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Prevention, Pesticides and Toxic Substances (7508C)

April 2002

Report of the FQPA Tolerance Reassessment Progress and Risk Management Decision (TRED)

Difenzoquat

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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CERTIFIED MAIL

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 (TRED) for difenzoquat", which was approved on April 19, 2002. A Notice of Availability of this tolerance reassessment decision will be published in the *Federal Register* (FR) shortly.

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 date of the enactment of the FQPA, which was in August of 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 aggregate risks are not of concern, the tolerances are considered reassessed. A reregistration eligibility decision (RED) for difenzoquat was completed in September 1994, prior to FQPA enactment. Therefore, the tolerances need to be reassessed to meet the FQPA standard.

The Agency has evaluated the dietary risk associated with difenzoquat and has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to difenzoquat when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, no mitigation measures are needed, and the twenty two (22) tolerances established for residues of difenzoquat in/on raw agricultural commodities are now considered reassessed as safe under section 408(q) of the FFDCA.

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 reason for considering other substances is because of the possibility that 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. EPA did not perform a cumulative risk assessment as part of this review of difenzoquat, because the Agency has not determined that there are any other chemical substances that have a mechanism of toxicity common with that of difenzoquat. If EPA identifies other substances that share a common mechanism of toxicity with difenzoquat, then a cumulative risk assessment will be conducted that includes difenzoquat once the final framework EPA will use for conducting cumulative risk assessments is available. Further, EPA is in the process of developing criteria for characterizing and testing endocrine disrupting chemicals and plans to implement an Endocrine Disruptor Screening Program. Difenzoquat will be reevaluated at that time and additional studies may be required.

The Agency's human health findings for the pesticide difenzoquat, were discussed in a closure conference call, and are summarized in the enclosed chemical overview and summary of the risk assessments. The risk assessments and other documents pertaining to the difenzoquat tolerance reassessment decision are listed at the end of this document and are available on the Internet at http://www.epa.gov/pesticides/reregistration/status.htm and the public docket for viewing.

Tolerances are established for residues of difenzoquat, derived from application of the methyl sulfate salt and calculated, in/on barley, wheat, and animal commodities [Source: 40 CFR §180.369]. Current tolerances range from 0.05 to 20 ppm for residues in/on barley and wheat commodities, and are 0.05 ppm for residues in livestock commodities. Adequate enforcement methods are available for the determination of difenzoquat residues in/on plant and animal commodities.

The Agency has recommended establishing tolerances in processed commodities, barley bran, wheat bran and wheat shorts at 0.25 ppm and has reassessed the tolerances for wheat straw, barley straw, and barley grain at 5.0, 5.0 and 0.05 ppm, respectively. Fat, meat, and meat byproducts of poultry are being reassessed each at 0.05 ppm. (See Table I)

The available livestock feeding data suggest that the established tolerances for residues of difenzoquat in ruminant meat are adequate. However, actual reassessment of ruminant meat tolerances will be made when the requested residue data for all major livestock feed (wheat forage and hay; and barley hay) items have been submitted and a re-calculation of maximum dietary burden has been performed. Meanwhile, the label restriction against the grazing of livestock on treated fields and the cutting of treated forage for silage/hay should remain on the label until forage and hay data are submitted and evaluated.

The Codex Commission has not established or proposed maximum residue limits (MRLs) for residues of difenzoquat in/on various raw agricultural and processed commodities. Therefore, there are no inquiries with respect to compatibility of U.S. tolerances with Codex MRLs.

Table I. Tolerance Reassessment Summary for Difenzoquat

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment
Tolerances listed under 40 CFR §180.369			
Barley, grain	0.2	0.05	
Barley, straw	20	5.0	
Cattle, fat	0.05	TBD	
Cattle (mbyp)	0.05	TBD	*[Cattle, meat byproducts]*
Cattle, meat	0.05	TBD	
Goats, fat	0.05	TBD	*[Goat, fat]*
Goats (mbyp)	0.05	TBD	*[Goat, meat byproducts]*
Goats, meat	0.05	TBD	*[Goat, meat]*
Hogs, fat	0.05	TBD	*[Hog, fat]*
Hogs (mbyp)	0.05	TBD	*[Goat, meat byproducts]*
Hogs, meat	0.05	TBD	*[Hog, meat]*
Horses, fat	0.05	TBD	*[Horse, fat]*
Horses (mbyp)	0.05	TBD	*[Horse, meat byproducts]*
Horses, meat	0.05	TBD	
Poultry, fat	0.05	0.05	
Poultry (mbyp)	0.05	0.05	*[Poultry, meat byproducts]*
Poultry, meat	0.05	0.05	
Sheep, fat	0.05	TBD	
Sheep (mbyp)	0.05	TBD	*[Sheep, meat byproducts]*
Sheep, meat	0.05	TBD	
Wheat, grain	0.05	0.05	
Wheat, straw	20	5.0	

Tolerances That Need To be Proposed Under 40 CFR §180.369			
Wheat, bran	None	0.25	
Barley, bran	None	0.25	
Wheat, shorts	None	0.25	

Note that technical registrants will be sent a Section 3(c)(2)(B) Data-Call-In (DCI) letter under the Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) in a separate mailing. If you have questions on this document, please contact the Chemical Review Manager, Tawanda Spears, at (703) 308-8050.

Sincerely,

Lois A. Rossi

Lois A. Rossi, Director
Special Review and
Reregistration Division

Enclosures: "Difenzoquat Overview" and "Difenzoquat Summary"

OVERVIEW OF DIFENZOQUAT RISK ASSESSMENT

April 18, 2002

Introduction

This document summarizes EPA's human health risk and drinking water exposure assessments for the methyl sulfate pesticide difenzoquat, (broadly classified as a pyrazole) as presented fully in the documents, "Difenzoquat: HED Human Health Risk Assessment for the Tolerance Reregistration Eligibility Decision (TRED)," dated February 11, 2002, and "EFED Drinking Water Exposure Assessment for the Tolerance Reregistration Eligibility Decision on Difenzoquat," dated October 29, 2001. The purpose of this overview is to assist the reader by identifying the key features and findings of these risk assessments, and to better understand the conclusions reached in the tolerance reassessment. References to relevant sections in the complete documents are provided to allow the reader to find the place in these assessments where a more detailed explanation is provided. This overview was developed in response to comments and requests from the public which indicated that the risk assessments were difficult to understand, that they were too lengthy, and that it was not easy to compare the assessments for different chemicals due to the use of different formats.

The difenzoquat risk assessment and additional supporting documents, are posted on EPA's Internet website (http://www.epa.gov/pesticides/difenzoquat.html) and are available in the Pesticide Docket for public viewing. The Agency's report on the FQPA tolerance reassessment decision for difenzoquat will be announced and made available to the public through a Federal Register Notice. Prior to publication of the Notice, the Agency plans to conduct a closure conference call to describe the risk and tolerance reassessment findings that will be presented in the TRED.

The Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act (FQPA) of 1996, requires EPA to review all the tolerances for registered chemicals in effect on or before the date of the enactment of FQPA. In reviewing 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. The tolerances are considered reassessed once the safety finding has been made or a revocation occurs. A reregistration eligibility decision (RED) for difenzoquat was completed in September, 1994 prior to FQPA enactment; therefore, tolerances needed to be reassessed to reflect the provisions of FQPA.

Risks summarized in this document are those that result only from the use of difenzoquat. The FQPA requires that 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." The reason for consideration of other substances is due to the possibility that 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. The Agency did not perform a cumulative risk assessment as part of this tolerance reassessment of difenzoquat because the Agency has not yet identified any other chemical substances that have a mechanism of toxicity common with that of difenzoquat. If the Agency identifies other substances that share a common mechanism of toxicity with difenzoquat, then a cumulative risk assessment will be conducted that includes difenzoquat.

Use Profile

- **Herbicide:** Registered for use on the following crops/sites: selective control of wild oats in wheat and barley. In addition, there are Special Local Needs [24(c)] registrations for the states of Washington, Oregon, and Idaho to control wild oats in Kentucky bluegrass grown only for seed production.

- **Formulations:** Formulated as a 2 lb cation/gal soluble concentrate (SC/L; EPA Reg. No. 241-266) and a 92.5% water dispersible granule (WDG; EPA Reg. No. 241-354).

- **Methods of Application:** Difenzoquat may be applied by broadcast ground or aerial applications in water spray volumes of 5-20 gal/A and 3-10 gal/A, respectively.

- **Timing:** These products are registered for a single post-emergence application per growing season to barley and wheat at a maximum rate of 1 lb cation/A. Application may be made to: (i) barley when plants are in the 2- to 7-leaf stage; (ii) fall-seeded wheat when plants are in the 4-leaf to tiller stage; and (iii) spring-seeded wheat when plants are in the 5- to 6-leaf stage.

- **Annual Poundage:** Based on data from 1995 through 2000, an annual estimate of difenzoquat total domestic usage averaged 235,000 pounds of active ingredient for over one million acres treated. The largest market in terms of total pounds of active ingredient is allocated to wheat (65%) and barley (35%); use on bluegrass grown for seed is very low. Most of the usage is in Minnesota, Montana, North Dakota, and Washington. Weighted average percentile of crop treated is 2% for both barley and wheat.

- **Registrants:** BASF Corporation

Human Health Risk Assessment

Acute Dietary (Food) Risk

Acute dietary risk is calculated considering what is eaten in one day. Acute dietary exposure that is less than 100% of the acute Population Adjusted Dose (aPAD) does not exceed the Agency's level of concern. The aPAD is the reference dose (RfD) adjusted for the FQPA Safety Factor. The acute RfD is the dose at which an individual could be exposed in a single day with no adverse health effects.

An acute dietary risk assessment was not conducted for difenzoquat because the Agency has established there is no acute hazard (no adverse effects were associated with exposure to a single dose). Therefore, an acute reference dose (aRfD) was not established. The only acute effects noted in the database (suggestive of irritation) were considered to be attributed to the method of administration of the test article (gavage) or did not result from a single dose.

Chronic Dietary (Food) Risk

Chronic dietary risk is calculated by using the average consumption values for food and average residue values on those foods over a lifetime or the duration of exposure assessed (i.e., 1 year for infants, 6 years for children ages 1-6 years and 37 years for females of childbearing age 13-50 years old.). Chronic dietary exposure that is less than 100% of the chronic Population Adjusted Dose (cPAD) does not exceed the Agency's level of concern. The cPAD is the chronic reference dose (cRfD) adjusted for the FQPA Safety Factor. The chronic RfD is the dose at which an individual could be exposed over the course of a lifetime with no adverse health effects.

The chronic dietary analysis for difenzoquat was conducted using a conservative, deterministic (Tier I) analysis which assumes tolerance level residues based on existing and/or reassessed tolerances and 100 % crop treated. The chronic dietary exposure analysis is conducted using the Dietary Exposure Evaluation Model (DEEM™). A three-day average of consumption for each subpopulation is combined with tolerance residues in commodities to determine average exposures in mg/kg/day.

- Chronic dietary (food) risk is below the Agency's level of concern for the general U.S. population and all population subgroups (<1% of the cPAD).

- The toxicity endpoint for the chronic dietary is consistent decreases in body weight and body weight gain in the absence of decreased food consumption based on a combined chronic/oncogenicity toxicity study in rats (NOAEL=25 mg/kg/day). The effects were observed at 125 mg/kg/day (LOAEL).

- The uncertainty factor is 300x; 10x for intraspecies variability and 10x for interspecies extrapolation. An additional 3x was added due to lack of an acceptable multigeneration reproduction toxicity study.

- The FQPA Safety Factor was reduced to 1X for chronic exposures because (i) there is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* exposure; (ii) although the two-generation reproductive toxicity study in the rat is unacceptable, the lack of this study has been considered and reflected in the application of a 3x database uncertainty factor to the cRfD; (iii) a developmental neurotoxicity study is not required; and (iv) the dietary (food and drinking water) assessments will not underestimate the potential exposures for infants and children.

- The chronic RfD (cRfD) is 0.083 mg/kg/day. Because the FQPA Safety Factor was reduced to 1X, the cPAD is equal to the cRfD.

- Based on available data, difenzoquat is not carcinogenic, and has been classified as a Group E "not likely" carcinogen. Likewise, there is no mutagenic or genotoxicity activity, therefore no chronic (cancer) dietary risk assessment was conducted.

- There is no evidence of endocrine disruption upon exposure to difenzoquat.

Drinking Water Dietary Risk

Exposure to pesticides in drinking water can occur through surface and/or ground water contamination. EPA considers both acute (one day) and chronic (lifetime) drinking water risks and uses either modeling or monitoring data, if available, to estimate those risks. To determine the maximum allowable contribution of treated water allowed in the diet, EPA first looks at how much of the overall allowable risk is contributed by food, then calculates a "drinking water level of comparison" (DWLOC) to determine whether modeled or monitoring levels exceed this level.

The Agency uses a DWLOC as a surrogate to capture risk associated with exposure from pesticides in drinking water. The DWLOCs represent the maximum contribution to the human diet (in ppb or µg/L) that may be attributed to residues of a pesticide in drinking water after dietary exposure is considered. Risks from drinking water are assessed by comparing the DWLOCs to the estimated environmental concentrations (EECs) in surface and/or ground water. When the EECs are less than the DWLOCs, the Agency is not concerned with drinking water risks. Drinking water modeling is considered to be an unrefined assessment and provides high-end estimates of exposure. In the absence of reliable monitoring data, a DWLOC is used as a point of comparison against conservative model estimates of pesticide concentrations on water. In this case, no monitoring data is available for difenzoquat, therefore the Agency is relying solely on the modeling estimates for drinking water dietary risks.

- Estimated drinking water concentrations for ground water are based on the Screening Concentration in Ground Water (SCI-GROW) model, which is a conservative, Tier I assessment that provides a high-end estimate.

- Estimated drinking water concentrations for surface water are based on the Index Reservoir Screening Tool (FIRST) using the PRZM/EXAMS model, which is a refined Tier-II assessment that provides a high-end estimate.

- As previously discussed, because adverse effects were not associated with exposure to a single dose, only chronic risk was assessed.

- For chronic risk, potential exposure to difenzoquat from drinking water derived from surface water results in a chronic EEC of 12.3 ppb, which again does not exceed the DWLOC of 800 ppb for children, 1-6 years old, the most highly exposed population subgroup. The Agency is therefore, not concerned with potential chronic exposure to difenzoquat through surface water.

- For chronic risk, potential exposure to difenzoquat from drinking water derived from ground water results in a chronic EEC of 0.006 ppb, which does not exceed the DWLOC of 800 ppb for children, 1-6 years old, the most highly exposed population subgroup. The Agency is therefore, not concerned with potential chronic exposure to difenzoquat through ground water.

Residential Risk

There are currently no registered residential uses of difenzoquat. Therefore, there is no expected exposure of homeowners to difenzoquat and aggregation with dietary sources of exposure is not necessary.

Aggregate Risk

The aggregate risk assessment for difenzoquat examines the combined risk from exposure through food and drinking water. The Agency concludes with reasonable certainty that no harm to any population will result from chronic dietary (food and water) exposure to difenzoquat residues. DWLOCs that correspond to potential chronic consumption of water by the general population and specific population subgroups (i.e., infants, children, and females of childbearing age) were compared to the EECs. The calculated DWLOCs for all populations are greater than surface and ground water chronic EECs. Also, chronic dietary (food only) risk estimates for all population subgroups are less than 1% of the cPAD based on a Tier I assessement. Therefore, residues of difenzoquat in drinking water are not expected to represent a chronic human health risk. Additionally, the chronic aggregate exposure from residues of difenzoquat in food and drinking water are expected to be far less than the Agency's level of concern for chronic aggregate exposure of any U.S. population subgroup.

Occupational Risk

No new data have been received to warrant a reevaluation of the decision in the1994 difenzoquat RED.

Ecological Risk

No new data have been received to warrant a reevaluation of the decision in the 1994 difenzoquat RED.

Summary of Pending Data

Several data deficiencies have been identified for difenzoquat. Studies required by the Agency include: (i) UV/visible absorption (830.7050); and (ii) wheat and barley hay and wheat forage field trial residue studies (860.1500). The deletion of the current forage/hay grazing/cutting restriction will be deferred until tolerances for hay and forage are established following the submission and review of the field trial data listed above.

Difenzoquat Summary

Uses

- Difenzoquat is a herbicide used for selective control of wild oats in wheat and barley.
- There are Special Local Needs registrations for difenzoquat in the states of Washington, Oregon, and Idaho to control wild oats in Kentucky bluegrass grown only for seed production.
- Approximately 235,000 pounds of active ingredient of difenzoquat are used annually for over one million acres treated, according to Agency and registrant estimates.
- Difenzoquat may be applied by broadcast ground or aerial applications in water spray volumes of 5-20 gal/A and 3-10 gal/A, respectively.

Health Effects

- No acute hazard endpoint (no adverse effects were associated with exposure to a single dose) was identified.
- Chronic effects were consistent decreases in body weight and body weight gain in the absence of decreased food consumption.
- The mutagenicity database for difenzoquat indicates that this chemical has no mutagenic or genotoxicity activity and it is not a carcinogen.
- There is no evidence of endocrine disruption upon exposure to difenzoquat.

Risks

- Acute and Chronic Dietary (food and water) Risks from exposure to difenzoquat are not of concern.
- Residential Risk is not of concern because there are no residential uses currently registered for difenzoquat.

- Aggregate (food and water) Risk is below the Agency's level of concern. The chronic aggregate exposure from residues of difenzoquat in food and drinking water are expected to be far less than the Agency's level of concern for aggregate exposure of any U.S. population subgroup.

- Worker /Ecological Risks previously assessed in the difenzoquat RED issued in September 1994.