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MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Simazine (080807), Reregistration Case No. 0070 and Special Review. Registrant Ciba-Geigy Corporation. Guideline 171-4a, Simazine Corn Field Metabolism Study. CBRS No. 13439, DPBarcode No. D200940, MRID 43159001.

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In response to an Agency DCI of 9/91, registrant Ciba-Geigy Corporation submitted data on a field metabolism study with simazine in corn. Assignment instructions are to review the submission. Conclusions and Recommendations below pertain only to data pertinent to the present submission.

Tolerances are established for residues of the herbicide simazine, 2-chloro-4,6-bis(ethylamino)-*s*-triazine, in or on various raw agricultural commodities (40 CFR 180.213), and for combined residues of simazine and its metabolites 2-amino-4-chloro-6-ethylamino-*s*-triazine, and 2-chloro-4,6-diamino-*s*-triazine, in or on the specific commodities bananas and fish (40 CFR 180.220(b)). Designations for the metabolites in the tolerance expression are G-28279 and

G-28273, respectively (see Figure 1). Simazine is a List A Chemical. The Residue Chemistry Chapter to the Registration Standard was issued 10/13/83, a Reregistration Standard (Guidance Document) was issued 3/84, and a Second Round Review Residue Chemistry Chapter was issued 1/30/89. Special Review has been initiated on triazine herbicides, including simazine (59 FR 60412, 11/23/94, PD1).

Conclusions

1. The application rate was 1.7 lb ai/A preemergence, less than half the label maximum of 4 lb ai/A. If the data from this submission are used in exposure assessment, residue magnitudes should be adjusted accordingly.

2. Simazine undergoes significant metabolism in corn. The Registrant has identified chloro, hydroxy, and amino metabolites, each containing an intact triazine ring (for details, see Table 4 and Figure 1 of this review). Using Extraction Method I, residues assigned represented 45% TRR in silage forage, 28% TRR in final harvest fodder, and 19% TRR in final harvest grain. Simazine and other chloro compounds combined represented 8% TRR in silage and 2% TRR in final harvest grain.

3. With Extraction Method II, an acid autoclave procedure, 73% TRR in silage and more than half the TRR in each of final harvest fodder and grain was converted to cyanuric acid and the simazine hydroxy metabolites G-30414, GS-17792, and GS-17791 (see Table 4 and Figure 4). This observation indicates that the position of the HED Metabolism Committee, that TRR should represent total residues containing the triazine ring, is a reasonable assumption.

4. The corn metabolism data reviewed here are consistent with the summary data submitted as part of the Registrant's comments on the triazine PD1 (CBRS 15634, 8/1/95, J. Abbotts). There is no need to revise that previous review because of metabolism data.

5. The present submission is a corn field metabolism study at a single site in IL. Data in the present submission, along with data on atrazine metabolism in corn, will allow dietary exposure assessment to be conducted using conservative assumptions.

Recommendations

Guideline 171-4a, Nature of the Residue in Plants, is satisfied for corn.

We recommend that the Registrant be provided a copy of this memo.

DETAILED CONSIDERATIONS

Background

In 1990, Dietary Exposure Branch determined anticipated residues for simazine, based on parent and chloro metabolites only (Memo, 1/19/90, M.S. Metzger). A subsequent residue chemistry review noted that for triazine herbicides including simazine, all metabolites containing the intact triazine ring were considered of toxicological concern (Memo, 2/15/90, M.S. Metzger). Consequently, anticipated residues for simazine were revised to reflect total residues containing the triazine ring; much of this revision depended on the translation of data from atrazine to simazine (Memo, 6/15/90, M.S. Metzger). The Agency later issued a DCI, received by registrant in 9/91, requiring additional data on simazine metabolism.

The HED Metabolism Committee noted that Agency DCIs, including the 9/91 DCI, required radiolabel field studies for crops on which atrazine or simazine were registered. Accordingly, the Committee decided that exposure assessment for dietary cancer risk from atrazine or simazine would be conducted on the basis of total radioactive residues from radiolabel field trials, or if such data were not available, then with the best data available for estimating total triazine ring residues. The Committee noted that this decision could be altered, depending on the results of the cancer/chronic feeding study with hydroxyatrazine (Memo, 8/7/92, M.S. Metzger).

During a telephone conversation in 1992, CBRS clarified requirements for simazine plant metabolism studies. Radiolabel field studies were required on corn, citrus, apples, and a small fruit or berry (Memo, 9/30/92, M.S. Metzger). The memo of the conversation reported the following information (Ibid.):

"Mr. Parshley [Ciba-Geigy] stated that the radiolabel field studies for atrazine showed no variability in either the level of the total radioactive residue or in the ratio of metabolites among the 3 geographical locations in which studies were done. Based on this information, as well as on the similar structures of atrazine and simazine, CBRS agreed that a single radiolabel field study for simazine on corn performed in IL would suffice for this commodity."

In response to Agency DCIs, registrant Ciba-Geigy submitted data on radiolabeled field metabolism studies for atrazine and simazine. As part of its comments on the PD1, the Registrant submitted a summary of metabolism data, including data on simazine in plants. Although the submitted simazine studies were not yet reviewed, the summary was evaluated, with the provision that additional conclusions and recommendations upon full review would not be precluded (CBRS 15634, 8/1/95, J. Abbotts).

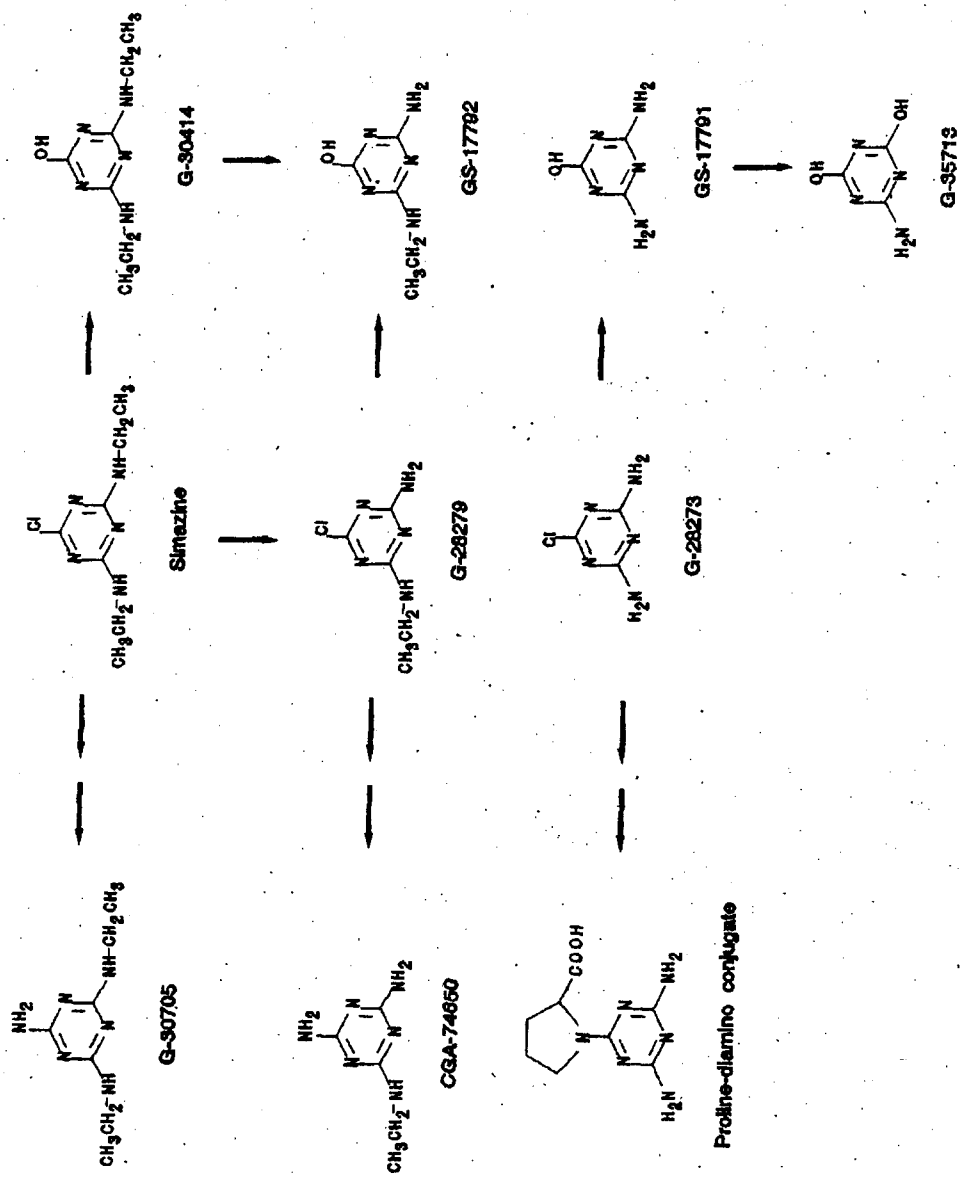


Figure 1. Simazine metabolites reported in plants.

With additional reviewed data on atrazine plant metabolism and submissions on hydroxyatrazine toxicology, the HED Metabolism Committee revisited its provisional conclusions and recently issued two decisions pertaining to triazine chemicals. The first decision was that the residues of concern for cancer dietary risk from atrazine are parent and chloro metabolites (Memo, 9/29/95, J. Abbotts); pending review of submitted metabolism studies, parent and chloro metabolites were also of concern for dietary cancer risk from simazine. Parent and chloro metabolites are those in the central pathway in Figure 1.

The second decision for atrazine was that for chronic non-cancer dietary risk from atrazine, evaluations should be performed on two different sets of residues. One evaluation should be based on anticipated residues of combined free hydroxy metabolites, using the RfD for hydroxyatrazine; this RfD will be assigned by TOX for the purposes of dietary risk assessment. The second evaluation should be based on anticipated residues for all other metabolites (total radioactive residues minus free hydroxy metabolites), using the RfD for parent atrazine. (Memo, 11/28/95, J. Abbotts)

For simazine, the Metabolism Committee decided that pending review of submitted metabolism studies, assessment of non-cancer chronic dietary risk should initially be based on total radioactive residues (TRR), with the RfD for simazine. This assessment would be considered conservative because the RfD for simazine is lower than the expected RfD for hydroxyatrazine, and would generate an estimated risk greater than either risk generated from the two residue subset approach used with atrazine. If it ultimately becomes necessary to conduct dietary risk using the same approach as for atrazine, the RfD value assigned to hydroxyatrazine would be translated to hydroxysimazine (Ibid.). The simazine free hydroxy metabolites are those on the right side of Figure 1; hydroxysimazine is designated G-30414.

In response to the 9/91 DCI, the Registrant provided the following document:

^{14}C-Simazine: Nature of the Residue in Corn, Laboratory Project HWI 6117-210, Ciba-Geigy Corporation, February 2, 1994 (MRID 43159001).

Review of the present submission will be conducted with recognition of the recent decisions of the Metabolism Committee.

Field Procedures

Plots 6 x 14 ft, consisting of silty clay loam soil, were prepared for field corn at the Ciba-Geigy Midwest Research Station, Dewey IL. Each of a control and a treatment plot were

planted in April 1992 with field corn seed, Funk's G-4160 from Ciba Seeds. The test substance was the 4L formulation, containing ^{14}C-simazine uniformly labeled in the aromatic ring, at a specific activity of 46,620 dpm/μg and a radiochemical purity of 98%.

The 4L formulation was applied pre-emergence after planting on the same day using hand sprayers at a target rate of 2 lb ai/A; analysis of spray aliquots indicated an actual rate of 1.70 lb ai/A. The control plot was treated in the same manner, but with formulation containing no simazine. Corn forage samples were collected at 30 days after planting and application, corn silage samples at 120 days, and corn grain and fodder were harvested at maturity (162 days). At maturity, ears were removed from the stalk, husks were removed from ears and discarded, and stalks and leaves were collected as fodder samples. Control samples were harvested and processed in the same fashion as treated samples. Soil samples were also taken. Samples were collected by hand, placed into prelabeled plastic bags, and stored in a walk-in freezer, kept at approximately -20°C. Samples were packed and shipped frozen to the performing laboratory, Hazleton Wisconsin, Madison, WI; all samples were shipped within two months of field collection. Upon arrival at Hazleton, samples were placed into frozen storage, and stored at approximately -20°C when not being analyzed.

CBRS Comment, Field Procedures

The present submission described the rate of application as the maximum label rate. However, a label of 3/13/95 for Princep 4L, the applied formulation, contains a maximum rate of 4 lb ai/A, preemergence. The Second Round Review Residue Chemistry Chapter (1/30/89) also indicates 4 lb ai/A as the maximum label rate for corn. These considerations lead to the following comment:

Conclusion 1: The application rate was 1.7 lb ai/A preemergence, less than half the label maximum of 4 lb ai/A. If the data from this submission are used in exposure assessment, residue magnitudes should be adjusted accordingly.

Laboratory Analysis

Plant samples were frozen in liquid nitrogen and ground in a mill. Total radioactive residues (TRR) of corn samples were determined by combustion of aliquots in a sample oxidizer and liquid scintillation counting (LSC). Results are summarized in Table 1; forage, silage, and fodder samples are described above under Field Procedures.

Table 1. TRR in Corn Samples.

Sample	Days after Treatment	TRR, ppm
Forage	30	0.158
Silage	120	0.209
Fodder	162	0.493
Grain	162	0.044

Table note: Study location was IL.

The most extensive extraction protocol was Method I applied to mature corn fodder, shown in Figure 2. Plant samples were placed into methanol:water, 80:20, ground in a Tissumizer, and filtered. The methanol in the extract fractions was removed by rotary evaporation, and the extract was partitioned with equal volumes of chloroform. For corn silage, the extraction ended at this point.

For final harvest fodder and grain, the solid after methanol:water extraction was placed in a Soxhlet apparatus, and soaked in water overnight. Methanol was added and residues were extracted by Soxhlet for 4 h. The Soxhlet extract was concentrated by rotary evaporation and redissolved in water. After Soxhlet extraction, the remaining nonextracted residue was refluxed in 1% sodium chloride solution for 4 h, cooled, and filtered. The filtrate was concentrated and redissolved in water. For the grain sample, the mixture was brought to 0.5 M HCl, stirred for 2 h on a hot plate, centrifuged, and the filtrate decanted. The extraction ended at this point for the grain.

For the fodder sample, the nonextracted residue after sodium chloride extraction was resuspended in buffer and treated successively by ß-glucosidase, α-amylase, protease, and cellulase. As will be seen below, treatment by all enzymes combined released only a small portion of the TRR. The nonextracted residue following enzyme treatments was split into two approximately equal samples. One sample was added to 200 ml of 1 N HCl; the second sample was added to 200 ml of 1 N HCl with 40 g thioglycolic acid. Each sample was separately refluxed for 6 h, cooled, and filtered. Each filter cake was washed with 95% ethanol, and the acid, thioglycolic acid, and ethanol extracts were concentrated separately. The nonextracted residue following thioglycolic acid treatment was added to 6N HCl and refluxed for 4 h, cooled, and filtered. The remaining unextracted residue was analyzed by combustion and liquid scintillation counting.

Silage, fodder, and grain were also extracted by Method II, shown in Figure 3. Plant samples were incubated in 0.5 N HCl in an autoclave for approximately 24 h, filtered, and rinsed with water. The extract was concentrated and partitioned three times with equal volumes of chloroform. The chloroform layers were combined and partitioned once with an equal volume of water. The water layer was combined with the aqueous fractions.

For both Methods I and II, radioactivity in solids was determined by combustion and liquid scintillation counting, and radioactivity in aqueous and organic fractions was determined by liquid scintillation counting directly. The distributions of TRR with Methods I and II are summarized in Tables 2 and 3:

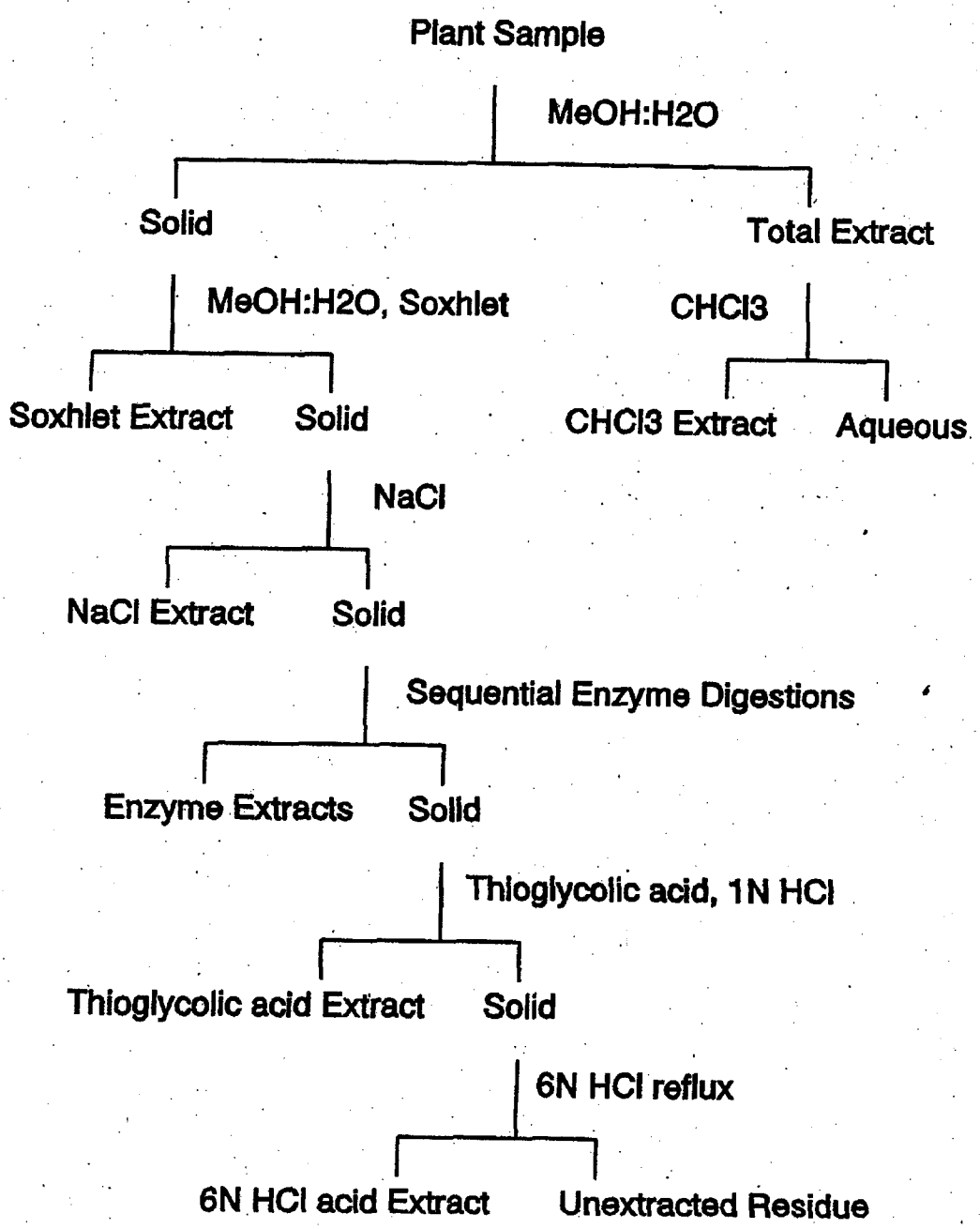


Figure 2. Extraction Method I for corn samples.

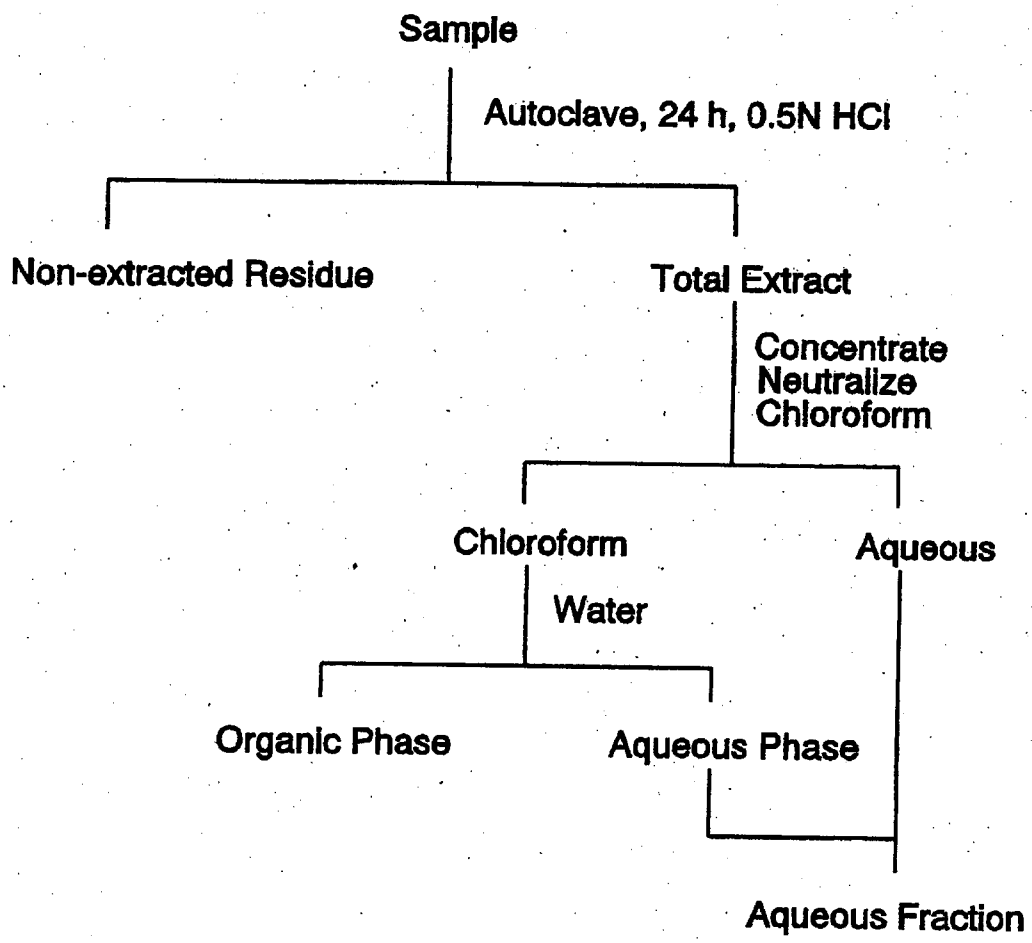


Figure 3. Extraction Method II for corn.

Table 2. Extraction of TRR from corn samples by Method I.

Fraction	% TRR (ppm) for [100% TRR]:		
	Silage [0.209 ppm]	Final harvest fodder [0.493 ppm]	Final harvest grain [0.044 ppm]
Chloroform	2.9 (0.006)	3.9 (0.019)	0.2 (<0.001)
Aqueous	69.7 (0.146)	53.7 (0.265)	58.0 (0.026)
Soxhlet		12.9 (0.064)	8.1 (0.004)
NaCl		9.6 (0.047)	23.5 (0.010)
Combined Enzyme		1.6 (0.008)	
Thioglycolic acid		10.4 (0.051)	
1N HCl		5.6 (0.028)	
6N HCl		0.7 (0.004)	
Unextracted	22.8 (0.048)	5.0 (0.025)	8.9 (0.004)

Table notes: Method I is outlined in Figure 2 and described in the text. Combined enzyme and subsequent treatments were performed only on fodder.

Table 3. Extraction of TRR from corn samples by Method II.

Fraction	% TRR (ppm) for [100% TRR]:		
	Silage [0.209 ppm]	Final harvest fodder [0.493 ppm]	Final harvest grain [0.044 ppm]
Chloroform	0.2 (<0.001)	0.3 (0.001)	0.6 (<0.001)
Aqueous	86.9 (0.182)	75.6 (0.373)	77.3 (0.034)
Unextracted	13.0 (0.027)	18.5 (0.091)	24.3 (0.011)

Table notes: Method II is shown in Figure 3.

Residue Analysis

Fractions extracted by Method I were analyzed to identify residues. Organic and aqueous fractions were analyzed by 2-dimensional thin layer chromatography (2-D TLC) using silica gel plates. The solvent in the first dimension was

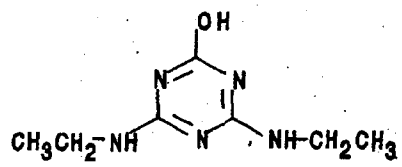
chloroform:methanol:formic acid:water (75:20:4:2), and the solvent in the second dimension was butanol:acetic acid:water (80:10:10). One-dimensional TLC was also used to purify radioactive residue fractions and to verify the results of other analyses.

Organic (chloroform) fractions from extraction Method I were analyzed by 2-D TLC and by reverse phase HPLC using a YMC-Pack ODS column, eluted with gradients in 1% acetic acid in water and 1% acetic acid in acetonitrile (HPLC Method I). Peaks from TLC and HPLC were assigned based on similar mobilities with standards. Residues assigned in the organic fractions were parent simazine, the chloro metabolites G-28279 and G-28273, and G-30705 (see Figure 1 for structures). As can be seen from Table 2, organic soluble residues were always a relatively small portion of TRR.

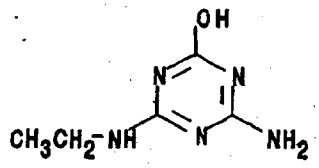
Aqueous fractions, including aqueous fractions from the extended versions of Extraction Method I (Figure 2), were analyzed by Aminex A-4 cation exchange chromatography and by HPLC, using HPLC Method I or using a Whatman Partisil PAC column in series with a Phenomenex SCX (strong cation exchange) column, eluted with gradients in acetonitrile:0.1 M ammonium formate (94:6) and acetonitrile:0.1 M ammonium formate:methanol (70:20:10) (HPLC Method II). Peaks were assigned based on similar mobilities with standards. Residues assigned from aqueous fractions were the hydroxy metabolites G-30414, GS-17792, and GS-17791 (see right side of Figure 1), G-28273, and CGA-74650. Identification of these metabolites was confirmed by a second method, either HPLC or TLC. The additional extraction steps starting with Soxhlet allowed the assignment of an additional 6% TRR with corn fodder, and an additional 8% TRR with corn grain.

The aqueous fractions produced by Extraction Method II, acid autoclave, were also analyzed; organic fractions from this method each represented less than 1% TRR and were not further evaluated. The major residues identified by Aminex cation exchange chromatography were three hydroxy compounds and cyanuric acid (see Figure 4). When corn fodder was treated by reflux in acid for 16 h, some residues were assigned as metabolite G-35713; this metabolite was not identified after the acid autoclave treatment, however. Identification of cyanuric acid was confirmed by HPLC.

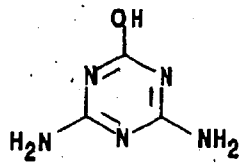
Table 4 provides a comparison of residues assigned under Extraction Methods I and II. For the purposes of Table 4, free hydroxy residues were assigned based on extraction with neutral solvents. Extraction with acidic solvents released an additional 3% of hydroxy residues in fodder, which could have been due to cleavage of conjugates.



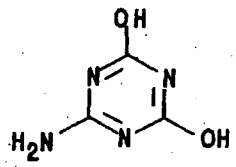
G-30414



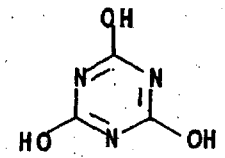
GS-17792



GS-17791



G-35713



Cyanuric acid

Figure 4. Simazine residues detected after extensive treatment in acid.

Table 4. Assignment of Residues by Extraction Method I or II.

Residue	Corn silage [TRR=0.209 ppm]		Final harvest fodder [TRR=0.493 ppm]		Final harvest grain [TRR=0.044 ppm]	
	Method I, % TRR (ppm)	Method II, % TRR	Method I, % TRR (ppm)	Method II, % TRR	Method I, % TRR (ppm)	Method II, % TRR
Simazine	<0.1 (<0.001)		0.1 (<0.001)			
G-28279	1.5 (0.003)	0.2	0.4 (0.002)			
G-28273	6.9 (0.014)		4.0 (0.019)		2.2 (<0.002)	
[Total chloros]	[8.4]		[4.5]		[2.2]	
G-30414	1.8 (0.004)	7.7	2.7 (0.013)	7.7	1.0 (<0.001)	1.5
GS-17792	27.9 (0.058)	8.5	15.6 (0.077)	5.0	3.6 (0.002)	
GS-17791	5.5 (0.011)	2.1	2.4 (0.012)	0.8	11.9 (0.005)	3.6
[Total free hydroxy]	[35.2]		[20.7]		[16.5]	
G-30705	0.2 (<0.001)		0.3 (0.002)			
CGA-74650	0.8 (0.002)		2.5 (0.012)		0.4 (<0.001)	
Cyanuric acid		54.7		45.2		51.7
Total Assigned	44.6 (0.092)	73.0	28.0 (0.138)	58.7	19.1 (0.008)	56.8

Table notes: See Figures 1 and 4 for structures. Values for ppm are shown for Method I only. Blank spaces indicate residues not detected. Free hydroxy assignments were based on extraction with neutral solvents.

The Registrant provided data on corn sample extracts generated using Method I, from analyses in January 1993, three months after final harvest, and after frozen storage until December 1993, near the end of laboratory work. Data were presented on the 2-D TLC profile of the organic fraction from silage, and on the Aminex A-4 profiles of aqueous fractions from silage, fodder, and grain. The chromatographic profiles and quantity of radioactive residues were comparable for each sample at the two different times, indicating acceptable storage stability of residues during the course of laboratory analysis.

CBRS Comments, Residue Analysis

Conclusion 2: Simazine undergoes significant metabolism in corn. The Registrant has identified chloro, hydroxy, and amino metabolites, each containing an intact triazine ring (for details, see Table 4 and Figure 1 of this review). Using Extraction Method I, residues assigned represented 45% TRR in silage forage, 28% TRR in final harvest fodder, and 19% TRR in final harvest grain. Simazine and other chloro compounds combined represented 8% TRR in silage and 2% TRR in final harvest grain.

Conclusion 3: With Extraction Method II, an acid autoclave procedure, 73% TRR in silage and more than half the TRR in each of final harvest fodder and grain was converted to cyanuric acid and the simazine hydroxy metabolites G-30414, GS-17792, and GS-17791 (see Table 4 and Figure 4). This observation indicates that the position of the HED Metabolism Committee, that TRR should represent total residues containing the triazine ring, is a reasonable assumption.

As noted above in the Background section, the Registrant has previously submitted a summary of metabolism data as part of its comments on the PD1. The metabolism data reviewed here are nearly identical to the data in the summary (compare Table 4 here with Table 1 in CBRS 15634, 8/1/95, J. Abbotts). These considerations lead to the following comments:

Conclusion 4: The corn metabolism data reviewed here are consistent with the summary data submitted as part of the Registrant's comments on the triazine PD1 (CBRS 15634, 8/1/95, J. Abbotts). There is no need to revise that previous review because of metabolism data.

Atrazine Corn Metabolism Data

As noted in the Background section, CBRS amended data requirements for simazine to a single corn metabolism study in IL, based on information from the registrant during a telephone conversation (Memo, 9/30/92, M.S. Metzger):

"Mr. Parshley [Ciba-Geigy] stated that the radiolabel field studies for atrazine showed no variability in either the level of the total radioactive residue or in the ratio of metabolites among the 3 geographical locations in which studies were done. Based on this information, as well as on the similar structures of atrazine and simazine, CBRS agreed that a single radiolabel field study for simazine on corn performed in IL would suffice for this commodity." :

However, review of the atrazine corn metabolism studies reached the following conclusion:

"The present submission indicates variability in the composition of the total residue in corn with location and commodity, and variability in residues detected with method of extraction. In the present studies, the percent of TRR represented by organic soluble residues ranged from 0.5% to 3.7% in grain and from 2.6% to 49.8% in forage and fodder; the percent of TRR assigned to known hydroxy metabolites ranged from 3.9% to 16.6% in grain, and from 13.6% to 40% in forage and fodder." (CBRS 10980, 6/3/93, J. Abbotts, Conclusion 1g)

The higher percentages noted in this conclusion were generally associated with Extraction Method II of that study, which used mildly acidic conditions during initial extraction. Table 5 summarizes data with Extraction Method I of that study, which used initial extraction with methanol:water followed by partitioning with chloroform, similar to the initial steps of Method I in the present simazine submission. The data in Table 5 are based on extraction with neutral solvents, and therefore are considered an appropriate assignment of free hydroxy residues.

Although the data in Table 5 are generally comparable across geographical location, there are cases where the variability is considerable: TRRs vary by 2-fold among grain, and by 5-fold among early forage samples. There is a 3-fold variation among percent TRR represented by total free hydroxy compounds in grain, and a variation of more than 10-fold among percent TRR represented by chloro compounds in early forage. In the atrazine study, the registrant could not rule out the possibility that Unknown 1 was a chloro triazine (Ibid.), and it is summed in Table 5 with the known chloro compounds. These considerations lead to the observation that whatever the reason for miscommunication, the material reported in the memo of a telephone conversation (9/30/92, M.S. Metzger) was not an accurate description of the atrazine field metabolism studies on corn as reviewed (CBRS 10980, 6/3/93, J. Abbotts).

Table 5. Assignment of Atrazine Residues in Corn, Extracted by Method I.

Residue	Percent of TRR assigned by location and sample [100% TRR in ppm]:											
	MS				IL				NY			
	30-Day Forage [0.694]	Silage Forage [0.660]	Mature Fodder [0.850]	Mature Grain [0.045]	30-Day Forage [0.466]	Silage Forage [0.710]	Mature Fodder [1.809]	Mature Grain [0.071]	30-Day Forage [2.840]	Silage Forage [0.499]	Mature Fodder [1.549]	Mature Grain [0.034]
Organic Fraction	(9.2)	(5.2)	(2.6)	(0.5)	(8.4)	(14.6)	(5.4)	(1.5)	(49.8)	(9.2)	(9.1)	(1.0)
Atrazine	0.4	<0.1	<0.1		2.0	1.3	0.2		43.2	1.1	0.8	
G-28273	0.2	0.2	0.1		0.1	0.2	<0.1		0.1	0.1	<0.1	
G-28279	0.2	0.1	<0.1		0.3	0.2	0.1		0.2	0.1	0.2	
G-30033	0.3	0.1	<0.1		0.3	0.1	0.1		0.4	0.2	0.5	
Unknown 1	1.1	0.8	1.0		2.3	2.1	2.7		1.6	2.6	4.1	
Total, known chloros plus Unknown 1	[2.2]	[1.2]	[1.1]		[5.0]	[3.9]	[3.1]		[45.5]	[4.1]	[5.6]	
GS-17791	1.4	1.3	0.7	0.7	1.1	1.8	1.0	2.3	0.7	0.6	<0.1	1.2
GS-17792	4.4	4.5	3.3	0.5	4.1	5.2	4.5	1.3	1.1	2.0	1.7	0.9
GS-17794	18.5	19.8	14.6	2.7	16.8	19.9	16.9	6.1	8.1	18.6	14.4	10.7
G-34048	8.1	2.9	0.6	<0.1	6.1	9.1	3.0	<0.1	3.7	2.1	2.0	0.3
Total free hydroxy:	[32.4]	[28.5]	[19.2]	[3.9]	[28.1]	[36.0]	[25.4]	[9.7]	[13.6]	[23.3]	[18.1]	[13.1]

Table notes: Data are adapted from CBRS 10980, 6/3/93, J. Abbotts. Assignments represent combined residues in organic and aqueous phases. Organic fractions from grains were not analyzed due to low levels of radioactivity.

At issue, then, is whether further data should be required on simazine in corn. Of the three locations for atrazine studies, (IL, MS, and NY) IL is most representative of corn-growing areas, and the simazine study was also conducted at this location. With the atrazine studies, TRRs were highest in IL for silage, mature fodder, and grain. The portion of TRR represented by potential chloro compounds was highest in IL for grain (where organic soluble residues are assumed to represent the maximum possible contribution from chloro residues), and was comparable to NY for silage and fodder. The portion of TRR represented by combined free hydroxy residues in IL was highest for silage and fodder, was higher than NY and comparable to MS for early forage, and was higher than MS and comparable to NY for grain.

Furthermore, when the simazine data from IL (Table 4) are compared with the atrazine data, the portion of TRR represented by chloro compounds is higher for simazine than for any atrazine sample in silage, fodder, and grain; and the portion represented by free hydroxy compounds is comparable for simazine in silage and fodder, and is higher for simazine than for any atrazine sample in grain. These considerations lead to the following comment:

Conclusion 5: The present submission is a corn field metabolism study at a single site in IL. Data in the present submission, along with data on atrazine metabolism in corn, will allow dietary exposure assessment to be conducted using conservative assumptions.

Recommendations: Guideline 171-4a, Nature of the Residue in Plants, is satisfied for corn.

cc:Circ, Abbotts, RF, Simazine List A File, Simazine SF
RDI:ARRathman:3/26/96:RBPerfetti:4/5/96:EZager:4/5/96
7509C:CBII-RS:JAbbotts:CM-2:Rm805A:305-6230:4/5/96
JA16\simazine.6

SIMAZINE (CASE NO. 70/CODE NO. 080807)
UNOFFICIAL RESIDUE CHEMISTRY DATA SUMMARY THROUGH 4/8/95[1]
REASSESSMENT OF U.S. TOLERANCES AND POTENTIAL FOR HARMONIZATION WITH CODEX[2]

Guideline Number and Topic[3]	Phase 5 data requirements satisfied?	MRID(s)[4]
171-3 Directions for use		
171-4(a) Plant Metabolism	N[5]	43159001
171-4(b) Animal Metabolism	N[6]	
171-4(c) Residue Analytical Methods - Plants	N	
171-4(d) Residue Analytical Methods - Animals	N	
171-4(e) Storage Stability	N[7]	42739102
171-4(k) Crop Field Trials		
171-4(k) Root and Tuber Vegetables Group		
Artichokes	N	
171-4(k) Citrus Fruits Group [see 171-4(l)]		
Grapefruit	N	
Lemons	N	
Oranges	N	
171-4(k) Pome Fruits Group		
Apples [see 171-4(l)]	N	
Pears	N	
171-4(k) Stone Fruits Group		
Cherries	N	
Peaches	N	
Plums (fresh prunes) [see 171-4(l)]	N	
171-4(k) Small Fruits and Berries Group		
Blueberries	N	
Cranberries	N	
Grapes [see 171-4(l)]	N	
Raspberries	N	
171-4(k) Tree Nuts Group		
Almonds	N	
Filberts	N	
Macadamia	N	
Pecans	N	
Walnuts	N	
171-4(k) Cereal Grains Group		
Corn (field) [see 171-4(l)]	N	
Corn (fresh) [see 171-4(l)]	N	
171-4(k) Forage, Fodder, and Straw of Cereal Grains		
Corn (field) forage and fodder	N	
Corn (fresh) forage	N	
171-4(k) Miscellaneous Commodities		

SIMAZINE (CASE NO. 70/CODE NO. 080807)
UNOFFICIAL RESIDUE CHEMISTRY DATA SUMMARY THROUGH 4/8/95[1]

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

Guideline Number and Topic[3]	Phase 5 data requirements satisfied?	MRID(s)[4]
Asparagus	N	
Avocados	N	
Bananas	N	
Olives [see 171-4(l)]	N	
Sugarcane [see 171-4(l)]	N	
171-4(l) Processed Food/Feed		
Apples	N	
Citrus	N	
Corn, Field	N	
Corn, Fresh	N	
Grapes	N	
Olives	N	
Plums	N	
Sugarcane	N	
171-4(j) Meat/Milk/Poultry/Eggs	Reserved	
171-4(f) Potable Water	N	
171-4(g) Fish	N	
171-4(h) Irrigated Crops	N/A	
171-4(i) Food Handling Establishments	N/A	
171-5 Reduction of Residues		

[1]Registration Standard issued 3/84. Second Round Review Residue Chemistry Chapter issued 1/30/89. A comprehensive DCI was issued 9/91.

[2]No Codex MRLs are established or proposed for simazine.

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

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

[5]Memo, 8/7/92, M.S. Metzger, Results of the HED Metabolism Committee Meeting of 7/9/92: In the absence of data on toxicity of metabolites, all metabolites containing a triazine ring with a substituent are of concern. Practical interpretation of this conclusion means that exposure assessments will be conducted using total radioactive residue.
CBRS 11000, 2/4/93, M.S. Metzger: Radiolabel field trial data would be limited to four commodities (corn, oranges, apples, and grapes) to represent the large number of commodities for which registrant plans to maintain registrations (corn, orchard fruits, tree nuts, small fruits and berries).
Memo, 9/29/95, J. Abbotts: The HED Metabolism Committee determined that, pending review of submitted metabolism studies, the residues of concern for cancer dietary risk are parent and chloro metabolites. Dietary risk assessment should also be conducted for non-cancer chronic risk; parameters will be designated subsequently.

Memo, 11/28/95, J. Abbotts: The HED Metabolism Committee determined that for simazine, pending review of submitted metabolism studies, non-cancer chronic dietary risk should initially be based on total radioactive residues, with the RfD for simazine.
CBRS 13439, 4/8/95, J. Abbotts, MRID 43159001: Simazine metabolism in corn is significant. Registrant has identified chloro, hydroxy, and amino metabolites, each containing an intact triazine ring. Data indicate that the position of the HED Metabolism Committee, that TRR should represent total triazine ring residues, is a reasonable assumption. This guideline is satisfied for corn.

[6]Memo, 8/7/92, M.S. Metzger, Results of the HED Metabolism Committee Meeting of 7/9/92: In the absence of data on toxicity of metabolites, all metabolites containing a triazine ring with a substituent are of concern. Practical interpretation of this conclusion means that exposure assessments will be conducted using total radioactive residue.

[7]CBRS 11813, 5/13/93, J. Abbotts: MRID 42739102 contains data on sample storage conditions and intervals for residue chemistry studies previously submitted to determine the magnitude of the residue of simazine and three chloro metabolites. CBRS declines review of this submission until the residues to be regulated for reregistration have been determined.

cc: Simazine List A Reregistration Standard File; Reregistration Branch Chief, SRRD
[redacted]70.2

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Chemical:	**Simazine**
PC Code:	***080807***
HED File Code	**11000 Chemistry Reviews**
Memo Date:	**04/05/96**
File ID:	**DPD200940**
Accession Number:	**412-03-0019**

HED Records Reference Center
01/03/2003