Subject File

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

APR 17 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Addendum #1 to the Naptalam Residue Chemistry Reregistration Standard and Product and Residue Chemistry Reviews of Additional Responses (MRID #'s 41664001, 00153372, 41664002, 00157184, and 41790500; CBRS #'s 7333 and 7743; Barcodes: D158499 and D162082).

FROM: E. Zager, Chief
Debra Edwards, for
Chemistry Branch II: Reregistration Support
Health Effects division (H7509C)

TO: Lois Rossi, Chief
Reregistration Branch
Special Review & Reregistration Division

and

Reto Engler, Ph.D., Chief
Science Analysis and Coordination Branch
Health Effects Divisiom (H7509C)

Attached are Addendum #1 to the Residue Chemistry Update of the Naptalam Reregistration Standard, along with a review of Product Chemistry submitted by the Registrant. These reviews were prepared by Ddynamac Corporation under supervision of CBRS, HED. they have undergone secondary review in the branch and have been revised to reflect Agency policies.

Revised data requirement tables are included.

The Registrant has also requested waivers for several guideline requirements (CBRS #7743, MRID #41790500). These are discussed below.

(1) 63-11 Octanol/Water Partition Coefficient: The Registrant explains that naptalam is a polar material.

CBRS notes however that the Registrant has already provided a coefficient for one of its naptalam products. The Branch

recommends against the granting of this waiver. The Registrant should be directed to footnote #8, Table A, in the naptalam product chemistry update (7/25/90).

(2) 171-4(a) Nature of the Residue in Plants: CBRS has reconsidered the Registrant's earlier argument against conducting plant metabolism studies using material labeled in the napthylamine moiety and in the phthalic acid ring or a single study using a double labeled compound. We have also reviewed a metabolism study in soybeans (See the attached document.). This study employed naphthylamine labeled naptalam. The experiment was not found to be adequate and additional studies are required. CBRS again recommends against the granting of this waiver. The Registrant should be directed to footnote #5 in the attached review for the present requirements for 171-4(a).

(3) 171-4(a) Nature of the Residue in Plants (Confirmatory Analysis): In light of the ongoing requirement above for 4 (or 2) additional metabolism studies this waiver request is probably not pertinent. CBRS however recommends against granting any such waiver. The registrant should again be directed to footnote #5 of the attached review.

(4) 171-4(e) Storage Stability. The Registrant requests a waiver for a storage stability study on peanuts based on a soybean storage stability study to which they have contributed. CBRS recommends that the peanuts storage stability study be reserved pending submittal and review of the soybean experiment.

Also, the Registrant has submitted additional data on a storage stability study on cantalope and cucumbers (CBRS #7743, MRID #41664002). This experiment was not acceptable. The Registrant should be directed to footnute #8 of the attached review.

(5) 171-4(e) and 171-4(b). Processing and Nature of the Residue in Livestock.

The Registrant should be directed to footnote numbers 6, 7, 10 and 11 in the attached review (CBRS #7743).

If you need additional input please advise.

Attachment 1: Review of Naptalam Product Chemistry

Attachment 2: Addendum #1 to the Naptalam Residue Chemistry Reregistration Standard

cc: (with Attachments 1 and 2): RBP, Naptalam Reregistration Standard File, Naptalam Subject File, C. Furlow/J Burrell (PIB/FOD) and Dynamac.

cc: (with Attachment 2): Circulation (7)

cc: (without Attachments): RF

Attachment #2

DYNAMAC
CORPORATION

Final Report

NAPTALAM
Task 4: Residue Chemistry Registration Standard Update

January 22, 1991

Contract No. 68-D8-0080

Submitted to:
Environmental Protection Agency
Arlington, VA 22202

Submitted by:
Dynamac Corporation
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NAPTALAM

REGISTRATION STANDARD UPDATE - ADDENDUM 1

RESIDUE CHEMISTRY

Task - 4

INTRODUCTION

The 3/85 Naptalam Guidance Document and/or the Naptalam Registration Standard Update of 7/25/90 identifies residue chemistry data gaps for the nature of the residue in plants and animals, residue analytical methods, storage stability, and the magnitude of the residue in processed products of peanuts and soybeans. Uniroyal Chemical Co., Inc. submissions containing data (DEB No. 7333) pertaining to the nature of the residue in soybeans (1976; MRID 00153372), storage stability (1990; MRID 41664002) and the magnitude of the residue in soybeans (1983; MRID 00157184) are considered here for their adequacy in fulfilling outstanding data requirements.

SUMMARY

The following Naptalam residue chemistry data are outstanding:

- Data on plant and animal metabolism, residue analytical methods, and storage stability.
- Data pertaining to the processing of peanuts and soybeans.

QUALITATIVE NATURE OF THE RESIDUE IN PLANTS

Conclusions:

The Naptalam Registration Standard Update of 7/25/90 concludes that the qualitative nature of the residue in plants is not adequately understood, and requires additional data depicting the distribution and metabolism of [1-naphthylamine-^{14}C]naptalam ring-labeled in the phthalic acid moiety and a separate study with the label in the 1-naphthylamine moiety (or one study using [1-naphthylamine-^{14}C]naptalam labeled in both moieties) in soybeans and a cucurbit vegetable.

Data pertaining to the metabolism of [1-naphthylamine-^{14}C]naptalam in soybeans, submitted by Uniroyal (1976; MRID 00153372) in response to the Guidance Document, do not satisfy outstanding data requirements for the following reasons: (i) only ca. 40-46% of detectable ^{14}C-residues in soybean seed were characterized; (ii) suitable confirmatory methods were not used

for those ^{14}C-residues which were identified; and (iii) raw data and supporting calculations for the reported concentration of ^{14}C-activity recovered in hexane-soluble, methanol-soluble, and insoluble fractions were not provided. The following additional data are required:

- Data depicting the distribution and metabolism of [1-naphthylamine-^{14}C]naptalam ring-labeled in the phthalic acid moiety and a separate study with the label in the 1-naphthylamine moiety (or one study using [1-naphthylamine-^{14}C]naptalam labeled in both moieties) in soybeans and a cucurbit vegetable. A completely characterized test substance representative of technical naptalam used in commercial formulations (including impurities) must be applied under conditions representing normal cropping practices and at levels sufficient to make residue identification and quantification possible. Residues must be characterized in edible mature plant parts. Confirmation of the identities of residues using a suitable method such as mass spectrometry (MS) or high-performance liquid chromatography (HPLC) is also required. In addition, representative samples from these tests must be analyzed by the residue analytical methods developed for data collection and tolerance enforcement to ascertain that these methods will recover and quantify all metabolites of concern.

Although incomplete, the available metabolism data indicate that naptalam is metabolized in cucumbers and soybeans to 1-naphthyl-phthalimide and/or 1-naphthylamine and phthalic acid; 1-naphthylamine may become conjugated to glucose. The molecular structures and chemical names of naptalam and its possible metabolites in plants are presented in Table 1.

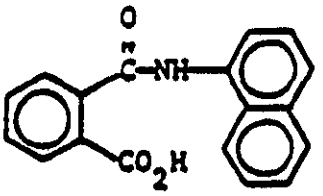
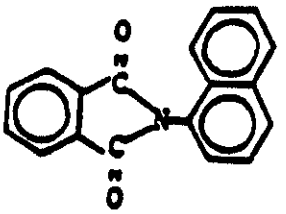
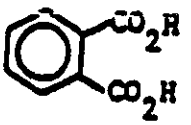
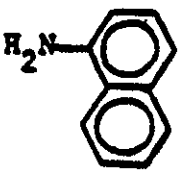
References (used):

MRID(s): 00153372.

Discussion of the data:

Uniroyal submitted data (1976; MRID 00153372) from two studies pertaining to the metabolism of naptalam in mature soybeans treated with [1-naphthylamine-^{14}C]naptalam in a formulation mixture containing unlabeled dinoseb.

Table 1. Naptalam and its metabolites in plants.[a]

Code	Chemical name Structure	Substrate	MRID Common name
I.	N-1-Naphthyl phthalamic acid		
		cucumber seedlings soybean callus	40274503 40274503 **Naptalam** **Alanap**
II.	N-1-Naphthyl phthalimide		
		**soybeans** cucumber seedlings soybean callus	**00153372** 40274503 40274503
III.	Phthalic acid		
		**soybeans** soybean callus	**00153372** 40274503
IV.	N-1-Naphthylamine		
		cucumber seedlings hydroponic cucumber soybean callus	40274503 40274503 40274053
V.	1-Naphthylamine glucose-conjugate		
		cucumber seedlings hydroponic cucumber soybean callus	40274503 40274503 40274503

[a] MRID 40274503 was reviewed in the Naptalam Registration Standard Update of 7/25/90.

Preemergence plus foliar treatment: Six-day-old potted soybean plants (crook stage) received [1-naphthylamine-^{14}C]naptalam (1.77 mCi/mM specific activity, radiochemical purity 96%) at a field equivalent rate of 3 lb ai/A. The potted plants were moved outdoors and at 69 days postplanting, they received an over-the-top treatment of [1-naphthylamine-^{14}C]naptalam at 2 lb ai/A; plants bore mature pods at the time of foliar application. Soybeans were harvested 48 days after the second treatment. Mature soybeans were separated from their pods and stored frozen at unspecified temperature for an unspecified interval prior to extraction.

Preemergence treatment: Five-day-old potted soybean plants (crook stage) received [1-naphthylamine-^{14}C]naptalam (specific activity 0.5 mCi/mM, radiochemical purity unspecified) as a spray application. A field equivalent rate in lb ai/A was not given. After treatment the plants were removed from the pots and transplanted outdoors, and the soil between the plants was treated with the same formulation of [1-naphthylamine-^{14}C]naptalam/*dinoseb*. Soybeans were harvested at maturity (posttreatment interval unspecified), and beans were separated from the pods, ground, freeze-dried and stored frozen (storage temperature and duration unspecified).

Total Radioactive Residue (TRR)

Soybean samples were analyzed for total radioactivity by liquid scintillation spectrometry (LSS) following combustion. The limit of detection of the radioassay was not specified. The total radioactive residue (TRR) in soybeans following preemergence and foliar application was 0.54 ppm; following preemergence application only TRR was 0.09 ppm. These TRR values are assumed to be expressed as naptalam equivalents; raw data and sample calculations were not provided.

Extraction

Details of the extraction procedures used for soybean treated with a single preemergence application were not provided. Soybean samples from the preemergence + foliar test were homogenized then Soxhlet-extracted with hexane for six hours to isolate the oil fraction. The hexane-soluble extract ("oil fraction") was reserved, and excess hexane was removed from the residue by rotary evaporation. Next, the hexane-insoluble residue was extracted with two volumes of 70% aqueous methanol. The methanol-soluble extracts were combined and stored frozen ("carbohydrate fraction"), and the unextractable residue ("protein fraction") was dried, weighed, and stored at room temperature. Data depicting the concentration of ^{14}C-activity in these extracts were reported as a percentage and as ppm (Table 2); however, neither raw data on weights of the samples nor examples of calculations were provided. Note that the values for

percent ^{14}C-activity in extracted fractions are not proportional to the reported ppm values.

Table 2. Distribution of radioactivity in extracts of soybeans treated with [1-naphthylamine-^{14}C]naptalam.

Component	% of ^{14}C-activity (ppm)	
	Pre + Foliar	Preemergence
Hexane (oil fraction)	15.3 (0.5)	14.3 (0.08)
Methanol (carbohydrate fraction)	43.5 (1.65)	19.8 (0.09)
Unextracted solids (protein fraction)	26.4 (0.26)	65.9[a](0.10)
Total recovery	85.2	100.0

[a] This value was reported as calculated by subtraction.

Characterization of residues

Hexane-soluble extracts: The hexane-soluble extract from the first preemergence + foliar treatment was concentrated and partitioned to acetonitrile (hexane:acetonitrile, 3:1, v/v). Acetonitrile layers were combined, evaporated to dryness, and the residue was chromatographed on activated silica gel using a hexane:dichloromethane gradient. The fraction which eluted with 50% dichloromethane in hexane was collected and further purified on a Zorbax high-performance liquid chromatography (HPLC) column. Resulting fractions were again collected, and were identified by cochromatography with known standards using GC (2' x 1/8" stainless steel column packed with 3% OV17 on Chromosorb WHP, 80-100 mesh) equipped with a flame ionization detector (FID) and a radioactive monitoring system (RAM), and by thin-layer chromatography (TLC) on silica gel using benzene:ethanol (95:5, v/v) as the solvent system. The retention time and R_f for the principle radioactive fraction corresponded to those for the N-1-naphthylphthalimide standard. The identity of the metabolite was "confirmed" by isotopic dilution involving dilution of a sample of the HPLC-purified extract with unlabeled N-1-naphthylphthalimide, followed by four recrystallizations from benzene, and analysis by LSS. We note that this method of identification is relative at best.

The registrant states that 67.7% of the ^{14}C-activity in the oil fraction from the preemergence + foliar treatment was extracted into acetonitrile, and that radioassay of the acetonitrile layer using TLC/LSS indicated that N-1-naphthylphthalimide represented 88.6% of the radioactivity in the layer; however, no raw data were provided. Based on the above figures the registrant has concluded that N-1-naphthylphthalimide accounted for 9.2% of the

TRR in the soybeans treated in the preemergence + foliar treatment study (67.7% x 88.6% x 15.3%). Results are summarized in Table 3.

The hexane-soluble fraction from the preemergence only study was partitioned to acetonitrile as above; however, the registrant concluded that N-1-naphthylphthalimide was not a major residue in the soybeans treated preemergence because only 4% of the radioactivity in the oil fraction was detected in the acetonitrile extract (radioassayed by LSS). The possibility that [1-naphthylamine-^{14}C]naptalam residues had been incorporated into fatty acids was investigated in a series of steps involving: (i) saponification of the hexane-soluble extract by refluxing for one hour with 6% potassium hydroxide in ethanol, followed by partitioning to benzene and two chloroform extractions; (ii) esterification of the resulting oil by stirring with methanolic-hydrochloric acid overnight at room temperature, and subsequent cleanup; and (iii) separation of the methyl esters--methyl oleate, linoleate, and linolenate--by column chromatography on silica gel eluting with hexane:ethyl ether (9:1, v/v) and hexane:ethyl ether:methanol (8:1:1, v/v/v). Methyl oleate and linoleate were quantitated by GC-FID (column specifications as in the preemergence + foliar treatment study except the column was packed with 10% ethylene glycol succinate on Chromosorb WHP). The registrant states that methyl esters accounted for 7.5% of the total [1-naphthylamine-^{14}C]naptalam in the mature bean, and that methyl linoleate accounted for 50% of the ester mixture by GC analysis, and represented 28.3% of the ^{14}C-activity in the oil fraction or 3.8% of the ^{14}C-activity in the mature bean; however, raw data were not provided.

Methanol-soluble extracts: The methanol-soluble extract from the preemergence + foliar treatment study was purified by solvent-solvent partition chromatography on Celite 545. The column was eluted with a mobile phase of n-butanol:ethanol (9:1, v/v), and fractions were radioassayed. Fractions containing ^{14}C-activity were collected, combined, dried and weighed, then acidified with 2N HCl and extracted three times with two-volume portions of ether. Aliquots of the ether extracts were radioassayed by LSS, and were co-chromatographed on Baker-flex TLC plates with phthalic acid standard using two solvent systems: ethyl acetate:formic acid (98:2) and ethanol:15% NH_4OH (2:1, v/v). The R_f values of the samples corresponded to those for the phthalic acid standard. The presence of phthalic acid in the ether extract was confirmed by isotopic dilution of the samples (as noted before, this method does not provide conclusive identification), and by treatment of a portion of ether extract with ethereal diazomethane followed by TLC cochromatography in two solvent systems with dimethylphthalate standard; the R_f values for the major radioactive bands of the sample corresponded to those for the dimethylphthalate standard.

The methanol-soluble extract from the preemergence only study was acidified with 2N HCl then extracted three times with ether. Ether layers were then combined and partitioned to 5% sodium bicarbonate; the resulting bicarbonate fraction was acidified with 6N HCl, and extracted again with ether. Phthalic acid was identified in the ether extracts by cochromatography of the samples with phthalic acid standard on silica gel plates developed in ethyl acetate:formic acid (98:2, v/v). The R_f of the major radioactive band corresponded to that of the standard.

Phthalic acid was quantitated from the methanol-soluble extract in the preemergence + foliar treatment study under a similar extraction scheme in which the acidified fractions from the purification step were extracted with ether in a continuous liquid-liquid extractor for 22 hours. The registrant states that 60.6% of the ^{14}C-activity from the carbohydrate fraction was extracted into ether in the preemergence + foliar treatment study and 30% in the preemergence only study, and that analysis of the ether layers from the two studies using TLC/LSS indicated that phthalic acid represented 64.0% of the radioactivity in the layer in the preemergence + foliar treatment study and 82.1% in the preemergence only study; however, no raw data were provided. Based on the above figures the registrant has concluded that phthalic acid from the methanol soluble-extract accounted for 16.9% of the TRR in the soybeans treated in the preemergence + foliar treatment study (60.6% x 64.0% x 43.5%) and 5.7% of the TRR in soybeans treated in the preemergence only study. Results are summarized in Table 3.

In the preemergence + foliar treatment study the registrant attempted to identify benzoic acid, a degradate of phthalic acid in soil, by treating the ether extract with ethereal diazomethane, followed by TLC cochromatography with methylbenzoate standard; however, no significant ^{14}C-activity was associated with the band whose R_f corresponded to methyl benzoate. The registrant also investigated the potential for incorporation of labeled CO_2 into sugars in the soybean. In the preemergence + foliar treatment study sugars were separated from the methanol-soluble extract on a column eluted with isopropanol:acetone:1.0M formic acid (4:4:2, v/v/v), collected, spotted on TLC plates, and radioassayed, or were separated from the extract following solvent-solvent partitioning, and eluted on a column with isopropanol:acetone:1.0M formic acid (4:4:2, v/v/v) followed by isopropanol:acetone:1.0M formic acid (2:2:1, v/v/v) then radioassayed. In the preemergence only study sucrose was isolated by TLC following solvent-solvent partitioning using similar procedures. Although sugars were not quantitatively isolated, the registrant concluded that labeled sucrose accounted for 1.1% of the ^{14}C-activity in the mature beans in the preemergence + foliar treatment study and 4.4% in mature beans in the preemergence only study, based on a standard soybean sucrose content of 6.6% (w/w).

The methanol-soluble extract from the preemergence + foliar treatment study was also subjected to enzyme hydrolysis to determine whether naptalam metabolites had been conjugated as glycosides. Following separation on a Silic AR CC-7 column packed with isopropanol:acetone (1:1, v/v), the fraction containing ^{14}C-activity was dissolved in 0.08M sodium acetate buffer at pH 5.0 and shaken for two hours with ß-glucosidase (Sigma), hesperidinase (from Aspergillus niger, Sigma), or Cellulase, Type I (from Aspergillus niger,Sigma) at 37 C, then extracted with ether. Radioassay of the ether layers by LSS indicated that no radioactive compounds were liberated by the enzymes.

Unextracted solids: Unextracted soybean meal from the preemergence + foliar treatment study was refluxed with 6N HCl for 24 hours, then filtered. The registrant notes that hydrolysis under these circumstances destroys tryptophan and partially destroys cystine. The filtrate was analyzed for amino acids by successive cation and anion exchange chromatography by diluting with acetic acid, then elution from an Amberlite IR-120 column with 0.1M acetic acid followed by 0.1M NH_4OH. An aliquot from each fraction was removed and spotted on a TLC plate and developed with ethanol:water:acetic acid (5:1:0.1). Amino acids were visualized by spraying the plates with 0.2% ninhydrin in butanol:10% aqueous acetic acid (95:5). Fractions containing amino acids were further purified on a Dowex 1 (40 g dry resin, 200-400 mesh) column eluted with 0.1N NaOH followed by 0.5N HCl and analyzed by TLC as above. Fractions containing the majority of amino acids were combined, acidified if basic, and radioassayed. The registrant concluded that, based on a standard crude protein content for soybeans of 43% (w/w) and uniform labeling in the amino acids recovered, labeled amino acids accounted for 10.3% of the ^{14}C-activity in the soybeans; however, no raw data were provided. Following the same procedure for the preemergence only study, the registrant concluded that labeled amino acids accounted for 28.2% of the radioactivity in the mature bean. Again, no raw data were provided.

The unextracted soybean meal from the preemergence + foliar treatment study was also analyzed for phthalic acid. Samples were hydrolyzed with 6N H_2SO_4 overnight at room temperature, filtered, and the filtrate was extracted three times with ether. Phthalic acid was identified in the ether phase by the TLC method described for the methanol-soluble extracts. The registrant states that 14.8% of the ^{14}C-activity in the protein fraction from the preemergence + foliar treatment study was extracted into ether, and that radioassay of the acetonitrile layer using TLC/LSS indicated that phthalic acid represented 85.8% of the radioactivity in the layer; however, no raw data were provided. Based on the above figures the registrant has concluded that phthalic acid from the unextracted solids accounted for 3.3% of

the TRR in the soybeans treated in the preemergence + foliar treatment study (14.8% x 85.8% x 26.4%). Results are summarized in Table 3. Attempts to isolate phthalic acid from the unextracted solids in the preemergence only study resulted in the removal of less than 2.4% of the radioactivity from the protein fraction.

Table 3. Characterization of radioactive residues in soybeans treated with [1-naphthylamine-^{14}C]naptalam.

Component	% of ^{14}C-activity	
	Pre + Foliar	Preemergence
N-1-naphthylphthalimide	9.2	--[a]
methyl linoleate	--	3.8
other methyl esters	--	3.7
phthalic acid	20.2[b]	5.7
sucrose	1.1	4.4
amino acids	10.3	28.2
Total	40.8	45.8

[a] The registrant did not attempt identification of this component.
[b] Composed of 16.9% from carbohydrate fraction plus 3.3% from protein fraction.

STORAGE STABILITY DATA

Conclusions:

The Naptalam Guidance Document dated 3/85, and the Naptalam Residue Chemistry Registration Standard Update of 7/90 conclude that additional data depicting the stability of naptalam residues in plant matrices are required.

In response to these requirements, Uniroyal (1990; MRID 41664002) submitted data depicting the stability of naptalam in cucumbers and cantaloupes stored for 12 months at sub-freezing temperatures. These data indicate that residues of naptalam are relatively stable in samples of cucumber stored frozen for up to 1 year. Residues are also relatively stable in samples of cantaloupe stored frozen for up to 6 months; however, a significant decline in stability (38-69% of initial fortifications) occurs after ca. 8 months in storage.

The data do not fulfill the requirements for the topic because: (i) details regarding the test compound used for fortification

(purity, concentration) were not supplied; (ii) specific details of storage conditions (containers, temperatures, lighting, humidity) were not indicated; and (iii) no data were supplied for soybeans and peanuts. The following additional data are required:

- The sample storage intervals and conditions must be supplied for all residue data submitted in support of tolerances, whether previously submitted or required in this addendum. Storage stability data in support of previously submitted residue data must reflect the actual storage conditions and intervals for samples used to generate the residue data. If residue depletion occurs, data will be required which depict the decline in levels of pesticide residues of concern in commodities stored under the range of conditions and for the range of intervals specified. Crop samples bearing measurable weathered residues or fortified with naptalam residues of concern must be analyzed immediately after harvest or fortification and again after storage intervals that allow for reasonable unforeseen delays in sample analysis. In laboratory tests using fortified samples, the pure active ingredient and pure metabolites must be used. However, if field-weathered samples are used, the test substance must be a typical end-use product. For additional guidance on conducting storage stability studies, the registrant is referred to an August, 1987 Position Document on the Effects of Storage Validity of Pesticide Residue Data available from NTIS under order no. PB 88112362/AS.

The nature of the residue in plants and animals is not adequately understood. If the requested data on plant and animal metabolism indicate the presence of additional metabolites of concern, data depicting the stability of those residues during storage will be required.

References (used):

MRID(s): 41664002.

Discussion of the data

Uniroyal (1990; MRID 41664002, supplement to MRID 40274505) submitted data on the stability of naptalam in or on cantaloupes and cucumbers during frozen storage. Commodities were macerated and fortified with naptalam at 0.1 or 0.4 ppm and stored frozen at unspecified temperatures for up to 373 days. Data were collected using a colorimetric method (Lane et al., 1958). The limit of detection was 0.05 ppm. Six control samples of cantaloupe and eight control samples of cucumber bore residues <0.05 ppm (nondetectable). Recoveries of initial fortification

levels at various storage intervals are detailed in Table 3; values obtained for the zero-day storage interval were fortified and analyzed at the time of the last analysis.

Table 3. Stability of naptalam in cantaloupes and cucumbers stored for various intervals under frozen conditions.

Commodity[b]	Storage Interval (days)	Recovery (%)[a] naptalam
Cantaloupe (0.1)	0	94, 100
	61	73, 93
	125	76, 88
	182	86, 92
	189	67, 88
	244	38, 69
	300	66, 66
	373	34, 62
Cucumber (0.4)	10	110, 116
	28	115, 116
	87	97, 120
	182	60, 78
	273	78, 82
	361	66, 74

[a] Method recoveries at time of analysis were 75-123%. [b] Initial fortifications given in parentheses.

In summary, these data indicate that residues of naptalam are relatively stable in samples of cucumber stored frozen for up to 1 year. Residues are also relatively stable in samples of cantaloupe stored frozen for up to 6 months; however, a significant decline in stability (38-69% of initial fortifications) occurs after ca. 8 months in storage.

These data do not fulfill the requirements for the topic because: (i) details regarding the test compound used for fortification (purity, concentration) were not supplied; (ii) specific details of storage conditions (containers, temperatures, lighting, humidity) were not indicated; and (iii) no data were supplied for soybeans and peanuts. Additional data are required.

MASTER RECORD IDENTIFICATION NUMBERS

Bibliographic Citations (used):

00153372 Uniroyal Chemical (1976) Nature of Residues-Plant Metabolism [Dyanap]. Unpublished compilation. 40 p.

41664002 Gaydosh, K. (1990) Storage Stability of Naptalam in Cantaloupe and Cucumber: Lab Project Number: 40787: 42693: UR301. Unpublished study prepared by Morse Labs. 33 p.

Bibliographic Citations (not used):

[The following document was not used because it does not contain data pertinent to a decision on the reregisterability of naptalam. The Naptalam Guidance Document dated 3/85 does not require additional data pertaining to the residues of naptalam in or on soybeans unless plant metabolism data reveal additional residues of concern.]

00157184 Uniroyal, Inc. (1986) Alanap Residues in Soybean Seed: Project UR101. Unpublished study prepared by Morse Laboratories. 14 p.

TABLE A. GENERIC DATA REQUIREMENTS FOR NAPTALAM.

Data Requirement	Test Substance[1]	Does EPA have data to satisfy this requirement?	Bibliographic Citation[2]	Must additional data be submitted under FIFRA Sec. 3(c)(2)(B)?
40 CFR §158.240 Residue Chemistry				
171-2. Chemical Identity[3]				
171-3. Directions for Use		(See Index)[4]		
171-4. Nature of the Residue (Metabolism) - Plants	PAIRA	Partially	00153372 40274503	Yes[5]
171-4. Nature of the Residue (Metabolism) - Livestock	PAIRA & plant metabolites	No	N/A	Yes[6]
171-4. Residue Analytical Methods	TGAI & metabolites	Partially	N/A	Yes[7]
171-4. Storage Stability	TEP & metabolites	Partially	40274505 41664002	Yes[8]
171-4. Magnitude of Residue in Plants				
Legume Vegetables				
- Soybeans	TEP	Yes		No[9]
(processed commodities)	TEP	Partially	N/A	Yes[10]
Foliage of Legume Vegetables				
- Soybean forage and hay	TEP	Partially	N/A	No[11]

(Continued, footnotes follow)

TABLE A. (Continued).

Data Requirement	Test Substance[1]	Does EPA have data to satisfy this requirement?	Bibliographic Citation[2]	Must additional data be submitted under FIFRA Sec. 3(c)(2)(B)?
Cucurbit Vegetables				
- Cantaloupes	TEP	Yes	40274504	No
- Cucumbers	TEP	Yes	40274504	No
- Muskmelons	TEP	Partially	N/A	No[12]
- Watermelons	TEP	Yes	40274504	No
Miscellaneous Commodities				
- Peanuts	TEP	No	N/A	No[13]
(processed commodities)	TEP	Partially	N/A	Yes[14]
171-4. Magnitude of residue in Meat/Milk/Poultry/Eggs	TGAI or plant metabolites	No	N/A	Reserved[15]

1. Test substance: PAI = purified active ingredient; PAIRA = purified active ingredient, radiolabeled; TEP = Typical end-use product; TGAI = technical grade of the active ingredient; MP = manufacturing-use product.

2. These references were submitted in response to the {Pesticide} Guidance Document dated {mm/dd/yy}. Underlining indicates documents that have been reviewed for this update.

3. The same chemical identity data are required as under 40 CFR §158.150-190, with emphasis on impurities that could constitute residue problems. Refer to Product Chemistry Data Requirements tables.

4. The 4/26/89 Update to the Naptalam Index was used to create this document.

TABLE A. (Continued).

5. Data are required depicting the distribution and metabolism of [^{14}C]naptalam ring-labeled in the phthalic acid moiety and a separate study with the label in the 1-naphthylamine moiety (or one study using [^{14}C]naptalam labeled in both moieties) in soybeans and a cucurbit vegetable. A completely characterized test substance representative of technical naptalam used in commercial formulations (including impurities) must be applied under conditions representing normal cropping practices and at levels sufficient to make residue identification and quantification possible. Residues must be characterized in edible mature plant parts. Confirmation of the identities of residues using a suitable method such as mass spectrometry (MS) or high-performance liquid chromatography (HPLC) is also required. In addition, representative samples from these tests must be analyzed by the residue analytical methods developed for data collection and tolerance enforcement to ascertain that these methods will recover and quantify all metabolites of concern.

6. No data have been submitted in response to the Guidance Document. Metabolism studies utilizing ruminants and poultry must be conducted. Animals must be dosed orally for a minimum of 3 days with both ring-labeled [phthalic acid- and 1-naphthylamine-^{14}C]naptalam in the diet at a level sufficient to make residue identification and quantification possible. Eggs and milk must be collected twice daily during the dosing period. Animals must be sacrificed within 24 hours of the final dose. The distribution and identity of residues must be determined in eggs, milk, muscle, fat, kidney (except poultry), and liver. Representative samples from these studies must be analyzed using a suitable confirmatory method such as MS or HPLC. In addition, representative samples from these studies must be analyzed using a currently accepted or proposed enforcement analytical method in order to ascertain that the method is capable of adequately recovering and identifying all residues of concern.

7. If radiolabeled validation of existing analytical methodology for plants and animals (refer to "Qualitative Nature of the Residue in Plants" and "Qualitative Nature of the Residue in Animals" for additional details) reveals the presence of additional metabolites of concern or indicates a major portion of the total radioactive residue is not recovered and identified by the available methods, radiolabeled validation of new proposed methodology will be required.

8. The data do not fulfill the requirements for the topic because: (i) details regarding the test compound used for fortification (purity, concentration) were not supplied; (ii) specific details of storage conditions (containers, temperatures, lighting, humidity) were not indicated; and (iii) no data were supplied for soybeans and peanuts. Therefore, the sample storage intervals and conditions must be supplied for all residue data submitted in support of tolerances, whether previously submitted or required in this addendum. Storage stability data in support of previously submitted residue data are required only for those samples deemed to be useful for tolerance assessment. Data are also required which depict the decline

TABLE A. (Continued).

in levels of naptalam residues of concern in commodities stored under the range of conditions and for the range of intervals specified. Crop samples bearing measurable weathered residues or fortified with naptalam residues of concern must be analyzed immediately after harvest or fortification and again after storage intervals that allow for reasonable unforeseen delays in sample analysis. In laboratory tests using fortified samples, the pure active ingredient and pure metabolites must be used. However, if field-weathered samples are used, the test substance must be a typical end-use product. For additional guidance on conducting storage stability studies, the registrant is referred to an August, 1987 Position Document on the Effects of Storage Validity of Pesticide Residue Data available from NTIS under order no. PB 88112362/AS.

9. Data were not required by the Naptalam Guidance Document dated 3/85.

10. The Guidance Document did not require additional data pertaining to the processing of soybeans. However, the data reviewed for the Guidance Document concerned the processing of samples bearing no detectable residues from treatment at ca. 1x the maximum registered rate. Current Agency policy requires that processing studies be conducted using commodities bearing measurable weathered residues. Therefore, a processing study is required depicting the potential for concentration of naptalam residues of concern in products (meal, hulls, soapstock, crude oil, and refined oil) from the processing of soybeans bearing measurable, weathered residues. If residues concentrate in any product, an appropriate food/feed additive tolerance must be proposed.

11. No data are required, since a feeding restriction has been imposed.

12. The data submitted for cantaloupes will translate to muskmelons.

13. Additional data on peanut forage and hay are not required since a feeding restriction has been imposed.

14. The Guidance Document did not require additional data pertaining to the processing of peanuts. However, the data reviewed for the Guidance Document concerned the processing of samples bearing no detectable residues from treatment at ca. 1x the maximum registered rate. Current Agency policy requires that processing studies be conducted using commodities bearing measurable weathered residues. Therefore, a processing study is required depicting the potential for concentration of naptalam residues of concern in products (meal, soapstock, crude oil, and refined oil) from the processing of peanuts bearing measurable,

TABLE A. (Continued).

weathered residues. If residues concentrate in any product, an appropriate food/feed additive tolerance must be proposed.

15. The nature of the residue in animals is not understood. On receipt of the requested animal metabolism data, the need for and nature of tolerances for residues of naptalam in meat, milk, poultry, and eggs will be determined, and additional feeding trials may be required.

Attachment #1

DYNAMAC
CORPORATION

Final Report

NAPTALAM (DEB No. 7333)
Task 4: Registrant's Response to Product Chemistry Data Requirements

January 22, 1991

Contract No. 68-D8-0080

Submitted to:
Environmental Protection Agency
Arlington, VA 22202

Submitted by:
Dynamac Corporation
The Dynamac Building
11140 Rockville Pike
Rockville, MD 20852

NAPTALAM (DEB NO. 7333)

REGISTRANT'S RESPONSE TO PRODUCT CHEMISTRY DATA REQUIREMENTS

Task - 4

BACKGROUND

The Naptalam Registration Standard Update of 7/25/90 requires additional data for the Uniroyal Chemical Company 23.7% end-use product (EP; EPA Reg. No. 400-49) pertaining to product composition, discussion of the formation of impurities, preliminary analysis, certified limits, enforcement analytical methods, and physical/chemical characteristics. In response to these product chemistry requirements, Uniroyal Chemical Company has submitted one volume of product chemistry data (DEB No. 7333; 1990; MRID 41664001). These data and our conclusions apply only to the nitrosamine requirements for the 23.7% EP (EPA Reg. No. 400-49).

CONCLUSIONS

In response to the Naptalam Registration Standard Update of 7/25/90, Uniroyal has submitted (1990; MRID 41664001) a discussion of the potential for formation of nitrosamines and preliminary analysis for nitrosamines in the 23.7% EP (EPA Reg. No. 400-49), which are presented in Confidential Appendices A and B, respectively. These data partially satisfy the requirements of 40 CFR §158.167 and §158.170 (Guideline Reference Nos. 61-3 and 62-1) regarding the discussion of formation of and preliminary analysis for nitrosamines in the Uniroyal 23.7% EP (EPA Reg. No. 400-49). No additional nitrosamine data are required.

TABLE A. GENERIC DATA REQUIREMENTS FOR THE NAPTALAM/NAPTALAM SODIUM (UNIROYAL) TECHNICAL GRADE OF THE ACTIVE INGREDIENT.[1]

Data Requirement	Test Substance[2]	Guideline Status	Must additional data be submitted under FIFRA Sec. 3(c)(2)(B)? [Yes]	[No]	Reference (MRID No.)
40 CFR §158.155-190 Product Chemistry					
Product Composition					
61-2. Beginning Materials and Production Process	TGAI	R		X	
61-3. Formation of Impurities	TGAI	R	X[3]		41664001
Analysis and Certification of Product Ingredients					
62-1. Preliminary Analysis	TGAI	CR	X[4]		41664001
Physical and Chemical Characteristics[5]					
63-2. Color	TGAI	R		X	
63-3. Physical State	TGAI	R		X	
63-4. Odor	TGAI	R		X	
63-5. Melting Point	TGAI	R		X	
63-6. Boiling Point	TGAI	R		X[6]	
63-7. Density, Bulk Density, or Specific Gravity	TGAI	R		X	
63-8. Solubility	TGAI or PAI	R		X	
63-9. Vapor pressure	TGAI or PAI	R		X	
63-10. Dissociation Constant	TGAI or PAI	R	X[7]		
63-11. Octanol/Water Partition Coefficient	PAI	CR	X[7]		
63-12. pH	TGAI	CR	X[7]		
63-13. Stability	TGAI	R		X	

(Continued, footnotes follow)

TABLE A. (Continued).

Data Requirement	Test Substance	Guideline Status	Must additional data be submitted under FIFRA Sec. 3(c)(2)(B)? [Yes] [No]	Reference (MRID No.)
Other Requirements:				
64-1. Submittal of Samples	TGAI or PAI	CR	X[8]	

1. Data requirements pertain to the TGAI (solid naptalam sodium) of the Uniroyal Chemical Company 23.7% EP (EPA Reg. No. 400-49). Additional data requirements are listed in the following Table C, "Product Specific Data Requirements for the Naptalam/Naptalam Sodium End-Use Product".

2. Test substance: MP = manufacturing-use product; PAI = purified active ingredient; EP = end-use product; TGAI = technical grade of the active ingredient.

3. The registrant has responded to the requirement for discussion of formation of nitrosamines, and data are adequate. A discussion regarding the origin of the following potential impurities must be provided: (i) each impurity associated with the active ingredient which was found to be present in any analysis of the product conducted by or for the registrant, and (ii) each impurity which the registrant has reason to believe may be present at a level equal to or greater than 0.1% (w/w) based on the composition of each starting material; (iii) intended and side reactions which may occur during production; (iv) the possible degradation of ingredients after production, post-production reactions between ingredients, possible contamination from packaging materials or production equipment; and (v) process control, purification and quality control measures.

4. The registrant has responded to the requirement for preliminary analysis for nitrosamines, and data are adequate. However, the registrant must submit data regarding additional impurities of the TGAI present at 0.1% or greater, as listed on the CSF. If the discussion of formation of impurities reveals the potential for compounds of toxicological significance at levels <0.1% of the TGAI, these compounds too must be included in the preliminary analysis study. Additional preliminary analysis data may be collected using the 25% dilute naptalam sodium solution; however, the registrant will then be required to identify impurities present in the solution at ≥0.025% and compounds of toxicological significance at <0.025% as warranted by discussion of formation of impurities.

5. As required by 40 CFR §158.190 and more fully described in the Pesticide Assessment Guidelines, Subdivision D, Guidelines Reference Nos. 63-2 through 63-13, data must be submitted on physicochemical characteristics (color, physical state, odor, melting point, boiling point, specific gravity, solubility,

TABLE A. (Continued).

vapor pressure, dissociation constant, octanol/water partition coefficient, pH, and stability). There are additional data requirements listed in Table C pertaining to physicochemical characteristics of end-use products.

6. Data on boiling point are not required since the technical product is a solid at room temperature.

7. The registrant must specify which test substance was used for testing (PAI, TGAI, or EP).

8. The Agency will request samples if required.

TABLE C. PRODUCT SPECIFIC DATA REQUIREMENTS FOR THE NAPTALAM/NAPTALAM SODIUM (UNIROYAL) END-USE PRODUCT.[1]

Data Requirement		Test Substance[2]	Guideline Status	Must additional data be submitted under FIFRA Sec. 3(c)(2)(B)? [Yes]	[No]	Reference (MRID No.)
40 CFR §158.155-190 Product Chemistry						
Product Composition						
61-1.	Product Composition	EP	R	X[3]		
61-2.	Beginning Materials & Production/Formulation Process	EP	R		X	
61-3.	Formation of Impurities	EP	R	X[4]		41664001
Analysis and Certification of Product Ingredients						
62-1.	Preliminary Analysis	EP	CR	X[5]		41664001
62-2.	Certified Limits	EP	R	X[6]		
62-3.	Enforcement Analytical Methods	EP	R	X[7]		
Physical and Chemical Characteristics[8]						
63-2.	Color	EP	R		X	
63-3.	Physical State	EP	R		X	
63-4.	Odor	EP	R	X[9]		
63-7.	Density, Bulk Density, or Specific Gravity	EP	R	X		
63-12.	pH	EP	CR		X	
62-14.	Oxidizing/Reducing Action	EP	CR		X	
62-15.	Flammability	EP	CR		X	
63-16.	Explodability	EP	R		X	
63-17.	Storage Stability	EP	R	X[10]		
63-18.	Viscosity	EP	CR		X	
63-19.	Miscibility	EP	CR		X	
63-20.	Corrosion Characteristics	EP	R		X	

(Continued, footnotes follow)

TABLE C. (Continued).

Data Requirement	Test Substance	Guideline Status	Must additional data be submitted under FIFRA Sec. 3(c)(2)(B)? [Yes] [No]	Reference (MRID No.)
Other Requirements:				
64-1. Submittal of Samples	EP	CR	X[11]	

1. Data requirements pertain to the Uniroyal Chemical Company 23.7% EP (EPA Reg. No. 400-49). Additional data requirements are listed in the preceding Table A, "Generic Data Requirements for the Naptalam/Naptalam Sodium Technical Grade of the Active Ingredient".

2. Test substance: MP = manufacturing-use product; PAI = purified active ingredient; EP = end-use product; TGAI = technical grade of the active ingredient.

3. Since this product is formulated by an integrated system, nominal concentrations must be submitted for the impurities listed on the CSF and the nominal concentration of the active ingredient must be based on the nominal concentration of the active ingredient in the source product.

4. The registrant has responded to the requirement for discussion of formation of nitrosamines, and data are adequate. Since this product is formulated by an integrated system, a discussion regarding the origin of the following potential impurities must be provided: (i) each impurity associated with the active ingredient which was found to be present in any analysis of the product conducted by or for the registrant, and (ii) each impurity which the registrant has reason to believe may be present at a level equal to or greater than 0.1% (w/w) based on the composition of each starting material; (iii) intended and side reactions which may occur during production; (iv) the possible degradation of ingredients after production, post-production reactions between ingredients, possible contamination from packaging materials or production equipment; and (v) process control, purification and quality control measures.

5. The registrant has responded to the requirement for preliminary analysis for nitrosamines, and data are adequate. Since this product is formulated by an integrated system, the registrant must submit data regarding additional impurities of the TGAI present at 0.1% or greater, as listed on the CSF. If the discussion of formation of impurities reveals the potential for compounds of toxicological significance at levels <0.1% of the TGAI, these compounds too must be included in the preliminary analysis study.

TABLE C. (Continued).

6. Since this product is formulated by an integrated system, the registrant must submit upper certified limits for toxicologically significant impurities (as determined by preliminary analysis) and certified limits for the active ingredient based on the nominal concentration of the active ingredient in the source product. Certifications must be submitted on EPA Form 8570-4 (Rev. 2/85).

7. Analytical methods which are suitable for enforcement purposes must be provided for all impurities listed on the CSF which are determined to be of toxicological significance. Suitability for enforcement purposes shall be determined from validation studies of method accuracy and precision submitted by the registrant.

8. As required in 40 CFR §158.190 and more fully described in the Pesticide Assessment Guidelines, Subdivision D, Guidelines Reference Nos. 63-2 through 63-20, data must be submitted on physicochemical characteristics of each end-use product (color, physical state, odor, specific gravity, pH, oxidizing or reducing action, flammability, explodability, storage stability, viscosity, miscibility, and corrosion characteristics). Additional data requirements regarding physicochemical properties of the technical grade of the active ingredient are listed in Table A, "Generic Data Requirements for the Naptalam Technical Grade of the Active Ingredient."

9. The registrant must submit a more detailed description of the odor.

10. The registrant must submit the quantitative storage stability data.

11. The Agency will request samples if required.

NAPTALAM (UNIROYAL; DEB NO. 7333)

PRODUCT CHEMISTRY

TASK 4

(Final Report)

CONFIDENTIAL APPENDICES

Appendix A: 1 Page
Appendix B: 1 Page

Confidential Appendices to the Scientific Review of a Registration Standard Followup Report for the Pesticide Naptalam by the Dietary Exposure Branch [Confidential FIFRA Trade Secret/CBI].

Page _____ is not included in this copy.

Pages 33 through 34 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients.

__X__ Identity of product impurities.

__X__ Description of the product manufacturing process.

___ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

___ The product confidential statement of formula.

_____ Information about a pending registration action.

___ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

_____ Internal deliberative information.

_____ Attorney-Client work product.

___ Claimed Confidential by submitter upon submission to the Agency.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.