 S.F.

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

APR 6 1995

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: PP#4G4347. Temporary Tolerance Petition and Experimental Use Permit for Use of the Biochemical Plant Growth Regulator Aminoethoxyvinylglycine Hydrochloride (AVG) on Apples; 000275-EUP-IN. Evaluation of the Submitted Data Package.
MRID# 42722-01, -02, 427047-01, 432069-03.
DP Barcodes# D210538.
CBTS# 14884.

From: G. Jeffrey Herndon, Chemist
Tolerance Petition Section II
Chemistry Branch I - Tolerance Support
Health Effects Division (7509C)

G. Jeffrey Herndon

Through: Elizabeth T. Haeberer, Section Head
Tolerance Petition Section II
Chemistry Branch I - Tolerance Support
Health Effects Division (7509C)

Elizabeth T. Haeberer 4/6/95

To: Cynthia Giles-Parker/James Stone, PM# 22
Fungicide-Herbicide Branch
Registration Division (7505C)

and

Jane Smith, Acting Head
Registration Section
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

The registrant, Abbott Laboratories, is requesting an exemption from the requirements of a temporary tolerance for the residues of the biochemical ABG-3097 (L-AVG Technical, or [S]-trans-2-amino-4-(2-aminoethoxy)-3-butenoic acid hydrochloride) in/on apples (fresh market only). Associated with this temporary tolerance exemption petition, Abbott has requested an experimental use permit for the use of ABG-3168 (the 15% wettable powder end-use product) on apple trees in 13 states using 270 pounds of active ingredient over 2450 acres.

Aminoethoxyvinylglycine (AVG) received classification as a biochemical on 5/27/92 (see memo of R. Sjoblad). This classification was based on its proposed use pattern (as a regulator of the growth/maturation/ripening of the target plants) and its proposed low use rate (≤ 50g.ai./A./application), and to a lesser extent on its natural occurrence (although not necessarily in/on plants).

Abbott Laboratories intends to manufacture the L-AVG by utilizing Streptomyces sp. X-11085, which produces L-AVG only (no D-AVG is produced) in "moderate amounts" as a second metabolite when it is cultured in an appropriate medium. Abbott intends to use L-AVG as a plant growth regulator. L-AVG apparently inhibits ethylene production in plants by interfering with the plant enzyme aminocyclopropanecarboxylate (ACC) synthase. Abbott intends to register AVG on apples to act as a stop-drop agent when applied 4 weeks prior to harvest.

CBTS has provided previous guidance to Abbott concerning AVG; see memos of G.J. Herndon dated 12/9/92 (biochemical data requirements), 12/10/92 (position of label for conducting metabolism studies), 5/5/94 (follow up to 12/10/92 metabolism guidance), 10/28/94 (initial temporary tolerance submission), and memos of understanding from G.J. Herndon from meetings that took place on 3/2/93 (position of the label for conducting metabolism studies), and 7/19/94 (questions concerning how to conduct the metabolism studies on apples and goats).

TOX in their memo of 3/7/95 (R. Gardner), made the following conclusion:

> " There are adequate Toxicology data to support the request for an exemption from temporary tolerance for the use of AVG on apples assuming no residues are found (levels are below the limit of detection of 0.03 ppm)."

Therefore, CBTS is being asked to determine if, based on the proposed use pattern, detectable residues are likely to be present.

Abbott has provided product chemistry data, a Section B (proposed label), and Section F (asking for a exemption from the requirement of a temporary tolerance). An analytical method and magnitude of the residue studies (analyzed for parent compound only) were provided in the previous submission (see memo of G.J. Herndon dated 10/28/94).

Conclusions

CBTS does not routinely review residue data (magnitude of the residue) in the absence of a plant metabolism study outlining the nature of the residue. Abbott has initiated apple and goat metabolism studies, but they have not been completed. Normally with pesticides that have been classified as biochemicals, the biochemical classification is tied to a use pattern (in this case as a regulator of the growth/maturation/ripening of the target plants at rates ≤ 50g.ai./A./application) and not to a residue value that results from that use pattern and rate, provided that the results of the TOX Tier 1 data do not trigger additional studies.

In this case, due to its biochemical classification, low toxicity, and limited use through this EUP request, CBTS will provide a maximum expected residue value to be used by Toxicology Branch in determining the acceptability of the temporary tolerance exemption request for L-AVG. Based on the residue data provided, CBTS does not expect residues of L-AVG (parent only) to exceed 0.075 ppm (the limit of quantitation) as a result of the proposed use. If, for a future Section 3 request, CBTS is asked to provide a maximum expected residue level, Abbott will need to provide adequate data outlining the nature of the L-AVG in apples. In addition, to satisfy the product chemistry requirements for a Section 3 registration, Abbott will need to provide data on storage stability (63-17).

Recommendation

Provided a residue level of 0.075 ppm is still acceptable to TOX, CBTS can recommend in favor of the proposed EUP/exemption from the requirements of a temporary tolerance.

For a Section 3 registration, a decision will need to be made whether a permanent tolerance or an exemption from a tolerance is most appropriate.

Detailed Considerations

Product Chemistry

The review of the product chemistry data submitted with this petition is included as Attachments I and II (confidential appendix containing CBI). The submitted product chemistry data are sufficient to fulfill the requirements of this EUP/temporary tolerance exemption request. **For a future Section 3 request, Abbott will need to provide data on storage stability (63-17).**

Proposed Use

The end-use product, ABG-3168, is a water soluble powder formulation containing 15% active ingredient, A-80009, or [S]-trans-2-amino-4-(2-aminoethoxy)-3-butenoic acid hydrochloride. For use as a stop-drop agent for apples, ABG-3168 should be applied 4 weeks prior to anticipated harvest and applied at 0.74 lb (50 g.ai.) per acre in sufficient water to ensure adequate coverage.

Nature of the Residue

Metabolism in Plants

Abbott has not submitted any data addressing the nature of the residue in apples (or any other plants). CBTS does not routinely review residue data (magnitude of the residue) in the absence of a plant metabolism study outlining the nature of the residue. Abbott has initiated apple and goat metabolism studies, but they have not been completed. Normally with pesticides that have been classified as biochemicals, the biochemical classification is tied to a use pattern (in this case as a regulator of the growth/maturation/ripening of the target plants at rates ≤ 50g.ai./A./application) and not to a residue value that results from that use pattern and rate, provided that the results of the TOX Tier 1 data do not trigger additional studies.

In this case, due to its biochemical classification, low toxicity, and limited use through this EUP request, CBTS will provide a maximum expected residue value to be used by Toxicology Branch in determining the acceptability of the temporary tolerance exemption request for L-AVG. If, for a future Section 3 request, CBTS is asked to provide a maximum expected residue level, Abbott will need to provide adequate data outlining the nature of the L-AVG in apples.

Analytical Method

The petitioner has submitted the following method for the analysis of A-80009 ([S]-trans-2-amino-4-(2-aminoethoxy)-3-butenoic acid hydrochloride) in apples.

> "HPLC Method for the Analysis of A-80009 in Apple with Pre-Column Derivatization and Fluorescence Detection", ADC Report 1354-A-1, (pgs. 423-428 of MRID# 432069-03, vol. 2).

Apple samples are homogenized with 0.02M KH_2PO_4 buffer and filtered, first through cheesecloth, then through filter paper. The resulting filtrate is passed through a SCX Mega Bond SPE column. The compound is eluted from the column using 2M NaCl. The compound is analyzed on an HPLC system using a Regis Little Champ HPLC column, a mobile phase of 0.1M sodium acetate/methanol solution,

pre-column o-phthaldialdehyde derivatization, and fluorescence detection. Abbott estimates the limit of detection to be 0.03 ppm. Based on adequate recoveries at the lowest fortification level attempted, the limit of quantitation is estimated to be 0.075 ppm on apples (RAC).

Recoveries at fortifications ranging from 0.075 to 0.80 ppm (103 values) ranged from 72 -122% (ave. of 102%)

Residue Data

Storage Stability

The field residue samples were stored up to 60 days from harvest to extraction. No storage stability data were provided with this petition. Although our guidelines specify that storage stability data are required to support field residue samples that are stored longer than 30 days, due to its biochemical classification, low toxicity, limited use through this EUP request, and relatively short storage interval, CBTS will not require storage stability data for L-AVG **for this proposed EUP/temporary tolerance exemption request.**

Magnitude of the Residue

"Magnitude of the Parent Residue of A-80009 for Apple Field Trials and Processed Commodities", K.C. Chapin, 3/28/94, Abbott Laboratories, (MRID# 432069-01, 2 vols.).

Eight (8) field trials were conducted on apples in 6 states in 1993. The trials were conducted using ground equipment (airblast) and spray volumes of 150 gallons per acre.
For each field trial site, the following spraying/sampling scheme was used:

residue samples (all at 28 day PHIs)
controls, 50 g.ai./A. (1X), and 150 g.ai./A. (3X)
residue decline samples (0, 3, 7, 14, 21, 28, 35, and 42 day PHIs)
controls, 50 g.ai./A. (1X), and 150 g.ai./A. (3X)

In addition, for 2 of the sites (1-ACD-93 and 1-RBA-93) an additional 500 g.ai./A. (10X) rate was used and the resulting fruit were processed into apple juice, wet apple pomace, and dry apple pomace. In all cases, only 1 application of a ABG-3168 WSP formulation (15% active ingredient, A-80009) was made. Field residue samples were analyzed at Abbott Laboratories.

Since this proposed EUP use is for fresh market use only, only data from the 1X rate (50 g.ai./A.) and proposed 28 day PHI (except where noted) are shown in Table 1 below. The "NQ" values represent approximations of residue levels above the limit of detection, but

below the limit of quantitation.

Table 1

Maximum Residues of L-AVG in/on Apples Based on the Proposed Rate and PHI

trial	site	variety	rate (g.ai/A.)	PHI (days)	residues of L-AVG (ppm)
1-AGS-93	Conklin, MI	McIntosh	50 (1X)	28	ND
					ND
					ND
					ND
2-AGS-93	Conklin, MI	Golden Delicious	50 (1X)	28	ND
					NQ (0.040)
					ND
				35	NQ (0.040)
1-ACD-93	North Rose, NY	McIntosh	50 (1X)	28	ND
					ND
					ND
					ND
2-ACD-93	Alton, NY	Golden Delicious	50 (1X)	28	ND
					ND
					ND
					ND
1-HRF-93	Camino, CA	Red Delicious	50 (1X)	28	ND
					ND
					NQ (0.036)
					ND
1-FSA-93	Cana, VA	Red Delicious	50 (1X)	28	ND
					ND
					ND
					ND
1-RBA-93	Wapato, WA	Red Delicious	50 (1X)	28	ND
					ND
					ND
					ND
1-CAC-93	The Dalles, OR	Golden Delicious	50 (1X)	28	ND
					ND
					ND
					NQ (0.031) (0.043 at 35 day PHI)
1-CMS-93	Hereford, PA	Red Delicious	50 (1X)	28	ND
					ND
					ND
					ND

Comments

Based on the residue data provided in Table 1, CBTS cannot support TOX's use of the 0.03 ppm limit of detection (LOD) in a risk assessment for L-AVG on apples. Because of several residue values below the limit of quantitation (LOQ), but above the LOD, CBTS recommends that a value of 0.075 ppm (the limit of quantitation) of L-AVG on apples be used for any dietary risk assessment regarding this EUP/exemption from the requirements of a temporary tolerance request.

Attachment I - Product Chemistry Review of L-AVG

Attachment II - CONFIDENTIAL APPENDIX portion of the Product Chemistry Review of L-AVG

cc (without Attachments): circu., R. Gardner (TOX), E. Haeberer (section head)

cc (with Attachments): RF, SF, G.J. Herndon.

RDI: Section Head: E. Haeberer: 4/5/95,
Branch Senior Scientist: R.A. Loranger: 4/5/95,
Acting Branch Chief: E. Zager: 4/6/95.

H7509C: CBTS: G.J. Herndon: 305-6362: CM#2, Rm. 804C: 4/4/95.

FIFRA

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12356)

Some information in the attached material may be entitled to treatment as trade secret or proprietary data under section 7(d) and section 10 the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), as amended.

Any person handling or using the attached information in any way is responsible for preventing unauthorized disclosure while in his/her possession. Section 12(a)(2)(D) makes it unlawful for any employee to use for his/her own advantage or to reveal confidential information (except to persons needing the information for the performance of official duties). A penalty of up to $10,000 fine and up 3 years imprisonment may result from conviction of a violation of section 12(a)(2)(D).

Section 10(f) makes it a crime for any employee to disclose confidential information except as authorized by sections 7 and 10 of FIFRA. A penalty of up to $10,000 fine and up to one year in jail may result from conviction of a violation of section 10(f).

The attached information is not to be published, reproduced, publicly discussed, included in response to an FOI request or otherwise released without the explicit written authorization of the appropriate division or his designee.

REVIEW OF PRODUCT CHEMISTRY (SUBDIVISION D), GLN'S 61 TO 63

Chemical Name (IUPAC, ANSI, etc.)	Aminoethoxyvinylglycine hydrochloride or [S]-trans-2-amino-4-(2-aminoethoxy)-3-butenoic acid hydrochloride	
Chemical Number (CAS; PC Code)	129104	
Registration No.	275-EUP-IN	
Test Substance		
Type of Product (T, FI, MP, EP)	MP/TGAI	
CB No.	14884	
DP Barcode	D210538	
Reviewer	G.J. Herndon	
Approvals		
Section/Team	E. Haeberer	E. Haeberer
Branch Senior Scientist	R. Loranger	R. Loranger
Branch Chief	E. Zager	E. Zager

Table 1: Manufacturing and Impurity Data for (NAME), (REGISTRATION NUMBER).

GLN	MRID	Status[1]	Deficiency
61-1: Product Identity & Disclosure of Ingredients	426722-01C	A	
61-2: Starting Materials & Manufacturing Process	426722-01C	A	
61-3: Discussion of Impurities	426722-01C	A	
62-1: Preliminary Analysis	426722-01C 426722-02C	A	
62-2: Certification of Limits	426722-01C 426722-02C	A	
62-3: Analytical Methods	426722-02C	A	

[1] A = Acceptable. N = Unacceptable (see Deficiency).

Table 2: Physical and Chemical Properties for (NAME), (REGISTRATION NUMBER)			
GLN	MRID	Status[1]	Result[2] or Deficiency
63-2: Color	427047-01	A	beige
63-3: Physical State	427047-01	A	powder
63-4: Odor	427047-01	A	amine-like
63-5: Melting Point	427047-01	A	180°C
63-6: Boiling Point		N/A	
63-7: Density, Bulk Density, or Specific Gravity	427047-01	A	0.42 g/mL
63-8: Solubility	427047-01	A	42 g/100 mL water
63-9: Vapor Pressure		N/A	
63-10: Dissociation Constant		N/A	
63-11: Octanol/Water Partition Coefficient		N/A	
63-12: pH	427047-01	A	6.9 (0.1% solution)
63-13: Stability	427047-01	A	stable in various salts, light, dark, 60°C (7 day periods)
63-14: Oxidizing or Reducing Action		N/A	
63-15: Flammability		N/A	
63-16: Explodability		N/A	
63-17: Storage Stability		N	no data were supplied; data required for Section 3 registration
63-18: Viscosity		N/A	
63-19: Miscibility		N/A	
63-20: Corrosion Characteristics		N/A	

[1] A = Acceptable; N = Unacceptable (see Deficiency); N/A = Not applicable.
[2] For example, "brown" for 63-1; "155° C" for 63-4.

Attachment: Confidential Appendix A.

Page 11 is not included in this copy.

Pages _____ through _____ are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

__X__ Identity of product impurities.

__X__ Description of the product manufacturing process.

__X__ Description of quality control procedures.

__X__ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

__X__ The product confidential statement of formula.

_____ Information about a pending registration action.

__X__ FIFRA registration data.

__X__ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

__X__ Internal deliberative information.

__X__ Privileged attorney-client communication.

__X__ Claimed Confidential by submitter upon submission to the Agency.