UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 001331

CONFIDENTIAL 4-7-78

DATE: April 7, 1978

SUBJECT: Tolerance for Bolstar, Petition No. 8F2063
Caswell No. 453-AA

FROM: Reto Engler, Ph.D.
Toxicology Branch, RD (WH-567)

TO: Mr. Frank Sanders, RD
and
Chemistry Branch, RD (WH-567)

Tolerances Requested:

Cottonseed	-	0.5 ppm
Meat (all)	-	0.01 ppm
Milk	-	0.001 ppm
Eggs	-	0.001 ppm
Cottonseed oil	-	1.0 ppm
Cottonseed hulls	-	1.0 ppm

Petitioner:

MOBAY, Kansas City, Mo.

Residue Chemistry Considerations:

CB memo of June 21, 1978 indicates no objection to the proposed residue levels thus the toxicology considerations below are not affected by the CB reviews.

Recommendations: (Tolerance)

The tolerances can be toxicologically supported (see also freestanding memo on ADI, studies submitted, etc.).

Recommendation (Label):

According to Mr. Ritter's memo of Feb 2, 1977 the signal word should be changed to Danger based on eye effects, with commensurate changes in first-aid statements.

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

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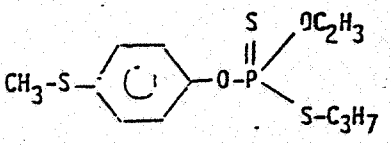
In the same memo Mr. Ritter also requested that the antidotal statement on the label should be revised since 2-PAM and atropine are only effective under very rigorous conditions. A medical expert should revise the statement so it conveys to the treating physician as best as possible what he may expect in an acute poisoning case.

It appears that these two items have not been addressed by the registrant. They should be resolved before the label receives final approval.

Substance Identification:

Bolstar
BAY NTN 9306
O-ethyl-O-(4-methylmercaptophenyl)-S-n-propyl-dithiophosphate



Referenced Petition:

6G1705

Formulation:

Bolstar (tech) 74.8%

[redacted]

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* Inerts are cleared for agricultural use

Review:

A. Prior studies

Studies previously submitted (PP #6G1705) were reviewed by Mr. D. Ritter, memos of Jan. 6, 1976, Jan. 27, 1977 and Feb. 2, 1977. The studies pertinent to evaluating the food tolerances are summarized below:

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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Neurotoxicity (hen)	- negative (dosed twice with LD_{50})
Teratology (rabbit)	- negative at 30 mg/kg
Dominant lethal mutagenicity (mouse)	- negative at 200 mg/kg
90-Day rat feeding study	- NEL (ChE) 10 ppm
90-Day dog feeding study	- NEL (ChE) 10 ppm

Review of Present Submission

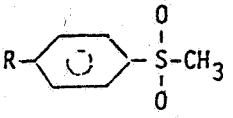
1. Acute oral toxicity of Bolstar, sulfone sulfoxide and oxygen (male and female rats).

   a) Technical Bolstar

   LD_{50} male 262 (211-326) mg/kg
   female 275 (201-376) mg/kg

   male 293 (213-417) mg/kg
   female 275 (204-370) mg/kg

   b) Sulfone:



   LD_{50} male 283 (222-361) mg/kg
   female 404 (329-496) mg/kg

   c) Oxygen analogue of sulfone

   LD_{50} male 74 (47-115) mg/kg
   female 133 (114-155) mg/kg

   d) Sulfoxide

   LD_{50} male 253 mg/kg
   female 283 (243-330) mg/kg

e) Bolster analytical standard

LD_{50} male 208 (172-251) mg/kg
female 356 (306-416) mg/kg

f) Oxygen analogue of Bolstar

LD_{50} male 73 (53-98) mg/kg
female 206 (142-299) mg/kg

g) Oxygen analogue of sulfoxide

LD_{50} male 62 (47-80) mg/kg
female 84 (67-104) mg/kg

2. 3-Generation reproduction study (rats)

Hazleton Lab, Report No. 339-105, Sept. 8, 1977

A standard 3-generation reproduction study protocol was used, with 10 male and 20 females per dose per generation. Two matings were performed at each generation. All animals not used in future generations were necropsied and discarded. In addition, 10 males and 10 females of the F_{3b} litters were analysed histologically examined (about 30 tissues). The feeding levels were 0, 30, 60 and 120 ppm.

Results:

Body weights and food consumption for all parental generations were unremarkable, some statistical significant deviations were observed but they were neither consistent nor dose related and thus are not biologically significant. Survival of animals was not affected by treatment.

Partuition, lactation survival, life birth, weaning, and sex ratio indexes were determined and statistically analyzed.

No biologically significant deviations from the norm were noted, although some measurements were statistically significantly different. All these deviations were not dose related and consistently observed in all generations.

Gross necropsy is reported and was found unremarkable. Histopathology performed on the designated F_{3b} weanlings is reported and does not show any adverse effects.

RBC, plasma and brain ChE was determined on P_3 rats of the control group and high dose group. All ChE measurements were significantly depressed for the exposed animals with exception of the male brain ChE.

Conclusion:

The NEL for reproductive effects is greater than 120 ppm for the rat. The study is classified as core minimum data.

3. Two-year feeding study on rats

Chemagro Agri. Division Tox Lab, Report No. 63058, March 1, 1978.

Fisher 344 rats were fed Bolstar at 0, 6, 60, and 250 ppm. Fifty rats per sex per dose were used. The customary clinical determinations were run, body weight and food consumption was determined. Gross pathology was performed on all rats and the tissues were preserved. All tissues of all rats at the control and high dose levels were prepared for histopathology as well as from all rats that died on study, plus 10 survivors per sex from the low and middle dose. Adrenals, thyroids, gonads, liver, spleen, lymph nodes, pituitary, femur, and gross lesions were examined histologically from all rats.

Results:

Body weights, organ weights and food consumption were not affected at any level, except for high dose females which consumed relatively more food but maintained the weight. Blood chemistry, hematology and urinalysis were normal for all groups with exception of ChE. Plasma and RBC ChE were depressed at 60 and 250 ppm for males and females, brain ChE was inhibited at 250 ppm for males and females. At 6 ppm no significant inhibition was noted. Gross and histopathology showed no compound related effects, or tumor formation.

Conclusion:

The ChE NEL for the rat is 6 ppm, no systemic effects were noted at 250 ppm. This study was audited in Stanley, Kansas on March 27 - 31, 1978, no significant discrepancies in the raw data were detected. Core minimum study.

4. Chronic feeding study on mice

Chemagro Tox Lab, Report No. 63059, March 3, 1978.

CD, Swiss mice were fed at levels of 0, 2.5, 25, 200, and 400 ppm for 22 months. Body weights, food consumption, hematology, blood chemistry, urinalysis were measured. Sixty animals per sex were used at each dose, 10 of these animals were set aside for blood taking and the remaining 50 animals were used for the other tests (body weight, food consumption, pathology, etc.). Gross pathology was performed on all animals. Complete histopathology on all control and high dose animals and on 10 per sex from the three middle doses (sacrificed at termination).

Results:

The only significant findings were related to ChE inhibition. Plasma and RBC ChE were significantly inhibited at 25 ppm and above, brain ChE inhibition was apparent at 400 ppm (female 74%, male 85%) and to some degree at 200 ppm (male 83%, female 83%). Plasma and RBC Che at 400 ppm were around 10% and as low as 0-1% of controls. The other parameter studied showed no compound related effect. Gross and histopathology showed no somatic or oncogenic effect.

Conclusion:

The ChE NEL for the mouse is 2.5 ppm. No somatic effects at 400 ppm. This study was also audited and no significant discrepancies were apparent. This study can be classified as a mouse feeding/oncogenicity study. Core minimum data.

5. Two-year feeding study on beagle dogs

Chemagro Tox Lab, Report No. 63100, Feb. 27, 1978.

Four dogs per sex per dose were fed at levels of 0, 10, 100, and 150 ppm. Body weight, food consumption, hematology, blood chemistry and urinalysis were studied. Gross and complete histopathology was performed on all animals.

Results:

The only parameter affectd was ChE; at 100 and 150 ppm plasma, RBC and brain ChE were inhibited. 10 ppm showed no effect. The other parameters were unremarkable at all levels.

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Conclusion:

The ChE NEL for the dog is 10 ppm with no somatic effects at 15 ppm. This study was also audited on the premises of MOBAY and no discrepancies were found. Core minimum study.

Over-all Conclusion:

Conversion of the ChE NEL into mg/kg/day for the three species tested is as follows:

mouse	0.375 mg/kg/day
rat	0.30 mg/kg/day
dog	0.25 mg/kg/day

For purposes of ADI calculation the lowest value will be chosen.

6. Exposure analysis and risk assessment

(See freestanding memo)

No RPAR criteria are exceeded in the studies submitted.

E for GEW 6/23/78

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