US EPA ARCHIVE DOCUMENT

Dr. Perkin

ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

003692

Date: July 10, 1972

Reply to XXXXXX

Subject: Request for residue tolerance for o-isopropoxyphenyl methylcarbamate (BAY 39007, Baygon) in or on alfalfa fresh at 65 ppm, alfalfa hay at 100 ppm, oat grain at 0.1 ppm, oat green fodder and forage at 2 ppm, oat straw at 1 ppm, pasture grass green at 35 ppm, pasture grass hay at 55 ppm, meat, fat, and meat by-products of cattle, sheep, and goats at 0.1 ppm, and milk at 0.01 ppm.

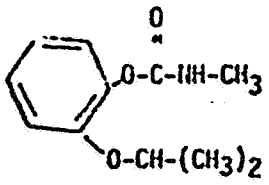
To: Mr. Drew H. Baker, Chief
Petitions Control Branch
Pesticides Tolerances Division

Pesticide Petition No. 2F1244

Related Petitions
9G0765

Chemagro Corporation
P.O. Box 4913
Kansas City, Missouri 64120

STRUCTURE




o-isopropoxyphenyl methylcarbamate

FORMULATIONS

I. Technical Baygon

o-Isopropoxyphenyl methylcarbamate 97.5%

[redacted]

INFORMATION WHICH MAY REVEAL AN INERT INGREDIENT IS NOT INCLUDED

1 7/22

[redacted] 03692

*Not detected

II. Baygon 70% Wettable Powder

o-Isopropoxyphenyl methylcarbamate 70%

Inert Ingredients [redacted]

TOXICOLOGICAL EVALUATION

I. PP# 9G0765 reviewed by Dr. M.L. Quaife, April 7, 1969.

Acute oral $LD_{50}$'s

| | |
|---|---|
| Rats-F | 87-110 mg/kg |
| Rats-M | 88-150 mg/kg |
| Guinea pig-M | 40 mg/kg |
| Hen | 150 mg/kg |
| Chick-M | 46.5 mg/kg |
| 28-Day intubation-M rats Systemic NEL | 7.5 mg/kg |
| 16-Week feeding study - rats NEL | >800 ppm |
| 2-Year feeding study - rats Systemic NEL = | 250 ppm |
| ChE NEL not established | |
| 2-Year feeding study - dogs Systemic NEL = | 250 ppm |
| ChE NEL not established | |
| $LD_{50}$ of metabolite | |
| o-hydroxyphenyl N-methylcarbamate | 1.1 g/kg |

INFORMATION WHICH MAY REVEAL AN INERT INGREDIENT IS NOT INCLUDED

Dr. Quaife found the requested temporary tolerances in this petition to be safe (0.5 ppm for barley, oats, and wheat grain; 1 ppm for their straws) but stated that the following would be required for the establishment of permanent or finite tolerances:

1) Histopathologic findings from the chronic studies or the the same from new 90-day rat and dog feeding studies.

2) Adequate characterization of "no-effect levels" for ChE inhibition (for plasma, RBC, and brain)

3) Knowledge of composition of toxic residues of Baygon on treated commodities plus adequate (sub-acute and/or effect-on-reproduction) toxicity data on those toxic components which occur in significant amounts, or else, proof they occur as major metabolites in mammalian metabolism of Baygon.

4) Adequate rat reproduction study

5) Information on extent of transfer of toxic residues to meat, milk, poultry, or eggs.

II. Addendum (April 16, 1969) to previous review stated that a demyelination study would also be necessary for the establishment of permanent tolerances.

III. New Toxicology Data Submitted in Current Petition

A. Acute oral $LD_{50}$

| Species | Sex | No. of Animals | Formulation | Application Method | $LD_{50}$ |
|---|---|---|---|---|---|
| Rats | F | 32 | 1.5 lb/gal SC | Diluted with 20% ethanol-80% propylene glycol | 400 mg/kg |
| Rats | F | 32 | 1% oil spray 68-56-1A | Undiluted | 4.6 ml/kg |

(Table continued on Page 4)

003692

A. Acute oral $LD_{50}$ (con't.)

| Species | Sex | No. of Animals | Formulation | Application Method | $LD_{50}$ |
|---|---|---|---|---|---|
| Rats | F | 32 | 1% oil spray 68-56-1B | Undiluted | 4.3 ml/kg |
| Rats | M | 15 | Ant and Roach Killer 0.5% BAYGON | Undiluted | 17.5 ml/kg |
| Rats | M | 15 | UCC Cockroach Formulation 1.0% Baygon | Undiluted | 5.66ml/kg |
| Rats | M | 150 | Emulsion | Undiluted | 960 ul/kg |
| Rats | F | 24 | Technical | Diluted with 20% ethanol-80% propylene glycol | Single oral asymptomatic dose is 4 mg/kg. |
| Rats | F | 20 | 18% liquid | Undiluted | 1135.0 mg/kg |
| Rats | M | 24 | 18% liquid | Undiluted | 1144.2 mg/kg |
| Dogs | M&F | 18 | Technical | As dry powder in gelatin capsules. | Single oral asymptomatic dose is 4 mg/kg. |
| Dogs | M&F | 36 | Technical | Dissolved in acetone and mixed with ½ daily ration. standard dry dog food. | Total somatic "no-effect" dose 55 mg/kg. |
| Rats | M | 12 | 70% WP | Oral in $H_2O$. | Ca 125 |
| Rats | F | 8 | 70% WP | Oral in $H_2O$. | >125 |
| Rats | F | 24 | 50% Hopper Box Seed Treater | Homogenized in 0.2% aqueous carboxymethylcellulose. | 212.7 mg/kg |

(Table con't. on Page 5)

A. Acute oral $LD_{50}$ (con't.)

| Species | Sex | No. of Animals | Formulation | Application Method | $LD_{50}$ |
|---|---|---|---|---|---|
| Rats | M | 20 | 50% Hopper Box Seed Treater | Homogenized in 0.2% aqueous carboxymethylcellulose. | 223.9 mg/kg |
| Rats | F | 32 | 20% liquid concentrate | Diluted with 20% ethanol-80% propylene glycol. | 506.2 mg/kg |
| Rats | M | 36 | 20% liquid concentrate | Diluted with 20% ethanol-80% propylene glycol. | 545.2 mg/kg |

B. Acute dermal toxicity

| Sex | No. of Animals | Formulation | Dose | Remarks |
|---|---|---|---|---|
| Rats: | | | | |
| F | 10 | 1.5 lb/gal SC | 2000 mg/kg | Transient symptoms but no mortality. |
| F | 4 | 1% Oil Spray 68-56-1A | 5 ml/kg | No mortality. |
| F | 4 | 1% Oil Spray 68-56-1B | 5 ml/kg | No mortality. |
| M | 15 | Emulsion | 250 mg/kg<br>500 mg/kg<br>1000 mg/kg | No symptoms.<br>No symptoms.<br>Typical toxicity symptoms.<br>No mortality. |

(Table con't. on Page 6)

B. Acute dermal toxicity (con't.)

| Sex | No. of Animals | Formulation | Dose | Remarks |
|---|---|---|---|---|
| Rabbits: | | | | |
| - | 1 | 1% Oil Spray 68-56-1A | 2 ml | No mortality. No edema and erythema. |
| - | 1 | 1% Oil Spray 68-56-1B | 2 ml | No mortality. No edema and erythema. |
| M | 12 | Ant & Roach Killer 0.5% BAYGON | 5.0 ml/kg | $LD_{50}$ |
| M | 8 | UCC Cockroach Formulation 1.0% Baygon | 1.25 ml/kg<br>2.5 ml/kg<br>5.0 ml/kg | No mortality<br>Killed 4 of 4<br>Killed 2 of 2 |
| - | 2 | 18% Liquid Formulation | 1000 ml/kg | No pronounced cholinergic symptoms. No mortality. |
| M | 5 | 50% Hopper Box Seed Treater | 2000 mg/kg | No symptoms or mortalities. |
| - | 5 | 20% Liquid Concentrate | 200 mg/kg | No mortalities. |
| - | 5 | 20% Liquid Concentrate | 2000 mg/kg | No mortalities. |
| - | 3 | 70% WP | 2000 mg/kg | No symptoms or mortality. |
| - | 6 | Technical | 500 mg (abraded skin) | No irritation. |
| - | 6 | Technical | 500 mg (unabraded skin) | No irritation. |
| - | 6 | 70% WP | 0.5 ml (400 mg/ml) (abraded skin) | No irritation. |

(Table con't. on Page 7)

B. Acute dermal toxicity (con't.)

| Sex | No. of Animals | Formulation | Dose | Remarks |
|---|---|---|---|---|
| — | 6 | 70% WP | 0.5 ml (400 mg/ml) (unabraded skin) | No irritation. |
| Dogs: | | | | |
| - | 34 | 0.25% Pressurized Spray | Recommended Rate | No effect. |
| F | 1 | 0.25% Pressurized Spray | Sprayed for 1 minute. | No effect. |
| F | 4 | 0.25% Pressurized Spray | Each pup sprayed for 10 seconds. | No effect. |
| M | 1 | 0.25% Pressurized Spray | Each pup sprayed for 10 seconds. | No effect. |
| M | 1 | 50% WP | 19 gm formulation 1 gal. water sponged on. | No toxic symptoms. |
| - | 14 | 50% WP | 1500 ppm applied as a dogwash. | No effect. |
| - | 6 | 50% WP | 3000 ppm applied as a dogwash for puppies. | No effect. |
| M&F | 4 | 50% WP | 0.75% AI in water. | All animals exhibited slight cholinergic symptoms. |

(Table con't. on Page 8

B. Acute dermal toxicity (con't.)

| Sex | No. of Animals | Formulation | Dose | Remarks |
|---|---|---|---|---|
| M | 4 | 50% WP | 1.25% AI in water. | All animals exhibited slight cholinergic symptoms. |
| M&F | 3 | 50% WP | 0.75% AI solution | 1 dead at 5 hours, 1 exhibited cholinergic symptoms. |
| M | 4 | 50% WP | 1.25% AI solution | 1 dead at 5 hours. All exhibited cholinergic symptoms |
| Cats: | | | | |
| M | 2 | 50% WP | 0.25% AI in water. | No toxic symptoms. |
| F | 3 | 50% WP | 1.0% AI in water. | No toxic symptoms. |
| M&F | 3 | 50% WP | 1.25% AI in water. | No toxic symptoms. |
| F | 1 | 0.25% Pressurized Spray | Sprayed for 1 minute. | No effect. |
| F | 2 | 0.25% Pressurized Spray | Each kitten for 10 seconds. | No effect. |
| Chickens: | | | | |
| F | 11-12 | 1.5 lb/gal SC | 0.5% AI and sprayed to run-off. | No symptoms. No skin irritation. |
| F | 11-12 | 1.0 lb/gal SC | 1.0% AI and sprayed to run-off. | No symptoms. No skin irritation. |

(Table con't. on page 9)

003692

B. Acute dermal toxicity (con't.)

| Sex | No. of Animals | Formulation | Dose | Remarks |
|---|---|---|---|---|
| F | 11-12 | 1.5 lb/gal SC | 2.4% AI and sprayed to run-off. | No symptoms. No skin irritation. |
| F | 11-12 | 1.5 lb/gal SC | 4% AI and sprayed to run-off. | No symptoms. No skin irritation. |

C. Eye Irritation

| Species | No. of Animals | Formulation | Application Method | Remarks |
|---|---|---|---|---|
| Rabbits | 6 | Technical | 100 mg formualtion in eye. | No ocular irritation. |
| Rabbits | 6 | 70% WP | 100 mg formulation in eye. | Slight sclerotic congestion in 4 of 6 rabbits clearing by 48-hours post-treatment. |

D. Intraperitoneal Toxicity

| Species | Sex | No. of Animals | Formulation | $LD_{50}$ mg/kg |
|---|---|---|---|---|
| Rats | F | 25 | Technical | 11 |
| Rats | F | 28 | 1.5 lb/gal SC | 90 |

003692

E. Inhalation Toxicity

| Species | Sex | No. of Animals | Formulation | Exposure Time (min) | Observations |
|---|---|---|---|---|---|
| Rats | M | 20 | Technical | 60 | $LC_{50}$ > 14440 µg/L |
| Rats | M | 20 | Technical | 260 | $LC_{50}$ =832µg/L |
| Rats | - | 6 | Ant & Roach Killer (0.5% Baygon) | 240 | 33% mortality at 44330 mg/$m^3$ |
| Rats | - | 6 | U.C.C. Cockroach Formulation (1.0% Baygon) | 240 | 100% mortality at 41180 mg/$m^3$ |
| Rats | - | 6 | U.C.C. Cockroach Formulation (1.0% Baygon) | 240 | 17% mortality at 17240 mg/$m^3$ |
| Rats | F | 6 | 17.3% Liquid Formulation | 30 | $LC_{50}$ = 938 µg AI/L |
| Rats | M | 6 | 17% AI Liquid Formulation | 60 | $LC_{50}$ = 8000 µg/L |
| Rats | M&F | 40 | 1.4 lb/gal Oil Spray Concentrate | 60 | $LC_{50}$ = 3000 µg/L |
| Mice | M | 10 | 17.3% Liquid Formulation | 30 | $LC_{50}$= 612µgAI/L |
| Rats | M&F | 16 | 70% WP | 60 | 0% mortality at 2000 and 20000 µg/L |
| Rats | M&F | 18 | 50% Hopper Box Seed Treatment | 60 | 0% mortality at 2000 and 20000 µg/L |
| Rats | M&F | 12 | 20% Liquid Concentrate | 60 | 0% mortality at 20500 µg/L |
| Cat | - | 1 | Emulsion | 60 | 0% mortality at 2x40 ml |

(Table con't.) on page 11.

E. Inhalation Toxicity

003692

| Species | Sex | No. of Animals | Formulation | Exposure Time (min) | Observations |
|---|---|---|---|---|---|
| Rabbit | - | 1 | Emulsion | 60 | 0% mortality at 2x40 ml |
| Guinea pigs | - | 1 | Emulsion | 60 | 20% mortality at 2x40 ml |
| Rats | - | 5 | Emulsion | 60 | 0% mortality at 2x40 ml |
| Mice | - | 20 | Emulsion | 60 | 0% mortality at 2x40 ml |

F. Subacute Feeding Study (Farbenfabriken Bayer AG Institut Fur Toxikologie)

1. Procedure

Groups of 15 FB 30 (Elberfeld breed) male rats (4 weeks old) were fed diets containing 0, 1000, 2000, 4000, and 8000 ppm Bayer 39007 for 2 months. Female rats were likewise fed 0 or 4000 ppm Bayer 39007. Weekly weight gains and food consumption were recorded. Autopsies were performed on rats which died during the test.

2. Results

No pathological changes in appearance and behavior were noted in the M rats fed 1000 or 2000 ppm. Rats fed 4000 or 8000 ppm were less lively and had shaggier hair coats. Both the body weights and food consumption decreased as the dosage increaded. No deaths were compound-related.

3. The value of this test is limited since ChE activity, hematology, urinalyses, blood chemistry, and pathology (gross and histological) studies were not conducted. The no-effect level based on limited information available would be 2000 ppm Bayer 39007.

CORE – Supplementary 4/10/84 pb

G. Subacute Dermal Studies

| Species | No. of Animals | Formulation | Application | Results |
|---|---|---|---|---|
| Dogs | 15 | Invisible Flea Collar (1.0%AI) | Everyday for 14 consecutive days. (1 gm) | Slight erythema in 2 dogs. At days 6-14 in 1 dog and at 10-14 days in another dog. |
| Dogs | 5 | Invisible Flea Collar (1.0%AI) | Everyday for 14 consecutive days. (5 gm) | Slight erythema in 3 dogs beginning on day 6 and lasting through day 14. |
| Cats | 2 | 0.25% Pressurized Spray | Sprayed for 10 seconds on day 0 & 2 (kittens) | No effect |
| Cats | 4 | 50% WP | Dipped in 2.5% solution on Monday, Wednesday and Friday. | Asymptomatic. |
| Cats | 4 | 50% WP | Dipped in 1.25% solution on Monday, Thursday and Monday. | Asymptomatic. |
| Cats | 6 | Invisible Flea Collar (1.0%AI) | Twice weekly for 2 weeks.(IX Therapeutic) | No dermal or systemic toxicity noted. |
| Cats | 6 | Invisible Flea Collar (1.0%AI) | Twice weekly for 2 weeks.(5X Therapeutic) | No dermal or systemic toxicity noted. |
| Cats | 5 | Invisible Flea Collar (1.0%AI) | Twice weekly for 2 weeks.(0.2gm/kg) | No dermal or systemic toxicity noted. |
| Cats | 5 | Invisible Flea Collar (1.0%AI) | Twice weekly for 2 weeks.(1.0 gm/kg) | No dermal or systemic toxicity noted. |

003692

in utero rat and the immature rat were not therefore exposed to Baygon at these critical times. TB does not therefore consider this to be an adequate study.

5. Information on extent of transfer of toxic residues to meat, milk, poultry or eggs.

TB defers to CB regarding the transfer of toxic residues.

6. Demyelination study.

TB will accept the neurotoxicity study submitted as a demyelination study.

RECOMMENDATIONS

Toxicology Branch can not rule for the proposed tolerances for o-isopropoxyphenyl methylcarbamate (Baygon) until the deficiencies cited in the Discussion (#2, 3, 4,& 5) are corrected.

In 1970 Residue Toxicology Branch, Division of Pesticides, FDA initiated a 3 generation reproduction study and a 2 yr feeding study with Baygon in rats. The reproduction study has been completed and the chronic study is completed except for the pathological examination. PCB may want to inform petitioner that such experiments have been conducted.

William E. Parkin, D.V.M., Ph.D.
Toxicology Branch
Pesticides Tolerances Division

cc: JGCummings
PRD/EPA
Atlanta Branch (CLewis)
Perrine Branch
Division Reading File
Branch Reading File
PP# 2F1244

R/D Init:CHWilliams 7/7/72
WEParkin:dtb 7/25/72
Init:CHWilliams
7/27/72

H. Chronic Toxicological Studies on Dogs (Farbenfabriken Bayer AG; 669)

This study was reviewed by Dr. H. L. Quaife, April 7, 1969. The pathology report was submitted with this petition. The following tissues were taken from all the dogs (0, 100, 250, 750, and 2000 ppm BAY 39007) for histopathological examination (H & E stain)

heart - auricle & ventricle
lymph node - mesenteric
gall bladder
pancreas
urinary bladder
gonads
adrenals
various levels of gastrointestinal tract
lungs*
liver*
spleen
kidneys*
uterus
thyroids
central nervous system (5 sections)

*Oil Red O stain also.

Many of the animals of the 2000 ppm group showed evidence of post-mortem change. There were no changes in morphology seen which could be directly attributed to the compound under test, BAY 39007, in any of the animals examined in this experiment. TB still agrees with Dr. Quaife's findings that the systemic NEL is 250 ppm based upon abnormal behavior, mortality, body weight, food consumption, and increased liver-body weight ratios. No ChE NEL was determined since a suitable assay method was not used.

I. Chronic Toxicological Studies on Rats (Farbenfabriken Bayer AG; 726)

This study was reviewed by Dr. Quaife, April 7, 1969. The pathology report was submitted with this petition. The following tissues were examined by histopathological examination from 5 rats/sex/group (0,250,750,2000, and 6000 ppm)(H & E stain):

heart
eye
urinary bladder
spleen
thyroids
lungs
colon
kidneys*
gonads
liver*
brain
adrenals
stomach
together with all tumors occurring in the experimental animals

*Oil Red O stain also.

There were no changes in morphology seen which were considered to have a drug-induced etiology. TB concurs with Dr. Quaife's opinion that the NEL is 250

ppm based upon clinical or other symptoms. No ChE NEL was determined as an unsuitable assay method was used.

J. Generation Studies on Rats (Farbenfabriken Bayer AG; 798)

1. Procedure

Groups of 10 M and 20 F FB30 breed rats were fed on diets containing 0, 250, 750, 2000, or 6000 ppm BAY 39007 Technical (purity 98.4%). Except for the mating period, pregnancy, littering, and the raising period for the young rats, the animals were treated with BAY 39007 during the entire testing time. The rats were weighed weekly and food consumption was recorded during those periods when the compound was fed.

During the mating period, 2 F rats stayed with one M for 19 or 20 days. The M rats were alternated in such a way that each F was together with 3 different M longer than the duration of a cycle. After mating the F were placed in individual cages.

Immediately after birth, the number and weight of all the young were recorded. In litters with more than 10 young, the litters were reduced to 10 by culling the weak after 5 days (the weights were redetermined). The young rats were raised to 4 weeks and weighed weekly. The young from the first mating ($F_{1a}$, $F_{2a}$, $F_{3a}$) were then killed.

The young from the second mating were raised to 4 weeks, separated according to sex and raised to 8 weeks when the rats to be used as the next parental generation were selected ( and mated at an average age of 100 days). The remaining animals were killed.

The young rats were evaluated macroscopically immediately after birth for any deformities. The young rats from the $F_{3b}$ generation were killed at 3 weeks of age. Two M and 2 F young from each mother were dissected and evaluated macroscopically. The thymus, heart, liver, kidneys, adrenal glands, and testes were weighed.

The following tissues from 5 $F_{3b}$ rats/sex/group were taken for histopathological examination (H & E stain):

| | |
|---|---|
| heart | kidneys* |
| gonads | liver* |
| spleen | adrenals |
| uterus | thymus |

*Oil Red O stain also.

2. Results

Significant Reproduction Changes

| Parental Generation | $F_0$ | | $F_{1b}$ | | $F_{2b}$ | |
|---|---|---|---|---|---|---|
| Litter | $F_{1a}$ | $F_{1b}$ | $F_{2a}$ | $F_{2b}$ | $F_{3a}$ | $F_{3b}$ |
| Fertility | - | -. | - | b | - | - |
| Decreased litter size | b | b | b | - | a,b | b |
| Survival rate-4 weeks | b | a,b | b | - | b | - |
| Body weight-birth | a,b | a,b | b | b | b | b |
| Body weight-4 weeks | a,b | b | - | b | a,b | a,b |

2000 ppm rats = a  6000 ppm rats = b

No compound-related changes were observed by either macroscopic or microscopic examination of the tissues at necropsy. No compound-related malformations were observed. Organ weight reductions in the 2000 or 6000 ppm groups were directly related to decreased body weights.

3. Conclusions

The value of this study is restricted since BAY 39007 was not fed during the mating period, pregnancy, littering, and raising period for the young rats. Any abnormalities or deviations which occurred in the young were a result of damage to the parental generation prior to mating, etc. In order for the effects of BAY 39007 to be directly correlated to the young rats, the compound would have to be fed during these periods.

K. Examinations of Embryotoxic Effects Among Rats (Farbenfabriken Bayer AG; 2388)

1. Procedure

Ten F FB30 rats/group were fed either 0, 1000, 3000, or 10,000 ppm 98.4% technical BAY 39007 (+ 0.82% isopropoxphenol) during the entire period of gestation. The young fetuses were delivered by caesarian on the 20th day of gestation. The fetuses were examined for superficial deformations, determination of the weight, chest and abdominal organ abnormalities, and skeletal deformities (stain with Alizarin red S).

2. Results

Body weight gain and feed consumption were significantly less in the 3000 and 10000 ppm parental rats. The fertility rate was decreased in the 10000 ppm rats.

The number of implantations was normal among all fertilized animals. The rats which received 10000 ppm of BAY 39007 had significantly increased resorptions and correspondingly less living fetuses. The average weight of the fetus was significantly lower among the rats treated with 3000 and 10000 ppm (placentas were also lighter). The underdeveloped forms which are fetuses that weighed less than 3.0g and the fetus with slight bone changes were definitely increased in the group with 10000 ppm (only 3 values available). No deformed fetuses could be found.

3. Conclusion

Feeding BAY 39007 at 10000 ppm was embryotoxic based upon increased resorptions and decreased living fetuses. 3000 ppm produced less severe effects in the fetuses while 1000 ppm was tolerated without any damages. No teratogenic effects were observed from the feeding of BAY 39007 at levels up to 10000 ppm.

L. Mutagenic Study with Baygon in Albino Mice (Ind. Bio-Test Lab., Inc.; E8917)

1. Procedure

Groups of 12 male Charles River strain albino mice were injected once ip with 0, 2.5, or 5.0 mg/kg Baygon in corn oil. Each male mouse was placed in a cage with 3 virgin females/week for 6 weeks. The females were killed one week after their removal from the cage and the numbers of implantation sites, resorption sites, and embryos were recorded. Resorption sites, and embryos were recorded. Resorption sites were divided into 2 groups, early deaths (deciduomata) and late deaths. The proportion of early deaths is indicative of mutagenicity. Mutagenicity can also be measured by comparing the mean number of viable embryos in the test group to the number obtained in the control group.

2. Results

The mating indices were normal for the treated mice. The number of implantations, embryos, and deciduomata compare favorably with the control animals. Pre-implantation losses which occurred during the first week in the test animals are not attributed to mutagenic action for the following reason. Spermatozoa are at the same stage of development during the first 2 weeks and a positive result should have been seen in both weeks rather than in only one of these weekly periods.

3. Conclusions

003692

Single injections of 5.0 mg/kg (ip) of Baygon in male mice did not produce a mutagenic effect.

M. Neurotoxicity Studies

1. Procedure

Five groups of 8 chickens each (18-20 months old) were fed diets containing 0, 300, 1500, 3000, or 4500 ppm BAY 39007 for 30 days and then observed for 28 days.

Body weights and feed consumption were determined weekly. The ChE activity of the blood was determined by the method of Pilz and Kimmerle. Following the study, the chickens were killed and portions of the sciatic nerve and spinal cord in the cervical, thoracic, and lumbar regions were examined microscopically.

2. Results

The birds in the test groups weighed slightly less (probably due to lower feed consumption). No toxicity symptoms were observed nor were any signs of neurotoxic damages noted. No significant changes occurred in ChE activity (not reliable test per Dr. N. L. Quaife, PP# 9G0765, April 7, 1969). No histopathological effects were seen.

3. Conclusions

BAY 39007 does not produce neurotoxic effects in the chicken at up to 4500 ppm.

N. Cholinesterase Inhibition Studies

1. Cholinesterase Values of a Kennel Worker after Dipping Dogs and Cats in a BAY 9010 2.5% Dip Solution (Chemagro Corp.; 68-44)

RBC and plasma ChE activity was measured in a worker who dipped dogs and cats in a solution of BAY 9010 (BAY 39007) 2.5% on alternating days for 3 for 3 doses. The $\Delta$ pH of the ChE activity (method of Michel) was not essentially different during the exposure period than it was during the pre-exposure or post-exposure periods.

2. Specificity of Carbamate-Induced Esterase Inhibition in Mice (Toxicol. Appl. Pharmacol., 6-402-410, 1964)

White F mice (Dierolf Farms) were administered 20-26 mg/kg BAY 39007 by ip injection in corn oil. Warburg analyses were conducted on brain and liver

003692

homogenates after 0.5, 1.0, and 24.0 hours. Liver esterase activity at 24 hours and brain esterase activity at 1 and 24 hours were normal when compared with solvent-control mice.

| Substrate | 0.5 hours | 1.0 hours |
|---|---|---|
| Acetylcholine | 35* | 17 |
| Acetyl-β-methylcholine | 33 | 9 |
| Propionylcholine | 44 | 20 |
| Butyrylcholine | 40 | 20 |
| Benzoylcholine | - | 3 |
| Triacetin | 31 | 3 |
| Tripropionyn | 27 | 2 |
| Tributyrin | 15 | 0 |

* percentage inhibition of ester hydrolysis in solvent-treated control animals.

0. Pharmacodynamic Studies

1. Baygon, 39007 - Antidotal Effect (Farbenfabriken Bayer AG; 18514)

Before the appearance of acute symptoms from the oral application of BAY 39007 (50, 60, 75, 100, 125, 150, 175, 200, 250, 300, 350 mg/kg), 0.05 g/kg of atropine $SO_4$ and/or 0.05 g/kg of PAM and/or 0.02 g/kg of BH6 were injected ip.

| | $LD_{50}$ (mg/kg) |
|---|---|
| Without antidote | 91 |
| Atropine $SO_4$ | 295 |
| PAM | 140 |
| BH6 | 75 |
| Atropine $SO_4$ + PAM | 212 |
| Atropine $SO_4$+ BH6 | 127 |

2. A Study of the Acute Toxicity of Baygon in Combination with DDVP (Chemagro Corp.; 20789)

Adult, female Sprague-Dawley rats were injected ip with Baygon Technical and DDVP Technical to determine $LD_{50}$'s:

| | | |
|---|---|---|
| Baygon | $LD_{50}$ | 10.0 mg/kg |
| DDVP | $LD_{50}$ | 7.5 mg/kg |

Mixtures of the 2 compounds were then injected ip.

003692

| Percent of the Intraperitoneal $LD_{50}$ of each Compound given | Mortality | % Mortality |
|---|---|---|
| 25 | 0/4 | 0 |
| 50 | 13/20 | 65 |
| 75 | 3/4 | 75 |

Baygon and DDVP do not potentiate each other's toxic mechanisms.

3. The Use of 2-PAM Following Carbamate Poisoning (Chemagro Corp.; 24210)

Two dogs received oral administrations of Technical Baygon in Panasol $AN_2$ at 50mg/kg. One dog received 50mg/kg of 2-PAM ip after 7 minutes and again after 2 more minutes. The second dog received no 2-PAM. Cholinergic symptons, specifically copious salivation and noticeable tremor, were obvious in both animals. A moderation of symptoms began 7-9 minutes after treatment with 2-PAM although the dog died 30 minutes later. The other dog showed moderation of symptoms about 50 minutes after treatment and survived the 14 day observation period.

4. Comparison of the Antidotal Actions of Tetraethylammonium Chloride and Atropine in Acute Poisoning of Carbamate Insecticides in Rats (Arch. Toxikol., 27; 311-314, 1971)

LD50 rat oral (mg/kg)

| Without treatment | With TEAC 20mg/kg | With atropine sulfate 50mg/kg | With TEAC atropine |
|---|---|---|---|
| 191 (164-223) | 248 (210-293) | 543 (346-851) | 536 (381-802) |

P. Field Trials

1. Toxicological Observations on the Use of Baygon as a Malarial Control Insecticide in El Salvador-Babione, Quinby, and Moreira (WHO)

Baygon quickly caused mild reverible transient poisoning in baggers, spraymen, householders, and commensal animals. The vast majority in all groups except spraymen were not affected. The signs of toxicity in humans included: miosis, visual difficulties, headache, nausea, vomiting retching, dizziness, stomach ache, staggering, weakness, excess sweats, clamminess, sleeplessness, spitting, excess salivation,

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tightness in chest, respiratory irregularity and pain in heart or chest.

2. Thirty Months' Experience with Baygon at the Zoological Garden, Wuppertal (Pflanzenschutz-Nachrichten 18/1965,2; 82-92)

After more than 30 months of using Baygon, no fishes, reptiles, birds, or mammals have been affected although some species even eat the dead, poisoned cockroaches.

3. A Study of the Safety of O-Isopropoxyphenylmethylcarbamate in an Operational Field-trail in Iran (Bull WHO, 38; 609-623, 1968)

Minor reactions to over-exposure to Baygon were recorded among some spraymen and a few inhabitants. The incidence in spraymen was mainly associated with heavy skin contamination and insufficient washing during works while the inhabitants entered the house while it was being sprayed. No cumulative inhibitory effect could be demonstrated on whole-blood or plasma CHE activity. The symptoms and signs of toxicity seen were headache, nausea, giddiness, blurred vision, weakness, increased sweating, vomiting, and pin-point pupils.

4. Toxicology Consultant's Report on Cycle 5 of OMS-33(Bagyon) Spraying in El Salvador(Quinby, WHO)
Field Trial of OMS-33 Insecticide in El Salvador(Davies & Freal, WHO)

Observations on the Toxicity of Two Organo-Phosphorus and One Carbamate Insecticide in a Village Trial Performed by the WHO Insecticide Testing Unit in Lagos During 1964(Vandekar, WHO)

Preliminary Toxicological Report-Forth Round of Spraying OMS-33 ITT-El Salvador(Babione, WHO)

Ortho-Isopropoxyphenyl Methylcarbamate(OMS-33) as a Residual Spray for Control of Anopheline Mosquito (Bull. WHO, 40; 67-90, 1969)

Toxicological Studies of Baygon Insecticide in Shabankareh Area, Iran (Trop. Georgr. Med., 21; 186-190 (1969)

Assessment of Black fly 'Fogging' Insecticides, 1970 Season (West, Queen's Univ.)

The effects of spraying noted in these studies was essentially the same as those previously described. Signs of toxicity were noted in many of the spraymen and in only a few residents of the locales sprayed. Information was presented indicating the rapid return to normal of CHE activity and the rapid excretion of a Baygon metabolite (isopropoxyphenol IPP) in the urine.

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5. Performance of Baygon in Field Tests Against American Cockroaches at the Lincoln Park Zoo, Chicago (25043)

   Use of Baygon around snakes, turtles, lizards, and monkeys resulted in no observable adverse effects in these species.

6. Expert Opinion on a Disinfectant Treatment with Blattanex in the Heideberg General Hospital

   Baygon was used in this hospital without any adverse effects on the patients, including the seriously ill and the newborn (no details given as to amounts of Baygon or number of people exposed).

DISCUSSION

As was stated earlier, Dr. Quaife, in her review of PP# 9G0765 dated April 7, 1969 (and addendum of April 16, 1969), stated that 6 requirements would have to be fulfilled before permanent or finite tolerances could be granted:

1. Histopathologic findings from the chronic studies or the same from new 90-day rat and dog feeding studies. The petitioner has now submitted the histopathology reports from the chronic studies so TB considers this requirement fulfilled.

2. Adequate characterization of "no-effect levels" for ChE inhibition (for plasma, RBC, and brain). The ChE activity data submitted with this report does not fulfill these requirements. The petitioner is again referred to Mr. J.B. Lamb's letters of August 8, 1969 and May 5, 1969 (PP# 9G0765).

3. Knowledge of composition of toxic residues of Baygon on treated commodities plus adequate (sub-acute and/or effect-on-reproduction) toxicity data on those toxic components which occur in significant amounts, or else, proof they occur as major metabolites in mammalian metabolism of Baygon. TB defers to CB regarding the knowledge of the composition of residues of Baygon on treated commodities. However, we note that neither toxicity data on major residues nor mammalian metabolism studies have been submitted. Metabolic data was restricted to the identification of isopropoxyphenol as a human metabolite in the urine of Baygon spray applicators.

4. Adequate rat reproduction study.

A rat reproduction study was submitted in this petition but this study was deficient in that the test material was not fed during the mating period, pregnancy, littering, and the raising period for the young rats. The

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