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

MAR 24 1995

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Carbaryl (SEVIN XLR PLUS) - Review of a Dermal Absorption Study in Rats

PC Code: 056801 Tox. Chem. No.: 160
DP Barcode: D212592 Submission: S482663

FROM: Yiannakis M. Ioannou, Ph.D., Section Head
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

Y M. Ioannou 3/21/95

TO: Judith Loranger/Linda Propst, PM 73
SRRD (7508C)

THRU: Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (7509C) M van Gemert 3/22/95

Registrant: Rhone-Poulenc AG Co.

Action Requested: Review a dermal absorption study in rats with SEVIN brand XLR PLUS Carbaryl insecticide

Recommendations: Dr. R. Zendzian (Toxicology Branch I) has reviewed this dermal absorption study (DER attached) and his conclusions were as fellows:

Male rats (4/dose/time point)were exposed to SEVIN XRL PLUS at 35.6, 403 or 3,450 ug/cm^2 for 0.5,1,2,4,10 or 24 hours. The percent absorption ranged from 2.14 - 24.9 for the 35.6 ug/cm^2 dose, 1.01-24.7 for the 403 ug/cm^2 dose and 0.07-3.17 for the 3,450 ug/cm$_2$ dose. The results indicate saturation of absorption at the 403 and the 3,450 ug/cm^2, dose levels.

This study is ACCETABLE, and satisfies the Guideline Requirement (85-2) for a Dermal Absorption study.

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PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

March 20, 1995

SUBJECT: Carbaryl, (XLR Plus formulation) dermal absorption in rats

TO: Mike Ioannou Ph.D.
Head Rev Sec I
Toxicology Branch II
Health Effects Division (7509C)

3/30/95

FROM: Robert P. Zendzian Ph.D.
Senior Pharmacologist
Toxicology Branch I
Health Effects Division (7509C)

Compound; Carbaryl — Tox Chem #

Registration # 056801 — MRID 435529-01

Registrant; Rhone-Poulenc — DP Barcode; D212592

Action Requested

Review the following study;

Citation
Dermal Absorption of ^{14}C-Carbaryl (XLR Plus) in male rats (Preliminary and definitive phases) T. Cheng, Hazleton Wisconsin, HWI 6224-206, Jan 18, 1995, MRID 435529-01

Core Classification Acceptable

Conclusions
Male rats were dosed at 35,6, 403 or 3,450 ug/cm^2. Four animals per dose were exposed for 0.5, 1, 2, 4, 10 or 24 hours. Percent absorbed ranged from 2.14 to 24.9, 1.01 to 24.7 and 0.07 to 3.17 for the respective doses. Saturation of absorption was observed at 403 and 3,450 ug/cm^2. See DER for detailed data.

Discussion

This is the second study on a formulation of carbaryl. Data are now available on the dermal absorption of carbaryl

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from the 80S1 and the XLR Plus formulations. In both cases absorption is relatively low with indications of saturation with the XLR Plus formulation. However, the patterns of absorption from the two formulations are distinctly different. Figure 1 plots the percent absorbed against the dose for the two formulations at 4, 10 and 24 hour exposures. The dose-related patterns of absorption clearly show differences by formulation with absorption being less for the XLR Plus formulation. No obvious explanation is available for the differences.

1. Dermal Absorption of ^{14}C-Carbaryl (80S) in male rats (Preliminary and definitive phases) T. Cheng, Hazleton Wisconsin, HWI 6224207, July 27, 1994, MRID 433397-01

Attachment
DER

——— 80S
– – – – XLR Plus

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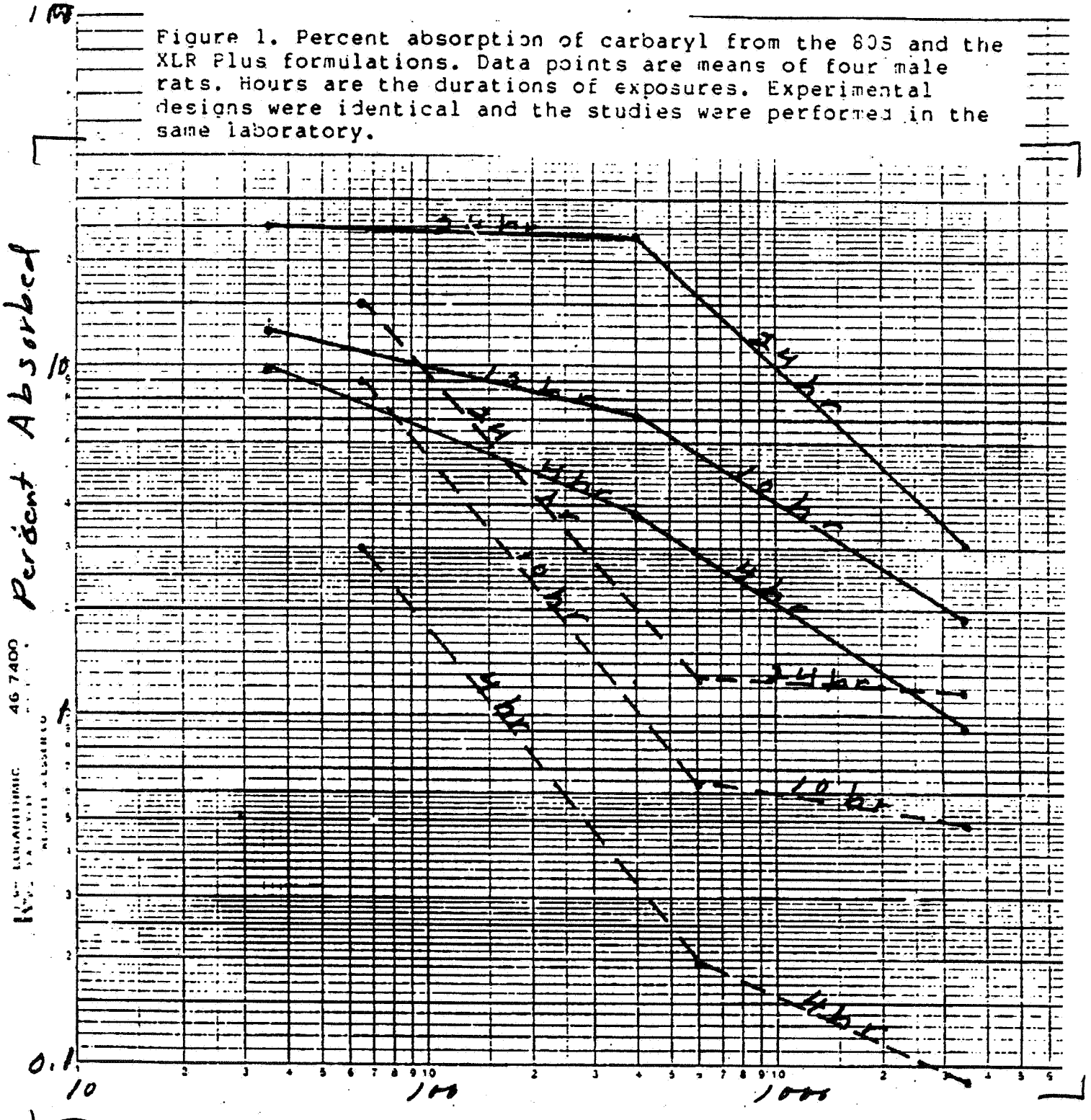
Figure 1. Percent absorption of carbaryl from the 80S and the XLR Plus formulations. Data points are means of four male rats. Hours are the durations of exposures. Experimental designs were identical and the studies were performed in the same laboratory.



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Data Evaluation Report

Compound Carbaryl

Study type Dermal Absorption, FIFRA guideline 85-3

Citation

Dermal Absorption of ^{14}C-Carbaryl (XLR Plus) in male rats (Preliminary and definitive phases) T. Cheng, Hazleton Wisconsin, HWI 6224-206, Jan 18, 1995, MRID 435529-01

3/30/95

Reviewed by Robert P. Zendzian PhD
Senior Pharmacologist

Core Classification Acceptable

Conclusions

Male rats were dosed at 35.6, 403 or 3,450 ug/cm^2. Four animals per dose were exposed for 0.5, 1, 2, 4, 10 or 24 hours. Percent absorbed ranged from 2.14 to 24.9, 1.01 to 24.7 and 0.07 to 3.17 for the respective doses. Saturation of absorption was observed at 403 and 3,450 ug/cm^2.

Materials

Carbaryl CAS name 1-naphthylcarbamate
CAS number 63-25-2
Molecular formular $C_{12}H_{11}NO_2$
Molecular weight 201.2
Physical state colorless solid
Lot # 60408302

^{14}C-Carbaryl
Lot # CSL-92-360-5-31
^{14}C purity 100%
Specific activity 22.04 mCi/mmol

Carbaryl XLR Plus
Lot # E01302183
Chemical Purity 43.9%

Male Charles river Crl:CD®BR rats
approximately 7 weeks of age
from Charles River

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Experimental Design

Phase	Group	Number of Animals	Dose (dilution of 80S)	Dose ai (mg/rat)
Preliminary	1	4	1:99 dilution	0.4
	2	4	Concentrate	44
Definitive	3	2	carrier only	0
	4	24	1:99 dilution	0.8
	5	24	1:9 dilution	8.0
	6	24	Concentrate	40.0

Preliminary phase (1&2) animals were used to test application and collection procedures. Group 3 (control animals) were maintained for 24 hours. Group 4, 5 and 6 animals were exposed, in groups of four animals, for 0.5, 1, 2, 4, 10 and 24 hours.

Dose preparation

"Dose suspensions were prepared by combining known amounts of ^{14}C-Carbaryl, XLR Plus, and 1.0% carboxymethylcellulose (CMC). The carrier, 1.0% CMC, was used for group 3 (control). The actual measurements are listed below. Components were mixed with magnetic stir bars and vortex-mixing. Radioactivity levels and homogeneity were determined immediately after preparation. The dose suspensions were stirred at 4° C overnight until dosing. Aliquots collected before and after dosing were analyzed to confirm radioactivity levels, homogeneity and radiochemical and chemical purities.

Group	^{14}C-Carbaryl(mg)	XLR Plus(g)	1% CMC(g)
1	0.374[a]	0.0091	0.9963
2	0.344[a]	1.1719	none
4	1.200	0.0286	3.1403
4[b]	1.570	0.0299	3.0293
5	1.30	0.3680	2.7856
6	1.19	3.6014	none

a. calculated values
b. due to low recovery 8 animals were redosed on July 14, 1994"

Dose Administration

"One day before dosing (preliminary and definitive), the back and shoulders of each animal were shaved, and the shaved area was washed with water. Care was taken not to abrade the skin. The site for application of the test material was defined by a plastic enclosure (approximately 12.5 cm^2), which was affixed with cyanoacrylate-based glue. Medical

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silicone adhesive Type A was applied on the outside of the enclosure for sealing purposes. An Elizabethan collar was placed on the animal's neck to prevent ingestion of the test material.

The radiolabeled dosing suspensions were sonicated and mixed using a vortex mixer before aliquots were taken. At dosing, 100 ul of the dosing suspension was applied within the enclosure along the midline of the skin site. The weight of the dosing syringe was recorded before and after dosing. The test material was spread across the skin site using a glass stirring rod (spreader). The spreader was then rinsed with approximately 5 ml of menthanol (2:1, v/v) and wiped with a guaze pad, the rinse and wipe were collected for analysis. Duplicate predose and post dose aliquots for each treated group were taken for dose verification.

After adminiatration of the test material, the application site was covered with a nonocclusive (filter Paper) cover. The animals had Elizabethan collars put on to protect the dose application site."

Animals were placed individually in metabolism cages and total urine and feces collected for the duration of the exposure period.

Termination

Animals were anesthetized with ketamine i.m. and the Elizabethan collar removed. The nonocclusive cover was collected and the application site washed with soap and water in situ. The following samples were collected for analysis;

nonocclusive cover
wash
urine and residual bladder urine
feces
skin at the application site
enclosure
blood
residual carcass
cage wash
cage wipe

Results

Dose distribution of the definitive study, as percent of dose, is presented in Table A. Doses are presented as actual dose applied based on analysis of dosing suspensions and quantitation of individual doses applied. Data indicate that absorption is saturated at the doses of 403 and 3,450 ug/cm^2.

Table A. Mean dose distribution of carbaryl from the XLR Plus formulation. Mean of
6, 7 and 8 of the report.

Exposure Duration (hours)	Cover[1]	Skin Wash	Application Site Skin	Blood	Carcass	Urine	Feces	Cage[2]
35.6 ug/cm^2								
0.5	0.34	86.3	9.07	0.09	1.79	0.26	ND	ND
1	0.73	83.5	7.73	0.16	4.03	0.24	<0.005	0.21
2	0.87	75.7	11.4	0.13	3.50	1.29	ND	0.47
4	0.63	77.2	6.18	0.14	4.76	4.65	0.03	0.25
10	0.99	74.0	8.38	0.06	4.13	7.28	0.07	1.15
24	1.25	60.9	9.09	0.03	2.78	16.4	1.60	4.05
403 ug/cm^2								
0.5	0.32	90.9	2.89	0.04	0.92	0.05	ND	ND
1	0.28	89.9	2.03	0.05	1.45	0.19	<0.005	0.04
2	0.39	87.7	2.39	0.04	1.27	0.62	ND	0.15
4	0.57	87.7	2.70	0.06	1.97	1.55	ND	0.23
10	0.56	82.3	3.39	0.10	3.28	3.02	0.03	1.02
24	1.09	64.6	3.15	0.06	3.12	16.1	1.92	3.46
3,450 ug/cm^2								
0.5	0.26	97.5	0.63	<0.005	0.06	0.01	ND	ND
1	0.28	97.2	0.66	0.01	0.65	0.03	ND	ND
2	0.23	95.7	0.92	0.01	0.56	0.06	ND	0.03
4	0.26	95.1	0.72	0.01	0.60	0.30	ND	ND
10	0.20	94.3	0.56	0.01	0.70	1.04	<0.005	0.16
24	0.82	90.5	0.80	0.01	0.71	1.72	1.72	0.46

1. sum of Non-occlusive cover and enclosure rinse.
2. Sum of cage wash and cage wipe.
3. Sum of blood, carcass, urine, feces and cage.

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Table A. Mean dose distribution of carbaryl from the XLR Plus formulation. Mean of f
6, 7 and 8 of the report.

Exposure Duration (hours)	Cover[1]	Skin Wash	Application Site Skin	Blood	Carcass	Urine	Feces	Cage[2]
35.6 ug/cm^2								
0.5	0.34	86.3	9.07	0.09	1.79	0.26	ND	ND
1	0.73	83.5	7.73	0.16	4.03	0.24	<0.005	0.21
2	0.87	75.7	11.4	0.13	3.50	1.29	ND	0.47
4	0.63	77.2	6.18	0.14	4.76	4.65	0.03	0.25
10	0.99	74.0	8.38	0.06	4.13	7.28	0.07	1.15
24	1.25	60.9	9.09	0.03	2.78	16.4	1.60	4.05
403 ug/cm^2								
0.5	0.32	90.9	2.89	0.04	0.92	0.05	ND	ND
1	0.28	89.9	2.03	0.05	1.45	0.19	<0.005	0.04
2	0.39	87.7	2.39	0.04	1.27	0.62	ND	0.15
4	0.57	87.7	2.70	0.06	1.97	1.55	ND	0.23
10	0.56	82.3	3.39	0.10	3.28	3.02	0.03	1.02
24	1.09	64.6	3.15	0.06	3.12	16.1	1.92	3.46
3,450 ug/cm^2								
0.5	0.26	97.5	0.63	<0.005	0.06	0.01	ND	ND
1	0.28	97.2	0.66	0.01	0.65	0.03	ND	ND
2	0.23	95.7	0.92	0.01	0.56	0.06	ND	0.03
4	0.26	95.1	0.72	0.01	0.60	0.30	ND	ND
10	0.20	94.3	0.56	0.01	0.70	1.04	<0.005	0.16
24	0.82	90.5	0.80	0.01	0.71	1.72	1.72	0.46

1. sum of Non-occlusive cover and enclosure rinse.
2. Sum of cage wash and cage wipe.
3. Sum of blood, carcass, urine, feces and cage.