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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carbaryl - Registration Standard Data Call-In
TOX Chem. No. 160

FROM: Ray Landolt
Review Section #1
Toxicology Branch
Hazard Evaluation Division (TS-769C)

5/14/86

TO: Larry Schnaubelt
Acting Product Manager 12
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

THRU: Robert B. Jaeger, Section Head
Review Section #1
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant: Union Carbide Agricultural Products Co.
Letter of July 20, 1984 (No. 261-84)

Registration No.: 264-324

Action Requested:

Review of the following studies in response to the Data Call-In of the Carbaryl Registration Standard Guidance Document.

1. Metabolism of Carbaryl in the Rat No. 25051, 1978.

2. Metabolism of Carbaryl in the Dog No. 25050, 1978.

3. Metabolism of Carbaryl in the Dog Following Oral Dosing No. 40-104, 1977.

4. Metabolism of Carbaryl in the Dog Following Intravenous Dose No. 40-105, 1977.

The two metabolism studies (25050 and 25051) submitted with the Union Carbide letter of July 20, 1984, made reference to two earlier metabolism studies No. 40-104 and 40-105. These two studies (40-104 and 40-105) were requested with the review of R. Landolt, September 28, 1985. These four studies have been evaluated with this review.

Recommendation:

1. The significance of the possible recovery of mercapturic acid conjugates in the polar fraction of urinary metabolites of the dog, but not the rat, should be characterized relative to the human metabolism of carbaryl.

2. It is not clear whether the quantitative differences reported in the percent of radioactivity recovered in the urine and feces is related to species differences between the rat and dog or as the result of the differences in the absorption of the oral doses of carbaryl dissolved in corn oil administered to rats as compared to the crystalline material administered in capsules to dogs.

   The resulting residue in food or feed will more likely be the crystalline form of carbaryl than carbaryl in corn oil.

3. The rat study conducted with female rats does not permit a quantitative comparison between rat and dog.

Metabolism - Rat
Union Carbide No. 811C20-25051, May 11, 1978, Accession No. 254104

A. Procedure

Three adult female Sprague-Dawley rats were dosed orally with 1-naphthyl-^{14}C-carbaryl (98% pure). To determine the effect of dosage on excretion and nature of metabolites, two rats were dosed with the test material in corn oil at 2.5 mg/kg. Another rat received the test material in aqueous methyl cellulose at 25 mg/kg. The treated animals were placed in individual metabolism cages for collection of urine and feces separately. Urine and feces were processed for identification of free and conjugated metabolites by thin-layer chromatography (TLC). Conjugated and water-soluble metabolites were subjected to enzyme or acid hydrolysis for identification and quantitation by two-dimensional TLC. The 25 mg/kg dose in methyl cellulose was administered for a comparison to the 25 mg/kg dose administered to dogs in gelatin capsules.

B. Results

1. Elimination

With reference to the following table (from this report) on the disposition of 1-naphthyl-^{14}C-carbaryl administered orally to the rat, a tenfold difference in the dose administered did not alter the total percent of the activity recovered in the urine and feces. However, a tenfold difference between dose levels is apparent in the percent of the administered dose recovered in the feces. This tenfold difference in percent of activity recovered was reported to account for the unabsorbed material eliminated unchanged in the feces. However, a greater percent of the 2.5 mg/kg dose may be recovered in the feces if administered in the crystalline form, i.e., methyl cellulose suspension.

Treatment	Fraction	% Applied Dose at Indicated Days 1	2	Total
2.5 mg/kg in corn oil (in solution)	Urine	74.1	17.2	91.3
	Feces	1.8	0.1	1.9
				93.2
25 mg/kg in aqueous methyl cellulose (suspension)	Urine	71.5	0.6	72.1
	Feces	18.1	0.4	18.5
				90.6

2. Identification and Quantitation of Urinary Metabolites

Urine collected from the 2.5 mg/kg level was analyzed for urinary metabolites. The unconjugated metabolites 5-hydroxy carbaryl, 5,6-dihydrodihydroxy carbaryl, 4-hydroxy carbaryl, and 5,6-dihydrodihydroxy naphthol comprised about 17 percent of the free metabolite fraction. Decarbamylated products of these metabolites, 1,6-naphthalenediol, 1-naphthol, 3,4-dihydrodihydroxy naphthol, carbaryl and 1,4-naphthoquinone represented less than 2 percent of the total radioactivity. The conjugated metabolites account for 81 percent of the total urinary radioactivity. Conjugated 1-naphthol accounted for 16 percent of the total as the result of enzyme hydrolysis. Conjugated carbaryl accounted for 4 percent of the total as the result of acid hydrolysis. Conjugated methylol accounted for 0.64 percent of the total as the result of acid hydrolysis to desmethyl carbaryl. The conjugated metabolites 1,5-naphthalenediol, 1,6-naphthalenediol, and 3,4-dihydrodihydroxy naphthol, previously unreported metabolites, accounted for about 3 percent of the total as the result of enzyme hydrolysis. Conjugated 3-hydroxy carbaryl, previously unreported, accounted for 0.06 percent of the total by acid hydrolysis. The highly polar materials comprised 27 percent of water-soluble radioactivity representing incomplete hydrolysis of the conjugates. This fraction designated as highly polar materials was not identified in this study.

Metabolic Products Present in 24-Hour Urine of A Rat Treated Orally with 2.5 mg/kg of 1-Naphthyl-^{14}C-Carbaryl in Corn Oil.

Products	% Total Radioactivity in Urine
1-Naphthol	16.61
Carbaryl	4.81
Methylol	0.64
1,5-Naphthalenediol	1.37
1,6-Naphthalenediol	0.45
5-Hydroxy Carbaryl	11.07
5,6-Dihydrodihydroxy Naphthol	6.15
5,6-Dihydrodihydroxy Carbaryl	13.41
1,4-Naphthoquinone[1]/	1.25
4-Hydroxy Carbaryl	5.25
3-Hydroxy Carbaryl	0.06
3,4-Dihydrodihydroxy Naphthol	2.24
Unknown 1	3.26
Unknown 2	3.46
Other Unknowns	2.67
Highly Polar Materials	27.30

1/ A decomposition product of 1,4-naphthalenediol during work-up.

The significant amounts of hydroxylated carbamates and their enzyme and acid hydrolysis products suggest that a major portion of the conjugates were present as sulfates and glucuronides of the primary metabolites.

3. Identification and Quantitation of Fecal Metabolites

With reference to the following table (from this report) the fecal elimination of the 25 mg/kg level was higher than the 2.5 mg/kg level as the result of decreased absorption from the intestinal tract.

Metabolic Products Eliminated in the 24-Hour Feces of Rats Treated Orally with 1-Naphthyl-^{14}C-Carbaryl

Products	% Total Radioactivity in Feces[1]/		% Applied Dose	
	Treatment 1	Treatment 2	Treatment 1	Treatment 2
1-Naphthol	0.87	1.57	0.017	0.290
Carbaryl	1.84	6.77	0.035	1.252
Methylol	0.68	0.69	0.013	0.128
1,5-Naphthalenediol	0.96	0.23	0.018	0.043
5-Hydroxy Carbaryl	1.57	0.77	0.029	0.142
5,6-Dihydrodihydroxy Naphthol	4.59	ND[2]/	0.087	ND[2]/
5,6-Dihydrodihydroxy Carbaryl	9.66	1.91	0.184	0.353
4-Hydroxy Carbaryl	0.79	0.58	0.015	0.107
Conjugated Metabolites	34.09	52.78	0.648	9.764
Unextractables	44.95	34.70	0.854	6.420

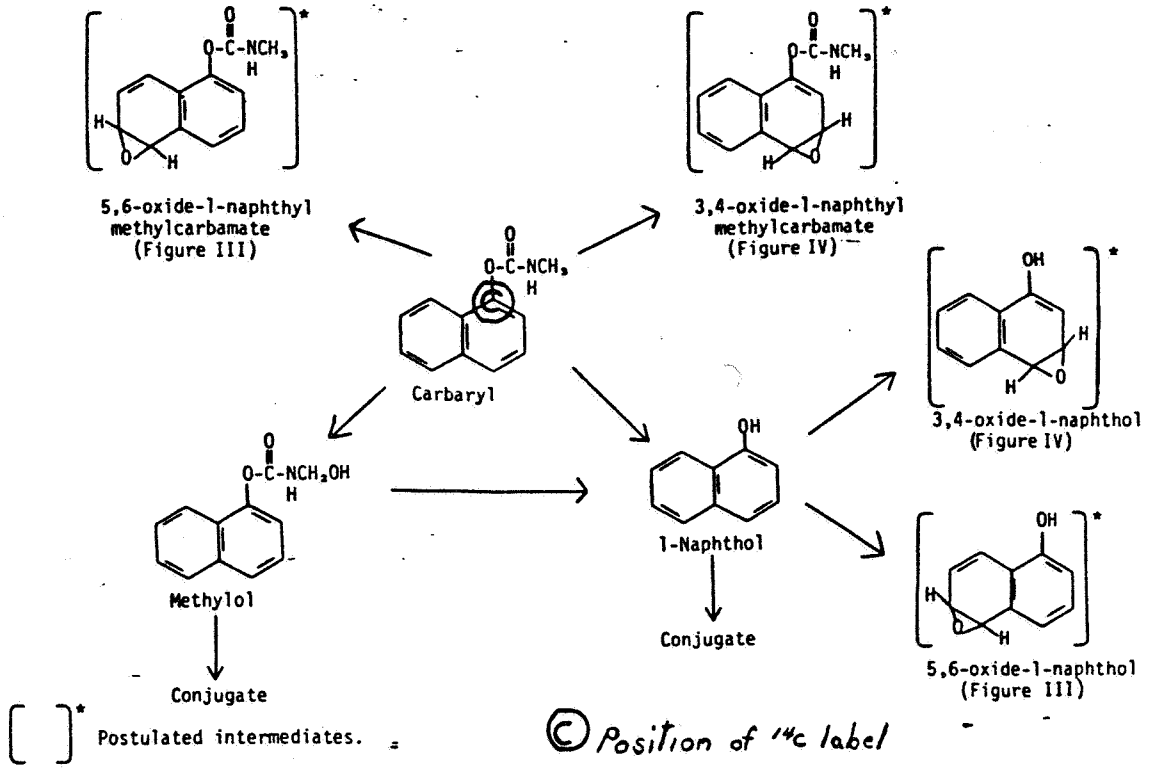
1/ Treatment 1 = 2.5 mg/kg in corn oil.
Treatment 2 = 25 mg/kg in 2% aqueous methyl cellulose.
2/ ND = None detected.

However, the administration of a 2.5 mg/kg dose of carbaryl dissolved in corn oil permitted recovery of a greater percent radioactivity in the feces for identification than the 25 mg/kg dose in a methyl cellulose suspension.

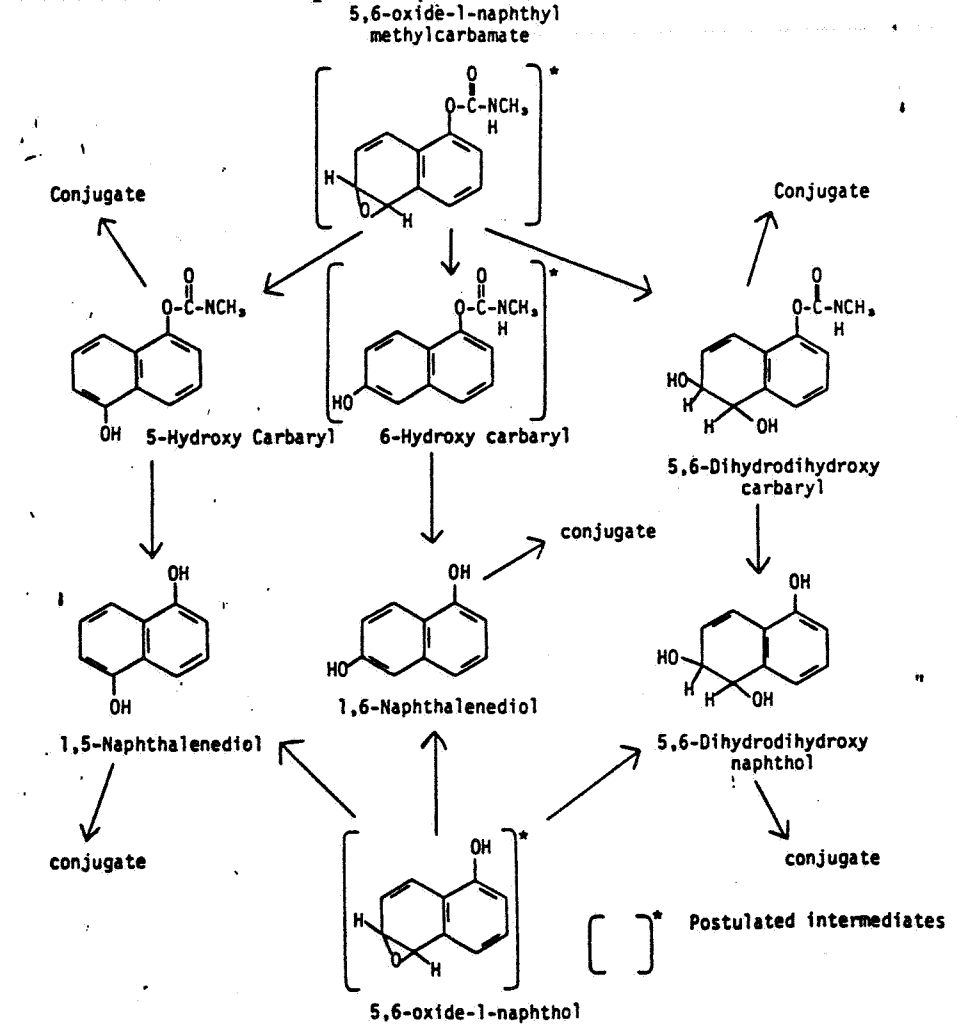
4. Metabolic Pathway in the Rat

Carbaryl (^{14}C-labeled in the 1-naphthyl position) appears to undergo biotransformation by hyrolysis, N-methyl oxidation, ring hydroxylation and conjugation through the metabolic pathway proposed in the following three figures.

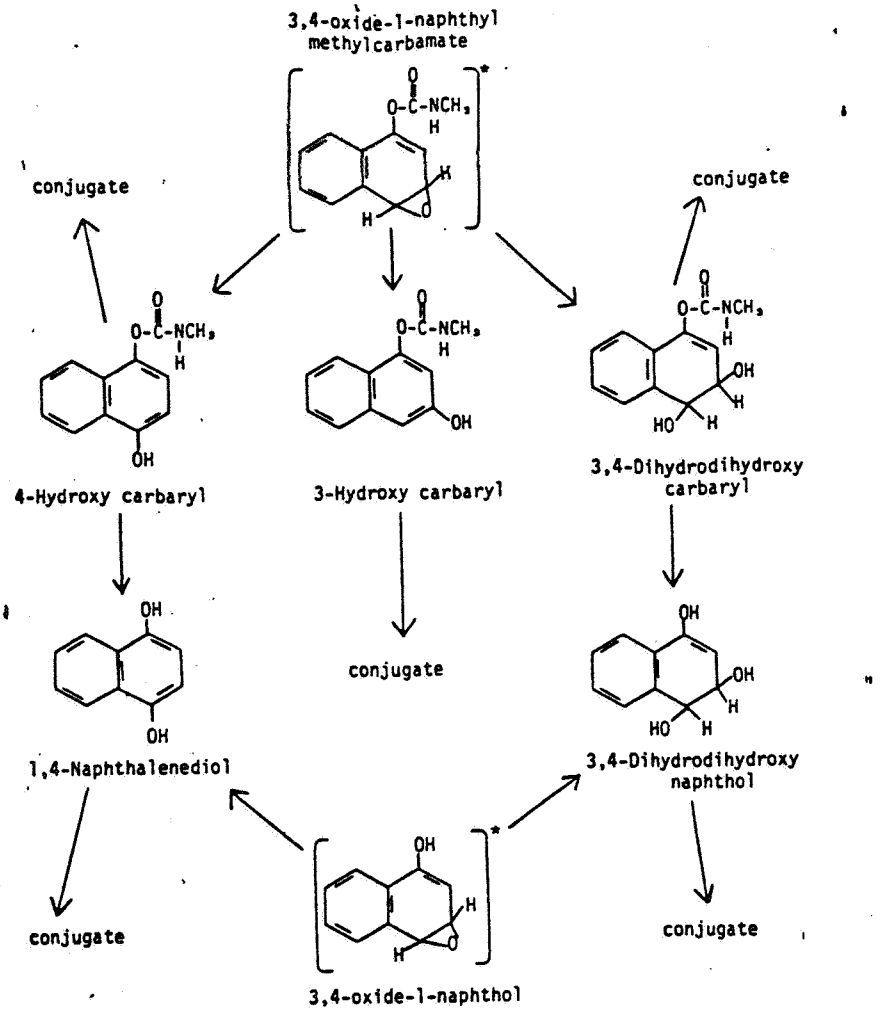
Metabolic athway of Carbaryl in the at, Part I



Metabolic Pathway of Carbaryl in the Rat, Part II



Metabolic Pathway of Carbaryl in the Rat, Part III



C. Conclusion

1. Classification of Data - Supplemental

a. Deficiency

i. The study conducted with female rats does not permit a comparison, if any, between sexes.

ii. The oral admini stration of the 2.5 mg/kg dose dissolved in corn oil used to identify and quantify the urinary metabolites (permitted a recovery of a greater percent of radioactivity to be identified) does not permit a comparison to the dog study conducted with the crystalline material.

2. Oral doses of 1-naphthyl labeled carbaryl dissolved in corn oil and administered to female rats at 2.5 mg/kg are rapidly eliminated within 24 hours with 74.1 percent of the dose accounted for in the urine and 1.8 percent in the feces. Within 48 hours 93.2 percent of the 2.5 mg/kg dose was recovered with 91.3 percent accounted for in the urine and 1.9 percent in the feces. The metabolic pathway of carbaryl in the female rat is presented along with qualitative evidence for the presence of four metabolites: 1,5-naphthalenediol, 1,6-naphthalenediol, 3,4-dihydro-3,4-dihydroxy-1-naphthol, and 3-hydroxy carbaryl that were not previously identified.

3. The observed possible enterohepatic cycling reported in the dog study (Report No. 40-105, 1977) has not been addressed in this rat study.

Metabolism - Dog
Union Carbide No. 811C20-25050, May 11, 1978, Accession No. 254104

A. Procedure

This report presents the metabolic pathway of 1-napthyl-^{14}C-carbaryl in the dog along with the quantitative elimination data previously reported in studies No. 40-104 and 40-105 (Accession No. 258271). Urine samples were lyophilized for scintillation counting. Feces samples were extracted by the acetonitrile-water solvent extraction method and the Soluene digestion procedure (Report No. 40-106, Accession No. 258271). Urine and feces were processed for identification by gel permeation column, thin-layer and two-dimensional chromatography. Conjugated and water-soluble metabolites were subjected to enzyme and/or acid hydrolysis for identification by two-dimensional TLC. Hydrolysis of the conjugates was accomplished by incubation with enzyme Glusulase and β-glucuronidase followed by acid to release the aglycones.

B. Results

1. A summary of the elimination in urine and feces of 1-naphthyl-^{14}C-carbaryl administered orally and intravenously to the dog is presented in the following table. There is approximately a twofold increase in the percent of the dose recovered in the urine of dogs treated intravenously as those treated orally. A three to sixfold increase in the percent of the dose recovered in the feces of the orally treated dogs as compared to those treated intravenously was observed.

Treatment (mg/kg)	Fraction	% Applied Dose at Indicated Days 1	2	Total
2.5 Oral, Male	Urine	34.8	7.7	43.2
	Feces	32.0	2.4	35.6
	Cage[1]/	7.2	1.1	8.5
				87.3
2.5 Oral, Female	Urine	30.1	2.3	32.8
	Feces	38.2	0.9	39.7
	Cage	10.8	0.6	11.6
				84.1
1.0 I.V., Male	Urine	55.8	3.1	59.5
	Feces	12.0	1.4	13.4
	Cage	11.6	0.6	12.4
				85.3
1.0 I.V., Female	Urine	61.3	2.8	64.8
	Feces	4.9	3.0	8.0
	Cage	16.6	1.0	17.7
				90.5

1/ Cage washing.

2. Identification and Quantitation of Urinary Metabolites

The unconjugated metabolite 5,6-dihydrodihydroxy carbaryl, 5,6-dihydrodihydroxy naphthol, and 5-hydroxy carbaryl comprised about 5 percent to 6 percent of the free metabolite fraction. Free carbaryl was not detected in the urine. The conjugated metabolites accounted for 90 to 95 percent of the total urinary radioactivity. Conjugated 1-naphthol accounted for about 5 percent of the total radioactivity in the urine as the result of enzyme and acid hydrolysis. Conjugated carbaryl accounted for between 9 and 12 percent of the urinary radioactivity as the result of acid hydrolysis. Conjugated methylol accounted for about 0.15 percent of the total urinary radioactivity as the result of acid hydrolysis and is considered a minor pathway of carbaryl metabolism. Conjugated 1,6-naphthalenediol, a previously unreported metabolite, accounted for up to 7 percent of the total urinary radioactivity as the result of enzyme hydrolysis. Conjugates of 4-hydroxy carbaryl, as the result of enzyme hydrolysis, accounted for about 4 percent of the urine radioactivity. Conjugated 3-hydroxy carbaryl, a previously unreported metabolite, accounted for about 0.3 percent of the total urinary radioactivity as the result of enzyme hydrolysis. The significant amounts of hydroxylated carbamates and their enzyme and acid hydrolysis products suggest that this portion of the conjugates were present as sulfates and glucuronides of the primary metabolites. The highly polar metabolites remaining after enzyme and acid hydrolysis represented incomplete hydrolysis of the conjugates. "Treatment of these conjugates with acid yielded the water-soluble naphthyl cysteine derivatives."

Metabolic Products Present in 24-Hour Urine of Both Dogs Treated Orally with 2.5 mg/kg of 1-Naphthyl-^{14}C Carbaryl

Products	% Total Radioactivity in Urine
1-Naphthol	4.80
Carbaryl	6.32
Methylol	0.19
1,5-Naphthalenediol	3.46
1,6-Naphthalenediol	6.34
5-Hydroxy Carbaryl	3.25
5,6-Dihydrodihydroxy Naphthol	11.28
5,6-Dihydrodihydroxy Carbaryl	6.18
1,4-Naphthoquinone[1]/	1.02
4-Hydroxy Carbaryl	3.43
3-Hydroxy Carbaryl	0.25
3,4-Dihydrodihydroxy Naphthol	0.70
Unknown 1	0.31
Unknown 2	1.48
Other Unknowns	1.87
Highly Polar Materials	49.44

1/ A decomposition product of 1,4-naphthalenediol during work-up.

3. Identification and Quantitation of Fecal Metabolites

Incomplete absorption of ^{14}C-carbaryl from the gastrointestinal tract following oral administration is apparent as compared to the lower fecal excretion values recorded for the intravenous treated dogs. However, the low amount of unchanged carbaryl along with the larger amounts of conjugates and unextractable radioactivity detected in the feces of interavenous treated dogs suggests that biliary excretion is a significant route of elimination.

Metabolic Products Present in 24-Hour Feces of Dogs Treated with 1-Naphthyl-^{14}C-Carbaryl

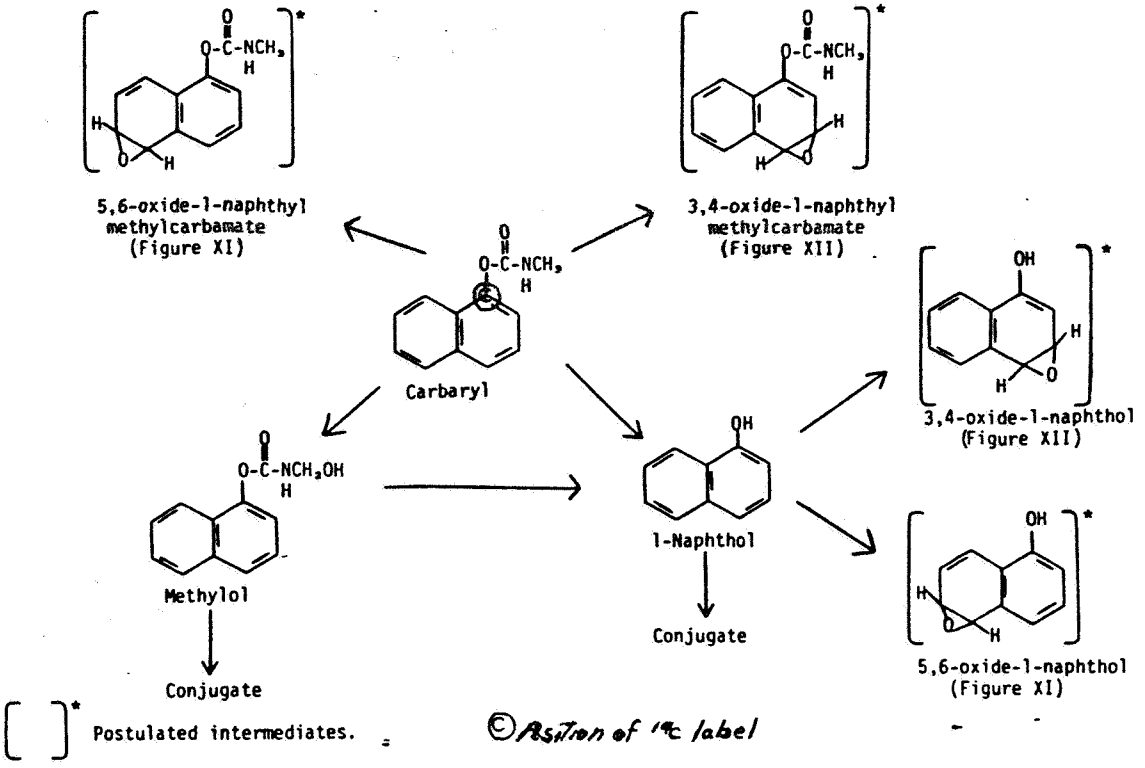
Products	% Total Radioactivity in the Feces of Indicated Treatments	
	Oral 2.5 (mg/kg)	I.V. 1.0 (mg/kg)
1-Naphthol	1.03	9.47
Carbaryl	87.07	4.24
Methylol	0.08	ND[1]/
1,5-Naphthalenediol	0.39	2.82
5-Hydroxy Carbaryl	0.20	2.02
5,6-Dihydrodihydroxy Naphthol	0.25	5.71
5,6-Dihydrodihydroxy Carbaryl	0.48	3.82
4-Hydroxy Carbaryl	0.43	4.22
Conjugated Metabolites	5.07	25.55
Unextractables	5.27	42.16

1/ND = None detected.

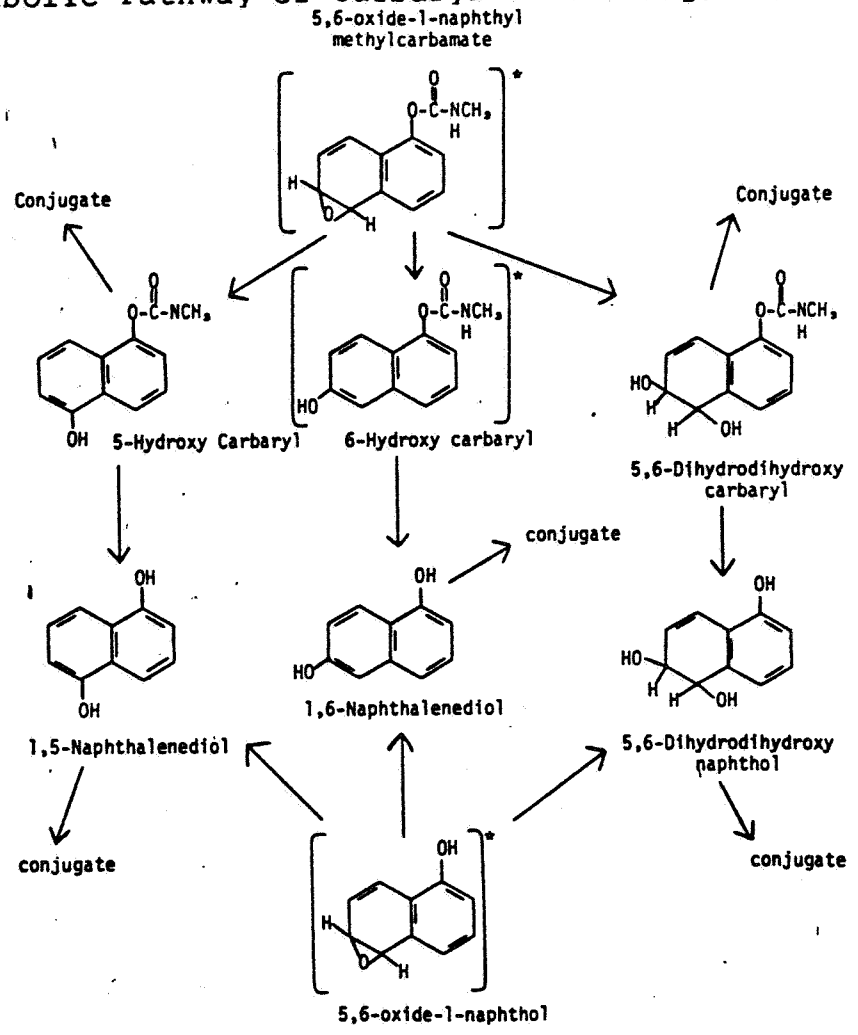
4. Metabolic Pathway in the Dog

Carbaryl (^{14}C-labeled in the 1-naphthyl position) appears to undergo biotransformation by hydroxylation of the N-methyl group to yield 1-naphthyl (hydroxymethyl) carbamate, hydrolysis to 1-naphthol and expoxidation of the 3,4 or 5,6 positions. From the metabolic products identified in the urine the following metbolic pathway of carbaryl is proposed.

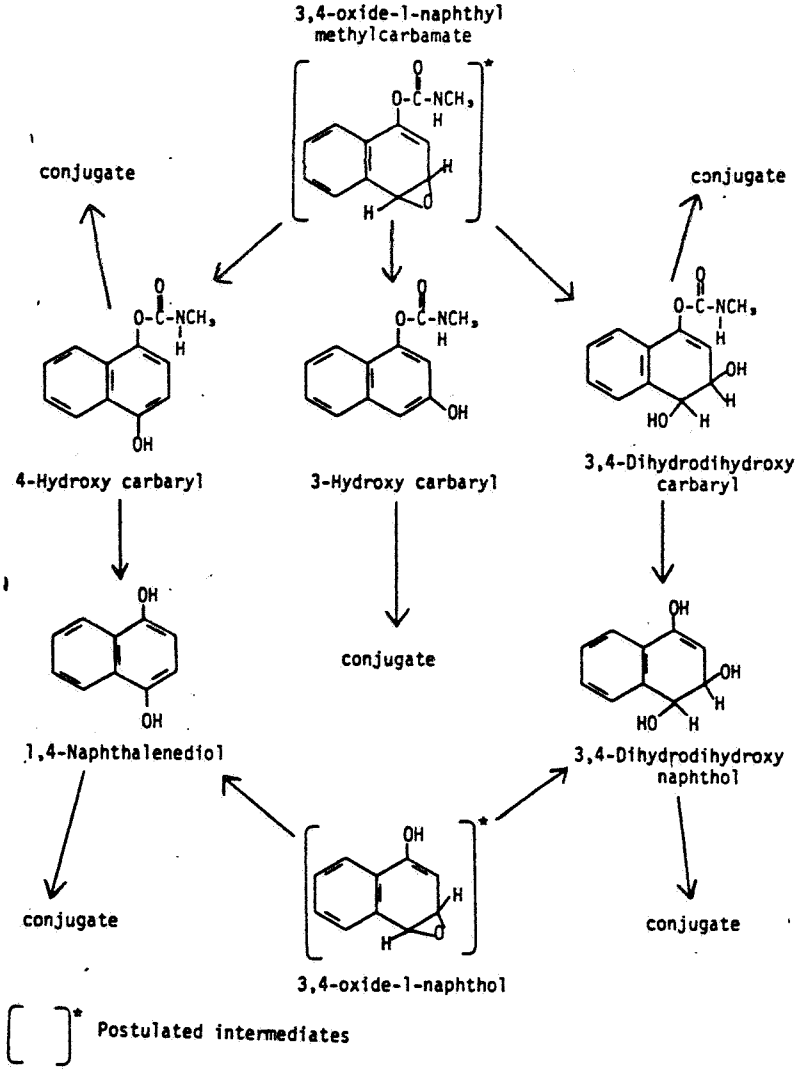
Metabolic Pathway of Carbaryl in the Dog, Part I



Metabolic Pathway of Carbaryl in the Dog, Part II



Metabolic Pathway of Carbaryl in the Dog, Part III



Comparison Between the Rat and Dog

In the rat (Report No. 25051) the principal route of elimination is the urine with 91 percent of the dose recovered as compared to 33 to 43 percent of the dose eliminated in the urine of the dog (Report No. 25050). In the dog (Report No. 25050) 36 to 40 percent of the dose was accounted for in the feces with less than 2 percent of the dose recovered in the feces of the rat (Report No. 25051). The high percent of the dose recovered in the feces of the dog appears to be related to the incomplete absorption of carbaryl from the gastrointestinal tract. Biliary excretion of carbaryl appears to be a significant route of elimination in the dog with 8 to 13 percent of the intravenous dose accounted for in the feces. The importance of biliary excretion was not addressed in the rat study. However, the importance of biliary elimination in the rat is suggested from the reported recovery of 97 percent of the total radioactivity in the portal blood within 66 minutes following an intragastric dose of 1-naphthyl-^{14}C-carbaryl administered to rats with the pylorus of the

stomach ligated (Casper, H.H. et al., Pestic. Biochem. Physiol. 2, 391, 1973).

No significant differences between male and female dogs were reported in the total radioactivity recovered in urine and feces. However, quantitative differences in the percent of metabolites identified as free 5-hydroxy carbaryl and conjugates of carbaryl and 4-hydroxy carbaryl were 3 to 5 times greater in the urine of female dogs than for male dogs dosed at the 2.5 mg/kg level. The conclusion drawn in the dog study that no significant differences were found between males and females in not compatible with the percent of metabolites identified between male and female dogs. With this difference noted between male and female dogs a comparison between species cannot be made with the metabolism study used for the comparison conducted on female rats.

Qualitative evidence for the similarity of the metabolic pathway of carbaryl in the rat and dog is presented in the following table as well as quantitative differences in the metabolites eliminated in the urine of the rat and dog.

Summary of the Urinary Metabolites of 1-Napthyl-^{14}C in the Dog and Rat

	% Total Radioactivity in Urine of Indicated Treatments (mg/kg)				
	Dog (crystalline)				Rat (in corn oil)
Products	2.5 Male	2.5 Female	25 Male	25 Female	2.5 Female
1-Naphthol	4.62	4.98	4.98	4.59	16.61
Carbaryl	3.21	9.42	10.44	11.77	4.81
Methylol	0.10	0.27	0.23	0.22	0.64
1,5-Naphthalenediol	3.73	3.18	3.56	3.17	1.37
1,6-Naphthalenediol	7.74	4.94	2.74	1.62	0.45
5-Hydroxy Carbaryl	1.39	5.11	1.91	3.48	11.07
5,6-Dihydrodihydroxy Naphthol	13.09	9.46	5.41	10.91	6.15
5,6-Dihydrodihydroxy Carbaryl	5.35	7.00	8.10	6.89	13.41
1,4-Naphthoquinone	1.23	0.81	2.42	2.60	1.25
4-Hydroxy Carbaryl	1.03	5.82	7.46	6.38	5.25
3-Hydroxy Carbaryl	0.28	0.21	0.14	0.05	0.06
3,4-Dihydrodihydroxy Naphthol	0.73	0.66	0.73	0.50	2.24
Unknown 1	0.29	0.32	1.06	0.82	3.26
Unknown 2	1.74	1.21	0.97	1.30	3.46
Other Unknowns	2.08	1.12	1.45	1.68	2.67
Highly Polar Materials	53.38	45.49	48.40	44.02	27.30

A two to threefold increase in the amount of free urinary metabolites was reported for the rat over those found for the dog. The higher levels of 4-hydroxy carbaryl, 5-hydroxy carbaryl, and 5,6-dihydrodihydroxy carbaryl in the rat urine account for this difference. The rat appears to be more efficient in hydrolyzing carbaryl to 1-naphthol than the dog. This quantitative difference may be accounted for by the vehicle used to administer the 2.5 mg/kg dose, i.e., corn oil to the rat and capsule to the dog. From the urinary metabolites identified in the preceding table, carbaryl appears to undergo biotransformation in the rat and dog by the pathway proposed in the attached figure. The metabolic pathway in the rat and dog appears to involve hydroxylation of the N-methyl group to 1-naphthyl (hydroxymethyl) carbamate, hydrolysis to 1-naphthol and epoxidation of the 3,4 or 5,6 positions of the naphthalene ring. The proposed metabolic pathways for rat and dog are identical.

C. Conclusion

From the data presented on the metabolic products identified in the urine and feces of rats and dogs receiving oral doses of 1-naphthyl-^{14}C-carbaryl, it appears that the metabolic pathways of carbaryl in these two species are qualitatively similar. The comparison is the result of data collected from the oral administration of 2.5 mg/kg to both rats and dogs with the difference being that the dose administered to female rats was dissolved in corn oil and the dose administered to male and female dogs was crystalline (in capsules).

A quantitative difference is noted in the percent of radioactivity accounted for in the highly polar fraction of urinary metabolites remaining after acid and enzyme hydrolysis of the conjugates of carbaryl. The fraction of total urinary radioactivity identified as highly polar materials was 2.7 percent for the rat as compared to 38 percent for the dog. In the dog the treatment of these unidentified conjugates with acid yielded water-soluble products, possibly mercapturic acid conjugates. "This behavior is similar to that observed for glutathion conjugates of carbaryl." The highly polar fraction of urinary metabolites was not identified in the rat. With reference to the literature cited (Chen 1976) the formation of glutathion conjugates and mercapturic acid metabolites was not evident in the urine of carbaryl treated rats. "Glucuronic acid and sulfate conjugates were the predominant type of metabolite found in the urine of rats dosed with carbaryl." The significance of this quantitative difference between the two species may be attributed to the percent recovery in the polar fraction. With this uncertainty the question of differences or similarity between the rat and dog still exists.

It would appear that any apparent differences in metabolism which are identified are more a consequence of the physical nature of the carbaryl administered (e.g., liquid vs solvent) than it is with species differences. For example, crystalline form administered via capsule to dog and crystalline material administered in the diet to rat, the excretion was primarily via the feces. When the rat was administered a more soluble form (carbaryl in corn oil) the excretion was essential via urine.

Excretion - Dog
Carnegie-Mellon Institute of Research No. 40-104, September 16, 1977, Accession No. 258271

A. Procedure

Male and female beagle dogs (one per sex per dose) received gelatin capsules containing 1-naphthyl-^{14}C-carbaryl (99%) and nonlabeled carbaryl (99.8%) at 2.5 and 25 mg/kg. Both sexes were 1.0 to 1.5 years of age with females weighing 8.2 and 8.6 kg, and males 9.0 and 11.8 kg. All animals were in good health based on physical examination and the results of clinical blood chemistry. Blood samples were collected initially, then at 15, 30 minutes, 1, 2, 4, 8, 12, 24 hours, and daily for determination of plasma radioactivity and cholinesterase levels. Urine and feces were collected separately at 12 and 24 hours then daily for 3 days.

B. Results

1. Cholinesterase Activity

a. At 25 mg/kg, a 40 to 50 percent reduction in both plasma and RBC values were reported at the 2-hour interval for both dogs, returning to normal values for the male within 48 hours and for the female within 96 hours. A transient (15 to 20%) decrease in plasma and RBC activity was observed for the female at the 24-hour interval.

b. At the 2.5 mg/kg level a decrease of 20 to 30 percent plasma and RCB values were observed within 1 to 2 hours after dosing returning to normal within 4 to 8 hours for both dogs.

2. Plasma Radioactivity

a. Plasma radioactivity of both dosage levels peaked within 2 hours then gradually decreased over the 4-day period.

b. The peak plasma radioactivity levels of the 2.5 mg/kg level were approximately five times higher than the 25 mg/kg level of activity suggesting "a higher proportion of the dose in the dogs treated with 2.5 mg/kg ^{14}C-carbaryl was absorbed."

3. Urinary Elimination

a. At the 25 mg/kg level 8.6 (F) and 11.8 (M) percent of the dose was recovered within 24 hours with 15.1 (F) and 14.3 (M) percent of the dose accounted for by day 4.

b. At the 2.5 mg/kg level 30.1 (F) and 34.8 (M) percent of the dose was recovered within 24 hours with 32.8 (F) and 43.2 (M) percent of the dose accounted for by day 4.

c. The poor resolution of the urinary metabolic profile of this study was attributed "to insufficent amounts of ^{14}C-metabolites in the urine samples."

4. Fecal Elimination

a. At the 25 mg/kg level 13.8 (F) (in addition to 24.4% cage wash) and 44.7 (M) percent of the dose was recovered within 24 hours with 19.2 (F) (25.4% cage wash) and 45.8 (M) percent of the dose accounted for by day 4.

b. At the 2.5 mg/kg level, 43.4 (F) and 29.5 (M) percent of the dose was recovered within 24 hours with 45 (F) and 33.2 (M) percent of the dose accounted for by day 4.

c. "Technical difficulties in sampling nonhomogeneous samples precluded meaningful quantitative recovery data in the feces."

5. No gross pathological changes were observed.

6. Tissue Distribution

a. The highest levels were found in the liver with less than 1 percent of the dose accounted for in the body of the animal by day 4.

b. Tissue distribution of ^{14}C-activity was the highest in the liver with 0.17 (F) and 0.10 (M) ppm reported for the 25 mg/kg dose and 0.029 (F) and 0.052 (M) ppm reported for the 2.5 mg/kg dosage level.

C. Conclusions

1. Classification of Data - Minimum, as a excretion/ elimination study.

2. Cholinesterase activity and plasma radioactivity peaked within two hours. Within 24 hours, 30.1 (F) and 34.8 (M) percent of the 2.5 mg/kg dose was recovered in the urine and 43.4 (F) and 29.5 (M) percent in the feces. Less than 1 percent of the dose was accounted for in the tissues at day 4 of the study.

Excretion - Dog
Carnegie-Mellon Institute of Research No. 40-105, September 16, 1977, Accession No. 258271

A. Procedure

One male (7.7 kg) and one female (7.7 kg) beagle dogs were dosed intravenously with 1-naphthyl-^{14}C-carbaryl in propylene glycol solution at 1.0 mg/kg. Animals were 1 to 1.5 years old. All animals were in good health based on physical examination and the results of clinical blood chemistry. Blood samples were collected at approximately 1, 5, 15, and 30 minutes, then at 1, 2, 4, 8, 12, 24, 48, 72, and 96 hours for determination of plasma and RCB cholinesterase levels. Urine and feces were collected separately at 12 and 24 hours then daily for 3 days.

B. Results

1. Cholinesterase Activity

a. Within 2 minutes of dosing, plasma and RCB levels were reduced by 30 to 50 percent followed by a gradual recovery to control values within 2 to 4 hours.

2. Plasma Radioactivity

a. During the first hour a lag period was apparent, for both dogs, when "plasma levels of radioactivity fluctuated in a manner as if the ^{14}C-carbaryl were released into the blood stream by a time-dependent mechanism" suggestive of plasma protein binding or other physiochemical processes.

b. Inspection of the 24-hour semilog plot of the plasma concentrations reveal "that the elimination kinetics during this period of time might involve two first order processes."

c. The estimated t 1/2 was approximately 6 hours for the female and 7 hours for the male dog.

3. Elimination

Within 24 hours 61.3 (F) and 55.8 (M) percent of the dose was recovered in the urine and 5.5 (F) and 11.7 (M) in the feces. By day 4 of the study 64.8 (F) and 59.5 (M) percent of the dose was accounted for in the urine and 8.4 (F) and 12.7 (M) in the feces. The study suggests that "with respect to carbaryl metabolism, biliary excretion may be a significant route of elimination in the beagle dog."

4. No gross pathological changes were observed.

5. Tissue Distribution

a. Tissue distribution of ^{14}C-activity was the highest in the liver with 0.033 (F) and 0.023 (M) ppm reported by day 4 following intravenous administration of 1.0 mg/kg.

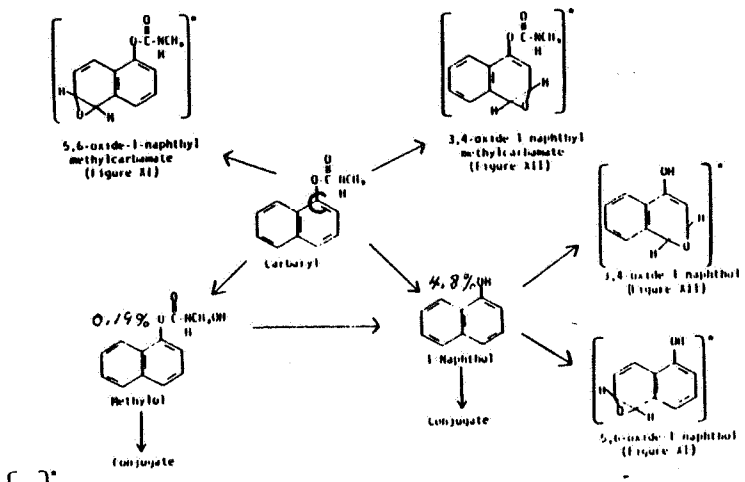
b. Approximately 1.0 percent of the dose was accounted for in the animal by day 4.

C. Conclusions

1. Classification of Data - Minimum, as an excretion/elimination study only.

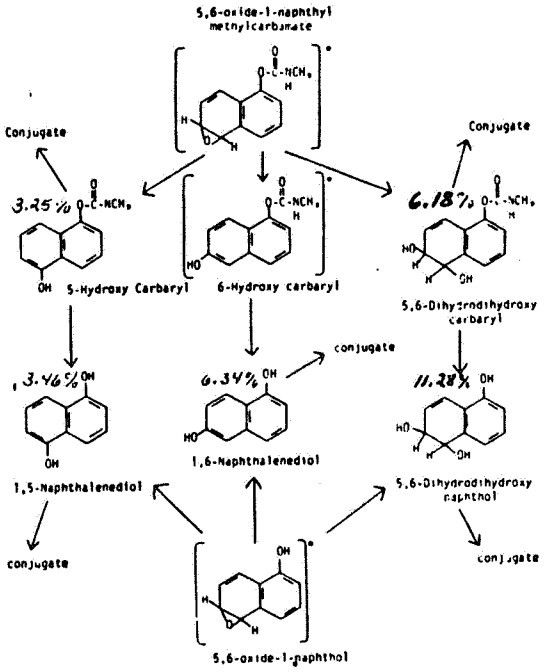
2. Plasma and RBC cholinesterase values were reduced by 30 to 50 percent followed by a return to control values within 2 to 4 hours. The estimated plasma half-life was approximately 6 hours for the female and 7 hours for the male. Within 24 hours 61.3 (F) and 55.8 (M) percent of the dose was accounted for in the urine and 5.5 (F) and 11.7 (M) percent in the feces. Approximately 1 percent of the dose was accounted for in the animals by day 4 of the study.

Metabolic Pathway of Carbaryl in the Dog, Part I

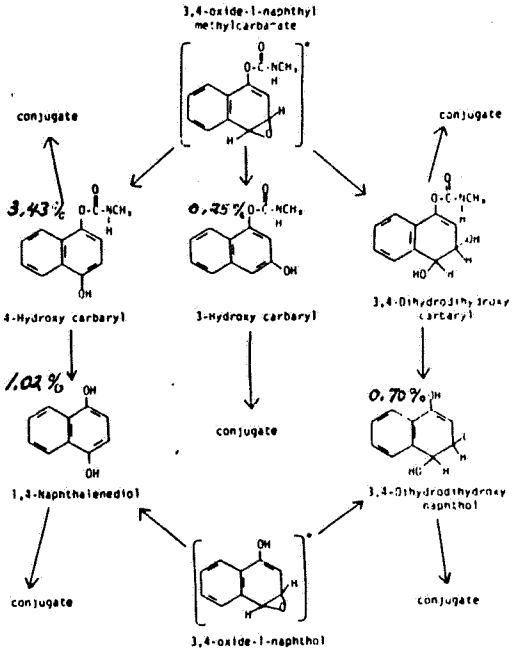


C-Position of ^{14}C label

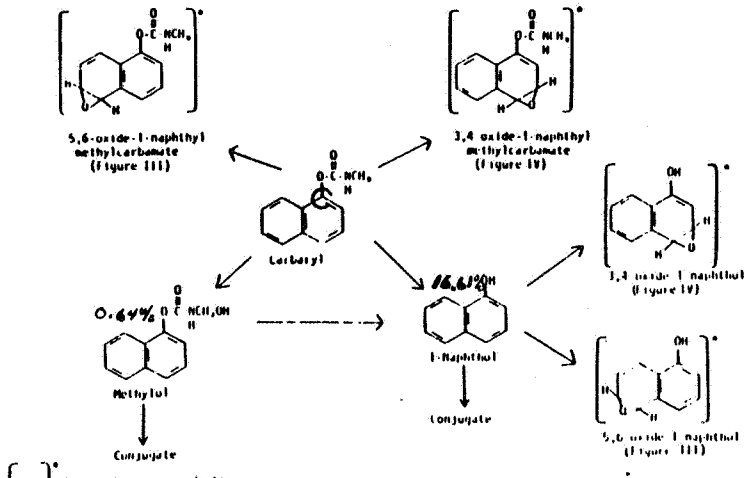
Metabolic Pathway of Carbaryl in the Dog, Part II



Metabolic Pathway of Carbaryl in the Dog, Part III

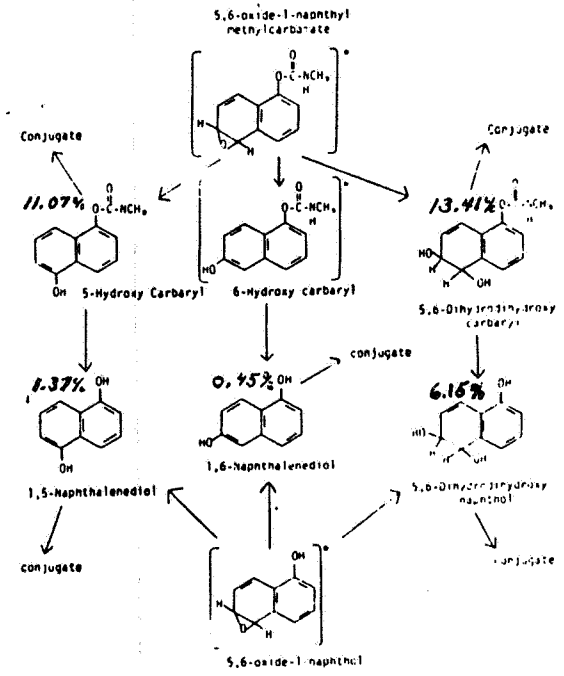


Metabolic Pathway of Carbaryl in the Rat, Part I

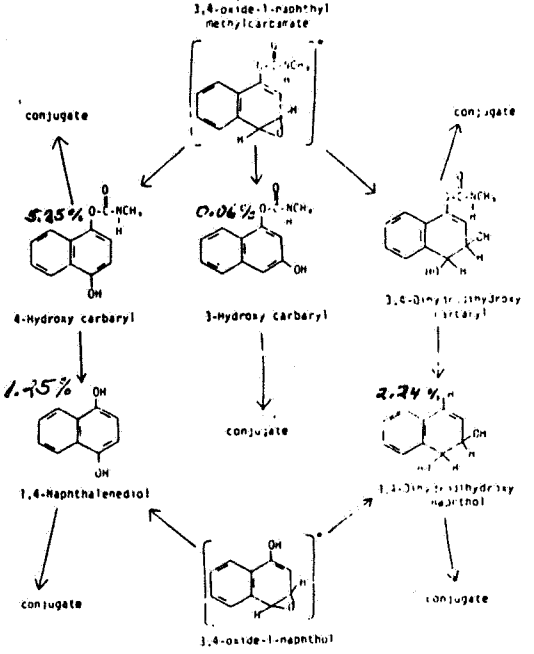


C-Position of ^{14}C label

Metabolic Pathway of Carbaryl in the Rat, Part II



Metabolic Pathway of Carbaryl in the Rat, Part III



Tox Chem No. 160 Carbaryl

File Last Updated _____

Current Data _____

Study/Lab/Study #/Date	Material	EPA Accession No.	LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Excretion - Dog; Carnegie-Mellon Inst. Res.; No. 40-104; September 16, 1977	naphthyl ^{14}C 99%	258271	2.5 mg/kg Oral Plasma and RBC cholinesterase decreased 20 to 30 percent within 2 hours, normal within 4 to 8 hours. Plasma ^{14}C-peaked within 2 hours. Urinary excretion within 2 hours - 30 to 35 percent, within 4 days - 33 to 43 percent Fecal recovery within 24 hours - 30 to 43 percent, within 4 days - 33 to 45 percent Tissue level by day 4, <1.0 percent of the dose. Levels tested 2.5 mg/kg and 25 mg/kg - Oral.		Minimum
Excretion - Dog; Carnegie-Mellon Inst. Res.; No. 40-105; September 16, 1977	naphthyl ^{14}C 99%	258271	1.0 mg/kg - IV Plasma and RCB cholinesterase decreased 30 to 50 percent within 2 minutes, normal within 4 hours. Plasma ^{14}C- t 1/2, 6 hours for female, 7 hours male. Urinary excretion within 24 hours - 56 to 61 percent within 4 days - 60 to 65 percent Fecal recovery within 24 hours - 6 to 12 percent within 4 days - 8 to 13 percent Tissue level by day 4-1 percent of the dose. Biliary excretion proposed as a significant route of elimination in the dog. Level tested 1.0 mg/kg		Minimum

Tox Chem No. 160 Carbaryl

File Last Updated _____

Current Data _____

Study/Lab/Study #/Date	Material	EPA Accession No.	LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Metabolism - Rat; Union Carbide No. 25051; May 11, 1978	naphthyl ^{14}C 98%	254104	2.5 mg/kg - Oral (Female rats only) Urinary excretion within 24 hours - 74.1 percent within 48 hours 93.2 percent Fecal recovery within 24 hours 1.8 percent within 48 hours 1.9 percent Levels tested 2.5 and 25 mg/kg Metabolites not identifed previously 1,5-naphthalenediol 1,6-naphthalenediol 3,4-dihydrodihydroxy naphthol 3-hydroxy-carbaryl Metabolic pathway proposed by hydrolysis, N-methyl oxidation, ring hydroxylation and conjugation.		Supplementary

Tox Chem No. 160 Carbaryl

File Last Updated _____ Current Data _____

Study/Lab/Study #/Date	Material	EPA Accession No.	LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Metabolism - Dog; Union Carbide No. 25050; May 11, 1978	naphthyl ^{14}C	254104	Metabolic pathway proposed: Hydrolysis, N-methyl oxidation, ring hydroxylation and conjugation. The highly polar fraction representing incomplete hydrolysis of the conjugates yielded (with acid) water-soluble products identified as possible mercapturic conjugates. These conjugates were not identified in the rat.		Minimum

87478:Little:HED/24:KENCO:4/14/86:4/22/86:SONJA:VO
92850:Little:HED/24/KENCO:4/21/86:5/1/86:SONJA