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CODEX COMMITTEE ON PESTICIDES RESIDUES
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European Union comments on

Agenda Item 5 (a)

Report on items of general consideration

(Section 2 of the 2023 JMPR Report)

European Union Competence
European Union Vote

The European Union (EU) would like to provide the following comments on section 2 of the 2023 JMPR Report on general consideration items:

2.1 Developments in dietary exposure methodology for pesticide residues in foods

The EU welcomes the JMPR initiative to improve the long-term dietary risk assessment methodology at Codex level and to harmonise methodologies between different food domains. The EU supports the JMPR decision to explore transition from IEDI to GECDE-mean, which might give a better estimate of the expected dietary exposure of the general population and of specific population groups that may have a higher exposure than the general population.

The EU notes that for the comparison presented in the 2022 report, the results obtained with IEDI and GECDE differed significantly. Also, within a cohort (e.g. children & adolescents), the results differed significantly (e.g., difenoconazole, GECDE mean ranges from 1 to 430% of the ADI) which could give an indication that the surveys do not contain all the relevant food commodities that contribute to the dietary exposure.

The EU also acknowledges that the JMPR investigates both the implementation and modification for the GECDE-high (for the assessment of dietary exposure for chronic and shorter-than-lifetime assessment) and the degree of conservatism of IEDI and GECDE (mean and high). Based on the preliminary results provided by JMPR on GECDE-high, the EU notes that the current chronic exposure estimates are increased by at least a factor of 2, in some cases even 10 or more, compared to the IEDI. The EU suggests that JMPR presents at the next CCPR the outcome of its assessment on the degree of conservatism of IEDI and GECDE (mean and high) and its investigation of implementation options.

The EU identified several points that need to be further addressed, to allow an informed discussion at risk management level whether in future the IEDI methodology can be replaced with the GECDE-mean and whether GECDE-high would be appropriate to assess the less-than lifetime dietary exposure.

i) Points to be addressed for GECDE-mean and GECDE-high model:

- Lack of transparency of GECDE exposure calculations;
- Level of stratification of calculation of exposure assessment: definition of suitable subgroups;
- Definition of a clear protection goal;
- Validation and plausibility check of the model and the consumption data used for the calculations

ii) Additional points for GECDE-high:

- Specification of the exposure duration and/or life stage that should be addressed in a less-than-lifetime assessment;
- Appropriateness of CIFOCOss summary data for less-than-lifetime exposure calculations;
- Need to consider a consumption frequency for chronic high consumers;
- Need to consider the frequency of the use of a pesticide in the individual commodities.

A detailed discussion of these bullet points can be found in the Annex to the EU comments.

It is also noted that at EU level, work has been initiated on the modification of the methodology used for long-term exposure. The European Food Safety Authority (EFSA) is concluding a new revision of the pesticide residue intake model (PRIMo revision 4), in which calculations are performed using mean consumption of the food commodities included in the diet, averaging the consumption for the duration of the food survey. For each relevant population subgroup (country/cohort) the calculation will derive the distribution of the exposure, presenting the mean exposure of the relevant subgroups and higher percentiles (e.g. P95). The percentile that will be the basis for risk management decisions has not yet been agreed.

EFSA will prepare an impact assessment, comparing the level of conservatism of calculations with the current PRIMo methodology (using the point estimate of the mean consumption of the pertinent food commodity of the relevant subgroup of the population, normalised by body weight) and the new PRIMo version, providing the distribution of the exposure estimates for the individual diets.

In future, further modifications of the chronic risk assessment methodology are expected at EU level, aiming at an alignment of the methodology across different food domains is envisaged. Recommendations of the alignment were elaborated in a report of the European Medicines Agency (EMA) and EFSA[1]

2.2. Development of guidance on the assessment and interpretation of nonlinear toxicokinetics

The EU welcomes the development of the guidance document on the assessment and interpretation of nonlinear toxicokinetics, as being prepared by the dedicated electronic working group (eWG) of JMPR. Toxicokinetic data are helpful in the interpretation of available toxicity studies and can provide support in the design of new ones.

[1] https://www.ema.europa.eu/en/documents/report/ema-efsa-report-development-harmonised-approach-human-dietary-exposure_en.pdf

At EU level, hazard classification is an important element to decide on the approval of an active substance. According to the European Chemical Agency (ECHA) the kinetically-derived maximum dose (KMD) approach is not suitable/not appropriate to fulfil the legislative needs for classification and labelling; instead, the maximum tolerated dose (MTD) approach, with inclusion of the non-linear kinetics as complementary information, is considered be the most appropriate methodology to derive selection of the high dose level for toxicological studies.

The EU will welcome more detailed information on the content of the guidance, including information whether the (draft) guidance will be open for commenting.

2.3 The need for sponsors to provide accurate chemical structures and related information on metabolites.

The EU supports the JMPR request to submit correct chemical structures of metabolites and acknowledge the importance of this information to perform in silico analysis to predict genotoxicity.

2.4 Resolving inconsistent assessment of common metabolites.

The EU supports the JMPR request of increasing the efforts in the coordinated submission of pesticides containing common metabolites to facilitate a consistent assessment. The EU suggests the use of metabolism databases, such as MetaPath[2], for identification of metabolites that could be also derived from other active substances. The database MetaPath can be updated with information related to metabolism studies for the active substances assessed by JMPR.

2.5 On the rolling submission of data

The EU fully supports the JMPR request to applicants on the correct submission of completed datasets and studies, both published and unpublished, for the toxicological and/or residue evaluations of active substances. The EU agrees with the view of JMPR that a comprehensive, state-of-knowledge assessment requires the timely submission of all relevant information. Incomplete dossiers are leading to inefficiencies, which should be avoided, considering the high workload of JMPR.

Only in 2023, there were two examples (permethrin and fluazinam) of incomplete dossiers that did not permit JMPR to perform a substantive re-evaluation. For active substances scheduled for periodic reviews, sponsors should have sufficient time to generate the necessary studies.

The EU consider that in the interest of efficiency of use of JMPR resources, the submission of incomplete dossiers needs to be avoided, since it leads to delays in the review process of setting new Codex MRLs. The EU suggests to develop an efficient procedure for cases where sponsors of substances scheduled for the periodic review program do not submit complete dossiers, precluding that existing Codex MRLs are maintained in the Codex system and avoiding that the compounds are scheduled at each Meeting, which is binding capacities at JMPR level.

[2] https://oasis-lmc.org/products/software/metapath.aspx

2.6 Why is a residue definition sometimes not agreed when there is an ADI/ARfD?

The EU welcomes the clarifications provided and have not further comments.

2.7 Enhancement of process

The EU welcomes the feedback of the discussion with the chair of the electronic working group on the Enhancement of CCPR and JMPR Operational Procedures and have not further comments.

2.8 Strategy and timing for JMPR re-evaluation of dithiocarbamates

The EU welcomes the initiative to prioritize the periodic review of dithiocarbamates within the CCPR system and calls the sponsors to contribute with the information requested by JMPR.
The EU is willing to contribute with the expertise gained on the recent MRL review of dithiocarbamates at EU level[3]

[3] Review of the existing maximum residue levels for dithiocarbamates according to Article 12 of Regulation (EC) No 396/2005. https://www.efsa.europa.eu/en/efsajournal/pub/7987

Annex to EU comments on Agenda item 5a
Detailed EU comments on GECDE model

The transition towards the GECDE-mean model based on actual consumption data, instead of summary trade statistics as used in the current GEMS Food based IEDI model mirrors the deterministic methodology used in EU and in many regulatory frameworks globally. However, prior to implementation we recommend to solve some shortcomings regarding the technical procedure:

• Currently, there is lack of transparency, both in how the calculation of the model works and how the results are presented. Background documentation is required as well as a source for the model to allow all stakeholders to conduct and repeat calculations. Moreover, an output format (either electronically or as a Report Annex) sufficient to identify all input data and parameters (residue data, relevant consumption data, involved recipe data) needs to be agreed. For GECDE-mean, an EXCEL-Spreadsheet similar to the current model is considered technically feasible and it would be highly appreciated, if WHO could provide it.

• Prior to implementation, scientific agreement needs to be achieved regarding the level of stratification used in the model. Currently, IEDI focusses on 17 cluster diets from multiple countries. In theory, CIFOCOss consumption data allow consideration of single countries, certain age groups per country (e.g. children) and certain genders by country (e.g. female). When narrowing down the target population too much (e.g. female children aged 0 - 3 years versus all children or even the general population), the robustness of the data decreases due to the much lower number of consumers for each food commodity. In view of potentially 200 population subgroups from approximately 40 countries in the CIFOCOss database, the selection and interpretation of suitable sub-populations becomes challenging. For the long-term ("life-time") dietary assessment, a clear protection goal in terms of description of the desired target population (general population, vulnerable groups or even gender separation) is required by CCPR to allow a proper selection. . Thus the meeting is required to define the protection goal.

• Validation and plausibility check of the model and the underlying CIFOCOss data are required before GECDE-mean is used for decision making. If questionable consumption data are identified, the underlying survey needs to be cross-checked first to verify the values (as it was done for the JMPR IESTI-model). In parallel, the GECDE-mean model itself needs to be reviewed by third parties (e.g. Codex Member States) to ensure that it works as intended.

Regarding GECDE-high, current chronic exposure estimates are increased by at least a factor of 2, in some cases even 10 or more compared to IEDI, based on the preliminary results provided by JMPR. Some major aspects therefore have to be solved prior to implementation:

• One major objective of implementing the GECDE-high is to address potential "less-than-lifetime" dietary risks. Until now, no definition of "less-than-lifetime" was provided which would be suitable to conclude on a proper dietary model to achieve such a risk assessment. The range between the current acute (24h) and chronic (lifetime) exposure models is too broad. WHO is encouraged to specify the desired scenario in more detail in terms of exposure duration (days, week, months, seasons or life stages) and frequency (daily, weekly or longer) before the conclusion on an appropriate model can be drawn.

• The use of high percentiles for 'consumers only' in long-term assessments seems unusual and is not followed for pesticides in the EU or in any other regulatory framework so far. The CIFOCOss database only relies on summary statistics for the consumption while extrapolation of consumption survey data from a very limited number of days per individual (typically two) demands adjustment before using them in long-term assessments. The observed individual mean (OIM) is a simple method with drawbacks ("OIM is still popular because it gives conservative, i.e. too large, estimates of the upper percentiles of the usual intake distribution…", EFSA Supporting publications 2012:EN-300). Given the obvious increase in the model outcome compared to current methods, more sophisticated methodology (e.g. LNN, LNN0 or FFQ assisted methods)[5] is proposed to be explored to address high chronic consumers in sub-lifetime scenarios. If such advanced methodologies are considered scientifically necessary, CIFOCOss summary data might be unsuitable for the desired task to adequately assess less-than-lifetime risks.

• When aiming for chronic high consumers, the consumption frequency becomes a major aspect, but is still unsolved. Cited sources in the General Item[4], but also case studies in the EFSA Supporting publications[5] were based on single foods or commodity groups with a very high or even daily consumption frequency, whereas the GECDE-high approach targets single individual food commodities, many of them consumed with a frequency of less than 10 %. A similar procedure was considered by EFSA[6], when FoodEx Level 2 grouping (e.g. 'fruits', 'root and tuber vegetables' or 'meats') was successfully tested. Pesticide assessment normally deals with specific commodities (FoodEx level 4 or higher, e.g. potatoes, apples, bovine muscle). More research is required to demonstrate that the GECDE-high assumption on highest reliable percentiles ("HRP") is scientifically justified and can be applied on individual commodity level.

• When it comes to non-central long-term exposure tendencies (mean → high consumer), not only consumption aspects but also conservatism in the occurrence part has to be considered. In case of pesticides, the assumption to combine HRP-based portion sizes for 'consumers only' with median residues (STMR values) is highly conservative. In reality, detection frequencies of pesticides found on the market are very low. In the Electronic Working Group on Cumulative Risk Assessment of EU COM, it was discussed to introduce the 95th percentile of detection frequency from EU Monitoring data, which is 25 %, into prospective probabilistic risk assessments to avoid unnecessary overestimations. In GECDE-high, 100 % occurrence rates are assumed. It needs to be carefully discussed whether such a combination still reflects a conservative, but realistic scenario. For food additives such a conservative approach makes sense, as brand loyal high consumers may be exposed to the same agent on a daily basis, but for pesticides a comparable scenario appears unlikely and should not be applied unless clearly advised by risk managers as a desired protection goal. Given the low findings of pesticides in market samples, it should be discussed before GECDE-high implementation, whether IEDI or GECDE-mean already involve sufficient conservatism to cover also less-than-lifetime scenarios. The EU proposes to compare the results to higher tier exposure assessments based on realistic occurrence data (probabilistic assessments based on monitoring data or results from total diet studies).

[4] Pesticide Safety Directorate. 2004. Instructions for carrying out long term consumer risk assessment using CRD's ten consumer model.

[5] A European tool for usual intake distribution estimation in relation to data collection by EFSA. https://www.efsa.europa.eu/en/supporting/pub/en-300

6 EFSA Guidance: Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment. EFSA Journal 2011;9(3):2097