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

MAY 15 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Review of Carboxin Registration Standard

FROM: Bruce A. Kapner
Project Manager, CRB I
Special Pesticide Review Division (TS-791)

Bruce A. Kapner

TO: HED Carboxin Support Team Members (TS-769)
(See list below)

Please review the attached draft of the Carboxin Registration Standard. Assess your chapters in light of a use that was uncovered in the 24(c) labels, ie., above ground foliar application of a granular formulation and spraying of the flowable concentrate onto peanut foliage (see the attached labels).

In your review please determine if:

1. the text is consistent with the information you supplied to SPRD; and if

2. there are any changes in data requirements or text due to these above ground uses.

SPRD proposes to remove all the State restrictions and add these above ground foliar uses to the set of Federally registered uses. Please forward your comments to me, no later than May 21, 1981, in Room 711-I.

Attachment

Alex Arce
Ed Fite
Sam Howard
Ray Kent
Greg Weidemann

cc: Carolyn Gregorio
Bill Boodee
Lionel Richardson
Harry Craven
Ann Barton

IV. PRODUCT CHEMISTRY

A. Chemical Identity

B. Manufacturing Process

C. Active Ingredient Limits in Carboxin Products

D. Product Analytical Methods and Data

E. Physical and Chemical Properties

F. Summary of Major Data Gaps

A. CHEMICAL IDENTITY

Carboxin is the common name accepted by the American National Standards Institute (ANSI) for the chemical 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide. Alternative chemical names are: 2,3-dihydro-6-methyl-5-phenylcarbamoyl-1,4-oxathiin-3-carboxamide. Carboxin is also known by the trade name Vitavax^{R} and by the abbreviation DMOC and DCMO. The Chemical Abstracts Registry number is 5234-68-4; the Uniroyal, Inc. internal code numbers as D-735 and F-735; and the EPA Shaughnessy number is 090201. The common name will be used throughout this standard in lieu of other chemical or trade names.

B. MANUFACTURING PROCESS

The specific details of the synthesis process for technical carboxin are considered trade secrets. There are two procedures, and they are detailed in Uniroyal, 19??, MRID 00003296 and Uniroyal, 1976, MRID 00003084. The manufacturing process for the formulation - Vitavax^{R} Flowable Fungicide - has been submitted to the Agency (Uniroyal, 19??, MRID 00003231). This process is also considered a trade secret.

Manufacturing processes for the other products have not been submitted to the Agency.

C. ACTIVE INGREDIENT LIMITS IN CARBOXIN PRODUCTS

The upper and lower limits for the active ingredient have not been established and certified for any carboxin product.

D. PRODUCT ANALYTIC METHODS AND DATA

An infrared spectroscopic method for the assay of carboxin in the technical product and in formulations has been submitted to the Agency, (Puchalsky, 1968, MRID 00003172). The carboxin concentration is determined from the absorption at three wavelengths in comparison to absorptions of a standard. A modification of the method in which only two wavelengths are utilized has also been submitted to the Agency (Uniroyal, 19??,

MRID 00002995). A titrimetric method has also been submitted to the Agency for the determination of carboxin in the technical product (Uniroyal, 1960, MRID 00002978). The above mentioned infrared spectroscopic and titrimetric methods have been published by Stone, 1976, MRID 05005076.

Carboxin formulations may be analyzed for the active ingredient by an ultraviolet spectrophotometric method (Harda, 1978, MRID 05003778). This method has been validated to be accurate for the 75% wettable powder formulation.

The previously mentioned assay methods are of sufficient detail to satisfy Agency requirements. However, validation data and results of analysis on at least five typical samples of each product have not been submitted. This information will need to be submitted.

E. PHYSICAL AND CHEMICAL PROPERTIES

The following are the only data available on technical and end-use carboxin. Data which are not available but which are required to be submitted are listed in the tables in Chapter III. The following data are for technical carboxin, unless otherwise mentioned.

1. Color

Off-white (Uniroyal, 1977, MRID 00005859)

2. Odor

Described as "faint" (Uniroyal, 1977, MRID 00005859)

3. Melting Point

Two melting ranges of technical carboxin are given 91.5-92.5°C and 98.-101°C, reflecting two crystalline structures. In solution the two structures revert to one. It is reported that that there are no differences in biological activity between the two structures (Uniroyal, 1977, MRID 00005859).

4. Density or Specific Gravity

Product Type	Density/Specific Gravity
Technical	1.70 gm/ml
Technical	40-45 lbs/ft^3*
Formulation Intermediate	20-30 lbs/ft^3*
Ready to Use (Flowable)	1.05-1.13 gm/ml
Soluble Concentrate (Liquid)	1.13-1.18 gm/ml

*Bulk density

(Uniroyal, 1977, MRID 00005859)

5. Physical State

Product Type	Physical State
Technical	Crystalline solid
Formulation Intermediate	Solid
Wettable Powder/Dust	Powder
Ready-to-Use (Flowable)	Liquid
Soluble Concentrate	Liquid
Dust	Powder

(Uniroyal, 1977, MRID 00004849)

6. Solubility

Solvent	Gm Solute/100 gm solvent @ 25 C
Distilled Water	0.017
Benzene	15.0
Demethyl Sulfoxide	150.0
Acetone	60.0
Methanol	21.0
Ethanol	11.0

(Uniroyal, 1977, MRID 00005859)

7. Stability

Carboxin is readily inactivated by ultraviolet light and sunlight (Buchenous, 1975, MRID 05002823).

8. pH

There are two Ready-to-Use (Flowable) formulations. The pH range for one is 7.0-9.0, the other is 6.2-8.2. The pH for the soluble concentrate (liquid) formulation is 9.0-10.5 (Uniroyal, 1977, MRID 00005859).

9. Flammability

Product Type	Flash Point	Test Method
Technical	203 C	C.O.C.
Ready-to-Use (Flowable)	>200 F	Unreported
Ready-to-Use (Flowable)	215 F	Unreported
Soluble Concentrate (Liquid)	135 F	Unreported

(Uniroyal, 1977, MRID 00005859)

10. Storage Stability

Three years (Uniroyal, 1977, MRID 00005859).

F. Summary of Major Data Gaps

The major data gaps are as follows: a more detailed manufacturing process for the technical product and each end-use product except Vitavax^{R} Flowable Fungicide; details on the formation of unintentional ingredients; certification of ingredient limits; validation data and results from analysis on each product; and various physical/chemical properties.

V. ENVIRONMENTAL FATE

A. Use Profile

B. Environmental Fate Profile

C. Exposure Profile

D. Summary of Major Data Gaps

A. USE PROFILE

Carboxin is a systemic fungicide used as a seed treatment to protect barley, corn, wheat, oats, cotton and peanut seeds and seedlings. It controls smut diseases, seed rot and seedling blight. There are also state registrations in Alabama, Georgia, North Carolina, Oklahoma and Texas for use on peanut foliage.

At present six products with single active ingredients are registered for use: a dust (25% a.i.); a wettable powder/dust (75% a.i.); two ready-to-use liquids (34% and 17.1% a.i.); and two liquid soluble concentrates (both 29.5% a.i.). Carboxin may be used alone, or in combination with other seed protectants, e.g. thiram and captan. multiple active ingredients
Standard is for single active ingredient

Current seed treatment uses and application rates, by formulation are summarized in Table I, on page __.

Table 1

Use and Application Rates

Crop	RATE RANGE (oz/100 lb seeds) (oz. of a.i. per acre) WP/D	RTU	D	SC/L
Barley	2-3[b/] (1.5-2.5)	2-3 (0.7-1.0)		
Corn		2-4 (0.7-1.4)	4-6 (1-1.5)	
Cottonseed	3-6 (1.5-4.5)	16 (2.7)		20[a/] (1.2)
Oats	1-2 (0.75-1.5)	2-3 (0.7-1.0)		
Peanuts	2-6 (1.5-4.5)			
Wheat	2-3[c/]* (1.5-2.25)	2-3 (0.7-1.0)		

[a/] Seed treatment by professional applicators only

[b/] 4 oz./100 lbs. for seed production purposes only

*] No C

Label restrictions prohibit use of treated seed for food, feed or oil purposes. Cotton and peanut forages or hay grown from treated seed are not to be fed to livestock. Hogs should not forage peanut fields prior to harvest. Livestock are not to be grazed on treated barley, oats, wheat, or corn, for six weeks after planting.

Between 600,000 and 2,000,000 pound of active ingredient are used yearly in this country. The distributive extent of usage on the seven seed types is unknown. No extent of usage data are available concerning its use on peanut foliage (Preliminary Quantitative Ussage Analysis by BFSD)

B. ENVIRONMENTAL FATE PROFILE

1. Physico-Chemical Transformation - Photodegradation

In aqueous solution (under UV light and in the dark) carboxin was oxidized to carboxin sulfoxide, carboxin sulfone, and two unidentified compounds (Smilo et al.,1977, MRID 00003088). These? compounds appear to be the result of carboxin ~~in~~ sulfoxide photodegradation. Formation of the unidentified compounds under UV and black light in a 2 percent water-acetone solution exceeded that in the aqueous solution without acetone. Acetone, a photosensitizer, accelerated the formation of one of these unidentified compounds by approximately 30-200 percent (as compared to photolysis in water). This study does provide some

The unidentified

What is the photolytic half-life for carboxin

information on the photodegradation of carboxin in water, but does not identify the two unknown compounds. Degradation products of greater than 10 percent of the exposed activity require identification, [redacted].

2. Metabolism - Soil

Spare (1979, MRID 00005540) and Dzialo and Lacadie (1978, MRID 00003225) found that under aerobic soil conditions carboxin sulfoxide was the major degradation product of carboxin in loamy sand, silt loam and sand soils. The half-life for conversions of carboxin to carboxin sulfoxide was less than three days. Dzialo and Lacadie also found that in sandy soil, 6.7 and 16.7 percent of the radio-labeled carboxin had been degraded under laboratory conditions to $^{14}CO_2$ within 30 and 154 days, respectively. They also found several minor degradation products (less than 10%). Spare also found p-hydroxy carboxin sulfoxide, p-hydroxy carboxin, $^{14}CO_2$, and five unidentified products.

Four studies reported that carboxin (75% WP formulation) was completely oxidized to carboxin sulfoxide within two weeks under greenhouse conditions in a sandy loam soil (Chin et al., 1972, MRID 00002935; Chin et al., 1969, MRID 00003044; Chin et al., 1970 MRID 05002176 and Chin et al., 1970, MRID 05004996).

Dzialo et al. (1978, MRID 00003226) showed that carboxin sulfoxide and carboxin sulfone will persist in sandy soil under

anaerobic conditions. At 56 days after the establishment of anaerobic condition, 49.5 percent of the carboxin sulfoxide and 1.9 percent of the carboxin sulfone applied was still present.

No reference Point to determine The amount of carboxin sulfoxide Present who anaerobic conditions were established

3. Metabolism - Microbiological

Lyr et al. (1974, MRID 05003852) found that carboxin was oxidized to carboxin sulfoxide and carboxin sulfone by flavin enzymes found in fungal mitochondria. Ustilago mazdis was capable of oxidizing carboxin in dark and light condition; Trametes versicolor and Aspergillus niger were capable of oxidizing carboxin to the sulfoxide and sulfone products under dark conditions, with the reaction being accelerated under illuminated condition; Saccharomyces fragiles, Trichosporon fermentans, Geotrichum candedum, and Rhodotour amucilaginosa were all capable of oxidizing up to 10 percent of the carboxin to carboxin sulfoxide in the dark; and a species of Pseudomonas was capable of degrading carboxin to 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid-4,4-dioxide and aniline.

Spare (1979, MRID 00005540) found that 99 percent of the carboxin applied to silt loam soil was degraded in three days and 96 percent of that applied to loamy soil was degraded in seven days. Carboxin sulfoxide is the major degradation product; the minor products found were carboxin sulfone, p-hydroxy carboxin, p-hydroxy carboxin sulfoxide, and five unidentified products, each found at concentration of less than 10 percent.

A Nocardia - like bacterium was found to use carboxin as a sole source of nitrogen and carbon (Bachafer et al., 1973, MRID 05005110). Bacillus cereus oxidized carboxin to its analogs sulfoxide and sulfone in Nile River water containing sludge (El-Dib and Aly, 1976, MRID 05003218). A species of Pseudomonas isolated from a red sandy loam is capable of using carboxin or a sole source of carboxin and nitrogen (Bolasubramanza and Patit, 1976, MRID 05006789). Michail et al. (1975, MRID 05004129), using a bioassay, determined that carboxin (75% ai formulation) was degraded faster in nonsterile soil than in sterile soil.

Taken together, these six studies show how carboxin is degraded in the soil by common microorganisms, and satisfy guideline requirements for the effects of microbes on carboxin.

The effect of carboxin on soil microorganisms is varied. Spare (1979, MRID 00005540) found that carboxin (analytical grade) at 2 ppm did not inhibit the ability of Azotobactes chroococcum to fix nitrogen. Fisher (1976, MRID 05002575) found that carboxin (technical grade) at 10 ppm did not inhibit the growth of Rhizobium trifalii, a 5 percent inhibition at 50-100 ppm, and 10 percent inhibition at 200 ppm. Fisher also showed that carboxin sulfone inhibited the growth of R. trifolii by 47 percent at 200 ppm. Nitrogen fixation was decreased by

20-25 percent in the presence of 25-150 ppm of carboxin sulfone. Carboxin had no effect on oxygen consumption by A. chroococcum or R. trifolii.

When soybean seeds were treated with carboxin root nodulation was reduced 19, 45, and 83 percent when seeds were planted at 1,4, and 24 hours after seed treatment, respectively (Curley and Burton, 1975, MRID 05003947). It can be concluded that the nodulation bacteria, Rhizobium japonicum, was not significantly affected if the seeds were planted within four hours after treatment.

The time of inoculation can effect carboxin's inhibition of root nodulation. When carboxin is applied as a seed treatment prior to inoculation with rhizobia (planted in sterile sand), carboxin completely prevented Vigna angiuculata root nodulation. However, with uninoculated carboxin-treated seeds planted in rhizobia-containing sand there was no significant reduction in nodulation (Staphorst and Strijdom, 1976, MRID 05003657).

Carboxin severely inhibited dehydrogenase activity in Trameters versicolor and Aspergillus niger (Lyr et al., 1974, MRID 05003852). Kritzman et al. (1977, MRID 05002989) found that 75% carboxin dust at 50 ppm inhibited succinic dehydrogenase in Sclerotium rolfsii by 30%.

To examine the effects of carboxin on pure cultures of several bacteria, El-Dib and Aly (1976, MRID 05003218) used 10 ppm of

carboxin in cultures of Streptococcus faecalis, Staphylococcus albus, Sarcina urea, Bacillus cereus (representative of protein degraders), Escherichia coli, Klebsiella aerogenes (nitrogen fixers), and Pseudomonas aeruginosa a denitrifier). No inhibition or toxic effects were observed.

4. Mobility

A laboratory experiment on leaching of carboxin in clay loam soil columns showed that carboxin was very mobile in soil. It was also found that carboxin sulfoxide, the major degradation product, was also very mobile in the soil column (Lacadie et al., 1978, MRID 00003277). Soil thin-layer chromatography data (Dannak et al., 1976, MRID 00003114) showed that carboxin sulfoxide and sulfone were mobile in sandy loam, silt loam, and clay loam soils (Rf values were 0.9, 0.78, and 0.67, in the respective soil types, for both the sulfoxide and sulfone analogs). Using aged radio-labeled carboxin-treated sandy soil, Lacadie et al. (1978, MRID 00003229) found that 3-17 percent of the applied compound leached through the 12 inch column. One-third of the radioactivity was in the top three inches, and one-fourth was in the 3-6 inch region.

→ Review Format (Task 1) - Not Environmental Fate (Summary Format)

To determine the adsorption/desorption potential for carboxin in soil, Smyser (1979, MRID 00009541) found that there was a low potential for Carboxin adsorption to a sandy loam soil (Freundlich adsorption coefficient was K=0.78). The calculated desorption coefficient was K=1.10. El-Dib and Aly (1976, MRID 05003915)

Different formats in same Topic

determined the adsorption coefficient for three types of bentonite clay to be less than 0.5. This last study is considered supplemental data because field soil was not used.

The mobility studies mentioned show that carboxin is easily leached and not tightly adsorbed to the soil, indicating a potential to contaminate ground water.

5. Field Dissipation

inaccurate Field dissipation studies uses End use product

In a field dissipation ~~and mobility~~ experiment conducted by Cardona et al. (1976, MRID 00003087), radio-labeled carboxin was applied to the soil, and after one month only 4 percent of the carboxin had not degraded. The major degradation products were carboxin sulfoxide (31-33 percent) and an unidentified compound (6-18 percent). Two months after treatment the carboxin could not be detected and only 4 percent of the sulfoxide and 2-3 percent of the other compound remained. After one year, approximately 75-80 percent of the radioactivity remaining was found in the top six inches.

simulated field

What other compound? inaccurate

Leaching to at least 11 inches was indicated by the detection of radioactivity at that depth. The detection of the compound or its metabolites at a depth of 11 inches one year after application indicates that carboxin aged residues are persistent and mobile, and could potentially contaminate ground water.

6. Accumulation

Format

A laboratory experiment was conducted to see if carboxin residues could be bioaccumulated in wheat (seeds), beets (top and root) and lettuce. Using radio-labeled carboxin, the concentration of oxathiin-labeled residues present in those crops were 1.5-60 times higher than the concentration of aniline-labeled residues (Dannak et al., 1976, MRID 00003114).

A field study by Uniroyal Chemical (1978, MRID 00003224) showed that carboxin residues were not taken up in turnip roots. Carboxin residues were less than 0.2 ppm, the sensitivity of the method used, in turnip greens and rye seed planted after treatment. However, the analytical method was not sensitive enough to determine conclusively that residues less than 0.2 ppm were not taken up by rotational crops.

A flow-through fish bioaccumulation study using bluegill sunfish was conducted by Kuc and Doebbler (1979a, MRID 00005544). They found that levels of radio-labeled carboxin residues steadily increased throughout the 30-day uptake period. Maximum bioaccumulation factors of 45 in whole fish, 26 in edible tissues, and 53 in nonedible tissues were observed. After 14 days depuration, levels of labeled residues decreased to approximately 22 percent of the maximum accumulation in whole fish. The residues consisted of carboxin sulfoxide and some unidentified metabolites.

How many is some?

A state channel catfish bioaccumulation study conducted by Kuc and Doebbler (1979b, MRID 00005545) with aged soil residues of radiolabeled carboxin showed markedly lower bioaccumulation factors than the bluegill study. The maximum bioaccumulation factors ranged from 3 in edible tissues to 5 in nonedible tissues. After 14 days depuration, levels of labeled residues decreased to approximately one-third of the maximum accumulation level. Carboxin sulfoxide accounted for all extractable residues from both edible and nonedible tissues.

Based on the data from these studies and the use patterns, carboxin does not appear to present an accumulation problem in fish.

C. EXPOSURE PROFILE (All Formulations)

Exposure to humans, livestock, and wildlife via spray drift is unlikely because the chemical is not applied aerially. Carboxin and its residues have been shown to be mobile in soil indicating a potential to contaminate groundwater. Although the mobility of carboxin aged in soil was mitigated by its degradation to the sulfoxide and sulfone, the residues were also shown to be mobile in soil. However, since single active ingredient formulations of carboxin are used only as seed treatments, the use pattern minimizes the potential exposure of humans and domestic animals to carboxin and its residues via groundwater contaminiation. Carboxin residues indicated a potential to accumulate in

bluegill sunfish and catfish. However, since formulations containing carboxin as the single active ingredient are used primarily as a seed treatment, this potential hazard is minimized. Potential exposure of humans to carboxin residues by ingestion of contaminated rotated crops is also minimized by its use as a seed treatment.

Potential exposure of wildlife exists through the ingestion of treated seeds. Mechanically planted seeds may be left uncovered or partially uncovered at the end of rows, and therefore wildlife, especially birds, may ingest treated seeds. Data necessary to estimate the nature and extent of such exposure are unavailable. The greatest potential for human exposure exists during seed treatment, most of which is done by seed processors or seed companies. Respiratory exposures may be especially high from the use of dust formulations, and commercial applicators are switching to the flowable concentrate to reduce such exposure. Dermal exposure from handling treated seed is expected to be low since most seeds are mechanically planted, and further minimized by the use of protective gloves.

D. SUMMARY OF MAJOR DATA GAPS

A number of the guideline requirements have been partially fulfilled by the data submitted. However, data are still needed to adequately assess the environmental fate of carboxin. The

specific deficiencies can be found in the Data Requirements Charts in Chapter III. The major data gaps are: hydrolysis, photodegradation, aerobic and anaerobic soil metabolism, effects of carboxin on microbes, activated sludge metabolism, leaching, terrestrial field dissipation, and accumulation in rotational crops.

VI. TOXICOLOGY

A. Toxicology Profile

B. Human and Domestic Animal Hazard Assessment

C. Summary of Major Data Gaps

A. TOXICOLOGY PROFILE

1. Technical Carboxin

a. Acute Effects

A limited amount of information was available to assess the acute oral toxicity of technical carboxin. The oral LD_{50} in rats was 3.82 $\pm$ 0.35 g/kg which is sufficient to assign technical carboxin to Toxicity Category III, corresponding to a low acute oral toxicity (Carson, 1965a, MRID 00003065).

An acute dermal toxicity test was conducted in rabbits (Carson, 1965b, MRID 00003066). The data show that when applied as a 50% aqueous slurry, technical carboxin causes no mortality at levels of 8 g/kg, which is sufficient to assign it to Toxicity Category III, indicating a low hazard potential.

Babish (1977e, MRID 00003116) reported that exposure for one hour to a concentration of 20 ml/l of technical carboxin did not

cause mortality in rats in an acute inhalation toxicity test. However, due to inappropriate testing protocols, this study must be repeated.

In a primary dermal irritation study conducted on rabbits, 0.5 gm of technical carboxin was applied to the skin and did not cause irritation (Babish, 1977g, MRID 00003119). This study indicates that technical carboxin is not a potential skin irritant and may be assigned to Toxicity Category IV.

b. Subchronic Effects

Sufficient data were available to assess the subchronic effect of technical carboxin. In the rat 90-day feeding study the No Observable Effect Level (NOEL) was 200 ppm of carboxin in the diet. At the 600 ppm level, the effects noted were degenerative renal changes (Ozer, 1966, MRID 00003063). In the two-year dog feeding study the NOEL was 600 ppm (Holsing, 1969c, MRID 00003030). In addition, in a 21-day dermal study, rabbits treated with 3.0 g/kg did not produce any treatment related effects (Holsing, 1968b, MRID 00003216). No data were available to assess the subchronic inhalation toxicity of technical carboxin. However, these data may not be required, pending the final results of the acute inhalation study.

c. Chronic Effects

In a screening study, groups of rats were fed diets containing 0, 300, 1,000 or 3,000 ppm of carboxin technical for two years (Holsing, 1969b, MRID 00003152). A NOEL was not established in this study because the dose levels were too high. However, in a subsequent chronic feeding study, rats were fed diets containing 0, 100, 200, or 600 ppm of technical carboxin for two years (Holsing, 1969a, MRID 00003031). The NOEL of 200 ppm was observed after two years. At the 600 ppm level the effects were poor survival and weight gain depression. These data are sufficient to satisfy the requirements for chronic feeding.

No evidence of oncogenicity was indicated in either of the two-year feeding studies (Holsing, 1969a, MRID 00003031 and Holsing, 1969b, MRID 00003152). However, oncongenic testing in a second species (a mouse study is currently in progress) is required.

A teratology study was conducted in rats by Knickerbocker (1977, MRID 00003120). Technical carboxin at doses as high as 4.0 mg/kg/day did not produce any maternal toxicity. However, teratogenicity testing is still required in a second species.

In a three generation reproduction study, rats were fed diets containing 100, 200, and 600 ppm technical carboxin (Holsing,

1968c, MRID 00003032). There were no treatment related effects on reproductive performance. The NOEL was established at 200 ppm.

d. Mutagenicity

Mutagenicity testing is incomplete. In a study by Brusick (1977, MRID 00003118) two different types of tests for detecting gene mutations were reported. Carboxin was tested in the Salmonella typhimurium reversion assay with and without a rat liver microsome metabolic activation system. No increases in reversion frequency were detected on any of the treated plates. Carboxin was also tested in a mutation assay system using Saccharomyces cerevisiae, but procedures in this assay were inadequately described. Additional mutagenicity testing is required.

e. Metabolism

Kennedy (1971a, MRID 00002943) reported on the distribution and excretion of ^{14}C carboxin in rats. Between 88 and 99 percent of the compound was recovered, most within 24 hours of treatment. The urine contained 42-89 percent of the administered ^{14}C and the feces contained 10-45 percent. Very little was found in the animal's tissues and organs.

In a companion study, Kennedy (1971b, MRID 00002944) characterized the ^{14}C activity in urine and feces using thin

layer chromatography and liquid scintillation. Carboxin sulfoxide accounted for 27-45 percent of the ^{14}C in the 24 hour sample and 47-56 percent in the 72 hour sample. Three additional urinary components were detected but not identified, and the parent compound was not present. The major component found in the feces (19-36 percent of fecal ^{14}C) was tentatively identified as carboxin sulfone.

These studies collectively provide sufficient information about the metabolism of carboxin in animals.

2. End-Use Carboxin

Acute toxicity (oral, dermal, and inhalational), irritation (eye and dermal), and dermal sensitization testing is required for each formulation or substantially similar formulation.

a. Acute Effects- Oral

One test (Matthews, 1970a, MRID 00003317) is available on the acute oral LD_{50} of a 75% wettable powder/dust formulation. The LD_{50} value for this formulation in albino rats is greater than 2 g/kg. This is sufficient information to assign this formulation to Toxicity Category III corresponding to a low acute oral potential.

Two acute oral toxicity studies were conducted that together show that the LD_{50} for the 34% ready-to-use liquid formulation

in rats is greater than 5 ml/kg, or 5 g/kg (Babish, 1977a, MRID 00003081 and Babish, 1977b, MRID 00003082). This is sufficient information to place this formulation in Toxicity Category IV.

b. Acute Effects-Dermal

A dermal toxicity study was conducted on rabbits using a 75% wettable powder/dust formulation (Matthews, 1970b, MRID 00003314). No deaths and no signs of toxicity were observed at doses up to 10 g/kg. This is sufficient information to assign this formulation to Toxicity Category III.

The acute dermal LD_{50} value of a 34% ready-to-use formulation was found to be greater than 20 ml/kg or 20 g/kg in albino rabbits (Babish, 1977c, MRID 00003080). This is sufficient information to assign this formulation to Toxicity Category IV.

The acute dermal LD_{50} value of a 29.52% soluble concentrate/liquid formulation was found to be greater than 5 g/kg for albino rabbits (Stevens, 1979a, MRID 00005858). This information is sufficient to assign this formulation to Toxicity Category III, indicating a low acute dermal hazard.

c. Acute Effects- Inhalation

Binnes et al. (1969, MRID 00003034) found that the LC_{50} value of a 75% wettable powder/dust formulation is greater than 5 mg/l

for rats. No animals died, but test animals displayed a nasal discharge during exposure. This formulation can be assigned a Toxicity Category III, indicating a low hazard.

Rats were exposed to a concentration of 20 mg/l of a 34% ready-to-use formulation. No mortality was produced, but ataxia was observed (Babish, 1977f, MRID 00003083). These data indicate that this formulation can be assigned to Toxicity Category IV, indicating practically no hazard due to inhalation.

d. Acute Effects- Eye Irritation

Two studies were conducted using a 75% wettable powder/dust formulation. Holsing (1968a, MRID 00003035) placed 100 mg of the formulation in the eyes of rabbits and observed marked and persistent conjunctival effects, iris irritation, and corneal opacity. These results are sufficient to assign this formulation to Toxicity Category I, indicating that this is a strong eye irritant.

After 100 mg of the 75% wettable powder/dust formulation was instilled into one eye of each rabbit, Bailey (1976a, MRID 00003301) noted corneal opacity within 72 hours, and damage to the iris, although neither of these effects persisted for seven days. Conjunctival effects occurred and persisted for seven days. This information is sufficient to assign this formulation to Toxicity Category II, indicating a high potential for eye irritation.

Testing a 34% ready-to-use formulation for eye irritation, Babish (1976a, MRID 00003161) found no irritation to the conjunctiva, iris or cornea of the eyes of the test rabbits. This formulation can be assigned to Toxicity Category IV, indicating a very low potential for eye irritation.

Stevens (1979b, MRID 00005857) tested a 29.52% soluble concentrate/liquid formulation for eye irritation. Results show transient conjunctival effects, and no iris or cornea irritation was observed. These observations are sufficient to assign this formulation to Toxicity Category III, indicating a low potential for eye irritation.

e. Acute Effects- Dermal Irritation

No irritation was produced when a 75% wettable powder/dust formulation was applied to the skin of rabbits (Matthews, 1970d, MRID 00003311). These results are sufficient to assign this formulation to Toxicity Category IV, indicating a very low dermal irritation potential.

The 34% ready-to-use formulation produced moderate irritation to the intact and abraded skin of albino rabbits (Babish, 1976b, MRID 00003162). Erythema and edema were also noted. These results were sufficient to assign this formulation to Toxicity Category III, indicating a low irritation potential.

The 29.52% soluble concentrate/liquid formulation was severely irritating to the intact and abraded skin of albino rabbits. Moderate to severe erythema and edema were also noted (Stevens, 1979c, MRID 00005856). These results were sufficient to assign this formulation to Toxicity Category II, indicating a moderate irritation hazard.

B. HUMAN AND DOMESTIC ANIMAL HAZARD ASSESSMENT

1. Technical

The information available to assess potential hazard as a result of chronic exposure is incomplete (see the Toxicity Profile for details). However, the available data for oncogenicity, teratogenicity, and reproduction suggest a low hazard. In addition, the data on acute oral, acute dermal and primary dermal irritation indicate low hazard. No data were available to assess the acute inhalation, primary eye and primary dermal irritation potential.

2. Wettable Powder/Dust (WP/D)

The 75% WP/D formulation had low acute oral, acute dermal, acute inhalation and primary skin irritation potential. Five irritation studies show that this formulation is a severe eye

irritant and appropriate labelling and caution is necessary. No data were available to assess the dermal sensitization potential.

3. Ready-to-Use (RTU)

The 34% RTU formulation has low acute oral, acute dermal, acute inhalation, primary eye, and primary dermal irritation potential. No data were available to assess dermal sensitization.

4. Soluble Concentrate/Liquid (SC/L)

The 29.5% Sc/L formulation has low acute dermal and primary eye irritation potential. Primary dermal irritation studies show a moderate to severe skin irritation potential. No data were available to assess the acute oral, acute inhalation and dermal sensitization potential.

C. SUMMARY OF MAJOR DATA GAPS

The following tests are required for the reregistration of carboxin: acute inhalation toxicity (technical product, 25% dust, 29.5% soluble concentrate/liquid), primary eye irritation (technical product and 25% dust), dermal

sensitization (technical product and all formulations), and the following tests on the technical product only: oncogenicity, teratogenicity, and mutagenicity. Some of these data gaps have already been partially satisfied, see Chapter III for an explanation of what information is needed.

VII RESIDUE CHEMISTRY

A. RESIDUE CHEMISTRY PROFILE

1. Uptake and Distribution and Metabolism in Plants

Data obtained by a variety of methods show that carboxin is systemic in plants. Extracts of plants grown from carboxin-treated seed or immersed in a carboxin solution have been shown by bioassay methods to contain residues toxic to fungi (Verma and Vyas, 1976, MRID 05001172; Thapliyal and Sinclair 1971, MRID 05001304; Thapliyal and Sinclair, 1970, MRID 05001302; Bolkan and Milne, 1975, MRID 05002793). Fungitoxic residues persist up to 29 days in some plants (Bolkan and Milne, 1975, MRID 05002793).

The distribution of residues derived from phenyl-^{14}C- or oxathiin-^{14}C-carboxin in cotton, wheat, barley, soybean, and bean plants has been studied (Leroux and Gredt, 1972, MRID 05006363; Ambro-Balint, 1974, MRID 05013368; Briggs et al., 1974, MRID 05002886; Thapliyal and Sinclair, 1971, MRID 05001304; Kirk et al., MRID 1969, 05003664; Berggren and Pinckard, 1973; MRID 05003673; Snel and Edgington 1970, MRID 05003663; Chin et al., 1970, MRID 05002177; Chin et al., 1969, MRID 00003044; Chin et al., 1972, MRID 00002941). Carboxin is systemic in all species studies, in agreement with bioassay data. The pattern of residue distribution within plants is variable, depending upon the species examined, the length of exposure to the labeled compound, and the method of analysis. In general, data obtained by methods capable of detecting the total radiolabeled residue (combustion technique, radioautography) show that roots, lower stem and the earliest leaves contain the bulk of the radiolabeled chemical (Kirk et al., 1969, MRID 05003664;

Berggren and Pinckard 1973, MRID 05003673; Snel and Edgington 1970, MRID 05003663; Chin et al., 1969, MRID 00003044). Radiolabeled carboxin distribution within plants was similar whether the ^{14}C label was in the oxathiin or phenyl rings of carbon (Briggs et al., 1974, MRID 05002886; Chin et al., 1969, MRID 00003044).

The predominant metabolite of carboxin in wheat, beans, and barley plants grown from ^{14}C-carboxin-treated seed is the sulfoxide derivative of carboxin (Leroux and Gredt 1972, MRID 05006363; Ambro-Balint 1974, MRID 05013368; Snel and Edgington 1970, MRID 05006363; Chin et al. 1970, MRID 05002177). Small amounts of carboxin sulfone (oxycarboxin) have been found in treated barley and wheat (Chin et al. 1970, MRID 05002177), and the p-hydroxylated derivative of carboxin has been identified in barley (Briggs et al. 1974, MRID 05002886). As crops mature, insoluble anilide complexes (these complexes of carboxin or carboxin derivatives with macromolecules such as lignin are insoluble in water and organic solvent and liberate aniline upon hydrolysis) increase (Briggs et al. 1974, 05002886; Snel and Edgington 1970, MRID 05003663; Chin et al. 1970, MRID 05002177; Chin et al. 1972, MRID 00002941). Seven weeks after planting, acetone-insoluble residues were 23 percent of the total residue in barley and 40 percent in wheat (Chin et al. 1970, MRID 05002177). Polar metabolites of carboxin also increase during crop maturation (Leroux and Gredt 1972, MRID 05006363; Snel and Edgington 1970, MRID 05003663), but do not contribute significantly to the total residue in aerial portions of plants (Leroux and Gredt 1972, MRID 05006363).

The uptake, distribution and metabolism of carboxin in plants has been adequately defined for the currently registered uses of the fungicide. The residues of concern are: carboxin, carboxin sulfoxide, and insoluble anilide complexes.

2. Metabolism in Food-Producing Animals

Data on the metabolism of carboxin in food-producing animals have not been submitted to the Agency.

The Agency is not requiring an animal metabolism study to support seed treatment use of carboxin. Data from a feeding study (see Residues in Animals) in conjunction with data on residues in crops (see Residues in Plants) indicate that total residues would be low or undetectable in tissues of animals fed commodities grown from seed treated with carboxin at application rates now permitted.

3. Analytical Methods

A colorimetric method (Lane 1970, MRID 05002737), by which carboxin and carboxin derivatives are determined as aniline, has been used to obtain most residue data on growing crops. Sensitivity of the method is 0.2 ppm.

Some residue data were obtained by an earlier version of the aforementioned colorimetric method (Lane 1966, MRID 00003058).

A gas chromatographic method also based on determination of aniline has been

used to gather data on residues in mature crops (Sisken and Newell 1971, MRID 00003335). Sensitivity of the method is 0.2 ppm.

Recovery data for both methods are acceptable (cite references under Residues in Plants.) No pesticide with tolerances on commodities on which carboxin is used has been found to interfere with the GLC method are not likely to detect insoluble complexes. There have been no data submitted indicating the fraction of total residues determined by either method.

The colorimetric and GLC methods are subject to considerable interferences in untreated crop samples. A modified colorimetric method for residues hydrolyzable to aniline in meat, milk and eggs has been submitted (Uniroyal Chemical 1973, MRID 00002857). The method differs from that of Lane in that samples undergo extraction and column-chromatography clean up steps prior to steam distillation. Sensitivity of the method is 0.2 ppm for meat and meat by-products, 0.05 ppm for eggs, and 0.02 - 0.05 ppm for milk. Untreated sample blanks are low, recovery data are adequate and other pesticide and pesticides with tolerances on meat, milk, and eggs do not interfere with the determination of carboxin. The method has been successfully tried out in an EPA laboratory and is published in the Pesticide Analytical Manual (PAM). Validation data for commodities other than meat, milk and eggs have not been submitted.

In summary, both the colorimetric method of Lane and the GLC method of Sisken and Newell are suitable for obtaining residue data, although the latter method may not determine insoluble aniline complexes. Neither method is suitable for tolerance enforcement, but a modification of the colorimetric method is acceptable for enforcement of tolerances on meat, milk, and eggs. The modified method would be acceptable for tolerance enforcement on crops, if appropriate

validation data, including data showing that the method determines insoluble anilide complexes, were submitted.

4. Residues in Plants

The following tables of residue data reflect use of carboxin as a seed treatment. Residues in or on immature crops were analyzed primarily by the colorimetric method of Lane (Lane 1970, MRID 05002737), and residues in mature crops by the GLC method of Sisken and Newell (Sisken and Newell 1971, MRID 00003335).

The residue level on carboxin-fortified plant samples did not change after seven months of subzero storage (colorimetric method, Stone 1969 1012--001-04), or on fortified seed samples stored for 11 months at room temperature (GLC method, Sisken and Lane 1970, 1012-001-05).

Corn: Residue data have been obtained on fodder (whole immature plants), forage (stalks at harvest), ears (without husks), and grain. Data were gathered in Illinois, Iowa, Indiana, Minnesota, Washington, Nebraska and North Carolina:

RESIDUE SUMMARY

SAMPLE	PHI (weeks)	RATE(s) (oz/cwt seed)	RESIDUE DISTRIBUTION ppm (as carboxin) <0.2	0.2-0.5	>0.5
DUST [1]					
Fodder	4-21	1.5-3.0	12	0	0
Forage	22-23	1.0-3.0	6	0	0
Ears	21-25	1.0-3.0	8	0	0
grain	21-24	1.5-6.0	8	0	0
READY-TO-USE (FLOWABLE) [2]					
Fodder	4	1.4-2.7	0	1	1*
Fodder	5-9	1.4-2.7	11	1	0
Forage	15-26	0.7-4.0	10	0	0
Ears	15-26	0.7-4.0	10	0	0
SOLUBLE CONCENTRATE-LIQUID [3]					
Fodder	10-15	1.1	8	0	0
Forage	17-29	1.1	5	0	0
Ears	9-17	1.1	6	0	0
Grain	14-17	1.1	2	0	0

[*] (1.1 ppm)

[1] Uniroyal Chemical 197?, 1012-001-25

[2] Uniroyal Chemical 1973, 00005852

[3] Uniroyal Chemical 1975, 00003356

COTTONSEED: Data on residues in whole cotton plants, seed, and in proceeded fractions of seed were obtained in California, Georgia, Mississippi, and Florida:

SAMPLE	PHI (weeks)	RATE(s) (oz/cwt seed)	RESIDUE DISTRIBUTION ppm (as carboxin) <0.2	0.2-0.5	>0.5
FLOWABLE FUNGICIDE 1/					
Seed	28-30	2.8-12.8	9	0	0
WETTABLE POWDER 2/,3/					
Whole plant	2-4	3-12	0	0	13*
Whole plant	5-8	3-12	4	3	7**
Whole plant	10-14	3-12	6	2	0

[*] (2-32 ppm)

[**] (0.6-1.2 ppm)

[1] Uniroyal Chemical 1973, 00003129

[2] Uniroyal Chemical 1970, 1012-001-07

[3] Uniroyal Chemical 1967, 00003185

Residues declined with a half-life of 5 days. Residues were less than 0.2 ppm

in oil and meal from processed cottonseed grown from seed treated with 6 or 12 oz. carboxin per 100 lb. of seed (Sisken 1970, 00002938).

PEANUTS: Data on whole plants, peanut seed, meal and oil from processed seed, and on hulls were gathered from Georgia, North Carolina, Florida, and Texas:

SAMPLE	PHI (weeks)	RATE(s) (oz/cwt seed)	RESIDUE DISTRIBUTION ppm (as carboxin) <0.2	0.2-0.5	>0.5
WETTABLE POWDER					
Whole plant[1/,2/]	2-4	4.5-9.0	0	2	8*
Whole plant	4-7	4.5-9.0	3	2	3**
Whole plant	8-10	4.5-9.0	4	2	2***

Residues in whole plants declined with a half-life of 4-5 days.

Hay[3/]	20	4.5-9.0	4	0	0
Hulls[4/]	20	4.5-9.0	4	0	0
Hulls[5/]	17	2.25-4.5	4#	0	0
Whole seed[5/]	17	2.25-4.5	4#	0	0
Meal[5/]	17	2.25-4.5	4#	0	0
Oil[5/]	17	2.25-4.5	4#	0	0

#The formulation contained ^{14}C-carboxin. All residues were less than 0.05 ppm.

[*] (1.3-53 ppm)

[**] (1.3-3.6 ppm)

[***] (0.7-0.8 ppm)

[1] Uniroyal Chemical 1970, 1012-001-07

[2] Uniroyal Chemical 1969, 00003045

[3] Uniroyal Chemical 1974, 00002905

[4] Uniroyal Chemical 1974, 00002903

[5] Collier et al., 1974, 00003300

SMALL GRAINS: Data have been obtained in Idaho, Illinois, Utah, Kansas, North Dakota, Texas, and Manitoba on residues in whole plants and grain of oats, barley and wheat.

SAMPLE	PHI (weeks)	RATE(s) (oz/cwt seed)	RESIDUE DISTRIBUTION ppm (as carboxin) <0.2	0.2-0.5	>0.5
DUST					
Wheat-whole plants[1/]	6	1.5-3.0	2	0	0
Wheat-grain[2/]	17-19	1.5-3.0	4	0	0
Wheat-straw[2/]	17-19	1.5-3.0	4	0	0
Barley-grain[3/]	18	1.5-3.0	2	0	0
Barley-straw[3/]	18	1.5-3.0	2	0	0
Oats-grain[4/]	23	1.5-3.0	2	0	0
Oats-straw[4/]	23	1.5-3.0	2	0	0
READY-TO-USE (FLOWABLE)[5/]					
Wheat-whole plants	4	1.2-4.0	2	2	6*
Wheat-whole plants	6-12	1.2-2.0	6	3	0
Wheat-whole plants	6-12	2.4-4.0	4	1	4**
Wheat-grain	12-40	1.2-5.6	12	0	0
Wheat-straw	12-40	1.2-4.0	10	0	0
Barley-whole plants	4	1.2-4.0	2	4	0
Barley-whole plants	6-12	1.2-2.4	7	1	0
Barley-whole plants	6-12	4.0	2	1	0#
Barley-grain	12-34	1.2-4.0	6	0	0
Barley-straw	12-34	1.2-4.0	6	0	0

WETTABLE POWDER/DUST

Wheat-whole plants[6]	4-11	4	8	6	0
Wheat-whole plants	4-11	8	8	4	2##
Wheat-straw[7]	14-39	3-6	8	0	0
Barley-whole plants[6,8]	2-3	3-8	0	0	4■
Barley-whole plants	4-11	3-4	14	4	0
Barley-whole plants[8]	4-11	8	6	4	1■■
Barley-grain[8]	14-41	4-12	8	0	0
Oats-whole plants[8]	6-11	4-12	9	3	0

Residues in whole plants declined with an approximate half-life of 10 days[5,6,8]

[*] (0.8-1.8 ppm)

[**] (0.6-0.7 ppm)

[#] (0.8 ppm)

[##] (0.8 ppm)

[■] (0.9-13.3 ppm)

[■■] (0.6 ppm)

[1] Uniroyal Chemical 1978, 00003219

[2] Uniroyal Chemical 1978, 00003218

[3] Uniroyal Chemical 1977, 00003221

[4] Uniroyal Chemical 1978, 00003220

[5] Uniroyal Chemical 1973, 00003158

[6] Uniroyal Chemical 1969, 00003045

[7] Uniroyal Chemical 1972, 00002961

[8] Uniroyal Chemical 1970, 1012-001-07

SORGHUM: Data were obtained on growing plants, grain, and fodder (plants after harvest) in Nebraska, South Dakota, Kansas, Missouri, and Texas.

SAMPLE	PHI (weeks)	RATE(s) (oz/cwt seed)	RESIDUE DISTRIBUTION ppm (as carboxin) <0.2	0.2-0.5	>0.5
READY-TO USE (FLOWABLE) [1]					
Whole plants	4-9	3-6	6	0	0
SOLUBLE CONCENTRATE-LIQUID [2]					
Whole plants	4-14	1.1-2.2	22	2	0
Fodder	14	1.1-2.2	8	0	0
Grain	7-14	1.1-2.2	6	0	0
WETTABLE POWDER/DUST [1,3]					
Whole plants	2-4	3-6	2	0	14*
Whole plants	4-11	3	8	6	0
Whole plants	4-11	6	7	1	6**

Residues declined with a half-life of 11 days[3/].

[*] (0.6-10.8)

[**] (0.6-1.7)

[1] Uniroyal Chemical 1969, 00003045

[2] Uniroyal Chemical 1975, 00003054

[3] Uniroyal Chemical 1970, 1012-001-07

Data on residues in plants are adequate for the currently registered uses of carboxin, and are consistent with existing tolerances.

Residues of Carboxin in Animals

Three lactating cows were administered phenyl-^{14}C-carboxin in the diet. Milk, urine, and feces were monitored daily for radioactivity, and after 10 days of treatment the animals were sacrificed, and muscle, kidney, liver, and fat analyzed for radioactivity. Most of the radiolabel was excreted in the urine, the rate of excretion plateauing after day 2. Maximal radioactivity in feces was reached in the first week. Trace radioactivity in milk plateaued after the first few days. Less than 2 percent of the ingested carboxin was detected in tissues at sacrifice. Residue were distributed as follows (Kennedy and Jenkins 1971, 00002945).

TOTAL RESIDUE (PPB - EXPRESSED AS CARBOXIN)

PPM ADMINISTERED	LIVER	KIDNEY	MUSCLE	FAT	MILK (MAXIMUM)
0.5	22	18	4	3	1
1.5	78	71	23	7	4
5.0	147	81	39	13	8

The feeding study adequately depicts the distribution of tagged residues in animals ingesting carboxin. However, the nature of the residue in food-producing animals is not known.

Data on residues in poultry and eggs have not been submitted to the Agency, however, the Agency is not requiring a poultry feeding study to support the seed treatment use of carboxin. The feeding study described above indicates no propensity for residues to accumulate in animal tissues, and data on residues in crops (see Residues in Plants) demonstrate the absence of detectable residues in poultry feed items.

LABELING REQUIREMENTS

Labels on all carboxin formulations are required to prohibit use of treated seed for food, feed, or oil purposes. A restriction on grazing livestock on treated areas for six weeks after planting should remain on products used on barley, corn, oats and wheat. Formulations used on cottonseed are required to bear a prohibition against grazing of livestock on treated areas and feeding hay grown from treated seed. The wettable powder formulation used on peanuts should continue to bear a restriction against grazing treated areas, but the

current label restriction against feeding peanut hay (mature vines) to livestock is unnecessary because the established tolerance on peanut hay is adequate to cover permitted use.

SUMMARY OF MAJOR DATA GAPS

Data demonstrating that the enforcement method is capable of determining the residue of concern in crops are required.

VIII. ECOLOGICAL EFFECTS

A. Ecological Effects Profile

B. Ecological Effects Hazard Assessment

C. Summary of Major Data Gaps

A. ECOLOGICAL EFFECTS PROFILE

Scientifically sound data on the toxicity of technical or end-use carboxin to nontarget organisms is very limited. One study (Fink, 1974, MRID 00003139) showed that technical carboxin is practically nontoxic to mallard ducks, with an LC_{50} value greater than 4640 ppm.

B. ECOLOGICAL EFFECTS HAZARD ASSESSMENT

Insufficient information is available on the technical, end-use products, or their degradants to evaluate the potential impacts from carboxin to nontarget organisms.

All existing uses are for seed treatment, which could expose nontarget organisms to the parent compound or its degradates, carboxin sulfoxide and carboxin sulfone. However, in the absence of appropriate data the significance of the exposure cannot be addressed.

C. SUMMARY OF MAJOR DATA GAPS

The following studies are needed to determine carboxin's acute and subacute toxicity to some test species believed to be representative of nontarget organisms: avian single-dose oral LD_{50}; avian dietary LC_{50} (one one upland game bird); fish acute LC_{50}; and acute toxicity to aquatic organisms.

Further data may be required depending upon the examination of the above data and adequate environmental chemistry data on the parent compound as well as its degradates.

Carboxin

Product Specific Manufacturing-Use Products Data Requirements: [redacted] (See Chapter IV)

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
163.61-3	Product Identity & Disclosure of Ingredients	yes	Each Product	partially 1/	-	yes 1/
163.61-4	Description of Manufacturing Process	yes	Each Product	partially 2/	-	yes 1/
163.61-5	Discussion on Formation of Unintentional Ingredients	yes	Each Product	no	-	yes 1/
163.61-6	Declaration & Certification of Ingredients Limits	yes	Each Product	partially	-	yes/July '82 1
163.61-7	Product Analytical Methods & Data	yes	Each Product	partially 3/	00003172 00002995	yes/July '82
163.61-8	Physical/Chemical Properties	yes	Technical or Manufacturing-Use Product	partially	-	yes 1/

These data requirements are current as of June, 1981. Refer to the guidance package for updated requirements.

1/ These requirements must be fulfilled by each applicant. Data from other applicants may not be cited. Therefore, even if the requirement has been partially or completely fulfilled for some products, no references are given. Except for 163.61-6 these requirements must be filled at the time of registration or reregistration.

2/ The manufacturing process is not sufficiently detailed.

3/ The analytical methods are of sufficient detail to satisfy the Agency's requirements. However, validation data and results of analysis on at least five typical samples of each product must be submitted

Carboxin

Product Specific End-Use Products Data Requirements: Product Chemistry (See Chapter IV)

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
163.61-3	Product Identity & Disclosure of Ingredients	yes	Each Product	partially	-	yes 1/
163.61-4	Description of Manufacturing Process	yes	Each Product	partially 2/	-	yes 1/
163.61-5	Discussion on Formation of Unintentional Ingredients	yes	Each Product	no	-	yes 1/
163.61-6	Declaration & Certification of Ingredients Limits	yes	Each Product	no	-	yes/July '82 1/
163.61-7	Product Analytical Methods & Data	yes	Each Product	partially 3/	00003778	yes/July '82
163.61-8	Physical/Chemical Properties	yes	Each Product	partially	-	yes 1/

These data requirements are current as of June, 1981. Refer to the guidance package for updated requirements.

1/ These requirements must be fulfilled by each applicant. Data from other applicants may not be cited. Therefore, even if the requirement has been partially or completely fulfilled for some products, no references are given. Except for 163.61-6, these requirements must be filled at the time of registration or reregistration.
2/ Manufacturing process for Vitavax Flowable Fungicide is the only adequate process submitted.
3/ The analytical methods are of sufficient detail to satisfy the Agency's requirements. However, validation data and results of analysis on at least five typical samples of each product must be submitted.

CARBOXIN

Generic Manufacturing-Use Products Data Requirements: [redacted] (See Chapter V)

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
163.62-7(b)	Hydrolysis	yes	Technical Grade of Active Ingredient	no	00003040 1/	yes/ July '82
163.62-7(c)	Photodegradation	yes	Technical Grade of Active Ingredient	partial	00003088 2/	yes/ July '82
163.62-8(b)	Aerobic Soil Metabolism	yes	Technical Grade of Active Ingredient	partial 3/	00005540 00003225 05002176 00003041 00002935 05004996	yes/ July '82
163.62-8(c)	Anaerobic Soil Metabolism	yes	Technical Grade of Active Ingredient	partial 4/	00003226	yes/ July '82

These data requirements are current as of March, 1981. Refer to the guidance package for updated requirements.

1/ Not valid for hydrolysis because no recovery or sensitivity data provided. Also the Agency can not determine if the study was conducted in the dark.

2/ This study is useful and fills part of the requirements i.e., it provided information on photodegradation under natural and artificial lights. However it failed to identify the photo products. Thus further data are required. A study of photolysis on soil is also required.

3/ Data are required on aerobic soil metabolism of carboxin sulfoxide (preferably in silt loam, loamy sand or sandy soils). The data are insufficient to evaluate carboxin sulfoxide persistence in aerobic soil.

4/ Additional data are required to include 2 more soil types (preferably loam and silt loam soils).

CARBOXIN

Generic Manufacturing-Use Products Data Requirements: Environmental Fate (See Chapter V)

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
163.62-8(d)	Anaerobic Aquatic Metabolism	no				
163.62-8(e)	Aerobic Aquatic Metabolism	no				
163.62-8(f)	Microbial Metabolism:					
	(2) Effects of Microbes on Pesticides	yes	Technical Grade of Active Ingredient	all	00005540 05004129 05005110 05006789 05003218	no
	(3) Effects of Pesticides on Microbes	yes	Technical Grade of Active Ingredient	partial 5/	00005540 05002757 05003947 05003657 05003852 05003218	yes/ July '82

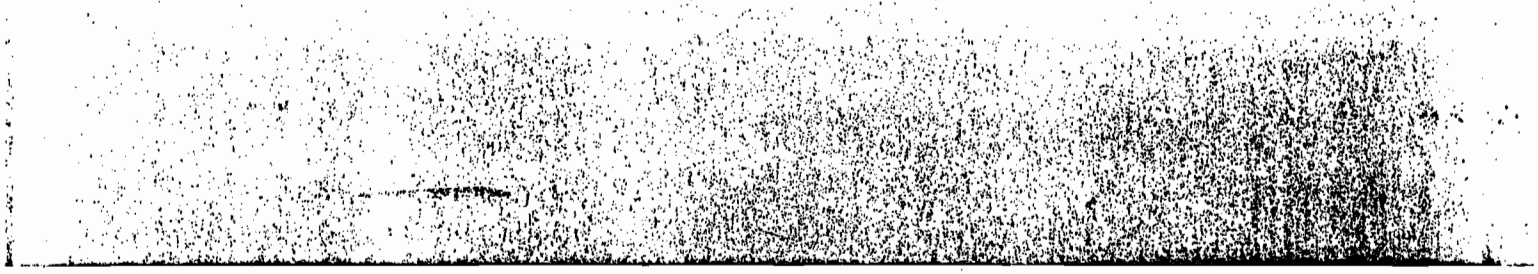
5/ Additional studies are required in order to evaluate effects of carboxin on blue-green algae, dehydrogenase activity, oxygen consumption, carbon dioxide evolution in soil, and ability of Rhizobium cowpea complex to form nodules and fix nitrogen in a symbiotic relationship with peanuts.

CARBOXIN

Generic Manufacturing-Use Products Data Requirements: Environmental Fate (See Chapter V)

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
163.62-8(g)	Activated Sludge Metabolism	yes	Technical Grade of Active Ingredient	no	-	yes/ July '82
163.62-9(b)	Leaching	yes	Technical Grade of Active Ingredient	partial 6/	00003237 00003114 00003229 00003227	yes/ July '82
163.62-9(c)	Volatility	no				
163.62-9(d)	Adsorption/Desorption	yes	Technical Grade of Active Ingredient	all	00009541 05003915	no
163.62-9(e)	Water Dispersal	no				
163.62-10(b)	Terrestrial Field Dissipation:					
	(1) Field & Vegatable Crops	yes	A Typical Formulation	partial 7/	00003087	yes/ July '82
	(2) Tree Fruit & Nut Crop Uses	no				
	(3) Pasture Land Uses	no				
	(4) Domestic Outdoor Parks, Ornamental & Turf Uses	no				

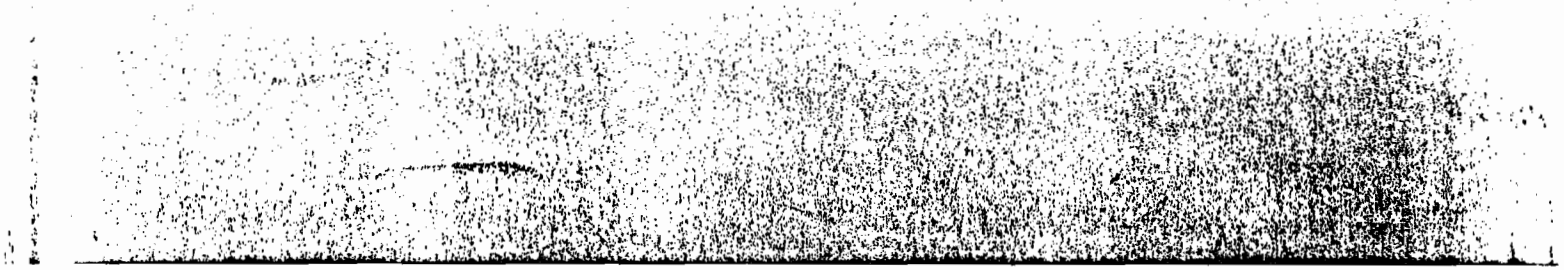
6/ Rapid leaching studies are needed using two additional soil types (sandy loam, silt loam or clay soils preferred).
7/ Dissipation and mobility rates for carboxin formulations are required.



CARBOXIN

Generic Manufacturing-Use Products Data Requirements: Environmental Fate (See Chapter V)

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
	(5) Rights of Way, Shelterbelts & Related Uses	no				
163.62-10(c)	Aquatic Field Dissipation:					
	(1) Aquatic Food Crop Uses	no				
	(2) Aquatic Nonerop Uses	no				
	(3) Specialized Aquatic Uses	no				
163.62-10(d)	Terrestrial/Aquatic (Forest) Field Dissipation	no				
163.62-10(e)	Aquatic Impact Uses:					
	(1) Direct Discharge	no				
	(2) Indirect Discharge	no				
	(3) Wastewater Treatment	no				



CARBOXIN

Generic Manufacturing-Use Products Data Requirements: Environmental Fate (See Chapter V)

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
163.62-10(f)	Combination & Tank Mix Field Dissipation	no				
163.62-10(g)	Long Term Field Dissipation Study	no				
163.62-11(b)	Accumulation in Rotational Crops	yes	Technical Grade of Active Ingredient	partial 8/	00003114 00003224	yes
163.62-11(c)	Accumulation in Irrigated Crops	no				
163.62-11(d)	Fish Accumulation	yes	Technical Grade of Active Ingredient	all	00005544 00005545	no
163.62-11(e)	Special Studies Accumulation in Aquatic Noncrop Uses	no				
163.62-13	Disposal & Storage	no				

8/ The available data satisfy the lab data requirements, however a field study is needed to determine if residue will be taken up by rotational crops.

A10

CARBOXIN

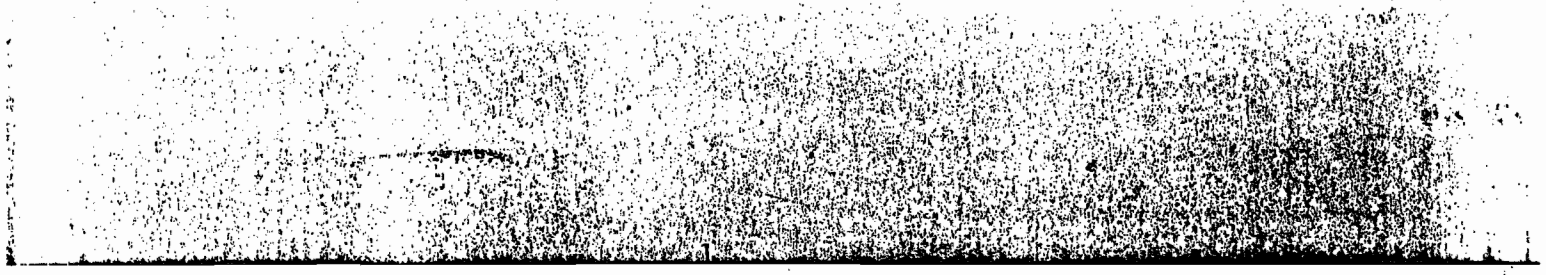
Generic Manufacturing-Use Product Data Requirements: [redacted] (See Chapter VI)

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
163.81-1	Acute Oral Toxicity	yes	Each Product	all	00003065	no
163.81-2	Acute Dermal Toxicity	yes	Each Product	all	00003066	no
163.81-3	Acute Inhalation Toxicity	yes	Each Product	partial 1/	00003116	yes/ July '82
163.81-4	Primary Eye Irritation	yes	Each Product	no	-	yes/ July '82
163.81-5	Primary Skin Irritation	yes	Each Product	all	0003119	no
163.81-6	Dermal Sensitization	yes	Each Product	no	-	yes/ July '82
163.81-7	Acute Delayed Neurotoxicity	no 2/				
163.82-1	Subchronic 21-Day Oral	yes	Technical Grade of Active Ingredient	all	00003063 00003030	no
163.82-2	Subchronic 21-Day Dermal Toxicity	yes	Technical Grade of Active Ingredient	all	00003216	no

These data requirements are current as of June, 1981. Refer to the guidance package for updated requirements.

1/ Since the study gave neither the particle size nor the actual concentration of carboxin in the inhalation chamber, further testing is required.

2/ This test is not required because carboxin is not expected to cause esterase depression nor is it related to substances that induce delayed neurotoxicity.



All

CARBOXIN
Generic Manufacturing-Use Products Data Requirements: Toxicology (See Chapter VI)

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
163.82-3	Subchronic 90-Day Dermal Toxicity	no [3]				
163.82-4	Subchronic Inhalation Toxicity	no [4]	Technical Grade of. Active Ingredient	no	-	no [4]
163.82-5	Subchronic Neurotoxicity	no				
163.83-1	Chronic Feeding	yes	Technical Grade of. Active Ingredient	all	00003031 00003152	no
163.83-2	Oncogenicity	yes	Technical Grade of. Active Ingredient	partial	00003031 00003152	yes [5] July '84
163.83-3	Taratogenicity	yes	Technical Grade of. Active Ingredient	partial	00003120	yes [6] July '84
163.83-4	Reproduction	yes	Technical Grade of. Active Ingredient	all	00003032	no
163.84-2 through -4	Mutagenicity	yes	Technical Grade of. Active Ingredient	partial	00003118	yes [7] July '84
163.85-1	Metabolism (Identification of Metabolites)	yes	Technical Grade of. Active Ingredient	all	00002945 00002943 00002944	no

These data requirements are current as of June, 1981. Refer to the guidance package for updated requirements.

The footnotes can be found on the next page.

3/ Not required because carboxin is not intentionally applied to the skin, and its use will not result in long-term exposure.

4/ Will depend on results of an acute inhalation test for technical carboxin.

5/ An eighteen-month mouse oncogenicity study is needed to meet this requirement.

6/ A teratogenicity test is needed on a second mammalian species, i.e. in addition to the test on rats.

7/ Test choices within these categories must be accompanied with rationale.

(1) At least 1 more test for detecting gene mutations from among these types:

- Insects e.g. sex-linked recessive lethal test.
- Mammalian somatic cells in culture with and without metabolic activation.
- Mouse specific locus test.

(2) At least 3 test for detecting chromosomal aberrations (see 163.84-1(b)(2)(ii).
(3) At least 2 tests for detecting primary DNA damage (see 163.84-1(b)(2)(iii)).

CARBOXIN
Product Specific End-Use Products Data Requirements: Toxicology (See Chapter VI)

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
163.81-1	Acute Oral Toxicity	yes	Each Formulation[7] or Substantially Similar Formulation	partial	00003317[8] 00003081[9] 00003082[9]	yes[11] July '82
163.81-2	Acute Dermal Toxicity	yes	Each Formulation[7] or Substantially Similar Formulation	partial	00003314[8] 00003080[9] 00005858[10]	yes[12] July '82
163.81-3	Acute Inhalation Toxicity	yes	Each Formulation[7] or Substantially Similar Formulation	partial	00003034[8] 00003083[9]	yes[11] July '82
163.81-4	Primary Eye Irritation	yes	Each Formulation[7] or Substantially Similar Formulation	partial	00003301[8] 00003035[8] 00003161[9] 00005857[10]	yes[12] July '82
163.81-5	Primary Skin Irritation	yes	Each Formulation[7] or Substantially Similar Formulation	partial	00003311[8] 00003162[9] 00005856[10]	yes[12] July '82
163.81-6	Dermal Sensitization	yes	Each Formulation[7] or Substantially Similar Formulation	no	-	yes[13] July '82

These data requirements are current as of June, 1981. Refer to the guidance package for updated requirements.
7/ See Guidance Package for requirements for each formulation or substantially similar formulation.
8/ This study is adequate for the testing of a 75% a.i. wettable powder/dust formulation.
9/ This study is adequate for the testing of a 34% a.i. ready-to-use formulation.
10/ This study is adequate for the testing of a 29.52% a.i. soluble concentrate/liquid formulation.
11/ Further testing is required for a 29.52% soluble concentrate/liquid and 25% dust formulations.
12/ Further testing is required for a 25% dust formulation.
13/ Testing is required for the following formulations: 75% wettable powder/dust; 34% ready-to-use; 29.52% soluble concentrate/liquid; and a 25% dust.

A12

CARBOXIN

Generic Manufacturing-Use Products Data Requirements: [redacted] (See Chapter VII)

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
	Metabolism in Plants	yes	Technical Grade of Active Ingredient	all	05001172 05001304 05001302 05002793 05006363 05013368 05002886 05003664 05003673 05003663 05002177 00003044 00002941 GS-0012-07	no
	Metabolism in Animals	no				
	Analytical Methods	yes	Technical Grade of Active Ingredient	partial	05002737 1/ 00003058 00003335 1/ 00002919 00003054 00002905 00002940 00002857 2/ GS-0012-02 GS-0012-03 GS-0012-04	yes

1/ Suitable for obtaining residue data, but not suitable for tolerance enforcement.

2/ This method is acceptable for tolerance enforcement on meat, milk, and eggs. This same method may be acceptable for enforcement of tolerances on crops if supported by validation data that showed detection of insoluble anilide complexes.

A13

CARBOXIN

Generic Manufacturing-Use Products Data Requirements: Residue Chemistry (See Chapter VII)

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
	Residue Data: Crops -				00003335 05002737	
	Corn	yes	Technical Grade of Active Ingredient	all	00005852 00003356 GS-0012-04	no
	Cottonseed	yes	Technical Grade of Active Ingredient	all	00003129 00003185 GS-0012-03	no
	Peanuts	yes	Technical Grade of Active Ingredient	all	00003045 GS-0012-03	no
	Wheat	yes	Technical Grade of Active Ingredient	all	00003219 00003158 00003045	no
	Barley	yes	Technical Grade of Active Ingredient	all	00003158 GS-0012-03	no
	Oats	yes	Technical Grade of Active Ingredient	all	GS-0012-03	no
	Sorghum	yes	Technical Grade of Active Ingredient	all	00003045 00003054 GS-0012-03	no

CARBOXIN

Generic Manufacturing-Use Products Data Requirements: Residue Chemistry (See Chapter VII)

Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
Residue Data: Processed Crops -					
Cotton seed	yes	Technical Grade of Active Ingredient	all		
oil				00002938	no
meal				00002938	
Peanuts	yes	Technical Grade of Active Ingredient	all		
hay				00002905	no
hulls				00002903 00003300	
meals				00003300	
oils				00003300	
Residue Data:					
milk	yes	Technical Grade of Active Ingredient	all	00002945	no
meat	yes	Technical Grade of Active Ingredient	all	00002945	no
poultry and eggs	no				
Storage Stability	no				

CARBOXIN

Generic Manufacturing-Use Products Data Requirements: [redacted] (See Chapter VIII)

Guidelines Citation	Name of Test	Are Data Required?	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement?	Bibliographic Citation	Must Additional Data be Submitted Under FIFRA 3(c)(2)(B)? If So, due when?
163.71-1	Avian Single-Dose Oral LD_{50}	yes	Technical Grade of Active Ingredient	no	-	yes
163.71-2	Avian Dietary LC_{50}	yes	Technical Grade of Active Ingredient	partial	00003139	yes
163.71-3	Mammalian Acute Toxicity	no				
163.71-4	Avian Reproduction	no				
163.71-5	Simulated and Actual Field Testing for Mammals & Birds	no				
163.72-1	Fish Acute LC_{50}	yes	Technical Grade of Active Ingredient	no	-	yes
163.72-2	Acute Toxicity to Aquatic Invertebrates	yes	Technical Grade of Active Ingredient	no	-	yes
163.72-3	Acute Toxicity to Estuarine & Marine Organisms	no				
163.72-4	Embryolarvae & Life-cycle Studies of Fish & Aquatic Invertibrates	no				
163.72-5	Aquatic Organism Toxicity & Residue Studies	no				
163.72-6	Simulated or Actual Field Testing for Aquatic Organisms	no				

These data requirements are current as of June, 1981. Refer to the guidance package for updated requirements.