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

NOV 16 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: New Chemical/First Permanent Food Use:
Carcinogenic and Chronic Dietary Risk Analysis
for the Proposed Use of Fenbuconazole
(Fenethanil) a.k.a Indar™ 2F
in or on bananas.
(PC Code 129011; CAS No. 114369-43-6;
Caswell # 723Q)

FROM: Teung F. Chin, Ph.D., Biologist
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Teung F. Chin

TO: Cynthia Giles-Parker / Dolphine Wilson, PM-22
Fungicide-Herbicide Branch
Registration Division (7505C)

THROUGH: Elizabeth Doyle, Ph.D., Acting Section Head
DRES/SAB
Health Effects Division

E. A. Doyle
W.D. Wassell

Action Requested

The Fungicide-Herbicide Branch has requested that a Dietary Risk Evaluation System (DRES) analysis be performed assessing the chronic dietary and carcinogenic risks resulting from proposed use of the herbicide fenbuconazole ((ANSI/ISO) or RH-7592 [alpha-(2-(4-chlorophenyl)-ethyl)-alpha-phenyl-3-(1H-1,2,4-triazole)-1-propanenitrile] and its metabolites RH-9129 and RH-9130, at a tolerance of 0.3 ppm on raw agricultural commodity bananas (whole fruit) of which not more than 0.05 ppm is contained in the banana pulp (8/1/94 and 8/8/94 CBTS memos W.D. Wassell to C. Giles-Parker and A. Kocialski). Rohm and Haas Company, Philadelphia, PA filed the petition for permanent tolerance (PP# 2F04154) amended 3/31/94, 6/30/94, and 7/19/94.



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Discussion

1. Toxicological Information: For chronic toxicity, the reference dose (RfD) (rats, strain not indicated) was 0.03 mg/kg/day, based on body weight decrease in females and increased liver weights with centrilobular to midzonal hepatocellular enlargement and vacuolization in males and females. An uncertainty factor of 100 was used for the inter-species extrapolation and intra-species variability (4/25/94 TB2 memo; M. Van Gamert to J. Kariya et al. and 7/7/93 RfD/QA Peer Review Memo; G. Z. Ghali to C. Giles-Parker).

No acute dietary risk assessment was necessary (4/25/94 TB2 memo; M. Van Gamert to J. Kariya et al.).

The chemical was classified as a Group C carcinogen (possible human carcinogen) (4/25/94 TB2 memo; M. Van Gamert to J. Kariya et al.). The unit risk, Q_1^* (mg/kg/day)⁻¹ of fenbuconazole, based upon male rat (Sprague-Dawley) thyroid follicular cell (adenomas and/or carcinomas) tumor rates, is 1.65×10^{-2} (mg/kg/day)⁻¹ in human equivalents (2/7/94 SAB memo; H. M. Pettigrew to S. Williams).

2. Residue Information: Bananas and plantain were the food uses evaluated in this analysis. Since this is a new chemical, there are no tolerances listed in §186 for meat, milk, poultry and eggs covering possible secondary residues resulting from feed additives and no § 185 tolerances, resulting its from use as a food additive. A new tolerance, set at 0.05 ppm in the pulp was incorporated into the DRES for the following foods: bananas - fresh; bananas - unspecified; bananas - dried; and plantains. Not included in the assessment was 0.3 ppm since it relates to the whole banana (i.e. with skin on). A summary of the residues used in the chronic exposure analysis is attached as Table 1.

Exposures being calculated in this analysis are from fenbuconazole (RH-7592) and its metabolites RH-9129 and RH-9130, expressed as parent equivalent residues (8/1/94 and 8/8/94 CBTS memos W.D. Wassell to C. Giles-Parker and A. Kocialski). It is also noted that CBTS recommended a tolerance with an expiration date only, at this time (8/8/94 CBTS memo W.D. Wassell to C. Giles-Parker and A. Kocialski). For a permanent tolerance, samples from additional field trials should be analyzed for the metabolite RH-4911 in addition to the other methbolites RH-9129 and RH-9130.

No processing studies were mentioned in the CBTS memos.

i. Percent Crop Treated - No percent crop treated information was utilized for the carincogetic risk assessment and chronic exposure analyses. None would be available since this is a new chemical/new use pattern. It was assumed that 100 percent of the bananas and plantains were treated with fenbuconazole.

ii. Anticipated Residues (AR) - No anticipated residues (AR) were utilized for the carcinogenic risk assessment and chronic exposure analyses. None would be available since this is a new chemical/new use pattern.

Discussion of Results

1. Chronic Exposure

The DRES chronic exposure analysis used tolerance level residues and 100 percent crop treated to estimate the Theoretical Maximum Residue Contribution (TMRC) for the overall U.S. population and 22 population subgroups. Because fenbuconazole is a new chemical, there are no anticipated residues and percent crop treated information, and therefore no estimated Anticipated Residue Contribution (ARC). The ARC is considered as the more refined estimate of exposure over the TMRC. A summary of the TMRCs and their representations as percentages of the RfD is in Table 2. It should be noted again that the residue of interest in this analysis is the parent compound (RH7592) and the two metabolites, RH-9129 and RH-9130.

The TMRC from the proposed new use of fenbuconazole for the general population of the 48 states is 0.000011 mg/kg bwt/day, which represents less than 1% of the RfD. The TMRC for the most exposed subgroups, non-nursing infants (< 1 year old), nursing infants (< 1 year old) and children (1-6 years old), was, respectively, 0.000054, 0.000046, and 0.000036 mg/kg bwt/day; neither exposure scenario exceeds 1% of the RfD. Therefore, minimal risk is expected from chronic dietary intake of fenbuconazole since the RfD is not exceeded for either the general population or any subgroup.

2. Carcinogenic Risk

Upper bound cancer risk from the proposed use of fenbuconazole on bananas does not exceed the de minimis value of 10^{-6} that the Agency generally considers negligible. Table 3 provides the total oncogenic risk from each commodity for the entire U. S. Population (48 states). A value of 1.89×10^{-7} was derived.

Attachments

cc: DRES, FHB, CCB, Tox 2, CBTS, Caswell # 723Q

TABLE 1: Food-Tolerances

CHEMICAL INFORMATION FOR CASWELL NUMBER 723Q

DATE: 10/20/94

PAGE: 1

CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES		DATA GAPS/COMMENTS	STATUS
			PADI	UF		
Fenbuconazole (Fenethanil) Caswell #723Q CAS No. 114369-43-6 A.I. CODE: 129011 CFR No.	2yr feeding - rat NOEL= 3.0300 mg/kg 80.00 ppm LEL= 30.6200 mg/kg 800.00 ppm ONCO: Pending	Decr body wts (F); incr liver wts with centrilob- ular to midzonal hepato- cellular enlargement & vacuolation (M&F).	OPP RfD= 0.030000 EPA RfD= 0.000000	-->100	Developmental tox- rabbit (current study maybe up- graded) Chemical was referred to HED Carcinogenicity Peer Review Committee.	RfD/PR reviewed 04/15/93 RfD/PR reviewed 04/29/93

FOOD CODE	FOOD NAME	TOLERANCE (PPM)		
		PETITION NUMBER	NEW	PUBLISHED

06002AA	BANANAS-UNSPECIFIED	2F04154	0.050000	
06002AB	BANANAS-FRESH	2F04154	0.050000	
06002DA	BANANAS-DRIED	2F04154	0.050000	
06106AA	PLANTAINS	2F04154	0.050000	

TABLE 2: Theoretical Maximum Residue Contributions

TOLERANCE ASSESSMENT SYSTEM ROUTINE CHRONIC ANALYSIS

DATE: 10/20/94

PAGE: 1

CHEMICAL INFORMATION		STUDY TYPE	EFFECTS		REFERENCE DOSES		DATA GAPS/COMMENTS		STATUS
Fenbutazone (Fenethaniol)	2yr feeding - rat	Decr body wts (F); incr liver wts with centrilobular to midzonal hepatocellular enlargement & vacuolation (M&F).	PADI	UF -->100	OPP RfD= 0.030000	EPA RfD= 0.000000	Developmental tox- rabbit (current study maybe up-graded)	RfD/PR reviewed 04/15/93	RfD/PR reviewed 04/29/93
Caswell #723Q	NOEL= 3.0300 mg/kg								
CAS No. 114369-43-6	80.00 ppm								
A.I. CODE: 129011	LEL= 30.6200 mg/kg								
CFR No.	800.00 ppm								
	ONCO: Pending								
POPULATION SUBGROUP		TOTAL TMRC (MG/KG BODY WEIGHT/DAY)		NEW TMRC AS PERCENT OF RFD		DIFFERENCE AS PERCENT OF RFD		EFFECT OF ANTICIPATED RESIDUES	
		CURRENT TMRC*	NEW TMRC**					ARC	%RFD
U.S. POPULATION - 48 STATES		0.00000	0.000011	0.038183		0.038183			
U.S. POPULATION - SPRING SEASON		0.00000	0.000011	0.036097		0.036097			
U.S. POPULATION - SUMMER SEASON		0.00000	0.000012	0.039023		0.039023			
U.S. POPULATION - FALL SEASON		0.00000	0.000012	0.038677		0.038677			
U.S. POPULATION - WINTER SEASON		0.00000	0.000012	0.038933		0.038933			
NORTHEAST REGION		0.00000	0.000011	0.036600		0.036600			
NORTH CENTRAL REGION		0.00000	0.000011	0.035113		0.035113			
SOUTHERN REGION		0.00000	0.000010	0.033700		0.033700			
WESTERN REGION		0.00000	0.000016	0.052613		0.052613			
HISPANICS		0.00000	0.000019	0.063673		0.063673			
NON-HISPANIC WHITES		0.00000	0.000011	0.038240		0.038240			
NON-HISPANIC BLACKS		0.00000	0.000007	0.023997		0.023997			
NON-HISPANIC OTHERS		0.00000	0.000016	0.053767		0.053767			
NURSING INFANTS (< 1 YEAR OLD)		0.00000	0.000046	0.153633		0.153633			
NON-NURSING INFANTS (< 1 YEAR OLD)		0.00000	0.000054	0.180627		0.180627			
FEMALES (13+ YEARS, PREGNANT)		0.00000	0.000006	0.020767		0.020767			
FEMALES 13+ YEARS, NURSING		0.00000	0.000006	0.021427		0.021427			
CHILDREN (1-6 YEARS OLD)		0.00000	0.000036	0.121543		0.121543			
CHILDREN (7-12 YEARS OLD)		0.00000	0.000015	0.049613		0.049613			
MALES (13-19 YEARS OLD)		0.00000	0.000008	0.025823		0.025823			
FEMALES (13-19 YEARS OLD, NOT PREG. OR NURSING)		0.00000	0.000007	0.022040		0.022040			
MALES (20 YEARS AND OLDER)		0.00000	0.000007	0.024063		0.024063			
FEMALES (20 YEARS AND OLDER, NOT PREG. OR NURS)		0.00000	0.000007	0.024533		0.024533			

*Current TMRC does not include new or pending tolerances.

**New TMRC includes new, pending, and published tolerances.

5

TABLE 3: Oncogenic Risk

TOLERANCE ASSESSMENT SYSTEM ROUTINE CHRONIC ANALYSIS

DATE: 10/20/94

PAGE: 1

CHEMICAL INFORMATION		STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Fenbutazone (Fenethanil)	2yr feeding - rat	3.0300 mg/kg	Deer body wts (F); incr liver wts with centrilobular to midzonal hepatocellular enlargement & vacuolation (M&F).	PADI UF -->100 OPP RfD= 0.030000 EPA RfD= 0.000000	Developmental tox- rabbit (current study maybe up-graded) Chemical was referred to HED Carcinogenicity Peer Review Committee.	RfD/PR reviewed 04/15/93 RfD/PR reviewed 04/29/93
Caswell #723Q	NOEL=	80.00 ppm				
CAS No. 114369-43-6	LEL=	30.6200 mg/kg				
A.I. CODE: 129011	ONCO: Pending	800.00 ppm				
CFR No.						

LISTING OF EXPOSURE BY RAC FOR: U.S. POPULATION - 48 STATES

FOOD CODE	FOOD NAME	-----TOLERANCE (PPM)-----		--EXISTING TOLERANCES--		-NEW & PENDING TOLERANCES-		TOTAL ONCOGENIC RISK
		NEW	PENDING	TMRC	%RfD	TMRC	%RfD	
06002AA	BANANAS-UNSPECIFIED	0.05000				0.000165	0.0005	0.000000003
06002AB	BANANAS-FRESH	0.05000				0.011202	0.0373	0.000000185
06002DA	BANANAS-DRIED	0.05000				0.000088	0.0002	0.000000001
06106AA	PLANTAINS	0.05000				0.000000	0.0000	0.000000000
CROP GROUP TOTALS FOR UNSPECIFIED:								
GRAND TOTAL TMRC:	0.011455	GRAND TOTAL % OF THE RfD:		0.0382		0.011455	0.0382	0.000000189

POPULATION SUBGROUP TOTALS

POPULATION TOTAL TMRC 0.011455 POPULATION TOTAL % OF THE RfD 0.0381

0.000000

0.000000

0.000000

0.000000

0.000000

0.000000

0.000000

0.000000

0.000000

0.000000

6