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Chemical:	**Carbofuran (ANSI)**
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CASWELL FILE

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

JUN 26 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

PC 090601

SUBJECT; Carbofuran; EPA Reg.#279-2875 (Furadan 75 WP) and EPA Reg.#279-2876 (Furadan 4 F); also FMC 35001 4 EC (unregistered Carbofuran analog). CASWELL #160A

FROM: Amal Mahfouz, Toxicologist
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Amal Mahfouz 5/13/81
FDC 5/13/81

TO: Jay Ellenberger (12)
Registration Division (TS-767)

THRU: Chris Chaisson, Acting Chief
Toxicology Branch, HED (TS-769)

Action Requested:

FMC has submitted the following human oral and dermal studies for review and inclusion in the Carbofuran file:

I. Human oral study with Carbofuran analytical grade (a.g.). Accession#241303

MRID 00092826

A. Acute Oral (QRC, 9/17/76)
B. Carbofuran Metabolites in Urine (MRI#4230-B, 7/15/77).

II. Human dermal studies with Furadan 75 WP. Accession#241303

A. Single Dermal Dose, at high temperature and humidity (QRC, 3/18/77)
B. Single Dermal Dose, at low temperature and humidity (QRC, 3/18/77)
C. Multiple Dermal Dose, at high temperature and humidity (QRC, 3/18/77)
D. Carbofuran Metabolites in Urine (MRI#4230-B, 7/15/77)

°Toxicity data on two subjects treated at the mid-dose level (0.1 mg/kg) in the oral study (I-A) need to be reported (4 subjects treated at 0.1 mg/kg in the MRI report, only 2 subjects reported in the QRC report).

°Clarification are also needed concerning the difference of the actual dosages 23 and 29 mg/kg from the nominal dosage 32 mg/kg in the (dermal study with Furadan 75% WP (II-B).

°Analysis of Carbofuran/metabolites in urine demonstrated that less than 50% of the initial dosage was eliminated in urine in the oral study (I-B) and less than 3.5% in the dermal study (II-D). Data on the level of Carbofuran/metabolites in blood should be submitted for review (blood samples were taken to be analyzed, see I-A, p. 17 and II-A, p. 22 of the submitted reports).

°Data were not adequately reported for some parameters. The individual data for each subject are required at each monitoring interval. The following data should be submitted:

Oral study (I-A Carbofuran analytical grade) Individual data for hematology, urinalysis and blood chemistry; and the preadmission values for these parameters. Also clear documentation of baseline and 0-hour values.

Dermal Study (II-A, B, C - Furadan 75 WP)

1. Symptoms
2. Pupil size and Eye accommodation
3. Pulse rate, blood pressure, and EKG
4. Respiration rate and body temperature
5. Fukuda test and Romberg
6. Laboratory values (hematology, urinalysis, and blood chemistry) pre- and post-treatment; and clear documentation of baseline and 0-hour values.
7. Age and weight for subjects in part B only.

Dermal Study (III-A - Furadan 4F and III-B - FMC 35001 4EC)

1. Pupil size* and Eye accommodation
2. Pulse rate*, blood pressure*, and EKG
3. Respiration rate and body temperature
4. Laboratory values (hematology, urinalysis, and blood chemistry) pre- and post-treatment; and clear documentation of baseline and 0-hour values.

*Only the average of all determinations was presented at the end of the 24-hours monitoring period.

III. Human dermal studies with Furadan 4F and FMC 35001 4EC (a Carbofuran analog). Accession#241305

A. Single Dermal, Furadan 4F (QRC#152.03; 2/15/78)
B. Single Dermal, FMC 35001 (QRC#152.03; 2/15/78)

IV. Human dermal study with Furadan 75 WP (IBT Study#F-9426; 8/12/71). Accession#241304.

This study is currently under validation by Clement Associate Inc.

Related Petitions: 6F1875, 6F1803, 6F1789, 6F1787, 6F1701, 6F1672, 5F1527 and 5F1530.

Recommendations:

These studies(I-III listed above)are classified as supplementary data.

No effect except for a marginal RBCChE inhibition (22% and 11% in two subjects respectively) was noted at 0.05 mg/kg in the oral Carbofuran study (I-A) listed above. This level was 20 times lower than the NOEL of 1 mg/kg/day for Carbofuran based on a two-year rat feeding study.

Acute responses were also noted at 0.25 mg/kg Carbofuran in this study; 2.0 mg/kg Furadan 75 WP in the dermal (II-A above). Acute responses were also observed at 4.0 mg/kg in the Furadan 4F study after dermal exposure (III-A above) and at 16 mg/kg in the FMC 35001 4EC - dermal study (III-B above).

These studies are classified as supplementary data due to of the following findings:

°Baseline values were erratic for some parameters in all these studies in the control subjects and some test subjects i.e. vestibular mechanisms and PChE in study I-A p. 2, 3 and 5 of the review; PChE in study II-A p. 4; RBCChE in study II-C p. 7; blood chemistry in study III-B p. 5. Other erratic baseline and control values were not discussed in the reviews because more data were needed.

°PChE determinations were generally erratic. RBCChE determinations were erratic in the FMC 35001 4EC study (III-B, dermal). These data indicate that some blood samples may not have been immediately analyzed after collection. Voss and Sachsse method used for blood ChE determinations in all these studies uses propionylthiocholine for substrate, this substrate is non-specific for AChE and may have affected the RBCChE data especially in the FMC 35001 4EC study.

Summary of Carbofuran Toxicity Data

	Study	Formulation	Results	Core-Classification
I-A	Single Oral Dose Human (M)	Analytical grade	0.05 mg/kg - lowest dose level (2 subjects): No effect noted except for a nominal decrease in ChE activity. RBCChE - 11% adn 22%. PChE - 32% and 36%. 0.1 mg/kg - mid dose (2 subjects): Symptoms - headache in one subject and lightheadedness in the other. RBCChE inhibition - 33% and 31%. PChE inhibition - 56% and 35%. 0.25 mg/kg - highest dose level (4 subjects): Symptoms - Severe cholinergic poisoning. RBCChE inhibition - 46% and 63%. PChE inhibition - 33% and 100%. (Pre-admission data are required before assessing hematology, blood chemistry, and urinalysis data)	Supplementary
I-B	Metabolism - Human (M)	Analytical grade	7-phenol is the major metabolite in urine as a result of oral exposure; less than 50% of the test compound was recovered in urine.	Supplementary

	Study	Formulation	Results	Core-Classification
II-A	Single Dermal Dose Human (M)	Furadan 75% WP	NOEL or LEL was not determined because data for doses (0.5 and 1.0 mg/kg) lower than the highest level were not completely reported (2 subjects/dose). 2.0 mg/kg - highest dose level (2 subjects): Symptoms - Severe cholinergic poisoning requiring atropine administration. RBCChE inhibition - 46% and 65%. Traces of protein in urine, and slightly increased SGOT. (exposure: 4 hrs at 85-95°F and 68%-89% RH).	Supplementary
II-B	Single Dermal Dose	Furadan 75% WP	No symptoms at any dose level tested (2.0, 4.0, 8.0 and 32.0 mg/kg; 2 subjects/dose). No significant effect was noted at 2, 4 or 8 mg/kg dose levels. At 32 mg/kg (actually 23 and 29 mg/kg), RBCChE inhibition was 24% in one subject (29 mg/kg) and GGT increased by 300% in the other subject (23 mg/kg). (exposure: 4 hrs at 70-75°F and 35%-40% RH).	Supplementary
II-C	Multiple Dermal Dose Human (M)	Furadan 75% WP	1.0 mg/kg/day applied for 4 hrs at 85-95°F and 68-89% RH on 3 consecutive days (2 subjects): caused 26%-29% RBCChE days inhibition in the second day of treatment in both subjects, 80% increased in BUN value at the end of the third day in one subject.	Supplementary

	Study	Formulation	Results	Core-Minimum
II-D	Metabolism - Human (M)	Furadan 75% WP	7-phenol is the major metabolite in urine as a result of dermal exposure; 0.0 to 3.8% of the test compound was recovered in urine.	Supplementary
III-A	Single Dermal Dose - Human (M)	Furadan 4F	LEL = 0.5 mg/kg - Lowest dose level (2 subjects): Symptoms - burning sensation at application site in one subject, and stomach discomfort in the other. RBCChE - 22% and 7%. PChE - 46% and 33%. 4 mg/kg - highest dose level (2 subjects): Symptoms - Severe cholinergic poisoning requiring atropine administration. RBCChE - 69% and 49%. Increased total protein in one subject. (exposure: 4 hrs at 90-95°F and 70%-80% RH).	Supplementary
III-B	Single Dermal Dose - Human (M)	FMC-35001-4EC	LEL = 0.5 mg/kg - Lowest dose level (2 subjects): Symptoms - Headache PChE inhibition - 12% and 46%. 16 mg/kg - highest dose level (2 subjects): Symptoms - Severe cholinergic poisoning (both subjects). RBCChE inhibition - 34% and 35%. (exposure: 4 hrs. at 90-95°F and 70%-80% RH).	Supplementary
IV	Single Dermal Dose - Human (M)	Furadan 75% WP	IBT study - under validation by Clement Associates.	

I. Human Acute Oral Toxicity

"Evaluation of the Safe Exposure Levels to Carbamate, Administered Orally to Healthy Adult Normal Male Volunteers"; John D. Arnold; Quincy Research Center (QRC), 9/17/76; and MRI Project No. 4230-B, 7/15/77. Accession#241303

I. Material and Methods

Test Substance - Carbofuran, analytical grade.

Nine caucasian, healthy male subjects were selected for this study from a pool of volunteers at Quincy Research Center. The subjects, were 23-47 years old and weighed 60-95 kg.

Three single oral doses of Carbofuran were tested: 0.05, 0.1, and 0.25 mg/kg. One dose level was evaluated at a time on two subjects starting with 0.05 mg/kg. Data generated from the 24-hour post-treatment were evaluated before proceeding to the next higher dose level. Different subjects were used at each dose level.

According to the investigators the dose which produced noticeable side effects (0.25 mg/kg) was further evaluated on two more subjects and one control subject. The control subject was given placebo.

All subjects took a breakfast before dose administration, then were confined to their beds for two hours and were permitted only minor ambulatory activity from 2-8 hours post drug administration. Cigarette smoking was permitted during this study.

The subjects remained under observation for 24 hours. During this time they were monitored for signs and symptoms of toxicity i.e. headaches, nausea, lightheadedness, dry mouth, salivation, vomiting, drowness, dizziness, unsteadiness, abdominal pain, diaphoresis, nervousness and weakness. The subjects were also monitored for the following parameters:

Blood cholinesterase activity* i.e. plasma and erythrocytes: 0-hour (pre-dosing), 1/2, 1, 2, 3, 6 and 24 hours.

EKG: 0-hr (pre-dosing), 1, 4 and 24 hrs. Measurements were also done at 2 and 3 hours for the high dose group and control subject.

Blood pressure, heart rate, temperature, and respiration: -1, -1/2 and 0 hr (pre-dosing), 1/4, 1/2, 3/4, 1, 1 1/2, 2, 3, 4, 5, 6, 7, 8, and 24 hrs.

Vestibular function (Fukuda step test and Romberg test): 0-hr (pre-dosing), 1, 2, 3, 4, 5, 6, 7, 8, and 24 hrs.

Pupil size and eye accommodation: 0-hr, 1, 2, 3, 4, 5, 6, 7, 8 and 24 hrs.

Hematology, urinalysis and blood chemistry: 0-hr and 24 hrs after dosing (baseline is within 14 days of pre-dosing)

Carbofuran and metabolites in urine: -6, and 0-hr (pre-dosing), 1, 2, 3, 4, 5, 6, 8, 16 and 24 hrs.

All subjects had a complete physical before selection for this study and after the 24-hours monitoring period. During the study, the subjects were under a physician's care.

*Cholinesterase activities were determined according to the method described by Voss, G. and Sachsse, K. "Toxicology and Applied Pharmacology, 16:764-777, 1970".

II. Results

A. Symptoms

0.05 mg/kg dosage: No overt symptoms or effects were noted.

0.10 mg/kg dosage: One subject had headache, and the other was lightheaded.

EKG for one subject reflected 25% decrease in the sinus rate as compared to the basline and the 0-hr determination. This subject also exhibited Sinus Arrhythmia (SA) and Sinus Bradycardia (SB); both SA/SB were noted at 4 and 24 hours post-treatment as compared to a normal baseline.

This subject also exhibited deterioration in the vestibular mechanism at the end of the 24-hour observation; however his baseline response was already abnormal (measured by the Fukuda step test*). These effects could not be fully assessed because of erratic data on the second subject and the control. Cigarette smoking may have affected these data.

The effect of Carbofuran was insignificant on pupil size and eye accommodation at this dose level.

0.25 mg/kg dosage: Symptoms analogous to those usually attributed to cholinesterase inhibition (drowziness, nausea, dizziness, nervousness, vomiting, headaches, weakness, dry mouth, salivation, unsteadiness, abdominal pains, and diaphoresis) were observed within the first 3 hours in three of the four subjects; the fourth subject exhibited nausea only within the first half hour post-treatment.

Changes in heart rate, lower body temperatures, and lower respiration rate were also noted in these subjects. The symptoms could be correlated in their severity and incidence with the extent and duration of RBC ChE inhibition.

EKG results reflected SB in 3 subjects after 3 to 4 hours post-treatment. One test subject did not recover after 24-hours. The noted SB in these subjects was paralleled by an average of 25% decrease in the Sinus rate; the subject that did not recover from the SB at the end of the study also a exhibited sharp increase (54%) in sinus rate in the first hour before the subsequent decrease (25%) stated above.

Vestibular mechanisms* were abnormal and deteriorating after one hour post-treatment in two** of the four subjects. One of these two subjects had a positive Romberg (could not stand up) after one hour post-treatment, this effect paralleled a 54% increase in Sinus rate. The other two subjects did not show any deterioration in vestibular mechanisms; however their response was abnormal prior to dosing and one of them remained with abnormal response until the end of the 24 hours monitoring period.

*The vestibular mechanism reflects the ability of the subjects to stand up, The Fukuda Step Test Results were reported as 3 sets of responses:

1. Normal, Borderline, or Abnormal
2. Same, Improved, or Deteriorating
3. Positive Romberg

**These two subjects were the only non-smokers in this study

All 4 subjects treated at 0.25 mg/kg dosage level had constricted pupils and increased eye accommodation. Pupil constriction and eye accommodation did not completely return to normal at 24 hours post-treatment in two subjects, one of these two subjects remained with severe pupil constriction even after 24 hours post-exposure.

B. Blood Cholinesterase

1. Red Blood Cells Cholinesterase (RBC ChE)

The RBC ChE inhibition reflected a dose response relationship i.e. 22% and 11% decrease at 0.05 mg/kg; 35 and 31% decrease at 0.10 mg/kg; 62%, 63%, 46% and 59% decrease at 0.25 mg/kg; and 10% for placebo.

At 0.05 mg/kg dose level, 11% is the maximum decrease in RBCChE activity in one subject tested. This decrease is within the normal range of RBCChE activity fluctuation as discussed in Ref(1)*. The 22% decrease in the second subject reflects a marginal effect.

At 0.1 mg/kg dose levels the maximum RBC ChE depression was detected one hour post-treatment and returned almost to normal after three hours post-treatment.

At 0.25 mg/kg dose level the maximum RBC ChE inhibition occcurred after three hours in one subject and one hour in the other three subjects; RBC ChE activity was almost back to normal after six hours treatment.

2. Plasma Cholinesterase (PChE)

PChE determinations reflected a maximum reduction in activity of 36% and 32% after 1 hour post-treatment at 0.05 mg/kg; 56% and 35% after 1/2 hour post-treatment at 0.1 mg/kg; and 53%, 33%, 100% and 81% after 2-6 hours post-treatment at 0.25 mg/kg.

Plasma cholinesterase activity levels were low prior to dosing in some subjects, which imply a greater degree of actual cholinesterase depression. The control subject showed 42% to 54% maximum reduction in PChE activity in the first hour. Conditions causing such reduction in the control subject and among subjects prior to dosing with Carbofuran were not explained in this study and should be clarified by the registrant.

*Ref(1) Toxicology of Anticholinesterase Pesticides by Elsa Reiver, Yogoslav Academy of Sciences and Arts. Zagreb. EPA-600/1-77-031, June 1977.

C. Hematology, Urinalysis and Blood Chemistry

Because the determinations of these parameters demonstrated erratic values prior to dosing, these findings are not considered useful. Individual data for each determination and the subjects health history are requested from the registrant.

D. Carbofuran Metabolites in Urine (MRI Report)

7-phenol was the major metabolite in urine of subjects treated at 0.05, 0.10, 0.25 mg/kg dose levels. The maximum level of 7-phenol was 23.7 ug/ml; this level was detected in urine of a subject exhibiting serious toxic symptoms at 0.25 mg/kg dose level. According to the MRI investigators, 7-phenol found in urine of some Furadan plant workers was 3 times higher than this maximum level (23.7 ug/ml) without indication of any illness.

Small amounts of unmetabolized Carbofuran, 3-keto-7-phenol, 3-hydroxy-7-phenol, 3-keto carbofuran and 3 hydroxycarbofuran were detected in all samples at a level of 1% to 8% of the administered dosages. Most of the detected 7-phenol metabolite was found in the first 8 hours post-treatment.

The total amount of Carbofuran metabolites detected in urine at the end of 24-hour monitoring period was 38.05% at 0.05 mg/kg dosage; 49.40% at 0.10% mg/kg dosage (one of the four subjects treated at 0.1 mg/kg dose level in this MRI section was not included in this average because of the exceptionally high 74% recovery level); and 38.55% at 0.25 mg/kg dose level.

Considering that the level of carbofuran/metabolites in urine is less than 50% of the actual Carbofuran dosages, and considering that the study indicates that the blood will be analyzed for Carbofuran/metabolites levels (p. 17 of this report, last paragraph), the registrants are asked to submit the data on the Carbofuran/metabolites in blood.

III. Conclusion

Based on the data presented in the Quincy and MRI report, the 0.25 mg/kg dose level caused serious toxic symptoms typical of cholinergic poisons in three of the four exposed subjects, and a high level of RBCChE inhibition of 46% to 63%. Also PChE inhibition was as high as 80% to 100% in two of these subjects.

Two subjects treated at the 0.1 mg/kg dose level exhibited headache, lightheadness, and moderate reduction in RBC ChE (31% and 35%) and PChE (35% and 56%). A decrease of 38-52% in platelets level was also noted in one of these two subjects.

Four subjects treated at the 0.1 mg/kg dose level were monitored for Carbofuran metabolites in urine according to the MRI report. Consequently, toxicity data should have been available in the QRC report on 2 other subjects and the registrants should be asked to submit these data.

The two subjects treated at the lowest dose level 0.05 mg/kg, demonstrated a marginal response to Carbofuran (11% and 22% RBCChE inhibition, and 32% and 36% PChE inhibition). This dose level is 20 times lower than the NOEL of 1 mg/kg/day for Carbofuran based on a two year rat feeding study, (TOX tolerance printout 9/11/80).

Effects on PChE, EKG, and vestibular mechanism could not be fully assessed in this study because of the inconsistent and erratic values obtained for the control and test subjects.

More than 50% of the administered Carbofuran was not detected in urine. The registrants are asked to submit available data on Carbofuran/metabolites in blood.

The method used for blood ChE determinations, Voss and Schsse, uses propionylthiocholine for substrate. This substrate is non-specific for RBCChE. Also the report (MRI#4230-B, report#1 p. 13) indicates that the procedure as used in this study "may be result in obtaining figures which do not reflect the maximum quantity of circulating Carbofuran" in the blood.

This study is classified supplementary data because data on the control subject and the baseline values for some test subjects were inadequate. Individual data for hematology, urinalysis and blood chemistry determinations, and the subjects preadmission values for these parameters should be requested from the registrant.

II. "Carbamate (Carbofuran) Human Dermal Study - Final Report" John D. Arnold; Quincy Research Center (QRC), 3/18/77; and MRI Project No. 4230-B; 7/15/77; Accession No. 241303

I. Materials and Methods

Test Substance - Furadan 75 WP, a Carbofuran formulation with 75.0% active ingredient.

Eighteen healthy adult males, age 18-55 years, were selected from a Quincy Research volunteer pool for this study. The study was conducted in three parts (A, B, C) to determine the threshold toxicity level to simple and multiple doses of Carbofuran under normal and elevated temperature and humidity.

Eight subjects were arbitrarily assigned to part A, another eight to part B, and the last two were assigned to part C. Different subjects were used at each dose level in each part of this study.

Baseline blood and urine laboratory determinations were done for each subject after overnight fast; they were then given a standard breakfast before Carbofuran administration. The test compound was applied directly to the subject's backs and liquid (water, artificial sweat, or saline) was added to give a 50% mixture (1g powder/ml liquid). The mixture was spread on a designated area of the upper back. The subjects immediately began a mild work cycle of 5 minutes excercise and 15 minutes rest; this cycle was repeated 11 times over a four hour period. The test substance was then removed and the subjects were monitored for the remainder of the 24-hour post-treatment period in part A and B, and for 3 days in part C (multiple dose). Tobacco smoking was permitted during this study.

Part A

Ascending dermal doses of Furadan 75% WB were tested under conditions of high temperature 85-95°F and humidity 68-89% RH. Eight subjects, age 25-53 years, weighing 63-78 kg and 156-182 cm tall were tested in groups of two per dose level.

The first group received a placebo application, the second group received a 0.5 mg/kg dose level, the doses were then doubled for subsequent groups until a minimum effect level *(threshold toxic level) was reached.

*Minimum effect level: level which produces mild but definite clinical symptoms.

The following doses were used in this part:

Dose mg/kg (a.i.)	Medium	Actual Dose per subject mg/kg (a.i.)
0.5	water	0.302, 0.502
1.0	water	1.007, 0.969
2.0	Artificial sweat	2.070, 2.007

Part B

The subject's weights and ages were not identified in this part. The subjects were also tested in groups of two in ascending order under conditions of normal temperature 70-75°F and humidity 35-40% RH. The first group received 2.0 mg/kg Carbofuran (the highest dose tested under conditions of high temperature and humidity). The doses were generally doubled for subsequent groups until toxicity was noted. All doses were spread on the subject's backs with saline. The following doses were used in this part:

Dose mg/kg (a.i.)	Actual Dose per subject mg/kg (a.i.)
2.0	1.566, 1.616
4.0	3.990, 4.090
8.0	8.033, 8.002
32.0	23.047, 29.287

The actual dosage/subject at 32 mg/kg dose level is low in both subjects (23.047 mg/kg in one subject and 29.047 mg/kg in the second subject), explanation of this difference is needed from the registrant.

Part C

Two subjects were treated at 1 mg/kg dose level on 3 consecutive days, under conditions of high temperature 85-95°F and humidity 68-89% RH as in Part A. All doses were spread on the subject's back with normal saline. The following table represents the actual dose level per subject in the three consecutive days of treatment:

Subject	Dose mg/kg/day (a.i.),	Actual Dose per Subject
1st	1.0	0.946; 1.007; 0.968
2st	1.0	1.030; 0.986; 1.010

All subjects in parts A, B and C remained under observation for 24 hours. During this time they were monitored for signs and symptoms of toxicity i.e. Lightheadedness headaches, nausea, dry month, salivation, vomiting, drowziness, dizziness, unsteadiness, abdominal pain, diaphoresis, nervousness and weakness. The subjects were also monitored for the following parameters:

-Blood cholinesterase activity* i.e. plasma and erythrocytes: 0-hour (pre-dosing), 1/2, 1, 2, 3, 6 and 24 hrs (0-hr is the baseline).

-EKG: 0-hr. (pre-dosing), 1, 4 and 24 hrs. Measurements were also done at 2 and 3 hours for the high dose group and control subject.

-Blood pressure, heart rate, temperature, and respiration: -1, -1/2, and 0-hr (pre-dosing), 1/4, 1/2, 3/4, 1, 1 1/2, 2, 3, 4, 5, 6, 7, 8, and 24 hrs.

-Vestibular function (Fukuda step test and Romberg test): 0-hr (pre-dosing), 1, 2, 3, 4, 5, 6, 7, 8 and 24 hrs.

-Pupil size and eye accommodation: 0-hr., 1, 2, 3, 4, 5, 6, 7, 8 and 24 hrs.

-Hematology, urinalysis and blood chemistry: 0-hr and 24 hrs after dosing. Baseline values determined before breakfast.

-Carbofuran and metabolites in urine: -6, 0-hr (pre-dosing), 0-1, 1-2, 2-4, 4-8, 8-16 and 16-24 hrs.

All subjects underwent a complete physical before selection for this study and after the 24 hours monitoring period. During the study, the subjects were under a physician's care.

*Cholinesterase activities were determined according to the method described by Voss, G and Sachsse, K "Toxicology and Applied Pharmacology, 16:764-777, 1970".

II. Results

A. Part A

1. Blood Cholinesterase

Except for one subject treated with 1.0 mg/kg dose level RBCChE inhibition reflected a dose-response relationship i.e.:

0.5 mg/kg - 20% and 23% inhibition
1.0 mg/kg - 39% and 9% inhibition
2.0 mg/kg - 46% and 65% inhibition

Cholinesterase data were compared to the 0-hour pretreatment data as baseline.

RBCChE inhibition decreased substantially by the 8th hour of exposure at all dose levels, and the enzyme activity returned almost to normal in all subjects by the end of the 24-hour monitoring period.

It is important to note that the two subjects treated at the 2 mg/kg dose level experienced a severe enough cholinergic effect as to require atropine administration after 5 hours post-treatment in one subject, and after 4 1/4 hours, 5 hours and 5 1/4 hours post-treatment in the other. This second subject was removed from treatment after 2 hours and 50 minutes of exposure and the test substance washed from his back.

PChE values were erratic at all dose levels (including placebo) in this study (including part A, B and C), and were inconclusive in assessing the effect of Carbofuran on ChE inhibition.

2. Symptoms, Hematology, Blood Chemistry and Urinalysis

No symptoms were reported for subjects treated at the 0.5 and 1.0 mg/kg dose levels. The investigators reported also that no effects were noted at these levels in hematology, blood chemistry and urinalysis data. The two subjects treated at 2.0 mg/kg experienced classical cholinergic inhibition symptoms that paralleled in severity the degree of RBCChE inhibition in these subjects. The report states that hemograms were not affected but no data was presented.

One subject (RE) at 2 mg/kg was weak and shaky after 3 1/2 hours of exposure; these symptoms paralleled a 29% to 46% RBCChE inhibition level. This subject was given 2 mg of atropine-IM 5 hours post-treatment, however a 44% RBCChE inhibition level was maintained through the 6th hour of exposure. RBCChE activity was normal at the end of the 24 hour monitoring period. Traces of protein were detected in urine at the end of the 24 hour monitoring period.

The second (CB) subject reported lightheadedness, "hazy vision" and hunger 2 1/2 hours post-treatment, which paralleled 33% to 53% RBCChE inhibition level, twenty minutes later he began to vomit. This subject was directly removed from the excercise regimen, and the test substance was washed from his back. However, he still experienced an urge for defecation and severe muscle cramps with his bowel movement. By the 4th hour post-treatment the subject was vomiting, shaking, chilling and extremely weak, these symptoms paralleled an increase in RBCChE inhibition from 53% to 65%. Subsequently the subject was administered 2 mg atropine-IM at 4 1/4 hours, 5 hours, 5 1/4 hours post-treatment. For the rest of the day the subject remained tired and exhausted, the RBCChE inhibition dropped to 17% and 10% by the 8th and 10th hour and returned completely to normal after 24 hours post-treatment.

This subject was asymptomatic by the end of the monitoring period, but had a slightly increased SGOT value of 61 IU at the end of the monitoring period. This increase reflects 7% higher SGOT than the baseline.

3. Other Effects

A summary was reported in this study concerning the results associated with the effect of the test substance on the vital signs, vestibular function and eyes of the subjects.

a. Electrocardiograms: No effect was noted. However, the condition of the two subjects treated at 2 mg/kg was serious enough to require atropine administration. EKG data were obtained after this administration which may explain why no Carbofuran related effect was noted at 2 mg/kg dose level.

b. Vital Signs: Subject (RE) manifested elevated erect pulse rate long after his excercise had ended at 4 hours post-treatment i.e. 144, 150 and 130 bpm at 4, 5, and 8 hours respectively; subject (CB) experienced supine tachycardia with pulse rates of 100, 105, 120, 110, and 102 bpm at 2, 3, 4, 6, and 8 hours respectively. It is important to note that these data were affected by atropine administration to subject (RE) after 5 hours of exposure and to subject (CB) after 4 1/4, 5 and 5 1/4 hours of exposure.

c. Pupil Size and Eye Accommodation: No effect was noted except for the two subjects (RE) and (CB) treated at 2.0 mg/kg. However, measurement for these 2 subjects were unavailable to the investigator after 2 and 4 hours respectively "therefore, no assessment of their response could be made". This reviewer notes that these two subjects were the only subjects in this study (Part A, B and C) reported with severe cholinergic inhibition symptoms. Lack of data on pupil size and eye accommodation appears to be related to the difficulty of measuring these parameters due to the subjects illness.

d. Vestibular Function: No effect was noted except for the two subjects (RE) and (CB) treated at 2.0 mg/kg. Those two subjects were unable to stand for the Fukuda and Romberg procedures after 2 and 4 hours respectively. No data were available for review to assess the status of these two subjects at the end of the 24-hour monitoring period.

B. Part B

Subjects in this part were reported asymptomatic at all dose levels tested (2.0, 4.0, 8.0, and 32.0 mg/kg).

RBCChE data were erratic and inconsistent. Only two subjects reflected a maximum RBCChE inhibition level of 20% or slightly higher, i.e., one subject treated at 2.0 mg/kg dose level reflected a maximum RBCChE inhibition of 20% after 6 hours posttreatment, and another subject treated at 32 mg/kg dose level reflected a maximum RBCChE inhibition of 24% after 8 hours of exposure. RBCChE inhibition was every low or insignificant in the other subjects. PChE data were also erratic at all dose levels.

Blood analysis indicated that one subject (GK) treated at the 4 mg/kg dose level had a slightly lower total protein value of 5.5g% at the final check up as compared to a 5.9g% baseline value and a 5.6g% value for the lower normal range. The two subjects treated at the 32 mg/kg dose level also reflected some difference in the 24-hour blood analysis: one subject (SB) had a slightly lower glucose value of 61 mg/dl as compared to a 0-hour value of 67 mg/dl and to the lower normal range value of 65 mg/dl; the second subject (DR) had an increase of 391% in GGT* value (47 IU) as compared to the 0-hour value (12 IU) and 223% as compared to the maximum normal range value (21.0 IU). The increase in GGT value is associated with hepatic and/or pancreatic pathology which indicates adverse effects despite the lack of symptoms at this dose level.

No other effects were noted in this part B of the study. However individual data were not presented.

It was also noted that the two subjects treated at 32 mg/kg received only 23 and 29 mg/kg Carbofuran respectively. The registrant should be asked to explain this difference.

*GGT: Gama Glutamic transpeptidase.

C. Part C

The two subjects in this part of the study were reported asymptomatic during the 3 days of testing at 1.0 mg/kg.

Maximum RBCChE inhibition was 26% for one subject and 29% for the other. These moderate inhibition levels were noted in both subjects on the second day of exposure i.e. 23%, 22% and 26% inhibition after 4, 8, and 24 hours post-treatment in one subject, and 29%, 28%, 24% and 29% inhibition after 3, 4, 6 and 24 hours post-treatment in the second subject.

Baseline RBCChE activities for both subjects in the first and third day of testing were 30% lower than the mean normal activity detected by the Voss and Sachsse method (for a random sample of the population). The higher level of inhibition noted in both subjects on the second day as compared to the first day, and the low baseline RBCChE activity level determined on the third day may suggest a pattern of slightly cumulative response.

The registrant are asked to explain the 30% lower than normal level of RBCChE baseline activity noted on day one.

Blood analysis indicated that one subject (RC) reflected a 27 mg/dl BUN value at the end of the study, an 80% increase as compared to the 0-hour value (15 mg/dl) and a 35% increase over the maximum normal range (20 mg/dl). This increase represents an adverse effect.

No other effects were noted in this part C of the study. However individual data were not presented.

D. Carbofuran Metabolites in Urine (MRI Report)

7-phenol is the major Carbofuran metabolite. The amount detected in urine was insignificant in all three parts A, B, C of this study.

The percentage of 7-phenol recovered in part A did not exceed 3.8% at any dose level; in part B the recovery did not exceed 0.11% at any dose level. Urine was not analyzed for other metabolites in these two parts (A, B). These data indicate that Carbofuran is dermally absorbed at a higher rate at high temperature and humidity.

In part C, traces of unmetabolized Carbofuran and 3-hydroxy-carbofuran were detected in the third day of exposure. In the second subject traces of unmetabolized Carbofuran were detected in each day of exposure, and traces of 3-keto-7-phenol (0.1 ug/ml) were noted on the third day of exposure. The percentage of total Carbofuran recovery in this part C did not exceed 0.48% at any of the 3 days of exposure.

Considering that the level of Carbofuran/metabolites in urine does not exceed 3.8% of the actual Carbofuran dosages in this study, and considering that blood was frozen to be analyzed for levels of Carbofuran/metabolites in this study (this report, p. 22, last paragraph), the registrant are asked to submit the data on the Carbofuran/metabolites in blood.

III. Conclusion

This study is unacceptable because the crucial individual data for each subject were not fully reported. Except for the cholinesterase results, all data were reported as a summary.

The classical, severe cholinergic poisoning noted in the two subjects treated at 2.0 mg/kg dose level under conditions of high temperature and humidity in Part A make it unusual that no symptoms, or other effects were noted at the lower dose levels,or in subjects treated at much higher dose levels under conditions of low temperature and humidity in Part B while one subject reflected 300% increase in GGT activity at 32 mg/kg.

It seems also unlikely that no symptoms were noted in Part C (multiple application) while one subject reflected 80% increase in BUN value over the 0-hr determination and the two subjects reflected 26-29% RBCChE inhibition.

Conflicting definitions exist between the protocol and the final report of this study concerning the baseline values and the 0-hour values. Clarifications of these values including tabulated data are requested from the registrant (especially for Ch.E data).

Clarification is also needed concerning the high dose (32 mg/kg) in part B of this study (low temperature and low humidity). The actual dosage administered to one subject is 23 mg/kg and to the second subject 29 mg/kg. The registrants are requested to explain the reason for this decreased rate of application.

It is also noted that an extremely low level (0.0% to 3.0%) of Carbofuran/metabolites was detected in urine. These data may indicate that a small fraction of the test substance was dermally absorbed. Data on the level of Carbofuran/metabolites in blood are requested from the registrant to assess these findings.

In conclusion, all the individual data for each subject are required for the review of this study. This means tabulated results for the following effects:

1. Symptoms
2. Pupil Size and Eye Accommodation
3. Pulse rate, blood pressure, and EKG; respiration rate and body temperature
4. Fukkuda test and Romberg
5. Laboratory values (hematology, urinalysis, and blood chemistry) pre-and post-treatment and clear documentation of baseline and 0-hour values.
6. Carbofuran/metabolites in blood.

Also identification of age, weight and height of each subject in part B and C.

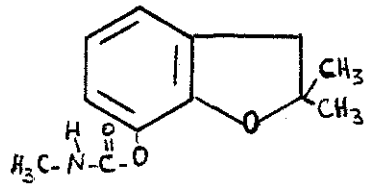
III. Human Dermal Toxicity

"Comparison of Cholinesterase Inhibition and Effects of Furadan 4F and FMC 35001 4 EC"; John D. Arnold; Quincy Research Center (QRC); Act 152.03; 2/15/78; Acc.#241305

I. Materials and Methods

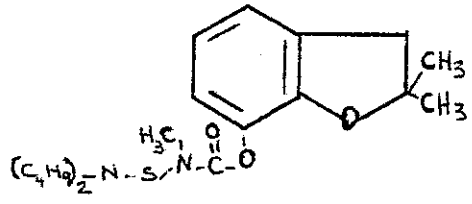
Test Substances - Two formulations: Furadan 4F (Carbofuran) and FMC 35001 4EC (Carbofuran analog). Each formulation contained 480 mg a.i./ml.

Furadan



2,3-Dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate

FMC 35001



2,3-Dihydro-2,2-dimethyl-7-benzofuranyl [(dibutylamino) thio]methylcarbamate

Twenty males 18-53 years old weighing within 15% of the ideal weight for their height were selected from a Quincy Research volunteer pool for this study. The baseline cholinesterase activity level did not reflect remarkable differences between these selected subjects.

The subjects were arbitrarily assigned to receive Furadan 4F or FMC 35001 4 EC in groups of two; no subject received more than one treatment of either compound.

Compounds were diluted to 50% of their original concentration and applied to a designated area of the subject's backs at a level of 0.5 mg per square centimeter. The dose levels used were as follows:
Furadan 4F - 0.5, 1.0, 2.0 and 4.0 mg/kg
FMC 35001 4 EC - 0.5, 1.0, 2.0, 4.0, 8.0 and 16.0 mg/kg

Each dosage was administered 1 1/2 hour after breakfast and the subjects were not allowed to smoke from 1/2 hour before treatment until 2 1/4 hours after dose administration.

From 1 hour pre-treatment until 4 hours post-treatment, subjects were confined in a controlled environmental room with temperature between 33-36°C (90-96°F) and relative humidity 70-80%. From 0-4 hours after treatment subjects alternated 5 minutes of mild ergometer excercise with 15 minutes of rest, this cycle was repeated 11 times in this 4-hour period.

Four hours after treatment the subjects were removed from the environmental room and their backs were washed with soap and water to remove the compounds; normal activity was permitted for the rest of the 24-hour post-treatment period. The subjects were fasted 9 hours before the 24-hour final blood and urine samples collection for routine tests, i.e., hematology, blood chemistry and urinalysis.

The subjects were monitored at regular intervals for 24 hours post-treatment for symptoms, plasma and erythrocytes cholinesterase (PChE and RBCChE) inhibition, pupil size and eye accommodation, arterial pressure, heart rates, electrocardiogram, respiration rates and temperature. Routine laboratory determination for blood and urine, and physical examinations were performed at the end of the 24-hours post-exposure period. The overall schedule of measurements was as follows:

Physical Examination - preadmission, 24 hours post-treatment

Cholinesterase activity - preadmission, 0 (pre-test), 1/2, 1, 2, 4, 6 and 24 hours post-treatment (0-hr was used as baseline)

Pupil size, eye accommodation - preadmission, 0, 1/2, 1, 2, 3, 4, 6, 8 and 24 hours post-treatment

Arterial pressure, heart rate, respiration rate, temperature - preadmission, 0, 1/2, 1, 2, 3, 4, 6, 8 and 24 hours post-treatment

Electrocardiogram - preadmission, 12 hours post-treatment

Routine blood and Urine tests - preadmission, 24 hours

Cholinesterase activities were determined according to the method described by Voss, Guenther and Sachsse, Klans in "Toxicology and Applied Pharmacology 16:764-777, 1970".

II. Results

A. Furadan 4F

1. Blood Cholinesterase

Maximum RBCChE inhibition was noted at the highest dose level 4.0 mg/kg, 49% in one subjects and 61% in the other. RBCChE inhibition was maximum four hours post-treatment at all dose levels. Recovery was noted 24-hour post-treatment in all subjects. RBCChE inhibition reflected a dose-response relationship:

0.5 mg/kg - 22% and 7% inhibition in two subjects respectively
1.0 mg/kg - 29% and 21% inhibition in two subjects respectively
2.0 mg/kg - 42% and 40% inhibition in two subjects respectively
4.0 mg/kg - 61% and 49% inhibition in two subjects respectively

PChE inhibition was inconsistant and erratic. Moderate PChE inhibition was noted in the two test subjects treated at the lowest dose level 0.5 mg/kg (33% and 46%) and in one subject treated at 2.0 mg/kg (44%).

PChE was insignificant at 1.0 mg/kg (4% and 15%), at 2.0 mg/kg for one subject (6%) and at the highest dose level 4.0 mg/kg for the two test subjects (6% and 9%).

No effect was noted at the end of the 24-hour monitoring period.

2. Symptoms, Hematology, Blood Chemistry and Urinalysis

0.5 mg/kg dose level - One subject had a burning sensation at the application site, the other had two episodes of unsettled stomach. No other effects were noted at this dose level.

1.0 and 2.0 mg/kg dose levels - No symptoms were reported; however decreased SGOT determination were reported for one subject at 1.0 mg/kg level in both final (6 IU) and baseline values (5 IU) as compared to the normal SGOT range of 8-100 IU. At 2.0 mg/kg level, SGOT decreased to 7 IU after 24 hours post-treatment as compared to 18 IU for the baseline value.

4.0 mg/kg dose level - The two subjects treated at this dose level had classical symptoms of cholinergic poisoning. The symptoms were severe enough that one subject had to be removed from the environmental room after 3 hours post-treatment, his back washed, and he was given 0.4 mg atropine. The other subject was given 1.2 mg atropine after 4 hours post-treatment; he also had a slightly increased final total protein value of 8.5 g/dl as compared to 6.9 g/dl baseline and 5.9-8.1 g/dl normal range.

3. Other Effects

The effects of Furadan 4F on pupil size and eye accommodation, and on erect and supine heart rate and blood pressure were not adequately reported, only mean values and standard deviations were summarized. Respiration rates, body temperatures and results of the Electrocardiograms (EKG) were not reported.

B. FMC 35001 4EC

1. Blood Cholinesterase

Maximum RBCChE inhibition of 35% and 34% was noted in the two subjects treated at the highest dose level, 16 mg/kg. Maximum inhibition occurred 1/2 to 6 hours post-treatment at the different dose levels tested. Recovery was noted 24-hour post-treatment. RBCChE inhibition reflected a dose-response relationship at the higher dose levels tested:

0.5 mg/kg - 5% and 0%	inhibition	in	two	subjects	respectively
1.0 mg/kg - 11% and 9%	"	"	"	"	"
2.0 mg/kg - 8% and 12%	"	"	"	"	"
4.0 mg/kg - 10% and 18%	"	"	"	"	"
8.0 mg/kg - 22% and 25%	"	"	"	"	"
16.0 mg/kg - 35% and 34%	"	"	"	"	"

PChE inhibition was inconsistant and erratic. Maximum inhibition of 46% was noted in one subject treated at 0.5 mg/kg (the lowest dose level); the other subject had only 12% inhibition. No inhibition was noted at 1.0 mg/kg; minimal inhibition of 14% and 6% was reported at 2.0 to 8.0 mg/kg dose levels; low inhibition of 24% and 18% was reported at 16.0 mg/kg (the highest dose level).

No effect was noted at the end of the 24-hour monitoring period at any dose level.

2. Symptoms, Hematology, Blood Chemistry and Urinalysis

0.5 mg/kg dose level - Headache was reported for one subject. No symptoms were noted for the second subject; however the baseline and final leucocyte values (3.6-3.3 K/mm^3) were within the low end of the normal range (1.3-13.3 K/mm^3).

1.0 mg/kg dose level - Severe headache was reported for one subject after 5 hours post-treatment. No symptoms were reported for the second subject; however a slight decrease in SGOT (7 IU) was noted as compared to the baseline (16 IU) and the normal range (8-100 IU).

2.0 mg/kg dose level - Slight redness was noted at the application site after 1 1/2 hour post-treatment. No symptoms were noted for the second subject; however a slightly increased BUN level (20 mg/dl) was determined at the end of the 24 hours monitoring period for this subject as compared to the baseline (15 mg/dl) and the normal range (5-19 mg/dl).

4.0 mg/kg dose level - One subject experienced a dry mouth effect at 2 3/4 hours post exposure. A slightly increased BUN (20 mg/dl) was noted as compared to the baseline (15 mg/dl) and the normal range. No effect was reported for the second subject.

8.0 mg/kg dose level - Weakness and fatigue when exercising were reported for both subjects at this dose level at 3 1/2 hours post-treatment. One of the subjects had an increased total protein (8.3 g/dl) as compared to the normal range (5.9-8.1 g/dl) , and decreased levels of SGOT (7 IU) and leucocytes (4.2 K/mm^3) as compared to baseline (SGOT 12 IU, Leucocytes 5.2 k/mm^3), and the normal range. No baseline total protein value was reported.

16.0 mg/kg dose level - The two subjects treated at this dose level had classical symptoms of cholinergic poisoning at 1 1/4 to 2 1/2 hours post-treatment. No other data were reported at this dose level.

3. Other Effects

The effect of FMC 35001 4 EC on pupil size and eye accommodation, and on erect and supine heart rate and blood pressure were not adequately reported; only mean values and standard deviations were summarized. Respiration rates, body temperatures and results of the Electrocardiograms (EKG) were not reported.

III. Conclusions

Furadan 4F and FMC 35001 4EC cause severe cholinergic poisoning symptoms in male human volunteers at the highest dose levels tested, i.e., 4.0 mg/kg for Furadan and 16 mg/kg for FMC 35001. These subjects were exposed to the compounds for only four hours under conditions of mild exercise, 90-96 °F and 70-80% RH. The symptoms were paralleled by 49% to 61% RBCChE inhibition with Furadan and 34% to 35% inhibition with FMC 35001. The lowest effect level (LEL) noted for Furadan 4F is 0.5 mg/kg. Mild toxicity was manifested at this level by 22% RBCChE inhibition in one subject, 33% and 46% PChE in the two subjects respectively; and symptoms like burning sensation at the site of application in one subject, and stomach discomfort in the second subject.

The lowest effect level noted for FMC 35001 4EC is also 0.5 mg/kg. Mild toxicity was manifested by 46% PChE inhibition in one subject and symptoms i.e. headache in one subject.

FMC 35001 4EC is not a potent RBCChE inhibitor as compared to Furadan 4F. However, toxicity of this compound appears not to be closely related with the extent of ChE inhibition. Symptoms experienced by the subjects treated with FMC 35001 were more pronounced (i.e. severe headaches) than the subjects treated with Furadan at the same low dose levels of 0.5, 1.0, and 2.0 mg/kg despite that RBCChE average inhibition was higher with Furadan (15%, 25% and 42% respectively) than FMC 35001 (3%, 10%, and 11% respectively) at these dosages.

The following data are requested for review:

1. Individual data at 0, 1/2, 1, 2, 3, 4, 6, 8 and 24 hours post-treatment for pupil size, eye accommodation, supine and erect heart rates and blood pressure.

2. Data on respiration rates and body temperatures.

3. EKG data.

4. Preadmission data and medical history.

CASWELL FILE

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

JUN 23 1981

MEMORANDUM

DATE: June 3, 1981

SUBJECT: FMC response to data requests of 1/9/81 relative to the EPA Reg.#279-2875; "Carbamate (Carbofuran) Human Dermal Study QRC 3/18/77", and Clarifications Relative to Cholinesterase Determinations in Carbofuran Oral and Dermal Toxicity Human Studies "Industrial Hygiene Studies, MRI Project#4230-B page 104, 7/15/77" CASWELL #160A
Accession#241303

FROM: Amal Mahfouz, Toxicologist
Toxicology Branch, HED (TS-769) Amal Mahfouz 6/3/81

TO: Jay Ellenberger (12)
Registration Division (TS-767)

IDC 6/3/81

Recommendations

The information requested by this reviewer from Don Carlson (FMC) on 1/9/81 (See attached memo of 2/17/81) concerning dosage concentrations and applications in the Carbofuran 75% WP - human dermal study [QRC - final report, 3/18/77] and clarification relative to notes on the cholinesterase analytical methodology [MRI - Industrial Hygiene Studies - Project#4230-B, p. 104, 7/15/77] have been submitted and reviewed.

This information, provided on 3/26/81, was considered in my original review of 5/13/81 from Amal Mahfouz to Jay Ellenberger EPA Reg.#279-2875 (Furadan 75 WP) and EPA Reg.#279-2876 (Furadan 4 F); also FMC 35001 4 EC (unregistered Carbofuran analog).

TS-769:th:TOX/HED:AMahfouz:6-3-81:#2

B's Jefferat Dykstra

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

MEMORANDUM

JUN 16 198

SUBJECT: Carbofuran; 279-EUP-TA; PP #0G2304, 1 H52 97; for use in/on soybeans 16.0A

CASWELL FILE

FROM: Sami Malak, Chemist Sami Malak
Environmental Fate Branch, HED (TS-769)

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Jay Ellenberger (12)
Registration Division (TS-769)

Toxicology Branch
Hazard Evaluation Division (TS-769)

TOX

Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU: Dr. Willa Garner, Chief WG
Review Section #1
Environmental Fate Branch, HED (TS-769)

This is to address the question raised by the Toxicology Branch as to whether or not carbofuran would contaminate ground water under the proposed use pattern in/on soybeans.

A simulated PESTAN leaching model was carried out for a typical soybean field under Illinois conditions [silt loam: pH 6.2, OM 3.9%, bulk density 1.5, and porosity 0.485]. The simulation was for a single application at 2.235 Kg/ha, assuming a soil recharge rate of 17 inches of water per year. Hydraulic parameters for this texturial group were obtained from Clapp and Hornberger. An experimental K_d of 0.305 was used. Considering an average $t_{1/2}$ of 80 days for carbofuran and a correction factor of three to correct for PESTAN's assumption that biodegradation is depth independent when, in fact, it is not, we calculated a degradation rate coefficient of 1.2×10^{-4} hrs^{-1}.

Predictions obtained showed that carbofuran would leach below 3 feet at a maximum concentration of 35 ppb after 560 days and below 5 feet at a maximum concentration of 5 ppb after 700 days of application. It has been estimated that the leachate from surface runoff would increase the ground water flow by 10%. Using a dilution factor of 10 X, concentrations of carbofuran in ground water of about 3.5 ppb would be expected. This is approximately 10% of the previous PESTAN predictions (40 ppb) for Long Island. The 1980 ground water monitoring data from Long Island were consistent with those predicted.

EFB believes that carbofuran will leach to the saturated zone at levels equivalent of 4 ppb and as such, it is expected to contaminate ground water under the prescribed use in/on soybeans.

Note to PM: In an attempt to duplicate the Long Island predictions using the same parameters, the inputs obtained were not consistent with those previously recorded. Present predictions were below the previous predictions by a factor of 500 to 650 X. Accordingly, we recommend that field monitoring for carbofuran contamination to ground water must be included under the proposed permit, noting that monitoring should continue for a period of 2 years.

CASWELL FILE

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

JUN 16 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: June 16, 1981

SUBJECT: EPA Reg #279-2712; 279-2876; Carbofuran; Rabbit Teratology
CASWELL#160A Accession#245268

FROM: William Dykstra, Toxicologist
Toxicology Branch, HED (TS-769)
WWD for LDC 6/16/81

TO: Jay Ellenberger (12)
Registration Division (TS-767)
RDJ for WB

Recommendations:

1. Carbofuran was not teratogenic or fetotoxic in rabbits at gavage dosages up to 2.00 mg/kg/day during gestation days 6-18. The study is acceptable as Core-Minimum Data.

Review:

1. Teratology Study in the Rabbit with Technical Carbofuran (IRDC#167-156; April 20, 1981)

   Groups of 20 pregnant New Zealand White rabbits were used to determine the teratogenic potential of Carbofuran. Dosage levels of 0.12, 0.50 and 2.00 mg/kg/day were administered orally by gavage as a single daily dose on gestation days 6 through 18 at a constant volume of 1 ml/kg. The control group received the vehicle only, 0.5% aqueous Methocel on a comparable regimen at a volume of 1 mg/kg.

   Cesarean sections were performed on all surviving females on gestation day 29.

Results:

Survival was 100% in the control group and in the 0.12 and 0.50 mg/kg/day dosage groups. Three dams aborted near the end of the gestation period; one each in the Carbofuran treated groups. One dam in the 2.00 mg/kg/day dosage group died on gestation day 11; a cause of death could not be determined at necropsy. During gestation, matting and/or staining of the anogential haircoat was noted in all groups, with an increase in duration observed in 2.00 mg/kg/day dosage group.

Mean maternal body weight gain in the 0.12 and 0.50 mg/kg/day dosage groups was comparable to the control group throughout gestation. A 20% reduction in mean maternal body weight gain was noted in the 2.00 mg/kg/day dosage group during the treatment period when compared to the control group; mean gain thereafter was comparable to the control group.

There were no biologically meaningful differences or statistically significant differences in mean Cesarean section values or in the number of litters with malformations (or developmental and genetic variations) in any of the Carbofuran treated groups when compared to the control group.

Conclusion:

Carbofuran was not teratogenic or fetotoxic in rabbits at gavage dosages up to 2.00 mg/kg/day during gestation days 6-18.

Classification: Core-Minimum Data

TS-769:th:TOX/HED:WDykstra:6-16-81:#2