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

Office of Prevention, Pesticides
and
Toxic Substances

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

May 1, 2002

TXR: 0050582

MEMORANDUM

SUBJECT: CARBARYL - Review of three dermal toxicity studies in rats (MRIDs 45630601-4563603)

PC Code: 056801
DP Barcode: D281853
Submission: S612723

FROM: Virginia A. Dobozy, V.M.D., M.P.H., Veterinary Medical Officer
Reregistration Branch I, Health Effects Division (7509C)

Virginia A Dobozy 5/1/02

THRU: Whang Phang, Ph.D., Branch Senior Scientist
Reregistration Branch I, Health Effects Division (7509C)

TO: Betty Shackleford/Anthony Britten
Special Review and Reregistration Division (7508C)

Action Requested: Review above referenced studies

Recommendation: None of the studies were conducted according to the dermal toxicity guidelines (OPPTS 870.3200); however, RRB1 determined the study with technical material (MRID 45630601 is acceptable (non-guideline) and can be used for risk assessment. The other two studies were classifed as unacceptable (non-guideline) and cannot be used for risk assessment. The Executive Summaries for the studies follow; the DERs are attached.

1) MRID 45630601

Citation: Austin, E.W. (2002). 4 Week Repeated-Dose Dermal Toxicity Study with Carbaryl Technical in Rats. Covance Laboratories, Madison, WI. Laboratory Study Identification Number 6224-268, March 8, 2002. MRID 45630601. Unpublished.

EXECUTIVE SUMMARY: In a non-guideline four-week dermal toxicity study (MRID 45630601), Carbaryl Technical (99.49% a.i., Lot 211048078) was applied to the shaved skin of 10 Crl: CD (SD)IGS BR rats/sex/dose at dose levels of 0, 20, 50 or 100 mg/kg bw/day, 6 hours/day for 5 days/week during a 4-week period. The parameters measured included the following: clinical observations, body weight, body weight gain, food consumption, RBC and brain cholinesterase and signs of dermal irritation.

There was no treatment-related effect on mortality, clinical observations, body weight or dermal irritation. The only statistically significant body weight gain changes were a decrease (27%) in the 100 mg/kg/day males during Days 5 to 12 and an increase (37%) in 50 mg/kg/day males during Days 19 to 26. However, there were non-significant decreases in the 100 mg/kg/day males at Days -3 to 5 (16%), 12 to 19 (17%) and -3 to 26 (12%) which are considered toxicologically significant.

The only statistically significant decreases in food consumption were in the 50 mg/kg/day females on Days 12 to 19 and 50 and in the 100 mg/kg/day females on Days 19 to 26. The effects are not considered treatment-related as there was no dose-response and the decreases were minimal (9% and 8% in the 50 and 100 mg/kg/day groups, respectively).

RBC cholinesterase was measured before dosing on Day -4 and on Days 1, 8, 15 and 22. The only statistically significant effects were in the 100 mg/kg/day males at Days 8 (11% decrease) and 22 (13%). Using the repeated measures statistical test, there were also significant decreases in the 50 and 100 mg/kg/day females (11% and 10%, respectively) on Day 22. These effects were determined to be not toxicologically significant because they were inconsistent.

Measurements were also performed within 1 hour after test material removal on Days 5, 12, 19, and 26. Statistically significant decreases were observed in the 50 mg/kg/day (12% decrease) and 100 mg/kg/day (15%) males on Day 5 and in the 100 mg/kg/day males on Days 12 (21%) and 19 (16%). Using the repeated measures statistical test, there was also a significant decrease (10%) in the 50 mg/kg/day males on Day 12. In females, statistically significant decreases were observed in the 50 and 100 mg/kg/day groups on Days 5 (13% and 12%, respectively) and Day 12 (20% and 13%, respectively).

Brain cholinesterase was statistically significantly decreased in the 50 mg/kg/day males (15%) and in the 100 mg/kg/day males (15%) and females (24%). There was also a non-significant decrease in the 50 mg/kg/day females (9%).

The systemic LOAEL is conservatively established at 50 mg/kg/day based on statistically

significant decreases in RBC cholinesterase in males and females and brain cholinesterase in males. The systemic NOAEL is 20 mg/kg/day.

The dermal LOAEL was not established. The dermal NOAEL was 100 mg/kg/day.

This 4-week dermal toxicity study in the rat is **acceptable (non-guideline).** The study was intended to establish endpoints for short-term and intermediate-term occupational and residential postapplication dermal exposure. Although the study does not meet guideline requirements, it is useful for risk assessment for the following reasons: 1) in all oral studies in which cholinesterase was measured, it was the most sensitive endpoint; therefore, other guideline parameters would most likely not establish a lower LOAEL; 2) plasma cholinesterase was not measured; however, in all the oral studies in rats, all three compartments (plasma, RBC and brain) were affected at the same dose level. Therefore, it is likely that plasma cholinesterase would not have been inhibited at a lower level, especially given the minimal effects on RBC and brain cholinesterase.

2) MRID 45630602

Citation: Austin, E.W. (2002). 4 Week Repeated-Dose Dermal Toxicity Study with SEVIN® XLR Plus in Rats. Covance Laboratories, Madison, WI. Laboratory Study Identification Number 6224-267, March 7, 2002. MRID 45630602. Unpublished

SPONSOR: Aventis CropScience

EXECUTIVE SUMMARY: In a non-guideline four-week dermal toxicity study (MRID 45630602), Sevin® XLR Plus (44.82% a.i., Lot 60618902) was applied to the shaved skin of 8 Crl: CD (SD)IGS BR rats/sex/dose at dose levels of 0, 20, 50 or 100 mcL/kg bw/day (0, 9.6, 24 or 48 mg/kg/day), 6 hours/day for 5 days/week during a 4-week period. The parameters measured included the following: clinical observations, body weight, body weight gain, food consumption, RBC cholinesterase and signs of dermal irritation.

There were no treatment-related effects on clinical observations or body weight or evidence of dermal irritation. Females treated at 100 mcL/kg/day gained 167%, 65%, 144% and 40% of control values for Days -3 to 5, 5 to 12, 12 to 19 and 19 to 26, respectively. Overall (Days -3 to 26) body weight gain was not affected. It is difficult to determine if there was a treatment-related effect immediately after dosing as the first body weight measurement was not done until Day 5 of dosing. Although not statistically significant, there does appear to be a treatment-related decrease on the body weight gain (Days 5 to 12) of females treated at 100 mcL/kg/day.

RBC cholinesterase was measured before dosing on Week -1 and on Days 1, 8, 15 and 22. There was no evidence of a treatment-related effect at these time periods. Measurements were also performed within 1 hour after test material removal on Days 5, 12, 19, and 26. In males, the only statistically significant difference from control values was on Day 26 in the animals dosed at 50 mcL/kg/day; the decrease was only 8%. Although not statistically significant, the RBC cholinesterase on Day 12

in males treated at 100 mcL/kg/day was decreased by 10%. In females treated at 100 mcL/kg/day, values were significantly decreased on Day 5 (12%), Day 12 (12%) and non-significantly decreased on Days 19 (5%) and Day 26 (7%). There were also significant decreases in the 50 mcL/kg/day females on Days 19 (9%) and 26 (14%) and in the 20 mg/kg/day group on Day 26 (10%). Although statistically significant, the RBC cholinesterase decreases are not judged to be toxicologically significant due to the small magnitude of the effect and the lack of a dose-response on Days 19 and 26.

The systemic LOAEL in females was 100 mcL/kg/day (48 mg/kg/day) based on decreased body weight gain. The systemic NOAEL was 50 mcL/kg/day (24 mg/kg/day). The systemic LOAEL in males was not established. The systemic NOAEL was 100 mcL/kg/day (48 mg/kg/day).

The dermal LOAEL was not established. The dermal NOAEL was 100 mcL/kg/day (48 mg/kg/day).

This 4-week dermal toxicity study in the rat is **unacceptable (non-guideline)**. The study was intended for use in the short-term and intermediate-term occupational and residential handler risk assessments for the liquid formulations of carbaryl. It is considered unacceptable and **not upgradeable** because RBC cholinesterase results were inconsistent and plasma and brain cholinesterase were not measured. In another dermal toxicity study (MRID 45630601), brain cholinesterase inhibition was the most sensitive and reliable endpoint. Determination of cholinesterase inhibition in all three compartments would have helped define the effect level.

3) MRID 45630603

Citation: Austin, E.W. (2002). 4 Week Repeated-Dose Dermal Toxicity Study with SEVIN® 80S in Rats. Covance Laboratories, Madison, WI. Laboratory Study Identification Number 6224-266, March 8, 2002. MRID 45630603. Unpublished.

EXECUTIVE SUMMARY: In a non-guideline four-week dermal toxicity study (MRID 45630603), Sevin® 80S (80.07% a.i., Lot C8I168025A) was applied to the shaved skin of 8 Crl: CD (SD)IGS BR rats/sex/dose at dose levels of 0, 20, 50 or 100 mg/kg bw/day, 6 hours/day for 5 days/week during a 4-week period. The parameters measured included the following: clinical observations, body weight, body weight gain, food consumption, RBC cholinesterase and signs of dermal irritation.

There was no treatment-related effect on mortality, clinical observations, body weight or dermal irritation. Body weight gain (relative to control values) in the 100 mg/kg/day males was highly variable between time periods. There were non-significant decreases of 15% and 20% on Days -3 to 5 and 19 to 26, respectively but increases of 9% and 53% were observed on Days 5 to 12 and 12 to 19, respectively. Since body weight was not measured at treatment initiation, it is difficult to determine if there was an effect during the first time period. However, food consumption was significantly decreased by 12% on Days -1 to 5 in this group, which correlates with an initial

treatment-related effect. Therefore, the decrease in body weight gain in the 100 mg/kg/day males is considered treatment-related.

RBC cholinesterase was measured before dosing on Week -1 and on Days 1, 8, 15 and 22. Statistically significant decreases were observed in the 50 and 100 mg/kg/day females on Day 8 (10% and 12%, respectively). These effects are not considered toxicologically significant given the inconsistency of the findings. Measurements were also performed within 1 hour after test material removal on Days 5, 12, 19, and 26. In males, statistically significant decreases were observed in animals treated at 50 mg/kg/day on Days 12 (10%), 19 (13%) and 26 (8%). In males treated at 100 mg/kg/day, there were significant decreases on Days 12 (20%), 19 (19%) and 26 (19%). Although not statistically significant, there was also a 12% decrease on Day 5 in this group. In females, statistically significant decreases were observed in animals treated at 50 mg/kg/day on Days 12 (16%) and 19 (12%). Using the repeated measures ANOVA test, there was also a significant decrease on Day 5 (12%) in this group. In females at 100 mg/kg/day, there were significant decreases on Days 12 (18%) and 19 (15%) and Day 26 (15%).

The systemic LOAEL is 50 mg/kg/day based on statistically significant decreases in RBC cholinesterase in males and females. The systemic NOAEL is 20 mg/kg/day.

The dermal LOAEL was not established. The dermal NOAEL was 100 mg/kg/day.

This 4-week dermal toxicity study in the rat is **unacceptable (non-guideline)**. The study was intended for use in the short-term and intermediate-term occupational and residential handler risk assessments for the solid formulations of carbaryl. It is considered unacceptable and not upgradeable because only RBC cholinesterase was measured. In the dermal toxicity study with the technical chemical (MRID 45630601), brain cholinesterase inhibition was the most sensitive and reliable endpoint. While this study does support the RBC cholinesterase effects in MRID 45630601, the lack of plasma and brain cholinesterase measurements makes the study unacceptable for use in risk assessment.

[CARBARYL/PC Code 056801]

EPA Reviewer: Virginia A. Dobozy, VMD, MPH
Reregistration Branch I, Health Effects Division (7509C)
Branch Senior Scientist: Whang Phang, PhD
Reregistration Branch I, Health Effects Division (7509C)
Secondary Reviewer: William Sette, PhD
Toxicology Branch, Health Effects Division (7509C)

Signature: Virginia a. Dobozy
Date 4/9/02
Signature: Whang Phang
Date 4/9/02
Signature: William Sette
Date 4-9-02

DATA EVALUATION RECORD

TXR#: 0050582

STUDY TYPE: Four-Week Dermal Toxicity - rat

PC CODE: 056801

DP BARCODE: D281853
SUBMISSION NO.: S612723

TEST MATERIAL (PURITY): Carbaryl Technical (99.49% a.i.)

SYNONYMS: 1-naphthyl methylcarbamate

CITATION: Austin, E.W. (2002). 4 Week Repeated-Dose Dermal Toxicity Study with Carbaryl Technical in Rats. Covance Laboratories, Madison, WI. Laboratory Study Identification Number 6224-268, March 8, 2002. MRID 45630601. Unpublished.

SPONSOR: Aventis CropScience

EXECUTIVE SUMMARY:

In a non-guideline four-week dermal toxicity study (MRID 45630601), Carbaryl Technical (99.49% a.i., Lot 211048078) was applied to the shaved skin of 10 Crl: CD (SD)IGS BR rats/sex/dose at dose levels of 0, 20, 50 or 100 mg/kg bw/day, 6 hours/day for 5 days/week during a 4-week period. The parameters measured included the following: clinical observations, body weight, body weight gain, food consumption, RBC and brain cholinesterase and signs of dermal irritation.

There was no treatment-related effect on mortality, clinical observations, body weight or dermal irritation. The only statistically significant body weight gain changes were a decrease (27%) in the 100 mg/kg/day males during Days 5 to 12 and an increase (37%) in 50 mg/kg/day males during Days 19 to 26. However, there were non-significant decreases in the 100 mg/kg/day males at Days -3 to 5 (16%), 12 to 19 (17%) and -3 to 26 (12%) which are considered toxicologically significant.

The only statistically significant decreases in food consumption were in the 50 mg/kg/day

females on Days 12 to 19 and 50 and in the 100 mg/kg/day females on Days 19 to 26. The effects are not considered treatment-related as there was no dose-response and the decreases were minimal (9% and 8% in the 50 and 100 mg/kg/day groups, respectively).

RBC cholinesterase was measured before dosing on Day -4 and on Days 1, 8, 15 and 22. The only statistically significant effects were in the 100 mg/kg/day males at Days 8 (11% decrease) and 22 (13%). Using the repeated measures statistical test, there were also significant decreases in the 50 and 100 mg/kg/day females (11% and 10%, respectively) on Day 22. These effects were determined to be not toxicologically significant because they were inconsistent.

Measurements were also performed within 1 hour after test material removal on Days 5, 12, 19, and 26. Statistically significant decreases were observed in the 50 mg/kg/day (12% decrease) and 100 mg/kg/day (15%) males on Day 5 and in the 100 mg/kg/day males on Days 12 (21%) and 19 (16%). Using the repeated measures statistical test, there was also a significant decrease (10%) in the 50 mg/kg/day males on Day 12. In females, statistically significant decreases were observed in the 50 and 100 mg/kg/day groups on Days 5 (13% and 12%, respectively) and Day 12 (20% and 13%, respectively).

Brain cholinesterase was statistically significantly decreased in the 50 mg/kg/day males (15%) and in the 100 mg/kg/day males (15%) and females (24%). There was also a non-significant decrease in the 50 mg/kg/day females (9%).

The systemic LOAEL is conservatively established at 50 mg/kg/day based on statistically significant decreases in RBC cholinesterase in males and females and brain cholinesterase in males. The systemic NOAEL is 20 mg/kg/day.

The dermal LOAEL was not established. The dermal NOAEL was 100 mg/kg/day.

This 4-week dermal toxicity study in the rat is **acceptable (non-guideline)**. The study was intended to establish endpoints for short-term and intermediate-term occupational and residential postapplication dermal exposure. Although the study does not meet guideline requirements, it is useful for risk assessment for the following reasons: 1) in all oral studies in which cholinesterase was measured, it was the most sensitive endpoint; therefore, other guideline parameters would most likely not establish a lower LOAEL; 2) plasma cholinesterase was not measured; however, in all the oral studies in rats, all three compartments (plasma, RBC and brain) were affected at the same dose level. Therefore, it is likely that plasma cholinesterase would not have been inhibited at a lower level, especially given the minimal effects on RBC and brain cholinesterase.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Carbaryl Technical
   Description: slightly pink powder
   Lot/Batch #: 211048078
   Purity: 99.49% a.i.
   Compound Stability: not provided
   CAS #: not provided

2. Vehicle control: reverse osmosis (RO) water

3. Test animals:
Species: rat
Strain: Crl:CD® (SD)IGS BR
Age/weight at study initiation: 59-65 days; weight on Day-3: males: 248-331 g; females: 178-231 g
Source: Charles River Laboratories, Portage, MI
Housing: Individually in stainless steel cages
Diet: #8728C Harlan Teklad *ad libitum*
Water: source not provided *ad libitum*
Environmental conditions: Temperature: 18-26^{0}C
Humidity: 30-70%
Air changes: not stated
Photoperiod: 12 hrs dark/ 12 hrs light
Acclimation period: 7 days

B. STUDY DESIGN:

1. In life dates - Start: April 2, 2001 End: April 27, 2001

2. Animal assignment: Animals were assigned using a computerized blocking procedure to the test groups noted in Table 1.

TABLE 1: Study design.

Test Group	Dose (mg/kg bw/d)	# Male	# Female
Control	0	10	10
Low	20	10	10
Mid	50	10	10
High	100	10	10

3. Dose selection rationale

No information on dose selection rationale was provided.

4. Preparation and treatment of animal skin

Shortly before the first application and as needed thereafter, the fur of each test animal was clipped from the dorsal area of the trunk over an area of at least 10% of the body surface. Daily doses were based on the most recently recorded body weights. Dose preparations were made fresh weekly. RO water (1 ml) was placed onto a gauze pad and applied to the test site prior to administering the test material. The test material was then placed on the intact skin and held in contact by a gauze dressing, secured with a nonirritating tape and over wrapped with bandage and tape. Animals were exposed at least 6 but no more than 7 hours/day, 5 days/week for at least 4 weeks. For the control group, 1 ml of RO water was used in place of the test material; the application site was covered using the same procedure as with the test material. At the end of the treatment period, the coverings were removed and the application site was wiped with a towel moistened with RO water.

5. Statistics - Levene's test was used to test for variance homogeneity. If there was a heterogeneity of variance at $p \leq 0.05$, transformations were used to stabilize the variance. One-way analysis of variance (ANOVA) was used to analyze body weights, body weight changes, food consumption and cholinesterase activity. ANOVA was done on the homogeneous or transformed data. If the ANOVA was significant, Dunnett's multiple comparison t-test was used for control vs. treated group comparisons. For each sex, Groups 2 through 4 were compared to Group 1 at the 5.0%, two-tailed probability level. In addition, RBC cholinesterase values for each animal were compared (using the average of the Day -3 and predose Day 1values) by repeated measures ANOVA test.

C. METHODS:

1. Observations:

1a. Cageside Observations

Animals were observed twice daily for signs of mortality and moribundity.

1b. Clinical Examinations

Once prior to treatment, on the first day of treatment and weekly thereafter, detailed observations were made prior to dosing with animals outside the cage. Observations included, but were not limited to, changes in skin, fur, eyes and mucous membranes; occurrences of secretions and excretions; and autonomic activity (lacrimation, piloerection, pupil size and unusual respiratory patterns). Changes in posture and reactivity to handling and the presence of clonic or tonic movements, stereotypies or bizarre behavior were recorded weekly. Animals were also allowed to walk freely to allow a weekly evaluation of gait.

Dermal irritation was scored before dosing on Days 1, 8, 15, 22 and 26. The scoring system graded skin reactions for erythema, edema, atonia, desquamation/fissuring from none/normal (0) to slight (1), to moderate (2), to severe/marked (3) for the presence of eschar and exfoliation.

1c. Neurological Evaluations

No evaluations were conducted.

2. Body weight

Animals were weighed once prior to treatment for randomization on Day -3 and on Days 5, 12, 19 and 26.

3. Food consumption

Food consumption was recorded for Days 1-5, 5-12, 12-19 and 19-26.

4. Ophthalmoscopic examination:

Eyes were not examined.

5. Hematology & Clinical Chemistry:

No parameters were measured except RBC and brain cholinesterase. Blood was collected in potassium EDTA tubes from the jugular vein in non-fasted animals once during the week before treatment initiation, before dosing on Days 1, 8, 15 and 22 and within one hour after removal of

test material on Days 5, 12, 19 and 26. Blood was chilled until analyzed. At the scheduled sacrifice, the right half of the brain was placed in individual cryotubes, flash frozen in liquid nitrogen and kept on dry ice until stored in a freezer set to maintain -60 to -80°C. The left half of the brain was stored for future analysis. The analytical method for cholinesterase determinations was not stated in the study report; however, a fax dated April 4, 2002, from Ronald Markevitch, supervisor of the clinical pathology laboratory at Covance stated that the Modified Ellman method was used.

6. Urinalysis

Urine was not examined.

7. Sacrifice and Pathology

No postmortem examinations were conducted.

II. RESULTS

A. OBSERVATIONS:

1. Clinical signs of toxicity - No treatment-related clinical signs were observed.

2. Mortality - All animals survived until the end of the study.

3. Dermal Irritation - There was slight atonia for one male on Day 8 and four females on Day 15 in the 100 mg/kg/day groups. This effect is not considered treatment-related as it did not persist as dosing continued.

B. BODY WEIGHT AND WEIGHT GAIN: There was no treatment-related effect on body weight. The only statistically significant body weight changes were a decrease (27%) in the 100 mg/kg/day males during Days 5 to 12 and an increase (37%) in 50 mg/kg/day males during Days 19 to 26. However, there were non-significant decreases in the 100 mg/kg/day males at Days -3 to 5 (16%), 12 to 19 (17%) and -3 to 26 (12%) which are considered toxicologically significant.

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TABLE 2. Mean body weight gain during 4 weeks of treatment

Dose rate (mg/kg/day)	Body Weight Gains (g±SD)				
	Days -3 to 5	Days 5 to 12	Days 12 to 19	Days 19 to 26	Days -3 to 26
Male					
0	32 ± 9.9	33 ± 6.9	18 ± 6.8	19 ± 3.5	101 ± 18.6
20	28 ± 14.1	35 ± 9.4	21 ± 4.5	20 ± 8.2	104 ± 18.3
50	32 ± 9.3	34 ± 8.4	21 ± 5.6	26 ± 6.3* (137)	114 ± 23.1
100	27 ± 10.6 (84)	24 ± 7.7* (73)	15 ± 4.6 (83)	23 ± 4.1 (121)	89 ± 20.8 (88)
Female					
0	14 ± 7.7	22 ± 9.5	8 ± 7.7	12 ± 5.0	56 ± 7.8
20	18 ± 4.7	17 ± 7.9	12 ± 6.8	14 ± 6.8	62 ± 10.6
50	16 ± 8.3	18 ± 5.8	11 ± 5.1	10 ± 7.5	54 ± 7.4
100	15 ± 9.7	17 ± 7.0	9 ± 8.6	13 ± 7.0	55 ± 14.9

[a] Data obtained from page 34 of MRID 45630601.
* Statistically different ($p < 0.05$) from the control.
(Percent of control value)

C. FOOD CONSUMPTION:

The only statistically significant decreases in food consumption were in the 50 mg/kg/day females on Days 12 to 19 and 50 and 100 mg/kg/day females on Days 19 to 26. The effects are not considered treatment-related as there was no dose-response and the decreases were minimal (9% and 8% decreases in the 50 and 100 mg/kg/day groups, respectively).

D. BLOOD ANALYSES:

RBC cholinesterase was measured before dosing on Day -4 and on Days 1, 8, 15 and 22. The only statistically significant effects were in the 100 mg/kg/day males at Days 8 (11% decrease) and 22 (13%). Using the repeated measures statistical test, there were also significant decreases in the 50 and 100 mg/kg/day females (11% and 10%, respectively) on Day 22. These effects were determined to be not toxicologically significant because they were inconsistent.

Measurements were also performed within 1 hour after test material removal on Days 5, 12, 19, and 26. Statistically significant decreases were observed in the 50 mg/kg/day (12% decrease) and 100 mg/kg/day (15%) males on Day 5 and in the 100 mg/kg/day males on Days 12 (21%) and 19 (16%). Using the repeated measures statistical test, there was also a significant decrease (10%) in

the 50 mg/kg/day males on Day 12. In females, statistically significant decreases were observed in the 50 and 100 mg/kg/day groups on Days 5 (13% and 12%, respectively) and Day 12 (20% and 13%, respectively).

The interpretation of the RBC cholinesterase data is difficult because there no dose response at some time periods (e.g., Days 5 and 12), high variability of measurements on some days (i.e., larger standard deviations on Days 19 and 26 for females) and minimal effects. It can be argued that the effects at 50 and 100 mg/kg/day are toxicologically significant based on the following: 1) there were statistically significant decreases at these doses in both males and females; 2) in MRID 45630603, decreases in RBC cholinesterase were observed at 50 and 100 mg/kg/day with an 80% formulation.

Brain cholinesterase was statistically significantly decreased in the 50 mg/kg/day males (15%) and in the 100 mg/kg/day males (15%) and females (24%). There was also a non-significant decrease in the 50 mg/kg/day females (9%). Data are presented in Table 5.

The LOAEL is conservatively determined to be 50 mg/kg/day based on RBC cholinesterase inhibition in males and females and brain cholinesterase in males.

Table 3: RBC Cholinesterase Values (UMOL/L) - Before Dosing[a]

Dose (mg/kg/day)	Day -4	Day 1	Day 8	Day 15	Day 22
Males					
0	1283 ± 82	1334 ± 95	1136 ± 82	1162 ± 117	1273 ± 90
20	1272 ± 71	1373 ± 125	1081 ± 135	1183 ±134	1304 ± 151
50	1338 ± 97	1382 ± 122	1150 ± 123	1221 ± 104	1269 ±90
100	1305 ± 92	1326 ± 102	1012 ± 51* ♮ (89)	1194 ± 103	1113 ± 86* ♮ ♮ (87)
Females					
0	1323 ± 92	1410 ± 81	1075 ± 82	1172 ± 117	1362 ± 92
20	1302 ± 97	1398 ± 74	1144 ± 94	1146 ± 87	1291 ± 120
50	1300 ± 131	1513 ± 143	1125 ± 187	1252 ± 78	1215 ± 143 ♮ ♮ (89)
100	1299 ± 91	1405 ± 124	1199 ±135 ♮	1254 ±70	1232 ± 142 ♮ (90)

a Extracted from Tables 6 (pages 36-37), 7 (pages 38-39), 9 (pages 42-43), 11 (pages 46-47) and 13(pages 50-51) of MRID 45630601

* Significantly different from control using Dunnett's test, $p \leq 0.05$

♮ Significant at 5% using a repeated measures ANOVA test

♮ ♮ Significant at 1% using a repeated measure ANOVA test

(percent of control value)

Table 4: RBC Cholinesterase Values (UMOL/L) - 1 Hour After Dosing[a]

Dose (mg/kg/day)	Day 5	Day 12	Day 19	Day 26
Males				
0	1281 ± 99	941 ± 111	1199 ± 142	1266 ± 124
20	1308 ± 114	918 ± 114	1191 ± 111	1360 ± 124
50	1122 ± 63* ♮♮(88)	851 ± 84 ♮ (90)	1164 ± 113	1280 ± 146
100	1089 ± 79* ♮♮ (85)	740 ± 93* ♮♮(79)	1002 ± 119* ♮♮ (84)	1282 ± 170
Females				
0	1339 ± 121	996 ± 92	1211 ± 101	1465 ± 133
20	1363 ± 108	961 ± 69	1330 ± 97♮	1412 ± 144
50	1165 ± 116* ♮♮(87)	801 ± 112* ♮♮ (80)	1199 ± 116	1394 ± 146
100	1172 ± 177* ♮♮ (88)	865 ± 120* ♮(87)	1188 ± 282	1492 ± 220

a Extracted from Tables 8 (pages 40-41), 10 (pages 44-45), 12 (pages 48-49), 14 (pages 52-53) of MRID 45630601
* Significantly different from control, p≤0.05 using Dunnett's test
♮ Significant at 5% using a repeated measures ANOVA test
♮♮ Significant at 1% using a repeated measures ANOVA test
(Percent of control value)

Table 5: Brain Cholinesterase Levels (UMOL/G) at Day 26[a]

	Dose Levels (mg/kg/day)							
	Males				Females			
	0	20	50	100	0	20	50	100
Day 26	40 ± 4.8	41 ± 3.8	34 ± 4.0* (85)	34 ± 7.1* (85)	45 ± 2.9	45 ± 4.0	41 ± 4.4 (91)	34 ± 6.0* (76)

a Extracted from Table 14 (pages 52-53) of MRID 45630601
* Significantly different from control, p≤0.05
(Percent of control value)

III. DISCUSSION and CONCLUSIONS

A. <u>INVESTIGATORS' CONCLUSIONS</u>: The study author concluded that there were mild reductions in RBC and brain cholinesterase in male and female rats at doses of 50 and 100 mg/kg/day of the test material. However, due to the lack of clinically observed toxicity, the modest reductions in RBC and brain cholinesterase for animals receiving 50 or 100 (males only) mg/kg/day and consistent with the interpretation of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 1998), the NOAEL was 100 mg/kg/day in males and 50 mg/kg/day in females.

B. REVIEWER COMMENTS:

In a non-guideline four-week dermal toxicity study (MRID 45630601), Carbaryl Technical (99.49% a.i., Lot 211048078) was applied to the shaved skin of 10 Crl: CD (SD)IGS BR rats/sex/dose at dose levels of 0, 20, 50 or 100 mg/kg bw/day, 6 hours/day for 5 days/week during a 4-week period. The parameters measured included the following: clinical observations, body weight, body weight gain, food consumption, RBC and brain cholinesterase and signs of dermal irritation.

There was no treatment-related effect on mortality, clinical observations, body weight or dermal irritation. The only statistically significant body weight changes were a decrease (27%) in the 100 mg/kg/day males during Days 5 to 12 and an increase (37%) in 50 mg/kg/day males during Days 19 to 26. However, there were non-significant decreases in the 100 mg/kg/day males at Days -3 to 5 (16%), 12 to 19 (17%) and -3 to 26 (12%) which are considered toxicologically significant.

The only statistically significant decreases in food consumption were in the 50 mg/kg/day females on Days 12 to 19 and 50 and 100 mg/kg/day females on Days 19 to 26. The effects are not considered treatment-related as there was no dose-response and the decreases were minimal (9% and 8% decreases in the 50 and 100 mg/kg/day groups, respectively).

RBC cholinesterase was measured before dosing on Day -4 and on Days 1, 8, 15 and 22. The only statistically significant effects were in the 100 mg/kg/day males at Days 8 (11% decrease) and 22 (13%). Using the repeated measures statistical test, there is also a significant decrease in the 50 and 100 mg/kg/day females (11% and 10%, respectively) on Day 22. These effects were determined to be not toxicologically significant because they were inconsistent.

Measurements were also performed within 1 hour after test material removal on Days 5, 12, 19, and 26. Statistically significant decreases were observed in the 50 mg/kg/day (12% decrease) and 100 mg/kg/day (15%) males on Day 5 and in the 100 mg/kg/day males on Days 12 (21%) and 19 (16%). Using the repeated measures statistical test, there was also a significant decrease (10%) in the 50 mg/kg/day males on Day 12. In females, statistically significant decreases were observed in the 50 and 100 mg/kg/day groups on Days 5 (13% and 12%, respectively) and Day 12 (20% and 13%, respectively).

The interpretation of the data is difficult because there was no dose response at most of the time periods (e.g., Days 5 and 12), high variability of some measurements on some days (i.e., larger standard deviations on Days 19 and 26 for females) and minimal effects. It can be argued that the effects at 50 and 100 mg/kg/day are toxicologically significant based on the following: 1) there were statistically significant decreases at these doses in both males and females; and 2) in MRID 45630603, decreases in RBC cholinesterase were observed at 50 and 100 mg/kg/day with a 80% formulation; and 3) the inhibition was seen 1 hour after demal application; in contrast, no significant effect was observed before application of the test material.

Brain cholinesterase was statistically significantly decreased in the 50 mg/kg/day males (15%) and in the 100 mg/kg/day males (15%) and females (24%). There was also a non-significant decrease in the 50 mg/kg/day females (9%).

The LOAEL is conservatively determined to be 50 mg/kg/day based on RBC cholinesterase inhibition in males and females and brain cholinesterase in males. The measurement of plasma cholinesterase would have helped in establishing the LOAEL.

The systemic LOAEL is 50 mg/kg/day based on statistically significant decreases in RBC cholinesterase in males and females and brain cholinesterase in males. The systemic NOAEL is 20 mg/kg/day.

The dermal LOAEL was not established. The dermal NOAEL was 100 mg/kg/day.

This 4-week dermal toxicity study in the rat is **acceptable (non-guideline)**. The study was intended to establish endpoints for short-term and intermediate-term occupational and residential postapplication dermal exposure. Although the study does not meet guideline requirements, it is useful for risk assessment for the following reasons: 1) in all oral studies in which cholinesterase was measured, it was the most sensitive endpoint; therefore, other guideline parameters would most likely not establish a lower LOAEL; 2) plasma cholinesterase was not measured; however, in all the oral studies in rats, all three compartments (plasma, RBC and brain) were affected at the same dose level. Therefore, it is likely that plasma cholinesterase would not have been inhibited at a lower level, especially given the minimal effects on RBC and brain cholinesterase.

C. STUDY DEFICIENCIES:

1) No reason for not measuring plasma cholinesterase was provided. These measurements may have provided more convincing evidence for establishing the study LOAEL.

2) Three animals in the 50 mg/kg/day female group were repeatedly found "out of their wraps" during the study.

Animal C65337 - Days 16, 23, 24 and 26
Animal C65338 - Days 4, 16, 22 and 26
Animal C65339 - Days 9 and 26

RBC cholinesterase was measured after dosing on Day 26. Compared to their measurements on Day 19 (the closest time period when cholinesterase was measured after dosing), there was no evidence that losing their wraps had an effect, except for Animal C65339. On Day 19, its RBC cholinesterase was 1118 UMOL/L, wherease on Day 26, it was 1503 UMOL/L. Pretreatment, it was 1534 UMOL/L.

3) Deviations from the 21/28 day dermal toxicity guidelines (OPPTS 870.3200) included the following:

1) assessment of motor activity, grip strength and sensory reactivity to different types of stimuli was not conducted

2) no clinical pathology testing was conducted

3) plasma cholinesterase was not measured

4) no postmortem examinations were conducted

DATA FOR ENTRY INTO ISIS

Subchronic Dermal (28 day) Study - rodents (870.3200)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
056801	45630601	subchronic	rat	4 week	dermal	dermal	20 - 100	0, 20, 50, 100	20	50	RBC cholinesterase inhibition (ChEI) in males and females; brain ChEI in males	Systemic
056801	45630601	subchronic	rat	4 week	dermal	dermal	20 - 100	0, 20, 50, 100	100	not established		Dermal

EPA Reviewer: Virginia A. Dobozy, VMD, MPH
Reregistration Branch I, Health Effects Division (7509C)
Branch Senior Scientist: Whang Phang, PhD
Reregistration Branch I, Health Effects Division (7509C)
Secondary Reviewer: William Sette, PhD
Toxicology Branch, Health Effects Division (7509C)

Signature: Virginia A Dobozy
Date 4/15/02
Signature: Whang Phang
Date 4/15/02
Signature: William Sette
Date 4-15-02

DATA EVALUATION RECORD

TXR#: 0050582

STUDY TYPE: Four-Week Dermal Toxicity - rat

PC CODE: 056801

DP BARCODE: D281853
SUBMISSION NO.: S612723

TEST MATERIAL (PURITY): Sevin® XLR Plus (44.82% a.i.)

SYNONYMS: Carbaryl; 1-naphthyl methylcarbamate

CITATION: Austin, E.W. (2002). 4 Week Repeated-Dose Dermal Toxicity Study with SEVIN® XLR Plus in Rats. Covance Laboratories, Madison, WI. Laboratory Study Identification Number 6224-267, March 7, 2002. MRID 45630602. Unpublished

SPONSOR: Aventis CropScience

EXECUTIVE SUMMARY:

In a non-guideline four-week dermal toxicity study (MRID 45630602), Sevin® XLR Plus (44.82% a.i., Lot 60618902) was applied to the shaved skin of 8 Crl: CD (SD)IGS BR rats/sex/dose at dose levels of 0, 20, 50 or 100 mcL/kg bw/day (0, 9.6, 24 or 48 mg/kg/day), 6 hours/day for 5 days/week during a 4-week period. The parameters measured included the following: clinical observations, body weight, body weight gain, food consumption, RBC cholinesterase and signs of dermal irritation.

There were no treatment-related effects on clinical observations or body weight or evidence of dermal irritation. Females treated at 100 mcL/kg/day gained 167%, 65%, 144% and 40% of control values for Days -3 to 5, 5 to 12, 12 to 19 and 19 to 26, respectively. Overall (Days -3 to 26) body weight gain was not affected. It is difficult to determine if there was a treatment-related effect immediately after dosing as the first body weight measurement was not done until Day 5 of dosing. Although not statistically significant, there does appear to be a treatment-related decrease on the body weight gain (Days 5 to 12) of females treated at 100 mcL/kg/day.

RBC cholinesterase was measured before dosing on Week -1 and on Days 1, 8, 15 and 22. There was no evidence of a treatment-related effect at these time periods. Measurements were also performed within 1 hour after test material removal on Days 5, 12, 19, and 26. In males, the only statistically significant difference from control values was on Day 26 in the animals dosed at 50 mcL/kg/day; the decrease was only 8%. Although not statistically significant, the RBC cholinesterase on Day 12 in males treated at 100 mcL/kg/day was decreased by 10%. In females treated at 100 mcL/kg/day, values were significantly decreased on Day 5 (12%), Day 12 (12%) and non-significantly decreased on Days 19 (5%) and Day 26 (7%). There were also significant decreases in the 50 mcL/kg/day females on Days 19 (9%) and 26 (14%) and in the 20 mg/kg/day group on Day 26 (10%). Although statistically significant, the RBC cholinesterase decreases are not judged to be toxicologically significant due to the small magnitude of the effect and the lack of a dose-response on Days 19 and 26.

The systemic LOAEL in females was 100 mcL/kg/day (48 mg/kg/day) based on decreased body weight gain. The systemic NOAEL was 50 mcL/kg/day (24 mg/kg/day). The systemic LOAEL in males was not established. The systemic NOAEL was 100 mcL/kg/day (48 mg/kg/day).

The dermal LOAEL was not established. The dermal NOAEL was 100 mcL/kg/day (48 mg/kg/day).

This 4-week dermal toxicity study in the rat is **unacceptable (non-guideline)**. The study was intended for use in the short-term and intermediate-term occupational and residential handler risk assessments for the liquid formulations of carbaryl. It is considered unacceptable and **not upgradeable** because RBC cholinesterase results were inconsistent and plasma and brain cholinesterase were not measured. In another dermal toxicity study (MRID 45630601), brain cholinesterase inhibition was the most sensitive and reliable endpoint. Determination of cholinesterase inhibition in all three compartments would have helped define the effect level.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Sevin® XLR Plus
   Description: white liquid
   Lot/Batch #: 60618902
   Purity: 44.82% (wt/wt) a.i.
   Compound Stability: not provided
   CAS #: not provided

2. Vehicle and/or positive control: none

3. Test animals:
   Species: rat
   Strain: Crl:CD® (SD)IGS BR
   Age/weight at study initiation: 59-65 days; weight on Day -3: males: 248-293 g; females: 173-211 g
   Source: Charles River Laboratories, Portage, MI
   Housing: Individually in stainless steel cages
   Diet: #8728C Harlan Teklad *ad libitum*
   Water: source not provided *ad libitum*
   Environmental conditions: Temperature: 18-26^{0}C
   Humidity: 30-70%
   Air changes: not stated
   Photoperiod: 12 hrs dark/ 12 hrs light
   Acclimation period: 7 days

B. STUDY DESIGN:

1. In life dates - Start: February 26, 2001 End: March 23, 2001

2. Animal assignment: Animals were assigned using a computerized blocking procedure to the test groups noted in Table 1.

TABLE 1: Study design.

Test Group	Dose (mcL/kg bw/d)	# Male	# Female
Control	0	8	8
Low	20	8	8
Mid	50	8	8
High	100	8	8

The mcL/kg/day doses were converted to mg/kg/day using the following formula based on the Sevin XLR Plus formulation:

$$\frac{4 \text{ lbs a.i.}}{\text{gal}} \times \frac{454 \text{ g}}{\text{lb}} \times \frac{1000 \text{ mg}}{\text{g}} \times \frac{1 \text{ gal}}{3785 \text{ mL}} \times \frac{1 \text{ mL}}{1000 \text{ mcL}} = 0.4798 \text{ mg/mcL}$$

Therefore, the 20, 50 and 100 mcL/kg/day doses are equivalent to 9.6, 24 and 48 mg/kg/day.

3. Dose selection rationale

No information on dose selection rationale was provided.

4. Preparation and treatment of animal skin

Shortly before the first application and as needed thereafter, the fur of each test animal was clipped from the dorsal area of the trunk over an area of at least 10% of the body surface (approximately 25 cm^2). Daily doses were based on body weights recorded on Days -3, 5, 12 and 19 for Weeks 1 through 4, respectively. The test material was used as supplied by the registrant and was applied directly to the skin. Animals were exposed at least 6 but no more than 7 hours/day, 5 days/week for at least 4 weeks. The test material was held in place with a porous gauze dressing and non-irritating tape which was then covered with an elastic bandage. For the control group, 1 ml of reverse osmosis (RO) water was used in place of the test material; the application site was covered using the same procedure as with the test material. At the end of the treatment period, the coverings were removed and the application site was wiped with a towel moistened with RO water.

5. Statistics - Levene's test was used to test for variance homogeneity. If there was a heterogeneity of variance at $p \leq 0.05$, transformations were used to stabilize the variance. One-way analysis of variance (ANOVA) was used to analyze body weights, body weight changes, food consumption and cholinesterase activity. ANOVA was done on the homogeneous or transformed data. If the ANOVA was significant, Dunnett's multiple comparison t-test was used for control vs. treated group comparisons. For each sex, Groups 2 through 4 were compared to Group 1 at the 5.0%, two-tailed probability level.

C. METHODS:

1. Observations:

1a. Cageside Observations

Animals were observed twice daily for signs of mortality and moribundity.

1b. Clinical Examinations

Once prior to treatment, on the first day of treatment and weekly thereafter, detailed observations were made prior to dosing with animals outside the cage. Observations included, but were not limited to, changes in skin, fur, eyes and mucous membranes; occurrences of secretions and excretions; and autonomic activity (lacrimation, piloerection, pupil size and unusual respiratory patterns).

Dermal irritation was scored on the first day of treatment and before dosing on Days 1, 8, 15, 22 and 26. The scoring system graded skin reactions for erythema, edema, atonia, desquamation/fissuring from none/normal (0) to slight (1), to moderate (2), to severe/marked (3) for the presence of eschar and exfoliation.

1c. Neurological Evaluations

No evaluations were conducted.

2. Body weight

Animals were weighed once prior to treatment for randomization on Day -3 and on Days 5, 12, 19 and 26.

3. Food consumption

Food consumption was recorded for Days 1-5, 5-12, 12-19 and 19-26.

4. Ophthalmoscopic examination:

Eyes were not examined.

5. Hematology & Clinical Chemistry:

No parameters were measured except RBC cholinesterase. Blood was collected in potassium EDTA tubes from the jugular vein in non-fasted animals once during the week before treatment initiation, before dosing on Days 1, 8, 15 and 22 and within one hour after removal of test material on Days 5, 12, 19 and 26. Blood was chilled until analyzed. The analytical method for

cholinesterase determinations was not stated in the study report; however, a fax dated April 4, 2002, from Ronald Markevitch, supervisor of the clinical pathology laboratory at Covance stated that the Modified Ellman method was used.

6. Urinalysis

Urine was not examined.

7. Sacrifice and Pathology

No postmortem examinations were conducted.

II. RESULTS

A. OBSERVATIONS:

1. Clinical signs of toxicity - No treatment-related clinical signs were observed.

2. Mortality - One control animal died during the final week of the study. The cause of death was not reported but this animal was observed to have a ventral abdominal mass.

3. Dermal Irritation - There was no dermal irritation in treated or control animals.

B. BODY WEIGHT AND WEIGHT GAIN: There was no treatment-related effect on body weight. Body weight gain was variable between time periods in females. Those in the 100 mcL/kg/day group gained 167%, 65%, 144% and 40% of control values for Days 5-12, 12-19 and 19-26, respectively. Overall (Days -3 to 26) body weight gain was not affected.

TABLE 2. Mean body weight gain during 4 weeks of treatment

Dose rate (mcL/kg/day)	Body Weight Gains (g±SD)				
	Days -3 to 5	Days 5 to 12	Days 12 to 19	Days 19 to 26	Days -3 to 26
Male					
0	21 ± 7.8	25 ± 12.2	23 ± 10.7	17 ± 6.0	87 ± 19.2
Low	26 ± 7.7	23 ± 7.7	24 ± 3.7	21 ± 7.3	94 ± 12.9
Mid	24 ± 7.2	30 ± 8.5	17 ± 7.1	19 ± 5.0	90 ± 21.6
High	33 ± 7.1*	29 ± 7.7	23 ± 7.9	21 ± 4.8	105 ± 16.4
Female					
0	12 ± 3.9	23 ± 7.7	9 ± 9.6	10 ± 6.5	54 ± 10
Low	12 ± 6.1	20 ± 6.7	15 ± 5.1	4 ± 4.6	51 ± 7.7
Mid	17 ± 9.1	26 ± 6.5	9 ± 8.4	8 ± 5.4	60 ± 14.2
High	20 ± 6.7* (167)	15 ± 6.5 (65)	13 ± 7.1 (144)	4 ± 6.1 (40)	52 ± 9.9

[a] Data obtained from page 31 in the study report.
* Statistically different ($p < 0.05$) from the control.

C. FOOD CONSUMPTION:

There was no treatment-related effect on food consumption.

D. BLOOD ANALYSES:

RBC cholinesterase was measured before dosing on Week -1 and on Days 1, 8, 15 and 22 (Table 3). There was no evidence of a treatment-related effect at these time periods. Measurements were also performed within 1 hour after test material removal on Days 5, 12, 19, and 26 (Table 4). In males, the only statistically significant difference from control values was on Day 26 in the animals dosed at 50 mcL/kg/day; the decrease was only 8%. Although not statistically significant, the RBC cholinesterase on Day 12 in males treated at 100 mcL/kg/day was decreased by 10%. In females treated at 100 mcL/kg/day, values were significantly decreased on Day 5 (12%), Day 12 (12%) and non-significantly decreased on Days 19 (5%) and Day 26 (7%). There were also significant decreases in the 50 mcL/kg/day females on Days 19 (9%) and 26 (14%) and in the 20 mg/kg/day group on Day 26 (10%).

Table 3: RBC Cholinesterase Values (UMOL/L) - Before Dosing[a]

Dose (mcL/kg/day)	Week -1	Day 1	Day 8	Day 15	Day 22
Males					
0	1318 ± 74	1002 ± 122	1436 ± 118	1272 ± 149	1174 ± 137
20	1296 ± 117	975 ± 72	1519 ± 84	1297 ± 86	1211 ± 102
50	1293 ± 95	969 ± 58	1476 ± 92	1222 ± 142	1194 ± 80
100	1313 ± 91	930 ± 61	1372 ± 119	1239 ± 45	1219 ± 85
Females					
0	1371 ± 75	1088 ± 43	1520 ± 84	1363 ± 73	1210 ± 46
20	1370 ± 54	1056 ± 83	1456 ± 102	1285 ± 84	1251 ± 99
50	1364 ± 92	1028 ± 59	1473 ± 94	1274 ± 142	1235 ± 92
100	1343 ± 123	1024 ± 99	1451 ± 174 (95)	1239 ± 141 (91)	1277 ± 82

a Extracted from Tables 6 (pages 33-34), 7 (pages 35-36), 9 (pages 39-40), 13 (pages 43-44) and 15 (pages 47-48). (percentage of control value)

Table 4: RBC Cholinesterase Values (UMOL/L) - After Dosing[a]

Dose (mcL/kg/day)	Day 5	Day 12	Day 19	Day 26
Males				
0	995 ± 84	1001 ± 60	1388 ± 136	1173 ± 79
20	1058 ± 41	945 ± 100	1388 ± 94	1137 ± 56
50	973 ± 40	911 ± 85	1422 ± 100	1084 ± 36* (92)
100	1015 ± 59	906 ± 69 (90)	1367 ± 58	1088 ± 87
Females				
0	1063 ± 97	1043 ± 63	1471 ± 44	1255 ± 115
20	1031 ± 89	984 ± 69	1403 ± 120	1124 ± 60* (90)
50	961 ± 82	934 ± 94	1334* ± 58 (91)	1079 ± 82* (86)
100	931 ± 70* (88)	919 ± 118* (88)	1395 ± 113 (95)	1172 ± 83 (93)

a Extracted from Tables 8 (pages 37-38), 10 (pages 41-42), 12 (pages 45-46), 14 (pages 49-50)
* Significantly different from control, $p \leq 0.05$

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The study author concluded that there was no clear effect on RBC cholinesterase; therefore, the NOAEL was 100 mcL/kg/day.

B. REVIEWER COMMENTS:

In a non-guideline four-week dermal toxicity study (MRID 45630602), Sevin XLR Plus (44.82% a.i., Lot 60618902) was applied to the shaved skin of 8 Crl: CD (SD)IGS BR rats/sex/dose at dose levels of 0, 20, 50 or 100 mcL/kg bw/day (0, 9.6, 24 and 48 mg/kg/day), 6 hours/day for 5 days/week during a 4-week period. The parameters measured included the following: clinical observations, body weight, body weight gain, food consumption, RBC cholinesterase and signs of dermal irritation.

There were no treatment-related effects on clinical observations or body weight and no evidence of dermal irritation. Females treated at 100 mcL/kg/day gained 167%, 65%, 144% and 40% of control values for Days -3 to 5, 5 to 12, 12 to 19 and 19 to 26, respectively. Overall (Days -3 to 26) body weight gain was not affected. It is difficult to determine if there was a treatment-related effect immediately after dosing as the first body weight measurement was not done until Day 5 of dosing. Although not statistically significant, there does appear to be a treatment-related effect on the body weight gain of females treated at 100 mcL/kg/day.

RBC cholinesterase was measured before dosing on Week -1 and on Days 1, 8, 15 and 22. There was no evidence of a treatment-related effect at these time periods. Measurements were also

performed within 1 hour after test material removal on Days 5, 12, 19, and 26. In males, the only statistically significant difference from control values was on Day 26 in the animals dosed at 50 mcL/kg/day; the decrease was only 8%. Although not statistically significant, the RBC cholinesterase on Day 12 in males treated at 100 mcL/kg/day was decreased by 10%. In females treated at 100 mcL/kg/day, values were significantly decreased on Day 5 (12%), Day 12 (12%) and non-significantly decreased on Days 19 (5%) and Day 26 (7%). There were also significant decreases in the 50 mcL/kg/day females on Days 19 (9%) and 26 (14%) and in the 20 mg/kg/day group on Day 26 (10%). Although statistically significant, the RBC cholinesterase decreases are not judged to be toxicologically significant due to the small magnitude of the effect and the lack of a dose-response effect on Days 19 and 26.

The systemic LOAEL in females was 100 mcL/kg/day (48 mg/kg/day) based on decreased body weight gain. The systemic NOAEL was 50 mcL/kg/day (24 mg/kg/day). The systemic LOAEL in males was not established. The systemic NOAEL was 100 mcL/kg/day (48 mg/kg/day).

The dermal LOAEL was not established. The dermal NOAEL was 100 mcL/kg/day (48 mg/kg/day).

This 4-week dermal toxicity study in the rat is **unacceptable (non-guideline)**. The study was intended for use in the short-term and intermediate-term occupational and residential handler risk assessments for the liquid formulations of carbaryl. It is considered unacceptable and **not upgradeable** because RBC cholinesterase results were inconsistent and plasma and brain cholinesterase were not measured. In another dermal toxicity study (MRID 45630601), brain cholinesterase inhibition was the most sensitive and reliable endpoint. Determination of cholinesterase inhibition in all three compartments would have helped define the effect level.

C. <u>STUDY DEFICIENCIES:</u>

Deviations from the 21/28 day dermal toxicity guidelines (OPPTS 870.3200) included the following:

1) 8 rats/sex/group were used instead of the required 10/sex/group if the study is intended for risk assessment purposes

2) assessment of motor activity, grip strength and sensory reactivity to different types of stimuli was not conducted

3) no clinical pathology testing was conducted

4) plasma and brain cholinesterase were not measured

5) no postmortem examinations were conducted

DATA FOR ENTRY INTO ISIS

Subchronic Dermal (28 day) Study - rodents (870.3200)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
056801	45630602	subchronic	rat	4 week	dermal	dermal	20 - 100 mcL/kg/day (9.6 - 48 mg/kg/day)	0, 20, 50, 100 mcL/kg/day (0, 9.6, 24, 48 mg/kg/day)	females: 50 mcL/kg/day (24 mg/kg/day); males: 100 mcL/kg/day (48 mg/kg/day)	females: 100 mcL/kg/day (48 mg/kg/day); males: not established	body weight gain	Systemic
056801	45630602	subchronic	rat	4 week	dermal	dermal	20 - 100 mcL/kg/day (9.6 - 48 mg/kg/day)	0, 20, 50, 100 mcL/kg/day	100 mcL/kg/day (48 mg/kg/day)	not established		Dermal

[CARBARYL/PC Code 056801]

EPA Reviewer: Virginia A. Dobozy, VMD, MPH
Reregistration Branch I, Health Effects Division (7509C)
Branch Senior Scientist: Whang Phang, PhD
Reregistration Branch I, Health Effects Division (7509C)
Secondary Reviewer: William Sette, PhD
Toxicology Branch, Health Effects Division (7509C)

Signature: Virginia A Dobozy
Date 4/15/02
Signature: Whang Phang
Date 4/16/02
Signature: William Sette
Date 4-16-02

DATA EVALUATION RECORD

TXR# 0050582

STUDY TYPE: Four-Week Dermal Toxicity - rat

PC CODE: 056801

DP BARCODE: D281853
SUBMISSION NO.: S612723

TEST MATERIAL (PURITY): Sevin® 80S (80.07% a.i.)

SYNONYMS: Carbaryl; 1-naphthyl methylcarbamate

CITATION: Austin, E.W. (2002). 4 Week Repeated-Dose Dermal Toxicity Study with SEVIN® 80S in Rats. Covance Laboratories, Madison, WI. Laboratory Study Identification Number 6224-266, March 8, 2002. MRID 45630603. Unpublished.

SPONSOR: Aventis CropScience

EXECUTIVE SUMMARY:

In a non-guideline four-week dermal toxicity study (MRID 45630603), Sevin® 80S (80.07% a.i., Lot C8I168025A) was applied to the shaved skin of 8 Crl: CD (SD)IGS BR rats/sex/dose at dose levels of 0, 20, 50 or 100 mg/kg bw/day, 6 hours/day for 5 days/week during a 4-week period. The parameters measured included the following: clinical observations, body weight, body weight gain, food consumption, RBC cholinesterase and signs of dermal irritation.

There was no treatment-related effect on mortality, clinical observations, body weight or dermal irritation. Body weight gain (relative to control values) in the 100 mg/kg/day males was highly variable between time periods. There were non-significant decreases of 15% and 20% on Days -3 to 5 and 19 to 26, respectively but increases of 9% and 53% were observed on Days 5 to 12 and 12 to 19, respectively. Since body weight was not measured at treatment initiation, it is difficult to determine if there was an effect during the first time period. However, food consumption was significantly decreased by 12% on Days -1 to 5 in this group, which correlates with an initial treatment-related effect. Therefore, the decrease in body weight gain in the 100 mg/kg/day males is considered treatment-related.

RBC cholinesterase was measured before dosing on Week -1 and on Days 1, 8, 15 and 22. Statistically significant decreases were observed in the 50 and 100 mg/kg/day females on Day 8 (10% and 12%, respectively). These effects are not considered toxicologically significant given the inconsistency of the findings. Measurements were also performed within 1 hour after test material removal on Days 5, 12, 19, and 26. In males, statistically significant decreases were observed in animals treated at 50 mg/kg/day on Days 12 (10%), 19 (13%) and 26 (8%). In males treated at 100 mg/kg/day, there were significant decreases on Days 12 (20%), 19 (19%) and 26 (19%). Although not statistically significant, there was also a 12% decrease on Day 5 in this group. In females, statistically significant decreases were observed in animals treated at 50 mg/kg/day on Days 12 (16%) and 19 (12%). Using the repeated measures ANOVA test, there was also a significant decrease on Day 5 (12%) in this group. In females at 100 mg/kg/day, there were significant decreases on Days 12 (18%) and 19 (15%) and Day 26 (15%).

The systemic LOAEL is 50 mg/kg/day based on statistically significant decreases in RBC cholinesterase in males and females. The systemic NOAEL is 20 mg/kg/day.

The dermal LOAEL was not established. The dermal NOAEL was 100 mg/kg/day.

This 4-week dermal toxicity study in the rat is **unacceptable (non-guideline)**. The study was intended for use in the short-term and intermediate-term occupational and residential handler risk assessments for the solid formulations of carbaryl. It is considered unacceptable and not upgradeable because only RBC cholinesterase was measured. In the dermal toxicity study with the technical chemical (MRID 45630601), brain cholinesterase inhibition was the most sensitive and reliable endpoint. While this study does support the RBC cholinesterase effects in MRID 45630601, the lack of plasma and brain cholinesterase measurements makes the study unacceptable for use in risk assessment.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Sevin® 80S
   Description: off-white powder
   Lot/Batch #: C8I168025A
   Purity: 80.07% a.i.
   Compound Stability: not provided
   CAS #: not provided

2. Vehicle control: reverse osmosis (RO) water

3. Test animals:
   Species: rat
   Strain: Crl:CD® (SD)IGS BR
   Age/weight at study initiation: 56-62 days; weight - males: 226-281 g; females: 175-224 g
   Source: Charles River Laboratories, Portage, MI
   Housing: Individually in stainless steel cages
   Diet: #8728C Harlan Teklad *ad libitum*
   Water: source not provided *ad libitum*
   Environmental conditions: Temperature: 19-25^{0}C
   Humidity: 30-70%
   Air changes: not stated
   Photoperiod: 12 hrs dark/ 12 hrs light
   Acclimation period: 7 days

B. STUDY DESIGN:

1. In life dates - Start: January 29, 2001 End: February 23, 2001

2. Animal assignment: Animals were assigned using a computerized blocking procedure to the test groups noted in Table 1.

TABLE 1: Study design.

Test Group	Dose (mg/kg bw/d)	# Male	# Female
Control	0	8	8
Low	20	8	8
Mid	50	8	8
High	100	8	8

3. Dose selection rationale

No information on dose selection rationale was provided.

4. Preparation and treatment of animal skin

Shortly before the first application and as needed thereafter, the fur of each test animal was clipped from the dorsal area of the trunk over an area of at least 10% of the body surface. Daily doses were based on the most recently recorded body weights. Dose preparations were made fresh weekly. RO water (1 ml) was placed onto a gauze pad and applied to the test site prior to administering the test material. The test material was then placed on the intact skin and held in contact by a gauze dressing, secured with a nonirritating tape and over wrapped with bandage and tape. Animals were exposed at least 6 but no more than 7 hours/day, 5 days/week for at least 4 weeks. For the control group, 1 ml of RO water was used in place of the test material; the application site was covered using the same procedure as with the test material. At the end of the treatment period, the coverings were removed and the application site was wiped with a towel moistened with RO water.

5. Statistics - Levene's test was used to test for variance homogeneity. If there was a heterogeneity of variance at $p \leq 0.05$, transformations were used to stabilize the variance. One-way analysis of variance (ANOVA) was used to analyze body weights, body weight changes, food consumption and cholinesterase activity. ANOVA was done on the homogeneous or transformed data. If the ANOVA was significant, Dunnett's multiple comparison t-test was used for control vs. treated group comparisons. For each sex, Groups 2 through 4 were compared to Group 1 at the 5.0%, two-tailed probability level. In addition, RBC cholinesterase values for each animal were compared (using the average of the Day -3 and predose Day 1values) by repeated measure ANOVA.

C. METHODS:

1. Observations:

1a. Cageside Observations

Animals were observed twice daily for signs of mortality and moribundity.

1b. Clinical Examinations

Once prior to treatment, on the first day of treatment and weekly thereafter, detailed observations were made prior to dosing with animals outside the cage. Observations included, but were not limited to, changes in skin, fur, eyes and mucous membranes; occurrences of secretions and excretions; and autonomic activity (lacrimation, piloerection, pupil size and unusual respiratory patterns).

Dermal irritation was scored before dosing on Days 1, 8, 15, 22 and 26. The scoring system graded skin reactions for erythema, edema, atonia, desquamation/fissuring from none/normal (0) to slight (1), to moderate (2), to severe/marked (3) for the presence of eschar and exfoliation.

1c. Neurological Evaluations

No evaluations were conducted.

2. Body weight

Animals were weighed once prior to treatment for randomization on Day -3 and on Days 5, 12, 19 and 26.

3. Food consumption

Food consumption was recorded for Days 1-5, 5-12, 12-19 and 19-26.

4. Ophthalmoscopic examination:

Eyes were not examined.

5. Hematology & Clinical Chemistry:

No parameters were measured except RBC cholinesterase. Blood was collected in potassium EDTA tubes from the jugular vein in non-fasted animals once during the week before treatment initiation, before dosing on Days 1, 8, 15 and 22 and within one hour after removal of test material on Days 5, 12, 19 and 26. Blood was chilled until analyzed. The analytical method for

cholinesterase determinations was not stated in the study report; however, a fax dated April 4, 2002, from Ronald Markevitch, supervisor of the clinical pathology laboratory at Covance, stated that the Modified Ellman method was used.

6. Urinalysis

Urine was not examined.

7. Sacrifice and Pathology

No postmortem examinations were conducted.

II. RESULTS

A. OBSERVATIONS:

1. Clinical signs of toxicity - No treatment-related clinical signs were observed.

2. Mortality - All animals survived until the end of the study.

3. Dermal Irritation - There was no dermal irritation in treated or control animals.

B. BODY WEIGHT AND WEIGHT GAIN: There was no treatment-related effect on body weight. The only statistically significant body weight changes were increases in males treated at 20 mg/kg/day and at 100 mg/kg/day on Days 12 to 19. However, in males treated at 100 mg/kg/day, there were decreases relative to control on Days -3 to 5 (15%) and Days 19 to 26 (20%) and an increase on Days 5 to 12 (9%) which were not statistically significant.

TABLE 2. Mean body weight gain during 4 weeks of treatment

Dose rate (mg/kg/day)	Body Weight Gains (g±SD)				
	Days -3 to 5	Days 5 to 12	Days 12 to 19	Days 19 to 26	Days -3 to 26
Male					
0	41 ± 12.1	34 ± 7.0	19 ± 3.7	25 ± 3.7	117 ± 19.9
20	39 ± 6.3	36 ± 6.6	25 ± 5.2*	22 ± 6.2	122 ± 15.5
50	39 ± 6.6	37 ± 8.3	24 ± 3.7	21 ± 11.6	121 ± 18.4
100	35 ± 10.5 (85)	37 ± 7.3 (109)	29 ± 6.2 (153)	20 ± 6.0 (80)	120 ± 24.9
Female					
0	12 ± 10.0	17 ± 6.7	10 ± 4.7	10 ± 5.9	49 ± 13.1
20	17 ± 7.4	16 ± 4.7	7 ± 4.2	10 ± 8.5	50 ± 9.9
50	11 ± 6.3	12 ± 9.8	13 ± 6.4	5 ± 7.9	40 ± 6.7
100	15 ± 9.2	17 ± 7.3	11 ± 8.2	9 ± 7.3	51 ± 13.3

[a] Data obtained from page 34 in the study report.
* Statistically different ($p < 0.05$) from the control.

C. FOOD CONSUMPTION:

The only statistically significant effect was a decrease of 12% food intake in the 100 mg/kg/day males on Days -1 to 5.

D. BLOOD ANALYSES:

RBC cholinesterase was measured before dosing on Week -1 and on Days 1, 8, 15 and 22 (Table 3). Statistically significant decreases were observed in the 50 and 100 mg/kg/day females on Day 8 (10% and 12%, respectively). These effects are not considered toxicologically significant given the inconsistency of the findings. Measurements were also performed within 1 hour after test material removal on Days 5, 12, 19, and 26 (Table 4). In males, statistically significant decreases were observed in animals treated at 50 mg/kg/day on Days 12 (10%), 19 (13%) and 26 (8%). In males treated at 100 mg/kg/day, there were significant decreases on Days 12 (20%), 19 (19%) and 26 (19%). Although not statistically significant, there was also a 12% decrease on Day 5 in this group.

In females, statistically significant decreases were observed in animals treated at 50 mg/kg/day on Days 12 (16%) and 19 (12%). Using the repeated measures ANOVA test, there was also a significant decrease on Day 5 (12%) in this group. In females at 100 mg/kg/day, there were

significant decreases on Days 12 (18%) and 19 (15%) and Day 26 (15%).

Table 3: RBC Cholinesterase Values (UMOL/L) - Before Dosing[a]

Dose (mg/kg/day)	Week -1	Day 1	Day 8	Day 15	Day 22
Males					
0	1139 ± 86	1015 ± 50	1024 ± 44	853 ± 107	1266 ± 56
20	1156 ± 85	1020 ± 101	1063 ± 188	889 ± 77	1326 ± 106
50	1129 ± 83	1076 ± 136	1050 ± 104	876 ± 142	1294 ± 107
100	1090 ± 54	965 ± 112	990 ± 69	737 ± 171 (86)	1251 ± 106
Females					
0	1108 ± 33	1013 ± 74	1044 ± 62	843 ± 170	1278 ± 64
20	1148 ± 56	1045 ± 39	994 ± 99	816 ± 127	1349 ± 100
50	1149 ± 86	1013 ± 126	943 ± 76* ♮ (90)	868 ± 189	1289 ± 114
100	1142 ± 49	953 ± 119	918 ± 70* ♮(88)	800 ± 177	1222 ± 62

a Extracted from Tables 6 (pages 36-37), 7 (pages 38-39), 9 (pages 42-43), 11 (pages 46-47) and 13(pages 50-51).
* Significantly different from control, $p \leq 0.05$, using Dunnett's test
♮ Significant at 5% using a repeated measures ANOVA test
♮♮ Significant at 1% using a repeated measure ANOVA test
(percentage of control value)

Table 4: RBC Cholinesterase Values (UMOL/L) - After Dosing[a]

Dose (mg/kg/day)	Day 5	Day 12	Day 19	Day 26
Males				
0	897 ± 59	1289 ± 75	1275 ± 39	1290 ± 65
20	1095 ± 190* ♮ ♮	1251 ± 138	1307 ± 61	1288 ± 81
50	912 ± 77	1154 ± 55* ♮ ♮(90)	1105 ± 55* ♮ ♮ (87)	1191 ± 78* ♮ (92)
100	787 ± 118 (88)	1035 ± 70* ♮ ♮(80)	1028 ± 70* ♮ ♮ (81)	1051 ± 55* ♮ ♮ (81)
Females				
0	931 ± 114	1305 ± 74	1245 ± 72	1252 ± 79
20	1022 ± 224	1245 ± 76	1198 ± 58	1339 ± 86
50	819 ± 120 ♮(88)	1099 ± 58* ♮ ♮ (84)	1096 ± 66* ♮ ♮ (88)	1223 ± 56
100	956 ± 98	1075 ± 66* ♮ ♮ (82)	1060 ± 98* ♮ ♮ (85)	1066 ± 61* ♮ ♮ (85)

a Extracted from Tables 8 (pages 40-41), 10 (pages 44-45), 12 (pages 48-49), 14 (pages 52-53)
* Significantly different from control, p≤0.05, using Dunnett's test
♮ Significant at 5% using a repeated measures ANOVA test
♮ ♮ Significant at 1% using a repeated measure ANOVA test

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The study author concluded that there was a treatment-related decrease in RBC cholinesterase in animals receiving 50 and 100 mg/kg/day of the test material. However, due to the lack of clinically observed toxicity, the modest reductions in these animals and consistent with the interpretation of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 1998), the NOAEL was 100 mg/kg/day.

B. REVIEWER COMMENTS:

In a non-guideline four-week dermal toxicity study (MRID 45630603), Sevin® 80S (80.07% a.i., Lot C8I168025A) was applied to the shaved skin of 8 Crl: CD (SD)IGS BR rats/sex/dose at dose levels of 0, 20, 50 or 100 mg/kg bw/day, 6 hours/day for 5 days/week during a 4-week period. The parameters measured included the following: clinical observations, body weight, body weight gain, food consumption, RBC cholinesterase and signs of dermal irritation.

There was no treatment-related effect on mortality, clinical observations, body weight or dermal irritation. Body weight gain (relative to control values) in the 100 mg/kg/day males was highly variable between time periods. There were non-significant decreases of 15% and 20% on Days -3 to 5 and 19 to 26, respectively but increases of 9% and 53% were observed on Days 5 to 12 and 12 to 19, respectively. Since body weight was not measured at treatment initiation, it is difficult to determine if there was an effect during the first time period. However, food consumption was

significantly decreased by 12% on Days -1 to 5 in this group, which correlates with an initial treatment-related effect. Therefore, the body weight gain decrease in the 100 mg/kg/day males is considered treatment-related.

RBC cholinesterase was measured before dosing on Week -1 and on Days 1, 8, 15 and 22. Statistically significant decreases were observed in the 50 and 100 mg/kg/day females on Day 8 (10% and 12%, respectively). These effects are not considered toxicologically significant given the inconsistency of the findings. Measurements were also performed within 1 hour after test material removal on Days 5, 12, 19, and 26. In males, statistically significant decreases were observed in animals treated at 50 mg/kg/day on Days 12 (10%), 19 (13%) and 26 (8%). In males treated at 100 mg/kg/day, there were significant decreases on Days 12 (20%), 19 (19%) and 26 (19%). Although not statistically significant, there was also a 12% decrease on Day 5 in this group. In females, statistically significant decreases were observed in animals treated at 50 mg/kg/day on Days 12 (16%) and 19 (12%). Using the repeated measures ANOVA test, there was also a significant decrease on Day 5 (12%) in this group. In females at 100 mg/kg/day, there were significant decreases on Days 12 (18%) and 19 (15%) and Day 26 (15%).

While it can be argued that the decreases from control value in the 50 and 100 mg/kg/day groups were minimal, the effects are considered adverse for the following reasons: 1) there was a dose-response effect; 2) decreases were observed in both males and females; and 3) effects were observed within 1 hour of test material removal (in oral studies, 1 hour is the time of peak effect).

The systemic LOAEL is 50 mg/kg/day based on statistically significant decreases in RBC cholinesterase in males and females. The systemic NOAEL is 20 mg/kg/day.

The dermal LOAEL was not established. The dermal NOAEL was 100 mg/kg/day.

This 4-week dermal toxicity study in the rat is **unacceptable (non-guideline)**. The study was intended for use in the short-term and intermediate-term occupational and residential handler risk assessments for the liquid formulations of carbaryl. It is considered unacceptable and not upgradeable because only RBC cholinesterase was measured. In the dermal toxicity study with the technical chemical (MRID 45630601), brain cholinesterase inhibition was the most sensitive and reliable endpoint. While this study does support the RBC cholinesterase effects in MRID 45630601, the lack of plasma and brain cholinesterase measurements makes the study unacceptable for use in risk assessment.

C. STUDY DEFICIENCIES:

Deviations from the 21/28 day dermal toxicity guidelines (OPPTS 870.3200) included the following:

1) 8 rats/sex/group were used instead of the required 10/sex/group if the study is intended for risk assessment purposes

2) assessment of motor activity, grip strength and sensory reactivity to different types of stimuli was not conducted

3) no clinical pathology testing was conducted

4) plasma and brain cholinesterase were not measured

5) no postmortem examinations were conducted

DATA FOR ENTRY INTO ISIS

Subchronic Dermal (28 day) Study - rodents (870.3200)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
056801	45630603	subchronic	rat	4 week	dermal	dermal	20 - 100	0, 20, 50, 100	20	50	RBC cholinesterase inhibition	Systemic
056801	45630603	subchronic	rat	4 week	dermal	dermal	20 - 100	0, 20, 50, 100	100	not established		Dermal

13544

043564

Chemical:	**Carbaryl**
PC Code:	**056801**
HED File Code	**13000 Tox Reviews**
Memo Date:	**05/01/2002**
File ID:	**TX050582**
Accession Number:	**412-02-0282**

HED Records Reference Center
06/04/2002