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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA-HQ-OPP-2010-0845; FRL-8885-8]

Isoxaflutole; Pesticide Tolerances

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This regulation establishes tolerances for residues of isoxaflutole in or on Soybean, seed and Grain, aspirated fractions. Bayer CropScience requested these tolerances under the Federal Food, Drug, and Cosmetic Act (FFDCA).

DATES: This regulation is effective [*insert date of publication in the* **Federal Register**]. Objections and requests for hearings must be received on or before [*insert date 60 days after date of publication in the* **Federal Register**], and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I.C. of the

SUPPLEMENTARY INFORMATION:

ADDRESSES: EPA has established a docket for this action under docket identification (ID) number EPA-HQ-OPP-2010-0845. All documents in the docket are listed in the docket index available at *http://www.regulations.gov*. Although listed in the index, some information is not publicly available, e.g., Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available in the electronic docket

at *http://www.regulations.gov*, or, if only available in hard copy, at the OPP Regulatory Public Docket in Rm. S-4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. The Docket Facility is open from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305-5805.

FOR FURTHER INFORMATION CONTACT: Kathryn V. Montague, Registration Division (7505P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (703) 305-1243; e-mail address: *montague.kathryn@epa.gov*.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. Potentially affected entities may include, but are not limited to those engaged in the following activities:

- Crop production (NAICS code 111).
- Animal production (NAICS code 112).
- Food manufacturing (NAICS code 311).
- Pesticide manufacturing (NAICS code 32532).

This listing is not intended to be exhaustive, but rather to provide a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. The North American Industrial Classification System (NAICS) codes have been provided to assist you and others in determining

whether this action might apply to certain entities. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. How Can I Get Electronic Access to Other Related Information?

You may access a frequently updated electronicversion of EPA's tolerance regulations at 40 CFR part 180 through the Government Printing Office's e-CFR site at *http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?&c=ecfr&tpl=/ecfrbrowse/Title40/40tab_02.tpl*. To access the harmonized test guidelines referenced in this document electronically, please go to *http://www.epa.gov/ocspp* and select "Test Methods and Guidelines."

C. How Can I File an Objection or Hearing Request?

Under FFDCA section 408(g), 21 U.S.C. 346a, any person may file an objection to any aspect of this regulation and may also request a hearing on those objections. You must file your objection or request a hearing on this regulation in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2010-0845 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing, and must be received by the Hearing Clerk on or before [*insert date 60 days after date of publication in the* **Federal Register**]. Addresses for mail and hand delivery of objections and hearing requests are provided in 40 CFR 178.25(b).

In addition to filing an objection or hearing request with the Hearing Clerk as described in 40 CFR part 178, please submit a copy of the filing that does not contain any CBI for inclusion in the public docket. Information not marked confidential pursuant to

40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit a copy of your non-CBI objection or hearing request, identified by docket ID number EPA-HQ-OPP-2010-0845, by one of the following methods:

• *Federal eRulemaking Portal*: *http://www.regulations.gov*. Follow the on-line instructions for submitting comments.

• *Mail*: Office of Pesticide Programs (OPP) Regulatory Public Docket (7502P), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001.

• *Delivery*: OPP Regulatory Public Docket (7502P), Environmental Protection Agency, Rm. S-4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. Deliveries are only accepted during the Docket Facility's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Docket Facility telephone number is (703) 305-5805.

II. Summary of Petitioned-For Tolerance

In the **Federal Register** of December 15, 2010 (75 FR 78240) (FRL-8853-1), EPA issued a notice pursuant to section 408(d)(3) of FFDCA, 21 U.S.C. 346a(d)(3), announcing the filing of a pesticide petition (PP 0F7750) by Bayer CropScience, 2 T.W.Alexander Dr., Research Triangle Park, NC 27709. The petition requested that 40 CFR 180.537 be amended by establishing tolerances for combined residues of the herbicide isoxaflutole, 5-cyclopropyl-4-(2-methylsulfonyl-4-trifluoromethylbenzoyl) isoxazole and its metabolite 1-(2-methylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropyl propane-1,3-dione, (RPA 202248), calculated as the parent compound, in or

on soybean at 0.05 parts per million (ppm), and soybean, aspirated grain fractions at 0.25 ppm. That notice referenced a summary of the petition prepared by Bayer CropScience, the registrant, which is available in the docket, *http://www.regulations.gov*. There were no comments received in response to the notice of filing.

Based upon review of the data supporting the petition and the preferred crop terminology, EPA has made two changes to the requested tolerances. First, EPA has changed the commodity descriptions for the tolerances to soybean, seed and grain, aspirated fractions. Second, EPA is raising the grain, aspirated fractions tolerance from 0.25 ppm to 0.30 ppm.

III. Aggregate Risk Assessment and Determination of Safety

Section 408(b)(2)(A)(i) of FFDCA allows EPA to establish a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if EPA determines that the tolerance is "safe." Section 408(b)(2)(A)(ii) of FFDCA defines "safe" to mean that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." This includes exposure through drinking water and in residential settings, but does not include occupational exposure. Section 408(b)(2)(C) of FFDCA requires EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in establishing a tolerance and to "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue. . . ."

Consistent with section 408(b)(2)(D) of FFDCA, and the factors specified in section 408(b)(2)(D) of FFDCA**,** EPA has reviewed the available scientific data and other

relevant information in support of this action. EPA has sufficient data to assess the hazards of and to make a determination on aggregate exposure for isoxaflutole including exposure resulting from the tolerances established by this action. EPA's assessment of exposures and risks associated with isoxaflutole follows.

A. Toxicological Profile

EPA has evaluated the available toxicity data and considered its validity, completeness, and reliability as well as the relationship of the results of the studies to human risk. EPA has also considered available information concerning the variability of the sensitivities of major identifiable subgroups of consumers, including infants and children.

Isoxaflutole exhibited low acute toxicity via oral, dermal, and inhalation routes of exposure and it is not a dermal sensitizer. In long-term studies via the oral route, isoxaflutole caused ocular toxicity in rats, hepatotoxicity (including liver tumor formation) and thyroid tumors in rats and mice, and hematotoxicity (toxicity to blood) in dogs and mice at high doses. The liver and ocular toxicities observed in rats were consistent with the mode of action of isoxaflutole in mammals (i.e., inhibition of the hepatic enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD)) that leads to a buildup of tyrosine in the blood and the eye.

Developmental toxicity was observed in rats and rabbits primarily as growth retardations, including delays in skeletal ossification, effects that have been observed with other HPPD inhibitors (e.g., pyrasulfotole). There was no evidence of reproductive toxicity in the 2-generation reproductive toxicity study in rats; however, both adults and offspring exhibited ocular and liver toxicities as seen in long-term studies.

In the acute and subchronic neurotoxicity studies in rats, mild changes in functional-observation battery (FOB) parameters (grip strength and/or landing foot splay) were observed in adult animals. However, similar effects were not observed either in pregnant animals or in offspring in a developmental neurotoxicity (DNT) study in rats. In both maternal animals and offspring, changes in body weight and/or food consumption were the primary effects seen in the DNT study and at the same dose tested. Decreased brain weights were observed in offspring on post-natal day (PND) 11 at the high dose only, but not at a later time point, an indicator of a developmental delay and/or a secondary effect of the decreased body weight. Although morphometric analyses were not performed in the study, there were no effects on pup swimming ability, learning, memory, motor activity, or auditory startle response at any dose, nor was there any evidence of neuropathology in the study at any dose. As a result, the missing morphometric measurements, while required, are unlikely to affect the tentative lowest-observed adverse-effect level (LOAEL) of the study (highest dose tested).

Isoxaflutole was negative in a variety of genotoxicity screening assays. In carcinogenicity studies, isoxaflutole induced liver and thyroid tumors in rats and liver tumors in mice. Isoxaflutole was classified as "likely to be a human carcinogen." The method of quantification was linear cancer slope factor (Q_1*).

Specific information on the studies received and the nature of the adverse effects caused by isoxaflutole as well as the no-observed-adverse-effect-level (NOAEL) and the lowest-observed-adverse-effect-level (LOAEL) from the toxicity studies can be found at *http://www.regulations.gov* in document "Isoxaflutole. Section 3 Registration for Use on

Soybeans. Human-Health Risk Assessment," p. 13 in docket ID number EPA-HQ-OPP-2010-0845.

B. Toxicological Points of Departure/Levels of Concern

Once a pesticide's toxicological profile is determined, EPA identifies toxicological points of departure (POD) and levels of concern to use in evaluating the risk posed by human exposure to the pesticide. For hazards that have a threshold below which there is no appreciable risk, the toxicological POD is used as the basis for derivation of reference values for risk assessment. PODs are developed based on a careful analysis of the doses in each toxicological study to determine the dose at which no adverse effects are observed (the NOAEL) and the lowest dose at which adverse effects of concern are identified (the LOAEL). Uncertainty/safety factors are used in conjunction with the POD to calculate a safe exposure level - generally referred to as a population-adjusted dose (PAD) or a reference dose (RfD) - and a safe margin of exposure (MOE). For non-threshold risks, the Agency assumes that any amount of exposure will lead to some degree of risk. Thus, the Agency estimates risk in terms of the probability of an occurrence of the adverse effect expected in a lifetime. For more information on the general principles EPA uses in risk characterization and a complete description of the risk assessment process, see *http://www.epa.gov/pesticides/factsheets/riskassess.htm.*

A summary of the toxicological endpoints for isoxaflutole used for human risk assessment is shown in the Table of this unit.

Table 1.—Summary of Toxicological Doses and Endpoints for isoxaflutole for Use in Human Health Risk Assessment

Exposure/Scenario	Point of Departure and Uncertainty/Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute dietary (Females 13-49 years of age)	LOAEL = 5 milligrams/kilograms/day (mg/kg/day) UF_A = 10x UF_H = 10x FQPA SF = 3 (includes UF_L)	Acute RfD = aPAD = 0.02 mg/kg/day	Prenatal developmental toxicity (rabbit) LOAEL = 5 mg/kg/day based on mg/kg/day based on increased incidence of fetuses with 27^{th} pre-sacral vertebrae.
Acute dietary (General population including infants and children)	NOAEL = 125 mg/kg UF_A = 10x UF_H = 10x FQPA SF = 1x	Acute RfD = aPAD = 1.25 mg/kg	Acute neurotoxicity (rat) LOAEL = 500 mg/kg based on significant decreases in hind limb grip strength and landing foot splay on day 15.
Chronic dietary (All populations)	NOAEL= 2 mg/kg/day UF_A = 10x UF_H = 10x	Chronic RfD = cPAD =	Combined chronic toxicity/carcinogenicity (rat) LOAEL = 20

	FQPA SF = 1x	0.02 mg/kg/day	mg/kg/day based on liver, thyroid, ocular, and nervous system toxicity (M) and liver toxicity (F).
Cancer (Oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans". Q_1* $(mg/kg/day)^{-1}$ of 1.14×10^{-2} from the male CD-1 mouse liver for the linear low-dose extrapolation based on statistically significant increases in liver tumors in both sexes of mice and rats.		

UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of data or other data deficiency. FQPA SF = Food Quality Protection Act Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

C. Exposure Assessment

1. *Dietary exposure from food and feed uses*. In evaluating dietary exposure to isoxaflutole, EPA considered exposure under the petitioned-for tolerances as well as all existing isoxaflutole tolerances in 40 CFR 180.537. EPA assessed dietary exposures from isoxaflutole in food as follows:

i. *Acute exposure*. Quantitative acute dietary exposure and risk assessments are performed for a food-use pesticide, if a toxicological study has indicated the possibility of an effect of concern occurring as a result of a 1-day or single exposure.

Such effects were identified for isoxaflutole. In estimating acute dietary exposure, EPA used food consumption information from the United States Department of Agriculture (USDA) 1994-1996 and 1998 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII). As to residue levels in food, EPA assumed that 100% of the crop was treated and that for all commodities residues were at tolerance levels.

ii. *Chronic exposure*. In conducting the chronic dietary exposure assessment EPA used the food consumption data from the USDA 1994-1996 and 1998 CSFII. As to residue levels in food, EPA assumed that 100% of the crop was treated and that for all commodities residues were at tolerance levels.

iii. *Cancer*. EPA determines whether quantitative cancer exposure and risk assessments are appropriate for a food-use pesticide based on the weight of the evidence from cancer studies and other relevant data. If quantitative cancer risk assessment is appropriate, Cancer risk may be quantified using a linear or nonlinear approach. If sufficient information on the carcinogenic mode of action is available, a threshold or non-linear approach is used and a cancer RfD is calculated based on an earlier non-cancer key event. If carcinogenic mode of action data are not available, or if the mode of action data determines a mutagenic mode of action, a default linear cancer slope factor approach is utilized. Based on the data summarized in Unit III.A., EPA has concluded that isoxaflutole should be classified as “Likely to be Carcinogenic to Humans” and a linear approach has been used to quantify cancer risk.

In conducting the cancer dietary exposure assessment EPA used the same food consumption data from the USDA and assumptions for residue levels in food as the Chronic Exposure in Unit III. C. 1. ii., of this unit.

2. *Dietary exposure from drinking water*. The Agency used screening level water exposure models in the dietary exposure analysis and risk assessment for isoxaflutole in drinking water. These simulation models take into account data on the physical, chemical, and fate/transport characteristics of isoxaflutole. Further information regarding EPA drinking water models used in pesticide exposure assessment can be found at *http://www.epa.gov/oppefed1/models/water/index.htm.*

Based on the First Index Reservoir Screening Tool (FIRST) and Screening Concentration in Ground Water (SCI-GROW) models , the estimated drinking water concentrations (EDWCs) of isoxaflutole and metabolite RPA 202248 are estimated to be 8.68 parts per billion (ppb) for surface water and 0.255 ppb for ground water for acute exposures, 1.26 ppb for surface water and 0.255 ppb for ground water for chronic exposures for non-cancer assessments, and 0.53 ppb for surface water and 0.255 ppb for ground water for cancer assessments.

Modeled estimates of drinking water concentrations were directly entered into the dietary exposure model. For acute dietary risk assessment, the water concentration value of 8.68 ppb was used to assess the contribution to drinking water. For chronic dietary risk assessment, the water concentration of value 1.26 ppb was used to assess the contribution to drinking water. For cancer dietary risk assessment, the water concentration of value 0.53 ppb was used to assess the contribution to drinking water.

3. *From non-dietary exposure*. The term “residential exposure” is used in this document to refer to non-occupational, non-dietary exposure (e.g., for lawn and garden pest control, indoor pest control, termiticides, and flea and tick control on pets).

Isoxaflutole is not registered for any specific use patterns that would result in residential exposure.

4. *Cumulative effects from substances with a common mechanism of toxicity*. Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Pyrasulfotole, mesotrione, isoxaflutole, and topramezone belong to a class of herbicides that inhibit the liver enzyme HPPD, which is involved in the catabolism (metabolic breakdown) of tyrosine (an amino acid derived from proteins in the diet). Inhibition of HPPD can result in elevated tyrosine levels in the blood, a condition called tyrosinemia. HPPD inhibiting herbicides have been found to cause a number of toxicities in laboratory animal studies including ocular, developmental, liver and kidney effects. Of these toxicities, the ocular effect (corneal opacity) is highly correlated with the elevated blood tyrosine levels. In fact, rats dosed with tyrosine alone show ocular opacities similar to those seen with HPPD inhibitors. Although the other toxicities may be associated with chemically induced tyrosinemia, other mechanisms may also be involved.

There are marked differences among species in the ocular toxicity associated with inhibition of HPPD. Ocular effects following treatment with HPPD inhibitor herbicides are seen in the rat but not in the mouse. Monkeys also seem to be recalcitrant to the ocular toxicity induced by HPPD inhibition. The explanation of this species-specific response in ocular opacity is related to the species differences in the clearance of

tyrosine. A metabolic pathway exists to remove tyrosine from the blood that involves a liver enzyme called tyrosine aminotransferase (TAT). In contrast to rats where ocular toxicity is observed following exposure to HPPD-inhibiting herbicides, mice and humans are unlikely to achieve the levels of plasma tyrosine necessary to produce ocular opacities because the activity of TAT in these species is much greater compared to rats. Thus, humans and mice have a highly effective metabolic process for handling excess tyrosine.

HPPD inhibitors (e.g., nitisinone) are used as an effective therapeutic agent to treat patients suffering from rare genetic diseases of tyrosine catabolism. Treatment starts in childhood but is often sustained throughout patient's lifetime. The human experience indicates that a therapeutic dose (1 mg/kg/day dose) of nitisinone has an excellent safety record in infants, children, and adults and that serious adverse health outcomes have not been observed in a population followed for approximately a decade. Rarely, ocular effects are seen in patients with high plasma tyrosine levels; however, these effects are transient and can be readily reversed upon adherence to a restricted protein diet. This indicates that an HPPD inhibitor in and of itself cannot easily overwhelm the tyrosine-clearance mechanism in humans.

Therefore, due to an efficient metabolic process to handle excess tyrosine, exposure to environmental residues of HPPD inhibiting herbicides is unlikely to result in high blood levels of tyrosine and ocular toxicity in humans; and EPA has concluded that a cumulative risk assessment with other HPPD inhibitors is unnecessary.

D. Safety Factor for Infants and Children

1. *In general*. Section 408(b)(2)(C) of FFDCA provides that EPA shall apply an additional tenfold (10X) margin of safety for infants and children in the case of threshold

effects to account for prenatal and postnatal toxicity and the completeness of the database on toxicity and exposure unless EPA determines based on reliable data that a different margin of safety will be safe for infants and children. This additional margin of safety is commonly referred to as the FQPA Safety Factor (SF). In applying this provision, EPA either retains the default value of 10X, or uses a different additional safety factor when reliable data available to EPA support the choice of a different factor.

2. *Prenatal and postnatal sensitivity*. Developmental toxicity was observed in rats and rabbits as growth retardations including delays in skeletal ossification; effects that have been observed with other HPPD inhibitors (e.g., pyrasulfotole). There was evidence of increased susceptibility in the rabbit study in the form of increased incidence of fetuses with 27th pre-sacral vertebrae at a dose much lower than those causing maternal deficits in body weight and food consumption. Neither the rat developmental study nor the rat 2-generation reproductive toxicity studies revealed any evidence of increased susceptibility. However, both adults and offspring in the 2-generation reproductive toxicity study exhibited ocular and liver toxicities seen in long-term studies.

3. *Conclusion*. EPA has determined that reliable data show the safety of infants and children would be adequately protected if the FQPA SF were reduced to 1x for all exposure scenarios, except acute dietary for females 13-49 years of age for which an FQPA SF is retained but reduced to 3X. That decision is based on the following findings:

i. The toxicity database for isoxaflutole is complete.

ii. There are not residual concerns regarding neurotoxicity, including developmental neurotoxicity, based on the results of acute, subchronic, and developmental neurotoxicity studies.

iii. There is no evidence that isoxaflutole results in increased susceptibility following *in utero* exposure in a rat developmental study or in young rats in the 2-generation reproduction study. However, there was evidence of increased susceptibility following *in utero* exposure in a rabbit developmental study and a NOAEL for developmental effects was not identified in that study. To address the concern for increased *in utero* susceptibility and the lack of a NOAEL in the rabbit study, this study was selected for the acute dietary endpoint for females of 13-49 years of age and a 3X FQPA SF was retained for that population subgroup. Use of a 3X FQPA SF applied to the LOAEL yielded a point of departure that is comparable to the point of departure for the chronic dietary exposure scenario and the offspring effects in the rat 2-generation reproductive toxicity study . Therefore, all dietary exposure scenarios are considered protective of developmental effects.

iv. There are no residual uncertainties identified in the exposure databases. EPA made the very conservative, health-protective assumption that all commodities for which tolerances exist or are proposed contain residues at the tolerance level. Additionally, EPA made conservative (protective) assumptions in the ground and surface water modeling used to assess exposure to isoxaflutole in drinking water. These assessments will not underestimate the exposure and risks posed by isoxaflutole.

E. Aggregate Risks and Determination of Safety

EPA determines whether acute and chronic dietary pesticide exposures are safe by comparing aggregate exposure estimates to the acute PAD (aPAD) and chronic PAD (cPAD). For linear cancer risks, EPA calculates the lifetime probability of acquiring cancer given the estimated aggregate exposure. Short-, intermediate-, and chronic-term risks are evaluated by comparing the estimated aggregate food, water, and residential exposure to the appropriate PODs to ensure that an adequate MOE exists.

1. *Acute risk.* Using the exposure assumptions discussed in this unit for acute exposure, the acute dietary exposure from food and water to isoxaflutole will occupy 2.4% of the aPAD for females 13 to 49 years old, the population group receiving the greatest exposure.

2. *Chronic risk*. Using the exposure assumptions described in this unit for chronic exposure, EPA has concluded that chronic exposure to isoxaflutole from food and water will utilize 1% of the cPAD for all infants (<1 year old) the population group receiving the greatest exposure. There are no residential uses for isoxaflutole.

3. *Short-term risk*. A short-term adverse effect was identified; however, isoxaflutole is not registered for any use patterns that would result in short-term residential exposure. Short-term risk is assessed based on short-term residential exposure plus chronic dietary exposure. Because there is no short-term residential exposure and chronic dietary exposure has already been assessed under the appropriately protective cPAD (which is at least as protective as the POD used to assess short-term risk), no further assessment of short-term risk is necessary, and EPA relies on the chronic dietary risk assessment for evaluating short-term risk for isoxaflutole.

4. *Intermediate-term risk*. An intermediate-term adverse effect was identified; however**,** isoxaflutole is not registered for any use patterns that would result in intermediate-term residential exposure. Intermediate-term risk is assessed based on intermediate-term residential exposure plus chronic dietary exposure. Because there is no intermediate-term residential exposure and chronic dietary exposure has already been assessed under the appropriately protective cPAD (which is at least as protective as the POD used to assess intermediate-term risk), no further assessment of intermediate-term risk is necessary, and EPA relies on the chronic dietary risk assessment for evaluating intermediate-term risk for isoxaflutole.

5. *Aggregate cancer risk for U.S. population*. The aggregate cancer risk assessment for the general population takes into account exposure estimates from dietary consumption of isoxaflutole from food and drinking water sources. Average food plus water source dietary exposure was used. Estimated cancer risk for the U.S. population includes infants and children. The aggregate cancer risk estimate for isoxaflutole is 8×10^{-7}. This risk estimate is based, in part, on the conservative assumption that 100% of all crops for which isoxaflutole is registered or proposed for registration are treated. Additional refinement using percent crop treated estimates would result in a lower estimate of cancer risk.

EPA generally considers cancer risks in the range of one in one million (1×10^{-6}) or less to be negligible. Accordingly, EPA has concluded the cancer risk for all existing isoxaflutole uses and the uses associated with the tolerances established in this action is negligible.

6. *Determination of safety*. Based on these risk assessments, EPA concludes that there is a reasonable certainty that no harm will result to the general population, or to infants and children from aggregate exposure to isoxaflutole residues.

IV. Other Considerations

A. Analytical Enforcement Methodology

Adequate enforcement methodology (liquid chromatography with tandem mass spectrometry (LC/MS/MS) method (IS-004-P10-02)) is available to enforce the tolerance expression.

The method may be requested from: Chief, Analytical Chemistry Branch, Environmental Science Center, 701 Mapes Rd., Ft. Meade, MD 20755-5350; telephone number: (410) 305-2905; e-mail address: *residuemethods@epa.gov*.

B. International Residue Limits

In making its tolerance decisions, EPA seeks to harmonize U.S. tolerances with international standards whenever possible, consistent with U.S. food safety standards and agricultural practices. EPA considers the international maximum residue limits (MRLs) established by the Codex Alimentarius Commission (Codex), as required by FFDCA section 408(b)(4). The Codex Alimentarius is a joint U.N. Food and Agriculture Organization/World Health Organization food standards program, and it is recognized as an international food safety standards-setting organization in trade agreements to which the United States is a party. EPA may establish a tolerance that is different from a Codex MRL; however, FFDCA section 408(b)(4) requires that EPA explain the reasons for departing from the Codex level.

The Codex has not established a MRL for isoxaflutole.

V. Conclusion

Therefore, tolerances are established for residues of isoxaflutole, 5-cyclopropyl-4-isoxazolyl)[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]methanone and its metabolite 1-(2-methylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropyl propane-1,3-dione, in or on soybean, seed and grain, aspirated fractions at 0.05 ppm and 0.30 ppm, respectively.

VI. Statutory and Executive Order Reviews

This final rule establishes tolerances under section 408(d) of FFDCA in response to a petition submitted to the Agency. The Office of Management and Budget (OMB) has exempted these types of actions from review under Executive Order 12866, entitled *Regulatory Planning and Review* (58 FR 51735, October 4, 1993). Because this final rule has been exempted from review under Executive Order 12866, this final rule is not subject to Executive Order 13211, entitled *Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use* (66 FR 28355, May 22, 2001) or Executive Order 13045, entitled *Protection of Children from Environmental Health Risks and Safety Risks* (62 FR 19885, April 23, 1997). This final rule does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA), 44 U.S.C. 3501 *et seq.*, nor does it require any special considerations under Executive Order 12898, entitled *Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations* (59 FR 7629, February 16, 1994).

Since tolerances and exemptions that are established on the basis of a petition under section 408(d) of FFDCA, such as the tolerance in this final rule, do not require

the issuance of a proposed rule, the requirements of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*) do not apply.

This final rule directly regulates growers, food processors, food handlers, and food retailers, not States or tribes, nor does this action alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of section 408(n)(4) of FFDCA. As such, the Agency has determined that this action will not have a substantial direct effect on States or tribal governments, on the relationship between the national government and the States or tribal governments, or on the distribution of power and responsibilities among the various levels of government or between the Federal Government and Indian tribes. Thus, the Agency has determined that Executive Order 13132, entitled *Federalism* (64 FR 43255, August 10, 1999) and Executive Order 13175, entitled *Consultation and Coordination with Indian Tribal Governments* (65 FR 67249, November 9, 2000) do not apply to this final rule. In addition, this final rule does not impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act of 1995 (UMRA) (Public Law 104-4).

This action does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA), Public Law 104-113, section 12(d) (15 U.S.C. 272 note).

VII. Congressional Review Act

The Congressional Review Act, 5 U.S.C. 801 *et seq*., generally provides that before a rule may take effect, the agency promulgating the rule must submit a rule report

to each House of the Congress and to the Comptroller General of the United States. EPA will submit 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 United States prior to publication of this final rule in the **Federal Register**. This final 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: November 21, 2011.

Lois Rossi,

Director, Registration Division, Office of Pesticide Programs.

Therefore, 40 CFR chapter I is amended as follows:

PART 180--[AMENDED]

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

Authority: 21 U.S.C. 321(q), 346a and 371.

2. Section 180.537 is amended in paragraph (a) by revising the introductory text and alphabetically adding the following commodities to the table to read as follows:

§ 180.537 Isoxaflutole; tolerances for residues.

(a) *General*. Tolerances are established for residues of the herbicide, isoxaflutole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of isoxaflutole ((5-cyclopropyl-4-isoxazolyl)[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]methanone) and its metabolite 1-(2-methylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropyl propan-1,3-dione (RPA 202248), calculated as the stoichiometric equivalent of isoxaflutole, in or on the commodity:

Commodity	Parts per million
* * * * *	
Grain, aspirated fractions	0.30
Soybean, seed	0.05

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