Atrazine Sub; File

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

AUG 1 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Atrazine (080803), Reregistration Case No. 0062, and Simazine (080807), Reregistration Case No. 0070. Special Review. Ciba-Geigy Comments on the Triazine PD1; Metabolism in Plants and Animals. CBRS No. 15634, DPBarcode No. D215329, MRID 43598602.

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Special Review of triazine herbicides, including atrazine and simazine, has been initiated (59 FR 60412, 11/23/94, PD1). Ciba-Geigy Corporation has submitted comments in response, including an overview of the nature of the residues in plants and animals; the present submission represents Volume 3 of the Registrant's comments. Assignment instructions are to review the present submission and provide an evaluation for development of a PD2/3. Conclusions below pertain only to the present submission, and its relation to the Agency position in the PD1.

Tolerances are established for residues of the herbicide atrazine, 2-chloro-4-ethylamino-6-isopropylamino-*s*-triazine, in or on various agricultural commodities (40 CFR 180.220(a)), and for combined residues of atrazine and its metabolites 2-amino-4-chloro-6-ethylamino-*s*-triazine, 2-amino-4-chloro-6-isopropylamino-s-triazine, and

2-chloro-4,6-diamino-*s*-triazine, in or on specified plant commodities (40 CFR 180.220(b)). Designations for the metabolites in the tolerance expression are G-28279, G-30033, and G-28273, respectively; structures are indicated in Figure 1. Atrazine is a List A Chemical. The Residue Chemistry Chapter to the Registration Standard was issued 7/25/83; the Registration Standard (Guidance Document) was issued 9/85; a Second Round Review (SRR) Residue Chemistry Chapter was issued 10/18/88.

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. 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.

Conclusions on This Submission

1. Assignment instructions indicate that a copy of this document was also provided to Toxicology Branch. CBRS defers to TOX with regard to information on metabolism in rats and humans.

2. The present submission summarizes data presented as separate volumes of the Registrant's comments. CBRS has separately reviewed the comments on atrazine metabolism in corn and sorghum (CBRS 15633, 7/6/95, J. Abbotts) and in sugarcane (CBRS 15632, 7/6/95, J. Abbotts). For both submissions, CBRS concluded that metabolism data on these crops did not contradict the Agency position in the PD1, and in fact reinforced it.

3. The remaining data on atrazine in plants summarized in the present submission were on metabolism in rotational crops. CBRS has already reviewed the study that is the source for the data summary. The review concluded that atrazine undergoes extensive metabolism in rotational crops; metabolic pathways are similar for rotational crops and primary crops, at least for early metabolites; and the position of the HED Metabolism Committee, that total radioactive residues (TRR) should represent total residues containing the triazine ring, is a reasonable assumption for rotational crops (CBRS 12889, 6/29/95, J. Abbotts).

4. The present submission summarizes data on simazine metabolism in plants and metabolism of hydroxyatrazine and hydroxysimazine in goats. CBRS has not yet reviewed the studies that are sources for these data summaries. Comments on the present submission are based on the data summaries provided, and do not preclude

additional conclusions and recommendations once the applicable studies are fully reviewed.

5. The reported data indicate that simazine metabolism in plants can be extensive. The Registrant has reported chloro, hydroxy, and amino metabolites, along with a conjugated metabolite, each containing an intact triazine ring (for details, see Tables 1 through 7 and Figure 2 of this review).

6. The reported simazine metabolite profile is clearest with grapes: A proline-diamino conjugate and the hydroxy metabolite GS-17791 together represent 74% TRR. In citrus, these two residues together also represent 84% TRR in juice, 73% TRR in pulp, and 54% TRR in peel.

7. The simazine metabolite profile reported for other crops was more complicated. With extraction by neutral solvent, assigned residues in corn ranged from 11% TRR in grain to 45% TRR in forage, and assigned residues in apples represented 50% TRR. Assigned residues in wheat as a rotational crop ranged from 12% TRR in grain to 61% TRR in forage. In the rotational crops spinach and garden beets, assigned residues ranged from 35% TRR in mature beet roots to 64% TRR in immature spinach leaves.

8. Extraction Method II, an extended acid autoclave procedure, or Method III, an extended acid reflux procedure, converted residues to cyanuric acid and the simazine hydroxy metabolites G-30414, GS-17792, GS-17791, and G-35713 (see Figure 3). Method III converted 33% TRR in apples to these metabolites, but nearly 50% TRR in apples was assigned to known residues with neutral solvent extraction. For the other crops reported in the present submission, Method II or III converted from 44% TRR (wheat straw) to 83% TRR (mature grapes) to a few hydroxy metabolites. These data indicate that the Agency position, that TRR should represent total residues containing the triazine ring, is a reasonable assumption for simazine metabolism in plants.

9. Although Extraction Methods II and III converted a major portion of simazine TRR in plant commodities to five hydroxy triazine compounds, the Registrant has acknowledged that it may not be practical to use these techniques for an enforcement method to determine total triazine ring residues.

10. The summary material in the present submission is consistent with the description of atrazine and simazine metabolism in edible animal commodities contained in the Agency's PD1.

11. Data were reported on metabolism of hydroxyatrazine and hydroxysimazine in goats. These compounds are identified metabolites from the use of their respective parent chemicals on plants. In most goat tissues, approximately half of the TRR was represented by the hydroxy compound fed. However, up to six

metabolites of hydroxyatrazine were reported, and up to four metabolites of hydroxysimazine were reported (for details, see Tables 8 and 9 and Figure 4). Each metabolite reported contained an intact triazine ring. These data indicate that the plant metabolites hydroxyatrazine and hydroxysimazine undergo further metabolism when fed to ruminants.

Conclusion with Regard to the PD1

The Agency position can be summarized in the following manner: Metabolism of atrazine and simazine in plants and animals is extensive, no single metabolite represents a large portion of the total triazine residue consistently across plant and animal commodities, analytical methods to measure total triazine ring residues are not available, and therefore, total radioactive residues from radiolabel field studies and animal feeding or metabolism studies are the most appropriate data to use for risk assessment. The present submission summarizing metabolism of atrazine and simazine in plants and animals does not contradict the Agency position, and in fact reinforces it.

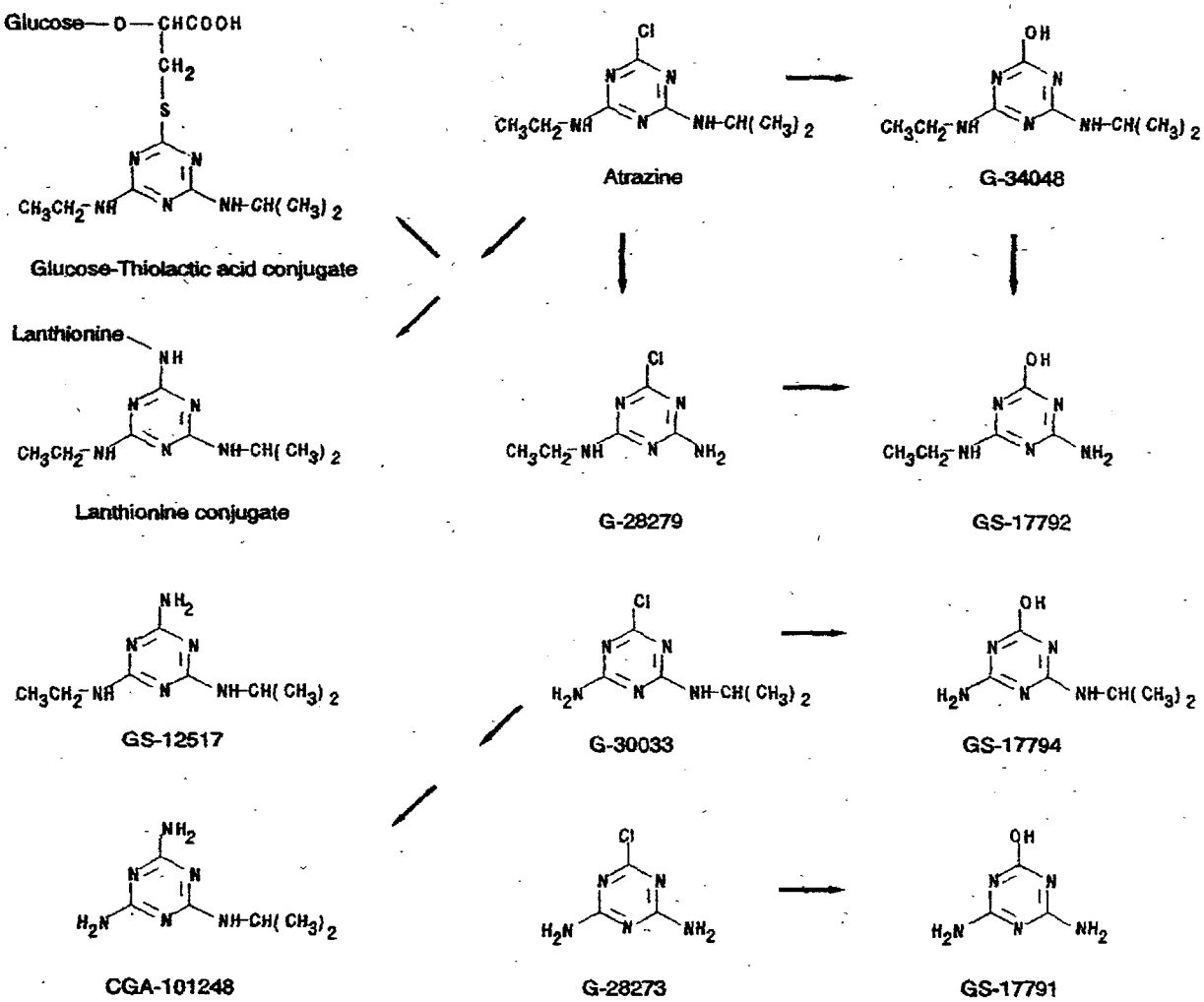

Figure 1. Atrazine metabolites identified in sugarcane cane.

DETAILED CONSIDERATIONS

PD1 Position on Metabolism

The initiation of special review on the triazines describes the Agency's position pertaining to triazine metabolism and residues of concern. The full FR notice contains more detail, but the following excerpts outline the Agency position on metabolism of atrazine and simazine (59 FR 60412, 11/23/94):

"In estimating triazine dietary risks, the Agency assumes that the total toxic residue of concern is the parent triazine compound plus all metabolites with a triazine ring, including among others, all chloro and hydroxy metabolites."

"In plants, atrazine and simazine are metabolized to numerous metabolites, no one of which has yet been shown to comprise a large portion of the total terminal residue. Metabolic processes include N-dealkylation and conjugation with endogenous plant components, particularly glutathione, and hydroxylation. Most metabolites have been shown to contain the intact triazine ring."

"In animals, data have been provided showing the animal metabolism of atrazine, simazine, and corn metabolites of atrazine (animals were fed corn which had been treated with atrazine). Higher tissue residues resulted from feeding atrazine or simazine, and numerous metabolites were identified resulting from N-dealkylation and conjugation with glutathione followed by modification of the glutathione moiety. In most cases, no single metabolite accounted for a significant percentage of the total residue. Exceptions to this were milk in which the di-N-dealkylated chloro metabolite (G-28273) comprised approximately 30 percent of the total residue for atrazine, and liver in which the cysteine conjugate of G-30033 comprised approximately 25 percent of the total residue. When corn treated with atrazine was fed to animals, much lower residues resulted in tissues indicating less absorption of metabolites than of the parent compounds."
(59 FR 60418)

"Based on its assessment of the structure-activity relationship and potential carcinogenicity of all registered triazine compounds, EPA believes metabolites which have been dechlorinated may be less potent carcinogens than the parent compounds.... However, in the absence of completed laboratory studies of the hydroxy metabolites, the Agency has relied on its equivalency policy and has made the assumption that all metabolites containing the triazine ring are equipotent as carcinogens as the parent compound when conducting its risk assessment." (59 FR 60418-60419)

"Since the registrants have been unable to develop analytical methodology which measures total triazine ring residues in non-radiolabel field trials, radiolabel field studies currently provide the best data to use for risk assessment. New radiolabel field studies for major dietary risk contributors for both atrazine and simazine have been submitted to the Agency and are currently under review." (59 FR 60419)

The Agency position can be summarized in the following manner: metabolism of atrazine and simazine in plants and animals is extensive, no single metabolite represents a large portion of the total triazine residue consistently across plant and animal commodities, analytical methods to measure total triazine ring residues are not available, and therefore, total radioactive residues from radiolabel field studies and animal feeding or metabolism studies are the most appropriate data to use for risk assessment. The present submission will be reviewed with regard to this Agency position.

Background

As part of its response (Volume 3 of 54) to the FR notice initiating special review, the Registrant submitted the following document:

Nature of Atrazine and Simazine Metabolism in Plants and Animals, Report ABR-95039, 3/9/95, Ciba-Geigy Corporation, Greensboro, NC (MRID 43598602).

The Registrant describes the submitted report as a "stand alone section" representing part of its response to the PD1, prepared to provide details on "the metabolism of Atrazine and Simazine in animal and plant systems as an aid to the Agency's toxicology and residue chemistry reviewers." This document includes information on metabolism of atrazine and simazine in rats and humans. Assignment instructions indicate that a copy of this document has also been provided to Toxicology Branch, and CBRS defers to TOX on these sections.

Conclusion 1: Assignment instructions indicate that a copy of this document was also provided to Toxicology Branch. CBRS defers to TOX with regard to information on metabolism in rats and humans.

The present submission also reports that some of the metabolism data discussed in this report are being submitted "for the first time to the Agency. Wherever this occurs, the original reports will be provided in a separate volume accompanying this submission." CBRS has already reviewed the metabolism data submitted as separate volumes of the Registrant's comments, and the following conclusion is appropriate:

Conclusion 2: The present submission summarizes data presented as separate volumes of the Registrant's comments. CBRS has separately reviewed the comments on atrazine metabolism in corn and sorghum (CBRS 15633, 7/6/95, J. Abbotts) and in sugarcane (CBRS 15632, 7/6/95, J. Abbotts). For both submissions, CBRS concluded that metabolism data on these crops did not contradict the Agency position in the PD1, and in fact reinforced it.

The remaining data on atrazine in plants summarized in the present submission are data on metabolism in rotational crops. The study from which these data are summarized has already been reviewed, leading to the following conclusion:

Conclusion 3: The remaining data on atrazine in plants summarized in the present submission were on metabolism in rotational crops. CBRS has already reviewed the study that is the source for the data summary. Review concluded that atrazine undergoes extensive metabolism in the rotational crops; metabolic pathways are similar for rotational crops and primary crops, at least for early metabolites; and the position of the HED Metabolism Committee, that total radioactive residues (TRR) should represent total residues containing the triazine ring, is a reasonable assumption for rotational crops (CBRS 12889, 6/29/95, J. Abbotts).

In addition to the material described above, the present submission also summarizes data on simazine metabolism in plants and animals, and atrazine metabolism in animals. The present submission includes summary data from studies recently submitted by the Registrant on simazine metabolism in corn, rotational crops, grapes, apples, and citrus; and on metabolism of hydroxyatrazine and hydroxysimazine in goats. We note that CBRS has not yet reviewed these studies, leading to the following provisional comment for this review:

Conclusion 4: The present submission summarizes data on simazine metabolism in plants and metabolism of hydroxyatrazine and hydroxysimazine in goat. CBRS has not yet reviewed the studies that are sources for these data summaries. Comments on the present submission are based on the data summaries provided, and do not preclude additional conclusions and recommendations once the applicable studies are fully reviewed.

<u>Simazine Metabolism in Plants</u>

Figure 2 shows the metabolites of simazine in plants reported in the present submission. For a field metabolism study in corn, ^{14}C-simazine was applied preemergence at 2 lb ai/A in IL. Samples were extracted by neutral solvent and partitioned into organic and aqueous soluble fractions (Method I). With this method, parent and 7 metabolites were identified, as shown in Table 1.

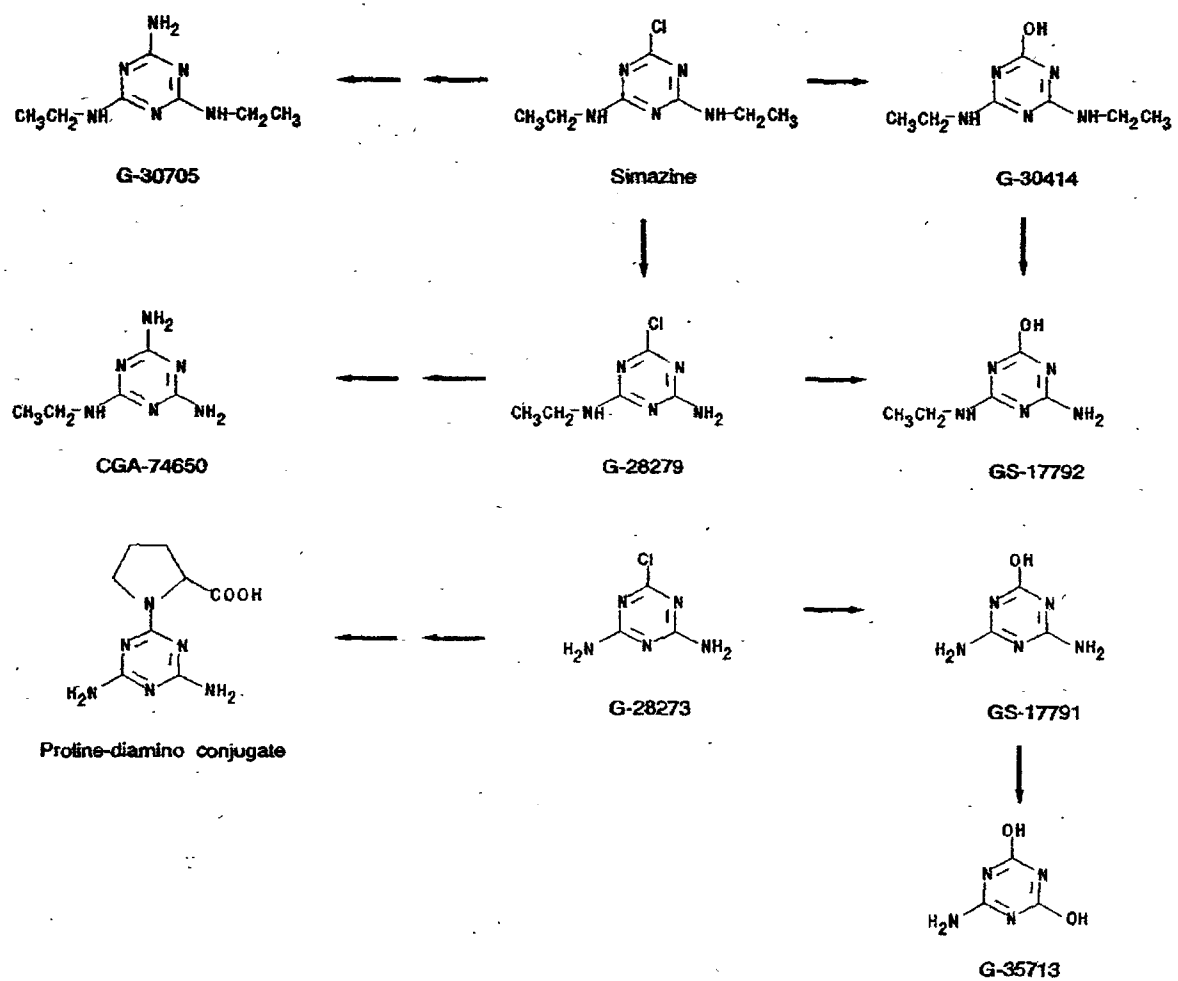

Figure 2. Simazine metabolites reported in plants.

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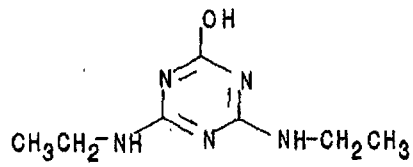
Table 1. Simazine residues reported in corn by extraction method.

Residue	% TRR assigned by method in [100% TRR in ppm]					
	Silage Stage Forage [0.209]		Mature Fodder [0.493]		Mature Grain [0.044]	
	I	II	I	II	I	II
Simazine	< 0.1		0.1			
G-28279	1.5		0.4			
G-28273	6.9		3.2		1.2	
G-30414	1.8	7.7	1.6	7.7	0.7	1.5
GS-17792	27.9	8.5	14.5	5.0	3.6	
GS-17791	5.5	2.1	2.4	0.8	5.9	3.6
Cyanuric acid		54.7		45.2		51.7
G-30705	0.2		0.3			
CGA-74650	0.8		1.7			
Total Assigned	44.6	73.0	24.2	58.7	11.4	56.8

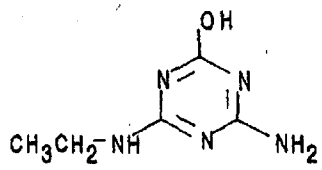
Table notes: Extraction Methods I and II were neutral solvent and extended acid autoclave, respectively. See Figures 2 and 3 for structures. Blank spaces indicate residues not detected.

Corn samples were also placed in acidic solution and extracted in an autoclave for approximately 24 h (Method II). After this method, residues were detected as the hydroxy metabolites G-30414, GS-17791, GS-17792, and cyanuric acid (see Figure 3 for structures). Table 1 provides a comparison of residues detected with extraction Methods I or II.

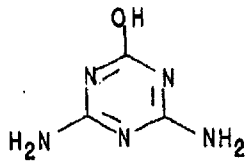
At the same site in IL as the corn metabolism study, wheat, spinach, and garden beets were planted as rotational crops following corn, and field metabolism studies were conducted on these crops. As with corn, samples were extracted by Method I, and Tables 2 and 3 summarize the residues reported with this extraction method. Selected mature crop samples were also extracted using reflux in 1N HCl for 16 h (Method III). Table 4 summarizes the residues reported with this method; residues were converted to several hydroxy metabolites, and small amounts of the chloro metabolite G-28273 were also detected.



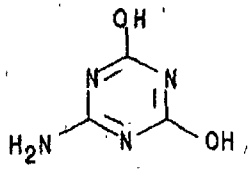
G-30414



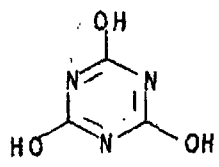
GS-17792



GS-17791



G-35713



Cyanuric acid

Figure 3. Simazine residues detected after Extraction Method II or III

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Table 2. Simazine residues reported in rotational crop wheat samples extracted by Method I.

Residue	% TRR for [100% TRR in ppm]:			
	60 DAP Forage [0.145]	Half-Mature Forage [0.029]	Mature Straw [0.135]	Mature Grain [0.020]
Simazine	30.2	6.9	0.5	
G-28279	20.7	25.3	1.6	
G-28273	6.5	11.8	8.3	2.1
G-30414	0.5	2.2	0.9	
GS-17792	0.7	3.8	1.1	8.4
GS-17791	2.8			0.5
G-30705		0.1		
CGA-74650				0.8
Total Assigned	61.4	50.1	12.4	11.8

Table notes: DAP=days after planting. See Figure 2 for structures. Blank spaces indicate residues not detected.

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Table 3. Simazine residues reported in rotational crop spinach and beet samples extracted by Method I.

Residue	% TRR for [100% TRR in ppm]:					
	Half-Mature Spinach Leaves [0.071]	Mature Spinach Leaves [0.130]	Half-Mature Beet Tops [0.101]	Mature Beet Tops [0.182]	Half-Mature Beet Roots [0.297]	Mature Beet Roots [0.126]
Simazine	5.1	3.2	32.7	20.4	10.6	6.1
G-28279	31.9	23.5	13.5	6.9	1.6	1.0
G-28273	23.8	19.0	15.2	9.8	0.7	2.0
G-30414	2.4	1.4	1.8	2.2	20.4	18.3
GS-17792	0.2	1.8	1.6	2.3	3.1	6.2
GS-17791	0.8	3.5	1.3	2.9		
G-30705		0.2		< 0.1	0.4	< 0.1
CGA-74650						1.3
Total Assigned	64.2	52.6	66.1	44.5	36.8	34.9

Table notes: See Figure 2 for structures. Blank spaces indicate residues not detected.

Table 4. Simazine residues reported in rotational crop commodities with Extraction Method III.

Residue	% TRR Assigned in Mature Commodity [100% TRR in ppm]:			
	Wheat Straw [0.135]	Spinach Leaves [0.130]	Beet Tops [0.182]	Beet Roots [0.126]
Cyanuric acid	17.2	18.4	8.4	8.7
G-28273	0.8		2.2	0.3
G-30414	1.1	7.1	19.9	48.1
GS-17792	12.8	32.8	14.7	9.1
GS-17791	11.6	21.1	17.7	3.4
Total	43.8	79.4	62.9	69.6

Table notes: See Figures 2 and 3 for structures. Blank spaces indicate residues not detected.

Data were also reported from a field metabolism study with apples in CA. A test apple tree received a single broadcast spray to the soil underneath the tree at approximately 4 lb ai/A. Leaf samples were taken 60 DAT (days after treatment), and leaf and fruit samples were taken at mature harvest, 6 months after treatment. When samples were extracted by Method I, parent and 8 metabolites were detected in immature leaves, and fewer metabolites were detected in mature samples. Mature samples were also extracted by Method III, by which residues were converted to three hydroxy metabolites, plus a small amount of G-28273 in leaves. Table 5 summarizes the metabolites reported with these extraction methods.

Data were also reported from a field metabolism study with grapes. A single broadcast spray at 4.8 lb ai/A was applied to the soil under grape vines. Leaves were sampled at 61 DAT and leaves and fruit were harvested at maturity, 4 months after treatment. Samples were extracted by Method I, and mature samples were also extracted by Method III. Table 6 summarizes the metabolites reported with these extraction methods.

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Table 5. Simazine residues reported in apples by extraction method.

Residue	% TRR assigned by method in [100% TRR in ppm]				
	60 DAT Leaves [0.244]	Mature Leaves [1.895]		Mature Fruit [0.021]	
	I	I	III	I	III
Simazine	9.8				
G-28279	10.7				
G-28273	18.0	3.4	1.6	1.1	
G-30414	< 0.1				
GS-17792	1.4	2.2	7.3	3.7	3.7
GS-17791	5.5	1.1	30.5	22.7	17.2
Cyanuric acid			18.3		11.9
G-30705	0.2				
G-35713	0.8	4.5		4.2	
Proline-diamino conjugate	0.6	2.6		16.2	
Total Assigned	47.0	13.8	57.7	49.7	32.8

Table notes: DAT=days after treatment. Extraction Methods I and II were neutral solvent and extended acid reflux, respectively; only mature samples were extracted by Method III. See Figures 2 and 3 for structures. Blank spaces indicate residues not detected.

Table 6. Simazine residues reported in grapes by extraction method.

Residue	% TRR assigned by method in [100% TRR in ppm]				
	60 DAT Leaves [1.029]	Mature Leaves [3.085]		Mature Fruit [0.098]	
	I	I	III	I	III
Simazine	17.8	0.5			
G-28279	9.6	0.5			
G-28273	2.5	1.4			
G-30414	1.9	0.6	24.4		
GS-17792	5.9	3.4	34.0	6.7	8.5
GS-17791	3.0	5.3	3.5	44.0	24.6
Cyanuric acid			17.3		50.3
G-30705		< 0.1			
G-35713	2.4	0.1	5.8		
Proline-diamino conjugate	2.7	4.1		29.9	
Total Assigned	45.8	15.9	85.0	80.6	83.4

Table notes: DAT=days after treatment. Extraction Methods I and II were neutral solvent and extended acid reflux, respectively; only mature samples were extracted by Method III. See Figures 2 and 3 for structures. Blank spaces indicate residues not detected.

In addition, data were reported from a field metabolism study with citrus. Two applications of radiolabeled simazine were made to the soil underneath a four year old navel orange tree, treated at 60 day intervals between sprays. Leaf samples were collected at 62 and 105 DAT; reported TRRs were 5.57 ppm and 4.72 ppm, respectively. Fruit was also harvested at 105 DAT, and separated into juice, peel, and pulp. Residues were extracted by neutral solvent and partitioned into organic and aqueous phases. Residues in the organic phases were less than 5% TRR for each of juice, peel, and pulp. The aqueous phases were analyzed for residues, with the results in Table 7:

Table 7. Simazine residues reported in citrus.

	% TRR Assigned in [100% TRR in ppm]:		
Residue	Peel [0.272]	Pulp [0.062]	Juice [0.105]
Unknown A1	5.4		
Unknown A2	5.4	9.3	6.6
Unknown B	8.3		
Proline-diamino conjugate	48.7	63.0	74.9
GS-17791	5.0	9.6	9.3
Unknowns I	3.9	5.8	
Total assigned to known residues	53.7	72.6	84.2

Table notes: See Figure 3 for structures. Blank spaces indicate residues not detected.

CBRS Comments, Simazine in Plants

Conclusion 5: The reported data indicate that simazine metabolism in plants can be extensive. The Registrant has reported chloro, hydroxy, and amino metabolites, along with a conjugated metabolite, each containing an intact triazine ring (for details, see Tables 1 through 7 and Figure 2 of this review).

For evaluation of the reported data, the applicable raw agricultural commodities for the fruits are apples, grapes, and whole citrus, respectively. Of the citrus fractions analyzed, processed commodities in the Updated Livestock Feeds Table (EPA 738-K-94-001, June 1994) are pulp as animal feed and juice.

Conclusion 6: The reported simazine metabolite profile is clearest with grapes: A proline-diamino conjugate and the hydroxy metabolite GS-17791 together represent 74% TRR. In citrus, these two residues together also represent 84% TRR in juice, 73% TRR in pulp, and 54% TRR in peel.

Conclusion 7: The simazine metabolite profile reported for other crops was more complicated. With extraction by neutral solvent, assigned residues in corn ranged from 11% TRR in grain to 45% TRR in forage, and assigned residues in apples represented 50% TRR. Assigned residues in wheat as a rotational crop ranged from 12% TRR in grain to 61% TRR in forage. In the rotational crops spinach and garden beets, assigned residues ranged from 35% TRR in mature beet roots to 64% TRR in immature spinach leaves.

Conclusion 8: Extraction Method II, an extended acid autoclave procedure, or Method III, an extended acid reflux procedure, converted residues to cyanuric acid and the simazine hydroxy metabolites G-30414, GS-17792, GS-17791, and G-35713 (see Figure 3). Method III converted 33% TRR in apples to these metabolites, but nearly 50% TRR in apples was assigned to known residues with neutral solvent extraction. For the other crops reported in the present submission, Method II or III converted from 44% TRR (wheat straw) to 83% TRR (mature grapes) to a few hydroxy metabolites. These data indicate that the Agency position, that TRR should represent total residues containing the triazine ring, is a reasonable assumption for simazine metabolism in plants.

Despite the ability to convert residues to a few metabolites, Extraction Methods II and III have limitations for applying them to an enforcement method for total triazine ring residues. The present submission has the following comments on such limitations:

"Cyanuric acid cannot be utilized as a viable residue method because it has been shown to be a degradation product of plant natural products."

"Note of caution that cyanuric acid is not a suitable marker residue due to its widespread occurrence in untreated samples (from previous work)." (MRID 43598602, p. 49)

In addition, previous review has noted that although cyanuric acid represents a common moiety, its detection does not distinguish between triazine herbicides as the original source of residues; in addition, cyanuric acid represents background levels on the order of 1 ppm in plant and animal commodities (CBRS 9167, 1/22/92, M.S. Metzger).

Conclusion 9: Although Extraction Methods II and III converted a major portion of simazine TRR in plant commodities to five

hydroxy triazine compounds, the Registrant has acknowledged that it may not be practical to use these techniques for an enforcement method to determine total triazine ring residues.

Metabolism in Ruminants and Poultry

The present submission summarized data on the metabolism of atrazine, simazine, and selected metabolites in ruminants and poultry. Two major metabolic pathways have been identified: One pathway involves dealkylation to produce the chlorometabolites G-30033, G-28279, and G-27873 (see center of Figures 1 and 2 for structures). A second pathway is by glutathione conjugation displacing the 2-chloro position of the triazine ring, with subsequent metabolism leading to cysteine conjugates, mercapturates, mercaptans, sulfides, sulfones, and disulfides of atrazine, simazine, and their principal chlorometabolites. Summaries of metabolism of atrazine and simazine were taken in the most part from studies conducted in the 1980s, which have been described in the Residue Chemistry Chapters to the Registration Standard (atrazine, 7/25/83; simazine, 10/13/83) and Second Round Review Residue Chemistry Chapters (atrazine, 10/18/88; simazine, 1/30/89).

The present submission also summarized the results of studies recently submitted on the metabolism of hydroxyatrazine and hydroxysimazine in goats. As noted in the discussion on metabolism in plants and in Figures 1 and 2 above, these hydroxy compounds are identified metabolites from use of their parent chemicals on plants. Also as noted above, these new studies in goats have not yet been reviewed, and review of the present submission is based on the data summaries provided. The reported metabolites of hydroxyatrazine, G-34048, are shown in Figure 4. Metabolites 1 and 2a are ring N-methylated compounds of hydroxyatrazine and GS-17792, respectively. Metabolite 8 is a ring N-glucuronide. The data summary did not include a detailed assignment of residues in goat tissues, but this was provided by the original submission, MRID 42925601, and data from that document are summarized in Table 8.

The present submission describes the metabolism of hydroxysimazine, G-30414, in goats as similar to Figure 4, with the obvious exception that one N-alkyl side chain differs between atrazine and simazine. In addition, the N-glucuronide was not reported with hydroxysimazine. The data summary did not include a detailed assignment of residues yin goat tissues, but this was provided by the original submission, MRID 43506801, and data from that document are summarized in Table 9.

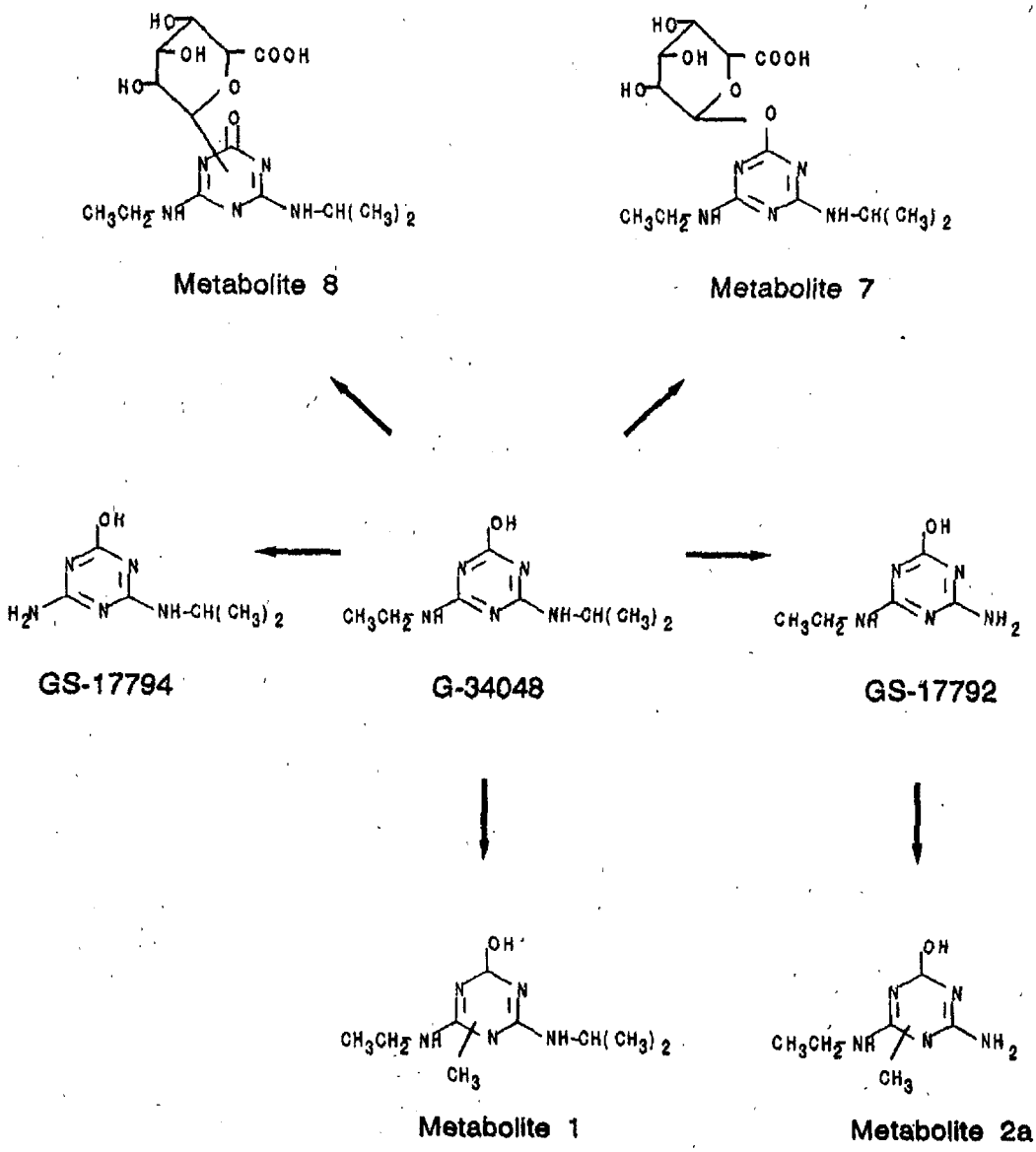

Figure 4. Metabolism of hydroxyatrazine (G-34048) reported in goat.

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Table 8. Residues of hydroxyatrazine (G-34048) reported in goat tissues.

Residue	% TRR assigned in [100% TRR in ppm]:				
	Milk [0.56]	Liver [1.18]	Kidney [2.57]	Tenderloin [0.21]	Perirenal fat [0.16]
Metabolite 1	3.9	44.0	6.4	5.4	4.3
Metabolite 2a	16.8	8.6	5.3	8.1	7.1
G-34048	46.5	20.2	47.7	54.8	49.2
GS-17794	4.6	3.3	3.0	3.9	3.1
GS-17792	9.0	3.3	8.4	13.8	11.8
Metabolite 7			8.6	2.0	9.1
Metabolite 8		2.2	6.3		5.1
Total assigned to known compounds	80.8	81.6	85.7	88.0	89.7

Table notes: Data are summarized from MRID 42925601, p. 27 and 38. Values are the average of data from two goats. Average feeding level was 113 ppm hydroxyatrazine in the diet for four consecutive days. See Figure 4 for structures. Blank spaces indicate residues not detected.

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Table 9. Residues of hydroxysimazine (G-30414) reported in goat tissues.

Residue	% TRR assigned in [100% TRR in ppm]:				
	Milk [0.48]	Liver [0.79]	Kidney [1.90]	Muscle [0.15]	Fat [0.02]
N-methylated G-30414	7.5	35.5	6.9	5.0	8.9
N-methylated GS-17792	14.3	12.5	6.0	9.2	8.0
G-30414	58.7	15.1	61.9	53.6	47.7
GS-17792	10.7	5.6	10.0	20.5	8.9
O-glucuronide of G-30414			2.7		1.4
Total assigned to known compounds	45.8	68.7	87.5	88.3	74.9

Table notes: Data are summarized from MRID 43506801, p. 62 and 71. Values are the average of data from two goats, except for kidney, where one sample was unusable, and liver, where extracts from both goats were combined. Average feeding level was 78 ppm hydroxysimazine in the diet for four consecutive days. Metabolites are hydroxysimazine analogues of compounds in Figure 4. Blank spaces indicate residues not detected.

CBRS Comments, Metabolism in Ruminants and Poultry

Determination of anticipated residues for atrazine and simazine included review of overview documents on animal metabolism (atrazine, DEB 5783, 5/8/90, M.S. Metzger; simazine, Memo, 1/19/90, M.S. Metzger). The descriptions of animal metabolism in those previous review are consistent with the Agency's position in the PD1 (see section above, PD1 Position on Metabolism, for excerpts), and with the summary material in the present submission.

Conclusion 10: The summary material in the present submission is consistent with the description of atrazine and simazine metabolism in edible animal commodities contained in the Agency's PD1.

The additional data reported on hydroxyatrazine and hydroxysimazine metabolism in goats lead to the following conclusion:

Conclusion 11: Data were reported on metabolism of hydroxyatrazine and hydroxysimazine in goats. These compounds are identified metabolites from the use of their respective parent chemicals on plants. In most goat tissues, approximately half of the TRR was represented by the hydroxy compound fed. However, up to six metabolites of hydroxyatrazine were reported, and up to four metabolites of hydroxysimazine were reported (for details, see Tables 8 and 9 and Figure 4). Each metabolite reported contained an intact triazine ring. These data indicate that the plant metabolites hydroxyatrazine and hydroxysimazine undergo further metabolism when fed to ruminants.

The Agency's position in the PD1 was described and summarized above (see section on PD1 Position on Plant Metabolism). The present submission does not contradict the Agency's position, and in fact reinforces it, leading to the following overall conclusion:

Conclusion with Regard to the PD1: The Agency position can be summarized in the following manner: Metabolism of atrazine and simazine in plants and animals is extensive, no single metabolite represents a large portion of the total triazine residue consistently across plant and animal commodities, analytical methods to measure total triazine ring residues are not available, and therefore, total radioactive residues from radiolabel field studies and animal feeding or metabolism studies are the most appropriate data to use for risk assessment. The present submission summarizing metabolism of atrazine and simazine in plants and animals does not contradict the Agency position, and in fact reinforces it.

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cc:Circ, Abbotts, RF, Atrazine List A File, Atrazine SF,
Simazine List A File, Simazine SF
RDI:FBSuhre:7/13/95:RBPerfetti:7/31/95:EZager:7/31/95
7509C:CBII-RS:JAbbotts:CM-2:Rm805A:305-6230:8/1/95
JA14\atrazine.12