Rec'd 9-23-92

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

SEP 23 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Triadimefon. List B Reregistration Case No. 2700/Chemical ID No. 109901. Raw data to upgrade metabolism studies reviewed in Phase 4. Phase 5 Review of subject studies. MRID Nos. 421234-00, -01, -02, -03, and -04. CBRS No. 9422. DP Barcode No. D174151.

FROM: Christina B. Swartz, Chemist
Reregistration Section II
Chemistry Branch II: Reregistration Support
Health Effects Division (H7509C)

Christina B. Swartz

THRU: William J. Hazel, Ph.D., Section Head
Reregistration Section II
Chemistry Branch II: Reregistration Support
Health Effects Division (H7509C)

W. J. Hazel

TO: Bruce Sidwell (PM 53)
Accelerated Reregistration Branch
Special Review and Reregistration Division (H7508W)

Triadimefon is a FIFRA 88 List B chemical which has undergone Phase 4 review by CBRS (memo, S.R. Funk, 1/31/91). Commonly known as Bayleton®, 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)-2-butanone is a systemic fungicide used to control rust and mildew on a variety of RACs. Tolerances are currently established for the combined residues of triadimefon and its metabolites containing chlorophenoxy and triazole moieties (expressed as the fungicide) in or on various fruits, cereal grains, and animal commodities, ranging from 0.04 ppm (milk) to 145 ppm (grass seed cleanings, including hulls).

Plant metabolism studies conducted on cucumbers, tomatoes, grapes and apples, and an animal metabolism study conducted on swine were found to be unacceptable for Phase 5 review, due to a lack of raw data supporting metabolite identification. The Phase 4 DCI required submission of GC/MS and TLC raw data, as well as an additional wheat metabolism study, and poultry and ruminant metabolism studies. In its 12/4/91 response to the Phase 4 DCI, Mobay Corporation has submitted raw data for tomatoes and cucumbers (MRID No. 421234-01), apples (MRID No. 421234-02), grapes (421234-03), and swine (MRID No. 421234-04).

1

Conclusions

1. Grapes: The submission of the raw data has rendered the grape metabolism study acceptable. No further information is required. A summary of triadimefon metabolism in grapes is presented in Appendix I.

2. Cucumber and tomato: The deficiencies identified in the Phase 4 review have not been resolved, since the registrant failed to submit GC/MS and MS spectra confirming identification of triadimefon and metabolite KWG 0519. The study is acceptable, pending receipt of the confirmatory spectra. A summary of triadimefon metabolism in cucumbers and tomatoes is presented in Appendix II.

3. Apples: The additional data submitted by the registrant did not include GC/MS or HPLC confirmation of metabolites identified using TLC; in addition, the TLC chromatogram submitted was difficult to read, and the location of the unidentified metabolite was not clearly indicated. Finally, the amount of radioactive residue available for characterization was claimed to be low (0.15 to 0.83 ppm); similar residues in the cucumber and tomato studies were deemed by the registrant to be too low for characterization. However, at this time, CBRS will not require an additional apple metabolism study, provided that the required confirmatory spectra are submitted for cucumber and tomato metabolites, and provided no new metabolites of concern are identified in the required wheat metabolism study. The need for an additional apple metabolism study will be reevaluated upon receipt of the wheat metabolism study. A summary of apple metabolism is included in Appendix III.

4. Swine: The single dose experiment cannot be used to support reregistration, and the multi-dose experiment is not acceptable since the animal was fed a mixture of unlabeled and radiolabeled triadimefon 7 days prior to dosing. In addition, the registrant did not submit GC/MS or HPLC confirmation of metabolite identification. CBRS will not require an additional swine metabolism study at this time, however, since both ruminant and poultry metabolism studies have been required in the Phase 4 review. If ruminant or poultry metabolism differ significantly from each other or from that in the rat, a swine metabolism study will be required. The swine metabolism results summarized in Appendix IV will contribute to an overall understanding of the nature of the residue in animals.

RECOMMENDATION

The registrant should be advised to submit the GC/MS and MS spectra confirming identification of cucumber and tomato metabolites. The requirement for an additional apple metabolism study is reserved pending receipt of the required wheat metabolism study, and the required cucumber and tomato spectra. The registrant should submit GC/MS or HPLC data confirming identification of apple metabolites, if such data are available. If the registrant opts

to conduct an additional apple metabolism study, CBRS strongly recommends that application of the radiolabeled material should include foliar contact. The grape metabolism study is acceptable. The swine study is not acceptable, but an additional swine metabolism study will not be required unless metabolism in poultry and/or ruminant differ significantly from each other or from that in the rat.

DETAILED CONSIDERATIONS

GRAPES

Mobay submitted data on the metabolism of uniformly, phenyl-ring-labeled [^{14}C]triadimefon in grapes (MRID No. 150893). The grape metabolism study (Mobay Report No. 88790) was not discussed in the List B Inventory. The Phase 4 review cited supporting raw data and sample chromatograms as a data gap for the grape metabolism study. A summary of the metabolism study, along with the additional data submitted under MRID No. 421234-03, is presented herein.

The radiolabeled triadimefon was formulated into a 50%WP formulation, which was subsequently diluted in water and applied to a 12-foot section of an established grape vine, using a hand-pump spray bottle. The zero-time sample was collected 1 hr later, after the vine had dried; additional samples were taken at 1, 3, 7, 14, 21, and 28 days after treatment. Fully mature grapes were harvested at the last sampling, 56 days after treatment. Samples were homogenized with acetone, and filtered; solids were homogenized with methylene chloride, and filtered. The two filtrates were combined and partitioned, and the organic phase, consisting primarily of methylene chloride, was filtered through sodium sulfate, evaporated, and redissolved in ethyl acetate. The solution was placed on a silica gel column, and eluted first with ethyl acetate, and then with methanol. The two fractions were then analyzed using TLC.

The aqueous phase, consisting primarily of acetone, was concentrated as an azeotrope with acetonitrile (ACN), and diluted with water. An aliquot was subjected to low pressure liquid chromatography, the ^{14}C fractions combined and subjected to additional liquid chromatography, and the ^{14}C fractions combined once again. The resulting fractions were cleaned up using preparative TLC, and radioactivity located using autoradiography. Radioactive bands were eluted with methanol, and aliquots were analyzed using autoradiography, and compared to available analytical standards.

The extracted solids were refluxed for 24 hours in MeOH/HCl, subjected to enzyme hydrolysis, and analyzed using TLC or HPLC. Three solvent systems consisting of ethyl acetate, ACN:H_2O:NH_4OH (80:18:2), and Chloroform:MeOH:NH_4OH (75:24:1) were used for TLC. Non-radiolabeled standards were available, and co-eluted with radioactive samples for metabolite identification. Radioactive bands were detected using autoradiography. Polar metabolites isolated during cleanup were subjected to enzyme hydrolysis, followed by analysis using TLC or HPLC. Radiocarbon analyses were performed using liquid scintillation counting

(LSC) or combustion.

A rapid decline in total radioactivity was observed in grapes, due to the volatility of triadimefon. The decline in the quantity of parent present was accompanied by a buildup of the metabolite KWG 0519 [1-(4-chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)-2-butanol]. Metabolism of triadimefon in grapes proceeds first through reduction of the carbonyl group to the alcohol forming KWG 0519, which exists as a pair of diastereomers. This first conversion appears to be quite rapid. The metabolism of KWG 0519 then proceeds through hydroxylation of the *t*-butyl group to form KWG 1342 [4-(4-chlorophenoxy)-2,2-dimethyl-4-(1H-1,2,4-triazol-1-yl)-1,3-butandiol], cleavage of the ether linkage to *p*-chlorophenol, and conjugation of KWG 0519, 1342, and *p*-chlorophenol with a variety of sugars. An unidentified metabolite (6.2% of the TRR) was released from the solids following mild acid hydrolysis; a more rigorous acid hydrolysis resulted in the release of *p*-chlorophenol. Base hydrolysis also resulted in release of *p*-chlorophenol. Attempts to identify the metabolite were unsuccessful, as it could not be eluted from the column.

Mobay has submitted the supporting raw data for the grape metabolism study (MRID No. 421234-03). Acceptable raw data depicting total radioactivity in grapes and in extracts reported as dpm were submitted, verifying the % distribution of radioactivity data in the original report. The data providing the distribution of organosoluble radioactivity following initial extraction of treated grapes with acetone and DCM were incomplete; data for grapes analyzed after 0 - 14 days and after 28 days could not be located, according to the registrant. In addition, the data provided did not exactly correspond to the figure for which the data were referenced in the original report. However, CBRS does not consider this to be a serious deficiency, since reporting for the remainder of the supporting data appears to be complete. The registrant submitted both TLC and HPLC chromatograms corresponding to various steps in the cleanup scheme applied to mature grapes harvested 56 days following treatment with [^{14}C]triadimefon. The HPLC chromatograms were accompanied by corresponding radioactivity traces, both of which were used to confirm the TLC results. CBRS considers the study to be acceptable, with the submission of the additional data. Summary tables depicting the metabolism of triadimefon in grapes are included in Appendix I.

CUCUMBER AND TOMATO

Mobay submitted data on the metabolism of uniformly, phenyl-ring-labeled [^{14}C]triadimefon in greenhouse-grown cucumbers (MRID Nos. 31440 and 31441). These MRIDs were discussed in the List B Inventory, Residue Chemistry (memo, R. Perfetti, 5/10/90). Phase 3 summaries of the studies were submitted to the Agency for Phase 4 review. The studies were found to be inadequate due to a lack of supporting data.

Ten cucumber seedlings were treated at 0.11 lb a.i./A (ca. 1X the maximum registered rate), with radiolabeled triadimefon in a 25% WP formulation. Four out of the 10 were treated two more times, beginning at fruit set, such that foliage and fruit could be collected from plants receiving either 1 or 3 treatments. In the 2nd and 3rd treatments, the fruit were sprayed to run-

off. Samples were extracted in methanol, and the extract acidified and partitioned twice with dichloromethane (DCM), and once with 60:40 DCM:ACN. An aliquot of the DCM phase was analyzed using liquid scintillation counting (LSC); solids from the extraction were analyzed by combustion. DCM extracts were then concentrated for TLC analysis. Aqueous-soluble residues were hydrolyzed with glucosidase and analyzed by TLC. Two different solvent systems were used for TLC analysis, ethyl acetate and DCM:MeOH:NH_4OH (70:25:1); radioactive bands were detected using autoradiography. An unidentified polar metabolite was subjected to GC/MS analysis, but the results were inconclusive; the registrant stated that the polar metabolite was a glucoside of metabolite KWG 0519 loosely bound to another naturally occurring moiety.

The study was found to be deficient, both in the List B inventory, and during Phase 4 review. The List B inventory stated that raw data supporting metabolite identifications in the fruit were not submitted. Supporting raw data and sample chromatograms were cited as specific data gaps in the DCI. The registrant has submitted additional raw data (MRID No. 421234-01). Much of the additional data submitted, as well as data in the original submission, were generated in a study in which hydroponically grown cucumbers and tomatoes were treated with [^{14}C]triadimefon. These data were not discussed in the List B inventory, or in the Phase 4 review. Raw data consisting of dpm/g (since sample sizes varied) were submitted to support data depicting the following: Distribution of total radiocarbon residue among the DCM and aqueous fractions and the plant tissue solids following a single application at the seedling stage; nature of the residue in the DCM extract of tomato and cucumber seedlings following a single application at the seedling stage; distribution of total radiocarbon residues among the DCM soluble and aqueous fractions and plant tissue solids following multiple applications; and nature of the residue in the DCM extract of tomatoes and cucumbers following multiple applications. There were several minor corrections to be made, but these did not affect the conclusions drawn from the results.

Metabolism of triadimefon in tomato and cucumber seedlings receiving a single foliar application appears to consist of rapid degradation of the parent, concomitant with an increase in metabolite KWG 0519; this degradation occurs more rapidly in cucumber seedlings than in tomato seedlings. Hydrolysis of water soluble radiocarbon and foliage samples from cucumber seedlings released Bayleton and KWG 0519, as well as low levels of the additional metabolites, KWG 1323 and KWG 1342 (TLC identification only). These additional metabolites were not detected in the tomato seedlings. Degradation of triadimefon in mature cucumber and tomato plants appeared to be similar to that in the seedlings, with minor differences. The fruit and foliage differed in their ability to metabolize the parent. In both tomato and cucumber fruit, the terminal degradation product was primarily KWG 0519, while the foliage of both tomato and cucumber exhibited a more complex series of degradation products.

TLC autoradiograms for organosoluble radioactive residues in cucumber shoots, and in cucumber and tomato tissues (foliage and fruit) were submitted. Although the registrant stated in the original report that TLC identifications of Bayleton and KWG 0519 were confirmed using GC/MS, only the spectra pertaining to the polar metabolite identification were submitted (MRID No. 31441). The registrant stated that identification of Bayleton and KWG 0519 were confirmed

using MS, but these spectra were not submitted. The data gap for confirmation of the TLC results with the GC/MS and MS spectra remains outstanding. Summary tables depicting the results of the original metabolism studies in cucumbers and tomatoes are presented in Appendix II.

APPLES

The Mobay study depicting metabolism of 3,5-C-triazol-ring (TR)- and uniformly, phenyl-ring-labeled [^{14}C]triadimefon in apples was discussed in the List B inventory, and found to be deficient, due to the fact that metabolite identifications made using TLC were not confirmed. The Phase 4 review data gap for Guideline 171-4(a) cited the lack of raw data and sample chromatograms supporting the apple metabolism study as deficiencies.

The radiochemicals were applied to apples alone (not foliage) in a 50%WP formulation, using a syringe; the runoff was collected, and excess formulation clinging to the stem was removed using a syringe. Zero day samples were collected after the apples were dry; apple samples consisting of 5 - 15 apples treated with the [^{14}C]triazole were collected 3, 7, 14, 21, 28, 35, 42 and 49 days post-treatment, while [^{14}C]phenyl-ring treated apples were collected 7, 14 and 35 days post-treatment. Prior to extraction, all apples were subjected to multiple benzene rinses (benzene rinses were analyzed using TLC), followed by separation of the pulp and peel for extraction.

Both peel and pulp were extracted with acetone/H_2O and filtered; remaining solids were re-extracted with chloroform and filtered. Remaining solids were then extracted with MeOH and filtered, and the filtrate evaporated to water (aqueous II). Aqueous II fractions were partitioned with chloroform:acetone, radioassayed, and the organic phase subjected to TLC analysis. Subsamples of the solids were retained for combustion analysis. Peel solids were extracted with methanol, filtered, and the aqueous filtrate partitioned with chloroform:acetone. The remaining aqueous phase was radioassayed, and the organic phase analyzed by TLC. Filtrates from the original extraction with acetone/H_2O were combined and partitioned, and the aqueous phase (aqueous I) was radioassayed. The organic phase was dried over sodium sulfate, and then evaporated. After the residue was redissolved in hexane, it was partitioned twice with acetonitrile (ACN). The ACN fractions were combined, evaporated, and redissolved in chloroform for TLC analysis. Negligible radioactive residues were found in the hexane fractions.

Various aqueous and solid fractions were also subjected to acid and enzyme hydrolysis. Only apples harvested on days 28 and 49 were subjected to the entire analysis scheme. Radiocarbon analyses were performed using either LSC or combustion. Four solvent systems were employed in TLC analysis: benzene/ethyl acetate (2:1); ethyl acetate/methylene chloride/toluene/EtOH (10:5:4:1); benzene/ethyl acetate (1:1); and ethyl acetate. Nonradiolabeled standards were eluted along with the radioactive samples. Radioactive bands were detected using autoradiography.

The results of the study were the same, whether [^{14}C]triazole metabolites or [^{14}C]phenyl-ring metabolites were characterized, indicating that metabolic products of triadimefon contain both moieties. Total apple residue declined from 0.83 ppm to 0.15 ppm during the first 21 days, and then remained constant; as in the other metabolism studies, the loss of residue was attributed primarily to volatilization. Residues in the peel decreased up to day 28, while residues in the pulp increased during this time. The lack of change after 28 days indicated that minimal residues were translocated from peel to pulp after that time. The distribution of radioactivity among the peel and pulp fractions appears to have changed little after 21 days. CBRS is concerned that such low levels of radioactivity were available for characterization; similar radioactive residues in cucumber and tomato samples were deemed to be too low for characterization.

The organosoluble residues, including the benzene washes, comprised 72 - 81% of the TRR for 21 - 49 day samples; aqueous fractions contained 3 - 11% of the TRR, and the solids approximately 10 - 19%, with most being found in the peel. Organosoluble fractions contained both diastereomers of KWG 0519, as well as an unidentified metabolite (4 - 5% of the TRR). The unidentified metabolite did not appear to be the same as an unidentified metabolite found in the barley metabolism study. The metabolite contained both the triazole and phenyl ring moieties, as it was identified in both apple studies. The registrant did not make additional attempts to identify the metabolite (i.e. HPLC or GC/MS).

The additional supporting data submitted by the registrant (MRID No. 421234-02) included raw data (i.e. sample weights and dpm data), as well as one set of TLC chromatograms for the benzene wash, and organosoluble fractions from the peel and pulp. The raw data support the values reported in Tables I through VII of the original submission, with a few minor corrections. The sample TLC is difficult to read, and locations of the unidentified metabolite were not clearly labeled. In addition, there were no data submitted for confirmation of the TLC results, i.e. HPLC or GC/MS. Consequently, the additional submission has not rendered the study acceptable for Phase 5 review. The requirement for an additional apple metabolism study is reserved. A new study may not be required, provided that no additional metabolites of concern [other than KWG 0519 (I and II), KWG 1342 (I and II), and KWG 1323] are identified in the required wheat study, and provided the remaining requirements for the cucumber and tomato metabolism studies are met. The need for an additional apple metabolism study will be reevaluated upon receipt of the required wheat metabolism study. If confirmatory GC/MS or MS spectra, or HPLC chromatograms confirming metabolite identities are available, they should be submitted to the Agency for review. If the registrant intends to conduct an additional apple metabolism study, CBRS strongly recommends that application of the radiolabeled formulation should include foliar contact. Apple metabolism presented in the subject MRIDs is summarized in Appendix III.

PIG METABOLISM (MALE AND FEMALE)

The study depicting metabolism of triadimefon in pigs under MRID No. 33058 was discussed in the List B inventory; the CBRS Phase 4 review of the study concluded that the

study might be acceptable for Phase 5 review, if the registrant provided raw data (TLC chromatograms, GC confirmatory chromatograms). The registrant has submitted additional information (MRID No. 421234-04), including additional summary data tables, tissue sample weights, dpm data, sample TLC chromatograms, and two GC radiochromatograms. The study is summarized and presented below, along with CBRS conclusions regarding the adequacy of the study.

Two pigs were treated with uniformly phenyl-ring-labeled [^{14}C]triadimefon. The animals were housed in dog metabolism cages, with minor modifications to accommodate swine. The study was comprised of both single dose and multi-dose phases. One male and one female pig were dosed with gelatin capsules containing a 5 mg/kg dose of the radiolabeled chemical which had been diluted with unlabeled triadimefon. The doses were administered using a balling gun. Urine and feces were collected over a period of 5 days (1, 2, 6, 24, 30, 48, 72, and 96 hours post-treatment), after which the female was sacrificed. This concluded the single-dose phase of the study. The multiple-dose phase was initiated 2 days later, when the male pig was fed radiolabeled triadimefon once daily for 5 consecutive days, with the same dose and formulation used in the single-dose phase. Urine and feces were collected at 6, 24, 30, 48, 54, 72, 78, and 96 hours post-treatment. The animal was sacrificed within 3 hours of the final consecutive dose.

Blood samples were collected during the multiple-dose study, but not following the single dose. Upon sacrifice of both the male and female pig, samples of the following tissues were taken for analysis: kidney, liver, heart, fat, muscle, skin, and brain. Composite urine samples were concentrated as an azeotrope with ACN, and evaporated to dryness. Residues were extracted with MeOH, evaporated, and dissolved in an acetate buffer in preparation for enzyme hydrolysis. The resulting hydrolysate was extracted with chloroform/ACN, and enzyme hydrolysis was repeated for the aqueous fraction. Organic fractions were analyzed using TLC. The aqueous fraction obtained from the second enzyme hydrolysis was then subjected to acid hydrolysis, and partitioned with chloroform/ACN. Both fractions were radioassayed, and the organic fraction was subjected to TLC analysis. Fecal samples were blended with methanol, filtered, and the filtrate concentrated for TLC analysis. The following solvent systems were used for TLC analysis: ethyl acetate; ethyl acetate/methylene chloride/toluene/EtOH (50:25:20:5); ACN/H_2O/Acetic Acid (90:8:2); and ACN/H_2O/NH_4OH (80:18:2). Nonradiolabeled standards were co-eluted with radioactive samples; radioactive bands were detected using autoradiography.

Liver, kidney, and fat samples were extracted with methanol very soon after sacrifice. Extracts were dried; and the residues dissolved in water for partition with chloroform/ACN. The aqueous fraction was acidified, and extracted again with chloroform/ACN. Organic and aqueous fractions were radioassayed, and the organic fraction analyzed using TLC. The remaining aqueous fraction was retained for enzyme hydrolysis. A sample isolated using preparative TLC, and suspected to be KWG 0519 Acid II, was subjected to reverse isotope dilution analysis. The sample was evaporated, and combined with pure unlabeled KWG 0519 Acid II; the mixture was dissolved in boiling ethyl acetate, and then cooled 24 hrs to enhance precipitation. The solution was filtered, and the crystals washed with ethyl acetate and dried.

8

Samples of the crystals were dissolved in methanol for LSC, and the remainder of the sample was recrystallized twice as described above, and analyzed for specific activity.

Metabolism in pigs was found to proceed through reduction of the carbonyl group, and then hydroxylation and oxidation reactions of the *t*-butyl functional group, to form metabolites KWG 0519, KWG 1323, KWG 1342, and KWG 0519 acid. More than 90% of the radioactivity was recovered from the urine within 72 hours of dosing, indicating rapid metabolism and elimination. The registrant noted that the KWG 1342 and KWG 0519 acid metabolites were found primarily in the II form, indication that swine enzymes exhibit some degree of stereoselectivity between the two isomers.

Although the registrant has submitted the required TLC chromatograms, along with raw data used to calculate ppm and % radioactivity (MRID No. 421234-04), the additional data do not render the study acceptable for Phase 5 review. Current Agency guidelines require that animals should be dosed orally for at least 3 days, and should have no preconditioning through feeding of unlabeled pesticide. The single dose experiments cannot be used to support reregistration; the multiple dose experiment cannot be used since the male pig was treated with a mixture of radiolabeled and nonradiolabeled material 7 days prior to initiation of the multiple-dose phase of the study. In addition, supporting raw data did not include HPLC or GC/MS confirmation of metabolite identifications. The Phase 4 review cited nature of the residue studies in the ruminant and poultry in the data gap. While the swine study alone is unacceptable, the results will contribute to our understanding of the metabolic profile of triadimefon in animals, once the required ruminant and poultry studies are submitted. Results of the swine metabolism study are summarized in Appendix IV.

cc (with appendices I - IV): CSwartz; Tridimefon List B File; SF; RF; Circulation
H7509C:CBRS:CSwartz:CM2:RM804F:703 305 5877:3/20/92
RDI:WJHazel:9/17/92 MSMetzger:9/22/92 EZager:9/22/92

APPENDIX I

GRAPE METABOLISM

Uniformly phenyl-ring-labeled [^{14}C]triadimefon

Distribution of [^{14}C]triadimefon Metabolites in Grapes 56 Days after Treatment[1]

Compound	% Distribution of ^{14}C organosoluble		% ^{14}C Watersoluble[3]	Total
	Initial Extract	Reflux Extract[2]		
Triadimefon	1.1 (0.06)			1.1 (0.06)
KWG 0519	33.8 (1.97)	21.2 (1.23)	0.6 (0.03)	55.6 (3.23)
KWG 1342	0.8 (0.05)			0.8 (0.05)
p-Chlorophenol		1.5 (0.09)		1.5 (0.09)
KWG 0519-conjugate I			0.6(0.03)	0.6 (0.03)
KWG 0519-conjugate II	1.8 (0.10)		2.0 (0.12)	3.8 (0.22)
KWG 0519-conjugate III	1.1 (0.06)		0.1 (0.01)	1.2 (0.07)
KWG 1342-conjugate I & II			2.0 (0.12)	2.0 (0.12)
KWG 1342-conjugate III & IV	5.9 (0.34)		6.8 (0.40)	12.7 (0.74)
p-Chlorophenol-conjugate I			3.8 (0.22)	3.8 (0.22)
p-Chlorophenol-conjugate II			0.3 (0.02)	0.3 (0.02)
p-Chlorophenol-conjugate III			0.6 (0.03)	0.6 (0.03)
Metabolite X		6.2 (0.36)		6.2 (0.36)
Diffuse Activity	2.1 (0.12)	2.1 (0.12)	0.6 (0.03)	4.8 (0.27)
Total Extractable Activity	46.6 (2.70)	31.0 (1.80)	17.4 (1.01)	95.0 (5.51)
Solids (unextractable activity)				5.0
Total				100

[1] Values are presented in the table as % radioactivity (ppm radioactivity).

[2] Reflux extraction of solids corresponds to mild acid hydrolysis (24 hours with 1% HCl in MeOH).

[3] Watersoluble radioactivity from initial extraction with acetone/methylene chloride is reported.

APPENDIX II

CUCUMBER AND TOMATO METABOLISM

Uniformly phenyl-ring-labeled [^{14}C]triadimefon

Table 1. Distribution of Radioactivity in Tomatoes and Cucumbers Following 1 Application to Seedlings

Crop	TSI[1] (Days)	% ^{14}C Organosoluble	% ^{14}C Water Soluble	% ^{14}C in Plant Solids	Total ppm ^{14}C
Tomato	0	98.5	1.2	0.3	12.25
	1	98.5	1.0	0.4	12.43
	3	98.0	1.3	0.7	13.68
	5	96.0	3.0	1.0	7.66
	7	93.8	4.4	1.8	5.73
	14	90.6	6.8	2.5	3.74
	21	86.7	9.6	3.7	2.92
	28	83.5	12.2	4.3	1.42
	70-foliage				0.36[2]
	70-fruit				0.04[2]
Cucumber	0	97.5	2.0	0.5	14.84
	1	95.9	3.1	0.9	11.87
	3	94.3	4.5	1.1	10.21
	5	91.5	6.6	1.9	6.70
	7	89.9	8.1	2.0	6.76
	14	75.2	20.8	4.0	3.68
	21	72.1	23.6	8.2	1.77
	28	61.3	20.4	12.4	1.53
	70-foliage				0.62[2]
	70-fruit				0.10[2]

[1] TSI = Treatment to sampling interval. Mature cucumber and tomato fruits were only available for day 70.

[2] Due to the low levels of radioactivity present in these samples, no attempt was made to characterize the residues.

11

Table 2. The Nature of ^{14}C Residues in Organosoluble Extracts of Tomato and Cucumber Seedlings Following 1 Application to Seedlings[1]

Crop	TSI (Days)[2]	Polar Metabolite[3]	KWG 0519 I	KWG 0519 II	Triadimefon (parent)	Total
Tomato	0	1.3	1.0	1.0	95.2	98.5
	1	1.7	3.4	3.1	90.1	98.3
	3	3.2	7.0	4.6	83.2	98.0
	5	3.3	12.8	8.4	71.3	95.8
	7	5.1	14.1	8.5	65.5	93.2
	14	6.3	14.7	7.9	61.2	90.1
	21	6.5	13.0	6.5	60.5	86.5
	28	7.8	14.8	6.5	54.4	83.5
Cucumber	0	1.1	0.6	1.4	94.4	97.5
	1	1.7	2.9	4.6	86.7	95.9
	3	2.7	11.2	15.1	65.3	94.3
	5	5.2	17.9	14.6	53.6	91.3
	7	8.0	22.5	18.9	40.5	89.9
	14	12.9	18.5	16.8	27.0	75.2
	21	19.5	20.9	20.3	11.4	72.1
	28	17.1	19.4	16.7	8.1	61.3

[1] All values are reported as % of the total radioactive residue (TRR).

[2] TSI = treatment to sampling interval.

[3] Attempts to identify the polar metabolite were unsuccessful; however, the registrant provided a reasonable argument that the metabolite was a glucoside of metabolite KWG 0519, loosely bound to "another naturally occurring moiety."

Table 3. Distribution of ^{14}C Radioactivity in Tomatoes and Cucumbers Following Multiple Applications[1]

Crop	Sample Type	TSI (Days)[2]	% ^{14}C Organosoluble	% ^{14}C Water-Soluble	% ^{14}C in Plant Solids	Total ^{14}C (ppm)
Tomato	Foliage	7	89.9	6.8	3.3	10.33
		14	91.8	4.1	4.1	17.39
		21	89.8	2.1	8.1	5.54
	Fruit	7	91.7	6.2	2.4	1.06
		14	83.3	14.6	2.1	0.58
		21	--	--	--	0.14[3]
Cucumber	Foliage	7	87.0	7.0	6.0	18.30
		14	87.2	5.9	6.9	39.18
		21	84.9	6.8	8.3	18.19
	Fruit	7	92.0	5.1	2.9	1.11
		14	84.0	11.0	5.0	0.53
		21	--	--	--	0.01[3]

[1] Three applications were made.

[2] TSI = treatment to sampling interval; the first sample was taken 7 days after the final application.

[3] Radioactive residues in these samples were too low to be characterized.

Table 4. The Nature of ^{14}C Residues in Organosoluble Extracts of Cucumbers and Tomatoes Following Multiple Applications[1]

Crop	Sample Type	TSI (Days)[2]	Polar Metabolite[3]	KWG 0519 I	KWG 0519 II	Triadimefon	Total
Tomato	Foliage	7	3.8	15.7	2.8	66.1	88.4
		14	5.3	13.6	2.3	70.6	91.8
		21	21.6	19.5	4.8	43.7	89.6
	Fruit	7	nd[4]	7.3	13.6	68.9	89.8
		14	nd	9.3	18.3	49.1	76.7

Table 4. The Nature of ^{14}C Residues in Organosoluble Extracts of Cucumbers and Tomatoes Following Multiple Applications[1]

Crop	Sample Type	TSI (Days)[2]	Polar Metabolite[3]	KWG 0519 I	KWG 0519 II	Triadimefon	Total
Cucumber	Foliage	7	3.9	11.3	9.6	60.4	85.2
		14	3.8	16.4	8.6	48.0	76.8
		21	19.8	16.8	11.7	36.0	84.3
	Fruit	7	nd	7.6	32.4	50.2	90.2
		14	nd	7.9	32.0	40.4	80.3

[1] A total of three applications were made; values presented represent % of the total radioactive residue (TRR).

[2] TSI = treatment to sampling interval; the first samples were harvested 7 days following the final application.

[3] Attempts to identify the polar metabolite were unsuccessful; however, the registrant provided a reasonable argument that the metabolite was a glucoside of metabolite KWG 0519, loosely bound to "another naturally occurring moiety."

[4] Samples contained less than 0.25% of the TRR.

APPENDIX III

APPLE METABOLISM

Uniformly phenyl-ring-labeled [^{14}C]triadimefon

Triazol-3,5-labeled [^{14}C]triadimefon

Table 1. Levels of ^{14}C Radioactive Residues in Apples[1]

TSI[2]	Peel[3]		Pulp		Total Apple	
	Triazol-^{14}C	Ring-^{14}C	Triazol-^{14}C	Ring-^{14}C	Triazol-^{14}C	Ring-^{14}C
0	8.44		<0.01		0.83	
3	3.12		0.02		0.30	
7	0.95	0.75	0.04	0.03	0.26	0.19
14	0.80	0.58	0.03	0.03	0.21	0.15
21	0.39		0.03		0.15	
28	0.63		0.06		0.15	
35	0.65	0.58	0.08	0.03	0.16	0.08
42	0.59		0.05		0.15	
49	0.75		0.07		0.16	

[1] All values reported are ppm radioactivity, based on fresh weight of the sample.

[2] TSI = treatment to sampling interval.

[3] Residue levels in the peel include radioactivity found in the benzene washes.

Table 2. Distribution of Radioactivity in Fractions Resulting from the First Extraction of [^{14}C]triazol-treated Apples[1]

TSI[2]	Peel				Pulp		
	Benzene Wash	Aqueous	Organic	Solids	Aqueous	Organic	Solids
0	83 (0.69)	<1 (<0.01)	16 (0.13)	<1 (<0.01)	<1 (<0.01)	1 (<0.01)	<1 (<0.01)
3	67 (0.20)	1 (<0.01)	22 (0.07)	4 (0.01)	1 (<0.01)	4 (0.01)	1 (<0.01)

Table 2. Distribution of Radioactivity in Fractions Resulting from the First Extraction of [^{14}C]triazol-treated Apples[1]

	Peel				Pulp		
TSI[2]	Benzene Wash	Aqueous	Organic	Solids	Aqueous	Organic	Solids
7	46 (0.12)	2 (<0.01)	36 (0.09)	6 (0.02)	1 (<0.01)	9 (0.02)	<1 (<0.01)
14	49 (0.10)	1 (<0.01)	28 (0.06)	8 (0.02)	1 (<0.01)	10 (0.02)	1 (<0.01)
21	15 (0.02)	<1 (<0.01)	42 (0.06)	14 (0.02)	3 (<0.01)	24 (0.04)	1 (<0.01)
28	5 (0.01)	4 (<0.01)	40 (0.06)	15 (0.02)	4 (<0.01)	29 (0.02)	2 (<0.01)
35	8 (0.01)	6 (0.01)	33 (0.05)	11 (0.02)	5 (<0.01)	36 (0.06)	1 (<0.01)
42	6 (0.01)	4 (<0.01)	40 (0.06)	17 (0.03)	5 (<0.01)	26 (0.04)	2 (<0.01)
49	10 (0.02)	6 (0.01)	34 (0.05)	13 (0.02)	4 (<0.01)	31 (0.05)	2 (<0.01)

[1] Values are reported as: % of the total radioactive residue (ppm radioactivity); values for ring-labeled apples are on a similar order of magnitude, however only 7-, 14-, and 35-day results are available.

[2] TSI = treatment to sampling interval.

Table 3. Distribution of [^{14}C]triazole Metabolites Following Extensive Fractionation of Peel and Pulp Samples[1]

Fraction	28-Day Apples			49-Day Apples		
	Peel	Pulp	Total	Peel	Pulp	Total
Organic (Combined)						
Triadimefon	10.8	2.1	13.0	10.4	2.1	12.5
KWG 0519 I	14.9	11.2	26.1	14.5	10.4	24.9
KWG 0519 II	13.6	7.1	20.7	14.8	9.4	24.2
Metabolite I[2]	2.8	3.1	5.9	1.5	2.1	3.6
Unidentified	8.5	7.1	15.6	5.1	9.5	14.6
Total	50.6	30.6	81.3	46.3	33.5	79.8
Aqueous (Combined)	5.7	5.3	11.0	4.8	6.4	11.2
Unextracted (Solids)	5.0	0.9	5.9	6.0	1.0	7.0
Total	61.3	36.8	98.2	57.1	40.9	98.0

[1] Values reported are expressed as % of the total radioactive residue (TRR); the complete fractionation scheme was performed for only these samples.

[2] Metabolite I was not identified, but contains both the triazole and phenyl ring moieties, since it was identified in both studies.

APPENDIX IV

SWINE METABOLISM

Uniformly phenyl-ring-labeled [^{14}C]triadimefon

Distribution of ^{14}C Radioactivity in Tissues of a Male Pig Sacrificed 3 Hours After the Last of 5 Consecutive Doses[1]

Metabolite	Kidney[2]	Liver[3]	Fat[4]
Triadimefon	0.6	3.4	24.0
KWG 0519 I	2.4	18.8	27.5
KWG 0519 II	1.4	11.8	20.5
KWG 1323	36.2	4.3	--
KWG 1342 I	--	--	5.5
KWG 1342 II	25.2	7.2	2.2
KWG 0519 Acid II	16.4	23.1	--
Unknown	--	7.4	--
Origin[5]	5.1	6.4	23.7
Residual Solids	5.9	11.9	6.6
Water soluble	6.8	5.7	--
Total	100.0	100.0	100.0

[1] All values reported are expressed as % of the total tissue residue.

[2] Total residue in kidney = 4.0 ppm (equivalents triadimefon); [3] Total residue in liver = 3.14 ppm; [4] Total residue in fat = 1.0 ppm.

[5] Origin in the ethyl acetate solvent system.

TRIADIMEFON (CASE 2700/CODE 109901) RESIDUE CHEMISTRY DATA SUMMARY THROUGH 09/17/92 (FOR AGENCY USE ONLY)[1]

REASSESSMENT OF U.S. TOLERANCES AND POTENTIAL FOR HARMONIZATION WITH CODEX[2]

Guideline Number and Topic[3]	Are data requirements satisfied?	MRID(s)[4]
171-3 Directions for use	N[5]	
171-4(a) Plant Metabolism	N[6]	42123401, -02, -03
171-4(b) Animal Metabolism	N[7]	42123404
171-4(c) Residue Analytical Methods - Plants	N[8]	42346601 42346701
171-4(d) Residue Analytical Methods - Animals	N	
171-4(e) Storage Stability	N[9]	
171-4(k) Crop Field Trials		
171-4(k) Root and Tuber Vegetables Group		
Sugar beets [see 171-4(l)]	Y	
171-4(k) Leaves of Root and Tuber Vegetables	Y	
Sugar beet tops		
171-4(k) Legume Vegetables (succulent/dried)		
Chick Peas	N	
171-4(k) Pome Fruits Group		
Apples [see 171-4(l)]	N	
Pears		
171-4(k) Cucurbit Vegetables Group	N	
171-4(k) Small Fruits and Berries Group		
Grapes [see 171-4(l)]	N	
Raspberries	Y	
171-4(k) Tree Nuts Group		
Almonds	Y[10]	
171-4(k) Cereal Grains Group		
Barley [see 171-4(l)]	N	
Wheat [see 171-4(l)]	N	
171-4(k) Forage, Fodder, and Straw of Cereal Grains		
Barley forage and straw	N	
Wheat forage and straw	N	
171-4(k) Grass Forage, Fodder, and Hay Group		
Grass, seed	N	

TRIADIMEFON (CASE 2700/CODE 109901) RESIDUE CHEMISTRY DATA SUMMARY THROUGH 09/17/92 (FOR AGENCY USE ONLY)[1]

REASSESSMENT OF U.S. TOLERANCES AND POTENTIAL FOR HARMONIZATION WITH CODEX[2]

Guideline Number and Topic[3]	Are data requirements satisfied?	MRID(s)[4]
171-4(k) Miscellaneous Commodities		
Pineapple [see 171-4(l)]	N[11]	
171-4(l) Processed Food/Feed		
	N[12]	42346601
Apples		42346701
Barley		42013201
Grapes		
Pineapple		
Sugar beets		
Wheat		
171-4(j) Meat/Milk/Poultry/Eggs	Y[13]	
171-4(f) Potable Water	N/A	
171-4(g) Fish	N/A	
171-4(h) Irrigated Crops	N/A	
171-4(i) Food Handling Establishments	N/A	
171-5 Reduction of Residues	N/A	
171-6 Proposed Tolerance	N[14]	

[1]List B Phase 4 Review issued 01/31/91. This summary is tentative and is subject to error and change.

[2]Codex has numerous MRL's for the combined residue of triadimefon and triadimenol. US tolerances add 1-(4-chlorophenoxy)-3-methyl-3-hydroxymethyl-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 1-(4-chlorophenoxy)-3-methyl-3-hydroxymethyl-1-(1H-1,2,4-triazol-1-yl-2-butanone to the residue of concern. The tolerance values and MRL's for a given commodity are comparable, but usually not identical.

[3]N/A = Guideline requirement not applicable.

[4]MRIDs that were reviewed in the current submission are designated in shaded type.

[5]Translated label supplied for almonds showed two crops with no US tolerances: sugar cane and coffee. L. Cheng, 06/15/92, CBRS No. 9851.

[6] CBRS No. 9422; CSwartz, 9/23/92. A wheat metabolism study remains outstanding. The Phase 4 review required additional information to upgrade the tomato and cucumber, grape, and apple metabolism studies.

Tomato and Cucumber (MRID No. 421234-01): The study is acceptable, pending receipt of the GC/MS and MS spectra confirming identification of triadimefon and KWG 0519.

Apples (MRID No. 421234-02): The study is not acceptable, since additional data submitted did not include GC/MS or HPLC confirmation of metabolites. CBRS will not require an additional apple metabolism study, provided the additional tomato/cucumber data are submitted, and provided no new metabolites of concern are identified in the required wheat metabolism study.

Grapes (MRID No. 421234-03): The additional information has rendered the study acceptable.

[7] CBRS No. 9422, CSwartz, 9/23/92. Ruminant and poultry metabolism studies were required in the Phase 4 review (SRFunk, 1/31/91). The registrant submitted additional information (MRID No. 421234-04) pertaining to a previously submitted swine metabolism study. The study is not acceptable. At this time, CBRS will not require a swine metabolism study. If the metabolism of triadimefon in the ruminant differs significantly from that in poultry, or if either differs significantly from metabolism in the rat, then a swine metabolism study may be required.

[8] Method summarized in MRID 92188042 has been validated for apples and grapes (See Phase 4 Review).

[9]Requirement of Phase 4 Review has been modified. See L. Cheng, 06/15/92, CBRS No. 9851.

[10]Registrant will not support this use (L. Cheng, 06/15/92, CBRS No. 9851). The tolerance must be revoked.

[11]Data depicting residues of triadimefon and the regulated metabolites in/on pineapple are required. The 50% a.i. DF formulation must be applied at the maximum label rate of 6.7 oz. a.i. in 100 gallons of water as a 3 minute postharvest dip for fresh pineapple.

[12] APPLE: Mass balance data required. Storage stability data required for grape processed commodities (to be translated to apple). See 171-6. S. Funk, 07/10/92, CBRS No. 10114.

GRAPE: Processing procedure must be described. Storage stability data required for grape processed commodities. See 171-6. S. Funk, 07/10/92, CBRS No. 10114.

BARLEY: Processing study required in Phase 4 Review has been deleted. Registrant may translate wheat processing to barley. L. Cheng, 06/15/92, CBRS No. 9851.

PINEAPPLE: Processing study is acceptable, pending submission of storage stability data for fresh pineapple and processed pineapple fractions. Concentration did not occur in juice, but did occur in bran (1.3X). The fresh pineapple tolerance of 3 ppm must be substantiated (field trials) before establishing a bran feed additive tolerance. The registrant has proposed 5 ppm. S. Funk, CBRS No. 8699, 09/xx/92; MRID No. 42013201.

[13]Storage stability data needed. See Phase 4 Review.

[14]The following food/feed additive tolerances are needed:
apple pomace (dry), 10 ppm; apple pomace (wet), 2 ppm; grape pomace (dry), 35 ppm; grape pomace (wet), 16 ppm; raisin waste, 10 ppm; raisins, 6 ppm. S. Funk, 07/10/92, CBRS No. 10114.

cc: CSwartz; Triadimefon List B File; J. Ellenberger, SRRD.