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

NOV 22 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#3F04177. Dimethenamid (129051 SAN 582H) Metabolism
in Soybeans. Issues to be Presented to the HED
Metabolism Committee on 12/1/93.
DB Barcode: D196871 Case: 284369
Submission: S434923

FROM: Martha J. Bradley, Chemist *Martha J. Bradley*
Chemistry Branch 1 - Tolerance Support
Health Effects Division (H7509C)

TO: Metabolism Committee
Health Effects Division (H7509C)

THRU: Debra Edwards, Branch Chief *Robert J. Quick*
Chemistry Branch 1 - Tolerance Support
Health Effects Division (H7509C)

In PP#3F04177, Sandoz Crop Protection Corporation is proposing a tolerance of 0.01 ppm on soybean grain.

Permanent tolerances have been established for dimethenamid on corn grain, fodder and forage at 0.01 ppm in 40 CFR 180.464. Temporary tolerances on soybeans, forage and hay at 0.01 ppm (PP#1G3980) expire 3/1/94.

The Metabolism Committee previously considered the adequacy of the metabolism data for dimethenamid in corn, ruminants and poultry and concluded that only the parent compound should appear in the tolerance expression for corn grain, forage and fodder (11/10/92 M.Flood memo).

The metabolism of dimethenamid in soybeans is similar to that in corn in that it is extensively metabolized and cannot be detected at a detection level of 0.01 ppm. The same metabolites identified in corn were also found in soybeans although at differing ratios. The primary difference is that the total radioactive residue in soybeans is 0.2 ppm whereas the total radioactive residue in corn grain was 0.02 ppm.

The present analytical enforcement method would only detect the parent compound in case of gross misuse. Attempts to develop a common moiety method have been unsuccessful. Attached are



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tables showing the total activity, the residue identified and the chemical structures of the identified metabolites from the use of 1.5 lb ai/A as is the recommended dosage on corn and soybeans.

Questions to the Metabolism Committee:

1. Given that residues of parent dimethenamid are not detected in soybeans at 0.01 ppm, that the metabolites are similar to those found in corn, should the tolerance expression for soybeans include only parent compound as was decided for corn?

2. Given that the total radioactive residue in soybeans is 10 times that in corn grain, that soybeans in infant formula contribute to a high percentage of infants diet, should the DRES run, or risk analysis for soybeans use the total radioactive residue of 0.2 ppm rather than the proposed tolerance of 0.01 ppm?

Attachments: Tables and Chemical Structures

cc with Attachments: Circu, RF, PP#3F04177, Bradley, SF
H7509C:CBTS:M Bradley:CM#2:Rm804:305-7324:11/18/93
RDI:RSQuick:11/18/93:RALoranger:11/18/93:DEdwards:11/18/93
A:\DIMETHEN.DYN

Total radiocarbon in plant tissues was determined by combustion followed by scintillation counting.

Table 1a. Radiocarbon in Corn Plants Grown in Treated Soil.

Appl Rate	Plant Part	PHI	Avg. ppm
1.5 lb ai/A	Forage	50	0.31
	Silage	116	0.40
	Cobs	116	0.012
	Grain	116	0.021
	Cobs	130	0.020
	Grain	130	0.023
	Fodder	130	0.50
	Roots	130	0.47
4 lb ai/A	Forage	50	1.05
	Silage	116	1.12
	Cobs	116	0.04
	Grain	116	0.05
	Cobs	130	0.06
	Grain	130	0.06
	Fodder	130	1.60
	Roots	130	1.69

3

Total radiocarbon in plant tissues was determined by combustion followed by scintillation counting. Total radiocarbon in plants is summarized in Table 1. Samples were analyzed for immature seed and straw, which are not RACs, for the purpose of isolation and identification of metabolites.

Table 1. Radiocarbon in Soybeans Grown in Treated Soil.

1988 Data				1990 Data			
Appl. Rate	Plant Part	DAT*	Avg. ppm**	Appl. Rate	Plant Part	DAT*	Avg. ppm**
1.5 lb ai/A	Forage	49	2.16	1.5 lb ai/A	Forage	42	0.30
	Hay	100	1.86		Hay	100	0.91
	Imm. Seed	100	0.09		Imm. Seed		NR
	Leaves	113	2.12		Leaves		NR
	Straw	118	1.22		Straw	128	0.89
	Seed	118	0.24		Seed	128	0.13
	Roots	118	2.64		Roots		NR
3.0 lb ai/A	Forage	49	3.72	3.0 lb ai/A	Forage	42	0.60
	Hay	100	2.94		Hay	100	2.28
	Imm. Seed	100	0.20		Imm. Seed		NR
	Leaves	113	5.12		Leaves		NR
	Straw	118	2.37		Straw	128	1.71
	Seed	118	0.48		Seed	128	0.27
	Roots	118	5.08		Roots		NR

Table notes:

*DAT = days after treatment

**Avg. ppm = average μg equivalent of ^{14}C -SAN-582H/fresh weight in g from multiple replicates

Imm. seed = immature seed

Leaves were collected from the soil surface

NR = not reported

4

Table 1b

Residue Identified from Corn Plants Treated at 1.5 lb ai/A with SAN-582H
 Residue Identified from Corn Forage Treated at 4.0 lb ai/A Using CCC Method -- Normalized to 1.5 lb ai/A

%TRR (ppm)

Crop Part	PHI(days)	Oxalamide	Sulfoxide of Thiolactic Acid Conj.	Sulfoxide of Thio-glycolic Acid Conj.	Thiolactic Acid Conj.	Thioglycolic Conj./M11/other	Sulfonate Conjugate
Forage	50	3.58 (0.011)	1.60 (0.005)	1.66 (0.005)	2.28 (0.007)	3.71 (0.011)	6.06 (0.019)
Forage CCC	50	6.8 (0.019)	10.2 (0.028)	5.7 (0.016)	6.8 (0.019)	4.7 (0.013)	<15.8 (<0.044)
Silage	116	0.57 (0.0023)	3.70 (0.015)	2.90 (0.012)	1.19 (0.005)	0.60 (0.002)	7.38 (0.03)
Grain	116	-----	-----	-----	-----	-----	-----
Fodder	130	1.43 (0.007)	2.0 (0.010)	0.67 (0.003)	1.43 (0.007)	5.62 (0.028)	2.50 (0.013)
Grain	130	-----	-----	-----	-----	-----	-----

* Oxalamide and thiolactic conjugate coeluted in TLC from CCC procedure.

21

Table 2. TLC characterization of 98% methanol extract of soybean seed (1988, 1.5 lb ai/A).

Tentative Identification	Characterization of Entire Extract							Further Characterization of Individual Extractable Residues ≥ 0.01 ppm				
	Initial Sample Analysis *			11-Month Sample Analysis				Residue	Initial Sample		11-Month Sample	
	TLC Rf Range	% TRR	ppm	TLC Rf Range	% TRR	ppm	% TRR		ppm	% TRR	ppm	
ND ^b	-0.026-0.0395	2.84	0.0055	-0.047-0.035	3.44	0.0067	N/A ^c	N/A	N/A	N/A	N/A	
Sulfonate	0.0395-0.145	4.58	0.0089				N/A	N/A	N/A	N/A	N/A	
ND	0.145-0.211	2.38	0.0048	0.035-0.113	2.39	0.00469	N/A	N/A	N/A	N/A	N/A	
				0.113-0.195	2.43	0.000476						
STLA	0.211-0.289	4.19	0.0082	0.195-0.277	2.93	0.00575	N/A	N/A	N/A	N/A	N/A	
ND	0.289-0.362	2.65	0.0052				N/A	N/A	N/A	N/A	N/A	
STGA	0.362-0.454	10.7	0.0210	0.277-0.362	10.3	0.0202	STGA	5.97	0.0116	5.71	0.0112	
ND	0.454-0.526	2.07	0.0040	0.362-0.443	0.51	0.00099	N/A	N/A	N/A	N/A	N/A	
ND	0.526-0.612	1.83	0.0036	0.443-0.552	2.26	0.00443	N/A	N/A	N/A	N/A	N/A	
ND	0.612-0.704	3.57	0.0070				N/A	N/A	N/A	N/A	N/A	
Oxalamide/TLA	0.704-0.789	4.63	0.0090	0.552-0.607	3.17	0.00621	N/A	N/A	N/A	N/A	N/A	
TGA/M11	0.789-0.849	6.17	0.0120	0.607-0.689	5.94	0.0116	TGA/M11	3.05	0.0060	2.94	0.0058	
ND	0.849-0.914	1.45	0.0028	0.689-0.770	<0.1	0.0001	N/A	N/A	N/A	N/A	N/A	
ND	0.914-1.00	1.11	0.0022	0.770-1.0	0.3	0.0007	N/A	N/A	N/A	N/A	N/A	
Total characterized ^{4*}	--	17.9	0.0351	--	<7.99	0.0114	--	17.90	0.0351	5.63	0.0114	
Total identified ^d	--	30.27	0.0591	--	25.78	0.0505	--	22.42	0.0437	18.19	0.0357	
Total ^{4*}	--	48.17	0.0942	--	<33.77	0.0618	--	40.32	0.0788	23.82	0.0470	

* Values are from the original metabolism study and are reiterated in the present submission.

^b ND = Not determined due to low (≤ 0.01 ppm) levels of radioactivity.

^c N/A = not applicable.

^d Calculated by study reviewer.

• All totals include zones designated as ND, whether or not they were further characterized by TLC.

Table 1. TLC characterization of 98% methanol extract of soybean forage (1988, 1.5 lb ai/A).

Metabolite	Characterization of Entire Extract						Further Characterization of Discrete TLC Bands					
	Initial Sample Analysis *			11-Month Sample Analysis			Scraped TLC Rf Range	Characterized Residues	Initial Sample		11-Month Sample	
	Rf Range	% TRR	ppm	Rf Range	% TRR	ppm			% TRR	ppm	% TRR	ppm
Sulfonate	-0.037-0.109	24.5	0.494	-0.044-0.119	20.1	0.360	0.04-0.14	Low Rf component	3.59	0.0726	2.95	0.0529
								Sulfonate	16.3	0.329	13.4	0.240
STLA	0.109-0.205	10.1	0.203	0.119-0.244	8.81	0.158	0.11-0.26	STLA	6.00	0.121	5.25	0.0942
STGA	0.205-0.351	15.3	0.309	0.244-0.359	11.7	0.210	0.25-0.41	STGA	2.51	0.0506	2.19	0.0393
								STGA	11.5	0.231	8.77	0.157
Diffuse zone	0.351-0.410	1.65	0.033 ⁴	0.359-0.431	3.32	0.059 ⁷	N/A ^b	Oxalamide	1.70	0.0343	1.30	0.0233
								N/A	N/A	N/A	N/A	N/A
Oxalamide/TLA	0.410-0.534	10.4	0.210	0.431-0.544	10.8	0.194	0.39-0.59	Oxalamide	6.45	0.130	6.72	0.121
								TLA	2.55	0.0515	2.66	0.0476
Diffuse zone	0.534-0.602	2.34	0.047 ³	0.544-0.613	2.96	0.053 ⁰	N/A	N/A	N/A	N/A	N/A	N/A
TGA/M11	0.602-0.708	4.13	0.083 ⁵	0.613-0.719	3.76	0.067 ⁴	0.63-0.77	TGA	1.67	0.0338	1.52	0.0273
Diffuse zone	0.708-0.814	<0.01	--	0.719-0.831	<0.01	--	N/A	M9	1.48	0.0298	1.34	0.0241
Diffuse zone	0.814-0.919	<0.01	--	0.831-0.938	<0.01	--		M11	0.73	0.0149	0.67	0.0119
Diffuse zone	0.919-1.00	<0.01	--	0.938-1.0	<0.01	--	N/A	N/A	N/A	N/A	N/A	N/A
Total characterized **	--	<4.00	4.081	--	<9.63	--	--	--	9.09	0.183	4.40	0.190
Total identified *	--	64.43	1.300	--	55.17	0.989	--	--	49.41	0.996	42.48	0.762
Total **	--	68.42	1.380	--	61.48	1.102	--	--	58.50	1.179	46.88	0.951

* Values are from the original metabolism study and are reiterated in the present submission.
 b N/A = not analyzed.
 c Calculated by the study reviewer.
 d All totals include diffuse zones, whether or not they were further characterized by TLC.

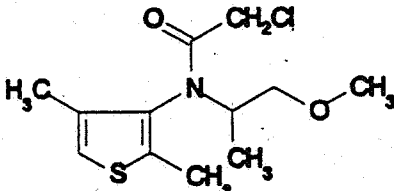
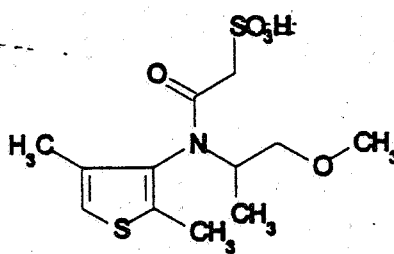
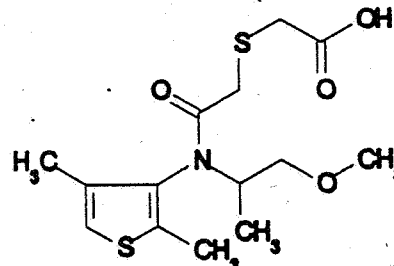
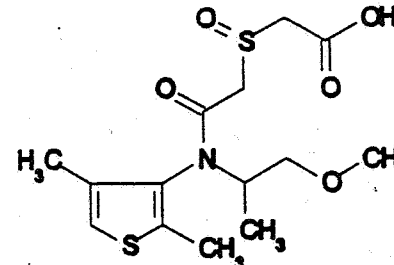
Table 3. Total radioactivity in fractions and metabolites extracted from soybean forage using the Sequential Extraction Procedure (1988, 3 lb ai/A).

Metabolites	Extrapolated TRR ^{a,b}											
	Methylene Chloride		Acetone		Methanol		Total Organic Extractable			Characterization of scraped and reanalyzed bands ^c		
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Extractable residues	7.53	0.202	45.4	1.22	21.4	0.573	74.3	2.00	N/A	N/A	N/A	N/A
Dimethenamid	ND	ND	ND	ND	ND	ND	ND	ND	N/A	N/A	N/A	N/A
TGA/M11 ^d	3.27	0.0875	2.54	0.0681	0.492	0.0132	6.30	0.169	2.49	0.0667		
Oxalamide/TLA ^d	1.83	0.0490	9.95	0.266	4.06	0.109	15.8	0.424	19.5	0.524		
STGA	1.11	0.0296	8.90	0.238	5.00	0.134	15.0	0.402	13.9	0.371		
STLA	0.6	0.0161	8.04	0.215	2.78	0.0744	11.4	0.306	7.90	0.211		
Sulfonate	0.37	0.0099	12.4	0.333	5.13	0.137	17.9	0.480	14.1	0.378		
Extremely Polar Component	ND	ND	3.36	0.090	3.87	0.104	7.23	0.194	6.63	0.178		
Total characterized ^e	7.18	0.192	3.36	0.090	3.87	0.104	7.23	0.194	6.63	0.178		
Total identified ^e	7.18	0.192	41.83	1.120	17.46	0.468	66.40	1.761	57.89	1.551		
Total ^e	7.18	0.192	45.19	1.210	21.33	0.572	73.63	1.975	64.52	1.729		

- ^a The petitioner stated that the TRR values were "extrapolated down" to estimate the TRR values that would have been obtained using samples obtained from plants treated at the 1x level. No calculations were presented.
- ^b Total forage TRR from the 2x treatment was 5.354 ppm (mean of four replicates).
- ^c Values represent collective characterization of bands obtained by analyses of methylene chloride, acetone, and methanol extracts by solvent system I; the bands were scraped and reanalyzed using TLC solvent system VI.
- ^d Components could not be resolved separately by TLC radioscan.
- ^e Calculated by the study reviewer.

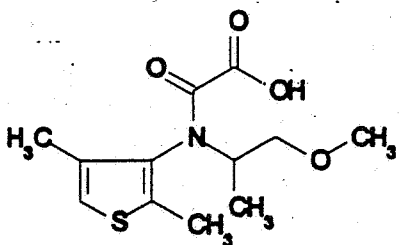
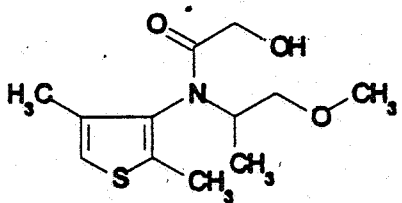
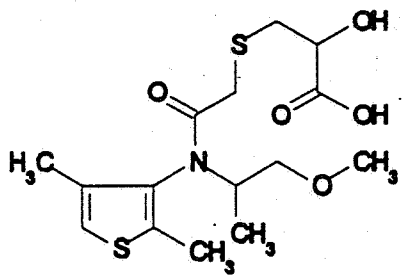
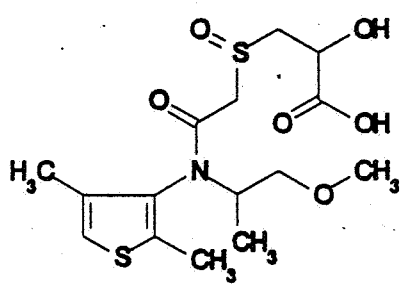
8

Table 4. Dimethenamid and its metabolites in soybeans and corn (MRID 42842501).

Code	Chemical Name Structure	Substrate	Common Name
I.	<p>2-chloro-N-(1-methyl-2-methoxyethyl)-N-(2,4-dimethyl-thien-3-yl) acetamide</p> 		SAN-582H, dimethenamid
II.	<p>N-(2,4-dimethyl-3-thienyl)-N-(2-methoxy-1-methylethyl)-2-sulfonyl acetamide</p> 	soybean seedlings, forage, and seed corn seedlings	sulfonate
III.	<p>N-(2,4-dimethyl-3-thienyl)-N-(2-methoxy-1-methylethyl)carboxymethylene thionylacetamide</p> 	soybean forage and seed corn forage	thioglycolic acid conjugate, TGA
IV.	<p>N-(2,4-dimethyl-3-thienyl)-N-(2-methoxy-1-methylethyl)carboxymethylene sulfinylacetamide</p> 	soybean seedlings, forage, and seed corn seedlings	sulfoxide thioglycolic acid conjugate, STGA

9

Table 4 (continued).

Code	Chemical Name Structure	Substrate	Common Name
V.	N-(2,4-dimethyl-3-thienyl)-N-(2-methoxy-1-methylethyl)oxamic acid 	soybean seedlings, forage, and seed corn seedlings	oxalamide
VI.	N-(2,4-dimethyl-3-thienyl)-2-hydroxy-N-(2-methoxy-1-methylethyl) acetamide 	soybean forage and seed <i>corn forage</i>	M11
VII.	N-(2,4-dimethyl-3-thienyl)-N-(2-methoxy-1-methylethyl)-2-carboxy-2-hydroxyethyl thionylacetamide 	soybean seedlings, forage, and seed corn seedlings	thiolactic acid conjugate, TLA
VIII.	N-(2,4-dimethyl-3-thienyl)-N-(2-methoxy-1-methylethyl)-2-carboxy-2-hydroxyethyl sulfinylacetamide 	soybean seedlings, forage, fodder, and seed corn seedlings	sulfoxide of thiolactic acid conjugate, STLA

10