2

U. S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

DATE: 11/26/2002

MEMORANDUM

SUBJECT: Prothioconazole (JAU 6476); EPA, PMRA, and Bayer Residue Chemistry Meeting. **Comments concerning Proposal for Dietary Burden Calculation (dated: 11/4/2002).**

DP Barcode:	D286914	PRAT Case:	None
Submission No.:	None	Caswell No.:	None
Chemical No.:	Not Available	Class:	Fungicide
Trade Name:	None	EPA Reg No.:	Not Registered
40 CFR:	Not Registered		
MRID No.:	None		

TO: Terri Stowe, PM Team 21
RSB/RD (7505C)

FROM: William D. Wassell, Chemist
RAB3/HED (7509C)

THRU: Stephen C. Dapson, Branch Senior Scientist
RAB3/HED (7509C)
12/03/2002

Introduction:

Members of HED (Clark Swentzel, Stephen Dapson, Amelia Acierto, and William Wassell), RD, PMRA (by teleconference), and representatives of Bayer met on September 10, 2002 to discuss residue chemistry issues associated with the new active ingredient prothioconazole or also known as JAU 6476. Bayer has submitted a Proposal for Dietary Burden Calculation (dated: 11/4/2002) which outlines Bayer's proposal for the ruminant feeding study utilizing JAU 6476. The proposal from Bayer is included as Attachment 1.

Detailed Considerations:

Immediately following the meeting, William Wassell of HED was asked to comment on Bayer's proposal for a livestock feeding study (ruminant) with JAU 6476 by Francis Duah of Bayer. Bayer has already conducted a ruminant feeding study in which the animals were dosed with the major plant metabolite of JAU 6476 (i.e. the desthio metabolite of JAU 6476). Dr. Duah proposed using the highest average field trial (HAFT) residue levels from the field trials to calculate the dietary burden for purposes of determining the dose levels for the ruminant feeding study. Bayer anticipates the residue of concern in plants will be determined to be the parent compound, the desthio metabolite of JAU 6476, the 4-hydroxy metabolites, and the conjugates of each of these three compounds. Further, the analytical method developed by Bayer for use in conjunction with the field trials measures total residues of JAU 6476 plus JAU 6474 conjugates, JAU 6476-4-hydroxy plus its conjugates, and JAU 6476-desthio plus its conjugates as JAU 6476, JAU 6476-4-hydroxy, and JAU 6476-desthio, respectively. The dietary burden was determined as the sum of the HAFT values of residues determined as JAU 6476 and determined as the desthio metabolite, but did not include the 4-hydroxy metabolite.

Based upon information presented at the meeting, Bayer has started to construct a risk assessment based upon toxicological endpoints chosen by Bayer and anticipates that a refined dietary exposure assessment may be needed in order to make a safety finding. The refined dietary exposure would be based on anticipated residues and project market share information.

HED Comments:

In the proposal, Bayer uses the terms anticipated [dietary burden] or maximum theoretical dietary burden (MTDB) interchangeably. These terms are not interchangeable. The MTDB is generally defined as the dietary burden to livestock that results from a diet constructed of feed items containing residue levels at the tolerance level and corrected for dry matter content if necessary. The dose level that is considered to be at the MTDB is used for tolerance setting purposes. A diet constructed of feed items containing residue levels at the HAFT would be used for estimating anticipated residue levels in meat, milk, poultry, and eggs in a refined dietary exposure assessment.

In the example calculation of the anticipated dietary burden provided by Bayer, the HAFT values for residues determined as JAU 6476 and the desthio metabolites were added together, but the calculation did not include the HAFT value for residues determined as the 4-hydroxy metabolite. Bayer should be informed that all residues of concern must be included in the calculation of the dietary burden for livestock.

The current submission makes no mention of dose levels other than that at the dietary burden. It is the understanding of this reviewer that the representatives of Bayer indicated that the feeding study in question would include additional animals dosed at exaggerated rates. The Residue

Chemistry Test Guidelines (OPPTS 860.1480) indicate that two exaggerated dose levels at 3x and 10x the MTDB should be included in livestock feeding studies.

HED concludes the proposal submitted by Bayer for determining the dietary burden to ruminants may result in an underestimate of the maximum theoretical dietary burden. HED urges Bayer to estimate the MTDB for livestock by the method specified in the Residue Chemistry Test Guidelines (OPPTS 860.1480) and use this value to determine the dose levels of the animals, since it is the MTDB dose level that will be used for tolerance setting purposes. If Bayer envisions that a refined dietary exposure assessment may be needed in order to make a safety finding for JAU 6476, then an additional dose level (other than 1x, 3x, and 10x) at the anticipated dietary burden may be included in the study to help facilitate the estimation of anticipated residues in ruminant commodities.

The issues discussed in this memorandum were the subject of a teleconference between EPA, HED (Bill Wassell), RD, and PMRA on 11/22/2002. Monique Thomas of PMRA has submitted PMRA's comments concerning the proposal. PMRA's comments are included as Attachement 2.

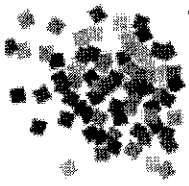
Bayer should be informed that the Agency cannot make formal agreements/decisions concerning data requirements for JAU 6476 until all data are submitted and reviewed. Additionally, if this chemical is submitted as a NAFTA Joint Review Chemical, then any decisions made concerning data requirements will be made in conjunction with input from representatives of Canada and Mexico. Every attempt will be made to harmonize the decisions with Canada and Mexico as this will facilitate sharing of reviews.

Attachments: 1: Correspondence from M.K. Tolliver, Bayer, to Terri Stowe, EPA, dated: 11/4/2002.
2. Comments on JAU 6476, Prothioconazole, Proposal for Dietary Burden Calculation; Monique Thomas, PMRA, Health Canada, dated 11/22/2002.

cc: WDWassell, RAB3 RF, AAcierto (RAB3)

RDI:GFKramer: 11/14/2002; SCDapson: 11/19/2002; PMRA, Heath Canada: 11/22/2002

Attachment 1



Terri Stowe
11/04/2002 03:17 PM

To: Clark Swentzel/DC/USEPA/US@EPA
cc: Richard Keigwin/DC/USEPA/US@EPA, Cynthia Giles-Parker/DC/USEPA/US@EPA, Carl Grable/DC/USEPA/US@EPA, Stephen Dapson/DC/USEPA/US@EPA, Amelia Acierto/DC/USEPA/US@EPA, William Wassell/DC/USEPA/US@EPA
Subject: JAU 6476, Prothioconazole Proposal for Dietary Burden Calculation

Clark,

Please see the e-mail below from Mel Tolliver from Bayer regarding their proposal for dietary burden calculation. Please let me know what you need to put it in the queue for review and about how long it will take to review.

MANY THANKS!

Terri

Terri Stowe
NAFTA Joint Review Coordinator
U. S. Environmental Protection Agency
Office of Pesticide Programs
Registration Division
(703) 305-6117 (voice)
(703) 305-6920 (fax)
stowe.terri@epa.gov

----- Forwarded by Terri Stowe/DC/USEPA/US on 11/04/2002 03:14 PM -----

Mel Tolliver <mel.tolliver@bayercropscience.com>
11/04/2002 11:50 AM

To: Terri Stowe/DC/USEPA/US@EPA, Lisa_Lange@hc-sc.gc.ca
cc:
Subject: JAU 6476, Prothioconazole Proposal for Dietary Burden Calculation

Terri and Lisa,

Attached is an electronic copy of a proposal being sent to you regarding the calculation of the dietary burden and the resulting rates for our livestock feeding study. Due to the slowness of the regular mail and the fact that we need the input from both agencies before we can begin the livestock feeding study in December, I am sending you an electronic copy of our proposal.

If you have any questions, please give me a call.

Mel Tolliver
Bayer CropScience
Phone: 919-549-2631
FAX: 919-549-2545

(See attached file: Proposal for Dietary Burden Calculation.pdf)

Proposal for Dietary Burden Calcula

Bayer CropScience

Document Processing Desk
Office of Pesticide Programs
Registration Division (H7505C)
Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Ave., NW
Washington, D.C. 20460-0001

Attention: Terri Stowe

November 4, 2002

Bayer CropScience
2 T.W. Alexander Drive
Research Triangle Park, NC 27709
Phone: 919 549-2000

Subject: JAU 6476, Prothioconazole
Proposal for Dietary Burden Calculation

Dear Ms. Stowe

On September 10, 2002, Bayer met with the PMRA (via telephone) and EPA at the EPA offices in Crystal City, Arlington, VA to discuss residue chemistry and toxicology issues regarding JAU 6476.

Immediately following this meeting, our Francis Duah discussed the anticipated dietary burden of the total JAU 6476 residue (JAU 6476 plus JAU6476-desthio) in ruminant feed with EPA's Bill Wassell. Mr. Wassell agreed with Francis Duah's suggestion that for the JAU 6476 dairy cattle feeding study, only the highest average field trial JAU 6476 residue from JAU 6476-treated crops should be used to calculate the anticipated or theoretical maximum dietary burden of JAU 6476 residue in livestock feed and the resulting dose rates. Mr. Wassell also suggested that Bayer submit a formal proposal for the calculation of the anticipated dietary burden to the EPA and PMRA for approval. The attached is our formal proposal requesting that for the JAU 6476 dairy cattle feeding study, only the highest average field trial JAU 6476 residue from JAU 6476-treated crops should be used to calculate the anticipated or theoretical maximum dietary burden of JAU 6476 residue in livestock feed and the resulting dose rates.

Since we would like to begin the feeding study early in December, we would appreciate comments from EPA and PMRA by December 1, 2002.

If you have any questions or need additional information, please contact me at (919) 549-2631.

Sincerely,

Melvin K. Tolliver

Melvin K. Tolliver
Product Manager, Fungicide Registrations

Attachment: JAU6476 Dairy Cattle Feeding Study - Calculation of Anticipated or Theoretical Dietary Burden.

cc: Carl Grable (with attachment)
EPA Office of Pesticide Programs

Lisa Lange (with attachment)
Executive Director's Office
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
Ottawa, Ontario K1A 0K9 Canada

JAU6476 Dairy Cattle Feeding Study - Calculation of Anticipated or Theoretical Dietary Burden.

1.0 Introduction

JAU 6476 is under development as a systemic DMI-fungicide for spray and seed treatment which demonstrates very good efficacy against a broad range of diseases in cereals, grapes, fruits, peanuts, rape, vegetables, bananas, rice, and turf. Bayer will seek the registration of this compound on wheat, barley, rice, canola, and peanuts in the US and Canada.

In a May 31, 2001 meeting with the EPA and PMRA to discuss the JAU6476 residue chemistry data package which also included a dairy cattle feeding study with the major plant metabolite (JAU6476-desthio), the Agencies asked Bayer to conduct a dairy cattle feeding study with the parent compound, itself.

Immediately following another meeting held on September 10, 2002 with the EPA and PMRA to discuss the JAU6476 residue chemistry data package, Francis Duah discussed the anticipated dietary burden of the total JAU6476 residue (JAU6476 plus JAU6476-desthio) in ruminant feed with Bill Wassell. Mr. Wassell agreed with Francis Duah's suggestion that for the JAU6476 dairy cattle feeding study, only the highest average field trial JAU6476 residue from JAU6476-treated crops should be used to calculate the anticipated or theoretical maximum dietary burden of JAU6476 residue in livestock feed and the resulting dose rates. Mr. Wassell also suggested that Bayer submit a formal proposal for the calculation of the anticipated dietary burden to the EPA and PMRA for approval.

Therefore, the purpose of this document is to officially request that for the JAU6476 dairy cattle feeding study, only the highest average field trial JAU6476 residue from JAU6476-treated crops should be used to calculate the anticipated or theoretical maximum dietary burden of JAU6476 residue in livestock feed and the resulting dose rates.

2.0 Highest Average Field Trial Residues

Based on the results of the plant metabolism studies, a crop residue analytical method was developed to measure the total JAU6476 residue (JAU6476 plus JAU6476-desthio) in crop matrices. Using this crop residue analytical method, the JAU6476 and JAU6476-desthio residues were measured, and these residues were summed to give the total JAU6476 residue in all target crop matrices from all the magnitude of the residue studies. The highest average field trial residue of JAU6476 and JAU6476-desthio and the total JAU6476 residue from all crop matrices are presented in Table 1.

Table 1. The highest average field trial residue of JAU6476, JAU6476-desthio, and total JAU6476 residue (JAU6476 plus JAU6476-desthio) found in crop matrices from the JAU6476 field residue trial conducted in the various EPA and PMRA crop regions.

Crop	Matrix	Residues (ppm)		
		HAFT JAU6476	HAFT JAU6476-desthio	HAFT Total JAU6476[a]
Barley	Hay	2.79	2.32	3.68
	Straw	0.51	1.02	1.32
	Grain	0.03	0.05	0.07
Canola				
	Seed	0.02	0.02	0.04
Peanut	Hay	0.25	3.62	3.68
	Nutmeat	<0.003 (0.001)	0.005	<0.01 (0.005)
Rice	Straw	0.35	0.72	0.94
	Grain	0.01	0.09	0.10
Wheat	Forage	1.00[b]	1.00	2.00
	Hay	1.06	1.70	2.22
	Straw	0.27	1.31	1.52
	Grain	0.005[c]	0.03	0.03
	AGF[d]	1.04	6.23	6.23

[a] The HAFT total JAU6476 plus JAU6476-desthio residue found in each matrix. These values will be used to set the tolerances for the various matrices. The HAFT residues for the individual analytes (JAU6476 and JAU6476-desthio) did not necessarily always occur in the sample having the HAFT total JAU6476 residue. Example: for barley hay, the HAFT values for JAU6476 (2.79) and total JAU6476 residue (JAU6476 plus JAU6476-desthio; 3.68 ppm) occurred in the same sample from one trial site, but the HAFT residue for JAU6476-desthio (2.32 ppm) occurred in another sample from a different trial site. Therefore, the individual HAFT residue for JAU6476 (2.79 ppm) and JAU6476-desthio (2.32 ppm) do not sum up to the HAFT total JAU6476 residue (3.68 ppm) for barley hay.

[b] All forage samples from the harvest trials were collected at a 1-day PHI. Since Bayer would like to request a 7-day feeding restriction for forage, additional trials have been initiated to collect forage samples at a 7-day PHI. The HAFT JAU6476 residue at a 7-day PHI from the two required decline trials was 0.16 ppm. Therefore, an HAFT residue of 1.00 ppm will be used to estimate the HAFT residue for JAU6476 in wheat forage. The actual HAFT residue from the additional trials will be used to calculate the final dietary burden.

[c] Although this value is less than the LOQ of 0.01 ppm, the measured value of 0.005 ppm and the concentration factor for aspirate grain fractions will be used to estimate the contribution of wheat grain aspirated grain fractions to the theoretical maximum dietary burden of JAU6476 residue.

[d] Aspirated grain fractions. The AGF residues were calculated from the concentration factor found in the aspirated grain fractions (207.7X) and the corresponding HAFT residue value for the analyte(s). Example: the HAFT Residue value for JAU6476 in the wheat AGF = 0. 005 ppm X 207.7 = 1.04 ppm.

3.0 Anticipated or Theoretical Maximum Dietary Burden of JAU6476 Residue in Ruminant Feed.

Bayer has already conducted a dairy cattle feeding study with the major plant metabolite, JAU6476-desthio, and this study will be submitted with the JAU6476 registration package. Since only JAU6476 will be fed in the JAU6476 dairy cattle feeding study, Bayer suggested (and Mr. Bill Wassell concurred) that the most accurate method to measure the transfer of JAU6476 residue from JAU6476-treated crops to milk and meat is to calculate the feeding level based on the actual JAU6476 residue in the treated crop matrices.

The anticipated or theoretical maximum dietary burden of JAU6476 residue in ruminant feed is 2.65 mg JAU6476/kg feed (Table 2).

Table 2. Anticipated or theoretical maximum dietary burden of JAU6476 residue in ruminant feed.

		% in Feed				Dietary Burden (ppm)	
Feed item	Percent Dry Matter	Beef Cattle	Dairy Cattle	Max. Res.[1] Ppm	Corrected Residues[2]	Beef Cattle	Dairy Cattle
Wheat Forage	25	25	60	1.00	4.000	1.00	2.40
Wheat Hay	88	10	0	1.06	1.205	0.12	0.00
Barley Hay	88	25	0	2.79	3.170	0.79	0.00
Aspirated Grain Fractions	85	20	20	1.04	1.224	0.24	0.24
Barley Grain	88	20	20	0.03	0.034	0.01	0.01
	Total	100	100		Total	2.16	2.65

[1] Maximum residue level of JAU6476 found in the matrices from the JAU6476 field residue trials conducted in the EPA and PMRA crop regions. See Table 1.
[2] Residues corrected to 100% dry matter.

4.0 Conclusion

Bayer is proposing to calculate the anticipated or theoretical maximum dietary burden of JAU6476 residue in ruminant feed by using the highest average field trial JAU6476 residue from JAU6476-treated crops. This maximum theoretical dietary burden will be used to calculate the dose rates for the JAU6476 dairy cattle feeding study. Bayer seeks the Agencies' (EPA and PMRA) concurrence with this proposal for theoretical maximum dietary burden calculation.

Attachment 2:

Health Canada / Santé Canada

Pest Management Regulatory Agency / Agence de réglementation de la lutte antiparasitaire

2250 promenade Riverside Drive
Ottawa, Ontario
K1A 0K9

Telephone/Téléphone:
Fax/Télécopieur:

PMRA ARLA

Your file *Votre référence*

Our file *Notre référence*

November 22, 2002

Memorandum To/Note adressée à: Ariff Ally, Ph.D.
Section Head,
FREAS, HED

From/De: Monique Thomas
Senior Evaluation Officer,
FREAS, HED

ACTION REQUESTED: Comments on JAU 6476, Prothioconazole, Proposal for Dietary Burden Calculation

---

Background

On September 10, 2002, a presubmission consultation meeting was held between Bayer USA and EPA (via teleconference), PMRA and Bayer Canada to discuss residue chemistry (i.e., plant metabolism, animal metabolism and definition of the ROC for animals and the feeding study) and toxicology issues (toxicology profile and proposed end points) pertaining to a new fungicide, prothioconazole (JAU 6476).

Following the meeting, Bayer submitted a proposal (see attachment) to both regulatory agencies requesting guidance on the calculation of the dietary burden and determination of the dosage rates for the ruminant feeding study. The proposal recommends using the highest average field trial (HAFT) residue levels for the feed items collected from the field trials to calculate the dietary burden which is used as the basis to determine the dose levels for the ruminant feeding study. Bayer expects the residue of concern in plants to be defined as the parent compound, the desthio metabolite of JAU 6476, the 4-hydroxy metabolites, and the conjugates of each of these three analytes. Accordingly, the analytical method developed to quantitate residues in treated samples collected from the supervised residue trials measures total residues of JAU 6476 plus JAU 6474 conjugates, JAU 6476-4-hydroxy plus its conjugates, and JAU 6476-desthio plus its conjugates as JAU 6476, JAU 6476-4-hydroxy, and JAU 6476-desthio, respectively. However, in the proposal, only the HAFT values for the parent JAU6476 were used in determining the dietary burden. A ruminant feeding study has already been carried out whereby animals were dosed with the predominant plant metabolite of JAU 6476 (i.e., the desthio metabolite).

Canada

PMRA's Position

According to the Residue Chemistry Guidelines, Dir98-02, the maximum theoretical dietary burden is calculated using the maximum expected residue in the feed item, the proportion in the diet of the feed item bearing the residue and the percentage dry matter in the feed. Should the parent comprise only a small proportion of the ROC, the animals in the feeding study should be administered a mixture of parent and plant metabolites. Furthermore, the feeding study should include the level of intake expected (1X) and two exaggerated levels (3X) and (10X).

In the summaries of the peanut and wheat metabolism studies, provided as part of the documentation in preparation for the presubmission consultation, the parent appears to be readily metabolized. As such, Bayer anticipates that the definition of the ROC for plant matrices should include the parent, the desthio metabolite, the 4-hydroxy metabolite and the conjugates of each of these analytes. These findings contrast the residue results reported in Table 1 of the proposal for dietary burden calculation, which indicates similar residue levels of the parent JAU 6476 and the desthio metabolite in feed items. Furthermore, the calculation of the anticipated dietary burden included highest average field trial (HAFT) residues of the parent, JAU6476, only and did not include the total residues (i.e., ROC for plant matrices) for each feed item. FREAS also noticed that feed items associated with pulses (i.e., vines, hay, silage) were not included in Table 1, nor were they considered in the calculation of the dietary burden, potentially underestimating the maximum theoretical dietary burden (MTDB). Additionally, Bayer did not provide any information pertaining to dose levels other than that at the dietary burden.

Therefore, FREAS encourages Bayer to conduct the feeding study as per the guidance provided in Dir98-02. This will ensure that the maximum residues of the ROC in feed items are used in determining the MTDB and that the feeding study is conducted at exaggerated dose levels (3X and 10X of the MTDB).

In the absence of a full review of the data package, FREAS is not in a position to make decisions or formal agreements concerning data requirements. Furthermore, should the request for registration of this chemical be submitted under the NAFTA Joint Review Program, any data requirements will be jointly decided upon with the US EPA and Mexico.

_____ **Date:**_____
Monique Thomas,
Evaluation Officer,
Food Residue Exposure Assessment Section, HED

_____ **Date:**_____
Mavis Cheng
Evaluation Officer,
Food Residue Exposure Assessment Section, HED

13544

057614

Chemical:

PC Code:
HED File Code 11000 Chemistry Reviews
Memo Date: 11/26/2002
File ID: DPD286914
Accession Number: 412-03-0019

HED Records Reference Center
01/17/2003