MEMORANDUM

SUBJECT: **Napropamide.** Reregistration Case No. 2450. Issues to be presented at the 3/16/93 meeting of the HED Metabolism Committee.

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TO: HED Metabolism Committee (H7509C)

Napropamide is a pre-emergence herbicide used to control annual grasses and some broad-leaved weeds. Tolerances are established (40 CFR 180.328) at 0.1 ppm or negligible residues (0.1 ppm) of napropamide (N,N-Diethyl-2-(1-naphthenyloxy) propionamide) in or on many raw agricultural commodities, including, almond hulls, artichokes, asparagus, avocados, basil, Brassica (cole) leafy vegetables, coffee beans, cucurbits vegetables, figs, fruits (citrus, pome, small, and stone), kiwifruit, marjoram, mint, nuts, olives, persimmons, pistachio nuts, rhubarb, rosemary, winter and summer savory, and fruiting vegetables.

The Phase 4 Review (1/16/91) of napropamide required the registrant, ICI Americas Inc., to provide new plant metabolism studies in three unrelated crops representing the highest percentage of use. In response to this requirement, the registrant has submitted metabolism studies in cabbage, tomatoes, and apples.

Cabbage Metabolism Study MRID #423939-01

Ring labeled napropamide was applied to soil in a pot at an exaggerated rate of 2.25 lb ai/A (1.125X). The PHI ranged from 55 to 63 days. A proposed metabolic pathway for napropamide in cabbage was presented (see Figure 1). The available data support the proposed metabolic scheme. Results for cabbage heart and whole cabbage are summarized in Tables 1 and 2.

The total radioactive residue (TRR) found in the cabbage heart sample was 0.125 ppm. Of this, 94.5% was extractable and a total of 90.7% of the TRR was characterized and 59.9% (0.075 ppm) of the TRR identified. Natural incorporation into sugars accounted for 50.1% (0.063 ppm) of the TRR. The major metabolites identified were naphthoxypropionic acid (3.0% TRR, 0.004 ppm), desethylnapropamide (2.5% TRR, 0.003 ppm), and 5-hydroxy-napropamide (1.2% TRR, 0.002 ppm). The parent compound accounted for 0.8% TRR, 0.001 ppm.

In whole cabbage, the total radioactive residue found was 0.457 ppm. Of this amount, 89.1% was extractable and a total of 77.0% of the TRR was characterized and 35.2% (0.161 ppm) of the TRR was identified. Natural incorporation into sugars accounted for 12.6% (0.058 ppm) of the TRR. The major identified metabolites were: 5-hydroxy-napropamide (6.7% TRR, 0.031 ppm); 1,4-naphthoquinone (4.9% TRR, 0.022 ppm); napthoxypropionic acid (2.9% TRR, 0.013 ppm); and desethylnapropamide (2.3% TRR, 0.011 ppm). The parent compound accounted for 0.9% TRR, 0.004 ppm.

Data depicting storage stability were not provided. This is a deficiency. The registrant stated that TLC profiles of extracts of cabbage hearts and whole cabbage taken at 3 months and up to 17 months post-harvest were qualitatively similar. Representative data were requested.

Tomato Metabolism Study MRID #423498-02

Ring labeled napropamide was applied to soil in a pot at an exaggerated rate of 2.25 lb ai/A (1.125X). Fruits were harvested when ripe (PHI ranged from 67 to 122 days). The total radioactive residue (TRR) found in tomatoes was 0.051 ppm. Of this amount, 92.3% was extractable, and total of 83.7% of the TRR was characterized and 43.9% (0.022 ppm) of the TRR identified. Natural incorporation into sugars accounted for 21.2% (0.011 ppm) of the TRR. The major metabolite found was o-phthalic acid (6.1% TRR, 0.0031 ppm), followed by 5-hydroxydesethyl-napropamide (4.5% TRR, 0.0023 ppm) and 5-hydroxynaphthoxypropionic acid (4.2% TRR, 0.0021 ppm). Storage stability data were not provided. This is a deficiency.

A proposed metabolic pathway for napropamide in tomatoes was presented (see Figure 1). The available data support the proposed metabolic scheme.

Apple Metabolism Study MRID #423498-01

Ring labeled napropamide was applied to soil in a $4m^2$ area around an apple tree. Two applications were made; the first at green cluster, at a rate of 4.11 lb ai/A (1.03X), and the second approximately five months later, at 4.04 lb ai/A (1.01X), to give a 35 day PHI for the first year crop. Application rate and timings adequately reflected label directions.

The first and second year's crop were harvested and analyzed for radioactive residue. The total radioactive residue (TRR) found in the first year's crop was 0.0032 ppm. The radioactivity was fractionated, an no fraction had a residue level greater than 0.002 ppm. Because of the low residues detected, additional analysis was not performed.

The TRR in the second year's crop was 0.0098 ppm. The radioactivity was fractionated, an no fraction had a residue level greater than 0.006 ppm. Because of the low residues detected, additional analysis was not performed.

Question for the Committee: For whole cabbage and tomatoes, the parent compound comprised less than 1% of TRR, and was the second least abundant of all radioactive components identified. 5-Hydroxynapropamide and 5-hydroxydesethyl napropamide together accounted for 8.7% TRR in whole cabbage and 6.9% TRR in tomatoes. In light of this data, is the current tolerance expression for napropamide adequate?

cc: Napropamide S.F., circ., R.F., List B File, S.Knizner
RDI: A.Rathman, 2/25/93 M.Metzger, 3/1/93
H7509C:CBRS:SAK:sak:305-6903:Napro1.met:CM#2:2/25/93

Figure 1. Proposed metabolic pathway of napropamide in cabbage and tomato.

Table 1. Summary of the characterization and identification of the radioactive residues in cabbage heart. The total residue was 0.125 ppm.

Component	% Total Residue	ppm
Extractable with Ethanol/Water		
Organosoluble:		
Napropamide	0.8	0.001
5-Hydroxynapropamide	1.2	0.002
Desethylnapropamide	2.5	0.003
o-Phthalic acid	0.5	0.001
1,4-Naphthoquinone	0.8	0.001
Naphthoxypropionic acid	3.0	0.004
5-hydroxynaphthoxypropionic acid	1.0	0.001
Unknowns	5.2	0.007
Remainder[1]	3.4	0.004
Aqueous Soluble Activity		
Glucose	18.6	0.023
Fructose	13.0	0.016
Remainder[2]	11.1	0.014
Aqueous 2 (not analyzed)	5.0	0.006
Activity Resulting from Enzyme Hydrolysis of Debris 1		
Sucrose	3.6	0.005
Glucose	12.4	0.016
Fructose	2.5	0.003
Remainder[2]	6.2	0.008
Aqueous-soluble activity not analyzed	1.6	0.002
Activity remaining in Debris 2	5.5	0.007
Activity Lost during Fractionation	2.2	0.003

[1]A mixture of machine noise and low levels of radioactivity uniformly streaked over the length of the chromato gram.

[2]Activity no co-chromatographing with ^{14}C-sugars (including activity not recovered from the column). No activity remaining was greater than 5.4% of the TRR (0.007 ppm).

Table 2. Summary of the characterization and identification of the radioactive residues in whole cabbage. The total residue was 0.457 ppm.

Component	% Total Residue	ppm
Extractable with Ethanol/Water		
Organosoluble:		
Napropamide	0.9	0.004
5-Hydroxynapropamide	6.7	0.031
Naphthoxypropionamide	0.2	0.001
Desethylnapropamide	2.3	0.011
5-Hydroxydesethylnapropamide	2.0	0.009
o-Phthalic acid	1.0	0.005
1,4-Naphthoquinone	4.9	0.022
Naphthoxypropionic acid	2.9	0.013
5-Hydroxynaphthoxypropionic acid	1.7	0.008
Unknowns[1]	14.4	0.066
Remainder[2]	12.5	0.057
Aqueous Soluble Activity		
Sucrose	0.2	0.001
Glucose	4.1	0.019
Fructose	3.1	0.016
Remainder[3]	1.7	0.014
Activity remaining in Aqueous 5[4]	5.8	0.027
Aqueous activity not analyzed	0.2	0.001Activity Resulting from Hydrolysis of Debris 3
Sucrose	1.4	0.006
Glucose/Fructose	3.8	0.017
Organosoluble activity not analyzed	0.7	0.003
Remainder	2.1	0.010
Activity in 50% Methanol 1[5]	6.2	0.028
Activity remaining in Debris 4	9.9	0.045
Activity Lost during Fractionation	12.2	0.056

[1]The major unknown was in Ether 5 (3.0% TRR, 0.014 ppm).
[2]Activity unassigned from linear scan data.
[3]Activity not co-chromatographing with ^{14}C-sugars (including activity not recovered from the column).
[4]Aqueous 5 contains at least two unknowns, the greatest of which accounts for 1.6% TRR, 0.007 ppm.
[5]50% Methanol 1 contains at least one unknown, the greatest of which accounts for 3.8% TRR, 0.017 ppm.

Table 3. Summary of the characterization and identification of the radioactive residues in tomato.

Component	% Total Residue	ppm
Extractable Activity		
Organosoluble:		
Napropamide	0.4	0.0002
5-Hydroxynapropamide	2.4	0.0012
4-Hydroxynapropamide	0.2	0.0001
Desethylnapropamide	1.6	0.0008
4-Hydroxydesethylnapropamide	0.6	0.0003
5-Hydroxydesethylnapropamide	4.5	0.0023
o-Phthalic acid	6.1	0.0031
Naphthoxypropionic acid	1.5	0.0008
5-hydroxynaphthoxypropionic acid	4.2	0.0021
4-Hydroxynaphthoxypropionic acid	1.2	0.0006
Unknowns	8.3	0.0042
Remainder[1]	5.1	0.0026
Aqueous Soluble Activity		
Glucose	8.6	0.0044
Fructose	9.6	0.049
Remainder[2]	7.0	0.0036
Remaining in Aqueous 5	9.6	0.0049
Aqueous Activity Not Analyzed	4.0	0.0020
Activity Resulting from Enzyme Hydrolysis of Debris 1		
Glucose/Sucrose	2.3	0.0012
Fructose	0.7	0.0004
Remainder[2]	6.2	0.008
Aqueous-soluble activity not analyzed	1.3	0.0007
Activity remaining in Debris 2	7.7	0.0039
Activity in Debris after Filtration	0.6	0.0033
Activity Lost during Fractionation	8.6	0.0044

[1]Activity unassigned from linear scan data.
[2]Activity not co-chromatographing with sugars (including activity not recovered from the column).