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SCIENTIFIC DATA REVIEWS
EPA SERIES 361

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 7, 2004

MEMORANDUM

SUBJECT: Naptalam (030702) and Naptalam Sodium (030703) Metabolism studies, Rotational Crop studies and summary of residue studies for Naptalam RED. Reregistration Case No. 0183. DP Barcode 266798, 307657. MRIDs 44295301, 44295302, 42087605

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Reregistration Branch 4
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Uniroyal Chemical Co., Inc. Crop Protection Division has submitted two plant metabolism studies additional information on their confined rotational crop study in response to reregistration requirements. These studies are reviewed in summary format. The plant metabolism studies are adequate. Naptalam metabolizes extensively, and is not found in mature plants. Naptalam, per se, remains the residue of concern, to be included in the tolerance expression. The remainder of the naptalam residue chemistry studies and the rat metabolism studies are briefly summarized as input to the Naptalam RED.

Plant Metabolism

Two plant metabolism studies in cucumber have been conducted. The first study (MRID 44295301) used naptalam uniformly labeled in the phthalic acid ring. Rates of 4 lb ai/A and 8 lb ai/A (1x and 2x) were used. Naptalam-sodium (14-C-Alanap-L, EPA Reg. No. 400-49) was applied twice according to label directions, one day after planting and at vining. The label

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directions allow application up to 2 days after planting and just before vining, when naptalam-sodium may be applied overtop of plants.

Table 1. Naptalam-Sodium. Total Radioactive Residues (TRR) in cucumber and cucumber foliage following treatment at 1x or 2x rate. (Phthalic acid label)

Plant part	TRR at 4 lb ai/A (1x rate)	TRR at 8 lb ai/A (2x rate)
cucumber fruit	0.369 ppm	0.491 ppm
cucumber foliage	10.5 ppm	16.2 ppm

The cucumber samples were extracted sequentially with water, weak base, weak acid, methanol, and ethyl acetate. The post extraction solids were treated with enzyme digestion, and sodium hydroxide. About 95% of the TRR was in the water extraction.

The extracts were analyzed by reverse phase HPLC. Four peaks were observed. The metabolites were identified by co-chromatography and LC/MS/MS. The following 3 metabolites were identified. The fourth peak contained 8% TRR, and contained many components, none of which exceeded 2% TRR. No naptalam residues were found.

Naptalam Metabolite	% TRR
Phthalic acid	80%
Phthalic acid monoamide (phthalamic acid)	3%
phthalic acid monomethyl ester	7%
Total identified	90%

The second study (MRID 44295302) used naptalam labeled at carbon one of the naphthyl ring. Rates of 4 lb ai/A and 8 lb ai/A (1x and 2x) were used. Naptalam was applied twice, one day after planting and at vining.

Table 2. Naptalam Sodium. Total Radioactive Residues (TRR) in cucumber and cucumber foliage following treatment at 1x or 2x rate. (Naphthyl label)

Plant part	TRR at 4 lb ai/A (1x rate)	TRR at 8 lb ai/A (2x rate)
cucumber fruit	0.107 ppm	0.272 ppm
cucumber foliage	18.5 ppm	37.2 ppm

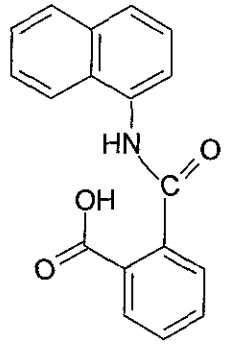
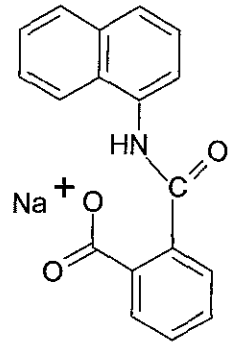
The cucumber samples were extracted sequentially with water, weak base, weak acid, methanol, and ethyl acetate. The post extraction solids were treated with enzyme digestion, and sodium hydroxide. More than 80% of the TRR was in the water extraction.

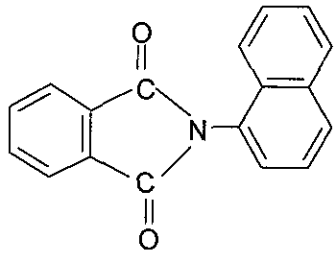
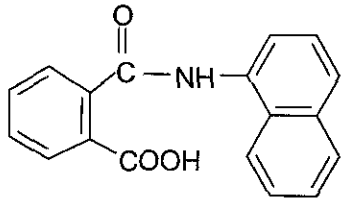
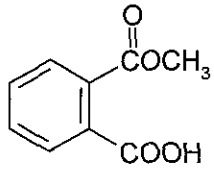
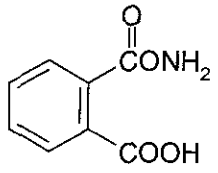
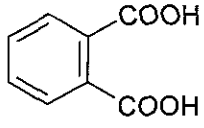
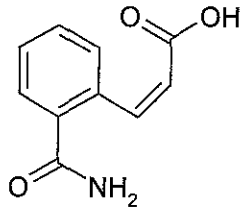
The extracts were analyzed by reverse phase HPLC. Eleven peaks were observed. The metabolites were identified by co-chromatography, LC/MS and LC/MS/MS. The following 7 metabolites were identified:

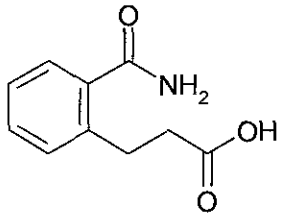
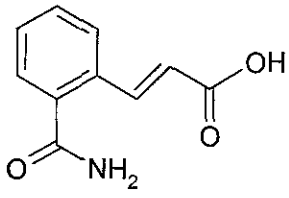
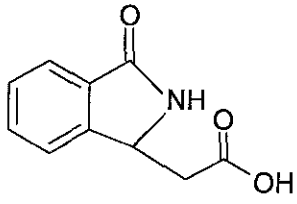
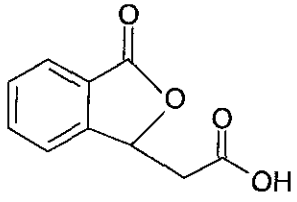
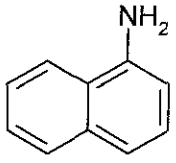
Naptalam Metabolite	% TRR
(Z)-3-[2-(aminocarbonyl)phenyl]-2-propenoic acid	9.13%
(Z)-3-[2-(aminocarbonyl)phenyl]-2-propanoic acid	12.3%
Phthalic acid	12.3%
(E)-3-[2-(aminocarbonyl)phenyl]-2-propenoic acid	5.64%
isoindolinone-3-acetic acid	<10%
3-phthalideacetic acid	<10%
phthalic acid monomethyl ester	<5%
Total identified	<65%

The balance of the metabolites were less than 6% TRR. No naptalam residues were found, and no residues containing the intact naphthalene group were found. In addition to the metabolites found, the following compounds was used as a standards and not found as a naptalam metabolite: 1-Aminonaphthalene.

Figure 1. Structures of Naptalam, Naptalam Sodium, and Metabolites

Naptalam	
Naptalam Sodium	

N-1-Naphthyl phthalimide (Found in cucumber seedlings, but not found in mature cucumber)	
N-1-Naphthyl phthalamic acid (Found in cucumber seedlings, but not found in mature cucumber)	
Phthamic acid Monomethyl ester (7% TRR - phthalic label <5% TRR - naphthyl label)	
Phthalic acid monamide or Phthalamic acid (3% TRR - phthalic label)	
Phthalic acid (80% TRR - phthalic label 12% TRR - naphthyl label)	
(Z)-3-[2-(aminocarbonyl)phenyl]-2-propenoic acid (9% TRR - naphthyl label)	

(Z)-3-[2-(aminocarbonyl)phenyl]-2-propanoic acid (12% TRR - naphthyl label)	
(E)-3-[2-(aminocarbonyl)phenyl]-2-propenoic acid (6% TRR - naphthyl label)	
Isoindolinone-3-acetic acid (<10 % TRR - naphthyl label)	
3-Phthalideacetic acid (<10 % TRR - naphthyl label)	
N-1-Naphthylamine (Found in cucumber seedlings, but not found in mature cucumber)	

Livestock Metabolism. Submitted livestock metabolism studies were inadequate. However, there are no longer naptalam sodium uses registered on livestock feeds, therefore a livestock metabolism study is not needed.

Confined Rotational Crop. A confined rotational crop study (MRIDs 40069102, 40274501) was submitted in response to the Registration Standard and found to be inadequate (H. Manning memo of 5/13/91). [C14]Naptalam residues accumulated in wheat planted 36 days after treatment (up to 0.16 ppm), and in lettuce and turnips planted 36 and 260 days after treatment (up to 0.026 ppm). None of the residues was identified.

Uniroyal submitted additional information on the confined rotational crop study; this information was assigned an MRID, 42087605. In response to the requirement that the metabolites in soils and crops be identified, Uniroyal responds that they intend to change the Alanap-L label to prohibit rotation to small grain crops. They claim that the residues in other crops were negligible. While the residues reported (0.026 ppm) exceed the Agency's trigger level, requiring identification, no naptalam residues, per se, were reported in the mature primary crop, and the metabolites identified were less toxic that the parent compound. The report also contains additional details about the study. No additional rotational crop data are needed.

Rat Metabolism. Two rat metabolism studies were submitted and both were considered supplementary (MRID 40274502, TXR 009803; MRID 41860003, TXR 010741). The following information is from the TOX 1-liners. The absorption, distribution, metabolism, and excretion of naptalam were studied in groups of male and female CD rats administered a single oral dose of 250 or 1000 mg/kb [C14] naptalam by gavage. [C14]Naptalam was rapidly absorbed, distributed, and excreted in rats at both dose levels. The 7 day recoveries were at least 84.85% of the administered dose. The elimination of the radioactivity in the urine (39.39 - 45.30%) was for all dose groups. The radioactivity in the feces was 59.13 - 67.73% in male groups and 41.46 - 43.10% in the female groups. The elimination data suggest that absorption of naptalam is rapid, bioaccumulation is low, and excretion occurs in the feces and urine. The urine contained one major radioactive band which was identified as the unmetabolized parent compound. No metabolites were identified in the urine. Since the metabolism was not evaluated in the feces, the complete metabolite pattern cannot be determined . The study also indicated that naptalam and/or its metabolites do not bioaccumulate to an appreciable extent following oral exposure since all tissues contained negligible levels of radioactivity at 7 days post-exposure. Based on the study results, absorption, distribution, and elimination of naptalam did not appear to be sex or dose related. No conclusions can be made regarding sex or dose-related differences in the metabolism of naptalam since radioactivity in the feces was not analyzed. Furthermore, no metabolic pathway could be determined for naptalam. The study showed that administration of 250 and 1000 mg/kg naptalam did not induce any apparent treatment-related clinical effects. This study does not satisfy the guideline requirement for a general metabolism study in rats. This study may be upgraded if additional data are provided. The company proposed a bridging study to help resolve questions of metabolism (DER 10741, 1/25/93).

Analytical Methodology. PAM II lists two colorimetric methods: (1) Smith and Stone (Method A), and (2) Lane, et. al. (Method B). Recovery of naptalam using FDA PAM I protocols A, D, and E is unlikely. FDA has not reported any analyses for naptalam from 1999 to 2002.

Crop Field Trials. A sufficient number of geographically representative field trials are available (MRID 40274504) for cantaloupe treated at 4 lb ai/A and harvested 47-54 days after treatment; cucumbers treated at 4 lb ai/A preemergent; and for watermelon treated at 4 lb ai/A and harvested 33-68 days after treatment. All residues reported in field trials were non-detectable (<0.1 ppm). The field trials are supported by storage stability data. The residue data support the currently established tolerances for cantaloupe, cucumber, muskmelon, and watermelon of 0.1 ppm.

Tolerances. Tolerances for naptalam are established in 40 CFR 180.297, as follows. Metabolism data reviewed for the RED indicate that there is no change needed in the naptalam tolerance expression.

180.297 N-1-Naphthyl phthalamic acid; tolerances for residues.

Tolerances are established for residues of the herbicide N-1-naphthyl phthalamic acid from application of its sodium salt in or on the following raw agricultural commodities:

Table 3. Tolerance Summary for Naptalam

Commodity	Established/Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Cantaloupe	0.1 (N)	Revoke	Tolerance should be revoked with the concomitant establishment of a tolerance for Melon (Crop Group 9A)
Cucumber	0.1 (N)	0.1	
Muskmelon	0.1 (N)	Revoke	Tolerance should be revoked with the concomitant establishment of a tolerance for Melon (Crop Group 9A)
Watermelon	0.1 (N)	Revoke	Tolerance should be revoked with the concomitant establishment of a tolerance for Melon (Crop Group 9A)
Melon subgroup (Crop Group 9A)		0.1	Tolerance should be established with the concomitant revocation of tolerances for Cantaloupe, Muskmelon, and Watermelon.

There are no established Codex maximum residue limits (MRLs) or tolerances for residues of naptalam. Therefore, international harmonization is not an issue.

MRIDs referenced

42087605 Uniroyal Chemical Co. (1991) Naptalam Sodium Salt: Supplemental Report (...) Confined Rotational Crops: Lab Project No. 8644: 8644A. Unpublished study. 13 p.

44295301 Gay, M.; Wang, R. (1997) Distribution and Metabolism of Naptalam (Phthalic-Ring-UL-(carbon 14)) in Cucumber: (Final Report): Lab Project Number: 95216. Unpublished study prepared by Uniroyal Chemical Co., Inc. 163 p. {OPPTS 860.1300}

44295302 Gay, M.; Wang, R.; Hull, L.; et al. (1997) Distribution and Metabolism of Naptalam ((carbon 14)-1-Naphthyl) in Cucumber: (Final Report): Lab Project Number: 95215. Unpublished study prepared by Uniroyal Chemical Co., Inc. 191 p. {OPPTS 860.1300}

Chemistry Reviews of Naptalam

RCB #	Barcode	ID No.	Date	Reviewer	Subject	Subject continued
	307657	030703	09/07/2004	SHUMMEL	ROTATIONAL CROP	42087605
	D237271	030703	09/07/2004	SHUMMEL	CUCUMBER METABOLISM	
	D237271	030702	09/07/2004	SHUMMEL	CUCUMBER METABOLISM	
	D237271	030703	09/07/2004	SHUMMEL	CUCUMBER METABOLISM	
15840	D217135	030703	07/13/1995	--	PROD CHEM 62-X 43702701	RETURN TO SRRD UNREVIEWED
14958	D210869	030703	04/19/1995	FFORT	PROTOCOL CUCUMBER METAB	
12345	D194016	030703	08/04/1994	FFORT	STORAGE STABILITY	
12159	D192766	030703	08/16/1993	KDOCKTER	PROD CHEM	42250101
9443	D174935	030703	07/30/1992	WSMITH	PROD CHEM	42194101 - -04, 42130102
7733	D162084	030703	02/04/1992	RPERFETT	PLANT METABOLISM	41790501--3
8322	D166854	030703	09/25/1991	RPERFETT	PRODUCT CHEM	41936301
	D157048	030703	05/13/1991	HMANNING	ROTATIONAL CROP	SEE EFED FILES 40274501
	D157048	030703	05/13/1991	HMANNING	ROTATIONAL CROP	SEE EFED FILES 40069102 - INTERIM REPORT
7333	D158499	030703	04/17/1991	RPERFETT	PRODUCT CHEMISTRY	41664001-NITROSAMINE
7743	D162082	030703	04/17/1991	RPERFETT	RESIDUE CHEMISTRY	00153372, 41664002, 00157184
7270		030703	01/31/1991	WSMITH	ANIMAL METABOLISM WAIVER	
0		030703	07/25/1990	WSMITH	REG.STD.UPDATE	00154116,00157183,40003301,41385501,40274503-05
		030702	01/09/1985	GBEUSCH	REG STD-PROD & RES CHEM	NAPTALAM (ACID) NO LONGER PRODUCED
		030703	01/09/1985	GBEUSCH	REG STD-PROD & RES CHEM	
		400-RAA	12/02/1982	LPROPST	SOYBEANS	
	180.297	0F2321	03/07/1980	LBRADLEY	PEANUT HULLS	
		400-75	01/23/1980	LBRADLEY	PEANUTS	
		400-75	09/29/1979	LBRADLEY	PEANUTS	
		400-75	09/27/1979	LBRADLEY	PEANUTS	
		MO-790000	09/27/1979	LBRADLEY	SOYBEANS	
		OK-790007	06/22/1979	JWORTHIN	PEANUTS	
		MS-790008	06/22/1979	JWORTHIN	SOYBEANS-ADDENDUM	
		MS-790008	06/06/1979	JWORTHIN	SOYBEANS	
		OK-790007	06/06/1979	JWORTHIN	PEANUTS	
		MO-780000	09/27/1978	EZAGER	SOYBEANS	
		400-87	08/21/1974	JSHAUGHN	SOYBEANS	
		400-85	08/21/1974	JSHAUGHN	SOYBEANS	
		400-75	08/07/1974	JSHAUGHN	PEANUTS, SOYBEANS	
	180.297	0F0904	10/23/1970	BHOPKINS	CANTALOUPE, CUCUMBERS,	MUSKMELON, WATERMELON, CRANBERRY, PEANUT
	180.297	0F0904	04/28/1970	BHOPKINS	CANTALOUPE, CUCUMBERS,	MUSKMELON, WATERMELON, CRANBERRY, PEANUT

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Chemical:	**Benzoic acid, 2-((1-naphthalenylamino)ca; Naptalam, sodium salt**
PC Code:	**030702; 030703**
HED File Code	**11000 Chemistry Reviews**
Memo Date:	**08/30/2004**
File ID:	**DPD266798; DPD307657**
Accession Number:	**412-05-0032**

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12/01/2004