

ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D. C. 20460

Dr. Parkin

001146

Date: August 17, 1972
Reply to Attn of: Request for a residue tolerance of 0.1 ppm
4-amino-6-tert-butyl-3-(methylthio)-as-triazin-5
Subject: (4H)-one (Sencor, BAY 94337) in or on soybeans.
To: Mr. Drew M. Baker, Chief
Petition Control Branch
Pesticides Tolerances Division

Pesticide Petition No. 2F1274

Chemagro
P. O. Box 4913
Kansas City, Mo. 64120

Related Petition: OG0940

TOXICOLOGICAL EVALUATION

I. PP No. OG0940 reviewed by Dr. G. E. Whitmore (March 10, 1970).

Acute Oral Toxicity:

× LD₅₀ Technical compound in 20% ethanol and 80% propylene glycol.

Male rats	1985 mg/kg
Female rats	1937 mg/kg
Male guinea pigs	198 mg/kg

LD₅₀ Technical compound-water emulsion.

Male rats	2200 mg/kg ✓
Female rats	2345 mg/kg ✓
Male mice	698 mg/kg ✓
Female mice	710 mg/kg ✓
Male guinea pigs	> 250 mg/kg ✓
Rabbits	> 500 mg/kg ✓
Cats	> 500 mg/kg ✓
Chickens	> 100 mg/kg ✓

Bayer AG
1574; 09/12/69
112052

× LD₅₀ 70% Wettable powder-aqueous suspension.

Bob White Quail	> 500 mg/kg
Female rats	> 1400 mg/kg

→ Should read 1,000 mg/kg

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90-Day Rat Feeding Study
90-Day Dog Feeding Study

NEL 150 ppm ✓
NEL 150 ppm

Dr. Whitmore found that the 150 ppm no-effect levels in the rat and dog supported the requested temporary negligible residue tolerances (0.02 ppm potatoes and 0.02 ppm soybeans).

- II. Mr. H. R. Gittes reviewed the above petition on December 21, 1970 for an extension of the temporary tolerances. No new data was presented at this time. Mr. Gittes approved the extension but stated that information regarding the metabolic fate of the herbicide was required before additional temporary tolerances or permanent tolerances could be granted.
- III. Dr. G. E. Whitmore reviewed the above petition on December 28, 1971 for an extension of the temporary tolerances.

Acute Oral Toxicity

DADK (metabolite of Sencor) - Female rats LD₅₀ 1100 mg/kg

Dr. Whitmore found the extension of the granted temporary tolerances to be safe but stated that animal metabolism data and possibly subacute toxicity data for DADK would be necessary for consideration of permanent negligible residue tolerances.

- IV. Toxicological data presented in this petition, PP No. 2F1274.

A. Acute Studies

(See Tables)

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ACUTE ORAL TOXICITY

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Species	Sex	No. of Animals	Formulation Tested	Administration Method	LD ₅₀	
					Formulation mg/kg	BAY 94337 mg/kg
Rat	Male	8	70% Wettable Powder	Suspended in water.	>2000 ✓	-
Rat	Male	16	50% Wettable Powder	Suspended in water.	4000 ✓	-
Rat	Female	16	50% Wettable Powder	Suspended in water.	4753 ✓	-
Guinea Pig	Female	16	Technical	Dissolved in 20% ethanol-80% propylene glycol.	-	274.5 ✓
Red-winged Blackbird	-	4	Technical	Propylene-glycol solution.	-	>100
Brown-headed Cowbird	-	2	Technical	Propylene-glycol solution.	-	>100
Common Grackle	-	2	Technical	Propylene-glycol solution.	-	>100
House Sparrow	-	2	Technical	Propylene-glycol solution.	-	>100
Cories	Female	6	Technical	Aqueous emulsion.	-	500-1000

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ACUTE DERMAL TOXICITY

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Species	Sex	No. of Animals	Formulation Tested	Method of Administration		LD ₅₀	LD ₅₀
Rabbits	Female	4	Technical	Formulation left in contact with skin for 24 hours.	-	>20,000 ✓	
Rabbits	Male	4	Technical	Formulation left in contact with skin for 24 hours.	-	>20,000 ✓	
Rats	Female	4	Technical	Skin abraded, moistened with saline, 24 hour contact.	-	>20,000 ✓	
Rats	Male	4	Technical	Skin abraded, moistened with saline, 24 hour contact.	-	>20,000 ✓	
Rabbits	Female	2	70% Wettable Powder	Formulation left in contact with skin for 24 hours.	>2000	-	
Rabbits	Female	6	70% Wettable Powder	Formulation left in contact with skin for 24 hours.	>20,000	-	
Rabbits	Male	4	50% Wettable Powder	Formulation left in contact with skin for 24 hours.	>2000	-	
Rabbits	Male	4	50% Wettable Powder	Formulation left in contact with skin for 24 hours.	>20,000 ✓	-	
Rabbits	Female	4	50% Wettable Powder	Formulation left in contact with skin for 24 hours.	>2000	-	
Rabbits	Female	4	50% Wettable Powder	Formulation left in contact with skin for 24 hours.	>20,000 ✓	-	
Rats	Male	4	50% Wettable Powder	Formulation left in contact with skin for 24 hours.	>20,000 ✓	-	

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ACUTE DERMAL TOXICITY (Continued)

Species	Sex	No. of Animals	Formulation Tested	Method of Administration	LD	
					Formulation mg/Kg	BAY 94337 mg/Kg
Rats	Female	4	50% Wettable Powder	Formulation left in contact with skin for 24 hours.	>20,000 ✓	-

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INHALATION TOXICITY

Species	Sex	No. of Animals	Type of Material	Daily Dose Theoretical µg/l	Daily Exposure Time (Min.)	No. of Exposures	Observations
Rat	Male	8	70% WP	2,000	60	1	No mortality
Rat	Male	8	70% WP	160,000 ✓	60 ✓	1	No mortality
Rat	Male	4	Technical	20,000 ✓	60	1	No mortality
Rat	Female	4	Technical	20,000 ✓	60	1	No mortality
Rat	Male	4	50% WP	2,000	60	1	No mortality
Rat	Male	4	50% WP	20,000 ✓	60	1	No mortality
Rat	Female	4	50% WP	2,000	60	1	No mortality
Rat	Female	4	50% WP	20,000 ✓	60	1	No mortality

Treatment Method:

Animals exposed in a rotating chamber to concentrations shown.

Intraperitoneal Toxicity

<u>Species</u>	<u>Sex</u>	<u>Formulation</u>	<u>Administration</u>	<u>LD₅₀ (mg/kg)</u>
Rats	Male	Technical	Water emulsion	363
Rats	Female	Technical	Water emulsion	363
Mice	Male	Technical	Water emulsion	247
Mice	Female	Technical	Water emulsion	275

Skin Sensitivity

<u>Species</u>	<u>Sex</u>	<u>No. Tested</u>	<u>Formulation</u>	<u>Dosage</u>	<u>Duration</u>	<u>Results</u>
Rabbits	-	2	Technical	Impreg- nated Cottonwool pads	7 days	No effect
✓ Rabbits	-	6	Technical	500 mg	72 hours	Slight ery- thema & edema on abraded areas
✓ Rabbits	-	6	50% Wettable Powder	500 mg	72 hours	"
Human	Males	8	Technical	Impreg- nated Cottonwool pads	24 hours	No effect

Eye Irritation

<u>Species</u>	<u>No. Tested</u>	<u>Formulation</u>	<u>Dosage</u>	<u>Duration</u>	<u>Results</u>
Rabbits	2	Technical	50 mg	--	No effect
✓ Rabbits	6	Technical	100 mg	72 hours	Slight erythe- ma in some animals after 24 hours

(Table continued)

Rabbits	6	50% Wettable Powder	100 mg	72 hours	No effect
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B. Repeated Oral Application to Rats

Sencor Technical was orally administered to 30 rats/sex/group at levels beginning at 100, 200, and 400 mg/kg. This dose was raised by the factor 1.5 on each successive day (5 administrations). The post-treatment observation period was concluded one week after the final dose. The average cumulative LD₅₀ was 450 mg/kg for male and female rats. The compound produces a cumulative effect.

C. Subchronic Toxicological Studies on Rats (Farbenfabriken Bayer AG Institut für Toxikologie; 2150)

1. Procedure

Wistar strain rats (groups of 15/sex/dose) were fed diets containing 0, 10, 25, and 60 ppm Sencor for 3 months. Body weights and food consumption were recorded weekly.

Laboratory examinations were conducted on 5 rats/sex/dose group after 4 weeks and 3 months.

Hematology - hemoglobin, hematocrit, RBC, total and differential WBC, medium cell hemoglobin, medium cell volume, reticulocytes, thrombocytes, and prothrombin time.

Blood Chemistry - SAP, SGOT, SGPT, sorbitol dehydrogenase, bilirubin concentration, total protein, blood sugar, cholesterin, BUN and creatinine.

Urine analysis - sugar, protein, blood, bile pigment, protein, and microscopic examination of the sediment.

All rats which died during the experiment or survived the study period were necropsied. The thyroids, thymus, heart, lung, liver, spleen, kidneys, adrenals, and gonads were weighed. The following tissues were studied histologically (H & E stain):

heart	ovaries	thymus	cerebral cortex
kidney*	uterus	stomach	thalamic nuclei

* Stained for fat with Oil Red O

lungs	cervix	duodenum	mid-brain
pituitary	liver*	adrenal	cerebellum
testes	spleen	thyroid	

* Stained for fat with Oil Red O

2. Results

There were no significant differences between the control and treatment groups by any of the following criteria:

~~body weights, food consumption, water consumption, hematology, clinical chemistry, gross pathology, histopathology, and organ/body weight ratios.~~

~~All other organ weights and organ/body weight ratios were not significantly different from those of the controls.~~

3. Conclusions

The increased liver weight of the 60 ppm females was not accompanied by either histological changes or abnormal liver function tests. The change in liver weights is therefore regarded as a physiological change rather than a toxic change. The no-effect level in this study is not determined since an effect was not produced at the highest dosage used, 60 ppm.

Systemic NOEL > 60 ppm (highest dose tested).

D. Mutagenic Study with BAY 94337 in Albino Mice (Ind. Bio-Test Lab., Inc.; E8922)

1. Procedure

Groups of 12 male Charles River strain albino mice were injected ip with 0, 10, or 20 mg/kg of Sencor Technical as a 0.2% suspension in corn oil. Three untreated virgin females were placed in a cage with each male for a week. For 6 consecutive weeks, new groups of 3 virgin females were kept with each male. The females were sacrificed approximately 1 week after removal from the breeding cage. The numbers

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of implantation sites, resorption sites (particularly early sites) and embryos were recorded.

2. Results

The mating indices (No. of pregnant mice ÷ No. of females mated X 100) and the number of surviving males/post-treatment week are essentially the same for test and control animals. No significant differences were observed in the number of implantations, resorptions, and embryos. The mutation rate and the number of preimplantation losses are normal and comparable to the control values.

3. Conclusions

Sencor Technical is not mutagenic for mice at levels up to 20 mg/kg.

E. Acute Oral Toxicity of Sencor Technical to Bobwhite Quail and Mallard Ducks (Chemagro; 33172)

Adult Bobwhite quail (5/sex) and mallard ducks (4/sex) were administered Sencor Technical in propylene glycol:ethanol via a stomach tube and observed for 21 days.

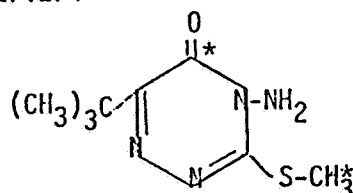
	Male LD ₅₀ (mg/kg)	Female LD ₅₀ (mg/kg)
Bobwhite quail	168 (138-206)	164 (141-190)
Mallard ducks	>460, <680	>680

F. Fish Toxicity (Chemagro; 33124)

Species	Formulation	Observations
Bluegill	Technical	96-hour LC ₅₀ - 80 ppm
Rainbow Trout	Technical	96-hour LC ₅₀ - 76 ppm
Bluegill	50% WP	96-hour LC ₅₀ - 131 ppm
Rainbow Trout	50% WP	96-hour LC ₅₀ - 147 ppm

G. The Metabolism and Excretion of Sencor in Rats (Chemagro; 33366)

Sprague-Dawley albino rats were intubated with Sencor at a dose rate of 20 mg/kg in 50% aqueous ethanol or 50 and 100 mg/kg in 0.5% aqueous gum tragacanth. The Sencor administered was labeled with ¹⁴C in the carbonyl group and with tritium in the S-methyl group for the 20 mg/kg study and with only the ¹⁴C labeled material for the 50 and 100 mg/kg doses.



The excretion of ^{14}C was essentially through the urine and feces. No radiocarbon was detected in the expired gases. Tritium activity was eliminated in increasing amounts in expired air suggesting S-demethylation and oxidative metabolism of the methyl group to tritiated water. The major metabolic pathway in the tissues appeared to be Sencor \longrightarrow deaminated (DA) Sencor \longrightarrow deaminated diketo (DADK) Sencor. A secondary, less active pathway was Sencor \longrightarrow diketo (DK) Sencor \longrightarrow deaminated diketo (DADK) Sencor.

H. The Metabolic Fate of Carbonyl C^{14} -Sencor in Dogs (Chemagro; 33361)

Male dogs were given a single oral dose of 10 mg/kg ^{14}C -Sencor. Peak gastrointestinal absorption occurred 4 hours after treatment. Recovery of administered radioactivity after 120 hours was 52-60% in the urine and 30% in the feces. Radioactive residues declined rapidly to low levels within 72 hours and at 120 hours residues were 7.3 ppm in liver and 0.1 ppm in muscle. Nearly all of the residues in the tissues were the deaminated diketo (DADK) metabolite and up to 70% in the urine was DADK. Lesser amounts of diketo and unmetabolized Sencor were found in the urine.

I. The Metabolism of Sencor in Soybean Plants (Chemagro; 29800)

Sencor, applied pre-emergence to soybeans, was metabolized first to deaminated Sencor and finally to DADK Sencor. Most of the material at harvest was in the DADK form.

J. The Acute Oral Toxicity of Two Metabolites of BAY 94337 to Adult Female Rats (Chemagro; 31656)

Adult, female Sprague-Dawley rats were dosed with DA Sencor and Sencor in 50% ethanol-50% propylene glycol as well as DK Sencor and Sencor in 20% ethanol-80% propylene glycol.

The rats were observed for 14 days.

Compound	50% - 50% diluent	20% - 80% diluent
Sencor	LD ₅₀ >1400 mg/kg	LD ₅₀ >1200, <1900 mg/kg
DA Sencor	LD ₅₀ > 275, <300 mg/kg	---
DK Sencor	---	LD ₅₀ > 600, < 900 mg/kg

DISCUSSION

The present petition requests a tolerance of 0.1 ppm Sencor in or on soybeans. Only toxicity data necessary to support negligible residue tolerances was submitted in this petition. If the petitioner desires a non-negligible tolerance, carcinogenicity studies, a reproduction study, and a teratology study would also be necessary. The present temporary tolerance for soybeans is a negligible residue tolerance. The requested tolerance is such that a negligible tolerance could readily be considered by TB in light of the submitted data and it is probable that the petitioner would prefer a negligible residue tolerance.

In Mr. W. S. Cox's memo of December 8, 1971 (PP #0G0940), he stated: "For the soybean meal which may be processed into the human food, soybean flour, and based on the tracer study, we estimate that residues of this herbicide could approach 2.0 ppm from the proposed use, but of this only about 0.25 ppm would be present as bound DADK with none of the parent compound present in any form. The remainder (ca. 1.75 ppm) will consist primarily of high molecular very polar complexes. We defer to TB as to whether this unidentified activity is of toxicological concern in connection with a temporary tolerance for soybeans and whether a tolerance expressed in terms of the parent compound and DADK metabolite would be safe."

Dr. G. E. Whitmore responded in his memo dated December 28, 1971 that these bound or conjugated metabolites were of no concern for the extension of the temporary tolerances. TB now feels that if CB finds the level of DADK (0.25 ppm) in soybean flour to be same as that stated in Mr. Cox's memo, we will require adequate data for the establishment of a non-negligible tolerance to cover soybean meal and flour. The additional studies should be conducted using the DADK metabolite since it is the compound present rather than the parent compound Sencor.

TB defers to CB regarding the transfer of residues of Sencor to meat, milk, etc. of livestock and poultry fed soybeans treated with Sencor.

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RECOMMENDATION

Toxicology Branch can not rule for the requested tolerance pending Chemistry Branch's review of the data and their evaluation of residues in soybean meal and flour.

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Toxicology Branch
Pesticides Tolerances Division

cc:
JGCummings
PRD/EPA
Perrine Branch
Atlanta Branch (CLewis)
Division Reading File
Branch Reading File
PP No. 2F1274

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