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ORED 12-20-96

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 12/20/96

SUBJECT: PP#5E4598 Time-Limited Tolerance for Inadvertent Residues of **Imidacloprid** in/on **Cucurbits.**

DP Barcode: D230568 Caswell: 497E
Chem#: 129099 PRAT Case#: 287031
Class: Insecticide 40 CFR: 180.472

TO: Hoyt Jamerson, PM Team 43
ERMUS/RSB/RD (7505W)

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INTRODUCTION

IR-4 is petitioning for an extension of the time-limited tolerance for indirect or inadvertent residues of imidacloprid and its regulable metabolites in/on cucurbit vegetables at 0.2 ppm. The existing tolerance for such residues in/on cucurbits expires 12/31/96 (40 CFR 180.472(f)). This tolerance allows growers to produce cucurbit vegetables in rotation with crops that are treated in accordance with registered uses of imidacloprid. The revised Section F of PP#5E4598 (dated 10/10/96) extends the tolerance expiration date to 12/31/97. A petition for a permanent tolerance for regulable residues of imidacloprid in/on cucurbits has been submitted to the Agency (PP#6E4766).

No new toxicology or residue chemistry data were provided with this petition. Previous FR Notices discussed the toxicology and residue chemistry data considered in establishing the time-limited tolerance (60 FR 64006, 12/13/95 and 61 FR 5711, 2/14/96). PIRAT has been asked to examine this petition with regard to criteria set forth in FQPA.

RECOMMENDATION

Aggregate chronic and acute risk estimates do not exceed HED's level of concern. Extension of this cucurbits tolerance should not pose an unacceptable dietary risk to infants and children. Therefore, HED has no objection to an extension of the time-limited tolerance (to expire on 12/31/97) for indirect or inadvertent residues of imidacloprid and its regulable metabolites in/on cucurbit vegetables at 0.2 ppm, when imidacloprid is used in accordance with registered use patterns on the following primary crops: fruiting vegetables, leafy vegetable leafy greens, and Brassica (cole) vegetables crop groups.

RISK CHARACTERIZATION

Both the chronic and acute dietary risk assessments are conservative and represent overestimates of risk because they assume tolerance level residues and 100% crop treated for all commodities having imidacloprid tolerances. Refinement of dietary exposure estimates using percent crop treated data and/or anticipated residue data would result in lower dietary exposure estimates. For chronic dietary risk estimates, the population subgroup with the largest percentage of the RfD occupied is children 1-6 years old at 32% of the RfD. For acute dietary exposure, the calculated MOE for the population subgroup of concern (females 13+ years old) is 480.

Because terrestrial field dissipation data for imidacloprid indicate a potential for leaching and slow degradation, exposure to residues potentially present in water were assumed to account for 10% of the aggregate chronic and acute risk. Based on analysis of water monitoring data for a large number of pesticides with varying toxicities, soil mobility characteristics, environmental stabilities, and physical/chemical properties, the assumption of 10% of the chronic and acute risk allocated to drinking water is considered conservative and protective of public health.

Minimal acute exposure to imidacloprid is expected to result from its termiticide and lawn uses. Calculated risks are negligible (MOEs were approximately 1000 or more) for these exposure scenarios).

PIRAT concludes that the total aggregate chronic risk for the most highly exposed population subgroup will be significantly less than the combined total of 42% of the RfD, and therefore does not exceed HED's level of concern. As for acute aggregate risk, the large dietary MOE of 480 demonstrates that the addition of acute risk from potential drinking water exposure or residential uses will not sufficiently lower the MOE to a level

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of concern to HED.

CONCLUSIONS

Hazard Assessment

1. Non-Dietary Exposure Endpoint Selection

   a) Short- and Intermediate-Term Risk. For short and intermediate-term Margin of Exposure (MOE) calculations, the Toxicology Endpoint Selection (TES) Committee (4/18/94) determined that available data do not demonstrate that imidacloprid has dermal or inhalation toxicity potential. Therefore, short term or intermediate-term dermal and inhalation risk assessments are not required. This decision was based on the fact that no effects were observed at the highest dose level tested (0.191 mg/L) in a Core-Minimum 28-day inhalation toxicity study (MRID #42273001) in rats, and that no systemic toxicity was observed at dose levels up to 1000 mg/kg/day in a 21-day dermal toxicity study (MRID #42256329) in rabbits.

   b) Chronic Risk. The TES Committee has not identified a chronic endpoint. Further, there is no chronic exposure scenario associated with this Section 18 request, therefore a chronic risk assessment is not required.

   c) Cancer Risk. Imidacloprid has been classified as a Group E (no evidence of carcinogenicity for humans) chemical by the RfD/Peer Review Committee (11/10/93).

2. Dietary Exposure Endpoint Selection

   a) Acute Risk. The TES Committee (4/18/94) recommended use of the NOEL of 24 mg/kg/day, based on decreased body weight, increased resorptions, increased abortions, and increased skeletal abnormalities at the LEL of 72 mg/kg/day, from the developmental toxicity study (MRID#: 42256339) in rabbits. This risk assessment should evaluate acute dietary risk to females 13+ years old.

   b) Chronic Risk. RfD = 0.057 mg/kg/day. The RfD was established based on a 2-year feeding/carcinogenicity study (MRIDs #42256331 and 42256332) in rats with a NOEL of 5.7 mg/kg/day and an uncertainty factor of 100. The LOEL of 16.9 mg/kg/day was based on increased thyroid lesions in males (RfD Committee, 11/10/93).

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c) Cancer Risk. Imidacloprid has been classified as a Group E (no evidence of carcinogenicity for humans) chemical by the RfD/Peer Review Committee (11/10/93).

d) Infants and Children

i) Developmental Toxicity Studies

Rat - From the developmental toxicity study (MRID #42256338) in rats, the maternal (systemic) NOEL was 30 mg/kg/day. The maternal (systemic) LOEL of 100 mg/kg/day was based on decreased weight gain. The developmental (pup) NOEL was 30 mg/kg/day. The developmental (pup) LEL of 100 mg/kg/day was based on increased wavy ribs.

Rabbit - From the developmental toxicity study (MRID #42256339) in rabbits, the maternal (systemic) NOEL was 24 mg/kg/day. The maternal (systemic) LOEL of 72 mg/kg/day was based on decreased body weight, increased abortions, and death. The developmental (pup) NOEL was 24 mg/kg/day. The developmental (pup) LOEL of 72 mg/kg/day was based on decreased body weight and increased skeletal anomalies.

ii) Reproductive Toxicity Studies

Rat - From the reproductive toxicity study (MRID #42256340) in rats, the maternal (systemic) NOEL was 55 mg/kg/day (HDT). The reproductive/developmental (pup) NOEL was 8 mg/kg/day. The reproductive/developmental (pup) LOEL of 19 mg/kg/day was based on decreased pup body weight during lactation in both generations.

Occupational Exposure

Based on the TES Committee recommendation, an occupational exposure risk assessment is not required.

Aggregate Exposure

Dietary Exposure

1. The nature of the residue in plants and animals, enforcement methodology and residue chemistry data in support of this petition were all previously evaluated by CBTS (F.Griffith, 11/3/95, PP#5E4598, D220603 and 220606, CBTS #16422 and 16423) in conjunction with establishment of the original time-limited tolerance. The residues of concern in plants and animals are combined residues of imidacloprid and its metabolites containing the 6-chloro-pyridinyl moiety, all

calculated as imidacloprid (as stated in 40 CFR 180.472). Adequate methods are available for the determination of the regulated imidacloprid residues. Bayer method 00200 for imidacloprid residues on plants and Bayer method 00191 for imidacloprid residues in animal tissues and milk have successfully completed an EPA Tolerance Method Validation. Copies of these methods have been forwarded to FDA for publication in PAM Volume II. Both of these methods are common moiety GC-MS methods.

2. CBTS previously concluded (F.Griffith, 11/3/95, PP#5E4598, D220603 and 220606, CBTS #16422 and 16423) that the petitioner has presented an adequate amount of limited geographically representative crop field trial data for imidacloprid on squash, cucumbers, and muskmelons to show that indirect/inadvertent residues of imidacloprid and its metabolites in/on cucurbit vegetables should not exceed the proposed 0.2 ppm time-limited tolerance when imidacloprid is used as directed on the fruiting vegetables, leafy vegetable leafy greens, and Brassica (cole) vegetables crop groups; and cucurbit vegetables are planted in rotation. Under such conditions, residues in cucurbits ranged from <0.05 to 0.15 ppm (see Additional Information, pages 9-10 for details). Also, 60 FR 64006, 12/13/95 and 61 FR 5711, 2/14/96 contain a discussion of residue chemistry considerations used in establishing the original time limited tolerance.

3. Acute Dietary Risk. The acute dietary exposure endpoints of concern for imidacloprid are decreased body weight, increased resorptions, increased abortions, and increased skeletal abnormalities. For the population subgroup of concern, females 13+ years old, the calculated Margin Of Exposure **(MOE) value is 480.** Corrections made to the imidacloprid dietary exposure database prior to calculating acute dietary exposure estimates are noted under "Additional Information".

4. Chronic Dietary Risk. The existing imidacloprid tolerances (published, pending, and including the current time-limited tolerance for cucurbits) result in a Theoretical Maximum Residue Contribution (TMRC) that is equivalent to the following percentages of the RfD:

U.S Population	16%
Nursing Infants	**12%**
Non-Nursing Infants (<1 year old)	**31%**
Children (1-6 years old)	**32%**
Children (7-12 years old)	**24%**
Non-Hispanic Others	17%
Western Region	17%

The subgroups listed above are: (1) the U.S. population (48 states); (2) those for infants and children; and, (3) the other subgroups for which the percentage of the RfD occupied is greater than that occupied by the subgroup U.S. population (48 states). Corrections made to the imidacloprid dietary exposure database prior to calculating chronic dietary exposure estimates are noted under "Additional Information".

5. Cancer Risk. Imidacloprid has been classified as a Group E chemical (no evidence of carcinogenicity for humans) chemical by the RfD/Peer Review Committee. Based on this finding, a quantitative dietary cancer risk assessment is not required.

6. International Harmonization. Because there are no Mexican, Canadian, or Codex Maximum Residue Levels and/or tolerances for imidacloprid on cucurbits, compatibility is not a problem at this time.

Exposure from Water

Review of terrestrial field dissipation data by the Environmental Fate and Effects Division indicates that imidacloprid is persistent and leaches into groundwater. There is no established Maximum Concentration Level (MCL) for residues of imidacloprid in drinking water. No health advisory levels for imidacloprid in drinking water have been established. The "Pesticides in Groundwater Database" (EPA 734-12-92-001, Sept 1992) has no entry for imidacloprid.

The petitioner noted that although imidacloprid product labels contain a statement that this chemical demonstrates the properties associated with chemicals detected in groundwater, they are not aware of imidacloprid being detected in any wells, ponds, lakes, streams, etc. from the use of imidacloprid in the U.S. The petitioner also noted that in 1995, imidacloprid was not detected in 17 wells on potato farms in Quebec, Canada. The petitioner stated that groundwater monitoring studies are currently underway in CA and MI.

HED does not have data to perform a quantitative drinking water risk assessment for imidacloprid at this time. Although the lack of detectable residues found in the available groundwater monitoring data suggest that water contamination due to imidacloprid use may be unlikely, it has not been determined whether these data are adequately representative of all sites at which imidacloprid would be likely to be found. Since imidacloprid data indicate the potential for leaching and slow degradation, water risks will be assumed to account for 10% of the total allowable chronic and acute risk until further data are

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provided. Based on analysis of water monitoring data for a large number of pesticides with varying toxicities, soil mobility characteristics, environmental stabilities, and physical/chemical properties, the assumption of 10% of the total acute and chronic risk allocated to drinking water is considered conservative and protective of the public health.

Non-occupational Exposure

Imidacloprid is registered for use on turfgrass, as a termiticide, and on pets for flea control.

A residential exposure and risk assessment for imidacloprid use on turfgrass was recently conducted by OREB in conjunction with the reregistration of imidacloprid (L. LaSota, 11/14/96, D223275, MRID #43923901). Dermal and inhalation exposures were measured using volunteers who performed a choreographed exercise routine on a turf plot treated with imidacloprid at the maximum registered rate. **Dermal** levels were measured using whole body dosimetry. Using the NOEL of 1000 mg/kg/day from the dermal toxicity study in rabbits (MRID #42256329), an **MOE corresponding to an upper bound risk of 7,587 was calculated for 10 year old and 6,858 for 5 year old children.** **Inhalation** levels were measured using quartz microfiber filters connected by polyvinylchloride tubing to portable air sampling pumps. Specific toxicological endpoints of concern for inhalation exposure have not been identified by the TES Committee (4/18/94). However, in the rat sub-acute inhalation study (28-day study in which rats were exposed 6 hours/day, 5 days a week for 4 weeks, MRID #42273001) the no observable effect concentration (NOEC) for imidacloprid was 5.5 mg/m^3. This **NOEC is approximately 800 times the concentration recorded in the immediate vicinity of the volunteers during the performance of their exercise routine. The OREB analysis concluded that "...risks to children are negligible from MERIT [imidacloprid]-treated turf as soon as the spray has dried."**

An exposure and risk assessment for the termiticide use of imidacloprid was also conducted by OREB (J. Tice, 3/29/94, D197419). Conservative estimates of maximum air concentrations to which humans could be exposed and continuous exposure (24 hours per day) were assumed in calculating MOEs. Adult exposure was calculated to be 1.24×10^{-5} mg/kg/day and infant exposure 3.3×10^{-5} mg/kg/day. As noted above under Hazard Assessment, specific toxicological endpoints of concern for inhalation exposure have not been identified by the TES Committee (4/18/94). For calculating MOEs, the sub-acute rat inhalation study (MRID #42273001) was used which had a NOEL of 0.191 mg/L, the highest dose tested (corresponding to 43.08 mg/kg/day). Based on the exposures and using this NOEL, **MOEs of 3.4×10^6 and 1.3×10^6 were calculated for adults and children**, respectively.

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Total Aggregate Exposure

Based on the available data and conservative assumptions used in making risk calculations for dietary (including potential drinking water exposure) and non-occupational exposures to imidacloprid, PIRAT concludes that the total aggregate chronic risk will be significantly less than 42% of the RfD and acute risks do not pose an unacceptable concern.

Cumulative Effects

The Agency has not made a determination whether imidacloprid and any other pesticide have a common mode of toxicity and require cumulative risk assessment. For the purposes of this Section 18 exemption, the Agency has considered only risks from imidacloprid. If required, cumulative risks will be assessed as part of Reregistration and tolerance reassessment, and when methodologies for determining common mode of toxicity and for performing cumulative risk assessment are finalized.

Determination of Safety for Infants and Children

The toxicological database for evaluating pre- and post-natal toxicity for imidacloprid is complete.

Concerning pre-natal effects, in the case of the developmental toxicity studies, the developmental and maternal NOELs for both rats and rabbits occur at the same dose level for each species (24 mg/kg/day for rabbits and 30 mg/kg/day for rats), which suggests that there are no special pre-natal sensitivities for unborn children in the absence of maternal toxicity. However, a detailed analysis of the developmental toxicity studies indicates that the skeletal findings (wavy ribs and other anomalies) in both the rat and rabbit fetuses are severe effects which occurred in the presence of slight toxicity (decreases of body weight) in the maternal animals. Additionally, in rabbits, there were resorptions and abortions which can be attributed to acute maternal exposure. This information has been interpreted by the Toxicology Endpoint Selection Committee (TESC) as indicating a potential acute dietary risk for pre-natally exposed infants. The acute dietary MOE for females 13+ years old is 480, using very conservative exposure assumptions. This large MOE demonstrates that the pre-natal exposure to infants is not a toxicological concern at this time.

Concerning post-natal effects, in the case of the 2-generation reproductive toxicity study in rats, the maternal NOEL is 55 mg/kg/day [HDT] and the NOEL for decreased pup body weight during lactation is 8 mg/kg/day with the LOEL at 19 mg/kg/day. Therefore, this study shows that adverse post-natal development of pups occurs at levels (19 mg/kg/day) which are lower than the

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highest levels tested for the parental animals (55 mg/kg/day), which was a NOEL. Therefore, the pups are more sensitive to the effects of imidacloprid than parental animals. The pup NOEL of 8 mg/kg/day in the reproductive toxicity study is slightly greater than the NOEL of 5.7 from the 2-year feeding study in rats which was the basis of the RfD. The TMRC value for the most highly exposed infant and children subgroup (children 1-6 years old) occupies 32% of the RfD.

PIRAT notes that both chronic and acute dietary exposure risk assessments are overestimates of risk in that they assume 100% crop treated and use tolerance level residues for all commodities. Consideration of anticipated residues and percent crop treated would likely result in an anticipated residue contribution (ARC) which would occupy a percent of the RfD that is likely to be significantly lower than the currently calculated TMRC value.

Should an additional uncertainty factor be deemed appropriate, when considered in conjunction with a refined exposure estimate, it is unlikely that the dietary risk would exceed 100 percent of the RfD and the MOE would likely be greater than the currently calculated value. Therefore, HED concludes that extension of this time-limited tolerance for cucurbits should not pose an unacceptable risk to infants and children.

Additional Information

Magnitude of the Residue - Crop Field Trials

The following summary of residue field trial data are reproduced exactly from a previous CBTS review (F.Griffith, 11/3/95, PP#5E4598, D220603 and 220606, CBTS #16422 and 16423). No new residue data were presented with this revised petition. The application rates used in these studies represent rates that are intended to be used when imidacloprid is registered for use on cucurbits as the primary crop. Therefore, the application rate is exaggerated compared to the amount of imidacloprid present in/on soil when cucurbits are grown as rotated crops.

SQUASH

The petitioner previously presented limited total imidacloprid magnitude of the residue data on squash from 4 field trials in Texas, California, Florida, and South Carolina from the 1992 crop year (see Section 18 Exemption 94TX0004). The trials received a maximum application of 0.5 lb ai/acre in-furrow at planting, as a soil drench or sidedress 14 day after planting/transplanting.

Total imidacloprid residues on squash ranged from < 0.05 ppm to 0.15 ppm averaging 0.044 ± 0.033 ppm, n = 24.

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CUCUMBER

The petitioner previously presented limited total imidacloprid magnitude of the residue data on cucumbers from 3 field trials in Texas, California, and South Carolina from the 1992 crop year. The trials received a maximum application of 0.5 lb ai/acre in-furrow at planting, as a soil drench or sidedress 14 day after planting/transplanting.

Total imidacloprid residues on squash ranged from < 0.05 ppm to 0.12 ppm averaging 0.039 ± 0.029 ppm, n = 18.

MELON

The petitioner previously presented limited total imidacloprid magnitude of the residue data on muskmelons from 4 field trials in Texas, California, Florida, and South Carolina from the 1992 crop year. The trials received a maximum application of 0.5 lb ai/acre in-furrow at planting, as a soil drench or sidedress 14 day after planting/transplanting.

Total imidacloprid residues on muskmelon ranged from < 0.05 ppm to 0.12 ppm averaging 0.043 ± 0.031 ppm, n = 24.

DRES Analysis

Corrections to the acute and chronic dietary exposure databases were made as follows prior to conducting the analysis:

- Ground Cherries at 1.0 ppm were added to the file to reflect the tolerance listed in the 40CFR.

- Fresh grapes at 1.0 ppm were added to the file to reflect the tolerance listed in the 40CFR.

- Grape juice and raisins were increased to 1.5 ppm to reflect food additive tolerances listed in the 40CFR.

- Apples were increased to 0.6 ppm to reflect the pome fruit crop group tolerance listed in the 40CFR.

- Cottonseed was changed from 9 ppm to 8 ppm to reflect the actual tolerance in the 40CFR.

- Leafy vegetable commodities at 3.5 ppm were added to reflect the leafy vegetable crop group tolerance in the 40CFR.

- Pears, crabapple and quinces at 0.6 ppm were added to reflect the pome fruit crop group tolerance listed in the 40CFR.

- Cucurbit commodities at 0.2 ppm were added to reflect the

cucurbit crop group tolerance listed in the 40CFR.

- Note: There is a tolerance for potato chips listed in the 40CFR, however, there is not an appropriate commodity definition associated with potato chips, therefore the value was not included in the run.

cc with Attachments: S.Knizner, D.Davis (PIRAT), PIRAT, DRES (B. Steinwand), D.McCall, (RCAB), CBTS (PP#5E4598)

cc w/o attachments: OREB (Chem File), Caswell #497E, TOX I
RDI:PIRAT:12/3/96