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CODEX COMMITTEE ON PESTICIDES RESIDUES
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Additional comments of the European Union on

Agenda Item 10

Establishment of Codex schedules and priority lists of pesticides for evaluation / re-evaluation JMPR

(CX/PR 24/55/9 – CL 2024/43-PR)

European Union Competence
European Union Vote

The European Union (EU) filed a concern form last year asking for a prioritisation of review of indoxacarb (last review 2005) as toxicological reference values (TRVs) are lowered in the EU (acute risks identified with current CXLs) and there is insufficient data on metabolite IN-JT333. JMPR in its report[1] stated that "The EU is invited to explain in more detail the basis for their conclusion that the NOAEL for findings in a rat developmental study is 0.5 mg/kg bw per day, and how these findings might be produced by a single dose".

As a response, the EU provided the following additional information to JMPR:

"During the Peer Review by EFSA[2], the EU replaced the previous ADI of 0.006 mg/kg bw per day by a new ADI of 0.005 mg/kg bw per day, based on the NOAEL of 0.5 mg/kg bw per day for maternal toxicity in a developmental toxicity study in rats, and applying an UF of 100. The ADI at Codex level is set at 0.01 mg/kg bw per day.

The previous EU ARfD of 0.125 mg/kg bw (based on an acute rat neurotoxicity study) was replaced by a new ARfD of 0.005 mg/kg bw, based on the same point of departure as the ADI and applying an UF of 100. The JMPR ARfD is set at the level of 0.1 mg/kg bw.

The Member States experts derived an overall NOAEL for maternal toxicity at 0.5 mg/kg bw per day from a developmental toxicity study in rats (study from 2004, the same study was reported in both the JMPR and the EU revised RAR). It is acknowledged that the EU peer review reports two pilot studies and three main studies in rats, the latest one dated 2005 presented a higher maternal NOAEL at 2 mg/kg bw per day.

[1] Report 2023: Pesticide residues in food – Joint FAO/WHO Meeting on Pesticide Residues. Rome. https://doi.org/10.4060/cc9755en

[2] EFSA (European Food Safety Authority), 2018. Peer review of the pesticide risk assessment of the active substance indoxacarb. EFSA-Q-2015-00023. DOI: 10.2903/j.efsa.2018.5140

The 2004 study was performed according to GLP and followed the OECD TG 414 (1981) without deviations. Indoxacarb was administered by oral gavage to female rats on gestation days (GD) 6 to 20 (22 rats/dose group) at dose levels of 0, 0.5, 1.0, 2.0 and 3.5 mg/kg bw/day. In this study, maternal body weight gains were statistically significantly reduced during GD 6-8 at the dose levels of 1 mg/kg bw per day and above by more than 60% compared to control animals (France, 2017, Table B.6.6.2-14 of the RAR: -62%, -67% and -67% of control animals at 1, 2 and 3.5 mg/kg bw per day respectively). The animals recovered during the study period, and the body weight gain during GD 6-21 (corrected for gravid uterine weight) was reduced by more than 10% at 1 and 2 mg/kg bw per day, and statistically significantly reduced at 3.5 mg/kg bw per day by 27.7% compared to control animals. These findings were considered as acute adverse effects, relevant to derive the ARfD and ADI (since this represents the lowest NOAEL of the dataset).

The JMPR monograph mentions maternal toxicity based on the same adverse effects but concluded that the maternal NOAEL is 2 mg/kg bw per day.

The EU also highlighted in the concern form that the JMPR residue definition for animal products (risk assessment) covers a metabolite IN-JT333 for which it is unclear whether the TRVs derived for the parent can be applied. According to JMPR it is not genotoxic and based on the available information, is seems to be more toxic than the parent.

In its response to the concern form, JMPR acknowledged that the toxicity could not be addressed. In order to demonstrate that the metabolite is unlikely to lead to an intake concern, a conservative intake calculation was performed which should demonstrate that the exposure will not exceed the TTC for non-genotoxic compounds (Cramer class III). To underpin its argumentation that the metabolite IN-JT333 is of no concern, JMPR also referred to the EFSA conclusion[3] where it was stated that residues of IN-JT333 are “unlikely to be above the limit of quantitation [...]". However, it should be clarified that the sentence was taken out of the context: this conclusion was derived for the limited number of representative uses evaluated in the renewal process. EFSA also highlighted that “for any future use leading to an increase of the dietary burden calculation, the validity of these feeding studies should be reconsidered and additional data might be needed to address the toxicity and the magnitude of all compounds included in the residue definitions for risk assessment set for poultry and ruminants matrices."

EFSA notes that the use of TTC approach is normally not accepted in the EU, but acknowledges that at JMPR level, it became a tool that is regularly applied to address metabolites for which insufficient toxicological data are available to perform a full hazard characterisation. Following the explanations of JMPR, formally, it would be appropriate to revise the JMPR residue definition, excluding the metabolite IN-JT333, since the toxicological reference values derived for the parent substance are not applicable.

With regards to the health issues, the EU has identified very important risks with 27 existing CXLs with the new TRVs, up to 2188% of the ARfD which was included in the concern form the EU had sent in 2023.

[3] EFSA (European Food Safety Authority), 2022. Targeted Review of the maximum residue levels for indoxacarb.; EFSA-Q-2022-00178. DOI: 10.2903/j.efsa.2022.7527

Acute risks were identified for the following CXLs proposed in 2023 using the new EU TRVs:

- Beetroot: 251% of ARfD
- Milk (cattle): 174% of ARfD
- Currants (red, black and white): 164% of ARfD
- Beans with pods: 135% of ARfD
- Blueberries: 190% of ARfD
- Gooseberries: 122% of ARfD
- Swine meat: 111% of ARfD

Processed products:

- Currants/juice: 331% of ARfD
- Beetroot/boiled: 195% of ARfD
- Beans with pods/boiled: 148% of ARfD

Furthermore, risks were identified for 20 other CXLs: apples, pears, apricots, cherries, peaches, plums, table and wine grapes, tomatoes, peppers, aubergines, cucumbers, gherkins, courgettes, melons, pumpkins, watermelons, broccoli, cauliflower, and lettuce, with exposure exceeding up to 2 188% of the ARfD.

Regarding chronic exposure, chronic risks were identified, with exposure exceeding up to 128% of the ADI."

In view of these, the EU requests indoxacarb to be prioritized for review. This would give the opportunity to JMPR to review all available studies to set TRVs.