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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of Carbaryl, 1-Naphthyl N-methylcarbamate

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Attached is an overview of the carcinogenic potential of Carbaryl prepared for the weight-of-the evidence consideration by the Health Effects Division Carcinogenicity Peer Review Committee.

Carbaryl

1/32

TABLE OF CONTENTS

2

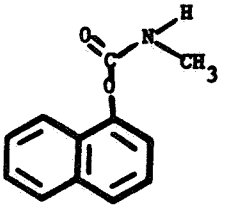
A. Material Reviewed

Data evaluation reports (DER) of studies submitted by Union Carbide and Rhone Poulenc. Statistical analysis by Lori Brunsman. Registration Standard of 1984 and 1988, Toxicology Chapter of the Registration Standard of August 10, 1983 (DER 003328) and February 22, 1988 (DER 006608), the Agency's Carcinogenic Assessment Group Report on Carbaryl, 1977, the Agency's Reproductive Effects Assessment Group, 1981 and Chernoff (Environmental Research center, RTP, NC) memo 1976.

B. Background Information:

Carbaryl with the trade name Sevin was registered by Union Carbide in 1958. Rhone Poulenc Ag Company and Makhteshim Agan Corporation are the two producers registered in the U.S.. Tolerances are established for residues of 1-naphthyl N-methyl carbamate in or on a wide range of raw agricultural commodities listed in 40 CFR 180.169. The insecticidal uses of carbaryl are registered for terrestrial food and nonfood, aquatic food and nonfood, greenhouse, forestry, and domestic indoor and outdoor use. The primary usage of this broad spectrum carbamate insecticide is agricultural; however, indoor and outdoor homeowner, plus livestock and poultry uses account for over 50% of the usage. (Registration Standard September 30, 1988).

The structure of carbaryl is shown below:



1-Naphthyl N-methylcarbamate

Chemical Abstracts Service Number: 63-25-2

Toxicology Chemical Number: 056801

Technical carbaryl is acutely, moderately toxic orally (LD_{50} 302 mg/kg) to low in toxicity by the dermal (LD_{50} > 2.0 g/kg) and inhalation (LC_{50} > 3.4 mg/L) route of exposure (DER 006608).

A notice of Determination Not to Initiate A Rebuttable Presumption Against Registration (RPAR) was published in Federal Register December 12, 1980. Carbaryl was under consideration for the RPAR process in 1967 primarily because two laboratory studies conducted in the late 1960's

indicated that carbaryl induced teratogenicity when administered in low doses to pregnant dogs. In addition to teratogenicity, the Agency was concerned that the use of carbaryl had potential carcinogenicity, mutagenicity, neurotoxicity and viral enhancement. The Agency concluded that the overall weight of evidence did not indicate that risk criteria warranting a RPAR had been met or exceeded.

C. Evaluation of the carcinogenicity Evidence

To determine the carcinogenic potential of carbaryl in experimental animals several studies were conducted in mice and rats prior to 1970. The studies, when considered individually, were deficient and of questionable value for drawing conclusions as to the carcinogenic potential of carbaryl. These studies were evaluated by the Agency's Carcinogenicity Assessment Group on September 28, 1977 with the conclusion that when these studies are considered collectively there is "no significant increase in tumor incidence in the treated groups as compared to the controls". The Scientific Advisory Panel was of the opinion (September 19, 1980) "that the current data are adequate to indicate that carbaryl is not carcinogenic". The Agency concluded, based on the available carcinogenic studies on carbaryl, that a rebuttable presumption was not warranted at this time (F.R. Vol. 45, No. 241, December 12, 1980).

Subsequently, the carcinogenicity data base on carbaryl was evaluated by HED (DER 007191) December 17, 1988, and in consort with the California Department of Food and Agriculture March 7, 1989 (DER 007190) with the conclusion that additional mouse and rat carcinogenicity studies should be performed.

1. Carcinogenicity Study in Mice

Hazleton Washington, Inc., Report No. HWA 656-138, dated December 17, 1991, MRID 421889-01.

a. Experimental Design

Four groups of 10 mice/sex/group for the 12 month sacrifice and 70 mice/sex/group for the 24 month sacrifice were fed dietary levels of 0,100, 1000, or 8000 ppm; equivalent to 15, 146 and 1249 mg/kg/day for males and 18, 181 and 1441 mg/kg/day for females. CRL:CD-1^{R} (ICR)BR mice were used in this study.

b. Adequacy of Dose Selection

The high dose was considered adequate for carcinogenicity testing based on clinical signs of toxicity, significantly decreased body weight in males (33%) and females (19%) during week 13, a significant decrease in erythrocyte hematology values in females, significant decrease in erythrocyte (males) and brain ChE activity in males and females and histopathology changes in males and females at this level.

Brain ChE of the high dose males and females was depressed during weeks 53 and 104 by 34 to 57% accompanied by a 30% decrease in erthrocytes ChE activity in males during week 53. At the mid dose brain ChE activity decreased by 13 to 18% during week 53 for males and females and during week 104 for females accompanied by a 23% decrease in erythrocyte ChE activity for males during week 53.

c. General Observations

Clinical signs of toxicity were observed for the high dose males and females to include tremors, hunched posture, languid appearance and urine stains. Eyes of females at the high dose were opaque in appearance during the last three weeks of the study.

During week 93, the animals in the 100 ppm group were fed what the study report refers to as a "non protocol specified compound" which caused the death of 17 animals (9 males and 8 females). This "compound" was identified as aldicarb in Table 4 of the preliminary report of adverse histopathological findings received from Rhone-Poulenc July 21, 1992 (DER 10092).

Mean body weight gain of the 8000 ppm level decreased during the 104-week study in males and females by 62-77% and 68-90%, respectively, accompanied by a 7-10% decrease in food consumption. There were significant decreases in HCT, HGB and RBC values in high dose females and males by weeks 53 and 104, respectively.

Absolute liver weights of the 8000 ppm females increased significantly by week 53. Relative liver weight of high dose males and females increased significantly at the 53 and 104 week intervals. Liver to brain weight ratio of the

8000 ppm males and females increased significantly by week 53. Kidney to body weight ratio increased significantly in the mid and high dose males at week 53 and in high dose males and females by week 104.

Statistical evaluation of mortality indicates no significant incremental changes with increasing doses of carbaryl in male and female mice. the following two tables summarize the statistical evaluation of mortality based upon the Thomas, Breslow and Gart computer program (Lori L. Brunsman, August 12, 1993).

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-26	27-52	53[i]	53-78	79-106[f]	Total
0	0/79[a]	3/79	10/76	13/66	16/53	32/69 (46)
100	2/80	2/78	10/76	9/66	26/57	39/70 (56)
1000	0/80	1/80	10/79	13/69	19/56	33/70 (47)
8000	1/80	1/79	10/78	12/68	26/56	40/70 (57)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[a]One accidental death at week 24, dose 0 ppm.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

7

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-26	27-52	53[i]	53-78	79-106[f]	Total
0	1/80	6/79	10/73	4/63	25/59	36/70 (51)
100	0/80	0/80	10/80	8/70	31/62	39/70 (56)
1000	0/80	3/79[a]	10/76	8/66	26/58	37/69 (54)
8000	6/79[b]	1/72[b]	10/71	12/61	17/49	36/68 (53)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[a]One accidental death at week 50, dose 1000 ppm.

[b]One accidental death each at weeks 11 and 48, dose 8000 ppm.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

8

d. Non-neoplastic lesions

Urinary bladder of the mid and high dose males and females was characterized by intracytoplasmic protein-like droplets (stained intensely eosinophilic)filling the cytoplasm of the superficial transitional epithelial cells during the interim and terminal sacrifice.

The increase incidence of chronic progressive nephropathy in the mid dose males and high dose males and females at the interim sacrifice was comparable between the test and control animals by the terminal sacrifice.

An increased incidence of extramedullary hematopoiesis and pigment in the spleens of the high dose males and females at the interim and terminal sacrifice was considered treatment related due to the decrease in erythrocyte values.

The increase incidence of unilateral and bilateral cataracts in the mid dose males and high dose males and females is summarized in the following table:

	Males			Females		
Group (ppm)	Unlist	Bilat	No. with Lesion	Unlist	Bilat	No. with Lesion
0	8	8	16	15	6	21
100	8	7	15	4	7	11
1000	11	7	18	11	4	15
8000	11	15	29	13	18	13

e. Neoplastic lesions of the kidney, liver and vascular system

Male mice had significant increasing trends in kidney tubule cell adenomas ($p<0.05$), carcinomas, (p0.05) and combined adenomas and/or carcinomas (,<0.05) and hemangiomas ($p<0.05$). There were also significant differences in the pair-wise comparisons of the 1000 ppm dose group with the controls for hemangiosarcomas and combined hemangiomas and/or hemangiosarcomas, and the 8000 ppm dose group

with the controls for combined kidney tubule cell adenomas and/or carcinomas and combined hemangiomas and/or hemangiosarcomas, all at $p<0.05$.

Female mice had significant increasing trends in hepatocellular adenomas, combined hepatocellular adenomas and/or carcinomas, hemangiosarcomas, and combined hemangiomas and/or hemangiosarcomas, all at $p<0.01$. There were also significant differences in the pair-wise comparisons of the 8000 ppm dose group with the controls for hepatocellular adenomas ($p<0.01$), combined hepatocellular adenomas and/or carcinomas ($p<0.01$), and hemangiosarcomas ($p<0.05$).

The following four tables (pages 11-14) summarize the tumor analysis for the kidney, liver and vascular neoplastic findings from feeding carbaryl at 100, 1000, and 8000 ppm to Crl:CD-1^{R} (ICR)BR mice for two years (Lori L. Brunsman, August 12, 1993).

f. Historical Control Data

The following table summarize the historical control tumor incidence (%) reported for the CD-1 mice at Hazleton Washington for April 84 to February 92.

	Spleen		Kidney		Liver	
	Male	Female	Male	Female	Male	Female
Hemangioma	0-3.1	0-2.0				
Hemangiosarcoma	0-4.2	0-6.1				
Tubule cell adenoma			0-1.7	0-0		
Tubule cell carcinoma			0-2.0	0-2.0		
Hepatocellular adenoma					0-14.9	0-6.0
Hepatocellular carcinoma					0-12	0-9.1

The incidence of tubule cell adenoma and carcinomas conbined (9%) in males and hepatocellular adenoma and carcinomas combined (16%) in females fed the 8000 ppm level exceeded the historical control incidence for these two tumors. The incidence of vascular hemangioma and hemangiosarcoma combined in males fed the 1000 and 8000 ppm level are 14 and 15%, respectively exceeding the historical control incidence for these tumors. For females fed the 8000 ppm level the incidence of vascular hemangioma and hemangiosarcomas combined (15%) exceeded the historical control incidence for these two tumors.

Male Blood Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	100	1000	8000
Hemangiomas (%)	0/66 (0)	1/66 (2)	1/69 (1)	3[a]/68 (4)
p =	0.046*	0.500	0.511	0.128
Hemangiosarcomas (%)	2/66 (3)	5/66 (8)	9[b]/69 (13)	7/68 (10)
p =	0.200	0.220	0.033*	0.090
Combined (%)	2/66 (3)	6/66 (9)	10/69 (14)	10/68 (15)
p =	0.063	0.137	0.019*	0.017*

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First hemangioma observed at week 72, dose 8000 ppm.

[b]First hemangiosarcoma observed at week 81, dose 1000 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Female Blood Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	100	1000	8000
Hemangiomas (%)	1/63 (2)	0/70 (0)	1[a]/66 (2)	0/61 (0)
p =	0.384	0.474	0.740	0.508
Hemangiosarcomas (%)	2/63 (3)	3/70 (4)	3/66 (5)	9[b]/61 (15)
p =	0.003**	0.550	0.522	0.024*
Combined (%)	3/63 (5)	3/70 (4)	4/66 (6)	9/61 (15)
p =	0.008**	0.609	0.526	0.056

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First hemangioma observed at week 93, dose 1000 ppm.

[b]First hemangiosarcoma observed at week 74, dose 8000 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Male Kidney Tubule Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	100	1000	8000
Adenomas (%)	0/66 (0)	0/66 (0)	0/69 (0)	3[a]/68 (4)
p =	0.016*	1.000	1.000	0.128
Carcinomas (%)	0/66 (0)	0/66 (0)	0/69 (0)	3[b]/68 (4)
p =	0.016*	1.000	1.000	0.128
Combined (%)	0/66 (0)	0/66 (0)	0/69 (0)	6/68 (9)
p =	0.000**	1.000	1.000	0.015*

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First adenoma observed at week 76, dose 8000 ppm.

[b]First carcinoma observed at week 105, dose 8000 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Female Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	100	1000	8000
Adenomas (%)	0/63 (0)	0/70 (0)	1/66 (2)	7[a]/61 (11)
p =	0.000**	1.000	0.512	0.006**
Carcinomas (%)	1/63 (2)	1/70 (1)	1/66 (2)	3[b]/61 (5)
p =	0.098	0.725	0.740	0.297
Combined (%)	1/63 (2)	1/70 (1)	2/66 (3)	10/61 (16)
p =	0.000**	0.725	0.518	0.004**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First adenoma observed at week 104, dose 8000 ppm.

[b]First carcinoma observed at week 74, dose 8000 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

14

2. Chronic Toxicity/Carcinogenicity Studies in Rats

a. Two-Year Feeding in Rats

Weil, C.S., et al., 1958, Special Reports on Chronic Oral feeding or Carbaryl to Rats. Mellon Institute report No. 21-88, submitted by Union Carbide Corp.

i. Experimental Design

Five groups of 20 CF-N rats/sex/group were fed dietary levels of 0, 50, 100, 200 or 400 ppm for two years.

ii. General Observations

After one year, cloudy swelling of the convoluted and loop tubules of the kidney was reported in males and females at the 400 ppm level. During the terminal sacrifice cloudy swelling of the hepatic cords about the central vein was observed in males at the 400 ppm level. In addition, a decrease in body weight was reported for males at the 400 ppm level. Concern for the cataractogenic property of 2-naphthol, a possible contaminant in the manufacture of 1-naphthyl N-methylcarbamate, was raised from the literature citation by Fitzhugh O.F. (Arch of Ophthalmal 41, p 572-582, 1949). No cataracts were observed in rats at any of the four dose levels when examined with a hand slit-lamp after 419 and 719 days of the study. Clinical chemistry and ChE activity were not determined.

Carbaryl was negative for carcinogenicity in this study. There was no effect on plasma, erythrocyte and brain ChE activity from feeding two groups of 5 rats/sex/group of 1500 and 2500 ppm for 96 days. However, in this 96-day study a decrease in body weight gain in females and a significant increase in male liver weight were reported for the 2500 ppm level. At the 1500 and 2500 ppm levels there was a significant increase in kidney weight of females accompanied by cloudy swelling of the kidney tubules (DER 003328).

The present RfD of 0.096 mg/kg/day is based on the 2-year rat feeding study NOEL of 9.6 mg/kg with a hundred-fold uncertainty factor (RfD for oral Exposure, February 3, 1988).

b. Two Year Feeding/Carcinogenicity Study in Rats Hazelton Washington, Inc., Report No. 656-139, December 12, 1991, MRID No. 421889-02.

i. Experimental Design

Four groups of 10 rats/sex/dose for the 53-week sacrifice and 70 rats/sex/dose for the 104-week sacrifice were fed dietary levels of 0, 250, 1500 and 7500 ppm equivalent to 10, 60 or 350 mg/kg/day respectively for male and 13, 79 or 486 mg/kg/day respectively for female Crl:CD® BR rats were used in this study.

To determine the extent of recovery from the 53-week study, additional dose levels of 10 rats/sex were fed 0 and 7500 ppm for 53 weeks then placed on control diet for 4 weeks. These animals were sacrificed during week 57 for complete necropsy, organ weights, clinical chemistry and histopathology.

ii. Adequacy of Dose Selection

The high dose was considered adequate for carcinogenicity testing based on a significant ($p<.05$) decrease in body weight during week 13 for males and females by 35 and 19% respectively as compared to controls. By weeks 52-53 plasma, erythrocyte and brain cholinesterase activities were significantly ($p<0.05$) decreased in males by 40%, 22% and 28%, respectively, and in females by 56%, 36% and 37%, respectively, as compared to controls.

By week 104 plasma, erythrocyte and brain ChE activities were significantly decreased in males by 42, 30 and 9%, respectively, and in females by 46, 38 and 22%, respectively.

In addition, by week 53 at the 1500 pmm level erythrocyte and brain ChE activities were decreased significantly in males by 19 and 10%, respectively, and in females by 26 and 13%, respectively. By week 105 erythrocyte and brain ChE activities in female rats fed the 1500 ppm level decreased significantly by 22 and 16%, respectively.

iii. General Observations

Clinical signs of toxicity observed for the high dose male and females include chromodacyorrhea, alopecia of the front limbs and urine stains. Body weight gain at the 7500 ppm level decreased by the 13, 52 and 104 week intervals in males to 60, 60 and 47% respectively, and in females by 48, 35 and 31%, respectively, of the control values. Body weight of females fed the 1500 ppm level decreased significantly at the 13, 53 and 105 week intervals by 26, 54 and 64%, respectively. Food consumption at the 7500 ppm level decreased by the 13, 52 and 102 week intervals in males and females to 83-86%, 79-84% and 88-96%, respectively of the control values.

The following table summarizes the incidence of unilateral and bilateral cataracts observed at week 104 of the study. A significant increase in the total incidence of cataracts in male and female rats at the high dose is apparent.

	Male			Female		
Group	Unilateral	Bilateral	Total	Unilateral	Bilateral	Total
1	3	1	4	2	1	3
2	5	1	6	2	0	2
3	6	1	7	4	0	4
4	9	3	12	5	5	10

Hematological findings were limited to decrease in leukocytes and lymphocyte in male and female rats at the 7500 ppm level. Significant increase in cholesterol and BUN were observed accompanied by significant decrease in AST, ALT and CK values in male and female rats at the 7500 ppm level. Cholinesterase activities of the recovery (plasma, RBC and brain) returned to control values when measured at week 56.

Survival in Rats Given Carbaryl in the Diet for 104 Weeks[a]

Week of Study	Males				Females			
	0	250	1500	7500	0	250	1500	7500
1	90/90	80/80	80/80	90/90	90/90	80/80	80/80	90/90
% mortality	0	0	0	0	0	0	0	0
13	90/90	79/80	80/80	90/90	90/90	80/80	80/80	89/90
% mortality	0	1	0	0	0	0	0	1
26	89/89	78/80	80/80	90/90	90/90	80/80	80/80	89/90
% mortality	0	2	0	0	0	0	0	1
52	85/88	77/80	79/80	86/90	84/90	80/80	79/80	88/90
% mortality	3	4	1	3	7	0	1	2
78	59/69	61/70	61/70	62/70	53/70	54/70	61/70	64/70
% mortality	14	13	13	11	24	23	13	9
104	41/68	31/69*	31/70*	43/70	23/70	28/70	28/70	48/70*
% mortality	40	55	56	39	67	60	60	31

* $p < 0.05$ vs control.

At week 53, organ weight of lung, spleen and kidneys were decreased in high dose male and female rats and organ/body weight ratios were also significantly increased at the high dose level. At terminal sacrifice, absolute weight of adrenal spleen, liver and kidneys were decreased in the high dose male and female rats, with significant increases in organ/body weight ratios for these organs in males and females.

iv. Non-Neoplastic Findings

Non-neoplastic histopathological findings were limited to the high dose for the liver, urinary bladder, lung, kidney, thyroid and sciatic nerve. An increase incidence of hepatocytic hypertrophy was observed in male and female rats accompanied by an increased incidence of eosinophilic foci of the liver in female rats. In the urinary bladder, an increased incidence of transitional cell hyperplasia in males and females was observed, along with increased incidence of squamous metaplasia, high mitotic index and atypia. An increase incidence of focal pneumonitis in males and females was reported. Increased incidence of transitional cell hyperplasia of the kidney was observed in males. An increased incidence of follicular cell hypertrophy was observed in males and females. Degeneration of the sciatic nerve was observed in males and females with increased incidence of degeneration of skeletal muscle.

Neoplastic Finding

Neoplastic histopahtological findings were limited to the high dose for the liver, urinary bladder, kidney and thyroid. A 10% increased incidence of liver adenoma was observed in female rats as compared to 1%, in the controls. Increased incidence of urinary bladder benign transitional cell papilloma was observed in males and females by 17 and 10%, respectively as compared to 0% in the controls for both sexes. Increased incidence of urinary bladder transitional cell carcinoma was observed in male and female rats by 15 and 9%, respectively as compared to 0% in the controls for both sexes. The single incidence of transitional cell carci- cinoma of the kidney in one male rat was considered treatment-related. Increased

The following table summarizes the incidence of neoplastic lesions in male and female rats fed carbaryl for 104 weeks

	MALES				FEMALES			
Dose (ppm)	0	250	1500	7500	0	250	1500	7500
Liver								
No. examined	71	70	70	71	70	70	70	70
Adenoma	1[b](1)[c]	1(1)	2(3)	1(1)	1(1)	0(0)	3(4)	7(10)
Urinary Bladder								
No. examined	70	69	69	71	69	69	69	69
Papilloma	0(0)	0(0)	0(0)	12(17)	1(1)	0(0)	0(0)	7(10)
Carcinoma	0(0)	0(0)	0(0)	11(15)	0(0)	0(0)	0(0)	6(9)
Kidney								
No. examined	70	69	70	71	70	70	70	70
Carcinoma	0(0)	0(0)	0(0)	1(2)	0(0)	0(0)	0(0)	0(0)
Thyroid								
No. examined	71	71	70	71	70	70	70	70
Adenoma	0(0)	2(3)	0(0)	8(11)	0(0)	0(0)	0(0)	1(1)
Carcinoma	0(0)	0(0)	0(0)	1(1)	1(1)	0(0)	0(0)	0(0)

b - number of rats with lesion ; c percent of rats with lesion

incidence of follicular cell adenoma of the thyroid of 11% as compared to 0% in the controls accompanied by a single incidence of thyroid follicular cell carcinoma was observed in the high dose males.

Historical Control Data

The following table summarizes the historical control tumor incidence (%) reported for Sprague Dawley rats at Hazelton Washington for March 1985 to May 92. Historical control data were not provided for the incidence of liver tumors in males or thyroid tumors in females.

	Males	Females
Liver		
Hepatocellular adenoma	-	0-6.3
Hepatocellular carcinoma	-	0-4.0
Thyroid		
Follicular cell adenoma	0-12	-
Follicular cell carinoma	0-8	-
Kidney		
Transitional cell papilloma	0-0	0-0
Transitional cell carcinoma	0-2.0	0-0
Urinary Bladder		
Transitional cell papilloma	0-1.1	0-1.4
Transitional cell carcinoma	0-1.4	0-0

The incidence of hepatocellular adenoma (0%) in females and thyroid follicular cell adenomas (11%) in males exceed the historical control values for these tumors, The incidence of urinary bladder transitional cell papilloma in males (17%) and females (10%) and carcinoma in males (15%) and females (9%) exceed the historical control values for these tumors. The single incidence of a kidney transitional cell carcinoma in one high dose male was within the historical control range, but considered treatment related due to the

"proliferative, changes present thoughout the urothelium in the high dose male".

D. Other Relevant Toxicity Data

1. Chronic Feeding Nonrodent

a. One Year Oral Toxicity in Dogs

Mellon Institute Report No. 21-89, October 3, 1958

i. Experimental Design

Four groups of 3 or 4 adults Basenji Cocker hybrid dogs/level, with a total of ten males and four females tested. The high level consisted of 4 males, no females. Oral doses were administered (gelatin capsule) at 0, 0.45, 1.8, Or 7.2 mg/kg five days a week for one year comparable to 25, 100 or 400 ppm).

ii. General Observation

No effects on body weight, food intake mortality, hematology, clinical chemistry, plasma or erythrocyte ChE, or liver and kidney weight were reported. Histopathology of the kidneys revealed diffuse cloudy swelling of the proximal convoluted and loop tubules at the 7.2 mg/kg level. These findings "were considered transitory and not related to carbaryl, but due to biological variability which was within the normal range for these dogs". The study does not satisfy the minimum data requirements for a nonrodent study and a replacement study was requested (DER 003328).

b. One-Year Oral Toxicity Study in Beagle Dogs

Hazelton Laboratories America, Inc. Report No. 400-715, March 18, 1987, MRID 401667-01. Five Week Subchronic Toxicity Study in Dogs, Hazleton Laboratories America, Inc. Report No. 656-152, March 28, 1991 MRID 420228-01.

i. Experimental Design

Four groups of 6 purebred beagle dogs/sex/group were fed dietary levels of 0, 125, 400, Or 1250 ppm for one year (DER 006401).

ii. General Observations

In the one-year feeding study a systemic NOEL of 400 ppm was established. The LOEL was 1250 ppm with a significant ($p<0.05$) decrease in body weight (50%), non-significant decrease in food consumption (23%) and a significant ($p<0.050$) decrease in albumin (11%) values at this level. The question of pathologic changes in the kidneys raised in the original dog study were addressed by HED pathologist, Dr. Kasza. His evaluation of this second dog study concluded that "compound-related changes in the urinary system in the present one-year dog study could not be established." A ChE NOEL was not determined in this study with a significant ($p<0.05$) decrease in plasma (23%) and brain (20%) ChE activity in female dogs at the 125 ppm level (DER 007086).

To derermine whether the marginal effects on cholinesterase activity at the 125 ppm level were reproducible, a 5-week subchronic feeding study was conducted at 20, 45 and 125 ppm. This 5 week dog feeding study was without affect on plasma, erythocyte or brain ChE activity. However, when considered with the one-year dog feeding study a NOEL of 45 ppm and a LEL of 125 ppm were demonstrated with a significant decrease in plasma (23%) and brain (20%) cholinesterase activity at the 125 ppm level (DER 009776).

2. Reproductive Toxicity

Mellon Institute, Report No. 36-65, August 31, 1972, "Comparative Study of Dietary Inclusion versus Stomach Intubation on Three Generations of Reproduction, and on Teratology and Mutagenicity" (MRID 00139647).

a. Experimental Design

For a comparison of the dietary vs intubation route of exposure five groups of 15 males and 25 females per group were dosed 5 days/week before and during mating, pregnancy and lactation for three generations. The dietary levels were 0, 7, 25, 100 or 200 mg/kg/day. The intubation levels were 0, 3, 7, 25 or 100mg/kg/day.

b. General Observation

Carbaryl was without effect on the reproductive indices of the rat when dosed by gavage or fed dietary levels up to 200 mg/kg/ day over three generations. In the dietary study the maternal LEL was 200 mg/kg/day with decrease body weight and increased in the average number of days from the first mating to birth of the litter. When administered by gavage the maternal LEL was 100 mg/kg/day with cholinergic signs of toxicity, decreased body weight and mortality. Fetotoxic LEL was 100 mg/kg/day with a decrease in viable fetuses in the F2a - F2b generations as well as a decrease in the number of pups born alive in the F1a - F2a and F2a - F3a generations.

3. Developmental Toxicity

Carbaryl was a candidate for the RPAR process primarily because of two teratology studies (Smalley, 1968 and Imming, 1969) which found carbaryl to be teratogenic when administered in low doses to pregnant beagle dogs. In addition, during the period between 1967 to 1979 the teratogenic potential of carbaryl was evaluated in the mouse, rat, gerbil, hamster, guinea pig, rabbit, swine, sheep and monkey. The Agency's determination not to initiate a RPAR was based on the weight of evidence of those studies which were valid and interpretable. Two general conclusions were drawn concerning the potential of carbaryl to affect mammalian development. The first is that the administration of carbaryl to pregnant animals (at sufficiently high dose levels and/or sufficient duration of treatment) may result in adverse effects to the embryo/fetus. Of those studies from which definite conclusions may be drawn, carbaryl has been shown to produce terata in the guinea pig, rabbit and dog and fetoxicity in the mouse, rat and gerbil. The second conclusion which may be arrived at is that these effects have generally occurred at dose levels which are toxic to the maternal animal. Adverse developmental effects have been seen at levels which resulted in maternal death in the guinea pig, cholinergic toxicity in the rabbit and weight loss in

the rat and mouse (the health status of the maternal gerbils was not given in the published study). The dog appears to be the only exception to this conclusion, and in this species the treated females had difficulty giving birth, a possible sign of carbryl-induced maternal toxicity. The quality of the two dog teratology studies did "not meet current scientific standards." The Agency concluded that "currently available data on carbaryl do not indicate that a rebuttable presumption on the basis of teratogenic and fetotoxic effects is warranted at this time. In the Agency's judgement, the extremely high doses of carbaryl used to elicit effects in the developing organism, coupled with the positive correlation of maternal and fetal toxicity in the multiple species tested (the dog being a possible exception), indicate that carbaryl would not constitute a potential human teratogenic or reproductive hazard under proper environmental usage." Carbaryl was returned to the registration process with Federal Register Notice Vol. 45, No. 241, December 12, 1980.

Questions have persisted for the last twenty-five years relative to the potential of carbaryl to elicit developmental effects. The dog teratology studies, while seriously flawed, suggested that the dog may be the most sensitive species. A new developmental study in the dog may confirm the species specificity of the dog to carbaryl and would no provide any additional information.

An additional dog teratology was requested in the Registration standard of 1984. Subsequently, the Agency determined that there was little scientific support for the requirement of a repeat dog teratology study. These results cannot be extrapolated to other species. The dog is not a species that is recommended for teratology testing by any regulatory Agency and is considered a poor model on which to base a teratology decision with regard to humans. The agency has determined that carbaryl has not demonstrated teratogenic potential to humans in any of the other approximately 24 animals teratology studies, including the monkey (Toxicology Chapter of the Registration Standard, February 22, 1988, DER006608).

The Peer Review Committee for Reproductive and Developmental Toxicity (R&D Tox.) June 16, 1989, requested a new dog teratology study. Rhone Poulenc requested a data waiver for a dog teratology study August 9, 1991. Subsequently, the FIFRA 88 Review Committee of September 17, 1992 recommended that the

Peer Review Committee for R&D Toxicity reconsider this data waiver request (Tox. Rev. October 3, 1992). On December 8, 1992 several members of the R&D Toxicity Peer Review Committee met and concluded that a dog teratology study is required (Tox. Rev. January 13, 1993). Subsequently, this data waiver request was the subject of a mini-review of the R&D Toxicity Peer Review Committee June 17, 1993 with the conclusion that the data waiver request by Rhone Pouenc is reasonable; thus a dog teratology study is not required (Tox. Rev. June 30, 1993).

The mammalian studies cited to assess the potential developmental toxicity of carbaryl have not been subject to current acceptance criteria for developmental and reproductive guideline data requirements (158.135) and may not conform to the Agency's standards for testing. No new developmental studies have been submitted for review.

Of the numerous studies on carbaryl that are negative for developmental effects the monkey, which is considered to be a more appropriate model for an evaluation of teratogenic potential to human, is cited in support of the RfD. This study was conducted with 16 pregnant Rhesus monkeys/group of control, vehicle control, 0.2, 2.0 and 20 mg/kg dosed twice daily by gavage during days 20 to 38 of gestation. The developmental NOEL is 20 mg/kg.

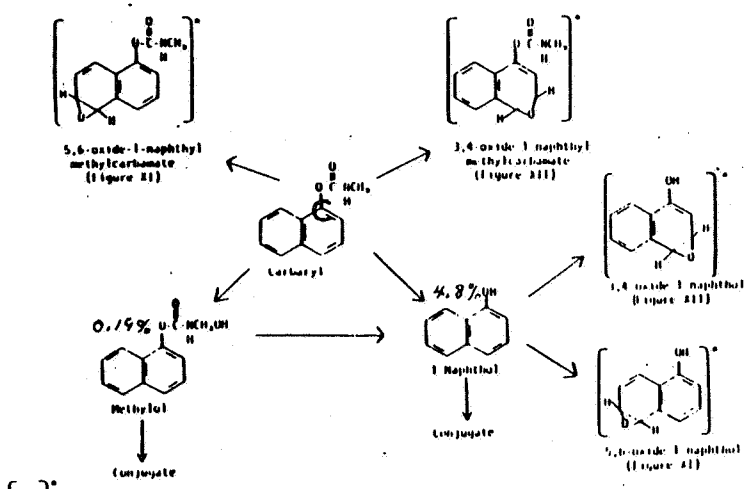
4. Metabolism

Metabolism of carbaryl has been investigated in numerous species including the rat, guinea pig, dog, pig, sheep, monkey and humans. These studies have not been subjected to current acceptance criteria for metabolism guideline data requirements (158.135) and may not conform to the Agency's standard for testing.

Although the metabolism of carbaryl has been studied in numerous mammalian species, including man, the Agency in the Carbaryl Registration standard of 1984 requested a metabolism study in rats and dog to clarify the claim that metabolism of carbaryl in the dog is unique and may account for the teratogenicity reported in two dog teratology studies. In response to the Registration Data Call-In, metabolism studies in the rat and dog were reviewed (DER 0052112) May 15, 1986.

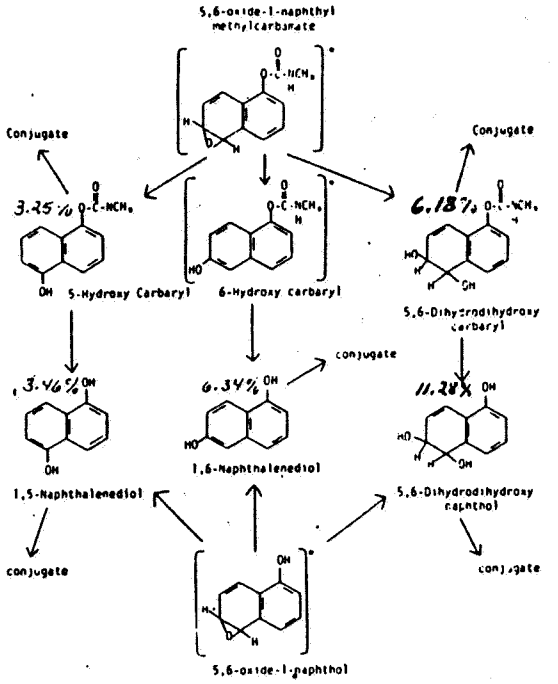
In these studies female rats, dosed orally with 1-napthyl-14_C-carbaryl in corn oil at 2.5 mg/kg, eliminated 74% of the dose in the urine and 1.8% in the

Metabolic Pathway of Carbaryl in the Dog, Part I

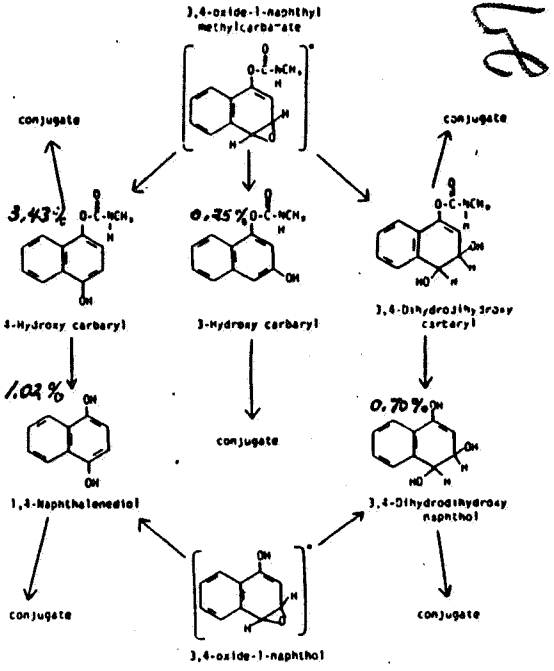


C-Position of ^{14}C label

Metabolic Pathway of Carbaryl in the Dog, Part II

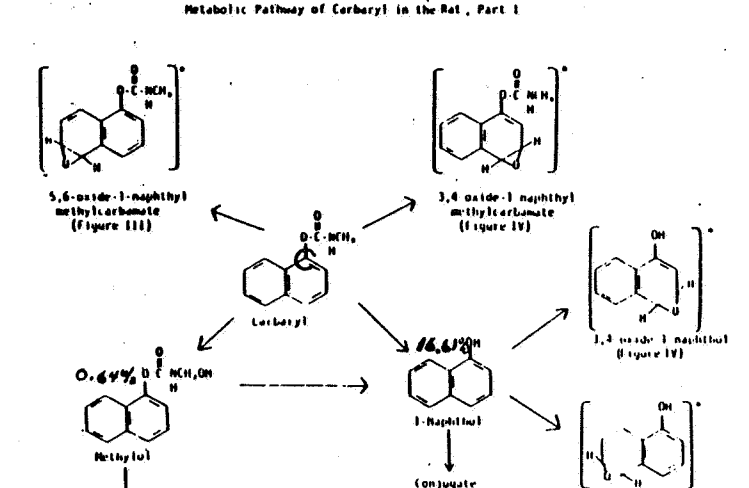


Metabolic Pathway of Carbaryl in the Dog, Part III



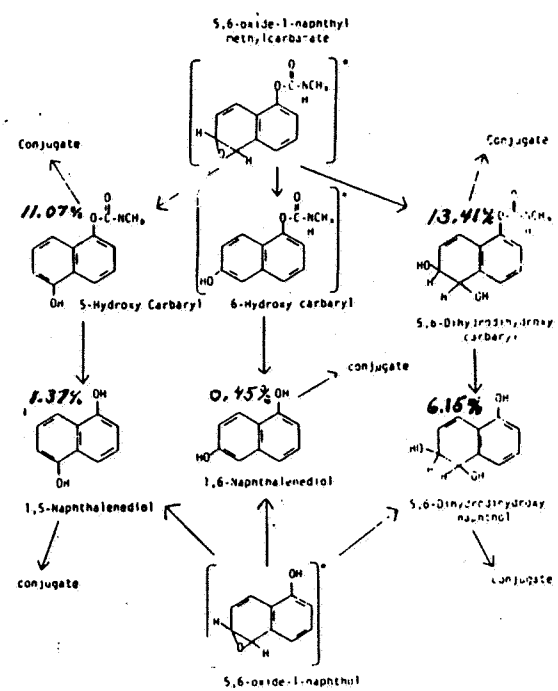
58

Metabolic Pathway of Carbaryl in the Rat, Part I



C-Position of ^{14}C label

Metabolic Pathway of Carbaryl in the Rat, Part II



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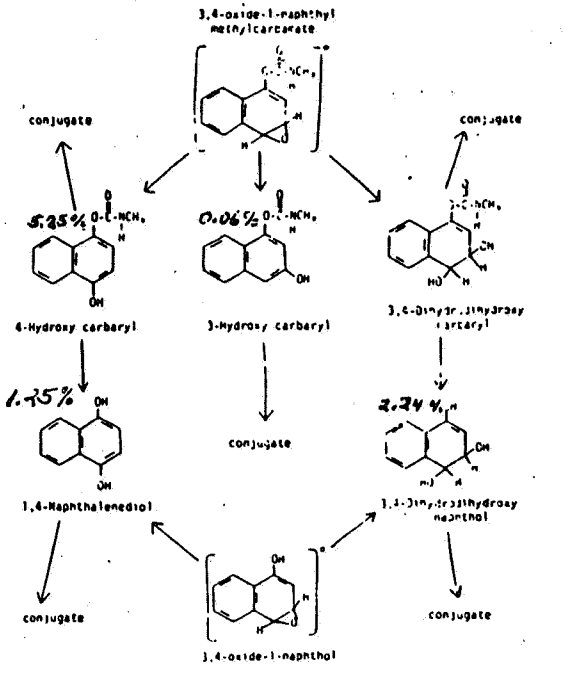
Metabolic Pathway of Carbaryl in the Rat, Part III



feces within 24 hours with 93% of the dose accounted for in urine and feces within 48 hours. For comparison, male and female beagle dogs dosed orally with 1-napthyl-14^{C}-carbaryl in gelatin capsules at 2.5 mg/kg eliminated 30-35% of the dose in the urine and 30-43% in the feces within 24 hours with 32-43% of the dose accounted for in the urine and 33-45% in the feces by day 4. Based on the existing rat and dog metabolism studies the proposed metabolic pathway of carbaryl, on the following page, is qualitatively similar for these two species (DER 005112).

These studies were deficient for the rat and acceptable for the dog. Data reviewed in these studies have not clarified whether there are species differences or similarities which can be identified quantitatively due to the physical form and vehicle used for oral administration of the test material. Rhone Poulenc, letter of November 12, 1991, is committed to provide an acceptable rat metabolism study.

5. Mutagenicity

The numerous mutagenicity studies conducted during the period of 1965 to 1978 were also reviewed as with the carcinogenicity and teratogenicity studies to determine whether a RPAR should be issued for carbaryl. The Agency reviewed these studies collectively and determined "that carbaryl is not a potent mutagen in the reported studies and probably acts as a weak mutagen" (Reproductive Effects Assessment Group Report No. EPA-600/6-81-001 January 1981). The mutagenicity data base on carbaryl was reviewed in consort with the California Department of Food and Agriculture March 7, 1989 (DER 007190) with a divergence opinion on the adequacy of the mutagenicity data base on carbaryl. Subsequently, four mutagenicity studies were submitted in response to a requirement by California Department of Food and Agriculture. These studies were reviewed (DER 008115 and 008450). Three of the four were acceptable and satisfy the guideline data requirements. Carbaryl was not mutagenic in the Salmonella typhimurium/Mammalian or the Unscheduled DNA Synthesis Assay, but was clastogenic in the Cultured Cytogenetic Assay CHO Cells with metabolic activation.

E. Structure-Activity Relationships

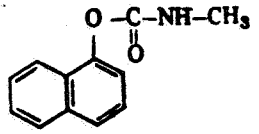
Carbaryl is structurally related to other carbamate insecticides possessing the carbamic acid ($HO-\overset{O}{\overset{\|}{C}}-NH_2$) moiety. As a N-methyl carbamate it is expected to behave biologically similar to other structurally related carbamates. The limited information provided by the toxicology one-liners indicate the following carcinogenic concerns for these N-methyl carbamates. Structural analogues of carbaryl are presented on the following page.

Aldicarb - No carcinogenic potential in mice or rats. Not mutagenic in the test systems assayed.

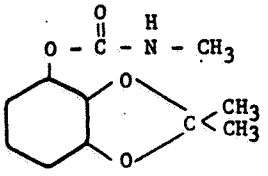
Bendiocarb - No carcinogenic potential in mice or rats. Positive, with increased chromosomal aberrations with activation and negative without S-9 activation.

Carbofuran - No carcinogenic potential in mice or rats. Positive in two separate studies in Ames Salmonella-Strain TA 1535 without activation. In two other Ames assays, a positive response was induced in strain TA 100 with and without activation, and a positive response in TA 98 and TA 100 with activation. In the mouse

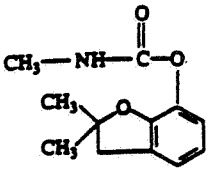
Structural Analogues of Carbaryl



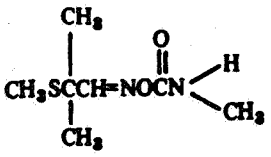
Carbaryl



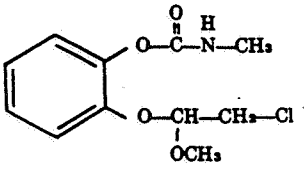
Bendiocarb



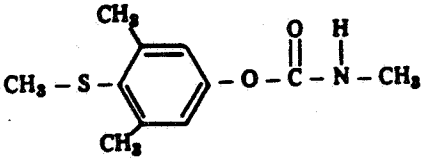
Carbofuran



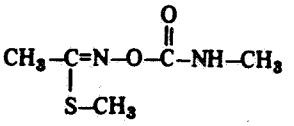
Aldicarb



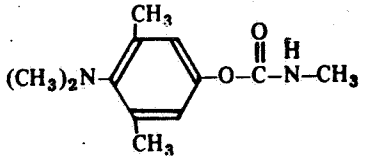
Cloethocarb



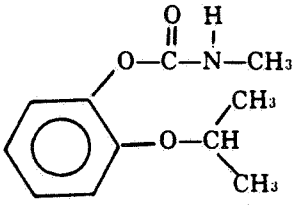
Methiocarb



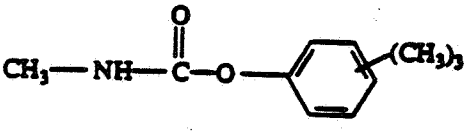
Methomyl



Mexacarbate



Propoxur



Trimethacarb

lymphoma assay a positive response was induced with and without activation.

Cloethocarb - No carcinogenic potential in mice or rats. Not mutagenic in the test systems assayed.

Methiocarb - No carcinogenic potential in rats; mouse data are not available. Not mutagenic in the test systems assayed.

Methomyl - No carcinogenic potential in mice or rats. Not mutagenic in the test systems assayed.

Mexacarbate - No carcinogenic potential in mice or rats. Positive in Chinese Hamster Ovary Cells with activation.

Propoxur - Classified as Group B2 carcinogen based on bladder tumors in male and female rats at 5000 ppm. In addition, carcinoma of uterus was reported in female rats at 5000 ppm. Not mutagenic in the test systems assayed.

Trimethacarb - No carcinogenic potential in mice or rats. Positive, with increase in chromosomal aberrations with and without activation.

E. Weight of Evidence Considerations

The Committee is requested to consider the following facts in the weight-of-the-evidence determination of the carcinogenic potential of carbaryl.

1. Male mice had significant increasing trends in kidney tubule cell adenomas ($p<0.05$), and carcinomas, ($p<0.05$). There were also significant differences in the pair-wise comparisons of the 1000 ppm dose group with the controls for hemangiosarcomas and combined hemangiomas and/or hemangiosarcomas, and the 8000 ppm dose group with the controls for combined kidney tubule cell adenomas and/or carcinomas and combined hemangiomas and/or hemangiosarcomas, all at $p<0.05$.

2. Female mice had significant increasing trends in hepatocellular adenomas, combined hepatocellular adenomas and/or carcinomas, hemangiosarcomas, and combined hemangiomas and/or hemangiosarcomas, all at $p<0.01$. There were also significant differences in the pair-wise comparisons of the 8000 ppm dose group with the controls for hepatocellular adenomas ($p<0.01$), combined hepatocellular adenomas and/or carcinomas ($p<0.01$), and hemangiosarcomas ($p<0.05$).

3. In the rat, neoplastic histopathological findings were limited to the high dose for the liver, urinary bladder, kidney and thyroid.

   a. A 10% increased incidence in liver adenoma was observed in female rats as compared to 1% in the controls.

   b. Increased incidence of urinary bladder benign transitional cell papilloma was observed in males and females by 17 and 10% respectively as compared to 0% in the controls for both sexes.

   c. Increased incidence of urinary bladder transitional cell carcinoma was observed in male and female rats by 15 and 9%, respectively as compared to 0% in the controls for both sexes.

   d. The single incidence of transitional cell carcinoma of the kidney in one male rat was considered treatment-related.

   e. Increased incidence of follicular cell adenoma of the thyroid of 11% as compared to 0% in the controls accompanied by a single incidence of thyroid follicular cell carcinoma was observed in the high dose males.

4. Carbaryl was not mutagenic in the Salmonella typhimurium/Mammalian Assay or the Unscheduled DNA Synthesis Assay, but was clastogenic in the Cultured Cytogenetic Assay in CHO Cells with metabolic activation.

5. Carbaryl is structurally related to Propoxur, a methyl carbamate, shown to cause bladder tumors in male and female rats.