SCIENTIFIC REPORT OF EFSA

Scientific and technical support for preparing a EU position in the 42nd Session of the Codex Committee on Pesticide Residues (CCPR)[1]

European Food Safety Authority[2]

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SUMMARY

The European Commission has the obligation to prepare a common EU position for the Codex Committee on Pesticide Residues (CCPR) and to obtain the agreement of the Council before presenting the EU position in CCPR.

The European Commission requested EFSA to provide comments on the CXLs and toxicological reference values proposed in the JMPR report 2009. These comments are to be taken into account for deriving the EU common position to be presented in the 42nd session of the CCPR in Xiang, China on 19 to 24 April 2010.

In the JMPR report 2009 the evaluations for the following 22 active substances were reported: Benalaxyl, bifenthrin, boscalid, buprofezin, cadusafos, carbofuran, chlorothalonil (and its metabolite SDS-3701), chlorpyrifos-methyl, cycloxydim, cypermethrin, fenbuconazole, fluopicolide (including its metabolite 2,6-dichlorobenzamide), haloxyfop, hexythiazox, indoxacarb, metaflumizone, methoxyfenozide, paraquat, prochloraz, prothioconazole (including the metabolite prothioconazole-desthio) spirodiclofen and zoxamide. Six of the active substances were assessed only with regard to the toxicological properties, and the derivation of toxicological reference values.

EFSA provides the requested background information, comparing the assessments performed at EU level in the framework of the peer review under Directive 91/414/EEC with the assessments performed by JMPR. EFSA takes into account the currently valid EU guidance documents for consumer risk assessment (European Commission, 1996, 1997a, 1997b, 1997c, 1997d, 1997e, 1997f, 1997g, 2008) and the agreed EU policies and provides comments in particular if the EU practice would lead to different conclusions regarding toxicological endpoints and MRL proposals compared with the JMPR methodology.

EFSA highlighted differences regarding the toxicological reference values derived by JMPR for bifenthrin, cadusafos, chlorothalonil, cycloxydim, fluopicolide and spirodiclofen in comparison with the values established at EU level. For metaflumizone currently no agreed European ADI and ARfD value is available since the peer review process under Directive 91/414/EEC is still ongoing.

EFSA identified potential consumer health risks related to the proposed CXLs for six substances evaluated (buprofezin (chronic exposure), carbofuran (chronic and acute exposure), chlorpyrifos-

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methyl (chronic exposure), cypermethrin (chronic exposure) fluopicolide (acute exposure) and haloxyfop (chronic and acute exposure)).

EFSA was also asked to provide comments on the four active substances (carbofuran, procymidone, lambda-cyhalothrin and flusilazole) for which the European Community has submitted concern forms to the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 2009 because of disagreement with the toxicological reference values established by JMPR.

The arguments presented in the concern forms have now been addressed by the 2009 JMPR and the European Commission is requesting advice from EFSA on the acceptability of these JMPR considerations. Taking into account the rational provided by the JMPR regarding the substances carbofuran, lambda-cyhalothrin and flusilazole, EFSA recommends to keep the EU position as expressed in the concern form submitted to JMPR since no additional arguments were provided which would require a changed position. Regarding procymidone EFSA has not been involved in the toxicological review. It is therefore recommended to consult the Rapporteur Member State France who was responsible for the assessment of the dossier.

KEYWORDS

Consumer risk assessment, CCPR meeting 2010, benalaxyl, bifenthrin, boscalid, buprofezin, cadusafos, carbofuran, chlorothalonil (and its metabolite SDS-3701), chlorpyrifos-methyl, cycloxydim, cypermethrin, fenbuconazole, fluopicolide (including its metabolite 2,6-dichlorobenzamide), haloxyfop, hexythiazox, indoxacarb, metaflumizone, methoxyfenozide, paraquat, prochloraz, prothioconazole (including the metabolite prothioconazole-desthio) spirodiclofen and zoxamide.

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BACKGROUND

The European Commission has the obligation to prepare a common EU position for the Codex Committee on Pesticide Residues (CCPR) and to obtain the agreement of the Council before presenting the EU position in CCPR. In the past the European Commission relied on the Member States for technical and scientific support as Member States were also giving such support to the European Commission in the process of MRL setting. Since Regulation (EC) No 396/2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin became applicable, the European Commission asked EFSA for scientific support for preparing the common EU position.

In January 2010, the European Commission already announced its intention to ask for the advice of EFSA on a limited number of subjects for the 2010 CCPR. On 11 March 2010, EFSA received the mandate explaining in detail the contributions that are expected from EFSA for the 2010 CCPR.

In particular, the European Commission requests advice on those substances for which there seems to be disagreement between the EU and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR). According to the procedure of CCPR, when there is a disagreement between a Member Country of Codex and JMPR about a recommendation, that country will submit a concern form in which the scientific objections are substantiated. JMPR will then comment on these issues and explain why it retains its original position or changes its position. For four active substances that were discussed at the 2009 CCPR (carbofuran, procymidone, lambda-cyhalothrin and flusilazole), the Delegation of the European Community raised concerns regarding the toxicological reference values established and concern forms were submitted to JMPR. These concern forms have now been considered by JMPR and a reply to the arguments put forward by the European Commission is now available in the report of the 2009 JMPR.

In addition, The European Commission requests EFSA to provide comments on chapter 2 of the JMPR report 2009 (General considerations) and on the proposed CXLs and toxicological endpoints (chapter 3 of the JMPR report), (WHO/FAO, 2009).

TERMS OF REFERENCE AS PROVIDED BY EUROPEAN COMMISSION

The European Commission asked EFSA to provide advice whether the arguments of JMPR outlined in the JMPR reports 2008 and 2009 section 3 (Responses to specific concerns raised by the Codex Committee on Pesticide Residues (CCPR)) in response to the concern forms submitted by the European Commission for carbofuran, procymidone, lambda-cyhalothrin and flusilazole are acceptable or whether the previously expressed concerns are still valid.

In addition, the European Commission asked for comments and EFSA's view regarding section 2 of the JMPR Report on the general considerations of JMPR and on the proposed Codex Levels (CXLs) and toxicological endpoints (section 5 of JMPR Report).

The deadline to provide the scientific report to the European Commission was 24 March 2010.

ASSESSMENT

1. Introduction

In order to derive a common EU position to be presented at the 42nd CCPR meeting held on 19 to 24 April 2010 in Xian, China, EFSA provides the requested background information, comparing the assessments performed at EU level in the framework of the peer review under Directive 91/414/EEC[3] with the assessments performed by JMPR. EFSA takes into account the currently valid EU guidance documents for consumer risk assessment (European Commission, 1996, 1997a, 1997b, 1997c, 1997d, 1997e, 1997f, 1997g, 2008) and the agreed EU policies and provides comments in particular if the EU practice would lead to different conclusions regarding toxicological endpoints and MRL proposals compared with the JMPR methodology.

2. Comments on JMPR responses to the concern forms submitted by the European Commission

In 2008 and 2009, the European Commission, on behalf of the European Community, and Belgium have submitted concern forms regarding the toxicological reference values for flusilazole, lambda-cyhalothrin, carbofuran and procymidone derived by JMPR (see Attachment A). JMPR has addressed the European concern in the JMPR reports 2008 and 2009. The European Commission is now requesting EFSA to evaluate the scientific arguments presented by a response to these concerns.

2.1. Carbofuran

2.1.1. EU position

During the review of carbofuran (EFSA, 2006), the Acceptable Daily Intake (ADI) was set at 0.001 mg/kg bw/day, with a safety factor of 100 applied, based on the No Observed Adverse Effect Level (NOAEL) of 0.1 mg/kg bw/day from the 1-year dog study, where testicular degeneration was observed at 0.5 mg/kg bw/day and inhibition of acetylcholinesterase (AChE) at 1 mg/kg bw/day. The Acute Reference Dose (ARfD) was 0.001 mg/kg bw, with a safety factor of 100, based on the NOAEL of 0.1 mg/kg bw/day in the developmental study in rat where neurotoxic signs were observed in the dams at 0.3 mg/kg bw/day as well as mortality at 1 mg/kg bw/day.

During the assessment of the dossier of carbofuran which was re-submitted with view of inclusion of the active substance in Annex I of Directive 91/414/EEC (EFSA, 2009a), it was concluded that the testicular damage and toxic effects on sperm were not replicated in a more recent study in rats. However, the absence of similar findings in the rat did not discount the effects observed in the dog. A new ADI was proposed, based on the Lowest Observed Adverse Effect Level (LOAEL) of 0.03 mg/kg bw observed in Post Natal Day (PND) 11 pups in a new submitted acute neurotoxicity study for which a significant inhibition of 20% of the brain AChE was observed. The use of a supplementary assessment factor of 2 was supported by a benchmark dose approach for a 10% decrease of brain AChE, resulting in an overall assessment factor of 200. The ADI was set at 0.00015 mg/kg bw/day as well as the ARfD (0.00015 mg/kg bw).

In the new acute neurotoxicity study (Hoberman 2007, main study, submitted during the resubmission process (Belgium, 2008)) thirty minutes after the single administration of carbofuran by gavage at dose levels of 0.03, 0.1 and 0.3 mg/kg bw to rat pups and young adults, brain (and to a lesser extent Red Blood Cell - RBC) AChE activity was inhibited. The effect was more marked into the pups than into the young adults. The inhibition of brain AChE activity subsided at 4h post-administration, at 0.1

[3] Council Directive 91/414/EEC of 15 July 1991, OJ L 230, 19.8.1991, p. 1-32.

mg/kg bw and above, but at the lowest dose level of 0.03 mg/kg bw, recovery was observed. In this study, the pup NOAEL was considered <0.03 mg/kg bw, based upon the brain AChE inhibition in rat pups (males and females) shortly after administration. As the decrease was <20% in rat adults, the adult neurotoxicity NOAEL could be established at 0.03 mg/kg bw. In principle, a statistically significant decrease by ≥20% of brain AChE represents a clear toxicological effect; in the case of the Hoberman study, clinical signs and motor activity impairments were not observed, but a full Functional Observation Battery (FOB) assessment or motor activity assessment was not conducted in the pups. A benchmark dose (BMD) was considered to estimate a plausible no-adverse effect level. A 5-10% response (in this case brain AChE inhibition compared to controls), was considered acceptable as a no-adverse-effect (US EPA, 2006a). The BMD10 was computed, i.e. the dose corresponding with a 10% brain AChE inhibition in the worst-case group (female pups, brain AChE inhibition at 30 minutes post-dosing), using the BMD software from the EPA (v 2.0, 2008).

For the female pups, the BMD10 was 0.01739 mg/kg bw. The BMDL10 (the one-sided 95% confidence limit of the BMD), was 0.0085 mg/kg bw. The limitations of the BMD10 were considered (a sigmoidal curve-fit using a model with 4 parameters may not be statistically demonstrable with ≤4 dose-groups), however, it was fairly comparable with the value obtained by extrapolating in a linear dose-response. Similarly, assuming a linear dose-response for the first three doses, a 10% inhibition would be assumed at 0.021 mg/kg bw (corresponding BMDL10= 0.018 mg/kg bw). Hence, an assessment factor of 2 was proposed to be applied to the LOAEL supporting the abovementioned BMD10, and was considered sufficient to derive the NOAEL in this study. Therefore, the NOAEL was calculated as half of the LOAEL (NOAEL = LOAEL (0.03 mg/kg bw)÷2 = 0.015 mg/kg bw/day).

In conclusion, the decrease of brain AChE was considered both statistically and biologically significant, and a clear dose-response was observed. Brain AChE activity decreases were also dose-dependent from the lowest dose on in the male adults, although the decrease at the lowest dose was <20%. It was acknowledged that clinical signs were absent at the lowest dose, but as a full FOB or motor activity assessment would be impossible in the pups, the implication on the level of the observed brain AChE decrease remained unexplained.

2.1.2. JMPR position

The Meeting established an ARfD of 0.001 mg/kg bw based on the overall NOAEL of 0.03 mg/kg bw per day identified on the basis of inhibition of brain acetylcholinesterase activity in rat pups aged 11 days (postnatal day 11) and a safety factor of 25 (WHO/FAO, 2008). This NOAEL was supported by the BMDL10 of 0.03 mg/kg bw extrapolated from data on inhibition of brain acetylcholinesterase activity in rat pups aged 11 days (postnatal day 11) in a second study. A safety factor of 25 was considered to be appropriate because the acute toxic effects of carbofuran are dependent on Cmax rather than area under the curve of concentration–time (AUC) and data indicated that the sensitivity of humans and laboratory animals (rats, dogs) to inhibition of acetylcholinesterase activity by carbofuran was similar. Given the apparent higher sensitivity of younger animals, the ARfD was considered to be adequately protective for infants and children since it was based on the NOAEL from a study in pups aged 11 days. The Meeting noted that this ARfD was lower than the current ADI of 0.002 mg/kg bw. This is plausible in view of the toxicological characteristics of inhibition of acetylcholinesterase activity by carbofuran, which shows very rapid recovery; long-term exposure can thus be likened to a series of acute exposures. The Meeting therefore concluded that the ADI and ARfD for carbofuran should be based on the same NOAEL and revised the ADI to 0.001 mg/kg bw based on the overall NOAEL of 0.03 mg/kg bw from the new studies of acute toxicity in rats and using a safety factor of 25.

Comparison

	Value	NOAEL, Study	Safety factor
ADI:			
EU	0.00015 mg/kg bw/day	0.03 mg/kg bw (LOAEL) Acute neurotoxicity	200
JMPR	0.001 mg/kg bw/day	0.03 mg/kg bw Acute neurotoxicity	25
ARfD			
EU	0.00015 mg/kg bw	0.03 mg/kg bw (LOAEL) Acute neurotoxicity	200
JMPR	0.001 mg/kg bw	0.03 mg/kg bw Acute neurotoxicity	25

Both JMPR and EFSA considered the same acute neurotoxicity study relevant for setting the reference values. However, EFSA considered a decrease of brain AChE of 20% biologically relevant, even in the absence of clinical signs in the affected pups, but also noting that an appropriate assessment of behaviour was missing as well. This resulted in a LOAEL of 0.03 mg/kg bw, whereas this was considered a NOAEL by JMPR. In addition, the EU assessment applied the standard uncertainty factor of 100 in view of the currently applied policy (plus an extra factor of 2 to take into account the use of a LOAEL), whereas JMPR lowered to 25 considering the dependence of carbofuran acute effects a to Cmax.

Noting that there is no agreed policy/general agreement at European level on how to apply reduced safety factors, EFSA recommends maintaining the EU position as expressed in the concern form submitted to JMPR. However, it should be noted that Regulation (EC) No 1107/2009[4] concerning the placing of plant protection products on the market, which entered into force on 14 December 2009 and which will become fully applicable on 14 June 2011, does not allow for the setting of toxicological reference values using a safety factor of less than 100 (Annex II, point 3.6.1. of the Regulation).

It is noted that US EPA used the same starting point BMDL10 = 0.03 mg/kg/day, based on cholinesterase inhibition in the brain of postnatal day 11 (PND11) male pups, with an uncertainty factor of 500, leading to an ARfD of 0.00006 mg/kg bw (US EPA, 2006b); a chronic RfD was not selected because the ARfD is considered protective of chronic exposures, given that carbofuran-induced inhibition of AChE activity is reversible (within 24 hours). The longer-term exposures could be considered a series of acute exposures.

2.2. Procymidone

2.2.1. EU position

In 2007, an ADI of 0.025 mg/kg bw/day was assigned, the value being based on the NOAEL of the rat multigeneration study, 2.5 mg/kg bw/day (50 ppm), and a safety factor of 100, based on reduced anogenital distance, hypospadias, testicular atrophy and undescended testes at 250 ppm (12.5 mg/kg bw/day) (European Commission, 2007).

For the purpose of renewal of the Annex I inclusion, the applicant submitted additional information which was assessed by the Rapporteur Member State France (France, 2007). The new information revealed increased weight of the testes and decreased weight of the prostate, epididymis and seminal

[4] Regulation (EC) No 1107/2009 of 27.11.2009, OJ L 309, 24.11.2009, p. 1-50

vesicles were seen even at 50 ppm. Thus, the following assessment factors were proposed by the RMS:

- a 3-fold factor (LOAEL → NOEL),
- a 3-fold factor for interspecies variability,
- a 10-fold factor for intraspecies variability and
- a 10-fold factor for the severity of the effects,

giving an ADI of 0.0028 mg/kg bw/day. It was agreed with Member States that this value is replacing the previously established ADI of 0.025 mg/kg bw/day.

The acute reference dose of 0.035 mg/kg allocated in 2007 in the framework of the peer review (European Commission, 2007) was based on one developmental toxicity study in rats (reduced anogenital distance, hypospadias, testicular atrophy, undescended testes) with a NOEL of 3.5 mg/kg bw/day. During the evaluation of the application for the renewal of the Annex I inclusion, the same toxicological end point was selected for deriving the ARfD but instead of using the safety factor of 100, the Rapporteur Member State France proposed to use the following assessment factors (France, 2007):

- a 3-fold factor for interspecies variability
- a 10-fold factor for intraspecies variability
- a 10-fold factor for the severity of the effects

giving an ARfD of 0.012 mg/kg bw/day. Further information could not be retrieved by EFSA.

2.2.2. JMPR position

The Meeting established an ADI of 0.1 mg/kg bw based on a NOAEL of 12.5 mg/kg bw per day in a two-generation study of reproductive toxicity and a study of developmental toxicity in rats, on the basis of hypospadias and alterations in testes, prostate and epididymis weights, and a safety factor of 100 (WHO/FAO, 2007). The ADI was supported by the NOAELs of 14 mg/kg bw/day in the 2-year study in rats and 15 mg/kg bw/day in the 2-year study in mice. The Meeting established an ARfD of 0.1 mg/kg bw based on a NOAEL of 12.5 mg/kg bw on the basis of hypospadias, which might have been a consequence of a single exposure, in a study of developmental toxicity in rats, and using a safety factor of 100. The Meeting concluded that the effects on organ weights observed in the multigeneration study were largely a consequence of postnatal exposure over a period of time and therefore not appropriate for the establishment of the ARfD. The Meeting considered that, on the basis of the observed differences between species in terms of kinetics, metabolism and toxicological sensitivity to procymidone, this ARfD might be conservative. However, uncertainties regarding potential responses in species other than rats were such that it was not possible to modify the default safety factor.

Comparison

	Value	NOAEL, Study	Safety factor
ADI:			
EU	0.0028 mg/kg bw/day	2.5 mg/kg bw/day rat multigeneration	900
JMPR	0.1 mg/kg bw/day	12.5 mg/kg bw/day Rat 2-generation, developmental	100
ARfD			
EU	0.012 mg/kg bw	3.5 mg/kg bw/day Rat developmental	300
JMPR	0.1 mg/kg bw	12.5 mg/kg bw/day Rat 2-generation, developmental	100

It is noted that procymidone was not assessed or peer reviewed by EFSA. In order to derive a common position to be presented at the CCPR meeting, EFSA recommends to consult the Rapporteur Member State familiar with the dossier presented in the EU peer review process to consider the ADI and ARfD values derived by JMPR.

2.3. Lambda-cyhalothrin

2.3.1. EU position

The 1-year subchronic feeding study of lambda-cyhalothrin in dogs was chosen during the peer review (finalised in 2000) for the calculation of the proposed ADI for lambda-cyhalothrin, since the critical effects of lambda-cyhalothrin noted for dogs (eg. neurological signs) were considered critical also for humans. The no observed effect level (NO(A)EL) was 0.5 mg/kg bw/day, based on clinical signs (ataxia, muscle tremors and convulsions) and decreased food consumption at 3.5 mg/kg bw/day. In view of the quality, extent and consistency of the data base, it was considered appropriate to apply the uncertainty factor of 100 and thus to derive an ADI of 0.005 mg/kg bw/day. No ARfD was proposed in the Draft Assessment Report of lambda-cyhalothrin as it was evaluated prior to the development of the guidance document. In 2000 a proposal for setting an ARfD for lambda-cyhalothrin was considered: the ARfD was set at 0.0075 mg/kg bw, based on decreased activity and tremors observed at 1.5 mg/kg bw/day in the 6-week oral study in dogs, and using an uncertainty factor of 100 (European Commission, 2001).

2.3.2. JMPR position

The most sensitive systemic effect of lambda-cyhalothrin/cyhalothrin was neurotoxicity (decreased motor activity), which was observed in a study of acute toxicity in rats given lambda-cyhalothrin orally, 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. On the basis of these effects, the Meeting established a group ADI for cyhalothrin and lambda-cyhalothrin of 0.02 mg/kg bw, 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 Cmax, the Meeting considered it appropriate to adjust the safety factor for the reduced variability in Cmax compared with AUC. The Meeting considered that the ADI of 0.02 mg/kg bw/day is adequately protective against the other, non-neurotoxic effects of lambdacyhalothrin/ cyhalothrin

observed in short- and long-term studies with repeated doses, and in studies of reproductive and developmental toxicity, where the use of a safety factor of 100 would be appropriate.

The Meeting 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/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 a safety factor of 25. For the same reasons as described above, the Meeting considered it appropriate to adjust the safety factor for the reduced variability in Cmax compared with AUC (WHO/FAO, 2007).

Comparison

	Value	**NOAEL, Study**	**Safety factor**
ADI:			
EU	0.005 mg/kg bw/day	0.5 mg/kg bw/day 1-year dog	100
JMPR	0.02 mg/kg bw/day	0.5 mg/kg bw/day 1-year dog	25
ARfD			
EU	0.0075 mg/kg bw	0.75 mg/kg bw 6-week oral dog study	100
JMPR	0.02 mg/kg bw	0.5 mg/kg bw/day 1-year dog	25

Both EU and JMPR selected the same study (1-year in dog) as relevant for setting the ADI. The different resulting value is due to the selection of different safety factor. As for the ARfD the endpoint is different in the two assessments; furthermore the applied safety factor is different as well.

Noting that there is no agreed policy/general agreement at European level on how to apply reduced safety factors, EFSA recommends maintaining the EU position as expressed in the concern form submitted to JMPR. However, it should be noted that Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market, which entered into force on 14 December 2009 and which will become fully applicable on 14 June 2011, does not allow for the setting of toxicological reference values using a safety factor of less than 100 (Annex II, point 3.6.1. of the Regulation).

2.4. Flusilazole

2.4.1. EU position

An ADI of 0.002 mg/kg bw/day was set based on effects on blood, liver and urinary bladder in a 1-year study in dogs, applying a SF of 100 to the NOAEL of 0.2 mg/kg bw/day.

The basis for the EU ARfD of 0.005 mg/kg bw (NOAEL 0.5 mg/kg bw/day, SF 100, considered relevant to women of childbearing age) is the rat oral developmental toxicity study submitted by the notifier and reviewed by the RMS (Ireland, 2004). A number of effects occurred in a dose and treatment-related manner from 2.0 mg/kg bw/day: red vaginal discharge during late gestation, mean placental weights significantly increased in a dose related manner (a similar observation with histopathological correlate was made in the dermal study), treatment-related increase in rudimentary

7th cervical ribs from 2 mg/kg bw, which was statistically significant from 10 mg/kg. The increase seen at 2.0 mg/kg bw/day was considered biologically relevant as it was the beginning of a dose-related finding.

In 2009 the EFSA Panel on Plant Protection Products and their Residues (PPR) confirmed this ARfD in the frame of the scientific opinion on "Risk Assessment for a Selected Group of Pesticides from the Triazole Group to Test Possible Methodologies to Assess Cumulative Effects from Exposure through Food from these Pesticides on Human Health".

2.4.2. JMPR position

The Meeting established an ADI of 0.007 mg/kg bw/day based on the NOAEL of 0.7 mg/kg bw/day based on gastric and liver effects and clinical chemistry in the 1-year dietary study in dogs, with a safety factor of 100. An ARfD of 0.02 mg/kg bw was established based on the NOAEL of 2 mg/kg bw/day for skeletal anomalies in the study of developmental toxicity in rats treated orally, applying a safety factor of 100.

Comparison

	Value	**NOAEL, Study**	**Safety factor**
ADI:			
EU	0.002 mg/kg bw/day	0.2 mg/kg bw/day 1-year dog	100
JMPR	0.007 mg/kg bw/day	0.7 mg/kg bw/day 1-year dog	100
ARfD			
EU	0.005 mg/kg bw *(Relevant to women of child bearing age)*	0.5 mg/kg bw/day Rat developmental	100
JMPR	0.02 mg/kg bw	2 mg/kg bw/day Rat developmental	100

As for the setting of the ADI, it seems that both the EU and JMPR assessors considered the same key study as well as the relevant endpoints; based on the available information it is not possible to explain the discrepenies; the differences may result from the selection of different NOAELs or from different conversion of dosing levels (conversion from ppm to mg/kg bw/day).

With regard to the ARfD the conclusion of the EU differs from that of JMPR as the JMPR reviewers only considered the rudimentary 7th rib as relevant for development at the dose level of 2 mg/kg bw/day. Findings of dose dependent vaginal discharge and increase of mean placental weights mentioned above were considered by JMPR to represent maternal toxicity.

In conclusion EFSA recommends to keep the EU position as expressed in the concern form submitted to JMPR.

3. Comments on general considerations (Section 2 of JMPR report)

3.1. Transparency in the maximum residue level estimation process

For deriving the CXL proposals presented in the JMPR report 2009, the JMPR tested the NAFTA MRL calculator, an electronic tool which should facilitate the statistical evaluation of residue data sets.

The JMPR experts concluded that evaluation of residue data is a complex task that requires the consideration of factors and parameters additional to the numerical residue values. Therefore, the JMPR experts are of the opinion that MRL estimates cannot be based solely on automatic calculation using any currently available "statistical" methods.

EFSA shares the view of the JMPR Panel that expert judgement plays an important role in deriving a MRL proposal. EFSA also notes that from the limited experience available at the moment it became evident that in most cases, the MRLs derived by using the NAFTA calculator were higher compared with the values derived with the EU MRL calculation methods.

EFSA therefore recommends investigating carefully the impact of the new methodology as implemented by the new OECD calculator which was recently released to replace the NAFTA calculator. Further testing is necessary before a final recommendation can be given whether or not to use the new developed calculation tool.

3.2. The OECD guidance document on livestock feeding

EFSA welcomes the decision by JMPR to adopt the latest available version of the OECD feed table and to include it in the FAO Manual, Second Edition (FAO, 2009).

3.3. Guidance for data submission for estimation of residue levels in/on spices

EFSA appreciates the further guidance given by JMPR on data submission for estimation of residue levels in/on spices.

3.4. Update of the FAO Manual on the submission and evaluation of data on pesticide residues for the estimation of maximum residue levels in food and feed

EFSA welcomes the publication of the second edition of the FAO Manual, describing the basic principles currently applied by the FAO Panel of JMPR in the evaluation of pesticide residues for recommending maximum residue levels.

4. Comments on the CXLs and toxicological reference values proposed by JMPR

The JMPR Meeting held from 16 to 25 September 2009 evaluated 22 pesticides. These 22 pesticides include among others three compounds evaluated by JMPR for the first time and eight compounds re-evaluated within the Codex Committee on Pesticide Residues periodic review programme for toxicity and/or residues. This JMPR meeting established ADI and ARfD values for 7 pesticides and estimated MRLs that are now recommended for use by the Codex Committee on Pesticide Residues (CCPR) for 18 compounds. STMR values and highest residue (HR) levels were also derived in order to perform dietary intake estimations. The results of the assessments are published in the JMPR Report (FAO/WHO, 2009a) while detailed evaluations can be found in the JMPR Evaluations (FAO/WHO, 2009b).

EFSA provides the requested background information, comparing the assessments performed at EU level in the framework of the peer review under Directive 91/414/EEC with the assessments performed by JMPR. EFSA takes into account the currently valid EU guidance documents for consumer risk assessment (European Commission, 1996, 1997a, 1997b, 1997c, 1997d, 1997e, 1997f, 1997g, 2008) and the agreed EU policies and provides comments in particular if the EU practice would lead to different conclusions regarding toxicological endpoints and MRL proposals compared with the JMPR methodology. In the following section EFSA addressed in particular the following issues:

- For the 7 active substances where new toxicological reference values were recommended by the 2009 JMPR, these toxicological reference values were compared with those established at European level. EFSA also assessed whether these values were established on the basis of the same toxicological data and whether the evaluation performed by JMPR was in compliance with the approaches applied at European level. For active substances for which toxicological reference values have been established in previous years, but which were assessed regarding the residue behaviour in the JMPR report, EFSA highlighted the differences regarding the ADI/ARfD values established by JMPR and at EU level.

- For all active substances where CXLs are recommended, EFSA compared the residues definitions that were applied by JMPR and the residues definitions currently in place at European level. This step was considered essential in view of inclusion of the CXLs in a European risk assessment. In case residue definitions were different, EFSA evaluated the relevance of the metabolites generating these differences.

- For all active substances where CXLs are recommended, EFSA also verified whether the draft CXLs are adequately supported by residues trials data and whether extrapolations applied by JMPR are in accordance with European guidance on this matter.

- At last, in order to assess whether the recommended CXLs might be of concern for European consumers, EFSA carried out both chronic and acute intake calculations using revision 2 of the EFSA PRIMo and appropriate HR and/or STMR values were used, when available. The acute intake calculations mainly refer to the CXLs at step 3 or 6 of the Codex adoption procedure (draft CXLs) but exceedances of the ARfD for CXLs already adopted by the CAC (existing CXLs) were also reported for information. Considering that chronic exposure of consumers is not resulting from the draft CXLs only, both draft and existing CXLs were considered for the chronic intake calculations. When appropriate STMR values were available to EFSA, the existing EC MRLs were considered for the chronic exposure as well.

4.1. Benalaxyl

4.1.1. Toxicological endpoints

Although no comments are requested at this stage, EFSA notes that JMPR has established an ARfD for women of childbearing age only whereas in peer review under Directive 91/414/EEC no ARfD was considered necessary. It is also noted that JMPR ADI value is higher than the EU ADI. (JMPR: 0.07 mg/kg bw/day; EU: 0.04 mg/kg bw/day).

4.1.2. Residue definitions

EU residue definition for risk assessment and enforcement: Benalaxyl including other mixtures of constituent isomers including benalaxyl-M (sum of isomers)

Residue definition derived by JMPR: Benalaxyl

4.1.3. CXL proposals

JMPR proposed higher CXLs compared with EU MRLs for:

- Grapes
- Lettuce head,
- Melons, except watermelons

JMPR proposed lower MRLs compare with EU MRLs for

- Onion, bulb,
- Potatoes (lower LOQ)
- Tomatoes

For peppers the existing CXL is proposed for withdrawal. The EU MRL for peppers is 0.2 mg/kg.

Grapes: The CXL is sufficiently supported by data. The EU MRL calculation method leads to the same MRL proposal as derived by JMPR.

Onions: A sufficient number of trials representing the critical EU GAPs is available. No residues above LOQ were observed. The EU MRL which is set at a level of 0.2 mg/kg may be considered for being lowered to the LOQ of 0.02 mg/kg.

Melons: Sufficient trials representing critical EU GAP are available. The EC methodology to calculate a MRL would result in 0.2 mg/kg whereas the JMPR proposal is 0.3 mg/kg.

Watermelons: A sufficient number of trials representing critical EU GAP (SEU) is available. The EU methodology to calculate MRL would result in 0.05 mg/kg whereas the JMPR proposal is 0.1 mg/kg.

Tomatoes: A sufficient number of trials to support the French GAP is available (for the most critical GAP (Spain) the number of trials was not sufficient to derive a CXL). The EU MRL calculation method leads to lower MRL (0.1 mg/kg) instead of 0.2 mg/kg as proposed by JMPR.

Lettuce: A sufficient number of trials representing the critical EU GAP is available. The EU MRL calculation methodology leads to a lower MRL of 0.05 mg/kg while JMPR proposed 0.1 mg/kg.

Potato: A sufficient number of trials, also at exaggerated dose rates, is available. In all cases residues were below the LOQ. The proposed CXL of 0.02 mg/kg, equivalent to the LOQ, is therefore justified.

4.1.4. Consumer risk assessment

Using the standard settings of EFSA PRIMo, no long-term consumer health risk is identified when the proposed CXLs are added to the EU MRLs and the lower EU ADI of 0.04 mg/kg bw/d is used.

Using the standard settings of EFSA PRIMo (standard variability factors of 7 or 5), no short-term health risk is identified for proposed CXLs using JMPR ARfD.

4.2. Bifenthrin

4.2.1. Toxicological endpoints

4.2.1.1. EU position

The reference values proposed in the EFSA conclusion issued on 30/9/2008 (EFSA, 2008) are 0.015 mg/kg bw/day for the ADI (based on the NOAEL from the 1-year study in dog, SF 100) and 0.03 mg/kg bw for the ARfD (derived from the 90-day neurotoxicity study in rats, SF 100).

4.2.1.2. JMPR position

JMPR assessed bifenthrin in 2009, setting an ADI of 0.01 mg/kg bw/day (based on the rat developmental toxicity NOAEL, SF 100) and an ARfD of 0.01 mg/kg bw (based on a rat motor activity assessment, with a SF 100).

Comparison

	Value	NOAEL, Study	Safety factor
ADI:			
EU	0.015 mg/kg bw/day	1.5 mg/kg bw/day 1-year dog	100
JMPR	0.01 mg/kg bw/day	1 mg/kg bw/day Rat developmental	100
ARfD			
EU	0.03 mg/kg bw	3 mg/kg bw/day 90-day neurotoxicity rats	100
JMPR	0.01 mg/kg bw	1 mg/kg bw/day Rat motor activity assessment	100

It is noted that in the EU peer review process the established developmental and maternal NOAELs from the rat study differ from the values used for setting the ADI by JMPR (whereas in the list of end points of the JMPR report the NOAELs correspond). Similarly, the acute motor activity assay was apparently not available to EFSA. According to the available information, the EU assessment is still supported with regard to the ADI; as for the ARfD the more conservative value of 0.01 mg/kg bw proposed by JMPR is acceptable. The EU ARfD should be reconsidered, taking into account the findings of JMPR in case the acute motor activity assay was not available in the EU assessment.

4.3. Boscalid

4.3.1. Toxicological endpoints

The EU ADI is identical with the value derived by JMPR (0.04 mg/kg bw/d). Both bodies did not establish an ARfD. No further comments are necessary at this stage.

4.3.2. Residue definitions

EU residue definition for risk assessment and monitoring (plants): boscalid;

For animal commodities (both for RA and monitoring): boscalid and M510F01 (including its conjugates) expressed as boscalid

JMPR established identical residue definitions.

4.3.3. CXL proposals

JMPR proposed higher CXLs compared with EU MRLs for:

- Brassica (except leafy brassica)
- Bulb vegetables
- Edible offal
- Fruiting vegetables, Cucurbits
- Fruiting vegetables, other that cucurbits
- Leafy vegetables (except lamb's lettuce)

- legume vegetables
- milks
- oilseed
- pulses,
- root and tuber vegetables

JMPR proposed lower CXLs compared with EU MRLs for:

- Banana
- Lambs lettuce
- Barley
- Strawberry
- Leafy brassica

For crops that can be grown in crop rotation, JMPR assessed the residues arising from direct treatment in combination with the root uptake of boscalid applied in previous years.

Brassica (except leafy brassica): The CXL proposal for brassica vegetables is derived from a combined dataset comprising trials on broccoli and cabbage. EFSA notes that the pooling of residue trials data from these crops and calculating an MRL proposal which is extrapolated to the whole group of brassica vegetables is not accepted at EU level. According to the EU assessment methodology, separate MRLs would be established for the individual crops provided that a sufficient number of trials are available for the individual crops.

Fruiting vegetables: The CXL proposal for fruiting vegetables was derived from cantaloupe (8 trials); this commodity showed the highest residue population in the fruiting vegetables group. For other fruiting vegetables lower MRLs would be sufficient. According to the EU policy, specific MRLs for the individual crops would be derived instead of deriving a group tolerance which is extrapolated from the dataset with the highest residues.

Leafy vegetables: The CXL proposal for leafy vegetables was derived from trials in mustard greens (8 trials); this commodity showed the highest residue population in the leafy vegetables group. (For other leafy vegetables lower MRLs would be sufficient). According to the EU policy, specific MRLs for the individual crops would be derived instead of deriving a group tolerance which is extrapolated from the dataset with the highest residues.

Legume vegetables: The CXL proposal for legume vegetables was derived from trials on green beans with pods. For other legume vegetables lower CXLs would be sufficient. According to the EU policy, specific MRLs for the individual crops would be derived instead of setting a group tolerance which is extrapolated from the dataset with the highest residues.

Pulses: The CXL for pulses was derived from combined data on beans and peas. The proposed CXL is acceptable.

Root and tuber vegetables: The CXL for root and tuber vegetables was derived from trials on carrots. According to the EU guidance document, an extrapolation from carrots is acceptable for parsley roots, salsify, parsnips, horseradish, beet roots, swedes and turnips, but not for the whole group (which comprises also the major crop potatoes).

4.3.4. Consumer risk assessment:

No long-term consumer health risk was identified for the proposed higher CXLs, including the existing EU MRLs in the refined intake calculation. No short-term consumer risk assessment was necessary since no ARfD was established.

4.4. Buprofezin

4.4.1. Toxicological endpoints

No comments are required at this stage but it is noted that the ADI established by EFSA is in the same range as the ADI derived by JMPR (EFSA: 0.01 mg/kg bw/day, JMPR: 0.009 mg/kg bw/day). The ARfD values established at EU level and by JMPR are identical (0.5 mg/kg bw).

4.4.2. Residue definitions

The residue definition for monitoring proposed by JMPR is identical with the EU monitoring residue definition.

In the EU no residue definition for risk assessment could be derived in the peer review. The lack of data finally was a reason not to include the active substance in Annex I of Directive 91/414/EEC. The dossier for the substance was resubmitted and is currently under assessment. A provisional residue definition for risk assessment for plants in the framework of the resubmission was derived: sum of buprofezin and BF-4 conjugates, measured as BF-9 and BF-12 under acidic conditions (draft EFSA conclusion for the resubmission). The toxicological relevance of the metabolite still needs to be further investigated

EFSA recommends that JMPR should consider the need to include the plant metabolites in the residue definition.

4.4.3. CXL proposals

JMPR proposed higher CXLs compared with EU MRLs for:

- Apples
- Cherries
- Fruiting vegetables (except cucumber)
- Nectarines
- Olives
- Peach
- Pear
- Peppers
- Plums

JMPR proposed lower CXLs compared with EU MRLs for:

- Almonds
- Cucumber

Apple: The CXL proposal is sufficiently supported by data but the EU MRL calculation method would result in a lower MRL (2 mg/kg instead of 3 mg/kg).

Pear: The CXL proposal is sufficiently supported data but the EU MRL calculation method would result in a lower MRL of 2 mg/kg instead of 6 mg/kg.

Peaches: The CXL proposal is sufficiently supported data.

Plums: The CXL proposal is based on 6 trials only. Since plums are a major crop worldwide as well as in NEU, at least 8 trials would be requested at EU level. It is also noted that the OECD MRL

calculator and the EU MRL calculation methodology would result in a lower MRL (1 mg/kg instead of CXL of 2 mg/kg).

Cherries: The CXL proposal is sufficiently supported by data and the EU MRL calculation method gives the same value as the proposed CXL.

Grapes: The CXL proposal is acceptable.

Strawberries: The CXL proposal is sufficiently supported by data but a CXL of 2 mg/kg would be sufficient (instead of 3 mg/kg).

Olives: The CXL proposal is based on 4 trials only. At EU level at least 8 trials would be requested to establish a MRL.

Fruiting vegetables/cucurbits: The CXL proposal is based on residue data for cantaloupes. For other cucurbits, lower MRLs would be sufficient. EFSA notes that according to the EU policy separate MRLs would be established for the individual cucurbits.

Pepper: The CXL proposal is based on combined data for bell peppers and non-bell peppers. The CXL proposal is acceptable.

Coffee: The CXL proposal is based on 4 trials only whereas at EU level at least 8 trials would be requested for coffee which is considered to be a major crop.

4.4.4. Consumer risk assessment

The risk assessment could only be performed for the parent compound, not including the additional metabolite which might be relevant for risk assessment (see 4.4.2):

In this indicative risk assessment, a potential long-term consumer health risk is identified with the EFSA PRIMo, if the proposed higher CXLs are added to the existing EU MRLs (STMR values for CXLs, supplemented with EU MRLs): the maximum exposure is 150% of ADI (compared with the JMPR ADI). The main contributors are oranges (EU MRL, without refinement: 42%), apples (CXL STMR 38%), olives (CXL STMR 42%). Further refinements of the intake calculations would be possible if data on STMR values and peeling factors for EU MRLs were available.

The total contribution of CXL (STMRs) is 60% of the ADI in the most critical diet.

The short-term risk assessment did not result in an exceedance of the ARfD. The highest ARfD exhaustion was identified for the proposed CXL for peaches (97% of ARfD).

EFSA concludes that because of the uncertainties regarding the residue definition for risk assessment a final consumer risk assessment is not possible. However, there are indications that the CXLs will significantly contribute to the chronic consumer exposure. Further refined intake calculations would be necessary to exclude that a potential long-term consumer health risk might occur.

4.5. Cadusafos

4.5.1. Toxicological endpoints

4.5.1.1. EU position

The ADI proposed in the EU peer review (2009) is 0.0004 mg/kg bw/day, based on the 2-year rat study NOAEL with a SF 100. The ARfD is 0.003 mg/kg bw and was based on a rabbit developmental

toxicity study, where the increase in early resorptions with no increase in late resorptions was considered consistent with the time at which administration of cadusafos starts (SF 100).

4.5.1.2. JMPR position

JMPR established an ADI of 0.0005 mg/kg bw/day based on a NOAEL of 0.045 mg/kg bw/day, on the basis of inhibition of erythrocyte cholinesterase activity at 0.222 mg/kg bw/day, in the long-term study in rats. A safety factor of 100 was applied.

JMPR established an ARfD of 0.001 mg/kg bw based on a NOAEL of 0.1 mg/kg bw per day identified on the basis of clinical effects in dams at 0.3 mg/kg bw/day in the study of developmental toxicity in rabbits. A safety factor of 100 was applied. The large dose spacing between the LOAEL and the NOAEL in the study of acute neurotoxicity made this study unsuitable for the derivation of an ARfD. The JMPR Meeting also noted that the ARfD established might be conservative because it was derived using clinical signs that occurred only after administration of several doses.

Comparison

	Value	**NOAEL, Study**	**Safety factor**
ADI:			
EU	0.0004 mg/kg bw/day	0.04 mg/kg bw/day 2-year rats	100
JMPR	0.0005 mg/kg bw/day	0.045 mg/kg bw/day 2-year rats	100
ARfD			
EU	0.003 mg/kg bw	0.3 mg/kg bw/day Developmental toxicity rabbits	100
JMPR	0.001 mg/kg bw	0.1 mg/kg bw/day Developmental toxicity rabbits	100

With regard to the ADI, both EU and JMPR based their assessment on the same relevant study and endpoint. As for the ARfD, EFSA concludes that the ARfD established at EU level should be reconsidered, taking into account the assessment of JMPR.

4.6. Carbofuran

4.6.1. Toxicological endpoints

See Section 2.1.

4.6.2. Consumer risk assessment

In view of the very low toxicological reference values that have been established by EFSA, EFSA performed both chronic and acute intake calculations using revision 2 of the EFSA PRIMo and STMR/HR values for all existing and/or draft CXLs. EU MRLs for carbofuran were not considered because the use of carbofuran and carbosulfan is no longer authorised in the EU. These calculations

revealed chronic and acute intake concerns with exceedances of the ADI up to 980% and ARfD up to 13000%.

EFSA therefore recommends the withdrawal of all draft CXLs as well as the revocation of all existing CXLs.

4.7. Chlorothalonil

4.7.1. Toxicological endpoints

Discrepancies were found with regard to the reference values set for the metabolite SDS-3701.

4.7.1.1. EU position

The ADI of 0.01 mg/kg bw/day was based on the NOAEL of 1.25 mg/kg bw/day, derived from a 90-days oral toxicity study in dogs, and this value was considered the overall NOAEL for rats, mice and dogs. No additional safety factor for exposure duration was applied. It should be noted that the available data on the genotoxic properties of SD-3701 is not complete since *in vitro* or *in vivo* gene mutation data are lacking. However, since there were no indications for carcinogenic properties of SDS-3701, it was considered acceptable to derive an ADI.

The ARfD was therefore set at the same level as ADI.

4.7.1.2. JMPR position

JMPR set an ADI of 0.008 mg/kg bw/d for the metabolite SDS-3701 based on the NOAEL of 0.83 mg/kg bw/d of a 1-year dog study. The critical effects identified were reduction of body weight gain in females, reduction in erythrocytes in males and increased serum concentration of glucose in males and females.

JMPR established an ARfD of 0.03 mg/kg based on a developmental toxicity study with SDS-3701 in rabbits. In this study early implantation loss was observed at 5 mg/kg bw/d dose level, NOAEL for this effect was 2.5 mg/kg bw/d. This study was evaluated in the EU process, and the same NOAEL was established for developmental toxicity based on the same effects as considered by JMPR. However, at that time no ARfD was set in the EU peer-review process.

Comparison

SDS-3701	Value	NOAEL, Study	Safety factor
ADI:			
EU	0.01 mg/kg bw/day	1.25 mg/kg bw/day 90-day dogs	100
JMPR	0.008 mg/kg bw/day	0.83 mg/kg bw/day 1-year dogs	100
ARfD			
EU	0.01 mg/kg bw	1.25 mg/kg bw/day 90-day dogs	100
JMPR	0.03 mg/kg bw	2.5 mg/kg bw/day Developmental toxicity rabbits	100

EFSA recommends to reconsider the ARfD, taking into account the evaluation done by JMPR.

With regard to the ADI, it is unclear whether the database considered by the EU and JMPR assessments is the same. Therefore, EFSA suggests to review the ADI established at EU level, taking into account the evaluation performed by JMPR.

4.8. Chlorpyrifos-methyl

4.8.1. Toxicological endpoints

Although no comments are requested at this stage, EFSA notes that JMPR and EU derived the same ADI of 0.01 mg/kg bw/day on the basis of the same study. A default safety factor of 100 was applied.

JMPR established an ARfD for chlorpyrifos-methyl in 2009 as 0.1 mg/kg bw based on the NOAEL of 1.0 mg/kg bw identified on the basis of absence of inhibition of erythrocyte acetylcholinesterase activity in a single dose study in human volunteers applying safety factor of 10. In the EU review process (2005) an ARfD of 0.1 mg/kg bw was established based on acute and delayed neurotoxicity in rats. The NOAEL of 10 mg/kg bw/day was based on the brain cholinesterase inhibition in the delayed neurotoxicity study, and supported by the NOAEL of 10 mg/kg bw in acute neurotoxicity study based on FOB, motor activity and neuropathology. A default safety factor of 100 was applied.

The assessment of the primary plant and mammalian metabolite chlorpyrifos-methyl, 3,5,6-trichloropyridinol (TCP) was considered in 1999 JMPR (review of chlorpyrifos). However, EFSA could not find the conclusion derived by JMPR regarding the toxicological relevance of this metabolite.

It is noted that TCP is a metabolite that is also observed for chlorpyrifos and triclopyr.

In the framework of the peer review of triclopyr EFSA derived a tentative ADI of 0.03 mg/kg bw/d (identical to ADI for triclopyr) and a tentative ARfD (0.25 mg/kg bw) for primary plant and mammalian metabolite of chlorpyrifos-methyl, 3,5,6-trichloropyridinol (TCP). JMPR discussed TCP in 1999, however the conclusion was not reported.

4.8.2. Residue definitions

EU residue definition for monitoring is identical with JMPR residue definition.

EU residue definition for risk assessment:

chlorpyrifos-methyl plus TCP plus conjugates expressed as chlorpyrifos-methyl;

For stored grain: sum of chlorpyrifos-methyl and desmethyl chlorpyrifos-methyl (soruce: list of end points available on CIRCA, March 2005.)

JMPR residue definition for risk assessment: chlorpyrifos-methyl.

JMPR concluded that human dietary exposure to TCP is not considered of toxicological concern.

EFSA recommends to ask JMPR for further clarifications regarding the decision not to include the metabolite in the residue definition, since the rationale is not clearly expressed in the JMPR reports.

4.8.3. CXL proposals

JMPR CXL proposals are higher than EU MRLs for :

- Citrus fruit
- Egg plant (aubergine)
- Grapes
- Meat fat
- Peppers
- Pome fruit
- Stone fruit
- Tomatoes

JMPR CXL proposals are lower than EU MRLs for:

- Edible offal (EU MRL at LOQ)
- Eggs (LOQ)
- Poultry meat
- Strawberries.

Citrus: the CXL proposal reflects EU GAPs; the CXL was derived from combined data from mandarins, clementines (7 trials) and oranges (8 trails). Although no GAP for the whole citrus group is established a proposal for a group tolerance was derived. With the combined data the EU methodology for calculating an MRL would lead to a lower MRL (1 mg/kg instead of 2 mg/kg).

Pome fruit: Trials are available for apples and pears reflecting the same GAP. The trials on apples showed higher residues. They were used to derive a group tolerance for pome fruit (1 mg/kg), although for pears a lower CXL would be possible. Using the EU MRL calculation methodology would lead to a lower MRL of 0.5 mg/kg. The NAFTA calculator leads to 0.6 mg/kg. This value was rounded up to 1 mg/kg because the trials were performed with application rates lower than the critical GAP, but within the acceptable deviation of 25% of the GAP rate.

Stone fruit: The CXL proposal is based on trials on peaches, where higher residues were observed compared with the trials on other stone fruits (trials were also available for apricots and cherries). At EU level, in this situation, specific MRLs for the different crops belonging to the stone fruit crop would be set. The result of the NAFTA calculator was 0.15 mg/kg. But since trials were performed at lower application rates (but within the 25% rule acceptable for deviations), JMPR recommended a group tolerance of 0.5 mg/kg. The EU MRL calculation method leads to a MRL of 0.3 mg/kg.

Grapes: The CXL derived with the NAFTA calculator (0.7 mg/kg) was rounded up (CXL proposal 1 mg/kg) because trials were conducted at the lower application rate than the critical GAP, but within the 25% range acceptable for deviations from the GAP. The EU methodology for calculating the MRL would lead to a lower MRL (0.5 mg/kg).

Strawberry: The CXL proposal derived for strawberries is 0.1 mg/kg, not 0.06 mg/kg as stated in the summary table. This CXL proposal is based on trials from SEU. The EU MRL is significantly higher (0.5 mg/kg). The data, on which the current EU MRL is based, are not available to EFSA since the PROFile has not yet been submitted.

Tomatoes: The proposed CXL is sufficiently supported by data.

Peppers: The CXL proposal is based on a Spanish GAP (indoor). The CXL proposal is acceptable.

Potatoes: no comment.

Cereal grains- post harvest use: The CXL proposal (3 mg/kg) is based on a Spanish GAP (2.2 g/t, no storage period specified.) Only 4 trials are available for this GAP. For the most critical GAP (UK: 4.5 g/t, 90 d) consumer health risks were identified.

Maize: The CXL proposal was extrapolated from wheat and barley (post-harvest use) to maize. For pre-harvest use no supporting trials were available.

4.8.4. Consumer risk assessment

The risk assessment was performed for parent chlorpyrifos-methyl only; the metabolite TCP was not included in the calculations.

No acute consumer health risk was identified for the proposed CXLs (refined calculations with HR/STMR values, standard EU variability factors). The maximum exposure value was calculated for apples: 55 % of ARfD.

The chronic risk assessment was performed with the existing EU MRLs, including the CXL proposals in case they are higher than the EU MRLs. For the crops where CXLs are higher than EU MRLs, the STMR values were used in the intake calculation.

A long-term consumer health risk could not be excluded (270% of the ADI). The major contributors were cereals (post-harvest use, accounting for up to 250% of the ADI).

Using the STMR of wheat flour (extrapolation also to rye) instead of the STMR for wheat and the STMR for beer instead of the STMR for barley significantly reduces calculated exposure, but still the ADI is exceeded (max. 128% of ADI, maize and wheat being the main contributors).

If the STMR for white bread is applied for wheat, the exposure is below the ADI (ca. 90%). However, it is noted that the STMR for wholemeal bread is significantly higher than the STMR for white bread.

EFSA performed an indicative long-term exposure calculation using the detailed consumption data for processed cereal based food that were submitted in the framework of an assessment of pirimiphos-methyl. Also in this calculation the total dietary intake for the cereal group was calculated to be around 90%, the major contributors were maize, for which no refined calculation could be performed (52% in WHO cluster diet B), wheat bran (40% for UK infant), and wheat flour (26 % in WHO cluster diet).

4.9. Cycloxydim

4.9.1. Toxicological endpoints

4.9.1.1. EU position

The proposed ADI is 0.07 mg/kg bw/day, based on the NOAEL of 7 mg/kg bw per day from the 24-month and 18-month studies in rodents, based on reduced body weights and serum triglycerides, SF 100; an ARfD of 2 mg/kg bw for the general population was set based on the rabbit and rat developmental toxicity studies (SF 100).

4.9.1.2. JMPR position

The proposed values are the same as the values derived in the EU assessment. However, the JMPR concluded that the establishment of an ARfD for the general population was not necessary on the basis of the low acute toxicity of cycloxydim, the lack of evidence for any acute neurotoxicity and absence of any other toxicologically relevant effect that might be attributable to a single dose; therefore the ARfD of 2 mg/kg bw was established for women of childbearing age.

4.10. Cypermethrin

4.10.1. Toxicological endpoints:

No comments are necessary at this stage, but it is noted that the EU ADI established for alpha-cypermethrin (0.015 mg/kg bw/day, cypermethrin compound with lowest reference values at EU level) is slightly lower than the ADI established by JMPR (0.02 mg/kg bw/day). The ARfD values are the same (0.04 mg/kg bw).

4.10.2. Residue definitions

The residue definitions (enforcement and risk assessment) used for the EU MRL setting are the same as those established by the JMPR. Consideration of the proposed CXLs in a European exposure calculation is therefore possible.

4.10.3. CXL proposals

All draft CXLs recommended by JMPR at step 3 are appropriately supported by data. The draft CXL on asparagus at step 6 (0.01* mg/kg) is also sufficiently supported by data. Last year this CXL was not advanced at step 5/8 because Thailand would provide additional data to the JMPR supporting a higher MRL on asparagus. However, the additional data were not submitted by Thailand.

4.10.4. Consumer risk assessment

Acute intake calculations were carried out by EFSA using revision 2 of the EFSA PRIMo, the HR values for all draft CXLs at step 3 or 6 and the ARfD of 0.04 mg/kg bw (EU, JMPR). No acute intake concerns were identified for the draft CXLs under discussion.

Although not under consideration for this year's CCPR, EFSA also performed acute intake calculations for all existing CXLs of cypermethrin. Acute intake concerns were identified for apples (137% ARfD), pears (128% ARfD), peaches (139% ARfD) and scarole (114% ARfD). A reservation of the EU regarding these CXLs was already expressed at last year's CCPR. Acute intake concerns are also identified for the temporary CXL on citrus fruits (663% ARfD) which was recommended for withdrawal by the JMPR last year but maintained for 4 years pending submission of data by Thailand. It is likely that residues in citrus pulp are much lower than for the whole fruit but no data are available to confirm this situation.

Chronic intake calculations were carried out by EFSA using revision 2 of the EFSA PRIMo, the STMR values for all draft/existing CXLs and the ADI of 0.015 mg/kg bw (EU, JMPR ADI is higher). EU MRLs were not considered in this intake calculation because residues trials supporting these MRLs are not available and existing EU MRLs will anyhow be reviewed in the framework of Article 12.2 of Regulation (EU) No 396/2005. Chronic intake concerns were identified for 5 European diets (up to 151% ADI) which are mainly driven by the temporary CXL for citrus fruits already discussed for acute intake concerns. However, the chronic intake concern for Danish children (109% ADI) is mainly driven by the draft CXL for wheat. Using the available processing factor for white flour, the chronic exposure for Danish children would drop to an acceptable level but this is not considered appropriate by EFSA because exposure to wholemeal flour cannot be excluded. Processing data on wholemeal flour should be made available in order to refine the calculation.

4.11. Fenbuconazole

4.11.1. Toxicological endpoints

No comments are necessary at this stage, but it is noted that toxicological reference values established by EFSA (ADI: 0.006 mg/kg bw/day, based on the NOAEL of the 1-year study in dogs, SF 100; ARfD: 0.3 mg/kg bw, based on the maternal NOAEL in the developmenbtal toxicity study in rats) are much lower than those established by JMPR (ADI: 0.03 mg/kg bw/day, ARfD: never considered).

4.11.2. Residue definitions

The residue definitions (enforcement and risk assessment) established by EFSA are the same as those established by the JMPR. Consideration of the proposed CXL in a European exposure calculation is therefore possible.

4.11.3. CXL proposals:

Plums (including prunes): The proposed CXL for plums (0.3 mg/kg) is based on a total of 5 Northern European trials while 8 residues trials are normally required at European level.

Edible offal (mammalian): The proposed CXL for mammalian edible offal (0.1 mg/kg) is based on the results for liver. The extrapolation from liver to all edible offal is normally not accepted at EU level. Based on the same dataset, EFSA would have concluded on a MRL of 0.01* mg/kg for mammalian kidneys and 0.1 mg/kg for mammalian liver.

All other draft CXLs recommended by JMPR at step 3 are appropriately supported by data.

4.11.4. Consumer risk assessment

Both chronic and acute intake calculations were carried out by EFSA, using revision 2 of the EFSA PRIMo, the HR/STMR values for all draft/existing CXLs and the European toxicological reference values. EU MRLs could not be considered in these calculations because risk assessment values for these MRLs are not available. Based on the draft and existing CXLs, no chronic or acute intake concerns were identified by EFSA (74% ADI and 11% ARfD).

4.12. Fluopicolide

4.12.1. Toxicological endpoints

Fluopicolide parent compound:

The EFSA conclusion was delivered in June 2009. The ADI was 0.08 mg/kg bw/day based on the NOAEL from the long term toxicity study in mice (78-week) supported by the 2-year study in rat, with a SF 100. The ARfD was 0.18 mg/kg bw based on the NOAEL of 17.7 mg/kg bw/day from the 28-day study in rats, SF 100, based on impaired growth and histopathological changes in the liver and kidney at 106 mg/kg bw/day.

In 2009 JMPR set the same ADI as the EU, whereas the ARfD was 0.6 mg/kg bw based on the rat developmental study, SF 100 (the same NOAEL was also available in the EU peer review**).**

Metabolite M1 (= 2,6-dichlorobenzamide):

EU established an ADI for metabolite 2,6-dichlorobenzamide (M1) at 0.05 mg/kg bw/day based on the 2-year rat and dog studies (SF 100). The ARfD was set at 0.3 mg/kg bw based on developmental rabbit study, SF 100.

An ADI of 0.02 mg/kg bw/day was established by JMPR based on the NOAEL of 2.0 mg/kg bw/day on the basis of microscopic changes in the liver in a 2-year dietary study of toxicity and carcinogenicity in rats, supported by the NOAEL of 4.5 mg/kg bw/day from the 2-year dietary study of toxicity in dogs, and with a safety factor of 100. JMPR based the ARfD for the metabolite on the study performed with the parent compound fluopicolide (0.6 mg/kg bw). Apparently JMPR had a different database.

With regard to the a.s. fluopicolide the assessment provided for the ARfD by the EU is supported as relevant effects were present in the key study.

Comparison

Fluopicolide	**Value**	**NOAEL, Study**	**Safety factor**
ADI:			
EU	0.08 mg/kg bw/day	8 mg/kg bw/day 78-week, mice	100
JMPR	0.08 mg/kg bw/day	8 mg/kg bw/day 78-week, mice	100
ARfD			
EU	0.18 mg/kg bw	17.7 mg/kg bw/day 28-day, rats	100
JMPR	0.6 mg/kg bw	60 mg/kg bw/day Developmental toxicity, rats	100

2,6-dichlorobenzamide	**Value**	**NOAEL, Study**	**Safety factor**
ADI:			
EU	0.05 mg/kg bw/day	5 mg/kg bw/day 2-year, rats supported by 2-year, dogs	100
JMPR	0.02 mg/kg bw/day	2 mg/kg bw/day 2-year, rats supported by 2-year, dogs	100
ARfD			
EU	0.3 mg/kg bw	30 mg/kg bw/day Developmental toxicity, rats	100
JMPR	0.6 mg/kg bw	60 mg/kg bw/day Developmental toxicity, rats with fluopicolide	100

With regard to the metabolite 2,6-dichlorobenzamide which is a common metabolite of different a.s., the EU assessment was based on a database which might have been different from the one considered by JMPR.

4.12.2. Residue definitions

EU and JMPR residue definitions for monitoring and risk assessment are identical (residue definition for monitoring: parent compound only, for risk assessment: separate residue definitions for fluopicolide and 2,6-dichlorobenzamide).

4.12.3. CXL proposals

CXL proposals are higher than EU MRLs for:

- Brussels' sprouts
- Cabbages, head
- Celery
- Flowerhead brassicas
- Fruiting vegetables: cucurbits
- Leafy vegetables
- Onion bulb
- Onion welsh

Currently no EU MRLs are established for products of animal origin, whereas JMPR derived proposals for eggs, edible offal mammalians and poultry, poultry meat (all LOQ) and milk (0.02 mg/kg).

Grapes: CXL proposal acceptable.

Onions, bulb: CXL proposal is acceptable.

Welsh onions: CXL proposal is based on 3 trials only. At EU level at least 4 trials would be required.

Cabbages, head: CXL is based on 7 US trials. Although at EU level at least 8 trials would be requested, CXL proposal is acceptable.

Brussels' sprouts: CXL proposal is acceptable.

Flowerhead brassicas: CXL is based on 6 US trials on broccoli. CXL proposal acceptable. However, 1.5 mg/kg would be sufficient (instead of 2 mg/kg).

Fruiting vegetables, cucurbits: CXL proposal is based on nine trials from USA. The results were extrapolated to the whole group although trials on other crops would result in lower CXLs.

Fruiting vegetables, other than cucurbits: The proposed CXL (1 mg/kg) is based on pooled trials performed on sweet and chilli peppers which were extrapolated to the whole group although for tomatoes a lower CXL would be possible.

Leafy vegetables: The proposed CXL (30 mg/kg) is based on 7 US trials performed on spinach which were extrapolated to the whole group, although trials on lettuce (head forming and open leaf varieties) matching the critical GAP would lead to lower residues (20 mg/kg for leaf lettuce). The CXL for leafy vegetables is also applicable to leafy brassica. An extrapolation of spinach to leafy brassica, scarole or witloof is not to acceptable according to EU guidance documents.

Celery: The proposed CXL for celery is based on 7 trials. The CXL proposal is acceptable.

Cereal straw: the proposed CXL is based on rotational crop studies. The value is acceptable.

Milks: The proposed CXL is acceptable.

4.12.4. Consumer risk assessment:

Risk assessment for fluopicolide:

Chronic intake calculations were carried out by EFSA using revision 2 of the EFSA PRIMo, including the STMR values for all draft/existing CXLs and the existing EU MRLs for crops for which no CXL proposals were made. No long-term consumer health risk was identified for the CXL (STMR).

Acute consumer health risk is identified using the JMPR ARfD (0.6 mg/kg bw) in EFSA PRIMo with variability factors 5 or 7, as appropriate, for the following commodities (Note: in case an exceedance was identified using the standard variability factors, EFSA also calculated the exposure using the variability factor of 3 which is the variability factor used by JMPR in its assessments):

All intake calculations reported in the table below refer to children. The intake is compared to the ARfD of 0.6 mg/kg body weight.

Commodity	**vf 7**	**vf 5**	**vf3**
scarole	Not relevant	250%	150%
kale	190%	140%	82%
witloof	130%	100%	Not relevant
celery	Not relevant	107%	64%
Chinese cabbage	Not relevant	105%	63%

If the EU ARfD of 0.18 mg/kg is applied, an acute consumer health risk is identified for:

Commodity	**vf 7**	**vf 5**	**vf3**
scarole	Not relevant	825%	297%
kale	640%	450%	275%
celery	Not relevant	350%,	128%
Chinese cabbage	Not relevant	350%,	210%
witloof	Not relevant	330%,	135%
lettuce	Not relevant	250%	150%
spinach	210% (variability factor 1)		
head cabbage	120%	70%	
purslane	Not relevant	110%	75%

The risk assessment for 2,6-dichlorobenzamide is performed only for the crops assessed by JMPR, because EFSA does not have the detailed information for the concentration of the metabolite resulting from other GAPs. The calculated long-term exposure to 2,6-dichlorobenzamide is less than 0.7% of the ADI derived by JMPR (0,02 mg/kg bw/d).

The short-term exposure to 2,6-dichlorobenzamide for the crops under consideration is in all cases below the ARfD (JMPR or EU ARfD). The maximum acute exposure is calculated for scarole (5.5% of EU ARfD, or 2.8% for JMPR ARfD).

4.13. Haloxyfop

4.13.1. Toxicological endpoints

No comments are necessary at this stage. It is noted that the ADI and ARfD values derived by JMPR are in the same range as the EU toxicological reference values (EU ADI 0.00065 mg/kg bw/day, JMPR ADI 0.0007 mg/kg bw/day, both based on the same chronic study in mice, SF 100; EU ARfD 0.075 mg/kg bw, JMPR ARfD 0.08 mg/kg bw, both based on the developmental toxicity NOAEL in rabbits, SF 100).

4.13.2. Residue definition

The residue definitions derived by JMPR and EU are substantially the same.

4.13.3. CXL proposals

The CXL proposals are generally higher than the MRLs established at EU level, except some MRLs at LOQ level, where the EU has defined higher LOQs.

Rape seed: Some of the GAPs for oilseed rape submitted to JMPR do not explicitly specify a growth stage or a PHI. Since the final residue level in rape seed depends to a large extent on the PHI, EFSA does not agree with the JMPR approach to pool residue results from trials with long PHI (autumn use) and PHI less than 100 days. The CXL proposal should reflect the worst case GAP (i.e. the spring use, PHI less than 100 day).

4.13.4. Consumer risk assessment

According to the calculations performed with the EFSA PRIMo model, the ADI is exceeded, indicating a chronic risk. The exposure calculation for the proposed CXLs plus the existing EU MRLs resulted in an exposure of ca. 450% of the ADI. The exposure related to the CXL proposals only amounts for up to 250% of the ADI and is mainly driven by the CXL for milk (using the STMR in the exposure assessment).

EFSA is concerned by the fact that levels far below the MRL proposals are used for acute risk assessment. For milk for which a MRL of 0.3 mg/kg is recommended, the acute risk assessment has been made for the STMR level which is 10 times below the MRL proposal.

4.14. Hexythiazox

4.14.1. Toxicological endpoints

Not comments necessary at this stage.

It is noted that the EU toxicological reference values have been set at the same level as the JMPR values (ADI 0.03 mg/kg bw/day, based on the NOAEL of the 2-year study in rats, SF 100; ARfD not necessary).

4.14.2. Residue definitions

The plant residue definitions for monitoring are identical. For animal commodities, the JMPR residue definition comprises additional metabolites. The EU residue definition for risk assessment is not yet established. Hexythiazox is a non-included active substance which was resubmitted. The peer review is ongoing.

4.14.3. CXL proposals

The JMPR CXL proposals are generally lower than the existing EU MRLs except the proposals for animal commodities and dates. The data are clearly evaluated by JMPR and comments are not needed.

4.14.4. Consumer risk assessment

No long-term consumer health risk is identified for hexythiazox based on the existing EU MRLs. Since the proposed CXLs are lower than the EU MRLs, the setting of CXLs will not influence the consumer exposure at EU level.

No acute consumer risk assessment was necessary since no ARfD was established.

4.15. Indoxacarb

4.15.1. Toxicological endpoints

No comments requested at this stage, but it is noted that the ADI established at EU level (0.006 mg/kg bw/day) is slightly lower than the one established by JMPR (0.01 mg/kg bw/day) and that the EU ARfD (0.125 mg/kg bw) is slightly higher than the one set by JMPR (0.1 mg/kg bw).

4.15.2. Residue definitions

The JMPR residue definition for plant commodities is the same as the EU residue definition. For food commodities of animal origin, however, the risk assessment residue definition established by the JMPR includes a metabolite which was not considered at EU level. For ruminants, the levels are very low compared to the parent compound and inclusion of this metabolite was not considered relevant by EFSA. In poultry, it is noted that the metabolite is present in higher amounts than the parent compound. This was not considered relevant at EU level because residues in poultry were anyhow expected to be very low. In the JMPR assessment the exposure of poultry to indoxacarb residues is much higher compared with the exposure assessment performed in the peer review. Consideration of this metabolite when assessing poultry CXLs is therefore essential. The European residue definition for risk assessment in poultry will be reconsidered by EFSA in the framework of Article 12 of Regulation (EC) No 396/2005.

4.15.3. CXL proposals

Fruiting vegetables, cucurbits: The proposed CXL for cucurbits (0.5 mg/kg) is based on a combined dataset of cucumber, cantaloupe and summer squash. This extrapolation is normally not accepted at EU level. Based on the same dataset, EFSA would have concluded on a MRL of 0.1 mg/kg for cucurbits with edible peel and 0.5 mg/kg for cucurbits with edible peel.

Stone fruit: The proposed CXL for stone fruits (1 mg/kg) is based on a combined dataset of peach, plums and cherries. This extrapolation is normally not accepted at EU level. Based on the same dataset, EFSA would have concluded on a MRL of 0.2 mg/kg for plums and 1 mg/kg for peaches, apricots and cherries.

All other draft CXLs recommended by JMPR at step 3 are appropriately supported by data.

4.15.4. Consumer risk assessment:

Acute intake calculations were carried out by EFSA using revision 2 of the EFSA PRIMo, the HR values for the draft CXLs and the ARfD of 0.125 mg/kg bw. No acute intake concern is identified for the CXLs under consideration.

Although not under consideration for this year's CCPR, EFSA also performed acute intake calculations for all existing CXLs of indoxacarb. Acute intake concerns are identified for the existing CXLs on lettuce (226% ARfD if a variability factor (VF) of 5 is used, 136% ARfD if VF 3 is used) and head cabbage (142% ARfD if VF 7 is used, 85.3% ARfD if VF 5 is used). EFSA notes that these CXLs are implemented in European legislation but a review of these MRLs in the framework of Article 12 of Regulation (EC) No 396/2005 is foreseen.

Chronic intake calculations were carried out by EFSA using revision 2 of the EFSA PRIMo, the STMR values for all draft/existing CXLs and the ADI of 0.006 mg/kg bw (EU, JMPR ADI is higher). STMR values for the existing EC MRLs were also considered and no chronic intake concerns were identified (highest chronic exposure: 80% ADI).

4.16. Metaflumizone

No comments are provided since this new active substance has not yet been peer reviewed at EU level.

4.17. Methoxyfenozide

4.17.1. Toxicological endpoints

No comments necessary at this stage. It is noted that the EU ADI is identical with the JMPR ADI (0.1 mg/kg bw/day based on chronic toxicity NOAEL in rats and the NOAEL of the 1-year study in dogs).

The EU ARfD (0.2 mg/kg bw) is lower than the JMPR ARfD (0.9 mg/kg bw).

4.17.2. Residue definitions

The residue definitions for monitoring and risk assessment derived by JMPR and in the peer review process (LoEP, April 2004) are identical: Parent compound is the residue of concern for plant and animal commodities.

4.17.3. CXL proposals

All proposed CXLs are higher than the current EU MRLs, except for citrus and peanuts (higher LOQ in EU list).

Citrus: The proposed CXL was derived from a combined dataset of residue trials on oranges and mandarins. The CXL proposal is acceptable. The higher EU MRL is probably related to the MRL classes commonly used.

Cranberries: The CXL proposal which was derived in 2006 is acceptable.

Papaya: The CXL proposal is based on 3 trials only. At EU level at least 4 trials would be requested.

Common bean (pods and/or immature seeds): corresponding with beans with pods in EU classification: The CXL proposal is based on 6 trials. At EU level at least 8 trials would be required.

Beans, dry: All results of the 9 supervised field trials were below the LOQ except one (0.22 mg/kg). CXL of 0.3 would be probably sufficient, but 0.5 is also acceptable.

Blueberries, strawberries, avocado, cow pea, dry, carrots, radish, sugar beet, sweet potato, peanut: CXL proposals are acceptable.

4.17.4. Consumer risk assessment:

No long-term intake concern was identified if the higher CXLs were added to the existing EU MRLs; even without refinement the maximum intake was below 40% of the ADI.

No short term consumer health risk was identified for the proposed CXLs.

4.18. Paraquat

4.18.1. Toxicological endpoints

No comments are necessary at this stage, but it is noted that toxicological reference values established at EU level (ADI: 0.004 mg/kg bw/day, based on the 1-year study NOAEL in dogs, SF 100; ARfD: 0.005 mg/kg bw, based on the 90-day study NOAEL in dog, SF 100) are slightly lower than those established by JMPR (ADI: 0.005 mg/kg bw/day based on the 1-year study NOAEL in dogs with a SF 100, ARfD: 0.006 mg/kg bw, based on the 90-day study NOAEL in dog, SF 100).

4.18.2. Residue definitions

The residue definitions for enforcement and risk assessment purposes established by the EU are the same as those established by the JMPR. Consideration of the proposed CXL in a European exposure calculation is therefore possible.

4.18.3. CXL proposals

Rice and rice straw: The proposed CXLs on rice grain and rice straw are sufficiently supported by residues trials data and it is agreed that the proposed CXLs will not affect the CXLs already established in commodities of animal origin.

4.18.4. Consumer risk assessment

EFSA does not agree with the proposal of JMPR to assume a rice STMR of 0 for both chronic and acute intake calculations. Nevertheless, using revision 2 of the EFSA PRIMo, the draft CXL for rice grain and the European toxicological reference values for paraquat, no chronic or acute intake concerns were identified by EFSA. For the chronic intake calculation, EFSA also considered the existing EU MRL and CXLs for paraquat.

Although not under consideration by this year's CCPR, EFSA notes that the existing CXLs for pulses (157% ARfD) and potatoes (154% ARfD) might present an acute risk to European consumers.

4.19. Prochloraz

4.19.1. Toxicological endpoints

Comments are not necessary at this stage. It is noted that the ADI derived by JMPR and in the peer review are identical (0.1 mg/kg bw/day).

JMPR has set an ARfD at the level of 0.1 mg/kg bw, whereas the RMS concluded in the DAR that no ARfD is necessary. (Prochoraz is a voluntarily withdrawn substance which was resubmitted; the peer review is not yet completed.)

4.19.2. Residue definitions

JMPR and EU residue definitions for monitoring are identical (sum of prochloraz and its metabolites containing the 2,4,6-trichlorphenol moiety, expressed as prochloraz).

The risk assessment residue definition proposed by the RMS in the DAR is identical with the risk assessment residue definition derived by JMPR (same wording as monitoring residue definition).

It is noted that the RMS proposed to consider simplifying the monitoring residue definition to parent compound only.

4.19.3. CXL proposals:

Mushrooms: the proposed CXL for mushrooms (3 mg/kg) is higher than the existing EU MRL. The proposed CXL was derived from 7 trials reflecting the alternative GAP, because the proposal derived for the most critical GAP resulted in an unacceptable CXL proposal. It is noted however that the CXL for straw is 40 mg/kg and it is not clear whether the JMPR considered the possible uptake of prochloraz from wheat straw when used as a substrate for growing mushrooms.

The MRL proposal is acceptable, provided that a contamination from straw can be excluded.

4.19.4. Consumer risk assessment:

The contribution of mushrooms to the chronic exposure is low (maximum 1.7% of the ADI). The short-term exposure is calculated to be ca. 12% of the ARfD.

The other commodities, for which MRLs are established at EU level, have not been included in this calculation.

4.20. Prothioconazole

4.20.1. Toxicological endpoints

No comments necessary at this stage. It is noted that JMPR derived an ARfD of 0.8 mg/kg bw for the parent compound only for women of childbearing age, whereas at EU level a lower ARfD (0.2 mg/kg bw) has been set which is applicable for the general population. The ADI values are identical (0.05 mg/kg bw/day, based on the NOAEL of 5 mg/kg bw/day, identified on the basis of gross and microscopic changes in the liver and kidneys in a 2-year study of toxicity and carcinogenicity in rats treated by gavage, and a safety factor of 100).
Regarding the toxicological reference values for the metabolite prothioconazole-desthio which is the only component in the residue definition JMPR derived two ARfDs, 0.01 mg/kg bw for women of childbearing age, and 1 mg/kg bw for the general except women of childbearing age. The EU ARfD is 0.01 mg/kg bw and is applicable to the general population.

4.20.2. Residue definitions

The EU residue definition for monitoring is identical with the JMPR residue definition.

The peer review has proposed a residue definition for risk assessment which comprises also metabolites (sum of prothioconazole-desthio and all metabolites containing the 2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl-2H-1,2,4-triazole moiety) expressed as prothioconazole-desthio. For cereal grain, oilseeds, milk, liver, muscle, kidney and fat conversion factors have been derived.

4.20.3. CXL proposals:

JMPR proposed higher CXLs compared with EU MRLs for:

- Edible offal
- Pulses
- Rape seed
- Sugar beet

The existing EU MRLs are higher for certain livestock commodities (mostly LOQ MRLs) and barley.

4.20.4. Consumer risk assessment

The risk assessment performed according to the JMPR residue definition does not indicate a chronic or acute risk associated to the JMPR proposals (refined intake calculations, using the STMR/HR values derived by JMPR). The maximum chronic exposure was calculated to account for 86% of the ADI, highest acute exposure for commodities under consideration was identified for sugar beet (31% of ARfD).

EFSA did not perform a risk assessment according to the residue definition as proposed in the peer review, because further detailed information would be required on authorised GAPs and residue trials.

4.21. Spirodiclofen

4.21.1. Toxicological endpoints

The EFSA conclusion was finalised in July 2009. The ADI of 0.015 mg/kg bw/day was based on the NOAEL of the 1-year study in dog, SF 100. The ARfD was considered unnecessary.

The JMPR ADI (0.01 mg/kg bw/day) was based on the same NOAEL and the same study. The ARfD was considered unnecessary by JMPR as well.

4.21.2. Residue definitions

The residue definitions for risk assessment monitoring for plants established by JMPR and EU are identical (parent compound only).

The EU residue definition for animal commodities (risk assessment and monitoring) comprises also the M01 metabolite (spirodiclofen-enol). JMPR included this metabolite only in the risk assessment residue definition, but not for the monitoring residue definition.

4.21.3. CXL proposals:

The proposed CXLs are higher than the existing EU MRLs for the following commodities:

- currants
- hops
- stone fruits

- tomatoes

The proposed CXLs are lower than the existing EU MRLs for:

- citrus fruits
- cucumber
- gherkins
- LOQ for coffee beans and fat

Pome fruit: The residue trials from apples and pears were used to extrapolate to the whole group. The proposed CXL is acceptable.

Stone fruit: The CXL proposal is based on a combined dataset of residue trials on cherries and peaches for which the same GAP is authorised. For plums the same GAP resulted in lower residues, therefore the data were not used to derive a group tolerance. It is noted that at EU level an extrapolation from peaches and cherries to the whole group would not be acceptable.

Grapes: It is noted that the EU MRL for table grapes is higher.

Other crops (citrus, currents, strawberries, papaya, cucumbers, gherkins, peppers, tomatoes, tree nuts, coffee: No comment

4.21.4. Consumer risk assessment:

The chronic risk assessment performed with the EU MRLs including the proposed higher CXLs (STMR values) did not raise a consumer health risk (max. 75% of the ADI, if the lower ADI established by JMPR is applied).

No acute risk assessment necessary since no ARfD has been established.

4.22. Zoxamide

4.22.1. Toxicological endpoints

No comments necessary at this stage, but it is noted that toxicological reference values established at EU level are the same as those established by JMPR (ADI: 0.5 mg/kg bw/day, ARfD: not required).

4.22.2. Residue definitions

The residue definitions for enforcement and risk assessment purposes established by the EU are the same as those established by the JMPR. Consideration of the proposed CXL in a European exposure calculation is therefore possible.

4.22.3. CXL proposals

Fruiting vegetables, cucurbits: The proposed CXL for cucurbits (2 mg/kg) is based on a combined dataset of cucumber, cantaloupe and summer squash. This extrapolation is normally not accepted at EU level. Based on the same dataset, EFSA would have concluded on an MRL of 0.5 mg/kg for cucurbits with edible peel and 2 mg/kg for cucurbits with edible peel.

4.22.4. Consumer risk assessment

Chronic intake calculations were carried out by EFSA, using revision 2 of the EFSA PRIMo and the STMR for all draft existing CXLs. EC MRLs for zoxamide were also considered in the chronic intake calculations, using the STMR where available). No chronic intake concerns are identified by EFSA (highest chronic exposure represented 0.8% ADI).

Acute intake calculations were not carried out because an ARfD for zoxamide is not considered necessary.

CONCLUSIONS AND RECOMMENDATIONS

Following the 2009 CCPR, the European Community submitted concern forms to JMPR for several active substances where the toxicological reference values established by JMPR are different from those established at European level. These concern forms have now been addressed by the 2009 JMPR and the European Commission is requesting advice to EFSA on the acceptability of these JMPR considerations, in particular with regard to carbofuran, procymidone, lambda-cyhalothrin and flusilazole.

In order to address the request of the European Commission, EFSA reviewed all available data related to the establishment of toxicological reference values both at European level and JMPR level. For each of the four compounds, a comparison between the different approaches was carried out and the following conclusions were reached:

- The toxicological reference values established by EFSA and by JMPR for carbofuran are based on the same toxicological study but different reference values were derived because a decrease of 20% brain AChE activity was considered biologically relevant at European level while it was not considered relevant by JMPR. Moreover, JMPR used a safety factor of 25 while there is no common understanding at European level on how to apply reduced safety factors. EFSA therefore recommends maintaining the European position as expressed in the initial concern form.

- The European toxicological reference values for procymidone are derived from a French proposal that was not peer reviewed at European level. EFSA therefore recommends consulting the Rapporteur Member State to derive background information relevant for the EU common position in CCPR.

- The different toxicological reference values established for lambda-cyhalothrin are mainly attributed to the use of reduced safety factors by JMPR while there is no common understanding at European level on how to apply reduced safety factors. EFSA therefore recommends maintaining the European position as expressed in the initial concern form.

- For deriving the ARfD of fluzilazole, EFSA and JMPR relied on the same developmental toxicity study. The main difference lies in the fact that the dose dependent vaginal discharge and the increase of mean placental weights were considered to represent developmental effects at European level while it was considered by JMPR to be the consequence of maternal toxicity only. EFSA therefore recommends maintaining the European position as expressed in the initial concern form.

In addition to the four above mentioned substances, EFSA was also requested to provide comments on the toxicological reference values and the draft CXLs that will be under discussion at the 2010 CCPR.

In the JMPR report 2009 the evaluations for the following 22 active substances were reported: Benalaxyl, bifenthrin, boscalid, buprofezin, cadusafos, carbofuran, chlorothalonil (and its metabolite SDS-3701), chlorpyrifos-methyl, cycloxydim, cypermethrin, fenbuconazole, fluopicolide (including its metabolite 2,6-dichlorobenzamide), haloxyfop, hexythiazox, indoxacarb, metaflumizone, methoxyfenozide, paraquat, prochloraz, prothioconazole (including the metabolite prothioconazole-desthio) spirodiclofen and zoxamide. Six of the active substances were assessed only with regard to the toxicological properties, and the derivation of toxicological reference values.

EFSA provided the requested background information, comparing the assessments performed at EU level in the framework of the peer review under Directive 91/414/EEC with the assessments performed by JMPR. EFSA took into account the currently valid EU guidance documents for consumer risk assessment (European Commission, 1996, 1997a, 1997b, 1997c, 1997d, 1997e, 1997f, 1997g, 2008) and the agreed EU policies and provides comments in particular if the EU practice

would lead to different conclusions regarding toxicological endpoints and MRL proposals compared with the JMPR methodology.

EFSA highlighted differences regarding the toxicological reference values derived by JMPR for bifenthrin, cadusafos, chlorothalonil, cycloxydim, fluopicolide and spirodiclofen in comparison with the values established at EU level. For metaflumizone currently no agreed European ADI and ARfD value is available since the peer review process under Directive 91/414/EEC is still ongoing.

EFSA identified potential consumer health risks related to the proposed CXLs for six substances evaluated (buprofezin (chronic exposure), carbofuran (chronic and acute exposure), chlorpyrifos-methyl (chronic exposure), cypermethrin (chronic exposure) fluopicolide (acute exposure) and haloxyfop (chronic and acute exposure).

DOCUMENTATION PROVIDED TO EFSA

1. Concern forms submitted by the European Community to JMPR (see Appendix A)

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APPENDIX

Concern forms submitted by the European Community to JMPR

CONCERNS WITH ADVANCEMENT OF AN MRL: Procymidone

Submitted by: European Community			
Date: 15 June 2008			
Pesticide/ **Pesticide Code Number**	**Commodity/** **Commodity Code Number**	**MRL** **(mg/kg)**	**Present Step**
Procymidone **136**	---	---	---
Is it a request for Clarification? **NO**			
Is it a Concern? **YES**			
Is it a Continuing Concern? **NO**			
Concern (*Specific* statement of reason for concern to the advancement of the proposed MRL). Regarding the endocrine disruptor properties of procymidone, new studies were provided and examined by Specialised Experts in the field of Reproductive Toxicity. PCM and PCM-CH2OH bind to the human androgen receptor in vitro indicating that PCM has antiandrogenic activity in humans. Since data on toxicokinetics in humans still do not exist, it was concluded that it cannot be excluded that human exposure to PCM would not lead to teratogenic effects. The previous conclusion that a Repr. Cat. 2 R61 is warranted for Procymidone was then confirmed (DG ENV – ECB - Ispra meeting of June 2007). A new safety factor was proposed in the addendum 6 to the draft monograph (August 2007), leading to the following revised ADI and ArfD: ADI =0.0028 mg/kg bw/day ArfD = 0.012 mg/kg bw/day.			
Request for Clarification *(Specific* statement of clarification requested).			
Do you wish this Concern to be Noted in the CCPR Report?			
Data/Information (Description of each separate piece of data/information which is attached or will be provided to the appropriate JMPR secretary within one month of the CCPR meeting.)			

Data provided by applicant are protected (see Annex attached)

FORM FOR EXPRESSING CONCERNS WITH ADVANCEMENT OF AN MRL/OR REQUEST FOR CLARIFICATION OF CONCERNS

Submitted by:
European Community

Date:
06.2008

Pesticide **Pesticide Code Number**	**Commodity/** **Commodity Code Number**	**MRL** **(mg/kg)**	**Present Step**
Flusilazole (165)			

Is this a Request for Clarification?
No

Is this a Concern?

Is this a Continuing Concern?

Concern *(Specific* statement of reason for concern to the advancement of the proposed MRL).

JMPR 2007 established an ARfD of 0.2 mg/kg/bw based on the oral rat developmental study and the Codex Committee on Pesticide Residues was informed at its 40th session that the EC had established a lower value for the ARfD based on the same study. This concern was also identified in CRD 14 at the CCPR meeting.

Request for Clarification *(Specific* statement of clarification requested).

Do you wish this Concern to be Noted in the CCPR Report?
This was already noted

Data/Information (Description of each separate piece of data/information which is attached or will be provided to the appropriate JMPR secretary within one month of the CCPR meeting.)

EU conclusion on the Developmental NOAEL for Flusilazole.

The basis for the EU ARfD is the rat oral developmental toxicity study submitted by the notifier and reviewed by the RMS in 2004. A number of parameters were affected in a dose and treatment-related manner from 2.0 mg/kg bw/day. The endpoints of relevance are as follows;

1. Evidence of an adverse effect of flusilazole on pregnancy was provided by the occurrence of a treatment and dose-related red vaginal discharge during late gestation from 2 mg/kg (see Table 1 below). This parameter was considered toxicologically relevant and related to pregnancy rather than maternal toxicity.
2. Mean placental weights were significantly increased from 2 mg/kg (24%, 61% and 83% greater than controls at 2, 10 and 50 mg/kg, respectively) (see Table 1 below). A similar observation (with histopathological correlate) was made in the dermal study. The extent of alteration of the placental architecture cannot be compared to that seen in the dermal study, as histopathology of the placental was not carried out in the current study.
3. There was evidence of embryotoxicity in that delayed ossification was statistically significant increased from 10 mg/kg. There was a treatment-related increase in rudimentary 7th cervical ribs from 2 mg/kg, which was statistically significant from 10 mg/kg (Table 2.). The increase seen at 2.0 mg/kg was considered related to treatment and biologically relevant as it was the beginning of a dose-related finding

Based on the above, the NOAEL/NOEL for maternal effects was found to be 2 mg/kg and the

NOAEL/NOEL for pregnancy and development was 0.5 mg/kg.

In the light of the new (Munley, 2000) oral study the previous developmental NOAEL of 2 mg/kg bw/day was adjusted to 0.5 mg/kg. A safety factor of x 100 was proposed as the 0.5 mg/kg is a clear NOEL.

The conclusion of the EU differs from that of the JMPR as the JMPR reviewers only considered the rudimentary 7th rib as relevant for development at the dose level of 2 mg/kg bw/day. Findings 1. and 2. above were considered by the JMPR to represent maternal toxicity.

Table 1. Summary of relevant reproductive parameters

Dose mg/kg bw	**0**	**0.5**	**2.0**	**10**	**50**	**0**	**50$_a$**	**50$_b$**
	Clinical observations)							
	25	*25*	*25*	*25*	*25*	*25*	*25*	*25*
Red vaginal discharge	**0**	**0**	**3***	**12***	**22***	**1**	**0**	**10***
	Reproductive outcome							
No. pregnant	25	24	24	25	24	25	25	24
No. delivered early	0	0	0	2	0	0	0	0
No. deaths	0	0	1	0	0	0	0	0
Total resorptions	0	0	0	0	0	0	0	0
No. litters	25	24	23	23	24	-	-	24
Mean corpora lutea	14.7 (1.70)	15.7 (2.08)	15.3 (2.17)	15.2 (1.85)	15.8 (2.04)	15.7 (1.95)	15.3 (1.95)	15.9 (2.13)
Mean implantations	13.7 (1.63)	14.1 (1.68)	13.8 (1.88)	14.1 (2.05)	14.4 (1.64)	14.6 (2.08)	14.0 (1.79)	14.6 (1.69)
Mean resorptions: Total Early Late	0.4(0.65) 0.4(0.65) 0.0	**0.3(0.56)** 0.3(0.56) 0.0	0.5(0.67) 0.5(0.67) 0.0	0.5(0.85) 0.3(0.78) 0.1(0.46)	1.8(3.19) 1.0(2.16) 0.8(1.43)	0.8(0.79) 0.8(0.79) 0.0	0.4(0.50) 0.4(0.49) 0.04(0.2)	1.5(1.79) 1.3(1.73) 0.3(0.69)
Dead foetuses	0.0	0.0	0.0	0.0	0.0	-	-	0.0
Live foetuses: Total Male Female	13.3(1.72) 6.9(2.24) 6.4(1.76)	13.8(1.8) 7.2(2.2) 6.6(2.3)	13.3(2.2) 7(2.65) 6.3(1.99)	13.7(2.0) 6.5(2.25) 7.2(1.9)	12.6(2.9) 6.9(2.61) 5.7(2.26)	- - -	 - -	13.1(2.0) 6.4(2.12) 6.7(1.59)
Sex ratio	0.51(0.14)	0.52(0.1)	0.52(0.1)	0.47(0.1)	0.54(0.1)	-	-	0.5(0.12)
Mean placental weight (gms)	0.54(0.1)	0.57(0.1)	0.67(0.2)*	0.87(0.2)*	0.99(0.2)*	0.3(0.04)	0.4(0.1)*	0.9(0.2)*
No. placental weight > 0.65 gms	1	4	12	20	24	0	0	23
Mean foetal wt:Total Males Females	5.71(0.29) 5.81(0.32) 5.58(0.27)	5.78(0.3) 5.93(0.3) 5.60(0.2)	5.75(0.3) 5.89(0.3) 5.69(0.5)	5.84(0.3) 6.01(0.3) 5.7(0.3)	5.63(0.6) 5.84(0.7) 5.4(0.64)	- - -	- - -	5.22(0.6)* 5.23(0.6) 5.22(0.6)

* Significant trend; $p < 0.05$

Table 2. Summary of relevant foetal malformations and variations.

Dose mg/kg bw	**0**	**0.5**	**2.0**	**10**	**50**	**0**	**50_a**	**50_b**
	Malformations							
	-	1(1)	-	-	3(2)	-	-	3(3)
	Variations							
External:	0	0	0	0	0	0	0	0
Visceral:								
Kidney- small papillae:-	25(16)	33(18)	27(16)	29(15)	36(19)*	-	-	34(19)*
-Size 1	1(1)	3(3)	-	2(1)	7(5)	-	-	8(5)
-Size 2	25(16)	21(14)	(27(16)	26(14)	36(19)	-	-	34(19)
-Size 3	24(12)	33(18)	23(13)	29(15)	28(18)	-	-	24(17)
Skeletal:								
Rudimentary cervical ribs:-	3(3)	4(4)	9(6)	27(15)*	141(22)*	-	-	124(22)*
Retarded ossification-skull:-	19(12)	32(10)	20(11)	27(12)	39(12)	-	-	73(18)*
-Sternebra:-	-	-	7(4)	15(10)*	49(16)*	-	-	82(19)*
-Vertebra:-	154(25)	138(22)	142(23)	147(23)	185(23)*	-	-	202(23)*

* Stat sig. : $p < 0.05$

FORM FOR EXPRESSING CONCERNS WITH ADVANCEMENT OF AN MRL/OR REQUEST FOR CLARIFICATION OF CONCERNS

Submitted by:
European Community

Date:
14.05.2008

Pesticide/ Pesticide Code Number	**Commodity/ Commodity Code Number**	**MRL (mg/kg)**	**Present Step**
Cyhalothrin (146) (lambda-cyhalothrin)			

Is this a Request for Clarification?
No

Is this a Concern?
Yes

Is this a Continuing Concern?

Concern *(Specific* statement of reason for concern to the advancement of the proposed MRL).

JMPR 2007 established a group ADI and a group ARfD for cyhalothrin and lambda-cyhalothrin, based on studies with lambda-cyhalothrin. The Codex Committee on Pesticide Residues was informed at its 40th session that the EC had established different (lower) ADI and ARfD for lambda-cyhalothrin. The EC consider an uncertainty factor of 100 to be relevant for setting both the ADI (0.005 mg/kg bw) and ARfD (0.0075 mg/kg bw/day) for lambda-cyhalothrin.

This concern was also identified in CRD 14 at the meeting.

Request for Clarification *(Specific* statement of clarification requested).

Do you wish this Concern to be Noted in the CCPR Report?

Data/Information (Description of each separate piece of data/information which is attached or will be provided to the appropriate JMPR secretary within one month of the CCPR meeting.)

ADI
In the EC the ADI for lambda-cyhalothrin (0.005 mg/kg bw) is based on the NOAEL (no observed adverse effect level) (0.5 mg lambda-cyhalothrin/kg bw/day) obtained from dog studies (1-year and 26 weeks). LOAEL (lowest observed adverse effect level): 3.5 mg lambda-cyhalothrin/kg bw/day (neurotoxic clinical signs). An uncertainty factor of 100 is considered to be relevant.
The ADI is usually based on long-term studies and not short-term studies, therefore the 1-year study on dogs seems to be the most relevant study. Moreover, undertaking a risk assessment for children, an extra safety factor could be necessary.

ARfD
In the EC the ARfD for lambda-cyhalothrin (0.0075 mg/kg bw/day) is based on the NOAEL (0.75 mg lambda-cyhalothrin/kg bw) obtained from a six week oral toxicity study in dog. LOAEL: 1.5 mg lambda-cyhalothrin/kg bw/day (tremor). The EC consider an uncertainty factor of 100 to be relevant also in this case. Moreover, undertaking a risk assessment for children, an extra safety factor could be necessary.

FORM FOR EXPRESSING CONCERNS WITH ADVANCEMENT OF AN MRL/OR REQUEST FOR CLARIFICATION OF CONCERNS

Submitted by: EC Member State Belgium

Date: 05/03/2009

Pesticide/ Pesticide Code Number	**Commodity/ Commodity Code Number**	**MRL (mg/kg)**	**Present Step**
Carbofuran (096)	-Cantaloupe (melons),	0.2	6
	-Cucumbers,	0.3	6
	-Potatoes,	0.2	6
	-Squash, summer (courgettes),	0.3	6
	-Sweet corn (corn-on-the-cob).	0.1	6
	-Banana	0.1	CXL
	-Edible offal (cattle, goats, horses, pigs and sheep)	0.05*	CXL
	-Maize	0.05*	CXL
	-Milks	0.05*	CXL
	-Potatoes	0.1*	CXL
	-Rice husked	0.1	CXL
	-Sugar beet	0.2	CXL
	-Sugar cane	0.1	CXL
	-Sunflower seed	0.1	CXL

Is this a Request for Clarification?

No

Is this a Concern?

Yes

Is this a Continuing Concern?

No

Concern *(Specific* statement of reason for concern to the advancement of the proposed MRL).

During the EU Resubmission for Peer Review of the a.s. Carbofuran, the applicant provided new acute neurotoxicity studies performed in 2007. The same studies were evaluated by the JMPR as well as older studies that were reevaluated and reported in 2008 ("2008 JMPR Report", point 5.5,

Carbofuran (096)).

1.Dog studies (4 and 13 wk):
- EU considers that in the 4wk dietary study the level of 5 ppm (0.22 mg/kg/day) is a LOAEL rather than a NOAEL, given the inhibition of RBC AChE increasing with duration of the study (10% day 1; 31% day 28) as well as the uncertainty concerning the experimental conditions to minimise enzyme reactivation.
- Agreement exists on the establishment of the 13 wk LOAEL=10 ppm (0.43 mg/kg bw/day).

2. Use of human study, are mainly flawed by the small sample and poor reporting, and their use as a source of information to substantiate interspecies equivalence of AChE inhibition for rat and human is not satisfying.

3. New acute neurotoxicity studies, considered as key studies for the determination of the reference doses ADI and ARfD:
In the pilot and full neurotoxicity study of Hoberman (2007a,c) , PND 11 pup brain AChE inhibition was demonstrated at the lowest dose of 0.03 mg/kg bw/d, reaching statistical significance in the full study, with inhibition of 20% (p 0.01) in the female pups and 13% in male pups. Therefore, the lowest dose should be considered a LOAEL for the *pups*.
EU proposal was based on:
a) A document of the US EPA (2007) who considered that brain AChE inhibition is a direct measure of the mechanism of toxicity and elected to use 10% inhibition in brain AChE as the response level. The 10% response level provides a point where functional or behavioural neurotoxicity is not expected.
b) Brain AChE activity demonstrates an age-related difference making children at greater risk from exposure to AChE inhibitors (Kousba, Poet and Timchalk, Toxicol. Sci., 95(1) 147-155, 2007).

EU is in line with the JMPR evaluation for what the *adult* NOAEL is concerned, i.e. 0.03 mg/kg bw/day.

Therefore, EU considers that the use of an ARfD and ADI of 0.001 mg/kg bw/d, based on the overall NOAEL of 0.03 mg/kg bw/day (and assessment factor of 25) is not sufficiently protective for neurotoxicity in children.

The JMPR chose to establish the lowest relevant NOAEL for brain AChE inhibition on an *overall* value, thus taking into account also the other two neurotoxicity studies conducted at higher doses (the Tyl study of 2005c, and the EPA-ORD study of Moser, 2007b). JMPR mentioned a BMD_{10} determination based on these 3 studies, which provided a value of 0.03 mg/kg bw/day. EU calculated the BMD_{10} and $BMDL_{10}$ values on the pooled data of the notifier's full studies (Tyl, 2005c and Hoberman, 2007c), which provided values from the same rat strain –exhibiting control brain levels in a comparable range i.e. 6.0-6.9 U/g–, using the same analytical method, and applying the Hill dose-response curve fitting function. In this case, the BMD_{10} was 0.014-0.016 mg/kg bw/day. EU is of the opinion that the use of these 2 GLP studies are more reliable for the estimation of a no-adverse effect level in a benchmark dose analysis, and considers the obtained value supportive for the extra 2 AF to extrapolate the pup LOAEL (0.03 mg/kg bw/day) to a NOAEL (0.015 mg/kg bw/day)

Finally, it should be noted that for reasons of consistency with the evaluation of other N-methyl carbamates (NMC), an assessment factor of 100 should be maintained to derive the reference doses ADI and ARfD. EU considers it insufficiently proven that a lower AF should be applied based upon the assumption that the NMC toxicity, dependent on a C_{max} rather than on an AUC effect, would exhibit lower inter or intraspecies variability. Also other regulatory bodies like the EPA maintain the position that, in the absence of robust evidence of such equivalence, e.g. on the basis of proven effects *in-vitro*, the application of lower AF is not recommended.

In conclusion, EU is of the opinion that the proposed reference dose for ADI=ARfD should be based upon the lowest relevant neurotoxic NOAEL= 0.015 100 = 0.00015 mg/kg bw/day, which is about 7 lower than the proposed value of the JMPR (0.001 mg/kg bw/day).

Using the EFSA PRIMo with the following inputs for the dietary intake risk assessment: HR values for all crops except for oranges(sweet and sour) and mandarins (EC used the recovered residue levels on citrus pulp from a carbosulfan metabolism study on citrus – submitted to the JMPR expert in

January 2009-cfr. Carbosulfan DAR, July 2004) and the EU established ADI and ARfD (0.00015 mg/kg bw/day), a chronic intake concern was identified: highest TMDI calculated: 4113 % of the ADI (UK toddler).
Acute intake concerns were identified for the following crops: melons/cantaloupe (13146%, BE child), cucumbers (11306%, NL child), potatoes (11275%, UK infant), courgettes/squash, summer (8058%, UK toddler), bananas (5573%, UK infant), cattle/goat milk and milk products (805-4140%, ES child-UK infant), sweet corn (corn-on-the-cob) (3916 %, DE child), sugar cane (322%, UK infant), bovine edible offal (242%, UK infant), maize (224%, UK infant), rice (210%, UK toddler), sunflower seed (205%, DE child) and sugar beet root (8513%, UK 4-6 year old).

Request for Clarification *(Specific* statement of clarification requested).

None.

Do you wish this Concern to be Noted in the CCPR Report?

Yes

Data/Information (Description of each separate piece of data/information which is attached or will be provided to the appropriate JMPR secretary within one month of the CCPR meeting.)

-Acute oral (gavage) dose range-finding study of cholinesterase depression from Carbofuran Technical in juvenile (Day 11) rats (Hoberman A.M., 2007)

-Acute Oral (Gavage) Time Course Study of Cholinesterase Depression from Carbofuran Technical in Adult and Juvenile (Day 11 Postpartum) Rats (Hoberman A.M., 2007)

-Cholinesterase Depression in Juvenile (Day 11) and Adult Rats Following Acute Oral (Gavage) Dose of Carbofuran Technical. (Hoberman A.M., 2007)

-Carbofuran Draft Assessment Report – Volume 3-Annex B-Toxicology and metabolism (September 2008)

ABBREVIATIONS

ADI	acceptable daily intake
AChE	acetilcholinesterase
ARfD	acute reference dose
a.s.	active substance
AUC	area under the curve of concentration-time
BMD	benchmark dose
BMDL	benchmark dose level
bw	body weight
C_{max}	maximum concentration
CAG	Cumulative Assessment Group
CAC	Codex Alimentarius Commission
CCPR	Codex Committee on Pesticide Residues
CRD	conference room document
CXL	codex maximum residue limit
d	day
EC	European Community
EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FOB	functional observation battery
HR	highest residue
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOAEL	lowest observed adverse effect level
MRL	maximum residue limit
NOAEL	no observed adverse effect level
NOEL	no observed effect level
PND	post natal day
ppm	parts per million (10^{-6})
PRIMo	Pesticide Residues Intake Model
PPR-Panel	Panel on Plant Protection Products and their Residues
RBC	red blood cell
SF	Safety factor
STMR	supervised trials median residue
TMDI	theoretical maximum daily intake

US EPA	Environmental Protection Agency of the United States
VF	variability factor
WHO	World Health Organisation