evaluation of studies on the metabolism of the active substance in crops, animals and rotational crops to identify the relevant metabolites, as well as studies on processed and stored commodities. Residue trials in crops, rotational crops and animal feeding studies are amongst others required to estimate the final residues levels of the active substance in food according to the intended agricultural practice. These residue levels are then to be used in mathematical models to calculate the human chronic and acute exposure, in relation to relevant human health toxicological threshold values, usually expressed as a contribution percentage of the acceptable daily intake (ADI) and Acute Reference Dose (ARfD), respectively.

The critical evaluation of the data provided and the data treatment are both crucial for a transparent and harmonised approach within PPPs residues risk assessment.

1.3. Combined dietary risk assessment of multiple pesticide residues

In the framework of PPPs authorisation, Article 4 of Regulation (EC) No 1107/2009 specifies that combined or as previously used, cumulative effects of the residues of the PPPs should not pose a risk to human health as long as a appropriate scientific methodology is available. Similarly, article 14 of Regulation (EC) No 396/2005 specifies that cumulative effects in the framework of MRL setting must be taken into account.

EFSA has published a guidance document on the probabilistic approaches that should be applied when evaluating the combined exposure to pesticides (EFSA PPR Panel, 2012). Similarly, the European Commission (2018) has agreed that the approach for combined risk should be a tiered level approach (Tier I and Tier II) starting from the most conservative scenario so as to screen the overall global exposure, progressively reaching more realistic scenarios, still including some degree of uncertainty.

Under European funding (7th Framework Programme for Research), the statistical software Monte Carlo Risk Assessment (MCRA) was released by the Dutch National Institute for Public Health and Environment (RIVM). This is a statistical software that allows probabilistic analyses with a tiered approach according to EFSA's recommendations and the Committee's requirements on the risk assessment of dietary exposure to multiple pesticides. Exposure estimates are calculated for specific cumulative assessment groups (CAG) (e.g. nervous system) as described by EFSA PPR Panel (2013) on grouping active substances on the basis of their toxicological profile. Exposure estimates are calculated for specific percentiles of exposure distribution and as suggested by the risk managers, conclusions should be drawn using the 99.9th percentile. The expression of exposure can be based on margin of exposure or other type of threshold values and measurements. Uncertainties can be found in all steps of the risk assessment, both in hazard characterisation (CAG formation and residue definition) and the exposure calculation. The high non-detect and missing values in the monitoring programs, the actual use of the authorised pesticides on each crop, the extrapolation that could potentially be used and the effect of processing on the residues of the consumed commodity are some of the uncertainties that are systematically being evaluated. In this respect processing factors are applied to each food commodity and active substance combination. A comprehensive European database of reliable processing factors for multiple active substances was recently published (Scholz et al., 2018) and should be applied in the framework of a combined risk assessment, even at Tier I level.

Being still in the pilot phase of the systematic implementation of probabilistic approach, RIVM will soon publish cumulative exposure assessments to pesticide residues in food regarding acute and chronic effects on nervous and thyroid systems using MCRA software and based on CAGs published by EFSA PPR Panel (2013). Similarly, EFSA will publish a similar report after public consultation duplicating the methodology of RIVM but using RAS software and taking into consideration an updated CAG and new approaches agreed at European level. RIVM will soon release the final version of MCRA 8.3 taking into consideration more parameters and the aforementioned approaches agreed at European level. Using probabilistic approaches to evaluate the risk caused by dietary exposure to multiple pesticides and set MRLs for PPP on a regulatory basis poses a challenge. Significant steps have been made to systematically approach a realistic characterisation of the risk to be evaluated towards a harmonised way of methodology as proposed by EFSA at a national and European level (EFSA Scientific Committee, 2019).

2. Description of work programme

2.1. Aims

The objective of the work programme was to work on the dietary risk assessment of (a) residues of PPPs (b) multiple residues of PPPs using a probabilistic approach.

During the first part of the project, the objective was to understand and familiarise with the risk assessment procedures and European regulations of active substances and PPPs at European and national/zonal level. During the second part of the project, the aim was to assess the dietary exposure of the French population to multiple pesticides using the MCRA software while looking into the effect of processing factors by incorporating the newly published European database of processing factors for pesticides in food (Scholz et al., 2018)

Integration in the projects and activities within the regulated products residue and consumer safety unit at ANSES was the core objective of the programme.

2.2. Activities/Methods

2.2.1. Dietary risk assessment of pesticide residues

In the framework of active substance renewal and PPP evaluation, there was a training period on EU regulations and technical guides concerning active substances and placing PPPs on the market. Using the Organisation for Economic Co-operation and Development (OECD) guidelines on crops, rotational crops and livestock metabolism, residue definition in plant and animal commodities, stability of residues, processing studies, residue and feeding trials was in the core of the methodology used for the evaluations.

Part of this work consisted of reviewing the residue section of two active substance monographs that were under the renewal period; one fungicide and one insecticide. All sections concerning the residue section were considered and the comments were made in a reporting table format, which was delivered to EFSA and the respective RMS. After the respective periods of consultation and addressing of comments, EFSA decided if the points made were adequately discussed and in some cases, that expert consultation is further needed. Numerous evaluations of PPPs containing one or more active substances were also undertaken in the framework of zonal authorisation and mutual recognition procedures under Regulation (EC) 1107/2009. Zonal and national evaluations were made providing opinions at both southern zonal European level and at national level concerning France (including northern and southern zones). Conformity to in-force EU MRLs was checked using the OECD MRL calculator as proposed by EFSA for a harmonised approach. Chronic and acute exposure assessments were undertaken using the calculation model developed by EFSA (PRIMo – Pesticide Residue Intake Model).

Participation at the preparative discussions within URSA to support the representative experts that participated at one pesticide peer-review experts meeting (PRAS) teleconference was a valuable experience and opportunity to understand the mechanisms and procedures of such meetings organised by EFSA at European level.

In both cases, during the evaluation of all aspects compromising the residue risk assessment section, consultation of fellow risk assessors was encouraged. The structure and expertise of the residue unit in ANSES offered a valuable opportunity for discussion and expertise exchange between risk assessors on a regular basis. Final evaluations were always discussed and validated by more experienced risk assessors within URSA.

2.2.2. Combined dietary risk assessment of multiple pesticide residues

The project on combined risk assessment started with a thorough understanding of EFSA's publications on harmonised methodologies for risk assessment to multiple chemicals. In parallel, there was training on the use and applications of MCRA software for probabilistic risk evaluations.

The project was focused on cumulative effects of acute exposure to pesticides in food on the human nervous system and it was in continuation of the work carried out within URSA in the framework of regulatory risk assessment. In the framework of this pilot project, the exposure studied was limited to the French population (consumption data 2006–2007; concentration data in food 2013–2015) and the CAG of human nervous system established by EFSA (EFSA PPR Panel, 2013). A tiered approach – starting with the most conservative to the most realistic – was followed, in accordance with

the approach agreed by the European Member States (European Commission, 2018). In view of refining and making more realistic the risk under evaluation, the effects of processing on the total residues have to be taken into account. The main objective of the current project was to incorporate in the analysis the processing factors published in the European food database (Scholz et al., 2018). The challenges arising were (a) translating the processing factor data (provided in a FOODEX2 system) to a form compatible with the available concentration and consumption data currently used by France (FOODEX1) and (b) interpreting the results taking into consideration that actually very limited information on the specific combination of process and active substance within each food commodity is actually available. Initially, communication with experts from RIVM, responsible for MCRA support was initiated in so as to correctly insert the data into the software. In view of the aforementioned challenges, a meeting with an expert of coding of food consumption and concentration data was organised within ANSES, in order to elucidate the possibilities of translating FOODEX 2 to FOODEX1 coding. On another occasion, a telephone meeting was organised with experts from the combined risk assessment team in EFSA to discuss possibilities and uncertainties of such translation but also overall limitations of the evaluation because of existing uncertainties.

Overall, the participation in the unit's working group of combined risk gave an insight of the work carried out so far by ANSES, RIVM and EFSA and allowed for discussions on the potential of a probabilistic approach of combined risk in the framework of regulatory pesticide risk evaluation.

3. Conclusions

This fellowship being part of the EU-FORA programme and taking place at URSA within the Regulated Products Department at ANSES gave the opportunity to gain not only knowledge on the regulatory procedures but also professional experience on the risk assessment of PPPs.

The initial training of the programme on chemical risk assessment was crucial for the better incorporation in this working programme. A comprehensive view of the procedures of chemical risk assessment fundamentally helped to apply the new knowledge and methodology acquired during the training.

The critical evaluation of active substance monographs and the PPP authorisation dossiers using harmonised European procedures, allowed for a profound understanding of the principles covering the risk assessment of PPP products. Furthermore, the participation in URSA's working group of combined risk assessment in parallel with the advancement of the probabilistic analysis approach with the refinement of the risk has given the opportunity to discuss on the potentials of setting a standard approach for the combined risk in the framework of regulatory pesticide risk evaluation.

The working environment and fellow colleagues were key to a pleasant and rewarding environment on a daily basis. The successful integration in the team has undoubtedly led to productive discussions, knowledge exchange and the foundations of a network and future collaborations between experts in food risk assessment.

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Abbreviations

ADI	acceptable daily intake
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
ARfD	Acute Reference Dose
CAG	cumulative assessment groups
EU-FORA	The European Food Risk Assessment Fellowship Programme
MCRA	Monte Carlo Risk Assessment
MRLs	maximum residue levels
OECD	Organisation for Economic Co-operation and Development
PPPs	plant protection products
PRAS	pesticides peer-review experts meeting
PRIMo	Pesticide Residue Intake Model
RIVM	Dutch National Institute for Public Health and Environment
RMS	Rapporteur member State
URSA	Residues and Food Safety Unit (ANSES, France)