

US EPA ARCHIVE DOCUMENT



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

April 2006



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Tolerance Reassessment
Progress and Risk
Management Decision (TRED)
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

CERTIFIED MAIL

Dear Registrant:

This is the Environmental Protection Agency's (hereafter referred to as EPA or the Agency) "Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision for Propazine," which was approved April 6, 2006. This document is also known as a Tolerance Reassessment Decision, or TRED. A Notice of Availability of this TRED will be published shortly.

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 or before the 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. Once a safety finding has been made that there is a reasonable certainty that no harm will result from aggregate exposure to propazine residues from dietary and other non-occupational exposures, the tolerances are considered reassessed. Existing tolerances associated with propazine must be reassessed in accordance with FFDCA, as amended by FQPA.

As part of the FQPA tolerance reassessment process, EPA assessed the risks associated with propazine. This assessment is for this individual chlorinated triazine pesticide propazine. FQPA also requires the Agency to evaluate food tolerances on the basis of cumulative risk from substances sharing a common mechanism of toxicity, such as the neuroendocrine mechanism of toxicity shared by structurally-related chlorinated triazines atrazine, simazine, propazine, and their three chlorinated degradates. The Agency has completed its cumulative risk assessment for the chlorinated triazine class of pesticides and has concluded that with the mitigation measures in the simazine Reregistration Eligibility Decision (RED) and atrazine Interim Reregistration Eligibility Decision (IRED) the cumulative risks associated with these pesticides are below the Agency's level of concern. Propazine was not incorporated into the assessment because exposure to propazine is not anticipated via any of the currently registered exposure pathways. The cumulative risk assessment and supporting documents are

available in the public docket EPA-HQ-OPP-2005-0481 located on-line in the Federal Docket Management System (FDMS), <http://www.regulations.gov>.

The Agency has evaluated all existing tolerances for sorghum (forage, grain, stover, and sweet) and has determined that the available data provide adequate support to conclude that there is a reasonable certainty that no harm to the general population, infants, children, or any other population subgroup, will result from these tolerances. This decision does not include an assessment of dietary exposure from drinking water because propazine is not currently registered for use on sorghum in the United States and the only registered use for propazine in the United States (a non-food use on container-grown ornamentals in greenhouses) will not result in exposure from drinking water. There are also no residential uses registered for propazine so aggregate risk estimates are the same as those for dietary exposure from food. Dietary exposure to propazine from food was determined to be essentially zero, or <1% of the aPAD and cPAD, and not of concern to the Agency. Therefore, no mitigation measures are necessary at this time for the pesticide propazine. The propazine risk assessment and supporting documents are available in the public docket EPA-HQ-OPP-2005-0496 located on-line in FDMS, <http://www.regulations.gov>.

The Agency has determined that the four tolerances established at 40 CFR 180.243 for residues of propazine in/on raw agricultural commodities are now considered reassessed and meet the safety standards under the FQPA amendments to Section 408(b)(2)(D) and 408(b)(2)(c) of the FFDCFA.

The Agency has also received a new use petition for sorghum from the Griffin Corporation (PP#7F4837 as announced in a *Federal Register* Notice published on June 22, 2005, 70 *FR* 36159) that requests the amendment of established tolerances for residues of propazine on sorghum. Potential risks resulting from this use will be assessed when the petition is considered.

Aggregate Risk Assessment

Propazine is a systemic herbicide that is usually applied to the soil, absorbed through leaves and roots, and acts by inhibiting photosynthesis within the targeted plant. It is used as a selective herbicide to control most annual grasses and broadleaf weeds before the weeds emerge or after removal of weed growth. Propazine is formulated as a flowable concentrate, is registered for use on container-grown ornamentals in greenhouses, and is to be applied through flood or drench nozzles only.

The toxicity database for propazine is considered complete for the assessment of toxicological endpoints for risk assessment purposes. Propazine has a low order of acute toxicity via the oral (Category IV), dermal (Category IV), and inhalation (Category III) routes of exposure. It is not an eye or skin irritant, or a dermal sensitizer.

In a sub-chronic developmental study, incomplete or absent bone formation or ossification was

observed in fetal rats following exposure of pregnant rats to propazine. These developmental effects are presumed to occur after a single exposure and are therefore appropriate for consideration in the acute exposure scenario for dietary risk from food. These adverse effects were the basis for identification of a developmental endpoint for acute dietary exposure to propazine in females ages 13 to 49. The corresponding highest dose or level of exposure at which these adverse effect were not observable in female rats (“no observed adverse effects level” or NOAEL) was 10 mg/kg/day.

After subchronic and chronic exposure to propazine, a variety of species were shown to exhibit neuroendocrine effects resulting in both reproductive and developmental consequences that are considered relevant to humans. These neuroendocrine effects are biomarkers of a neuroendocrine mechanism of toxicity that is shared by several other structurally-related chlorinated triazines including atrazine, simazine, and three chlorinated degradates – G-28279 (des-isopropyl atrazine or DIA), and G-30033 (des-ethyl atrazine or DEA), and G-28273 (diaminochlorotriazine or DACT) – the latter two which can result from the degradation of propazine. These six compounds disrupt the hypothalamic-pituitary-gonadal (HPG) axis, part of the central nervous system, causing cascading changes to hormone levels and developmental delays.

For propazine, a neuroendocrine endpoint was identified for chronic dietary exposure based on adverse effects of estrous cycle alterations and luteinizing hormone (LH) surge suppression observed in a LH surge study on female rats exposed to atrazine. The corresponding NOAEL was 1.8 mg/kg/day. Because the database for propazine’s potential neuroendocrine effects is less robust than the atrazine database, particularly for the young, the Agency concluded that atrazine data could be used as bridging data for propazine due to the fact that propazine and atrazine share the neuroendocrine mechanism of toxicity described above, and that these neuroendocrine effects are considered the primary toxicological effects of regulatory concern for chronic exposure.

Propazine’s two chlorinated degradates, DEA and DACT, are considered to have toxicity equal to the parent compound in respect to their common neuroendocrine mechanism of toxicity. Another degradate, hydroxy-propazine, was identified, which is expected to have a different toxicological profile from propazine based on the toxicological data available for an analogous metabolite for atrazine, hydroxy-atrazine. On the basis of the results of a risk assessment for hydroxy-atrazine that showed minimal exposure and risk, anticipated exposure, and consequently risk, to hydroxy-propazine in the diet would be expected to be very small. Therefore the degradate hydroxy-propazine was not included in the risk assessment.

Propazine was originally classified in 1989 as a Group C carcinogen, or possible human carcinogen, and was considered to have a non-threshold mechanism for tumor formation. In other words, a threshold, or dose below which the risk of developing cancer is negligible, had not been identified for propazine. Mode of action data were later received and examined by the Agency in regards to the ability of atrazine to induce mammary tumors in rats through the neuroendocrine mechanism of toxicity the compound shares with propazine. As a result of evidence that the events leading to the tumor formation are species/strain specific and not operative in humans, atrazine was reclassified in 2000 as “not likely to be carcinogenic to humans.” Propazine was similarly reclassified in 2005 based on weight-of-evidence that it is not genotoxic and operates via a mode of action for the development of mammary and pituitary tumors in female rats similar to atrazine. Consequently, cancer risks have not been assessed in the risk assessment.

EPA considers acute and chronic dietary risk from food. Acute dietary risk from food is calculated considering what is eaten in one day and maximum, or high-end, residue values in food. An acute risk estimate that is less than 100% of the acute Population Adjusted Dose (aPAD), the dose at which an individual could be exposed on any given day and no adverse health effects would be expected, is not of concern to the Agency. Chronic dietary risk from food is calculated using the average food consumption values for each population sub-group and average residue values in/on those foods over a 70 year lifetime to determine average exposure. A chronic risk estimate that is less than 100% of the chronic Population Adjusted Dose (cPAD), the dose at which an individual could be exposed over the course of a lifetime and no adverse health effect would be expected, generally meets the reasonable certainty of no harm standard in the FFDCA.

The aPAD and cPAD are the acute reference dose (aRfD) and the chronic reference dose (cRfD), respectively, adjusted for the Food Quality Protection Act (FQPA) safety factor, a method of accounting for the potential for increased susceptibility of infants and children to toxic effects. The total FQPA safety factor applied to the acute dietary assessment for propazine was reduced from the default 10X FQPA safety factor to 1X. The Agency believes that it has sufficient reliable data in the case of propazine to determine that a lower safety factor is safe. The Agency determined that it was unnecessary to retain a FQPA safety factor in the acute dietary assessment to account for hazard-based concerns because open literature data demonstrate that any neuroendocrine effect, the primary toxicological effects of regulatory concern, that could result from a single dose would only occur at a very high dose. Retention of the FQPA safety factor for exposure uncertainties is also unnecessary and not relevant to this decision because neither exposure through drinking water nor food sources occurs as a result of the registered uses of propazine. The total FQPA safety factor applied to the chronic dietary assessment was reduced from the default 10X to 3X. As was determined for the acute assessment, retention of an exposure-based FQPA safety factor for the chronic assessment is unnecessary and not relevant to this decision because neither exposure through drinking water nor food sources occurs as a result of the registered uses of propazine. The Agency has concluded that a 3X FQPA hazard-based safety factor is sufficient to account for residual uncertainty regarding the effects of the neuroendocrine mechanism of action on the developing child because available toxicological studies for the triazines indicate that the young are not likely to be an order of magnitude more sensitive than the adult. A 3X FQPA safety factor is retained due to the lack of studies on all possible outcomes

associated with exposures at every critical period of development in the young.

The aRfD and cRfD are derived from toxicity studies on animals and are equal to the NOAEL identified in the studies after an uncertainty factor of 100X is applied to account for both intraspecies variability (i.e., differences among humans) at 10X and interspecies extrapolation (i.e., uncertainty in extrapolating from animal data to humans) at 10X. The aRfD for propazine is 0.1 mg/kg/day and the resulting aPAD is 0.1 mg/kg/day. The cRfD for propazine is 0.018 mg/kg/day and the resulting cPAD is 0.006 mg/kg/day.

For the purposes of this TRED, exposure to propazine from food was determined to be essentially zero because there is no exposure to grain sorghum commodities reported in the human diet. Further, based on theoretical livestock diets and metabolism/feeding studies at exaggerated feeding levels, no human dietary exposure is expected due to consumption of meat or milk products. Thus, acute and chronic exposure from food are essentially zero, or <1% of the aPAD and cPAD, and are not of concern to the Agency. As there are no residential uses registered for propazine, the aggregate exposure assessment for propazine is the same as that for dietary exposure from food.

Cumulative Risk Assessment

FQPA requires that EPA consider “available information” concerning the cumulative effects of a particular pesticide’s residues and “other substances that have a common mechanism of toxicity.” The Agency considers other substances because low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect, as would a higher level of exposure to any of the other substances individually.

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>.

EPA evaluated propazine along with two other structurally-related chlorinated triazines, atrazine and simazine, and their three chlorinated degradates, as sharing a neuroendocrine mechanism of toxicity. After subchronic and chronic exposure to these compounds, a variety of species were shown to exhibit neuroendocrine effects resulting in both reproductive and developmental consequences that are considered relevant to humans. These compounds disrupt the hypothalamic-pituitary-gonadal (HPG) axis, part of the central nervous system, and cause cascading changes to hormone levels and developmental delays. The Agency has completed its cumulative risk assessment for the chlorinated triazine class of pesticides and has concluded that, with the mitigation measures in the simazine RED and atrazine IRED, the cumulative risks associated with these pesticides are below the Agency’s level of concern. The cumulative risk assessment and supporting documents are available in the public docket EPA-HQ-OPP-2005-0481 located on-line in FDMS, <http://www.regulations.gov>.

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 endocrine effects as the Administrator may designate.” Following recommendations of its Endocrine Disruptor Screening 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 EPA include evaluations of potential effects in wildlife. For pesticides, 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 for additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

There is evidence that propazine is associated with neuroendocrine disruption. Direct measurements of serum hormones such as luteinizing hormone, as well as changes in estrus cycling and histomorphologic changes in hormone responsive tissues, indicate neuroendocrine disruption. EPA has responded, in part, to propazine's known neuroendocrine disrupting capacity by regulating on endpoints based on neuroendocrine disruptor effects to ensure that potential risks of concern are below the Agency's levels of concern. When the appropriate screening and/or testing protocols being considered under the EDSP have been developed, propazine may be subject to additional screening and/or testing to better characterize effects related to endocrine disruption.

Tolerance Summary

Tolerances established under 40 CFR 180.243 are currently defined for residues of propazine (the parent compound) only. The Agency has received a petition from the Griffin Corporation (PP#7F4837 as announced in a *Federal Register* Notice published on June 22, 2005, 70 *FR* 36159) that requests a new use on sorghum and amendment of the tolerance expression for propazine. Consistent with the petition, the Agency has determined from available data that the tolerance expression for all tolerances should be revised to reflect combined residues of the parent compound, propazine (2-chloro-4,6-bis(isopropylamino)-*s*-triazine), plus its two chlorinated degradates (2-amino-4-chloro-6-isopropylamino-*s*-triazine and 2,4-diamino-6-chloro-*s*-triazine), the total residue to be measured in/on raw agricultural commodities for tolerance enforcement. Also, the Agency will propose revoking the tolerance for sorghum, sweet. This tolerance is not supported by the new use petition, and therefore the tolerance is no longer needed.

Table 1. Tolerance reassessment summary for propazine

| Current Commodity | Current Tolerance (ppm) | Tolerance Reassessment Decision (ppm) | Comments [Correct Commodity Definition] |
|---|-------------------------|---------------------------------------|--|
| Tolerances Listed Under 43 CFR 180.243 | | | |
| Sorghum, forage | 0.25 (N) ^a | 0.25 | No registered uses in the United States. [<i>Sorghum, grain, forage</i>] |
| Sorghum, grain | 0.25 (N) | 0.25 | No registered uses in the United States. [<i>Sorghum, grain, grain</i>] |
| Sorghum, grain, stover | 0.25 (N) | 0.25 | No registered uses in the United States. |
| Sorghum, sweet | 0.25 (N) | Revoke | No registered uses in the United States, and use is not supported in pending petition. |

^a (N) designation indicates negligible residues and EPA will propose to remove the “N” designation from all entries to conform to current Agency administrative practice.

This document summarizes the Agency’s decision on the tolerance reassessment for propazine. For a more detailed discussion of the potential risks associated with propazine, please refer to the human health risk assessment and supporting documents listed below which are available in the public docket EPA-HQ-OPP-2005-0496 located on-line in FDMS, <http://www.regulations.gov>. Please contact Diane Sherman of my staff with any questions regarding this decision. She may be reached by phone at (703) 308-0128 or by e-mail at sherman.diane@epa.gov.

Sincerely,

Debra Edwards, Ph.D.
 Director
 Special Review and Reregistration Division

Enclosures:

Propazine: Revised HED Risk Assessment for the Tolerance Reassessment Eligibility Decision (TRED) which includes a New Use on Grain Sorghum

Propazine: Revised Acute and Chronic Dietary Exposure Assessment for the Tolerance Reassessment Eligibility Decision (TRED) which includes a New Use on Grain Sorghum

Propazine. Revised Residue Chemistry Summary for the Tolerance Reassessment Eligibility Decision (TRED) and a Proposal to Reinstate Food/Feed Use on Grain Sorghum

Propazine: Fourth Report of the Cancer Assessment Review Committee

Propazine: Response to Error Only Review of Preliminary Human Health Risk Assessments