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

Good # 2-15-94 Keep the same see page 2

FEB 15 1994 What has changed?

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Diflubenzuron. Issues to be Presented at the 2/22/94 Meeting of the HED Metabolism Committee.** Estimates of Residue Levels of Diflubenzuron and p-Chloroaniline to be Used for Dietary Risk Calculations and Estimate of Dietary Risk. Reregistration Case No. 0144. Chemical No. 108201. No MRID #. No DP Barcode. No CBRS #.

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TO: HED Metabolism Committee

Tolerances for residues of the insecticide diflubenzuron (DFB, N-[[4-chlorophenyl)amino] carbonyl]-2,6-difluorobenzamide) are established in various racs (40 CFR 180.377) and feed additives (40 CFR 186.2000).

Metabolism studies indicate that in animals and mushrooms, DFB metabolites include p-chloroaniline (PCA), chlorophenylurea (CPU), p-chloroacetaniline (PCAA), and other moieties.

Conclusions

CBRS used results from metabolism studies to determine the percent of TRR present as PCA or related compounds (CPU and PCAA). Then, using tolerance levels for diflubenzuron, and assuming 100% crop treated, total levels of PCA and related compounds were estimated. Results are summarized in Table 1.

Using a Q_1^* for PCA of 0.059, as provided by Dr. Engler, and residue values for PCA as noted in Table 1, a potential upper bound cancer risk of 1.4×10^{-6} was calculated.

Question for the Committee After consideration of the risk assessment results, should the tolerance expression for diflubenzuron remain in terms of parent compound only?

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Background

At the 11/5/93 meeting of the HED Metabolism Committee, the following questions were discussed.

1. Because diflubenzuron per se is not considered a carcinogen by the Agency, for those commodities for which the presence of 4-chloroaniline (PCA) has been demonstrated (i.e., mushrooms and ruminants), should an estimate of the amount of PCA present together with the Q_1^* for PCA be used to generate the cancer risk resulting from the use of diflubenzuron?

2. For those commodities for which PCA was not detected in metabolism studies (i.e., all plants), should risk calculations be based solely on the diflubenzuron toxicological endpoint? yes

3. How should CPU (chlorophenylurea) and PCAA (p-chloroacetaniline) be regulated? ?

The Committee concluded that for commodities where no PCA, CPU or PCAA were present, the tox endpoint for diflubenzuron per se should be used for risk calculations. For those commodities that contain PCA, CPU and PCAA, the Q_1^* for PCA should be used for to calculate the cancer risk from the sum of the three metabolites. If a Q_1^* has not been determined for PCA, Dr. Reto Engler will be responsible for getting an acceptable Agency value to be used by DRES. Levels of PCA, CPU and PCAA in rac's will be estimated using information from the metabolism studies (A.Rathman, 11/15/93, memo entitled "Outcome of the HED Metabolism Committee meeting of 11/5/93). Keep the same! Especially for mushrooms & possibly for apples poultry? beyond level of detection?

Estimates of Residue Levels of Diflubenzuron and p-Chloroaniline to be Used for Dietary Risk Calculations

CBRS used results from metabolism studies to determine the percent of TRR present as PCA or related compounds (CPU and PCAA). Then, using tolerance levels for diflubenzuron, and assuming 100% crop treated, total levels of PCA and related compounds were estimated. Results are summarized in Table 1.

Table 1. Summary of commodities having DFB tolerances and levels of DFB or PCA (sum of PCA, CPU, and/or PCAA) to used by DRES for risk assessment purposes. Values to be used for risk assessment assume 100% crop treated.

Commodity	Tolerance (ppm)	Amount DFB to be used for Risk Assessment (ppm)	Amount PCA to be used for Risk Assessment (ppm)
Mushrooms	0.2	--	0.69
Soybeans	0.05	0.05	--
Walnuts	0.05	0.05	--

Commodity	Tolerance (ppm)	Amount DFB to be used for Risk Assessment (ppm)	Amount PCA to be used for Risk Assessment (ppm)
Cottonseed	0.2	0.2	--
Milk	0.05	0.05	--
Eggs	0.05	--	0.0056
Cattle, fat	0.05	0.05	--
Cattle, mbyp	0.05	--	0.005
Cattle, meat	0.05	0.05	--
Goat, fat	0.05	0.05	--
Goat, mbyp	0.05	--	0.005
Goat, meat	0.05	0.05	--
Hogs, fat	0.05	0.05	--
Hogs, mbyp	0.05	--	0.005
Hogs, meat	0.05	0.05	--
Horses, fat	0.05	0.05	--
Horses, mbyp	0.05	--	0.005
Horses, meat	0.05	0.05	--
Sheep, fat	0.05	0.05	--
Sheep, mbyp	0.05	--	0.005
Sheep, meat	0.05	0.05	--
Poultry, fat	0.05	0.05	--
Poultry, mbyp	0.05	--	0.025
Poultry, meat	0.05	--	0.011

Estimated Dietary Risk

Using a Q_1^* for PCA of 0.059, as provided by Dr. Engler, and residue values for PCA as noted above, a potential upper bound cancer risk of 1.4×10^{-6} was calculated.

Detailed Considerations

Mushrooms - A review of the metabolism study "Residues in Mushrooms grown from compost treated with radiolabeled diflubenzuron", dated 2/86, was completed by M. Nelson (4/22/87, CBTS #2085, Acces. No. 265703). In this study, mushroom compost, consisting mostly of horse and chicken manure, was spawned with mushroom culture and then was treated (day 1) with diflubenzuron, either ^{14}C-labeled in the 4-chlorophenyl ring of ^{3}H-labeled in the 2,6-difluorobenzoyl moiety. The dosage rate was 1 gm ai/m^2 (assuming a bed depth of 5 inches, this rate corresponds to 22 gm ai/m^3, or 0.05 lb ai/100 ft^3, which represents 0.5X the maximum application rate). An additional application was made at casing (day 13). Samples of mushrooms were collected at each of the first four flushes (day 32, 38, 46, and 55). Each flush was analyzed separately. TRR was determined by combustion analysis. Quantitation of diflubenzuron (DFB) and its metabolites CPU, DFBA, and PCA was via reversed phase isotope dilution, and TLC with autoradiography using reference compounds.

Residues of diflubenzuron (DFB), 4-chlorophenylurea (CPU), diflubenzoic acid (DFBA), and 4-chloroaniline (p-chloroaniline, PCA) were detected at levels up to 0.18, 0.6, 3.96, and 0.02 ppm respectively. No questions were raised concerning this study because the data gap which this study was submitted to fulfill had been previously considered fulfilled in a S.Malak memo of 7/28/86.

The tolerance for DFB in/on mushrooms is 0.2 ppm. If DFB were present in/on mushrooms at this tolerance level, combined residues of CPU and PCA could be expected to be present at 0.69 ppm.

Citrus - A CBTS review of a citrus metabolism study (S. Malak, 7/27/89, CBTS #5426-5429, in PP#F2507, MRID #41079301) noted several deficiencies, which were subsequently resolved (S.Malak, 10/2/89, CBRS #5706 and 5707; S.Malak, 11/21/89, CBRS #5913, 5978-5983). The reviews concluded that the vast majority of the residue in citrus fruit is composed of unchanged parent compound, and no detectable levels (< 1 ppb) of PCA, CPU, or DFBA were present.

No tolerances for DFB in/on citrus have been established. Results of the citrus metabolism study were presented only to demonstrate that PCA, CPU, and PCAA were not found at levels > 1 ppb.

Apples - An apple metabolism study has been previously submitted and reviewed in conjunction Diflubenzuron Registration Standard (11/16/84). By use of reverse phase isotope dilution analysis, PCA was detected in apple leaves and fruit at levels of 1.15 and 0.002 ppm respectively. Duphar contended that PCA found in leaves and fruit was an artifact that could have resulted due to extraction techniques in boiling methanol/water (1:1) (S.Malak, 2/25/88, PP#5F3270/FAP#5H5472), however, CBRS was unable to conclude if PCA found was actually a metabolite, or an artifact, or an impurity in the test substance (S.Malak, 8/24/88). Duphar submitted a new apple metabolism study which was reviewed by CBTS (J.Stokes,

5/27/93, CBTS #9703, MRID #42127700 and 42127701). This study was not adequate because: 1) low recoveries for PCA; 2) the application rate was too low; and 3) a PHI of 63 days instead of the proposed label PHI of 28 days was used. A new apple metabolism study was requested.

No tolerances for DFB in/on apples have been established. CBRS concludes that the presence of PCA as a DFB metabolite in apples remains unresolved.

Soybeans - Tolerances for residues of diflubenzuron in/on soybeans are established 0.05 ppm, and feed additive tolerances for residues of DFB in/on soybean hulls and soapstock have been established at 0.5 and 0.1 ppm respectively (40 CFR 186.2000). A recently submitted soybean metabolism study is currently under review (MRID #4265801, CBRS #11,501). Based on preliminary review of this study, the >90% of the TRR in soybean leaves was unchanged parent (ppm levels not provided). DFBA, CPU, and PCA were not detected, but the limit of detection for these compounds was not provided. In soybean hulls, 81.4% to 97.9% of the TRR (6.57 -17.5 ppm) was identified as unchanged parent. Again, DFBA, CPU, and PCA were not detected. The limit of detection for these compounds was 0.3 ppm. Residues in soybean seeds were too low to allow for metabolite characterization (<0.1 to 0.038 ppm).

Pending final review of the soybean metabolism study, CBRS tentatively concludes that PCA, CPU, and PCAA are not present in soybeans at levels $\geq$0.3 ppm.

Ruminants - CBTS has reviewed a goat metabolism study submitted by Duphar (J.Stokes, 12/30/92, CBTS #10,828, MRID #42494201, and J.Stokes 2/23/93, CBTS #11,183). The reviews concluded that based upon estimated dietary exposure of 9.0 ppm in the diet, the concentration of PCA in ruminant milk is below the limit of quantitation of 0.001 ppm and in liver is below the limit of quantitation of 0.005 ppm. Also based on this dietary exposure, CPU could be present in the liver at up to 0.003 ppm and in milk at 0.003 ppm. If present in liver or milk, PCAA would be below the limit of detection of 0.001 ppm.

CBRS concludes that based upon an estimated dietary exposure of 9.0 ppm PCA in ruminant milk is below 0.001 ppm and in the liver is below 0.005 ppm. Also based on this dietary exposure, CPU could be present in the liver at up to 0.003 ppm and in milk at 0.003 ppm. If present in liver or milk, PCAA would be below the limit of detection of 0.001 ppm.

Poultry - A poultry metabolism study (MRID #00070186), submitted by Thompson Hayward Chemical Co., was discussed in the Diflubenzuron Registration Standard. In this study, laying hens were dosed with uniformly double ring labeled ^{14}C-diflubenzuron at 0.05, 0.5, and 5 ppm in the diet for 1-28 days. At all dosing levels, ^{14}C residues plateaued in tissues and eggs by day 10 of dosing. TRR levels for tissues are presented in Table 2.

Table 2. TRR levels (ppm) in hens dosed with DFB at 0.05, 0.5, and 5 ppm in the feed for 1 to 28 consecutive days.

Tissue	Dosing level (ppm)		
	0.05	0.5	5
Fat	<0.0006 - 0.0067 ppm	<0.005 - 0.033 ppm	0.078 - 1.16 ppm
Kidney	<0.0006 - 0.0026 ppm	<0.005 - 0.013 ppm	0.68 - 0.338 ppm
Liver	<0.0006 - 0.0026 ppm	<0.005 - 0.044 ppm	0.059 - 0.453 ppm
Muscle	<0.0006 - 0.0029 ppm	<0.005 - 0.100 ppm	<0.032 - 0.833 ppm

Tissues and eggs collected after 7 days of continuous dosing at 5 ppm were extracted with ethyl acetate and residues were characterized by TLC. Of the total ^{14}C residues present in tissues and eggs, the percent TRR of DFB, DFBA and CPU present are shown in Table 3. Small amounts of PCA were tentatively identified in some samples.

Table 3. Identification of radioactive residues in hens dosed with DFB for 7 days at 5 ppm in the feed. Results are expressed as percent of TRR.

Tissue	% DFB	% DFBA	% CPU
Fat	100	0	0
Muscle	63.4 - 66.3	6.8 - 9.2	13 - 22.1
Liver	18.6	7.4	49.8
Kidney	23.8	0	40
Eggs	68.8	3.7	11.2

CBRS concludes that based upon established tolerances of 0.05 ppm in eggs, poultry fat, poultry meat, and poultry meat by-products, levels of PCA (CPU) could be 0.0056 ppm in eggs, 0.011 ppm in poultry meat, 0.025 ppm in meat by-products.

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