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Cumulative risk assessment with pesticides in the framework of MRL setting

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Abstract

This abstract presents a report on the proposed work programme, focus on cumulative risk assessment (CRA) for chemical risks, specifically pesticide residues in food. While not a scientific publication, this technical report aims to provide insights without including the fellow's data to avoid publication restrictions. This report focuses on addressing the question concerning the trigger value to perform a prospective CRA in case of a new maximum residue level (MRL) setting. The 1,000 margin of exposure (MOE) threshold value was tested and compared to preliminary ANSES results. Alternative thresholds were calculated and explored. The EU-FORA fellow selected two cumulative assessment groups (CAGs) related to acute craniofacial alterations and chronic thyroid effects. The fellow performed exposure assessments, integrating effects data, French monitoring data, processing factors, agricultural uses, MRLs and extrapolations into Monte Carlo risk assessment (MCRA). Retrospective cumulative exposures using MCRA were conducted for children, adults and a vulnerable group of childbearing women based on the French survey INCA3, identifying background levels at P99.9. The fellow also performed prospective assessments with MCRA, analysing results at P99.9 to evaluate the adequacy of the 1,000 MOE threshold. Alternative thresholds are discussed and proposed.

Keywords: cumulative risk assessment, pesticide residues, EU Commission working group trigger value, Monte Carlo risk assessment (MCRA), cumulative assessment groups (CAGs), retrospective and prospective cumulative risk assessment, MRL setting

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Summary

The EU-FORA programme offers motivated candidates to increase their knowledge and hands-on experience in food safety risk assessment. The programme's principal focus is on chemical and microbiological risk assessment. This report will focus on the proposed work programme as the fellow took part in cumulative risk assessment (CRA) work focusing on chemical risks in food, and in particular on pesticide residues in and on food.

For the implementation of CRA in the regulatory context, France represented by the French ministry in charge of agriculture and food, in cooperation with ANSES actively participates to the working group set up at EU Commission level. This group, coordinated by EU Commission, is preparing a note for risk managers to implement CRA in the evaluation process. The input of risk assessors is requested to decide on the parameters to be taken into account and also how to interpret the results obtained with Monte Carlo risk assessment (MCRA).

The harmonised European methodology for retrospective CRA among all Member States was taken note by the European Commission in September 2018 (SANTE-2015-10216 rev. 7).

European experts of the working group discussed the scenarios for CRA in the framework of maximum residue level (MRL) setting (prospective scenarios). As ANSES risk assessors are involved in both risk assessment for setting MRLs (Article 10, Article 12, SCOPAFF, CCPR) and CRA with MCRA, their participation in the working group is valuable for the development and implementation of the CRA methodology together with the participants of the other member states, EFSA and the European Commission.

In 2021, case studies were carried out by ANSES with residue trials in order to perform both chronic and acute prospective cumulative exposure assessments. Several cases with an increase of MRL for different commodities (plant or animal) on several active substance from a specific cumulative assessment group (CAG) has been conducted.

Experts of the EU working group were also asked to propose a threshold that would be used in order to identify the cases where a modification of an existing MRL or the setting of a new MRL will trigger the need to perform a prospective CRA.

This report will focus on this question. The threshold of 1,000 margin of exposure (MOE) was tested in the framework of the EU-FORA programme and another threshold could be suggested.

In order to achieve this objective, one CAG with acute effects on craniofacial alterations and one CAG with chronic effects on thyroid were selected. Data for exposure assessment (effects data, French monitoring data from 3 years, processing factors, agricultural uses, MRLs, extrapolations, etc.) were conducted by the fellow for implementation into MCRA. Retrospective cumulative exposures based on the French survey INCA3 were used for children, adults and a vulnerable group within MCRA. These allowed to identify the background levels at P99.9.

The fellow performed prospective assessments with MCRA Software. He analysed results at P99.9 in order to conclude whether the threshold of 1,000 MOE is an adequate trigger. Other trigger values were tested and discussed.

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1. Introduction

A pesticide is defined as a 'product used to prevent, destroy, or control harmful organisms (pests) or diseases, or to protect plants or plant products during their production, storage, and transport' (European Commission, 2009). The focus of this report was particularly on active substances (AS) used in the composition of plant protection products (PPPs).

The evaluation of PPPs and the active substances present in these PPPs has been regulated in the EU since 1993 by European Directive 91/414/EEC. In June 2011, this directive was updated with the entry into force of Regulation (EC) No 1107/2009. This regulation harmonised the approval procedures for active substances and the placing on the market of preparations among the Member States of the European Union (European Commission, 2009). Regulation (EC) No 396/2005 addresses the maximum residue limits (MRLs) for pesticides present in or on foodstuffs and feed of plant and animal origin (European Commission, 2005). MRLs are defined as 'the maximum legally permitted concentrations of pesticide residues in or on food intended for human consumption'. Their values reflect the authorised agricultural uses or good agricultural practices (GAPs) for PPPs in Europe, while adhering to the ALARA principle (As Low As Reasonably Achievable). Generally, a GAP is defined by the treated crop, the AS application rate, the number of applications, the minimum preharvest interval, and the growth stage. GAPs are production and post-production processes aimed at achieving 'safe and healthy agricultural products while considering economic, social, and environmental sustainability'.

According to Article 3 of Regulation (EC) No 1107/2009, a pesticide residue consists of 'one or more substances present in or on plants or animal products, drinking water, or elsewhere in the environment. It is the remaining result of the use of a plant protection product, including its metabolites and degradation or reaction products'.

Article 4 of Reg. 1107/2009 stipulates that for the approval of active substances 'they shall not have harmful effects on human health, including that of vulnerable groups or animal health, taking into account known cumulative and synergistic effects where the scientific methods developed by the authority to assess such effects are available'.

It was agreed that as soon as the methodology was developed by EFSA, cumulative and synergistic effects should be taken into account when setting MRLs for pesticide residues: Reg. 396/2005 states in Art.14 (2) (b) requirements, 'that for decisions on applications concerning MRLs, account shall be taken of the possible presence of pesticides residues arising from sources other than current plant protection uses of active substances and their known cumulative and synergistic effects when the methods to assess such effects are available'.

For the Retrospective assessment (= post-marketing), based on monitoring data, a consensus for a Tier I and Tier II retrospective approach was taken note during SCOPAFF meeting in September 2018. For the prospective assessment (= pre-marketing, e.g. application for MRLs), questions remained open. When the exposure of the focal substance in the focal commodity accounts for more than 10% of the acceptable daily intake/acute reference dose (ADI/ARfD) or less than 1,000 margin of exposure (MOE), should prospective cumulative risk assessment (CRA) be carried out?

1.1. Background and terms of reference as provided by the requestor

The fellow was already trained for pesticide risk assessment and coordinated European control plans, which is a prerequisite to conduct CRA. For further involvement in cumulative risk assessment, ANSES has already put in place training sessions. The fellow participated in different formations including theoretical presentations, reading and explanation of EFSA reference documents on the topic and practicing on MCRA supervised by experienced risk assessors. A training dealing with uncertainty analysis in accordance with EFSA guidance on EKE (Expert Knowledge Elicitation) was given. These sessions span over the whole period of the fellowship program.

A task of this program was to organize primary and secondary data for exposure assessment with MCRA in accordance with EFSA (EFSA 2020, EFSA 2022). Including individual data of the Third French Individual and National Food Consumption Survey (INCA3) into MCRA. Two databases of the selected acute and chronic toxicological effects (including lists and codes of active substances, NOAELs, Relative Potency Factors). Additionally, French monitoring occurrence data from 3 consecutive years in accordance with the list of active substances included in the CAGs (acute and chronic) were selected for this program. Processing factors from the available European database on processing factors (Scholz et al., 2018, update, Zincke F. 2022), MRLs, authorized used, extrapolation rules, variability factors.

The fellow performed retrospective cumulative exposure assessments with MCRA: for both acute and chronic exposures, Tier II scenario for whole french population or childbearing women depending on the population of interest for the CAG. Bootstrap was used in order to address the sampling uncertainty.

The fellow had to choose criteria and selected case studies in EFSA Reasoned Opinions in accordance with these criteria. Case studies include modification of MRLs on vegetable commodities only. Indeed, in order to calculate prospective cumulative exposure, MCRA uses results of Magnitude of Residue (MoR) trials. This kind of data is only available for crops. The deterministic acute or chronic consumer exposure was calculated with MCRA and the estimated MOE was compared to the threshold of 1,000.

Additionally, for all case studies, acute or chronic prospective cumulative exposure assessments were performed with MCRA using bootstrapping. The GAP scenario as mentioned in RIVM Report 2021 (RIVM, 2021), including the use frequency was used. Calculations were performed for several modifications of MRLs (fictive and real case studies).

The retrospective (= background) and prospective cumulative exposures at P99.9 were considered, the MOET were calculated and compared together as well as with the deterministic calculations.

1.2. Interpretation of the Terms of Reference

Deterministic Approach: Exposure assessment in regulatory dossiers can be conducted using either a deterministic or probabilistic approach. The deterministic approach is used when there is limited data, employing fixed values for statistical analysis to calculate an average or percentile. In contrast, the probabilistic approach considers variations in food consumption and contamination data, utilising a distribution of exposure based on a large data set. Consumer risk assessment in regulatory dossiers is typically performed deterministically. The EFSA's PRIMo model is widely employed at the European level for consumer risk assessment. It estimates short-term and long-term exposures to pesticide residues, comparing them with toxicological reference values (TRVs) to identify potential risks to consumer health. TRVs, established by international bodies, such as WHO, EFSA or national institutions, differ based on exposure duration and route. The PRIMo model incorporates algorithms for calculating dietary exposure to pesticide residues, which vary depending on whether assessing acute or chronic risk.

Cumulative Risk Assessment: The European approach to CRA of pesticide residues in food is guided by Regulation (EC) 396/2005 and Regulation (EC) 1107/2009. It requires consideration of residues from sources other than current pesticide uses and their cumulative and synergistic effects, provided suitable assessment methods exist. Three methods were outlined by the EFSA's Pesticides Peer Review Panel to combine the toxicity of multiple active substances: addition of responses, addition of doses and interaction. However, the addition of responses is deemed irrelevant for pesticide residues, and synergistic effects are considered highly unlikely due to the low levels of consumer exposure. Thus, the EFSA focuses on the additivity of effects (addition of doses) when assessing pesticide residues in food.

In 2009, EFSA published an opinion on the cumulative risk of triazole pesticides, presenting a methodology that involves the creation of a Cumulative Assessment Group (CAG), a tiered approach for hazard characterisation and exposure assessment, and the calculation of the Hazard Index (HI) using deterministic and probabilistic methodologies. This exercise highlighted the need for a tiered approach in CRA, but questions remain about the level of protection provided.

In 2012, EFSA released a guide on probabilistic approaches for modelling dietary exposure to pesticide residues, emphasising the use of tiered approaches with cautious assumptions to estimate exposure (EFSA, 2012).

Cumulative Assessment Groups: In 2013, EFSA published a scientific opinion on the identification of pesticide active substances (ASs) to be included in CAGs based on their toxicological profiles (EFSA 2013a). From 2022, EFSA will develop new CAGs for system/organs that require a refined assessment of cumulative risks (Biesebeek J, Sam M and Sprong R, 2021).

Monte Carlo Risk Assessment: The ACROPOLIS project, coordinated by the RIVM (Klaveren JDV, 2015), aimed to develop a framework for cumulative and aggregate risk assessment of pesticides. As part of this project, the MCRA (Monte-Carlo Risk Assessment) software was developed and validated to assess cumulative exposure to active substances within CAGs, following EFSA guidance (RIVM, 2019a,b). The MCRA software applies the concept of dose additivity through Relative Potency Factors (RPFs), which originated from Toxic Equivalent Factors (TEFs) used to assign toxicological values to mixtures of chemically similar compounds. The MCRA software provides probabilistic assessment for both acute and chronic cumulative exposures using various models and algorithms.

2. Data and methodologies

2.1. Data

To conduct the probabilistic assessment of cumulative risk, a substantial amount of data needs to be imported into MCRA. This data importation is performed through completed databases in Microsoft Excel and Access.

The fellow used R-software to create tables according to Standard Sample Description (EFSA 2013b) derived from Monitoring Data sourced from the Nations Surveillance and Control Plans (PSPC), Agricultural use data, Consumption data (INCA3), MRL history of the Pesticide Database. Tables for MCRA had to be established for CAG Database, Effects Database compiling the RPFs, which highlight the relative toxicity of the active substances present in the acute and chronic CAGs, based on the toxicity of a reference substance. Tables for the Variability Factors, Extrapolations, Processing Factors, Substance conversion from measured active substances and residue definitions as well as a food translation table for MCRA had to be created. For the prospective CRA tables including values from supervised residue trials (fictive and from current Art.10 MRL modifications) where uploaded to the MCRA software. Several Settings for the MCRA tool had to be learned and understood in alignment of the presentations from RIVM as well as the already gained knowledge from ANSES experts.

2.2. Methodologies

Cumulative Exposure – acute: The assessment of acute cumulative exposure is conducted using the 'person-day' approach in the MCRA software. This involves randomly selecting an individual and a consumption day from the INCA 3 food consumption diary. For each food item consumed on that day, a sample is randomly selected from the concentration database, taking into account all active substances measured in that sample. The concentrations of active substances are multiplied by the consumption of the food item and weighted by the RPF associated with each active substance. The process is repeated 100,000 times to obtain a distribution curve of the relative cumulative exposure.

Cumulative Exposure – chronic: For chronic cumulative exposure assessment, the MCRA software utilises the Observed Individual Means (OIM) model, which calculates the average exposure for each individual by multiplying their average consumption from the INCA3 food consumption diary with estimated average concentrations of active substances in the consumed food items.

The software also allows for an uncertainty analysis using the bootstrap method, which performs 100 resampling iterations to quantify the sampling uncertainty around the average exposure. This generates a 95% confidence interval, indicating the range within the true exposure value is likely to fall.

The margin of exposure total (MOET) is the chosen method for characterising cumulative risk associated with pesticide residue ingestion in Europe. It is calculated by dividing the no observed adverse effect level (NOAEL) of the substance of reference of the CAG by the cumulative exposure estimate. The MCRA software provides relative cumulative exposure values for different percentiles, with the 99.9th percentile being of particular interest for probabilistic assessment. An MOET value above 100 indicates an acceptable risk to consumer health, while a value below 100 suggests an unacceptable risk.

Retrospective CRA: In retrospective evaluation of cumulative risk, the focus is on examining cumulative exposure using surveillance data over a specific time period. It reflects the level of population exposure to pesticide residues after obtaining authorisation for their use. This is often referred to as background exposure.

Retrospective assessments should be repeated regularly to account for changes in exposure patterns and potential updates to CAGs. It is proposed to repeat retrospective CRAs every 3 years, which aligns with the 3-year cycle of the EU Multi-Annual Control Programme (MACP).

Prospective CRA: The methodology for prospective CRA focuses on the modification of MRLs and considers the existing background exposure to pesticide residues as well as the exposure associated with the potential authorisation of a new use. The MCRA software is used to combine data from residue trials and surveillance plans in five different scenarios. These scenarios involve replacing or appending concentration data, using concentration limit values, or removing measurements for specific active substance/focal commodity pairs. The European Commission and EFSA prioritise the harmonisation of this methodology across EU Member States.

The fellows work programme objectives include understanding the MCRA software, defining a threshold for prospective analysis, assessing the impact of RPF and/or high and low consumed food, and evaluating the cumulative risk resulting from modifications of MRLs. By achieving these objectives, the results aim to contribute to the development of a harmonised approach for CRA in the MRL setting process and support the safety of agricultural practices in the European Union.

3. Assessment

Report and interpretation of the results from MCRA are available. This technical report aims to provide insights without including the fellow's data to avoid publication restrictions.

Several questions were raised, including the relevance of the 1,000 MOE trigger value and the SCORE value proposed by ANSES in identifying cases requiring prospective CRA. Additionally, the limitations of using the MCRA software were discussed. The background contribution is not a reliable criterion for predicting the impact of MRL increases on background noise, but factors such as residue level, RPF, quantity consumed, and consumption frequency play a role. The report concludes by highlighting that the 1,000 MOE threshold and SCORE values are not robust enough, and additional thresholds need to be considered. The results from this work may impact the proposed thresholds, and further research is needed to validate the findings to establish more robust criteria for prospective CRA.

Questions asked:

- Is the 1,000 MOE trigger value a relevant threshold that will identify cases of MRL increases requiring prospective cumulative risk assessment?
- Is the SCORE value proposed by ANSES a relevant threshold that will identify cases of MRL increases requiring prospective cumulative risk assessment? It uses available data *a priori* and of the same nature as those used by MCRA, namely the new MRL, the RPF of the focal active substance, consumption of the focal commodity, and the use frequency.
- If not any of this trigger values is robust, can another threshold be proposed?

The fellow faced limitations associated with using the MCRA software corresponding to unspecific Residue Definition, FoodEx2 Code, Parameter Settings for Multiplication Factor according to the EKE for specific CAGs, double reporting of residue trials according to Occurrence Data/Monitoring Data from the Laboratories.

4. Conclusion

CRA is mandated by Article 14 of Regulation (EC) No 396/2005 on MRLs of pesticides. The methodology for assessing cumulative risks has been under development since 2008. Currently, consumer risk assessment for new MRL setting is conducted on a critical NOAEL of an active substance, conducted on a substance by substance basis using PRIMO.

The methodology for creating CAGs has been validated since 2013. CAGs have been formed by EFSA Expert Groups on Toxicology to be used for the Exposure Experts to use specific NOAELs for each active substance included in the CAG to derive RPFs (that put the toxicology of an active substance included in the CAG in relation to the one of reference within the CAG).

The European Commission, with the agreement of Member States and EFSA, also endorsed the characterisation of cumulative risk related to pesticide residues through the calculation of the cumulative exposure margin (MOET) at the 99.9th percentile, with a threshold of 100. The second part, which involves prospective assessment, is still under development and is a priority for the European Commission.

Retrospective assessment relies on 3-year surveillance data to evaluate past cumulative exposure of consumers associated with authorised pesticide uses.

Prospective assessment will use supervised residue trial data to estimate future cumulative exposure of consumers linked to new MRL setting. A use frequency that can be calculated from the information on monitoring data can be used in the prospective scenario as a way to estimate the extent of the future agricultural use.

Probabilistic assessment of cumulative risk requires substantial data and time. Therefore, it is crucial to identify in advance which data are truly necessary before launching a probabilistic prospective assessment. The fellow's work aimed to address the adequacy of two thresholds, the 1,000 MOE agreed by EFSA, COM and Member States and a SCORE derived and proposed by ANSES.

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Abbreviations

ADI	acceptable daily intake
ALARA	As Low As Reasonably Achievable
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
ARfD	acute reference dose
AS	active substance
CAG	cumulative assessment group
CCPR	CODEX Committee on pesticide residues
CRA	cumulative risk assessment
EKE	expert knowledge elicitation
EU-FORA	European Food Risk Assessment Fellowship Programme
FAO	Food and Agricultural Organization
GAP	Good Agricultural Practice
HQ	hazard quotient

JMPR	Joint Meeting on Pesticide Residues
LOAEL	lowest observed adverse effect level
MCRA	Monte Carlo Risk Assessment
MoA	mechanism/mode of action
MOE	margin of exposure
MOET	combined (total) margin of exposure
MoR	Magnitude of Residue
MRL	maximum residue level
NOAEL	no observed adverse effect level
OIM	Observed Individual Means
PF	processing factor
PPP	plant protection product
PRIMo	Pesticide Residue Intake Model
PSPC	Plan de Surveillance et Plan de Controle
RIVM	Dutch National Institute for Public Health and Environment
RPF	relative potency factor
SCoPAFF	Standing Committee on Plants, Animals, Food and Feed (European Commission)
TRV	toxicological reference value