UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 003712

DATE: October 26, 1977

SUBJECT: PP #2F1244 - Baygon In or On a Variety of Commodities 508

FROM: K. L. Bailey
Toxicology Branch

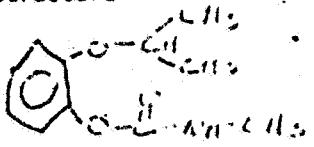
TO: F. Sanders, PM #12

Thru: Chief, Toxicology Branch EHWMB 11/24/78

I. Petitioner

Chemagro Ag. Div.
Mobay Chem. Corp.
Kansas City, Mo.

II. Chemical Structure



III. Chemical Name

2-(1-Methylethoxy) phenol
methylcarbamate

IV. Present Tolerances

There are no presently accepted tolerances for Baygon

V. Proposed Tolerances

Alfalfa (fresh)	6 ppm
Alfalfa (Hay)	22 ppm
Pasture Grass (Green)	8 ppm
Pasture Grass (Hay)	29 ppm
Meat, fat and meat by-products of cattle goats, hog, horses poultry and sheep	.2 ppm
Eggs	.04 ppm
Milk	.1 ppm

VI. Proposed Use

A. Control of adult mosquitoes over alfalfa and pasture grass fields.

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EPA FORM 1320-6 (REV. 3-76)

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To be applied at the rate of 1.25 - 4 fluid oz. per acre as necessary at 7 to 14 day intervals with no more than 10 applications per crop year.

g. For Fly Control in livestock and animal barns including dairy barns, milk rooms, horse sheep and swine barns and dog kennels as an aqueous 1% w/w solution.

VII. Maximum Theoretical Residue Contribution MTRC

Commodity	Tolerance	% diet	MTRC
Alfalfa	6 ppm	0	0
Pasture Grass	22 ppm	0	0
Meat, fat and meat by-products of cattle, goat, hogs, horses, poultry and sheep	.2 ppm	13.85	.042 mg/day
Eggs	.04 ppm	2.77	.0017 mg/day
Milk	.1 ppm	28.62	.0429 mg/day
			.086 mg/day

VIII. Acceptable Daily Intake, ADI, and Maximal Permissable Intake, MPI, of Baygon

No Effect Level = 250 ppm based on an increase in liver to body weight ratio in female rats.

Safety Factor = 100

250 ppm rat = (.05)(250) = 12.5 mg/kg/day
ADI = (1/100)(12.5 mg/kg/day)
ADI = .125 mg/kg/day
MPI (60 kg Adult) = (60 kg)(.125 mg/kg/day)
MPI = 7.5 mg/day

IX. Comparison of Maximum Permissable Intake MPI and Maximum Theoretical Residue Contribution, MTRC .

The MPI, 7.5 mg/day, is greatly in excess of the MTRC, .086 mg/day. Indeed, MTRC is< 2% of MPI.

X. Chemistry Review

The A. Rathmon Chemistry Review of August 23, 1977 has been read and considered and is of importance.

Specifically, the Chemistry Branch has concluded that 60-80% of the tissue residues in the cow are composed of an acid hydrolizable derrivative of o-isopropoxy phenol. In order to determine whether this unknown o-isopropoxy phenol derrivative is or is not of toxicologic concern we require the following information:

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a. The chemical identity of the metabolite.
b. Information as to whether the metabolism of Baygon is or is not essentially the same in both the rat and cow. If the chemical nature of the metabolite is of no concern and Baygon is metabolized in essentially the same way in both cow and rat we would conclude that this is of no toxicologic concern. However, if the chemical identity of the metabolite is of concern or Baygon is metabolized in a different manner in the cow and rat, additional studies will be necessary.

XI. RPAR Examination: The toxicologic data on hand have been examined and no RPAR criteria have been found to be exceeded.

XII. Conclusion

A. Tolerance Action

There is inadequate toxicologic data at hand to support this tolerance, considering that there are no presently accepted tolerances for Baygon. Specifically, we require the following:

1. A mouse chronic feeding / oncogenic study.
2. At such time as the agency determines a suitable protocol, an additio mutagenic study.
3. In relation to the rat 2 year feeding study (Studies 22991 and 2299! we require the pathology associated with each animal so that it may determined whether the study is or is not an acceptable oncogenic st
4. In relation to the teratogoenic study (Study 29035) we require clarification in relation to the following points:

   (a) What, specifically, is meant by the term slight bone changes?
   (b) Why, considering the number of fetuses examined, are no abnorma noted. One would, normally, expert some number of abnormalitic to be found.

B. Registration

In relation to the conclusion reached and the necessary data requirements for other than acute studies consult Section XIII (Toxicology Review A. Registration Actions) of this review.

C. Chemistry Review

In relation to Section X (Chemistry Review) of this review the Chemistry Branch has determined that in the cow 60-80% of the tissue residues are a acid hydrolizable derrivative of o-isopropoxy phenol.

In order to determine if this metabolite is or is not of toxicologic conc we require the following information.

(1) The chemical identity of the metabolite.

(2) Pertinent information as to whether Baygon is or is not metabolized in essentially the same manner in both the rat and cow.

If the metabolite is of toxicologic concern or if Baygon is metabolized in an entirely different manner in the rat as compared to the cow, furti toxicologic studies will be required.

XIII. Toxicology Review

A. Registration Actions

(Note: Only deficiencies in acute studies are noted here. Deficienc noted in relation to other studies are noted in general under Sectio (Conclusion, A. Tolernace Action) and specifically under Section XIII (Toxicology Review, B. Tolerance Action).

(Note to PM: A separate review is being prepared of the enormous num of studies at hand).

It is the petitioners contention that there is adequate data availabl such that, for purposes of registration, toxicologic label informatio may be readily extrapolated. While the basic concept, toxicologic extrapolation, is a sound principle, it is only feasable if we know t chemical composition of both the material used to perform the toxicol studies and the product for which the extrapolation is to be mode. I general, in the vast majority of submitted studies, only the Baygon concentration is specifie and not the concentration of the other ingredients (solvents, emulsifers, etc.)

Thus, it is impossible to extrapolate pertinent toxicological label information from many of the submitted studies as we do not know the actual chemical composition of the material used to perform the submi toxicological studies. It is recommended that the petitioner identif each toxicological study by the composition of the material actually to perform the study.

(A) Baygon 1.5 (EPA Reg. No. 3125-214)

(1) For purposes of registration, we require either actual acute toxicological studies or reference to particular studies alrea submitted including the chemical composition of the material u to perform these studies. It must be understood that, for pur of extrapolation, the referenced studies must have been perfor using material of sufficiently similar chemical composition to this product such that it is possible to reasonably determine appropriate label restrictions.

(2) As this product contains [redacted] suspected carcin we require conclusive evidence that this compound is not a carcinogen or that the material be replaced with some other suitable chemical.

(B) Baygon Spray Concentrate (EPA Reg. No. 3125-122)

In relation to this product see the previous comment A, (1) above.

(Note: There is no [redacted] in this product)

(C) Baygon MOS (EPA File Symbol 3125-GNA)

In relation to this product see the previous comment (A) (1) above.

(Note: There is no [redacted] in this product)

Baygon 70% WP (EPA Reg. No. 3125-146)

In relation to this product see the previous comment (1) (A), above.

(Note: There is no [redacted] in this product)

Baygon 2% Bait (EPA Reg. No. 3125-121)

In essence, this product is a granular mixture of Baygon and otherwise inacc inert ingredients. The toxicity is due essentially to Baygon and the word Caution is appropriate.

[redacted]

However, considering that the material [redacted] we require information that the product is not unreasonably attractive to either childr or domestic animals.

XIII. Toxicology Review

B. Tolerance Action

A. Two Year Dog Feeding Study Tab 22814, PP2F1244, Conducted by Bayer Institut fur Toxicologic; Pathology concuted by Huntingdon Research Cen

In this study 5 groups of beagles, each group composed of 4 males and 4 females, received the compound in their diet at levels of 0 ppm (contro 100,250 750 and 2000 ppm.

As all the female animals which received 2000 ppm died before terminatio the study, we have in effect 4 dosage levels for females and 5 for male The death of the high-level 2000 ppm females may, presumably, be attributed to the very marked reduction (=25% control) in food consumpt of this group.

The parameters measured were the following:

A. General Appearance
B. Body Weight
C. Food Consumption

D. Blood Tests
E. Kidney Function Tests
F. Liver Function Tests
G. Blood Glucose
H. Blood Cholinesterase Inhibition at 16 weeks
I. Mortality Rate
J. Macroscopic and Microscopic examination of the tissues of those animals which died or were sacrificed

The pertinent compound related effects noted are as follow:

1. 2000 ppm
   (a) Decreased food consumption in female dogs
   (b) Decrease in body weight of males and females
   (c) A 100% mortality in female dogs

It is to be noted that these is apparently a typographical error in the report i that it concludes the compound inhibits liver protein synthesis at all levels, ar observation clearly at odds with the results.

No observable cholinesterase inhibition was found for this compound. This lack o observable inhibition is probably the result of the method used rather than the lack of actual inhibition. However, considering that this compound is a carbama this is judged to be a minor deficiency.

The overall observable NEL is thus 750 ppm on the basis of mortality in the fema animals. The pathology is roughly what one would expect for animals of this a and the study is judged to be core-minimum. No serious hazards are indicated.

B. Supplement No. 5, Accession No. 111903

Rat 2 Year Feeding Study (Studies No 22991 and 11991a) Conducted by Bayer Institut fur Toxicologic and Huntingdon Research Center (Path.)

In this study 5 groups of rats, each group composed of 25 males and 25 female except the controls which contained 50 of each sex, were exposed to 0 (contro 250,750,2000 and 6000 ppm of the compound in their diet.

The following parameters were measured:

1. Behavior
2. Food Consumption
3. Body Weight
4. Hematologic Studies at 7 and 24 months
5. Urinalysis and Kidney Function at 7 and 24 months
6. Liver function at 24 months
7. Cholinesterase activity at 6 months
8. Mortality Rate
9. Pathology of Animals that were sacrificed or died of other causes.
10. Tissue weight and tissue to body weight ratio

The apparent compound related effects noted are as follows:

1. Decrease in food consumption in females - NEL 750 ppm
2. Decrease in body weight gain of females - NEL 750 ppm
3. Increase in liver to body weight ratio in females - NEL 250 ppm

4. Possibly, an increase in (SGPT) GPT in male rats - NEL 250 ppm.

The NEL for this study is thus 250 ppm an the basis of an increase in liver to body weight ratio in female rats.

While no cholinesterase inhibition was noted, this is probably due more to the lack of an appropriate technique than the lack of effect of the compound. Consi that the compound is a carbamate, this deficiency is judged to be of minor impo

The pathology is, roughly, what one would expect in relation to testicular atrop pituitary tumors and the other signs and symptoms associated with increasing age rats. There is however some confusion in relation to the pathology report in t the only reports submitted are for 5 animals per sex group and for those animal for which tumors were noted; the report suggests that all animals were examined. this basis the study is judged core-minimum as a feeding study and supplemental oncogenic study. Possibly, with more complete reporting, the study may be clas core-minimum as an oncogenic study. No serious hazards are, at present, sugges this study.

C. Hen Neurotoxicity Studies (Study No 17974 conducted b. Bayer Institute for Toxicology)

A. Pilot Studies

1. Oral Studies

In these two studies adult chicken were given the compound and observed in b the presence and absence of atropine for periods of 42 and 60 days respectiv No evidence of neurotoxic damage was found.

The design of the experiments are as follows:

Oral - No Atropine

dose mg/kg	acute toxicological* results	dead after no. of days	neurotoxic damages
100	0/0/1	-	none
200	0/1/1	-	none
500	0/1/1	-	none
1,000	2/5/5	1	none

Oral With Atropine

dose mg/kg	acute toxicological* results	dead after no. of days	neurotoxic damage
750	9/16/16	1 - 5	none
1,000	2/3/3	2	none

*death/ACH inhibition/No animals used

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2. Intraperitoneal Studies

These studies comprise two studies in which the compound was administered via intraperitoneal injection to adult cheickens both in the absence and presence : atropine. The animals were examined for periods of 42 and 60 days, respective and no neurotoxic damages were observed. The design of the experiments are as follows:

Intraperitoneal - No Atropine - 42 Days

dose mg/kg	acute toxicological* results	dead after no. of days	neurotoxic damages
25	0/0/1	-	none
37.5	0/5/5	-	none
50	1/1/1	2	-
100	1/1/1	1	-

Intraperitoneal - Atropine - 60 Days

dose mg/kg	acute toxicological* results	dead after no. of days	neurotoxic damages
50	0/0/1	-	none
75	0/1/1	-	none
100	3/13/13	1 - 2	none

*Deaths/Symptoms/No. Animals

Feeding Study

In this study 5 groups of 8 adult chickens were exposed respectively to 0 ppm (control), 300, 1500, 3000 and 4,500 ppm of the compound in their diet for a period of 30 days. Following dietary exposure, the animals were observed for period of 30 days and a variety of nervous tissues were subsequentially examin histologically.

No evidence of neurotoxic damage was found. It is to be noted that the tables body weight and food consumption, while mentioned, were not included in this r this is a very minor deficiency for the purposes at hand.

Summary

It is concluded that this Core-Minimum study demonstrates that the compound is a neurotoxin.

D. Supplement #5 Volume II of II Accession No. 11903

Histopathologic Report of Hen Neurotoxicity Study (Reports 20937 and 17974. performed by Bayer Toxicology Institute)

(Note: For further details consult Review C above)

Graduated sections of spinal cord from the cervial, dorsal and lumbar regio well as sciatic nerve were examined using hematoxylin -eosin and eosin. Wh some evidence of bacterial or viral infection was found, no evidence of com related neurotoxicity was noted.

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E. Supplement No. 5, Volume II of II, Accession No. 093225, Study 29035

Rat Teratogenic Study Conducted by Bayer Insitute of Toxicology.

It is not clear if the problems associated with this study relate to a poor translation from German, as has been the case in the 3-generation study, or are inherent deficiencies of the study.

In any case, we require the following information before the study can be evalua

(a) What, specifically, is meant by the term slight bone changes?
(b) Clarification is required why, considering the number of fetuses examine no deformaties of any kind are noted.

F. Supplement No. 5 Baygon Toxicology, Vol. II of II PP2F1244, Accession No. 093225

Study No. 23299

Rat Three Generation Reproduction Study conducted by Bayer Institute for Toxicol

In this typical rat three generation reproduction study, initially 5 groups of were each group composed of 20 female and 10 male FB 30 strain of rats, exposed respectively to 0 (control), 250, 750, 2000 and 6000 ppm of baygon in their diet The following parameters were measured:

(a) Body Weight
(b) Fertility
(c) Litter Size
(d) Survival Rate
(e) Examination for Deformities
(f) Dissection and Organ Weights (F.3b) including thymus, heart, liver, spl both kidneys, both adrenal glands, and both testes for 2 males and 2 f from each group.

In relation to general parameters there is a decrease in pup survival and body weight at 2000 and 6000 ppm.

In relation to reproduction, there is a clear and progressive decrease in the number pups per litter with a NEL of 250 ppm.

As high levels of the compound in this study and in chronic rat and dog studies produce marked decreases in body weight, it is possible that this decrease in number of pups per litter relates to decreased body weight in the dam; this study core-minimum.

II Study No. 23299

Rat Three Generation Reproduction Pathology Report - conducted by Huntingdon Research Centre

The only data reported is for liver tissue in which lymphocitic infiltration is be found in all groups including the control at essentially the same frequency i all groups. The pathology, while sketchy, is adequately covered in the Two Year Rat Feeding Study.

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G. Supplement No. 5, Volume II of II, Accession No. 093225

Study 30301

Mutagenic Study Using Mice Conducted By Industrial Bio-Test

In this mouse dominant lethal mutation study using Baygon IP, there is no discernable increase in mutation rate MR when measured using the following parameter:

$$MR = \frac{\text{Number of Early Resorption Sites X100}}{\text{Number of Implantation Sites}}$$

However, when measured using the following parameter the MR is observed to increase the first week and possibly the second:

$$MR = \frac{\text{(Embryos Test Group/Female) X100}}{\text{(Embryos Control Group/Female)}}$$

Considering the ambiguous results obtained in this study and the observation that the compound at high doses in a three generation reproduction study does modify reproduction, it is concluded that no weight should be given to this study at thi time. Rather, additional mutagenic studies should be instituted at such time as appropriate protocol s are determined.