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Report of the Food Quality
Protection Act (FQPA)
Tolerance Reassessment
Progress and Risk Management
Decision (TRED) for
Imazaquin

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Approved By:

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Date

I. Regulatory Determination

The Federal Food, Drug and Cosmetic Act (FFDCA), as amended by FQPA, requires EPA to reassess all the tolerances for registered chemicals in effect on the day before enactment of the FQPA on August 3, 1996. In reassessing these tolerances, the Agency must consider, among other things, aggregate risks from non-occupational sources of pesticide exposure, whether there is increased susceptibility to infants and children, and the cumulative effects of pesticides with a common mechanism of toxicity. When a safety finding has been made that aggregate risks are not of concern, the tolerances are considered reassessed. Existing tolerances associated with imazaquin must be reassessed in accordance with FFDCA, as amended by FQPA. Ecological and occupational assessments were originally conducted when imazaquin was first registered in 1986. Therefore, no further ecological or occupational assessments were conducted as part of this Report of the FQPA Tolerance Reassessment Progress and Risk Management Decision for Imazaquin (also referred to as a TRED).

Imazaquin is an imidazolinone herbicide which controls weeds by inhibiting the synthesis of specific amino acids (valine, leucine & isoleucine) necessary for plant growth. It is registered as a pre-plant, preemergence and early postemergence herbicide for use on soybeans, primarily across the central Midwest from Kentucky to Illinois and across the mid-South in Arkansas, Louisiana and Mississippi. It is also registered for pre- and postemergence weed control on ornamentals and warm season turfgrass in both residential and non-residential settings. The turf and ornamental uses are concentrated across the southern U.S. because of imazaquin's lack of selectivity on cool season grasses.

Imazaquin is a relatively low toxicity pesticide whose potential routes of exposure include food, drinking water and residential areas. Under the conditions of its current use, estimated health risks to the general population are below the Agency's level of concern. Estimated aggregate risk Margin of Exposures (MOEs) from the consumption of food and drinking water and from exposure to the pesticide in residential settings exceed 100 for all populations, including infants and children, and, therefore, are not of concern.

The Agency has evaluated the toxicity and exposure data bases for the pesticide active ingredient imazaquin, including its ammonium and monosodium salts, and has conducted a human health risk assessment in support of the Tolerance Reassessment Eligibility Decision (TRED) for this active ingredient. In making this determination, EPA has considered dietary exposure from food and drinking water and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, the one tolerance established for residues of imazaquin in or on soybean commodities is now considered reassessed as safe under section 408(q) of FFDCA, as amended by FQPA.

The Agency's human health and drinking water findings for the pesticide imazaquin are summarized in the following risk assessments: *Imazaquin and its Salts: HED Chapter of the Tolerance Reassessment Eligibility Decision Document (TRED)*, dated October 31, 2005 and

Drinking Water Assessment for Imazaquin and its Salts, dated June 21, 2005, and *Amendment to Drinking Water Assessment for Imazaquin and its Salts*, dated September 27, 2005. For further details, please refer to these risk assessments and other technical documents pertaining to the Imazaquin TRED, which are available on the Internet at <http://www.epa.gov/e-dockets> and in the public docket for viewing.

The Agency is issuing this TRED document for imazaquin as announced in a Notice of Availability published in the *Federal Register*. The Agency is providing a 30-day comment period for stakeholders to respond to this risk management decision. If substantive information is received during the comment period that indicates a need to refine any of EPA's assumptions or a need for risk mitigation, then this decision will be modified as appropriate through an amendment to the TRED.

II. Tolerance Reassessment

A. FQPA Assessment Supporting Tolerance Reassessment Decision

The Agency has conducted risk assessments to ensure that the imazaquin tolerances meet the new safety standards established by FFDCA, as amended by FQPA. These recent risk assessments for imazaquin include evaluation of potential susceptibility to infants and children; dietary, drinking water, and residential exposure of adults and children; and aggregate risk from these various exposure pathways.

EPA has determined that risk from exposure to imazaquin is within its own "risk cup." In other words, EPA is able to conclude today that the tolerance for imazaquin meets the FQPA safety standards. In reaching this determination, the Agency has considered the available information on the potential sensitivity of infants and children, as well as the chronic and acute food exposure. However, an endpoint attributable to a single dose was not identified for this chemical; therefore, an acute reference dose (RfD) was not established and an acute dietary assessment was not conducted. An aggregate assessment was conducted for exposures through food, residential uses, and drinking water. Results of this aggregate assessment indicate that the human health risks from these combined exposures are considered to be within acceptable levels; that is, combined risks from all exposures to imazaquin "fit" within the individual risk cup for this chemical. The Agency's risk assessment conclusions are summarized below.

FQPA Safety Factor Considerations. The FFDCA, as amended by the FQPA, directs the Agency to use an additional tenfold (10X) safety factor to take into account potential pre- and post-natal toxicity to infants and children. FFDCA authorizes the Agency to modify the tenfold safety factor only if reliable data demonstrates that the resulting level of exposure would be safe for infants and children.

EPA has determined that imazaquin does not cause developmental toxicity in rat or rabbit fetuses and does not adversely affect reproductive parameters in rats in a three-generation study. There is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses or

offspring after *in utero* and/or post-natal exposure to imazaquin in the developmental and reproduction studies. In addition, dose-response relationships are well-characterized and clear No/Lowest Observable Adverse Effect Levels (NOAELs/LOAELs) have been identified for the critical effects. Therefore, the Special FQPA Safety Factor can be reduced to 1X, since there are no concerns and no residual uncertainties for pre- and/or post-natal toxicity.

Further, no evidence of neurotoxicity was observed in any study. Based on the weight of evidence, a developmental neurotoxicity (DNT) study is not required for imazaquin. No evidence of carcinogenicity was seen in mice or rats, and imazaquin was non- mutagenic in available mutagenicity tests.

Toxicity Endpoint/Dose Selection. A chronic reference dose (cRfD) of 0.25 mg/kg/day was established for imazaquin, based on the NOAEL of 25 mg/kg/day in the dog chronic toxicity study and an uncertainty factor of 100 (10x for interspecies extrapolation and 10x for intraspecies variation). Effects seen at the LOAEL included body weight loss, clinical chemistry/hematology differences, slight anemia and skeletal muscle myopathy. Body weight decreases occurred in the first four weeks of the study and the hematology data from the earliest assessment at 13 weeks indicated statistically significant changes in hematology parameters, raising concern that the anemia effects of imazaquin may occur within a short or intermediate time frame. Therefore, the NOAEL of 25 mg/kg/day from this study was selected to assess oral, dermal and inhalation exposures of short-, intermediate- and long-term duration. An acute reference dose (aRfD) was not established, since an endpoint attributable to a single exposure was not identified from the available database.

Dietary Risks from Food and Drinking Water. Because an endpoint attributable to a single dose was not identified from the available toxicity database for imazaquin, an acute dietary assessment was not conducted. A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID), Version 2.03, which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The Tier 1 chronic analysis assumed 100% of the crop treated and tolerance-level residues for all foods. Drinking water exposure was incorporated directly into the dietary assessment using the Tier 1 estimated drinking water concentration for ground water generated by the SCI-GROW model.

EPA's Tier1 chronic dietary risk assessment indicates that dietary risk from imazaquin residues in food and drinking water is low and not of concern. The resulting chronic dietary exposure estimates using the DEEM-FCID model were less than 1.0% of the chronic Population Adjusted Dose (cPAD) for the U.S. general population and all population subgroups. Therefore, no mitigation measures are necessary to address dietary risks from food and drinking water.

Residential Risks. There is a potential for exposure in residential settings during the application process for homeowners who use products containing imazaquin on turf and ornamentals. There is also a potential for exposure of children and adults who enter residential areas previously treated with imazaquin. In both cases, the duration of exposure is expected to be short-term only. As a result, short-term risk assessments have been completed for both residential handler and

postapplication scenarios. The routes of exposure considered in the assessments included inhalation (residential handler exposure only), dermal (residential handler and postapplication exposures) and incidental oral (post-application exposure for children only). The Margin of Exposure (MOE) of concern for residential exposures is 100. The combined dermal and inhalation MOEs for residential handlers range from 1,700 (homeowners applying liquid concentrates to turf using a hose-end sprayer) to 15,400 (homeowners applying liquid concentrates to ornamentals with a hand held pump). Postapplication MOEs for adults range from 430 (high contact turf scenario, i.e., “jazzercise”) to 12,500 (mowing turf). The combined postapplication dermal and incidental oral (including hand-to-mouth, object-to-mouth and incidental soil ingestion exposures) MOE for children playing on treated turf is 260. The residential handler and postapplication exposure MOEs are all greater than 100 and are, therefore, not of concern. Therefore, no mitigation measures are necessary to address residential risks.

Aggregate Risk. Short- and long-term (chronic) aggregate risk assessments were conducted for imazaquin. The short-term assessment considered both dietary (food + water) and residential exposures. The long-term assessment considered dietary exposure only, since the current uses of imazaquin are not expected to result in long-term residential exposure. An intermediate-term aggregate assessment was not conducted, since the current uses of imazaquin are not expected to result in exposures of this duration. Also, since an endpoint attributable to a single exposure was not identified for imazaquin, an acute aggregate assessment was not conducted.

Short-term aggregate exposure takes into account short-term residential exposure plus average exposure levels from residues of imazaquin in food and water (considered to be a background exposure level). The results of the deterministic, Tier1 dietary assessment indicate that the chronic (average) dietary exposure to imazaquin from food and water is well below the Agency’s level of concern, with estimated exposures representing <1% of the cPAD for the U.S. population and all population subgroups, including infants and children. When the chronic (average) dietary exposure is combined with short-term residential exposure, the resulting short-term aggregate risk estimates for adults and children are also below the Agency’s level of concern. The MOE of concern for short-term aggregate risk is 100. Since the estimated short-term aggregate risk MOEs for adults and children (toddlers) are 340 and 257, respectively, short-term aggregate risk is not considered to be of concern for imazaquin.

The chronic aggregate risk assessment considered exposures from food and water only, because there are no residential uses expected to contribute to chronic exposures for this chemical. The chronic aggregate risk estimates for the U.S. population and all subgroups are < 1% of the cPAD and, therefore, below the Agency’s level of concern.

A cancer aggregate risk assessment is not required, since there was no evidence of carcinogenicity in the toxicology studies for imazaquin

In sum, therefore, since there are no aggregate risks of concern, no mitigation measures are necessary to address aggregate risks.

B. Cumulative Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to imazaquin and any other substances, and imazaquin does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that imazaquin has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at <http://www.epa.gov/pesticides/cumulative/>.

C. Endocrine Disruptor Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies with imazaquin, there was no evidence of estrogen or androgen mediated toxicity. Imazaquin, at higher doses, was demonstrated to increase thyroid stimulating hormone (TSH) and to have associated decreases in thyroxine (T4) and tri-iodothyronine (T3). However, the dose level at which these changes were noted is approximately 10-fold higher than the current reference dose for risk assessment. Therefore, the risk assessment should be protective of the observed endocrine/thyroid effects.

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, imazaquin may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

D. Tolerance Summary

The tolerance for residues of imazaquin in/on plant commodities is expressed in terms of residues of imazaquin *per se* 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1Himidazol-2-yl]-3-

quinoline carboxylic acid. Imazaquin has one tolerance for soybeans. A summary of the imazaquin tolerance reassessment for soybeans is presented below.

Tolerances Listed Under 40 CFR §180.426:

A tolerance has been established under 40 CFR §180.426 for residues of imazaquin in or on soybeans. Provided that the residue and product chemistry deficiencies cited in Section III of this document are resolved, the Agency supports the current tolerance of 0.05 ppm. The tolerance is set at the Limit of Quantitation (LOQ) of the analytical method, since all of the field trial residues were below this level.

Tolerance Summary for Imazaquin			
<u>Commodity</u>	<u>Current Tolerance (ppm)</u>	<u>Reassessed Tolerance (ppm)</u>	<u>Comments (correct commodity definition)</u>
Soybeans	0.05	0.05	<i>Soybean, seed</i>

Codex/International Harmonization

There are no Codex or Canadian maximum residue limits (MRLs) for imazaquin. Currently in Canada, a default MRL of 0.1 ppm applies when specific MRLs have not been established. Based on this consideration and the fact that detectable residues of imazaquin are not expected in soybeans from its current U.S. uses, the lack of compatible Codex and Canadian MRLs should not present a significant trade concern for U.S. growers.

III. Data Gaps and Confirmatory Data Requirements

There are residue and product chemistry deficiencies and data gaps for imazaquin. These data are not expected to change the regulatory conclusions for imazaquin described in this document. The following is the list of the required data:

Product Chemistry

- Additional data are required concerning product identity, certified limits, stability, storage stability, and UV/visible absorption (OPPTS 830.1550, 1750, 6313, 6317, and 7050) for the BASF Corporation imazaquin 95% T (EPA Reg. No. 241-287).
- Additional data are required concerning all generic product chemistry guidelines (OPPTS 830.1600, 1620, 1670, 1700, 6302, 6303, 6304, 6313, 7000, 7050, 7200, 7220, 7370, 7550, 7840, xxxx (solvent solubility, formerly 63-8), and 7950) for the BASF Corporation imazaquin ammonium salt TGAI and Ambrands imazaquin ammonium salt TGAI.

- Additional data are required concerning all generic product chemistry guidelines (OPPTS 830.1600, 1620, 1670, 1700, 6302, 6303, 6304, 6313, 7000, 7050, 7200, 7220, 7370, 7550, 7840, xxxx (solvent solubility, formerly 63-8), and 7950) for the BASF Corporation imazaquin sodium salt TGAI

Residue Chemistry

- 860.1380: Storage Stability Data / 860.1500: Crop Field Trials

The storage duration of the crop field trial soybean samples from harvest to analysis was not provided and should be submitted. Storage stability studies indicate that residues of imazaquin are stable on soybeans for up to 24 months of frozen storage. If the storage duration of the field samples was greater than 24 months, storage stability information should be submitted to cover the storage duration.

- 860.1360: Multiresidue Method

Multiresidue method data were not submitted. The registrant should submit data pertaining to the recovery of imazaquin via FDA Multiresidue Protocols (PAM Vol. I).