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

|| 22 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Difenoconazole: Dietary Exposure Analysis for the Proposed Time-Limited Use on Wheat (PP# 2F4107)

FROM: Jennifer M. Wintersteen *Jennifer Wintersteen*
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Science Analysis Branch/HED (7509C)

TO: C. Giles-Parker/J. Stone, PM Team 22
Registration Division (7505C)

THROUGH: William L. Burnam, Chief *W. Burnam*
Science Analysis Branch
Health Effects Division

Action Requested

Provide estimates of chronic dietary exposure and acute dietary risk for the proposed time-limited use of difenoconazole on wheat grain at 0.1 ppm (exp. 12/31/98) and animal products. This is the first food use petition for this chemical.

Discussion

1. Toxicological Endpoints: For chronic dietary exposure the Reference Dose (RfD) of 0.01 mg/kg bwt/day is based on a NOEL of 0.96 mg/kg/day and an uncertainty factor of 100. The NOEL is taken from a long term rat feeding study and the effect is hepatotoxicity at 24.12 mg/kg/day in males. The RfD has been approved by the HED RfD Peer Review Committee [G. Ghali memo, 2/24/94].

Based on weight of the evidence (WOTE), difenoconazole has been classified as a Category C (possible human) carcinogen. The Carcinogenicity Peer Review recommended that for the purposes of risk characterization, the Reference Dose approach should be used for quantification of human risk (E. Rinde Peer Review document, 7/94).

A Toxicology Endpoint Selection Document for difenoconazole (J. Rowland and M. VanGemert memo, 6/17/94) indicates that developmental toxicity is of concern. In order to calculate the acute dietary risk a NOEL of 25 mg/kg bwt/day was supplied in the same memo as appropriate for acute dietary assessment.



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2. Residue Information: Currently there are no published tolerances for difenoconazole in 40 CFR. CBTS recommends for the proposed uses on wheat grain (0.1 ppm), straw (0.1 ppm) and forage (0.1 ppm) as well as animal tolerances from resulting secondary residues as follows (G. Kramer memo, 6/16/94):

Eggs	0.05 ppm
Milk	0.01 ppm
Meat ¹	0.05 ppm
Fat ¹	0.05 ppm
Meat By-Products ¹	0.05 ppm

The DRES analysis is based on the parent compound only and not metabolites (G. Kramer memo to HED Metabolism Committee, 7/22/94).

No refinements of percent crop treated or anticipated residue data were made to the DRES analysis. Tolerance level residues and 100% crop treated assumptions were made for both chronic and acute analyses.

3. Chronic Exposure Analysis: For chronic dietary exposure the Theoretical Maximum Residue Contribution (TMRC) for the general U.S. population and the highest exposed subgroups is as follows (as percent of the Reference Dose):

U.S. population	4%
Children (1-6)	9%
Non-nursing Infants (<1)	9%

The TMRC from the proposed use on wheat is 4.1×10^{-4} mg/kg/day, representing 4% of the RfD. A summary of the chronic exposure estimates is attached as Table 2. Table 3 is a summary of the chronic exposure contribution by tolerance type.

4. Acute Exposure: The DRES detailed acute exposure analysis evaluates individual food consumption as reported by respondents in the USDA 77-78 Nationwide Food Consumption Survey (NFCS) and estimates the distribution of single day exposures through the diet for the U.S. population and certain subgroups. The analysis assumes uniform distribution of difenoconazole in the commodity supply.

Since the toxicological effect to which high end exposure is being compared to in this analysis is developmental toxicity the subgroup of concern is females (13+ years). For substances whose acute NOEL is based on animal studies, the Agency is not generally concerned unless the MOE is below 100.

Using the proposed wheat tolerance of 0.1 ppm and meat, milk and egg tolerances, the MOE for the subgroup females 13+ for high end exposure is 25,000 and 88,000 for mean exposure. The estimated percent of potential person days that are consumer days of any commodity for which difenoconazole has proposed tolerances is 99% of the population. The table below provides the calculated MOE for the females 13+ subgroup.

Table 1.

CHEMICAL INFORMATION FOR CASWELL NUMBER 955

DATE: 07/22/94

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CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Difenoconazole (Dividend) Caswell #955 CAS No. 119446-68-3 A.I. CODE: 128847 CFR No.	2yr feeding- rat NOEL= 0.9600 mg/kg LEL= 24.1200 mg/kg 500.00 ppm ONCO: Pending	Reductions in cumulative body weight gains. Referred to Carcinogenicity Peer Review Committee	ADI UF -->100 OPP RfD= 0.010000 EPA RfD= 0.000000	No data gaps.	RfD/PR reviewed 01/06/94

FOOD CODE	FOOD NAME	PETITION NUMBER	NEU	TOLERANCE (PPM)	PENDING	PUBLISHED
24007AA	WHEAT-ROUGH	2F4107	0.100000			
24007GA	WHEAT-GERM	2F4107	0.100000			
24007HA	WHEAT-BRAN	2F4107	0.100000			
24007MA	WHEAT-FLOUR	2F4107	0.100000			
50000DB	MILK-NON-FAT SOLIDS	2F4107	0.010000			
50000FA	MILK-FAT SOLIDS	2F4107	0.010000			
50000SA	MILK SUGAR (LACTOSE)	2F4107	0.010000			
53001BA	BEEF-MEAT BYPRODUCTS	2F4107	0.050000			
53001BB	BEEF(ORGAN MEATS)-OTHER	2F4107	0.050000			
53001DA	BEEF-DRIED	2F4107	0.050000			
53001FA	BEEF(BONELESS)-FAT	2F4107	0.050000			
53001KA	BEEF(ORGAN MEATS)-KIDNEY	2F4107	0.050000			
53001LA	BEEF(ORGAN MEATS)-LIVER	2F4107	0.050000			
53001MA	BEEF(BONELESS)-LEAN	2F4107	0.050000			
53002BA	GOAT-MEAT BYPRODUCTS	2F4107	0.050000			
53002BB	GOAT(ORGAN MEATS)-OTHER	2F4107	0.050000			
53002FA	GOAT(BONELESS)-FAT	2F4107	0.050000			
53002KA	GOAT(ORGAN MEATS)-KIDNEY	2F4107	0.050000			
53002LA	GOAT(ORGAN MEATS)-LIVER	2F4107	0.050000			
53002MA	GOAT(BONELESS)-LEAN	2F4107	0.050000			
53003AA	HORSE	2F4107	0.050000			
53005BA	SHEEP-MEAT BYPRODUCTS	2F4107	0.050000			
53005BB	SHEEP(ORGAN MEATS)-OTHER	2F4107	0.050000			
53005FA	SHEEP(BONELESS)-FAT	2F4107	0.050000			
53005KA	SHEEP(ORGAN MEATS)-KIDNEY	2F4107	0.050000			
53005LA	SHEEP(ORGAN MEATS)-LIVER	2F4107	0.050000			
53005MA	SHEEP(BONELESS)-LEAN	2F4107	0.050000			
53006BA	PORK-MEAT BYPRODUCTS	2F4107	0.050000			
53006BB	PORK(ORGAN MEATS)-OTHER	2F4107	0.050000			
53006FA	PORK(BONELESS)-FAT	2F4107	0.050000			
53006KA	PORK(ORGAN MEATS)-KIDNEY	2F4107	0.050000			
53006LA	PORK(ORGAN MEATS)-LIVER	2F4107	0.050000			
53006MA	PORK-LEAN	2F4107	0.050000			
55008BA	TURKEY-BYPRODUCTS	2F4107	0.050000			
55008LA	TURKEY-GIBLETS (LIVER)	2F4107	0.050000			
55008MA	TURKEY-FLESH(M/O SKIN)	2F4107	0.050000			
55008MB	TURKEY-FLESH(+SKIN)	2F4107	0.050000			
55008MC	TURKEY-UNSPECIFIED	2F4107	0.050000			
55013BA	POULTRY, OTHER-BYPRODUCTS	2F4107	0.050000			
55013LA	POULTRY, OTHER-(LIVER)	2F4107	0.050000			

DRES Subgroup	High End Exposure (mg/kg bwt/day)	MOE NOEL/High Exposure
Females (13+ years)	0.001	25,000

This is the first time that acute exposure has been calculated for difenoconazole. The calculated MOE is well above the level the Agency generally considers negligible for the females 13+ subgroup used in the DRES acute program and thus acute exposure is not expected to be a problem. A table of distribution of exposures in this analysis is attached as Table 4.

Conclusions

The chronic and acute dietary risk estimates are not of concern for the proposed time-limited tolerance for difenoconazole on wheat.

Attachments

cc: DRES, CBTS (G. Kramer), Tox II (J. Rowland), Caswell #955

¹ Meat of cattle, goats, horses, hogs, poultry, and sheep

Table 1.

CHEMICAL INFORMATION FOR CASWELL NUMBER 955

DATE: 07/22/94

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CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES		DATA GAPS/COMMENTS	STATUS
			ADI	UF		
Difencconazole (Dividend) Caswell #955 CAS No. 119446-68-3 A.I. CODE: 128847 CFR No.	2yr feeding- rat NOEL= 0.9600 mg/kg 20.00 ppm LEL= 24.1200 mg/kg 500.00 ppm ONCO: Pending	Reductions in cumulative body weight gains. Referred to Carcinogenicity Peer Review Committee	AD1	UF -->100	No data gaps.	RfD/PR reviewed 01/06/94

FOOD CODE	FOOD NAME	PETITION NUMBER	TOLERANCE (PPM)	
			NEW	PENDING PUBLISHED
55013MA	POULTRY, OTHER- FLESH(+SKIN)	2F4107	0.050000	
55014AA	EGGS-WHOLE	2F4107	0.050000	
55014AB	EGGS-WHITE ONLY	2F4107	0.050000	
55014AC	EGGS-YOLK ONLY	2F4107	0.050000	
55015BA	CHICKEN-BYPRODUCTS	2F4107	0.050000	
55015LA	CHICKEN-GIBLETS(LIVER)	2F4107	0.050000	
55015MA	CHICKEN-FLESH(W/O SKIN)	2F4107	0.050000	
55015MB	CHICKEN-FLESH(+SKIN)	2F4107	0.050000	

TOLERANCE ASSESSMENT SYSTEM ROUTINE CHRONIC ANALYSIS

DATE: 07/22/94

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CHEMICAL INFORMATION	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Difenconazole (Dividend) Caswell #95 CAS No. 119446-68-3 A.I. CODE: 128847 CFR No.	2yr feeding- rat NOEL= 0.9600 mg/kg 20.00 ppm LEL= 24.1200 mg/kg 500.00 ppm ONCO: Pending	Reductions in cumulative body weight gains. Referred to Carcinogenicity Peer Review Committee	ADI UF -->100 OPP RfD= 0.010000 EPA RfD= 0.000000	No data gaps.	RfD/PR reviewed 01/06/94
POPULATION SUBGROUP					
U.S. POPULATION - 48 STATES	0.000000	0.000412	4.123620	4.123620	
TOTAL THRC (MG/KG BODY WEIGHT/DAY)					
U.S. POPULATION - SPRING SEASON	0.000000	0.000401	4.006650	4.006650	
U.S. POPULATION - SUMMER SEASON	0.000000	0.000408	4.078560	4.078560	
U.S. POPULATION - FALL SEASON	0.000000	0.000424	4.238510	4.238510	
U.S. POPULATION - WINTER SEASON	0.000000	0.000417	4.170980	4.170980	
NORTHEAST REGION					
NORTH CENTRAL REGION	0.000000	0.000422	4.223980	4.223980	
SOUTHERN REGION	0.000000	0.000421	4.205300	4.205300	
WESTERN REGION	0.000000	0.000393	3.931640	3.931640	
	0.000000	0.000420	4.201670	4.201670	
HISPANICS					
NON-HISPANIC WHITES	0.000000	0.000479	4.790710	4.790710	
NON-HISPANIC BLACKS	0.000000	0.000409	4.087830	4.087830	
NON-HISPANIC OTHERS	0.000000	0.000400	4.002420	4.002420	
	0.000000	0.000445	4.449640	4.449640	
NURSING INFANTS (< 1 YEAR OLD)					
NON-NURSING INFANTS (< 1 YEAR OLD)	0.000000	0.000277	2.767560	2.767560	
FEMALES (13+ YEARS, PREGNANT)	0.000000	0.000946	9.461160	9.461160	
FEMALES 13+ YEARS, NURSING	0.000000	0.000294	2.941790	2.941790	
CHILDREN (1-6 YEARS OLD)	0.000000	0.000353	3.529530	3.529530	
CHILDREN (7-12 YEARS OLD)	0.000000	0.000946	9.455110	9.455110	
MALES (13-19 YEARS OLD)	0.000000	0.000643	6.430720	6.430720	
FEMALES (13-19 YEARS OLD, NOT PREG. OR NURSING)	0.000000	0.000458	4.582920	4.582920	
MALES (20 YEARS AND OLDER)	0.000000	0.000355	3.552030	3.552030	
FEMALES (20 YEARS AND OLDER, NOT PREG. OR NURS)	0.000000	0.000320	3.195410	3.195410	
	0.000000	0.000267	2.669120	2.669120	

*Current THRC does not include new or pending tolerances.
**New THRC includes new, pending, and published tolerances.

Table 3.

TOLERANCE ASSESSMENT SUMMARY FOR Difenoconazole (Dividend)
CASWELL #955

DATE: 07/22/94

ANALYSIS FOR POPULATION SUB-GROUP: U.S. POPULATION - 48 STATES

EXISTING TOLERANCES (PUBLISHED ONLY)		
RESULT IN A TMRC OF:	0.000000	MG/KG/DAY
THE EXISTING TMRC IS EQUIVALENT TO:	0.000	% OF THE ADI.
PROPOSED NEW TOLERANCES (CURRENT PETITION ONLY)		
RESULT IN A TMRC OF:	0.000413	MG/KG/DAY
THESE NEW TOLERANCES WILL OCCUPY:	4.124	% OF THE ADI.
IF THE NEW TOLERANCES (CURRENT PETITION ONLY)		
ARE APPROVED THE RESULTANT TMRC WILL BE:	0.000413	MG/KG/DAY
THE NEW TMRC WILL OCCUPY	4.124	% OF THE ADI.

NO OTHER PENDING TOLERANCES ARE IN THE FILE

ANALYSIS FOR POPULATION SUB-GROUP: NON-NURSING INFANTS (< 1 YEAR OLD)

EXISTING TOLERANCES (PUBLISHED ONLY)		
RESULT IN A TMRC OF:	0.000000	MG/KG/DAY
THE EXISTING TMRC IS EQUIVALENT TO:	0.000	% OF THE ADI.
PROPOSED NEW TOLERANCES (CURRENT PETITION ONLY)		
RESULT IN A TMRC OF:	0.000947	MG/KG/DAY
THESE NEW TOLERANCES WILL OCCUPY:	9.461	% OF THE ADI.
IF THE NEW TOLERANCES (CURRENT PETITION ONLY)		
ARE APPROVED THE RESULTANT TMRC WILL BE:	0.000947	MG/KG/DAY
THE NEW TMRC WILL OCCUPY	9.461	% OF THE ADI.

NO OTHER PENDING TOLERANCES ARE IN THE FILE

ANALYSIS FOR POPULATION SUB-GROUP: CHILDREN (1-6 YEARS OLD)

EXISTING TOLERANCES (PUBLISHED ONLY)		
RESULT IN A TMRC OF:	0.000000	MG/KG/DAY
THE EXISTING TMRC IS EQUIVALENT TO:	0.000	% OF THE ADI.
PROPOSED NEW TOLERANCES (CURRENT PETITION ONLY)		
RESULT IN A TMRC OF:	0.000946	MG/KG/DAY
THESE NEW TOLERANCES WILL OCCUPY:	9.455	% OF THE ADI.
IF THE NEW TOLERANCES (CURRENT PETITION ONLY)		
ARE APPROVED THE RESULTANT TMRC WILL BE:	0.000946	MG/KG/DAY
THE NEW TMRC WILL OCCUPY	9.455	% OF THE ADI.

NO OTHER PENDING TOLERANCES ARE IN THE FILE

