3. RESPONSES TO SPECIFIC CONCERNS RAISED BY THE CODEX COMMITTEE ON PESTICIDE RESIDUES (CCPR)

3.1 CARBARYL (008)

The insecticide carbaryl was last evaluated by the 2002 JMPR within the periodic review programme. The Meeting concluded that the IESTI for children exceeded the ARfD (130–1100% for several crops). The 40th Session of the CCPR[26] reiterated the decision by the 39th CCPR (Para 42 of Alinorm 08/31/24) to return to Step 6 the draft MRLs for cherries; citrus fruits; citrus juice; citrus pulp, dry; dried grapes (=currants, raisins and sultanas); grape juice; grape pomace, dry; grapes and stone fruits, awaiting the outcome of the 2008 JMPR evaluation.

The Meeting noted that the 2002 JMPR did not report an intake concern for citrus fruits.

Updated GAP information was provided by The Netherlands and United States. The GAP from the Netherlands could not be matched with any trial data. The updated US GAP was the same as previously reported by the 2002 JMPR. The sponsor announced that no additional data would be submitted; the evaluation was then rescheduled to the 2008 JMPR.

Results of supervised residue trials on crops

Citrus fruits

The GAP in USA for citrus is up to 8 applications of 2.42 to 8.4 kg ai/ha, with a maximum of 22.4 kg ai/ha per season and 5 days PHI.

Supervised trials reported by the 2002 JMPR performed according to maximum GAP resulted in highest residues of 10, 5.5 and 6.8 mg/kg in orange, lemon and grapefruit, respectively. The calculated short-term intakes based on the highest residue of 1.16 mg/kg in pulp estimated by the 2002 JMPR for children and adults consuming orange and grapefruit are 40% and 20% of the ARfD of 0.2 mg/kg, respectively. Mandarin and lemon short-term intake for children was estimated as 20% and 10% of the ARfD.

Based on the available information the Meeting concluded that there was no need to consider an alternative GAP for citrus fruits and processed products prepared from them.

Cherries

For stone fruit including cherries, the available supervised trials were performed according to the maximum US GAP only. No alternative GAP or new trial data was made available.

Consequently the Meeting could make no new proposals for stone fruits or cherries.

Grapes

Similarly, trials performed in grapes reflected the maximum US GAP. No alternative GAP or trial data were made available to the Meeting. Consequently the Meeting could make no new proposal for grapes.

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[26] Codex Alimentarius Commission. *Report of the 40th Session of the Codex Committee on Pesticides Residues, 14–19 April 2008, Hangzhou, China*, (ALINORM 08/31/24)

3.2 LAMBDA-CYHALOTHRIN (146)

Background

At the 40th Session of the CCPR,[27] the delegation of the European Community (EC) raised concerns regarding the ADI and ARfD for lambda-cyhalothrin, established by JMPR in 2007 on the basis of neurotoxic effects.[28] The ADI and ARfD established by the EC were both lower than the values established by the JMPR.

Evaluation of lambda-cyhalothrin by the JMPR

In 2007, the JMPR established a group ADI for cyhalothrin and lambda-cyhalothrin of 0–0.02 mg/kg bw on the basis of neurotoxicity observed in a study of acute toxicity in rats given lambda-cyhalothrin orally (decreased motor activity), with a threshold dose of 0.5 mg/kg bw; and in repeat-dose studies with cyhalothrin and lambda-cyhalothrin in dogs treated orally (ataxia, tremors, occasionally convulsions) with a NOAEL of 0.5 mg/kg bw per day, using a safety factor of 25. Because lambda-cyhalothrin is relatively rapidly absorbed and excreted and the neurotoxic effects are rapidly reversible and dependent on C_{max}, the Meeting considered it appropriate to adjust the safety factor for the reduced variability in C_{max} compared with AUC.

In 2007 the JMPR established a group ARfD for cyhalothrin and lambda-cyhalothrin of 0.02 mg/kg bw on the basis of systemic neurotoxicity (decreased motor activity) observed in a study of acute toxicity in rats given lambda-cyhalothrin orally with a threshold dose of 0.5 mg/kg bw per day; and in repeat-dose studies with cyhalothrin and lambda-cyhalothrin in dogs treated orally, in which neurotoxic effects (ataxia, tremors, occasionally convulsions) occurred during the first week, within a few hours after treatment, with an overall NOAEL of 0.5 mg/kg bw per day, and using an safety factor of 25. For the same reasons as described above, the JMPR considered it appropriate to adjust the safety factor for the reduced variability in C_{max} compared with AUC.

Evaluation of lambda-cyhalothrin by the EC

The ADI established by the EC for lambda-cyhalothrin (0.005 mg/kg bw) was based on the NOAEL of 0.5 mg/kg bw per day, identified in 1-year and 26-week studies in dogs, on the basis of clinical signs of neurotoxicity observed at 3.5 mg/kg bw per day, and using a safety factor of 100.

In the EC evaluation, the ARfD for lambda-cyhalothrin (0.0075 mg/kg bw) was based on the NOAEL of 0.75 mg/kg bw per day, obtained from a 6-week study in dogs treated orally, on the basis of neurotoxicity observed at 1.5 mg/kg bw per day, and a safety factor of 100. For both the ADI and the ARfD, the EC considered that an extra safety factor could be necessary when undertaking a risk assessment for children.

Comment by the JMPR

The JMPR and the EC identified the same overall NOAEL for neurotoxicity as the basis for the ADI. The difference between the ADI established by the EC and that established by the JMPR is determined by the safety factor used. The EC used the default safety factor of 100, while the JMPR considered that it was appropriate and scientifically justified in this case to adjust the safety factor for these substances that are rapidly absorbed and excreted and have effects that are rapidly reversible

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[27] Codex Alimentarius Commission. *Report of the 40th Session of the Codex Committee on Pesticides Residues, 14–19 April 2008, Hangzhou, China*, (ALINORM 08/31/24).

[28] In: Pesticide Residues in Food—2007. Report of the JMPR 2007, FAO Plant Production and Protection Paper, 191. Lambda cyhalothrin (146), pp 91–98.

and dependent on C_{max}, compared with AUC.[29] Thus, the kinetic portion of the inter- and intraspecies safety factors was reduced by half, yielding an overall safety factor of 25 (see general item 2.6 of the present report)

The difference between the ARfDs established by the EC and by the JMPR can be explained by the different studies used as a basis for this decision and the different safety factors used. The ARfD established by the EC for lambda-cyhalothrin was based on a NOAEL of 0.75 mg kg bw per day identified on the basis of tremors observed at 1.5 mg/kg bw per day in a 6-week pilot study in dogs treated orally. JMPR noted that in this study each dosing group comprised only one male and one female. In view of this limitation, JMPR did not identify a NOAEL from this study and did not consider it to be appropriate to establish the ARfD on the basis of the results of this study. The studies that formed the basis for the ARfD established by the JMPR are described above.

The reasoning behind the choice of safety factor for the ARfD used by the JMPR was the same as for the ADI. The JMPR considered that there were no indications for increased sensitivity of children to acute or long-term oral exposure to lambda-cyhalothrin. Therefore, JMPR considered that the applied safety factor of 5 for intraspecies variation was adequate to protect all sensitive groups, including children.

3.3 FLUSILAZOLE (165)

Background

At the 40th Session of the CCPR, the delegation of the European Community (EC) raised concerns regarding the ARfD for flusilazole established by the JMPR in 2007 on the basis of developmental effects (Annex 5, reference *191*), the ARfD established by the EC differing from that established by JMPR

Evaluation of flusilazole by the JMPR

In 2007, the Meeting established an ARfD for flusilazole of 0.02 mg/kg bw based on the NOAEL of 2 mg/kg bw per day for skeletal variations in a study of developmental toxicity in rats treated orally, with a safety factor of 100. The lowest-observed-adverse-effect level (LOAEL) for embryo and fetal toxicity was identified as 10 mg/kg on the basis of a higher incidence of skeletal variations – extra cervical ribs. The incidence of rudimentary cervical ribs was slightly, but not statistically significantly, increased at 2 mg/kg bw per day (3 fetuses out of 3 litters, 4 fetuses out of 4 litters, 9 fetuses out of 6 litters, 27 fetuses out of 15 litters, and 141 fetuses out of 22 litters in the groups at 0, 0.5, 2, 10, 50 mg/kg bw per day, respectively).

Evaluation of flusilazole by the EC

The ARfD established by the EC, described in the EC review report as being relevant to women of childbearing age, was established on the basis of the same study of developmental toxicity in rats as used by the JMPR, but was based on a NOAEL of 0.5 mg/kg bw per day, resulting in an ARfD of 0.005 mg/kg bw. The EC considered that the non-statistically significant increase in rudimentary cervical ribs at 2 mg/kg bw per day was treatment-related and an adverse effect, as it represented the beginning of a dose–response relationship. The EC also identified two additional developmental effects at 2 mg/kg bw per day that the JMPR considered to be maternal effects, and not adverse effects at that dose. The first effect was an increase in red vaginal discharge (0, 0, 3, 12 and 22 out of

[29] In: Pesticide Residues in Food—2000. Report of the JMPR 2000, FAO Plant Production and Protection Paper, 163. Annex 5. page 198

25 rats at 0, 0.5, 2, 10 or 50 mg/kg bw per day, respectively) and the second was an increase in mean placental weight (0.54, 0.57, 0.67, 0.87 and 0.99 g at 0, 0.5, 2, 10 and 50 mg/kg bw per day, respectively). In both cases, statistical significance was achieved at doses of 2 mg/kg bw per day and above. The red vaginal discharge occurred late in gestation and was not associated with adverse reproductive outcomes in the three dams at 2 mg/kg bw per day.

Comment by the JMPR

The JMPR and the EC identified the same critical effects in the same study of developmental toxicity as being the basis for the ARfD. The primary differences in the JMPR and EC assessments were the identification of the NOAEL for skeletal variations and the inclusion by the EC of the placental weights and vaginal discharge as critical effects. The JMPR considered that vaginal discharge late in gestation and changes in placental weights at 2 mg/kg bw per day were not toxicologically significant effects, and were not the result of a single exposure. The identification of the NOAEL for skeletal variations by the JMPR was reconfirmed on the basis of the lack of statistical significance.

3.4 OXAMYL (126)

At the 40th Session of the CCPR, the delegation of Ireland raised concerns regarding the ARfD for oxamyl, established by the JMPR in 2002. The ARfD of 0.001 mg/kg bw established by the EC was based on a study in rats. This ARfD differed from that set by the JMPR, 0.009 mg/kg bw, which was based on a study in humans. The EC as a policy does not accept data from studies in humans as a basis for setting health-based guidance values (e.g., ARfD) for plant-protection products.

The difference in the respective ARfDs is due to differences in policy with respect to the use of data from studies in humans, not to any differences in the data evaluated or their interpretation. The Meeting reaffirmed the basis of the ARfD established by the JMPR in 2002.

Evaluation for Alternative GAP

Oxamyl was evaluated for residues and toxicology by the JMPR in 2002 under the periodic review programme, where a residue definition was established as the sum of oxamyl and oxamyl oxime, expressed as oxamyl (for both animal and plant commodities). However the 2002 Meeting noted that for dietary intake estimation, this definition could result in an overestimate of the dietary intake calculations because the only residue of toxicological concern was the parent compound (oxamyl).

The 2002 JMPR estimated short-term intakes that exceeded the ARfD of 0.009 mg/kg bw for apple, cucumber, grapefruit, lemon, mandarin, melons, oranges, peppers and tomato.

At the 39th Session of the CCPR in 2007, the Committee requested JMPR to consider using alternative GAPs to recommend lower MRLs for citrus; cucumber; melon and pepper and at the 40th Session the CCPR (2008) noted that additional data would be available to support an alternative GAP assessment for tomato.

Information on current and proposed GAPs, analytical methods and new supervised trials data were submitted to the 2008 JMPR for citrus fruits (orange and mandarin), cucurbits (cucumbers, courgettes, melons), peppers and tomatoes.

The Meeting noted that while the accepted residue definition included both the parent compound and its oxime metabolite, the method used in the new supervised trials reported only the parent compound (oxamyl).

Bridging studies were reported to the meeting on the relative concentrations of oxamyl (parent compound) and total oxamyl (i.e., oxamyl plus oxamyl-oxime) in sweet peppers and lettuce following drip irrigation treatments to support the extrapolation of the oxamyl results reported in the

new supervised field trials to total oxamyl residues (this being the residue definition for MRL compliance).

In the plant metabolism studies reviewed by the 2002 JMPR, relative concentrations of oxamyl and oxamyl-oxime were measured in a tobacco plant 3 weeks after being transplanted into soil treated with oxamyl (6 mg/kg). Residues of the oxamyl-oxime were present at about 70% of the oxamyl residues (i.e., a total oxamyl/oxamyl ratio of 1.7).

In the bridging studies on lettuce and sweet peppers following five soil drip irrigation treatments, the ratio of total oxamyl/oxamyl residues ranged from 1.1 to 2.6 in lettuce sampled 0–7 days after the last application and from 5.5 to 35 in peppers sampled 1–28 days after the last application.

The Meeting concluded that these studies were insufficient to extrapolate residue values for oxamyl alone to total oxamyl residues in citrus fruits, cucurbits, peppers and tomatoes and concluded there was insufficient data to support alternative GAP assessments for these commodities.