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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

DATE: 7/11/2001

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

MEMORANDUM

SUBJECT: JAU 6476; EPA, PMRA, and Bayer Residue Chemistry Meeting. **Comments concerning Memorandum of Understanding (dated: 6/8/2001).**

DP Barcode:	D276098	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)

Introduction:

Members of HED (Stephen Dapson, Amelia Acierto, and William Wassell), RD, PMRA (by teleconference), and representatives of Bayer met on May 30, 2001 to discuss residue chemistry issues associated with the new active ingredient JAU 6476. Bayer has submitted a Memorandum of Understanding (MOU; dated: 6/8/2001) which outlines Bayer's understanding of what took place during the meeting. The MOU is included as Attachment 1.

Detailed Considerations:

Bayer stated that the purpose of the meeting was to seek agreements and/or guidance on the following issues concerning JAU 6476: (1) crop residue definition; (2) what to feed in the livestock feeding study; (3) animal residue definition; (4) waiver of the poultry feeding study; and (5) the

Agency's recommendations on conducting the second label metabolism study with triazole-labeled SXX 0665 or triazolinthione-labeled JAU 6476.

Bayer should be informed that the Agency cannot make formal agreements/decisions concerning JAU 6476 until all data are submitted and reviewed. Bayer should also be made aware that they have asked the Agency to make recommendations concerning the metabolism JAU 6476 with less than half of the data that is normally required to make these decisions. These decisions are normally made after review of toxicology and residue chemistry data. No toxicology data were summarized at the meeting and plant and livestock metabolism studies are available with only the chlorophenyl ring labeled. Additional metabolism studies with the triazolinthione ring labeled will be required in order to make final decisions concerning the residue of concern in plants and livestock. These points were emphasized at the meeting by the EPA representatives, but were not mentioned at all in the MOU.

Concerning Item 1:

Bayer should be made aware that since this chemical is being submitted as a NAFTA Joint Review Chemical, **any decisions made concerning the residue of concern will be made in conjunction with input from PMRA. Every attempt will be made to harmonize the residue of concern decisions with PMRA as this will facilitate sharing of reviews.**

Based upon PMRA's comments at the meeting, they are not be in favor of the tolerance expression including only SXX 0665 and not including the parent compound. Members of PMRA indicated that they are required (via regulation) to include the parent compound in the tolerance expression.

Based upon PMRA's comments, HED suggests that residue data for the parent compound may be required and that Bayer is encouraged to generate crop residue data using a method that measures residues of both JAU 6476 and SXX 0665 in plant commodities.

Concerning Items 2 and 3:

It should be noted that both EPA and PMRA stated that is premature to make this decision concerning the residues of concern in livestock since metabolism studies with the triazolinthione-labeled compound are not yet available.

Based upon the data that was presented, EPA stated that it seems reasonable to feed SXX 0665 in the cattle feeding study, but that a final decision concerning this cannot be made until the triazolinthione ring labeled studies are available. PMRA stated that JAU 6476 should be feed. Since this chemical is going to be submitted as a joint review chemical, PMRA's concerns will be considered when making any decisions concerning this new active ingredient.

Concerning Item 4:

Based upon the available data, EPA agrees that a poultry feeding study will not be required, but this decision could change once metabolism data with the triazolinthione-labeled compound are available.

Concerning Item 5:

EPA stated that the additional metabolism studies should be conducted with triazolinthione-labeled JAU 6476 and not with triazole-labeled with SXX 0665.

Attachment 1: Correspondence from M.K. Tolliver, Bayer to Terri Stowe, EPA, dated: 6/8/2001.

cc: WDWassell, RAB3 RF, New Chemical Correspondence File

RDI:RAB3 Res ChemTeam: 5/1/01; S.C. Dapson: xx/xx/01.

Attachment 1

Bayer

Agriculture Division

Bayer Corporation
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P.O. Box 4913
Kansas City, MO 64120-0013
Phone: 816 242-2000

June 8, 2001

Document Processing Desk
Office of Pesticide Programs (H7504C)
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202

Attention: Terri Stowe

Subject: JAU 6476
EPA and PMRA Residue Chemistry Meeting

Dear Ms. Stowe:

I want to again thank both EPA and PMRA for allowing Bayer to meet with the agencies on May 30, 2001 to present our residue chemistry proposals for our Negotiated Joint Review candidate, JAU 6476. As requested at the conclusion of the meeting, enclosed is Bayer's understanding of what took place.

If you have any questions or need additional information, please contact me at (816) 242-2150 or by e-mail at mel.tolliver.b@bayer.com.

Sincerely,
Bayer Corporation
Agriculture Division

Melvin K. Tolliver

Melvin K. Tolliver
Product Manager, Fungicide Registrations
Research and Development

MKT:gb

Enclosure: JAU 6476 Residue Chemistry Meeting with EPA and PMRA

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

Lisa Lange (with enclosure)
Pest Management Regulatory Agency
Sir Charles Tupper Bldg.
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Ottawa, Ontario, Canada K1A 0K9

June 8, 2001

JAU 6476 Residue Chemistry Meeting with EPA and PMRA

On May 30, 2001, Bayer Corporation met with the PMRA (via telephone) and EPA at the EPA offices in Crystal City, Arlington, VA to discuss residue chemistry issues regarding JAU 6476. Those present from the EPA included Carl Grable, Rick Keigwin, Cynthia Giles-Parker, Mary Waller, and Terri Stowe of the Registration Division and Bill Wassell, Amelia Acierto, and Stephen Dapson of the Health Effects Division. The PMRA participants by telephone were Stephane Lavigne of the Submission Coordination and Documentation Division, Ariff Ally and Louise Croteau of the Health Evaluation Division, and Lisa Lange (Joint Review Coordinator). Bayer personnel participating in the meeting included Otto Klein, John Murphy, Francis Duah, Ghona Sangha, Clive Halder, Tammy Sabbert, Norma Pangilinan (via telephone at PMRA), and Melvin Tolliver.

This was a follow-up to presubmission meetings Bayer had with the EPA on November 8, 2000 and June 15, 1999. Since Bayer decided to submit JAU 6476 as a negotiated joint review candidate, a meeting with both Agencies was requested.

Bayer began by stating that the purpose of the meeting was to seek agreement and/or guidance on the following issues for JAU 6476: (1) crop residue definition, (2) what to feed in the animal feeding study, (3) animal residue definition, (4) waiver of the poultry feeding study, and (5) the agencies' recommendations on conducting the second label metabolism studies with triazole-labeled SXX 0665 or triazolinthione-labeled JAU 6476. The agencies were informed that Bayer would be applying for registration of JAU 6476 on wheat, barley, canola, and turf in Canada and the U.S. and on peanuts and rice in the U.S.

Next, Dr. Klein presented Bayer's JAU 6476 wheat and peanut metabolism data, results from JAU 6476 cereal and peanut residue trials, and JAU 6476 and SXX 0665 storage stability data. The following conclusions were presented to the EPA as a result of these data:

1. SXX 0665 is the main plant metabolite. It occurs at ca. 14% of the given dose in rat feces.
2. The residue definition in wheat should be the desthio-derivative of JAU 6476, i.e. SXX 0665.
3. To include the unchanged parent compound in the residue definition is rendered unnecessary since its absolute amount as well as its percentage contribution in all wheat matrices and peanut hay is rather small.
4. Investigations have shown that it is difficult to analyse both JAU 6476 and SXX 0665 since the latter can also easily be formed as an artefact by nonenzymic conversion of JAU 6476. Presently available data from the storage stability study indicate a degradation of JAU 6476 under routine storage conditions.
5. Since only SXX 0665 can be analysed by gas chromatography, it can be easily incorporated in existing multiresidue methods.
6. That a possible misuse of JAU 6476 can be traced by analyzing SXX 0665, since high residues of SXX 0665 are found already on day 0.
7. From this, Bayer proposed that the parent compound not be included in the residue definition.

EPA and PMRA had the following comments.

1. EPA expressed concerns regarding the significant residue amounts of JAU 6476 at day 0. Bayer indicated that storage stability of JAU 6476 and SXX 0665 should not be a problem since samples were analyzed immediately.
2. Based on data presented on cereals, EPA inquired about our proposed PHI. In discussions that followed, Bayer agreed that we would propose a 7 to 14-day feeding restriction.
3. EPA agreed with our proposal to use SXX 0665 as the crop residue definition as long as we include the 7 to 14-day feeding restriction. However this may not be true for risk assessments where other metabolites may need to be included. EPA stated that they could not make an official decision until they could review our full data package.
4. PMRA did not agree with EPA on using SXX 0665 as the crop residue definition. PMRA's policy requires that the parent be included for enforcement purposes and that not using the parent would set a new precedent. Their regulations require a method able to detect the parent compound at day 0. PMRA also expressed concern that they would not be able to trace the misuse of JAU 6476 if method is based on metabolite only. PMRA stated that they have not had the opportunity to review the JAU 6476 toxicology data and could not establish ROC (residue of concern) based on PHI alone. They do not know if SXX 0665 is the only toxicologically significant metabolite without evaluating the full toxicology profiles of JAU 6476 and SXX 0665. Dr. Sangha indicated that Bayer would schedule another meeting with EPA and PMRA to discuss the proposed toxicology package for JAU 6476.
5. In response to Dr. Halder's question regarding if more than one method would be acceptable, PMRA indicated that more than one method would be acceptable as long as the enforcement method included the parent and metabolites. [PMRA, would you please clarify]
6. The EPA expressed a need for metabolism studies labeled in the triazole ring to determine the necessity of adding metabolites of concern to the residue definition.

Dr. Klein then presented data from Bayer's goat and rat metabolism studies. Based on these data, Bayer requested EPA and PMRA's agreement on the following proposals:

1. That only SXX 0665 (the major plant metabolite) be fed in the dairy cattle feeding study to support the registration of JAU 6476
2. If the Agencies agree that only SXX 0665 is to be fed in the dairy cattle feeding study, the residues of di-OH-diene SXX 0665, hydroxy SXX 0665, SXX 0665, and their corresponding glucuronides (converted to and measured as 3- and 4-hydroxy SXX 0665 and SXX 0665) be considered the residues of concern for animal matrices
3. That a conventional poultry feeding study should not be required for the registration of JAU 6476 for use on cereals, canola, and peanut.

EPA and PMRA had the following comments.

1. PMRA suggested that there are other methods to cleave glucoronides and achieve better recovery. Dr. Klein stated that Bayer had tried enzyme treatment but this is less practical than acid treatment and did not yield much more cleavage of the glucuronides.
2. EPA stated that the poultry feeding study was not needed at this time.
3. PMRA stated that JAU 6476 should be fed in the cattle feeding study.

4. Dr. Murphy asked what would the agencies be looking for if we were designing a feeding study today. EPA responded that it appeared reasonable to feed SXX 0665 only. However, Bayer would need to take into account PMRA's concerns of establishing the parent tolerance. PMRA added that on face value they could agree with EPA, however, Canadian regulations required feeding of the parent compound. They also stated that it was premature to make a determination at this time. The EPA also indicated that they might have to set different end points for JAU 6476 and SXX 0665 following their review of the entire registration package, and having only an SXX 0665 feeding study could cause a problem. In this case, a dairy cattle feeding study with JAU 6476 would be required.
5. EPA stated that they would be interested in seeing the different residue analytical methods attempted by Bayer to analyze for the parent and problems encountered. Bayer may need to establish higher risk factor for metabolites that cannot be recovered.

Bayer then asked the Agencies' response to the following question:

Bayer is planning to conduct livestock metabolism studies with the triazole-labeled compound. Based on the fact that Bayer is proposing to conduct the required cattle feeding study with only SXX 0665, do the Agencies recommend conducting the second label metabolism studies with triazole-labeled SXX 0665 or triazolinthione-labeled JAU 6476 (parent compound)?

1. EPA and PMRA both agreed that Bayer should conduct additional metabolism studies with triazole-labeled JAU 6476. Dr. Murphy asked if EPA would require triazole-labeled SXX 0665 studies at a later time. EPA responded that only the triazolinthione-labeled parent study would be required.
2. EPA stated they would also require triazolinthione-labeled JAU 6476 rat, livestock (goat and poultry), peanut, and wheat metabolism studies.

Dr. Halder asked what other procedures will be needed for joint review. EPA responded that a letter of understanding (meeting minutes) needed to be submitted to both agencies along with a statement requesting that JAU 6476 be considered as a candidate for a negotiated joint review. In addition, EPA also stated that they would also be interested in receiving E.U. monographs.

At the conclusion of the meeting, EPA asked whether Bayer still needed a response from EPA's Metabolism Assessment Review Committee (MARC) on our March 21, 2001 submission. Since EPA's Bill Wassell stated that the answers received from the MARC would be the same, Bayer agreed that a response from the MARC would not be necessary.

In a follow-up question submitted by e-mail on June 1, 2001 to Ariff Ally of PMRA and Bill Wassell of EPA, Bayer asked if the agencies would require a confined rotational crop study labeled in the triazolinthione ring. Both agencies stated that a confined rotational crop study with triazolinthione ring-labeled JAU 6476 will be required.