codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 11 **CX/PR 04/12**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON PESTICIDE RESIDUES
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PROPOSED PILOT PROJECT FOR THE EXAMINATION OF NATIONAL MRLs AS INTERIM CODEX MRLs FOR SAFER REPLACEMENT PESTICIDES

Prepared by the United States of America

1. BACKGROUND

1. The interim MRL concept was considered by the CCPR at its 34th Session (The Hague, The Netherlands, May 2002). It was one of several suggested methods to accelerate the MRL-setting process for new pesticides (CX/PR 02/11). The Codex Committee on Pesticide Residues (CCPR) at its 35th Session (Rotterdam, The Netherlands, April 2003) considered a paper on a pilot project proposal to test the interim MRL standard concept (CX/PR 03/14). That paper detailed the interim MRL process, the safeguards to protect the integrity of the process, and the interim standard criteria (including the requirement that interim standards only be considered for safer or reduced risk pesticides). It also identified possible candidates for interim MRL standard creation, based on the application of the defined criteria and the JMPR schedule (ALINORM 03/24, Appendix VII) and provided examples of summary data submissions for interim standard nominees for both toxicology and residue chemistry (Appendices III and IV). For ease of reference, these appendices have been reattached to the present paper as Appendices I and II.

2. The 35th Session discussed the paper (ALINORM 03/24A, par 176 – 186). Some delegations supported the pilot project and noted that there were sufficient safeguards to protect the integrity of the system and that there would be the opportunity to refine the details of the process during the pilot. Other delegations, while not opposing the project in principle, expressed major concerns:

- differences among national MRLs (for the same pesticide/crop);
- separation of risk assessment and risk management;
- status of the interim MRL with regard to the Codex Alimentarius Commission and the WTO-SPS;
- the level of independence and transparency associated with interim standard elaboration;
- additional burdens at the national level to assess Interim MRL submissions;
- uncertainty on data protection requirements;
- variability in the quality of national assessments provided in support of Interim MRLs;
- measurement of the success of the project.

3. The 35th Session resolved to initiate the project at the 36th Session, but to request work before that Session. Specifically, the existing Drafting group (Argentina, Australia, Canada, Chile, Egypt, New Zealand, Senegal, South Africa, Sudan, United States, European Community, Consumers International, and CropLife International), augmented by France, The Netherlands, and the JMPR Secretariat, was requested to revise CX/PR 03/14) based on the discussions. The United States was requested to continue as Chair of the drafting group. It was also agreed to seek the advice of the Codex Alimentarius Commission (par. 186).

4. The Joint FAO/WHO Food Standards Programme, Codex Alimentarius Commission (CAC) considered the pilot project for interim MRLs at its 26th Session in Rome, July 2003 (ALINORM 03/16/14, Annex 1; Agenda Item 13 and approved work on the pilot project on interim MRLs, "…with the understanding that the Proposed Interim (Step 8) MRLs would be submitted for the adoption by the Commission. The Commission drew the attention of the Committee to the need for scientific integrity and consistency with Principles for Risk Analysis for the Application in the Framework of the Codex Alimentarius. It also noted that national data requirements for the proposed Interim MRLs should meet criteria for the submission of data for JMPR and that procedural questions that might arise from this process should be considered carefully." (ALINORM 03/41, par. 199 – 202)

2. INTERIM MRL– REVISED PROCEDURE FOR CONSIDERATION BY CCPR

5. The criteria and attributes of the interim MRLs were defined in CX/PR 03/14. Among these was creation of the standard, designated Step 8(I), by the CCPR without the approval of the CAC (CX/PR 03/14, par. 11). As originally proposed, the CAC would be informed of the action and could move to reject specific CCPR approvals. In accordance with the opinion expressed by the 26th Session of the CAC, the approval process will be deferred to the CAC. In a process analogous to that for pesticides in the standard step process, CCPR recommendations for specific Step 8(I) MRLs will be sent to the CAC for acceptance or rejection. This modification provides an additional safeguard (CX/PR 03/14, par 24) and adds little time to the process, so long as the CAC continues its newly adopted practice of meeting annually.

3. CONCERNS OF THE 35TH CCPR (ALINORM 03/24A, PARA. 179)

3.1 Practical difficulties where significant differences exist among national MRLs

6. In the Interim MRL procedure, a national government nominates a pesticide meeting the selection criteria for consideration by the Priorties Working Group/CCPR. The manufacturer via the nominating national government submits a dossier including specific information on the proposed pesticide/commodity uses and summary toxicology and residue chemistry information. The manufacturer(s) has responsibility for deciding which uses it desires to support in the Codex system, for preparing the information in support of that nomination, and ultimately for providing the necessary complete scientific studies to the JMPR. This is exactly comparable to the existing Codex procedure. The manufacturer is cognizant of the various national registrations (uses) and associated MRLs (tolerances) and will supply data summaries and GAP (registration) information for those uses that it deems appropriate to support international standard proposals. These uses might extend to countries beyond the nominating nation, if the nominating nation is agreeable. The manufacturer is encouraged to select the GAPs for a given crop that give rise to the highest residues, in order to establish the most widely-applicable trading standard, but there is no constraint to do so.

7. The interim MRL will be based upon summaries of the supporting residue field trials conducted under an approved GAP, from the nominating country or from other countries. Ideally, these will be those that yield the highest residues globally This is the exact process used by the JMPR, i.e., the data made available with supporting GAP are evaluated. Those uses giving rise to the greatest residues are not necessarily considered (where the data or GAP are absent).

3.2 Separation of risk assessment and risk management

8. Under the established standard-setting process, JMPR performs the risk assessment and CCPR/CAC performs the risk management. Under the proposed interim MRL process, risk assessment and risk

management are being combined on a *temporary* basis within the CCPR. The CCPR will both assess the risk based on the data summaries provided by industry/national government and manage the risk by promulgating or rejecting certain interim standards. Independent oversight risk management will be exercised by the CAC. The CAC must approve or reject any temporary standards. Within the lifespan of the temporary standard, an independent risk assessment will be completed by the JMPR, followed by reevaluation of the risk management position within CCPR.

3.3 Status of the interim MRL with regard to the Codex Alimentarius Commission and the WTO-SPS

9. The 2003 Session of the CAC endorsed the interim MRL pilot project. The CAC will decide the fate of any proposed interim MRLs from the CCPR. Interim MRLs accepted at Step 8(I) by the CAC will have the same legal standing as CXLs. Under Article 3, para 2 of the WTO Agreement on the Application of the Sanitary and Phytosanitary measures, it is noted that sanitary and phytosanitary measures which conform to international standards, guidelines and recommendations shall be deemed to be necessary to protect human, animal, plant life or health, and presumed to be consistent with the relevant provisions of the GATT. In para 4, the Codex Alimentarius Commission is cited as one of the relevant international organizations. As the pilot project evolves, it will be for the CAC to make sure it remains consistent with the process of international harmonization.

3.4 The level of independence and transparency associated with interim standard elaboration

10. The interim MRLwill be generated without the independent review of the JMPR. It is based on the consideration by CCPR of summary information supplied by the manufacturer(s) via a national government. The process remains independent and transparent. Independence is maintained by relying upon the evaluation by the many CCPR member nations of the summary and recommendations made by the manufacturer(s) and nominating national government. Because the interim standard elaboration process runs parallel to the JMPR review process, the normal independent evaluation will be generated, although the interim standard may exist for a fixed period prior to that evaluation.

11. The process remains transparent and open in that the summary information will have adequate detail to allow a reasoned assessment and in that all CCPR members and observers will have the opportunity to participate in the process and offer comments.

12. Summary information will be provided via the Priorities Working Group and CCPR to all member nations. The summaries will contain sufficient detailed information to allow members to make informed recommendations. The summary information must be of the same level of detail as that found in JMPR Reports (Appraisals).

13. The process for considering new compounds as candidates for the Interim MRL Pilot Project is outlined as follows:

1. Nomination to the Working Group on Priorities by a national government (or governments) in conjunction with the manufacturer(s) for interim MRLs for a chemical already tentatively scheduled for review by the JMPR or being nominated simultaneously for consideration by the Working Group on Priorities.

2. Nominations should be accompanied by the following data:

   (i) National summary of toxicology and residues

   (ii) ADI and ARfD

   (iii) Chronic dietary intake calculations for the 5 or 9 Gems Food diets and point estimates for acute dietary intake calculations using JMPR methodology.

   (iv) Rationale for designation as a safer, reduced risk pesticide.

   (v) Commodities and respective MRLs to be considered.

3. The Working Group on Priorities considers whether the nominations should be recommended to CCPR to proceed. The nominations should proceed to Plenary if the data at paragraph 2 are provided, the ADI is not exceeded in any diet and the ARfD is not exceeded for any of the commodities considered. It would be possible for the nomination to be progressed by deleting one or more commodities where the ARfD has been exceeded. If the ADI is exceeded in any diet the nomination should not proceed.

4. CCPR agrees or disagrees that the Interim MRL nominations are to be progressed for consideration by member countries.

5. If agreed, information at paragraph 2 of this process description is circulated to all countries for comments. The comments are to be received by the Joint Secretariat and Chair Working Group on Priorities by 30 November of the same year.

6. Comments on Interim MRL nominations are to be collated into a circular letter to be circulated before the CCPR in the following year for discussion at the Working Group on Priorities/CCPR

14. For example:

- At CCPR 36 in 2004, bifenazate, trifloxystrobin, and fludioxinil are nominated and presumably agreed for consideration by CCPR.
- The data summaries accompanying bifenazate, trifloxystrobin, and fludioxinil are distributed to all member countries for comments to the Chair of the Working Group on Priorities and Joint Secretariat. Comments to the Chair of the Working Group on Priorities and Joint Secretariat are due by Nov. 30.
- A paper is prepared collating comments and is circulated in January 2005 for consideration by Working Group on Priorities and at CCPR 37 in 2005.
- If agreed by CCPR 37 in 2005, Interim MRLs are forwarded to CAC for ratification and implementation in 2005.
- The second cycle begins with the 2005 Working Group on Priorities considering further nominations for comment by countries in 2005 and CCPR agreement in 2006.

9. Additional burdens at the national level to assess Interim MRL submissions.

15. For the interim MRL process to function properly, national governments must allocate adequate resources to review the summary information that supports the nomination of interim MRLs. We expect this commitment and involvement to be very similar to the review of the JMPR findings (Reports), simply earlier in the process. In fact, the early review may save the governments some time in conducting their future reviews of the JMPR Reports as they will already have familiarity with the pesticide via the interim MRL nomination.

3.5 Uncertainty on data protection requirements

16. The information (toxicology and residue chemistry summaries and dietary intake assessment) submitted in support of the interim MRL will not be the actual studies conducted by the manufacturer, but rather summary data and information, per Appendices III and IV of CX/PR 03/14 (Agenda Item 11 at the 2003 CCPR) and repeated as Appendices I and II of this paper. The manufacturer must demonstrate/affirm that it has ownership or valid legal access to the underlying test reports.

17. The issue of data protection could arise when a member country considers the availability of some particular study report(s) as critical to their review of the nomination. This issue would be handled on a case-by-case basis among the nominating national government, the requesting party, and the manufacturer. We expect that the nominating government would facilitate/discuss the issue with the manufacturer. If the manufacturer makes the data reports available to the requesting government(s), the requesting national

government(s) have to ensure appropriate data protection. The supply of the full study report should not adversely effect any period of protection which would have been granted under a National Approval scheme.

3.6 Variability in the quality of national assessments provided in support of Interim MRLs

18. The national assessment from the nominating government is an ancillary document in the submission in support of the Interim MRLs. Summary information in all pertinent areas of toxicology and chemistry is supplied by the manufacturer. The CCPR members should base their recommendations on the particular interim MRL nomination on a critical review of all the available information, and not solely upon the conclusions of the national authority presenting the nomination.

3.7 Measurement of the success of the project

19. The purpose of the pilot project is to test the Interim MRL Proposal, and it is necessary to have some mechanism for measuring the degree of success of the test. While an exact quantitative measurement may not be possible, there are several possible indicators of the degree of the pilot project's success. These include:

- Ability of CCPR members to assess the nominations and conduct a scientific review that leads toward consensus-based MRL recommendations. Factors to be considered include the adequacy of the data base summaries, transparency, and validity of the dietary intake risk assessment. Members will be requested to provide feedback to the 2005 CCPR.

- Parallel proceedings and consistency of findings. Two pilot pesticides will be undergoing simultaneous review by the 2004 JMPR and the pilot project. A comparison of the ADIs, acute reference doses, and recommended MRLs can be made between the JMPR findings and the pilot project findings. The absolute values can be compared, and the extents of crops covered can be compared. A favorable comparison would be considered a validation of the interim MRL process.

- The objective of the pilot project is to develop a process that will permit accelerated international commercial exchanges of commodities containing new safer pesticides while protecting the health of consumers. The success of the Interim MRL process will be measured against its ability to shorten the time period to establish MRLs without infringing upon the scientific, transparent decision making process. This can be quantitated for the pesiticide(s) that is (are) not being considered simultaneously by the pilot project and the JMPR.

4. PILOT PROJECT FOR THE 2004 – 2005 CCPR

4.1 Proposal for the Pilot

20. Three compounds have been identified for the Pilot Project: bifenazate (2006 JMPR), trifloxystrobin (2004 JMPR), and fludioxinil (2004 JMPR). For purposes of the pilot project, the cooperating manufacturers have submitted the requisite nomination packages to the group Chair (USA) of this drafting group. The manufacturers were advised to use the formats shown in Appendices III and IV of CX/PR 03/14 and repeated as Appendices I and II of this paper. They were also supplied with the templates used by the JMPR to conduct chronic and acute dietary risk assessments. The submission deadline was March 1, 2004 to coincide with the deadline for submission to the FAO Panel of the JMPR. The packages will be forwarded to the Priorities Working Group for a review of completeness and subsequent scheduling. They will also be made available as an Annex to this paper.

21. Fludioxinil and trifloxystrobin are scheduled for review by the 2004 JMPR. Thus, a comparison of the recommendations from the Interim Pilot and the JMPR will be possible. It is *recommended* that the CCPR request the JMPR to make a summary comparison of recommendations and to comment briefly on discrepancies. CCPR members will have the same opportunity, utilizing the Report of the 2004 JMPR and the Annex of this document.

22. Bifenazate will be reviewed by the JMPR in 2006. Thus, no immediate comparison will be possible. Members are requested to consider carefully and critically the recommendations of Appendix III for bifenazate. This pesticide would be truly representative of the proposed Interim MRL process, where a comparison of the JMPR findings with the Interim MRL recommendations cannot be made for several years.

4.2 Next Steps

- Provide summary data packages for binfenazate, fludioxinil, and trifloxystrobin to the national CCPR Delegations and concerned NGOs. These will be distributed for the 2004 CCPR, as an Annex to this document.
- Place proposed interim MRLs for bifenazate, fludioxinil, and trifloxystrobin in the CCPR process at Step 3(I) at the 36th Session of the CCPR (2004), at the discretion of the Priorities Working Group and CCPR.
- Schedule the interim MRLs at Step 3(I) for consideration for advancement to Step 8(I) at the 37th Session of the CCPR (2005).
- Request the 2004 JMPR to compare its recommendations with those of the Interim Pilot Project for fludioxinil and trifloxystrobin, possibly as a General Report item in its Report.
- Ask CCPR Delegations for comments on the JMPR Report item and interim MRL proposals (e.g., by circular letter) and prepare a document on responses for the CCPR (2005).
- Consider inputs from CCPR members on the proposed specific Interim MRLs and on the process at the 37th Session of the CCPR (2005).
- Consider the comparison of JMPR recommendations and Pilot Project recommendations. Note similarities, differences, and rationale for differences.
- Refine the process, via a drafting group, based on comments at the 37thSession. This could include formalization of the process via detailed recommendations of the CCPR to the Codex Alimentarius Commission, or abandonment of the process with justification, or continuation of the Pilot (including new nominations) with/without modifications.
- If consensus is obtained (2005 CCPR) and if the project is continued, forward those interim MRLs recommended at Step 8(I) to the Codex Alimentarius Commission for final adoption at Step 8(I).
- If consensus is obtained (2004 CCPR/2005 CCPR) and if the project is continued, entertain additional Interim MRL nominations via the Working Group on Priorities at the 2005 CCPR.

APPENDICES

Appendix I and Appendix II are reproductions of Appendix III and Appendix IV, respectively, from CX/PR 03/14 discussed at the 2003 CCPR.

APPENDIX I: EXAMPLE OF TOXICOLOGY SUMMARY FOR STEP 8(I) NOMINEE PESTICIDES[1]

Summary Table of Toxicology Studies for XXXX (Technical)[1]

METABOLISM - XXXX

Absorption: With rats, radiolabeled. XXXX was rapidly and extensively absorbed in both sexes following single or repeat low-dose (0.97 mg/kg bw) administration and single high-dose (166 mg/kg bw) administration. Greater than 95% of the administered dose was absorbed following single or repeat low-dose administration and single high-dose administration. Data suggests that there was very little or no biliary absorption.

Distribution: The highest residues levels were observed in the fat, lungs, kidneys and liver, however, mean recovery of radioactivity in tissues/carcass at sacrifice (at 168 hours post-dosing) was less than 0.3% of administered dose for all dose groups indicating little potential for accumulation.

Metabolism: The major component in urine and faecal extracts was identified as XXXY, the free acid derivative of XXXX resulting from hydrolysis of the ester bond of the parent compound accounting for approximately 82.0-91.6% of the administered dose. The only other metabolite found (found in faecal extract only) was identified as the parent compound, XXXX, accounting for less than 0.1% of the administered dose.

Excretion: Excretion was rapid, with the majority of radioactivity being eliminated within 12 hours post-dosing via urine (greater than 85% of the administered dose at the low and high dose) and within 24 hours post-dosing via faeces (0.56-1.43 and 0.80-2.01% at the low and high dose, respectively). The major route of excretion was via urine, accounting for approximately 95% of administered dose at both dose levels. Faecal excretion accounted for approximately 1.0-2.4% of administered dose at both dose levels. By 72 hours less than 0.01% of the administered dose was recovered in expired air. Data suggests that there was very little or no biliary excretion

There were no significant qualitative differences in absorption, distribution, metabolism or excretion of XXXX between the sexes, between single and repeat low-dose administration or between single low-dose and high-dose administration.

STUDY	**SPECIES/STRAIN AND DOSES**	**NOAEL and LOAEL mg/kg bw/day**	**TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS**
ACUTE STUDIES - XXXX Technical			
Oral	Sprague-Dawley rats 5 animals/sex/dose **Dose Level**: 3,500 (females only), 4,000, 4,5000 (males only) or 5,050 mg/kg bw	**LD50 (95% confidence limits)**: males: 4,610 (4,450-4,790) mg/kg bw females: 4,210 (3,450-5,140) mg/kg bw sexes combined: 4,460 (4,180-4,750) mg/kg bw	No mortalities at 3500 mg/kg bw or in males at 4000 mg/kg bw; 3 females at 4000 mg/kg bw died by d 2; at 4500 mg/kg bw 1 male died by d 2; at 5050 mg/kg bw/d 5 males and 4 females died by d 2. No treatment-related clinical observations, necropsy findings or changes in bw. **LOW TOXICITY**

Dermal	SPF hybrid albino rats 5 rats/sex/dose **Dose Level**: 4,000 mg/kg bw	LD50 greater than 4,000 mg/kg bw for both sexes	No mortalities and no treatment-related necropsy findings or changes in bw. Clinical signs included dyspnea, ruffled fur, abnormal body position and reduced spontaneous activity, completely resolved by d 10. **LOW TOXICITY**
Inhalation - Limit Test (4-hour nose-only)	Tif: RAI f (SPF) albino rats 5 rats/sex **Dose Level**: Analytical Conc.- 5.3 mg/L air Nominal Conc. - 9.84 mg/L air (MMAD - 2.1 M; GSD - 2.7)	LC50 greater than 5.3 mg/L air	No mortalities and no treatment-related necropsy findings or changes in bw. Clinical signs included slight dyspnea and ruffled fur, completely resolved by d 7. **LOW TOXICITY**
Eye Irritation	New Zealand White rabbits 6 males and 3 females **Dose Level**: 0.1 mL undiluted test substance.	MIS: 5.33/110 at 1 hr for unwashed and washed eyes. MAS (for 24, 48 & 72 hrs): 0.67/110 for unwashed eyes and 0.89/110 for washed eyes.	Minimal (grade 1) conjunctival redness, chemosis and discharge in all animals (unwashed and washed) at 1 hour completely resolved by 72 hours. **MINIMALLY IRRITATING**
Skin Irritation	New Zealand White rabbits 3 males and 3 females **Dose Level**: 0.5 mL undiluted test substance.	MIS: 1.83/8 at 1 hour MAS (for 24, 48 & 72 hrs): 1.0/8	Very slight erythema in all animals at 1 hour, completely resolved by 72 hours. Very slight edema in 5 of 6 animals at 1 hour completely resolved by 7 days. **MILDLY IRRITATING**
Skin Sensitization (Optimization method)	Pirbright White guinea pigs 10 animals/sex in treatment and naive control group **Dose Levels**: <u>Intradermal Induction</u>: 0.1 mL of 0.1% solution of test substance in physiological saline (wk 1) or 0.1 mL of 0.1% solution of test substance in 1:1 formulation of physiological saline and Bacto Adjuvant (wk 2-3). <u>Intracutaneous Challenge</u>: 0.1 mL of 0.1% solution of test substance in physiological saline. <u>Epicutaneous Challenge</u>: 0.1 mL of 3% solution of test substance in vaseline.	No dermal reactions observed at 24 or 48 hrs after intradermal or epidermal challenge treatment.	**NOT A DERMAL SENSITIZER**

ACUTE STUDIES – XXXX Technical			
Oral	Sprague-Dawley rats 5 animals/sex **Dose Level**: 5,050 mg/kg bw	LD50 greater than 5,050 mg/kg bw for both sexes	One female found dead on day 1; no treatment-related necropsy findings or changes in bw; clinical signs included decreased activity, piloerection and sensitivity to touch, completely resolved by d 3. **LOW TOXICITY**
Dermal	New Zealand White rabbits 5 animals/sex **Dose Level**: 2,020 mg/kg bw	LD50 greater than 2,020 mg/kg bw for both sexes	No mortalities and no treatment-related necropsy findings or changes in bw; one female exhibited soft faeces two hrs after dosing, completely resolved by d 2. **LOW TOXICITY**
Inhalation	Sprague-Dawley rats 5 animals/sex **Dose Level**: Analytical Conc.- 2.57 mg/L air (MMAD - 2.1 M; GSD - 2.3-2.4)	LD50 greater than 2.57 mg/L air for both sexes	No mortalities and no treatment-related necropsy findings or changes in bw; all animals exhibited fur coated with faeces/ urine upon removal from chamber and piloerection on d 1, completely resolved by d 2. **LOW TOXICITY**
Eye Irritation	New Zealand White rabbits 6 males and 3 females **Dose Level**: 0.5 mL undiluted test substance.	**Unwashed eyes**: MIS: 18.3/110 at 48 hrs. MAS (for 24, 48 & 72 hrs): 15.5/110 **Washed eyes**: MIS: 21.7/110 at 24 hrs. MAS (for 24, 48 & 72 hrs): 19.9/110	Mildly Irritating to eye based on MIS/MAS for washed eyes, however, due to persistence of ocular irritation up to and including d 7 in both washed and unwashed eyes (not all d 7 scores equal 0), classification is upgraded to **MODERATELY IRRITATING**
Skin Irritation	New Zealand White rabbits 3 males and 3 females **Dose Level**: 0.5 mL undiluted test substance.	MIS: 0.17/8 at 1 hr. MAS (for 24, 48 & 72 hrs): 0/8	Very slight (grade 1) erythema noted in 1 animal at 1 hour, dermal irritation completely resolved by 24 hours. **MINIMALLY IRRITATING**
Skin Sensitization (Buehler method)	Hartley albino guinea pigs 5 animals/sex in treatment and naive control group **Dose Levels**: 0.4 mL of undiluted test substance for both the induction and challenge treatments.	No dermal reactions observed at 24 or 48 hrs after challenge treatment.	**NOT A DERMAL SENSITIZER**
SHORT TERM - XXXX Technical			

90-day dietary – mouse	15 CD-1 [Crl: CD-1 (ICR)BR] mice/sex/dose **Dose Level**: 0, 10, 100, 1,000 or 10,000 ppm (equal to 0, 1.6, 15.4, 161 and 1,552 mg/kg bw/d in males and 0, 2.0, 19.8, 194 and 1,970 mg/kg bw/d in females).	**NOAEL**: 10,000 ppm (equal to 1,552 and 1,970 mg/kg bw/d in males and females, respectively) **LOAEL**: Not determined.	There were no treatment-related findings in either sex at dose levels up to an including 10,000 ppm, the HDT **Control wk 13 bw** males: 34.3 g females: 29.3 g **Control wk 13 daily food cons.**: males: 4.9 g/animal; females: 5.2 g/animal
90-day dietary - rat	15 Sprague-Dawley rats/sex/dose **Dose Level**: 0, 50, 500, 5,000 or 20,000 ppm (equal to 0, 3, 34, 346 or 1,350 mg/kg bw/d for males and 0, 4, 38, 395 and 1,551 mg/kg bw/d for females)	**NOAEL**: 500 ppm (equal to 34 and 38 mg/kg bw/d in males and females, respectively) **LOAEL**: 5,000 ppm (equal to 346 and 395 mg/kg bw/d in males and females, respectively)	5,000 ppm - increased cytoplasmic accumulation of hyaline droplets in kidney (M). 20,000 ppm - lower bw, bwg and food cons. (M/F); lower urinary pH (M/F); increased urinary SG and urine volume (M); increased incidence of tubular basophilia, cytoplasmic accumulation of hyaline droplets and tubular casts in the kidney (M). Kidney histopathological findings considered to reflect early onset of spontaneous senile nephropathy (severity considered minimal). **Control wk 13 bw**: males: 557 g females: 318 g **Control wk 13 daily food cons.**: males: 25.4 g/animal females: 18.9 g/animal
90-day dietary – dog	4 beagle dogs/sex/dose **Dose Levels**: 0, 50, 1,000, 15,000 or 30,000 ppm (equal to 0, 2.0, 34.9, 516 and 927 mg/kg bw/d in the males and 0, 1.9, 39.8, 582 and 891 mg/kg bw/d in females)	**NOAEL**: 15,000 ppm (equal to 516 and 582 mg/kg bw/d in males and females, respectively). **LOAEL**: 30,000 ppm (equal to 927 and 891 mg/kg bw/day in the males and females, respectively).	30,000 ppm: lower bwg (M/F)
12-month dietary – dog	4 beagle dogs/sex/dose **Dose Levels**: 0, 40, 1,000, 10,000 or 20,000 ppm (equal to 0, 1.6, 31.6, 366 and 727 mg/kg bw/d in males and 0, 1.4, 39.5, 357 and 784 mg/kg bw/d in females)	**NOAEL**: 1,000 ppm (equal to 31.6 and 39.5 mg/kg bw/d in males and females, respectively) **LOAEL**: 10,000 ppm (equal to 366 and 357 mg/kg bw/d in males and females, respectively)	10,000 ppm and above: mucoid or bloody faeces, increased serum cholesterol and mild focal bilateral vacuolation of the dorsal medial hippocampus and/or lateral midbrain, secondary to altered glucose metabolism (M/F). 20,000 ppm: sporadic emesis (M/F); reduced RBC counts and haematocrit (M/F); reduced haemoglobin (F): lower bwg (M).

4-week dermal – rabbit	5 New Zealand White rabbits/sex/dose **Dose Levels**: 0, 10, 100 or 1,000 mg/kg bw/d	**Systemic Toxicity** **NOAEL**: 1,000 mg/kg bw/d **LOAEL**: Not determined.	No adverse treatment-related systemic findings in either sex. **Local irritation**: marginal increased severity of acanthosis and minimal to moderate increased incidence of inflammation, hyperkeratosis and crust formation in both sexes at 100 and 1,000 mg/kg bw/d.

CHRONIC TOXICITY/ONCOGENICITY - XXXX Technical			
78-week dietary – mouse	70 CD-1 [Crl:CD-1 (ICR)Br] mice/sex/dose **Dose Levels**: 0, 7, 70, 1,000, 3,500 or 7,000 ppm (equal to 0, 0.9, 9.0, 131, 451 and 912 mg/kg bw/d in males and 0, 1.1, 10.7, 154, 539 and 1,073 mg/kg bw/d in females)	**Chronic Toxicity:** **NOAEL**: 7,000 ppm (equal to 912 and 1,073 mg/kg bw/d in males and females, respectively). **LOAEL**: Not determined.	There were no treatment-related findings in either sex at dose levels up to an including 7,000 ppm, the HDT No evidence to indicate any carcinogenic potential of XXXX at any dose level up to and including 7,000 ppm, the HDT.

2-year dietary - rat	80-90 Sprague-Dawley rats/sex/dose (10 /sex/dose interim sacrifice, 20/sex/dose chronic toxicity, 50/sex/dose terminal sacrifice; 10/sex recovery group for control and 20,000 ppm groups only) **Dose Levels**: 0, 10, 100, 3,000, 10,000 or 20,000 ppm (equal to 0, 0.4, 3.9, 116, 393 and 806 mg/kg bw/d in males and 0, 0.5, 4.9, 147, 494 and 1,054 mg/kg bw/d in females).	**Chronic Toxicity**: **NOAEL**: 3,000 ppm (equal to 116 and 147 mg/kg bw/d in males and females, respectively). **LOAEL**: 10,000 ppm (equal to 393 and 494 mg/kg bw/d in males and females, respectively).	10,000 ppm and above: decreased urinary pH (M/F) and brown pigmentation in renal tubular epithelium (F; partially reversible after recovery; not observed at 104 wks). 20,000 ppm: lower bw, bwg and food consumption (M/F); increased incidence/severity hyaline droplets in kidneys and brown pigmentation in renal tubular epithelium (M,; reversible after recovery; not observed at 104 wks); bile duct hyperplasia (M); mammary gland galactoceles (F); acanthosis glandular stomach (F); low, but statistically significant, increased incidence of squamous cell carcinoma in non-glandular stomach (M), however, not considered to be biologically or toxicologically significant and likely not relevant to humans. Under conditions of this study, there was no biologically or toxicologically significant treatment-related increased incidence of tumours in the treatment groups compared to controls up to and including 20,000 ppm (HDT); therefore, under conditions of this study, trinexapac-ethyl not considered to be oncogenic. No treatment-related difference detected in total number of animals with tumours or in the total number of benign or malignant tumours at 52 or 104 weeks. No treatment-related effect on the time-dependent occurrence of tumour bearing animals.
REPRODUCTION / DEVELOPMENTAL TOXICITY - XXXX Technical			

Multi-generation - rat (1 litter/ generation)	30 Sprague-Dawley derived rats/sex/group Dose Levels: 0, 10, 1,000, 10,000 or 20,000 ppm (equal to 0, 0.6, 60, 594 and 1,212 mg/kg bw/d in males and 0, 0.9, 76, 751 and 1,484 mg/kg bw/d in females).	**Parental** NOAEL: 1,000 ppm (M = 60 mg/kg bw/d; F = 76 mg/kg bw/d) LOAEL: 10,000 ppm (M = 594 mg/kg bw/d; F = 751 mg/kg bw/d) **Offspring**: NOAEL: 10,000 ppm (M = 594 mg/kg bw/d; F = 751 mg/kg bw/d) LOAEL: 20,000 ppm (M = 1,212 mg/kg bw/d; F = 1,484 mg/kg bw/d) **Reproductive**: NOAEL: 20,000 ppm (M = 1,212 mg/kg bw/d; F = 1,484 mg/kg bw/d) LOAEL: Not determined.	**Parental**: 10,000 ppm: lower bw and bwg (F0/F1 males and females). 20,000 ppm: lower bw, bwg and food consumption (F0/F1 males and females). **Offspring**: 20,000 ppm: lower pup body weight (F1/F2 pups) and slight decreased pup survival (F1 pups). **Reproductive**: No adverse treatment-related effects on reproductive parameters up to & including 20,000 ppm (HDT).
Developmental toxicity – rat	24 sexually mature/nulliparous female Tif: RAIf (SPF) rats/dose **Dose Levels**: 0, 20, 200 or 1,000 mg/kg bw/d	**Maternal Toxicity**: NOAEL: greater than 1,000 mg/kg bw/d LOAEL: Not determined **Developmental Toxicity:** NOAEL: 200 mg/kg bw/d LOAEL: 1,000 mg/kg bw/d	**Maternal Toxicity** No treatment-related findings at any dose level up to & including 1,000 mg/kg bw/d (HDT). **Developmental Toxicity**: increased incidence of asymmetrically shaped vertebrae at 1,000 mg/kg bw/d. **Developmental toxicity**: No evidence of any treatment-related irreversible structural changes at any dose level up to & including 1,000 mg/kg bw/d (HDT); therefore, under the conditions of the study, XXXX did not show development toxicity.
Developmental toxicity - rabbit	16-17 sexually mature/ nulliparous female New Zealand White rabbits/dose **Dose Levels**: 0, 10, 60 or 360 mg/kg bw/d	**Maternal Toxicity**: NOAEL: greater than 360 mg/kg bw/d LOAEL: Not determined **Developmental Toxicity:** NOAEL: 60 mg/kg bw/d LOAEL: 360 mg/kg bw/d	**Maternal Toxicity** No treatment-related findings at any dose level up to & including 360 mg/kg bw/d (HDT). **Developmental Toxicity**: decreased live fetuses/litter and increased post-implantation loss at 360 mg/kg bw/d. **Developmental toxicity**: No evidence of any treatment-related irreversible structural changes at any dose level up to & including 360 mg/kg bw/d (HDT); therefore, under the conditions of the study, XXXX did not show developmental toxicity.
GENOTOXICITY - XXXX Technical			
STUDY	**Species/Strain or Cell Type**	**Dose Levels**	**Significant Effects / Comments**

Salmonella / Ames Test	*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537	0, 20, 78, 313, 1,250 or 5,000 g/plate. ± S9 metabolic activation.	**NEGATIVE**
Mammalian chromosomal aberration (*in vitro*)	mouse lymphoma L5178Y cells (at the TK locus)	0, 7.54, 30.16, 120.62, or 1930.00 g/mL ± S9 metabolic activation.	**NEGATIVE**
Mammalian cytogenetics (*in vitro*)	Human lymphocytes	0, 62.5, 125, 250, 500 or 1,000 g/mL ± S9 metabolic activation.	**NEGATIVE**
Micronucleus Assay (*in vivo*)	Male and female mouse bone marrow cells (erythrocytes)	0, 1,000, 2,000 or 4,000 mg/kg bw (sacrifice at 16, 24 and 78 hours)	**NEGATIVE**
Micronucleus Assay (*in vivo*)	Male and female mouse bone marrow cells (erythrocytes)	Initial assay: 0 or 3,000 mg/kg bw (sacrifice at 16, 24 and 48 hours) Confirmatory Assay: 0, 750, 1,500 or 3,000 mg/kg bw (sacrifice at 48 hours).	Significant increased frequency of MN-PCE's in males and sexes combined at 48 hours in the initial assay, however, values were within historical control range and not observed in the confirmatory assay at 3,000 mg/kg bw at 48 hours. In this study possible weak clastogen, however, weight-of-evidence suggest XXXX, not likely clastogenic.
UDS *in vitro*	Rat primary hepatocytes	Preliminary cytotoxicity assay: 0, 5, 10, 21, 41, 82, 164, 328, 656, 1,313, 2,625 or 5,250 g/mL Initial UDS assay: 0, 0.8, 4, 20, 100, 200 or 400 g/mL Confirmatory UDS assay: 0, 4, 20, 100, 150, 200, 300, 400 or 500 g/mL.	**NEGATIVE**
Compound-Induced Mortality: There was no significant increased incidence of treatment-related mortalities in any short-term, long-term or special studies.			

On the basis of the parental and offspring NOAEL's in the rat 2-generation reproductive toxicity study (one litter/generation) there was no indication that neonates were more sensitive than adults to the toxic effects of XXXX. However, the increased severity of the findings in the offspring compared to the severity of the findings in the dams at the respective NOAEL suggests that neonates may be slightly more sensitive to the toxic effects of XXXX.

On the basis of the maternal and developmental NOAEL's in the rat and rabbit developmental toxicity studies, there appears to an increased susceptibility of the fetus to in utero exposure to XXXX in both species.

In rats, the increased sensitivity was indicated by an increased incidence of asymmetrically shaped vertebrae at 1,000 mg/kg bw/d, the highest dose tested (maternal NOAEL greater than 1,000 mg/kg bw/d; developmental NOAEL = 200 mg/kg bw/d).

In rabbits, the increased sensitivity was indicated by decreased live fetuses/litter and increased post-implantation loss at 360 mg/kg bw/d, the highest dose tested (maternal NOAEL greater than 360 mg/kg bw/d; developmental NOAEL = 60 mg/kg bw/d).

There was no evidence of any irreversible structural changes in either species; therefore, XXXX was not considered to show developmental toxicity.

Recommended Acute RfD: Based on Endpoint:
Recommended ADI: Based on Endpoint:

[1] See also the summary tables at the end of the toxicology reviews of the JMPR *Report* and the *Evaluations* (Toxicology, ICPS). These may provide a simplified alternative in some cases.

Appendix II: Example of Residue Chemistry Summary for Step 8(I) Pesticide Nominee

Table: Food residue chemistry summary

NATIONAL USE PATTERN							
Crop	Formulation	Method and timing	Rate	Number per season	Maximum rate	PHI (days)	Restrictions
Maize(Field corn)	Water dispersible granular, 55% a.i.	Post-emergence. Broadcast	x g a.i./ha	#	x g a.i./ha	x	Do not harvest silage within x days after application

ANIMAL METABOLISM In goat and hen metabolism, the pesticide is rapidly excreted primarily as unchanged parent compound. Major compound identified is parent compound in urine, feces, liver and milk. Metabolites from Position 2 label were found in liver and feces. Major metabolite from Position 1 label is compound C in liver, feces and urine. Metabolic profile in plant and animal species suggest hydroxylation and conjugation of the rings; cleavage of the sulfonylurea bridge. The residue for dietary exposure and enforcement is the parent.		
Poultry metabolism (administration rate, method, no. of consecutive days, position(s) of radiolabel)		
Matrix	Identified Compounds or Components	Percent of TRR
Muscle (TRR, mg/kg)		
Fat (TRR, mg/kg)		
Eggs (TRR, mg/kg)		
Other (specify; TRR, mg/kg)		
Ruminant metabolism (specify goat or cow, administration rate, method, no. of consecutive days, position(s) of radiolabel)		
Matrix	Identified Compounds or Components	Percent of TRR
Muscle (TRR, mg/kg)		
Fat (TRR, mg/kg)		
Milk (TRR, mg/kg)		
Other (specify; TRR, mg/kg)		

CONFINED CROP ROTATION STUDIES 0.157 kg a.i./ha (5× gap); one foliar application post-emergent to maize (45 cm height)				
Crop	Crop fraction	Planting interval (DAT)	Harvest interval (DAT)	Equivalent to Position 1 ^{14}C-chemical X TRRs (mg/kg)
Winter wheat				
Corn				
Soybeans				

Sugar beets				
Leaf lettuce				

ANALYTICAL METHODS: PLANT AND ANIMAL MATRICES
HPLC method with UV detection at x nm; ILV . Example: Maize (field corn)

Residue: Pesticide parent *(or specify as indicated by metabolism studies and tox considerations)*

Matrix	Field corn				Corn processed fractions	
	Grain	Forage	Silage	Fodder	Oil	Presscake
LOQ (mg/kg)						
Recovery: mean ± SD (%)						
Matrix	Dairy cattle and Poultry					
	Milk	Muscle	Fat	Eggs	Liver	Kidney
LOQ (mg/kg)						
Recovery: mean ± SD (%)						

FREEZER STORAGE STABILITY TESTS FOR PLANT COMMODITIES
Stability of pesticide (parent) (*or specify as appropriate*) residues in corn substrates at –15 C
Field trial samples were stored for intervals consistent with these storage stability tests.

Storage interval (months)	Fortification level (mg/kg)	Freshly fortified % residues recovered			Stored fortified % residues remaining		
		Forage	Grain	Fodder	Forage	Grain	Fodder
0 day to x months							

FREEZER STORAGE STABILITY TESTS FOR ANIMAL COMMODITIES
Stability of pesticide (parent *or specify as appropriate*) residues in meat, milk and egg substrates at –15 C
Animal feeding study commodities and field trial residue samples were stored within the time periods studied

Storage interval (months)	Freshly fortified % residues recovered				Stored fortified % residues remaining			
	Beef liver (x mg/kg)	Milk (x ppm)	Poultry breast (x mg/kg)	Eggs (x ppm)	Beef liver (x mg/kg)	Milk (x mg/kg)	Poultry breast (x mg/kg)	Eggs (x mg/kg)
0 day to XX months								

SUPERVISED RESIDUE TRIALS ON MAIZE (FIELD CORN)

Commodity	Formulation	Application	PHI (days)	Residue (mg/kg)

		No.	Single rate (kg a.i./ha)	% GAP		
Forage (AF645)						
Fodder (AS645)						
Aspirated grain fractions						
Grain (GC645)						

PROCESSING STUDIES
Residue levels of pesticide parent *(or specify as appropriate)* in maize raw agricultural commodity (RAC) and processed fractions

Matrix and fraction	Rate (g a.i./ha)	PHI (days)	Residues (mg/kg)	Processing factor
Wet milling				
Maize grain (RAC)				
Oil, crude				
Oil, refined				
Milling by-product (specify)				
Dry milling				
Meal				
Oil, crude				
Oil, refined				
Milling by-products (specify)				

CATTLE FEEDING STUDY: Residues of (Specify) in Cattle Commodities
Dosed orally: 28 days
Maximum anticipated dietary burden: --- ppm (based on feed items, and consumptions per Appendix IX of FAO Manual…)

Feeding level (ppm in feed)	Maximum pesticide parent residues (mg/kg)			
	Milk	Muscle	Fat	Other

HEN FEEDING STUDY: Residues of (Specify) in Hen Commodities
Dosed orally: 28 days
Maximum anticipated dietary burden: --- ppm (based on feed items, and consumptions per Appendix IX of FAO Manual…)

Feeding level (ppm in feed)	Eggs (mg/kg)	Muscle (mg/kg)	Fat (mg/kg)	Other (mg/kg)

PROPOSED MRLs *(examples; all categories may not apply)*			
Crop	Codex Classification	Proposed Interim Codex MRL (mg/kg)	MRL in submitting Country (mg/kg or ppm)
Maize (Field corn) grain	GC645		
Maize forage	AF645		
Maize fodder	AS645		
Maize processed commodity (specify)	CF1255 CF645 OC645 OR645		
Milk of cattle, goats and sheep	ML107		
Eggs	PE112		
Poultry meat	PM110		
Poultry, Edible offal of	PO111		
Meat of cattle, goats, hogs, horses, pigs and sheep	MM96		
Cattle, edible offal of	MO812		
Liver of cattle, goats, pigs and sheep	MO99		
Kidney of cattle, goats, pigs and sheep	MO98		