1/27/97

MEMORANDUM

SUBJECT: PP#3F4187. Thiazopyr in/on Orange and Grapefruit. Request for Revised Section F Based On Petition Method Validation Results. No MRID#'s. CBTS#17727. DP Barcode #D232753. Chemical No. 129100. No Case No. assigned.

FROM: Jerry B. Stokes, Chemist
Chemistry Branch/Tolerance Petition Team 2
Health Effects Division (7509C)

THRU: Elizabeth Haeberer, Acting Chief
Chemistry Branch/Tolerance Support
Health Effects Division (7509C)

TO: Debbie McCall, Acting Section Head
Risk Characterization Analysis Branch
Health Effects Division (7509C)

CBTS has been asked to comment electronically on a proposed final Federal Register notice to establish tolerances for thiazopyr use on the RACs orange and grapefruit. Although most changes/ corrections can be completed by this method, CBTS has additional comments that will be supplied in this memorandum.

Background

The petitioner (Rohm Haas Company) submitted a revised Section F dated May 23, 1996 for proposed tolerances for orange and grapefruit. CBTS determined this revised Section F adequate for the proposed use (See memo of 07/16/96, J. Stokes). However, the residues included in the proposed tolerance expression were based on analytical methodology using two chemophores to show the expected levels of total thiazopyr residues including metabolites. The Agency has now accepted a slightly different analytical methodology using only one common chemophore. Thus based upon the HED Metabolism Committee decision that the appropiate tolerance expression would be based on the enforcement methodology available, the Section F must be revised to reflect the approved enforcement analytical methodology. This revised Section F should request that tolerances be established for the herbicide thiazopyr (3-pyridinecarboxylic acid, 2-(difluoromethyl)-5-(4,5-dihydro-2-thiazolyl)-4-(2-methylpropyl)-6- (trifluoromethyl)-, methyl ester) and its metabolites determined as 2-(difluoromethyl)-6-(trifluoromethyl)-3,4,5-pyridinetricarboxylic acid, all expressed as parent equivalents in or on the raw agricultural commodities orange and grapefruit. This revised Section F should be submitted by the petitioner.

Likewise the proposed final Federal Register notice should reflect the above decision of the HED Metabolism Committee. Corrections/ comments have been made on the attached copy of the draft FR notice.

Attachment: Draft Federal Register Notice, with CBTS comments

cc with Attachment: J. Stokes (CBTS); PP#3F4187; J. Miller/
E. Wilson (PM 23)
cc: without Attachmemnt: Circ; RF
RDI:RLoranger:01/23/97:EHaeberer:01/24/97
7509C:CBTS:CM#2:Rm803:JStokes:js:305-7561:01/27/97

ATTACHMENT

[Federal Register: [Rules and Regulations]
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ENVIRONMENTAL PROTECTION AGENCY
40 CFR Part 180

[PP 3F4187/R____; FRL-____-_]
RIN _____

Thiazopyr; Tolerances

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This document establishes time-limited tolerances for residues of the herbicide thiazopyr (3-pyridinecarboxylic acid, 2-(difluoromethyl)-5-(4,5-dihydro-2-thiazolyl)-4-(2-methylpropyl)-6- (trifluoromethyl)-, methyl ester) and its metabolites: 3-pyridinecarboxylic acid, 5-(aminocarbonyl)-2-(difluoromethyl)-4-(2-methylpropyl)-6-trifluoromethyl-, methyl ester and 3-pyridinecarboxylic acid, 2-(difluoromethyl)-4-(2-methylpropyl)-5-(((2-sulfoethyl)amino)carbonyl)-6-trifluoromethyl, determined as 2-(difluoromethyl)-6-(trifluoromethyl)-3,4,5-pyridinetricarboxylic acid, all expressed as the parent equivalents in or on the raw agricultural commodities oranges orange and grapefruit. Rohm and Haas Company submitted a petition to EPA under the Federal Food, Drug and Cosmetic Act (FFDCA) as amended by the Food Quality Protection Act of 1996 (Pub. L. 104-170) requesting the tolerances.

EFFECTIVE DATE: This regulation becomes effective (insert date of publication in the **Federal Register**). The tolerances expire and are revoked automatically without further action by EPA four years from the date of publication of this Final Rule.

ADDRESSES: Written objections and hearing requests, identified by the document control number, [PP 3F4187/R_____], may be submitted to: Hearing Clerk (1900), Environmental Protection Agency, Rm. M3708, 401 M St., SW., Washington, DC 20460. Fees accompanying objections and hearing requests shall be labeled ``Tolerance Petition Fees'' and forwarded to: EPA Headquarters Accounting Operations Branch, OPP (Tolerance Fees), P.O. Box 360277M, Pittsburgh, PA 15251. A copy of any objections and hearing requests filed with the Hearing Clerk should be identified by the document control number and submitted to: Public Response and Program Resources Branch, Field Operations Division (7506C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. In person, bring copy of objections and hearing requests to: Rm. 1132, CM #2, 1921 Jefferson Davis Hwy., Arlington, VA 22202.

A copy of objections and hearing requests filed with the Hearing Clerk may also be submitted electronically to the OPP by sending electronic mail (e-mail) to: opp-docket@epamail.epa.gov. Copies of objections and hearing requests must be submitted as an ASCII file avoiding the use of special characters and any form of encryption. Copies of objections and hearing requests will also be accepted on disks in WordPerfect in 5.1 file format or ASCII file format. All copies of objections and hearing requests in electronic form must be identified by the docket number [PP 3F4187/R_____]. No Confidential Business Information (CBI) should be submitted through e-mail. Electronic copies of objections and hearing requests on this rule may be filed online at many Federal Depository Libraries. Additional information on electronic submissions can be found below in this document.

FOR FURTHER INFORMATION CONTACT: By mail: Joanne I. Miller, Product Manager (PM) 23, Registration Division (7505C), Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. Office location and telephone number: Rm. 237, CM #2, 1921 Jefferson Davis Hwy., Arlington, VA 22202, (703)-305-6224; e-mail: miller.joanne@epamail.epa.gov.

SUPPLEMENTARY INFORMATION: In the Federal Register of October 21, 1993 (58 FR 54354), EPA issued a notice pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), announcing the filing of a pesticide tolerance petition by Monsanto Co., Suite 1100, 700 14th St., NW., Washington, DC 20005. The petition requested that 40 CFR 180 be amended by adding a regulation for tolernces tolerances for combined residues of the herbicide 3-pyridinecarboxylic acid, 2-(difluoromethyl)-5-(4,5-dihydro-2-thiazolyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-, methyl ester and its metabolites determined as 3-pyridinecarboxylic acid, 5-(aminocarbonyl)-2-(difuoromethyl)-4-(2-methylpropyl)-6-trifluoromethyl-, methyl ester and 3-pyridinecarboxylic acid, 2-(difluoromethyl)-4-(2-methylpropyl)-5-(((2-sulfoethyl)amino) carbonyl)-6-trifluoromethyl and expressed as parent equivalents, in or on the raw agricultural commodities: Citrus, whole fruit at 0.05 ppm; cotton seed at 0.05 ppm and cotton forage at 0.2 ppm. The proposed analytical method for determining residues was gas chromatogrphy chromatography with mass spectrometry.

In the Federal Register of August 24, 1994 (59 FR 43580) EPA issued a notice of an amendment to the petition. The tolerances requested were changed to residues of thiazophyr (pyridinecarboxylic acid, 2- [difluoromethyl]-5-(4,5-dihydro-2-thiazolyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-, methyl ester) and its metabolites determined as 3-pyridinecarboxylic acid, 5-(aminocarbonyl)-2-(difluoromethyl)-4-(2-methylproppyl)-6-trifluoromethl)-, methyl ester and 3-pyridinecarboxylic acid, 2-(difluoromethyl)-4-(2-methylpropyl)-5-(((2-sulfoethyl) amino) carbonyl)-6-(trifluoromethyl) acid and expressed as parent equivalents, in or on citrus whole fruit at 0.05 ppm, cotton seed at 0.05 ppm and cotton forage at 0.2 ppm. Monsanto Co. requested the petition be amended to read: tolerances of 0.05 ppm for orange, whole fruit and 0.05 for grapefruit, whole fruit. The proposed analytical method for determing determining residues was mass spectral multiple-ion detection.

In the Federal Register of November 22, 1996 (61 FR59440-59443) EPA issued a third Notice of Filing to amend the petition to bring the petition in conformity with the Food Quality Protection Act (FQPA) of 1996. The notice contained a summary of the petition prepared by the petitioner and this summary contained conclusions

and arguments to support its conclusion that the petition complied with FQPA. In this instance the petitioner proposed to amend 40 CFR 180 by establishing a regulation for tolerances for residues of thiazopyr in or on oranges orange and grapefruit at 0.05 ppm on the whole fruit, the same as proposed in the previous EPA Notices of Filing.

There were no comments or requests for referral to an advisory committee received in response to the notices of filing.

The data submitted in the petition and other relevant material have been evaluated. The toxicology data listed below were considered in support of these tolerances.

TOXICOLOGICAL PROFILE

1. A battery of acute toxicity studies placing technical thiazopyr in Toxicity Categories III and IV.

2. A 3 month feeding study in rats at dietary intakes of 0, 0.07, 0.67, 6.60, 68, or 201 mg/kg/day in males and 0.08, 0.79, 8.0, 79 or 227 mg/kg/day in females with a NOEL of 6.60 to 8.0 mg/kg/day, respectively based on increased liver, thyroid and kidney weights, changes in clinical chemistry and hematological parameters and on gross and microscopic changes observed in the liver and thyroid at the 68 mg/kg/day dosage. At the 201 mg/kg/day dose diffuse thyroid follicular cell hyperthophy/hyperplasia was observed.

3. A 3 month feeding study in dogs at 0, 3, 6, 35 and 175 mg/kg/day in males and 0, 2, 3, 35 and 160 mg/kg/day in females with a NOEL of 3 mg/kg/day. The thyroid hyperplasia and liver liver enlargment and discoloration with hepatocellular hyperthophy, oval cell proliferation and fatty content were observed at the 2 high dose levels along with several changes of clinical chemistry including AP, GGT, ALAT; and decreased chlosterol, triglyceride and proteins.

4. A 3 week dermal study in rabbits at 0, 100, 500 and 1000 mg/kg/day with a NOEL of 100 mg/kg/day. The effects were increased mean absolute and relative kidney weights and minimal multifocal or periportal hypatocyte vacuolation.

5. A 1 year feeding study in dogs at 0, 20, 200 or 2000 ppm with a NOEL of 20 ppm. The effects were a 10% increase in prothrombin time and several changes in blood chemistry: increased SGOT, SGPT, GGT and ALK levels and decreased cholesterol, lbumin and total protein and calcium. There were increases in absolute weights, liver and body weight and liver to brain weight, heptotoxicity characterized by enlargement and/or discoloration in some high dose animals and by hepatocellular hypertrophy/hyperplasia in the 200 ppm and 2000 ppm animals. The NOEL was based on hepatocellular hypertrophy and hyperplasia.

6. A developmental toxicity study in rats at 0, 10, 100 and 250 mg/kg/day with a maternal toxicity NOEL of 100 mg/kg/day. The effect were increased liver weight, increased slivation, significantly increased and decreased body weight gain and decreased food consumption. The developmental NOEL was also 100 mg/kg/day. The effects were increased incidence of unossified sternebrae and 7th cervical rib variation.

7. A developmental toxicity study in rabbits at 0, 10, 75 and 175 mg/kg/day with a maternal toxicity NOEL of 75 mg/kg/day. The effects were reduced body weight gain and reduced food consumption. The developmental NOEL was greater that 175 mg/kg/day, the highest dose tested.

8. A two-generation reproductive in rats at 0, 0.75, 7.5 and 75.0 mg/kg/day with a parental toxicity NOEL of 7.5 mg/kg/day. The toxic effects were increased absolute and relative liver weight, hepatic discoloration, histologic evidence of hepatic hypertrophy and vacuolization in females in both generations.

9. A mouse carcinogenicity study at doses of 0, 0.17, 1.6, 16.9 66.3 or 128.4 mg/kg/day (males) and 0,0.24, 2.6, 26.8, 108.1 or 215.9 mg/kg/day (female) with a systemic NOEL of 0.1 mg/kg/day. The effects at 1.0 mg/kg/day were hepatocellular hypertropy and amyloid depsition. At 4.0 mg/kg/day the same lesions plus increased liver weights, random and periportal hepatocellular vacuolation were observed. At 8 mg/kg/day the same lesions plus distended stomach, slight increase in ALP, SGOT and SGPT, abnormal coloration and enlargement of liver, decrease in absolute and relative spleen weights, increase in absolute and relative kidney weights, increase in eosinophilia in hepatocytes, kidney

nephropathy and lymphocytic hyperplasia of the nesenteric lymph nodes were observed.

10. A two year rat carcinogenicity study at doses of 0, 0.04, 0.4, 44.2 or 136.4 mg/kg/day (Males) 0, 0.06, 0.6, 5.6, 56.3 or 177.1 mg/kg/day (female) wih a NOEL of 4.4 mg/kg/day. The effects were protruding eyes, evidence of mild anemia, increased GGT and cholesterol, increased absolute and relative liver, kidney and thyroid weights and significant increase in microscopic lesions in the liver, hypertrophy and vacuolar changes, kidney (nephropathy) and thyroid (hypertrophy and hyperplasia); decreased mean body weight and body weight gain and food consumption. At six months, significant decrease in T4 in males and a significant increase in T3 in females. A statistically significant increase in thyroid follicular cell adenomas/cystadenomas were observed in males at 44.2 and 136.4 mg/kg/day.

The EPA Health Effects Division Carcinogenicity Peer Review Committee classified thiazopyr as a Group C, possible human carcinogen and recommended that for the purpose of risk characterization a Margin of Exposure (M.O.E.) approach should be used in evaluation of the consequences of human exposure.

11. An acceptable study for inducing reverse mutation in Ames Salmonella strains of bacteria exposed with or without activation at doses up to 10,000 micrograms per plate. The study showed negative results.

12. An acceptable study for inducing micronuclei in bone marrow cells of mice treated up to a lethal dose of 800 mg/kg. The study showed negative results.

13. A mutagenic study with Chinese hamster ovary cells exposed **in vitro** with or without activation to doses up to 1000 micrograms, the hightest dose tested. The study showed negative result for inducing forward mutation at the hypxanthine guanine phosphoribosyl transferase locus (HGPRT).

14. Two metabolism studies were conducted in rats with radio labeled radiolabeled thiazopyr. One with the 14C at the 4 position of the pyridine ring and one with the 14C at the 4' and 5' positions of the thiazole ring. The absorption of an orally administered dose was about 90%. The overall radiolabel recovery

for all study groups was 88.9, plus or minus 0.65%. No significant sex-related differences were observed in the total percent recovery. However, the distribution of recovery was sex-related. There was little radiolabel detected in tissues at study termination. Preferential sites for localization of the radiolabel included liver, adipose tissue, muscle and bone. The metabolic pathway is essentially an oxidative pathway. Vulnerable sites of the molecule are the thiazoline ring, the isobutyric side chain and the pyridine rings. Thiazapyr appears to be rapidly and extensively eliminated with low amounts of residues remaining in the tissues and carcasses. The percentage of radiolabel remaining in the carcasses following feeding thizoline thiazoline labeled thiozopyr thiazopyr was beween 6.9 and 10.8%.

METHOD OF DETERMINING RISKS

1. From Human Dietary Exposure

Residues in the agricultural commodities harvested from the crop cultured with the aid of the pesticide are determined by chemical analysis. To account for the diversity of growing conditions, culture practices, soil types, climatic conditions, crop varities and methods of use of the pesticide, data from studies that represent the resulting commodities are collected and evaluated to determine an appropriate level of residue that would not be exceeded if the pesticide is used as represented in the studies. The conduct of the field trial and guidelines for determining the residues are given in EPA "OPPTS Test Guidelines, Series 860, Residue Chemistry, August, 1996. See **Federal Register** Vol. 61:44308-44311 for availability of document.

The method of chemical analysis proposed for determining the residues in the various commodities is evaluated by a method "try-out" in EPA laboratories. If the method is found to be acceptable the Agency accepts the claim that a method of analysis is available for determining residues. The method must be appropriate for enforcement purposes.

The presence of the pesticide or degradates of the pesticide in potable water may also be a source of dietary exposure that must be considered in establishing a tolerance level for a agricultural

commodity.

The RfD is assumed to be the exposure at or below which daily aggregate exposure over a lifetime will not pose an appreciable risk to human health. To assure the adequacy of the RfD, the Agency uses an uncertainty factor in deriving it. The factor is usually 100, based on the assumption that certain segments of the human population could be as much as 100 times more sensitive than the species represented by the toxicology data.

If the pesticide is determined to be a human carcinogen, the toxicological end-point must be determined as a margin of exposure based on the nature of the carcinogenic response and a knowledge of its mode of action. The Agency may use a weight of evidence in classifying the potential of the pesticide as a human carcinogen. However, Thiazopyr thiazopyr has been determined to be a a Group C carcinogen and a margin of safety has been recommended for regulating this pesticide by the Office of Pesticide Programs
Peer Review Committee.

2. From Non-Dietary Exposure

Margins of Exposures (MOE's) are determined for non-dietary exposures based on toxicological end-points and measured or estimated exposures. There are no non-dietary uses registered under the Federal Insecticide, Fungicide and Rodenticide Act, as amended; therefore, no MOE has been determined.

AGGREGATE EXPOSURES

1. From Food and Feed Uses:

The primary source for human exposure to thiazopyr will be from ingestion of both raw and processed agricultural commodities as proposed in the November 22, 1996 Notice for Filing cited above. Based on tolerances of 0.05 ppm in or on oranges orange and grapefruit the Theoretical Maximum Residue Contributions (TMRC) for the U.S. adult population and for U.S. children (1-6 years of age) were determined. In deriving the dietary exposure to thiazopyr and its metabolites, EPA assumed that 100% of the orange and grapefruit crops were cultured with the aid of this herbicide. A chronic

exposure was used to estimate the Theoretical Maximum Residue Contribution. The TMRC for the U.S. population was estimated to be 0.000118 mg/kg/day. The TMRC for children (1-6 years of age was 0.000324 mg/kg/day.

2. From Potable Water:

There is presently no EPA Lifetime Health Advisory level for thiazopyr and its degradates as drinking water contaminates. Thiazopyr has not be found in ground water. A nonoacid degrate degradate was found in ground water at concentrations of up to 7.6 parts per billion (ppb). Using a standard potable water ingestion of 2 liters per day by adults and 1 liter per day by children, the exposure from potable water to adults was determined to be 0.000217 mg/kg/day. Exposure to children was determined to be 0.00076 mg/kg/day.

3. From Non-Dietary Uses:

There are no non-dietary uses registered under the Federal Insecticide, Fungicide and Rodenticide Act, as amended.

4. Cummulative Exposure To Substances with Common Mechanism of Toxicity.

The mechanism of toxicity as evidenced by thyroid growth, thyroid folicular cell hypertrophy and hyperplasia, thyroid and pituitary hormonal changes and liver hepatocellular hyperplasia and hypertrophy, inhanced liver metabolism and excretion of T4, indicates that thyzopyr disrupts the thyroid-pituitary hormonal balance in mammals. Other pesticide chemicals have been identified to have a similar mode of toxicity on the thyroid of mammals. The EPA has not made a determinatioon determination that thiazopyr and these other pesticides would have cumulative effects.

DETERMINATION OF SAFETY FOR U.S. POPULATION AND NON-NURSING INFANTS

The U.S. Population:

Based on a NOEL of 0.8000 mg/kg bwt/day from a two-year dog feeding study that showed a liver effect of hepatocellular hypertrophy and hyperplasia, and using an uncertainty factor of

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100 to account for the interspecies extrapolation and intraspecies variability, the Agency has determined a Reference Dose (RfD) of 0.008 mg/kg bwt/day for this assessment of risk. Based on the available toxicity data and the available exposure data identified above, the proposed tolerances will utilize 1.5% of the RfD for the U.S. population. Including an estimated exposure of 7.6 ppb in potable water, the dietary exposure for the U.S. adult population, assuming the ingestion of 2 liters of water per day, increases to 0.000325 mg/kg/day and utilizes 4.06% of the RfD.

Non-Nursing Infants:

Using the RfD of 0.008 mg/kg/bwt/day as described above and the TMRC of 0.000324 mg/kg/day determined of children, the proposed tolerances utilize 4.0% of the RfD. Adding an estimated exposure of 0.000324 mg/kg/day from ingestion of potable water, the percentage of the RfD utilized increases to 9.5.

From Nonfood Uses:

There are no monfood uses of thiazopyr registered under the Federal Insecticide, Fungicide and Rodenticide Act, as amended.

DETERMINATION OF SAFETY FOR INFANTS AND CHILDREN

Risk to infants and children was determined by use of two teratology studies. One in rats that had a NOEL for developmental toxicity of 100 mg/kg/day, based on an increase in the incidence unossified sternebrae and 7th cervical rib variations. The maternal NOEL was also 100 mg/kg/day based on toxic effects of increased liver weights, salivation, decreased body weight gains and food consumption. A second study with rabbits with a maternal NOEL of 75 mg/kg/day based on effects in reducing body weight gain and food consumptin consumption. There were no development effects at 175 mg/kg/day, the highest dose tested.

FFDCA section 408 provides that EPA shall apply an additional safety factor for infants and chidren in the case of threshhold effects to account for pre-and post-natal toxicity and the

completeness of the database unless EPA determines that such additional factor is not necessary to protect the safety of infants and children. Based on current data requirements, the database relative to pre- and post-natal toxicity is complete. The NOEL of 50.0 mg/kg/bwt/day from a 2-generation rat reproduction study did not adversely effect reproduction at 75 mg/kg/bwt/day, the highest dose tested. The NOEL of the study was about 62 times greater than the NOEL used for establishing the RfD. Effect on pups in the reproduction study did not indicate a greater sensitivity for infants and children. Therefore, EPA concludes that an additional uncertainity factor is not necessary to protect the safety of infants and children and that the RfD at 0.008 mg/kg/day is appropriate for assessing aggregate risk to infants and children.

The percent of the RfD that will be utilized by the aggregate exposure to thiazopyr will range from 11.66% for children 7-12 years old, up to 12.63 for non-nursing infants. Therefore, EPA concludes that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure.

OTHER CONSIDERATIONS

Endocrine Effects:

An evaluation of the potential effects on the endocrine systems of mammals was partially determined by chronic toxicology studies described above. There were observed pathology of the endocrine organs in those studies. Three rat studies were conducted to determine the subchronic effect of thiazopyr on thyroid function.

Thiazopyr was administered through the diet at 0 and 150 mg/kg/day rats to determine the subchronic effect on hormone level and other biochemical endpoints. Animals were assayed at 7, 14, 28, 56 or 90 days. Significant decreases in body weight gain were observed at 90 days. Early in the study the treated rats showed increases in TSH (ranging from 133 to 200% of controls) and decreases in T4 (ranging from 43% to 76% of controls). In addition there increases in liver and thyroid weights and increases in thyroid follicular cell pypertrophy/hyperplasia. Reverse T3 was increased at 28 days, and T3 was either not affected or increased. There were indications of increases in hepatic UDPGT

activity and significant increases in T4 UDPGT activity. Hepatic 5'-monodeiodinase activity was either not affected or decreased. The effects observed in this study were supportive of the theory that thiazopyr may induce thyroid tumors through a disruption in the thyroid-pituitary hormonal feedback mechanisms.

A second study on the effects of thiazopyr on the biochemical mechanisms of thyroid toxicity in rats at doses of 0, 0.5, 1.5, 5, 15, 50 or 150 mg/kg/day was conducted. Dose response effects on various biochemical parameters were observed. Two groups of the rats in the study were observed for reversibility of effects observed up to 56 and 112 days. Doses at 15, 50 and 150 mg/kg/day significantly increased the liver weights. Thyroid weights were increase at doses of 50 and 150 mg/kg/day. There were no significant effect on body weight or body weight gains during the study. The T4 UDPGT levels were increased by 117 and 376% above controls at the 50 and 150 mg/kg/day dosages. Effects of 150 mg/kg/day were increases in T3, TSH and rT3 serum concentrations, and increased incidence of follicular cell hypertrophy/hyperplasia at the 150 mg/kg/day dose. A NOEL of 1.5 mg/kg/day was determined based on liver weight increases. Thyroid weight was the only parameter that did not return to those similar to the controls. At the 56 and 112 day recovery periods the thyroid weights were 120 and 123% of control values, respectively.

A third thyroid function study on the biochemical mechanisms involved with disposition of T4 in rats fed dosages of 0 and 150 mg/kg/day for 56 days. Rats feed thiazopyr had increase T4 UDPGT activity and total deiodinase activity in their livers. There was also a two-fold increase in mixed function oxidase enzyme activity.

Results of the three studies suggest that increased glucuronidation, deiodination of T4 and T3, and increased rate of clearance of T4 from the blood and excretion of the hormone and its metabolites in the bile could significantly reduce the level of circulating T4 in the male rat.

Metabolism in Plants and Animals:

The metabolism of thiazopyr in plants and animals is adequately understood for the purposes of these tolerances. There were no crop residues found after the preemergence use is the

culture of oranges orange and grapefruit. The metabolites that were identified in a radio labeled radiolabeled thiazopyr study and converted to two common entities: amide acid and sulfonic diacid. are named as residues in this final rule. The use of these common entities in the analytical method for residues of thiazopyr and its metabolites of concern has been determined to be acceptable. However, the Agency has accepted enforcement analytical methodology that uses only one common entity to determine >70% of the expected thiazopyr residues.

Analytical Method:

There is a practical analytical method for detecting and measuring levels of thiazopyr and its metabolites in or on food with a limit of detection that allows monitoring of food with residues at or above the levels set in these tolerances. The proposed analytical method for determining residues is gas-liquid chromatography with mass selective detection. Thiazopyr and its metabolites are converted to a common moiety which is quantified. The limits of the method is 0.025 ppm for citrus whole fruits and processed fractions. The quantifiable limit of this method is 0.015 ppm for whole orange fruit. EPA has provided information on this method to FDA. Because of the long lead time from establishing these tolerances to publication, the enforcement methodology is being made available in the interim to anyone interested in pesticide enforcement when requested by mail from: Calvin Furlow, Public Response Branch, Field Operations Division (7506C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. Office location and telephone umber: Rm. 1130A, CM #2, 1921 Jefferson Davis Hwy., Arlington, VA 22202, (703)-305-5937.

International Tolerances:

There are no Codex Alimentarius Commission (Codex) Maximum Residue Levels (MRLs) for thiazopyr.

Data Gaps:

These tolerances are being established as time-limited tolerances with a expiration date of four years from the data of this Final Rule. This time limitation is believed to be

appropriate because these tolerances are being issed issued under a interim policy for implementation of the Food Quality Protection Act of 1996. During this time interval there may be new data requirements in order to meet the intent of this new law for regulating residues of pesticides in raw and processed agricultural commodities for which these tolerances are being established.

SUMMARY OF FINDINGS

The analysis for thiazopyr using tolerance level residues shows that the proposed uses in the culture of oranges orange and grapefruit will not cause exposure to exceed the levels at which the Agency believes there is an appreciable risk. All population subgroups examined by EPA are exposed to thiazopyr residues at levels below 100 percent of the RfD for chronic effects.

Based on the information cited above, the Agency has determined that the establishment of the time-limited tolerances by adding a new section to 40 CFR 180 will be safe; therefore, the time-limited tolerances are established as set forth below.

OBJECTIONS AND HEARING REQUESTS

The new FFDCA section 408(g) provides essentially the same process for persons to "object" to a tolerance regulation issued by EPA under new section 408(e) and (1)(6) as was provided in the old section 408 and in section 409. However, the period for filing objections is 60 days, rather than 30 days. EPA currently has procedural regulations which governs the submission of objections and hearing requests. These regulations will require some modification to reflect the new law. However, until those modifications can be made, EPA will continue to use those procedural regulations with appropriate adjustments to reflect the new law.

Any person may, by [insert date 60 days after publication of this document in the **Federal Register**], file written objections to any aspect of this regulation (including the automatic revocation provision) and may also request a hearing on those objections. Objections and hearing requests must be filed with the

Hearing Clerk, at the address given above (40 CFR 178.20). A copy of the objections and/or hearing requests filed with the Hearing Clerk should be submitted to the OPP docket for this rulemaking. The objections submitted must specify the provisions of the regulation deemed objectionable and the grounds for the objections (40 CFR 178.25). Each objection must be accompanied by the fee prescribed by 40 CFR 180.33(i). If a hearing is requested, the objections must include a statement of the factual issue(s) on which a hearing is requested, the requestor's contentions on such issues, and a summary of any evidence relied upon by the objector (40 CFR 178.27). A request for a hearing will be granted if the Administrator determines that the material submitted shows the following: There is a genuine and substantial issue of fact; there is a reasonable possibility that available evidence identified by the requestor would, if established, resolve one or more of such issues in favor of the requestor, taking into account uncontested claims or facts to the contrary; and resolution of the factual issue(s) in the manner sought by the requestor would be adequate to justify the action requested (40 CFR 178.32). Information submitted in connection with an objection or hearing request may be claimed confidential by marking any part or all of that information as Confidential Business Information (CBI). Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. A copy of the information that does not contain CBI must be submitted for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice.

Public Docket

A record has been established for this rulemaking under docket number [OPP _____]. A public version of this record, which does not include any information claimed as CBI, is available for inspection from 8 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The public record is located in Room 1132 of the Public Response and Program Resources Branch, Field Operation Division (7506C), Office of Pesticide Programs, Environmental Protection Agency, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA.

The official record for this rulemaking, as well as the public version, as described above, is kept in paper form. Accordingly, in the event there are objections and hearing requests, EPA will

transfer any copies of objections and hearing requests received electronically into printed, paper form as they are received and will place the paper copies in the official rulemaking record. The official rulemaking record is the paper record maintained at the address in "ADDRESSES" at the beginning of this document.

Regulatory Assessment Requirements

Under Executive Order 12866 (58 FR 51735, Oct. 4, 1993), this action is not a "significant regulatory action" and since this action does not impose any information collection requirements subject to approval under the Paperwork Reduction Act, 44 U.S>C. 3501 et seq., it is not subject to review by the Office of Management and Budget. In addition, this action does not impose any enforceable duty, or contain any "unfunded mandates" as described in Title II of the Unfunded Mandates Reform Act of 1995 (**P.L.** 104-4), or require prior consultation as specified by Executive Order 12875 (58**FR**58093, October 28, 1993), or special considerations as required by Executive Order 12898 (59 **FR** 7629, February 16, 1994).

Because tolerances established on the basis of a petition under section 408(d) of FFDCA do not require issuance of a proposed rule, the regulatory flexability analysis requirements of the Regulatory Flexability Act (RFA), 5 U.S.C. 604(a), do not apply. Prior to the recent amendment of the FFDCA, EPA had treated such rulemakings as subject to the RFA; however, the amendments to the FFDCA clarify that no proposal is required for such rulemakings and hence that the RFA is inapplicable.

Pursuant to 5 U.S.C. 801(a)(1)(A), EPA submitted a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives and the Comptroller General of the General Accounting Office prior to publication of the rule in today's Federal Register. This rule is not a major rule as defined by 5 U.S.C. 804(2).

List of Subjects in 40 CFR Part 180

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: _____

_____

Stephen L. Johnson,
Director, Registration Division, Office of Pesticide Programs.

Therefore, 40 CFR part 180 is amended as follows:

PART 180--[AMENDED]

1. The authority citation for part 180 continues to read as follows:

Authority: 21 U.S.C. 346a and 371.

2. By adding a new regulation for establishing tolerances for the following commodities, which reads:

Section 180._____ Thiazopyr; tolerances for residues.

Time-limited Tolerances are established for conbined residues of the herbicide thiazopyr (3-pyridinecaroxylic acid, 2-(difluoromethyl)-5-(4,5-dihydro-2-thiazolyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-, methyl ester) and its metabolites: 3-pyridinecarboxylic acid, 5-(aminocarbonyl)-2-(difluoromethyl)-4-(2-methylpropyl)-6-trifluoromethyl-, methyl ester and 3-pyridinecarboxylic acid, 2-(difluoromethyl)-4-(2-methylpropyl)-5-(((2-sulfoethyl)amino) carbonyl)-6-trifluoromethyl, determined as 2-(difluoromethyl)-6-(trifluoromethyl)-3,4,5-pyridinetricarboxylic acid, all expressed as the parent equivalents in or on the following raw agricultural commodities:

Commodities	Parts per million	Expiration date
Grapefruit	0.05	_____2001
Oranges Orange	0.05	_____2001

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