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

005849

APR 23 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Registration No. 3125-319 - Bayleton (MEB 6447)

Caswell No. 862AA

FROM: George Z. Ghali, Ph.D. G. Ghali 4.9.87
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Lois A. Rossi, Acting PM 21
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

THRU: Reto Engler, Ph.D., Chief
Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Petitioner: Mobay Chemical Corporation
Kansas City, MO 64120

Action Requested:

Review and evaluation of acute toxicity data and reassessment of the toxicity category for labeling purposes.

Conclusions and Recommendations:

1. The submitted data had been evaluated by the Toxicology Branch (TB). For conclusions and core classification of each study, please see individual data evaluation records.

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2. Technical Bayleton has been previously classified as Toxicity Category II based on the results of acute oral toxicity testing in rats (Bayer A.G. Institute of Toxicology, Report No. 4416, dated January 3, 1977). The new acute toxicity data recently submitted by Mobay should not affect this classification.

DATA EVALUATION RECORD 005849

Study Type: Acute Toxicity in Rats and Mice

Study ID: Nakazato, Y.; Iyatomi, A. (1977) MEB 6447 (Bayleton), Acute Toxicity Studies. An Unpublished Study Prepared by Nitokuno, Agricultural Chemical Institute, Laboratory of Toxicology, Report No. 88, Dated December 14, 1977. Submitted by Mobay Chemical Corporation (Mobay Report 63081). EPA Accession No. 261904.

Test Chemical: MEB 6447 (Bayleton) 1-p-chlorophenoxy-3,3-dimethyl-1-(1,2,4-triazol-1-yl)-2-butanon

Test Material: Active ingredient of Bayleton with a purity of 97.0% (PT 16002/75, eg 4/75)

Experimental Protocol:

"Male and female Wistar rats (weight of 100 to 130 grams), the male and female ddN mice (weight of 20.0 to 24.0 grams) were used. Throughout the experiment, animals were housed in an air-conditioned room and consumed food and water ad libitum."

This study included four acute toxicity testings: oral application, dermal application, intraperitoneal application, and subcutaneous application.

1. Oral Application

"Prescribed amounts of the compound were suspended in Lutrol and were administered to the animals. The prepared samples were applied by means of a stomach tube with the amounts of 0.5 mL per 100 g body weight for rats and 0.1 per 10 g body weight for mice, respectively."

2. Dermal Application

"Prescribed amounts of the compound were dissolved in acetone. They were applied on the dorsal skin which was clipped on the day before."

3. Intraperitoneal Application

"Prescribed amounts of the compound were emulsified in suitable amount of Lutrol with small amount of wetting agent and added with respective volume of physiological saline. These samples were applied into the abdominal cavity of the animals by mean of the injector."

4. Subcutaneous Application

"Prescribed amounts of the compound were emulsified in suitable amount of Lutrol with small amount of wetting agent and added with respective volume of physiological saline. These samples were applied into the dorsal subcutaneous part of the animals.

"The postapplication observation was carried out during 14 days. From the results of the mortality on final day, the mean lethal dose (LD_{50}) was calculated by the method of Bliss."

Results:

Acute Oral Toxicity in Rats

The results of the acute oral toxicity study in male and female rats are shown in table 1.

Poisoning signs were manifested as hyperactivity, hypersensitivity, lacrimation, salivation, piloerection and cramps. The onset of these symptoms varied with the dose level. Death occurred within 20 minutes up to 4 days after dosing. Spots of hemorrhage were observed in the intestine of several animals that died during the observation period. Adhesion of the liver to diaphragm was observed in the autopsy of animals that survived the treatment.

Acute Oral Toxicity in Mice

The results of the acute oral toxicity test in mice are shown in table 2. Signs of acute intoxication in mice were similar to those observed in rats, and were observed at about 4 to 20 minutes after dosing and continued for 1 to 5 days. Gross necropsy revealed spots of hemorrhage in the intestine of animals that died during the observation period, and enlargement of the liver and spleen of the surviving animals.

Acute Dermal Toxicity in Rats

The results of the acute dermal toxicity test in male and female rats are shown in table 3.

According to the authors, no poisoning symptoms were observed in any dose group except the highest two dose levels where deterioration of general health was observed. The authors also indicated that no abnormalities were observed in the internal organs in gross necropsy.

Acute Dermal Toxicity in Mice

The results of the acute dermal toxicity test in male and female mice are shown in table 4.

According to the authors, poisoning signs were manifested as early as 15 minutes after application and continued for one day. The poisoning symptoms are piloerection and deterioration in general health conditions.

Acute IP Toxicity in Rats

Results of IP toxicity in male and female rats are shown in table 5. According to the authors, the symptoms of acute intoxication manifested were hyperactivity, lacrimation, salivation and cramps. These signs were observed within 1 to 6 hours and lasted for up to 3 days. Death occurred in 25 minutes to 3 days after application. Gross examination of the animals that died during the observation period, were spots of hemorrhage in the intestine. Other signs observed were adhesion of liver to the diaphragm in addition to liver and spleen enlargement and dark color.

Table 1: Acute Oral Toxicity in Male and Female Rats

Dose mg/kg	Death	
	Males	Females
1300	15/15	15/15
1000	13/15	12/15
780	12/15	11/15
600	8/15	9/15
460	2/15	7/15
360	0/15	4/15
220	0/15	3/15
130	0/15	0/15
78	0/15	0/15
46	0/15	0/15

Table 2: Acute Oral Toxicity in Male and Female Mice

Dose mg/kg	Death	
	Males	Females
2800	-	15/15
2200	15/15	13/15
1700	14/15	11/15
1300	11/15	8/15
1000	9/15	5/15
780	5/15	2/15
600	1/15	0/15
460	0/15	-
360	-	0/15
280	0/15	-
220	-	0/15
170	0/15	-

Table 3: Acute Dermal Toxicity in Male and Female Rats

Dose mg/kg	Death	
	Males	Females
2000	0/10	0/10
1000	0/10	0/10
500	0/10	0/10
100	0/10	0/10

Table 4: Acute Dermal Toxicity in Male and Female Mice

Dose mg/kg	Death	
	Males	Females
1000	0/15	0/15
500	0/15	0/15
250	0/15	0/15
125	0/15	0/15
62	0/15	0/15

Table 5: Results of IP Toxicity in Male and Female Rats

Dose mg/kg	Death	
	Males	Females
1300	15/15	-
1000	14/15	15/15
780	12/15	13/15
600	11/15	11/15
460	9/15	9/15
360	7/15	8/15
280	3/15	4/15
220	0/15	1/15
170	-	0/15
130	0/15	-
100	-	0/15
78	0/15	-
60	-	0/15
46	0/15	-
36	-	0/15

Table 6: Results of IP Toxicity in Male and Female Mice

Dose mg/kg	Death	
	Males	Females
600	15/15	15/15
460	12/15	14/15
360	11/15	12/15
280	11/15	12/15
220	4/15	6/15
170	2/15	3/15
130	0/15	0/15
78	0/15	0/15
46	0/15	0/15

Table 7: Results of Subcutaneous Toxicity in Male and Female Rats

Dose mg/kg	Death	
	Males	Females
1000	3/10	3/10
780	2/10	2/10
600	2/10	1/10
460	0/10	1/10
360	0/10	0/10
220	0/10	0/10
130	0/10	0/10
78	0/10	0/10

Table 8: Results of Subcutaneous Toxicity in Male and Female Mice

Dose mg/kg	Death	
	Males	Females
1000	0/15	0/15
600	0/15	0/15
360	0/15	0/15
220	0/15	0/15
130	0/15	0/15
78	0/15	0/15

Conclusions:

The acute LD_{50}'s were determined by the authors as follows:

Acute oral LD_{50}, male rats = 630 (564 to 701) mg/kg.
Acute oral LD_{50}, female rats = 520 (446 to 605) mg/kg.

Acute dermal LD_{50}, male rats = > 2000 mg/kg.
Acute dermal LD_{50}, female rats = > 2000 mg/kg.

Acute IP LD_{50}, male rats = 463 (375 to 501) mg/kg.
Acute IP LD_{50}, female rats = 405 (352 to 464) mg/kg.

Acute Subcutaneous LD_{50}, male rats = > 1000 mg/kg.
Acute subcutaneous LD_{50}, female rats = > 1000 mg/kg.

Acute oral LD_{50}, male mice = 966 (855 to 1088) mg/kg.
Acute oral LD_{50}, female mice = 1271 (1119 to 1441) mg/kg.

Acute dermal LD_{50} male mice = > 1000 mg/kg.
Acute dermal LD_{50} female mice = > 1000 mg/kg.

Acute IP LD_{50}, male mice = 270 (238 to 305) mg/kg.
Acute IP LD_{50}, female mice = 239 (212 to 269) mg/kg.

Acute subcutaneous LD_{50}, male mice = > 1000 mg/kg.
Acute subcutaneous LD_{50}, female mice = > 1000 mg/kg.

Core Classification: Supplementary.

DATA EVALUATION RECORD

Study Type: Acute Oral Toxicity Studies

Study ID: Mihail, F. (1980) Acute Toxicity Studies. An Unpublished Report Prepared by Bayer, A.G. Institute of Toxicology. Report No. 9277, Dated June 27, 1980. Mobay Report No. 68922. EPA Accession No. 261904.

Test Chemical: MEB 6447 (Bayleton technical), Batch No. 816 854 682, Purity 92.6%

Experimental Protocol:

The study was done using male and female rats and mice and male rabbits. Male and female Wistar albino rats, NMRI mice, and male white albino rabbits were used in the study. Fifteen animals per sex per dose were used in the case of rats and mice, and five per group in the case of rabbits. The test material was prepared in polyethylene glycol 400 and administered by gavage to fasted and nonfasted rats and mice, and in distilled water for the treatment of male rabbits.

Rats and mice received a constant volume of 1.0 mL of the dosing solution per 100 g body weight. Rabbits received 0.5 mL per 100 g of body weight. The animals were observed for a period of 14 days after dosing.

Results:

Results are shown in tables 1, 2, 3, and 4.

According to the authors, symptoms of intoxication included apathy, labored breathing, increased or reduced mobility, staggering and cramped posture, and increased reaction to extraneous stimuli. In addition, severe behavioral disorder including aggressiveness and self-mutilation were seen in rats and rabbits. Onset of symptoms was within minutes postapplication in rats and mice, and in 2 to 6 hours postapplication in rabbits.

Gross pathology conducted on rats and mice that died during the course of the study revealed reddened and ulcerated glandular mucosa of the stomach, spotted lungs, pulmonary emphysemas, and reddened renal pelvises. These gross pathological symptoms were more pronounced in the fasted animals.

Gross pathology conducted on rabbits that died during the experiment revealed slight pulmonary emphysemas and spotted livers with distinct lobular pattern.

Table 1: Acute Oral Toxicity to Fasted Rats

Dose mg/kg	Death	
	Males	Females
250	-	0/15
350	-	2/15
500	-	5/15
750	2/15	6/15
1000	2/15	7/15
1500	6/15	10/15
2500	9/15	12/15
3500	14/15	15/15
5000	14/15	-

Table 2: Acute Oral Toxicity to Nonfasted Rats

Dose mg/kg	Death	
	Males	Females
250	-	1/15
500	0/15	4/15
750	2/15	9/15
1000	8/15	8/15
1500	9/15	9/15
2000	12/15	14/15
2500	15/15	-

Table 3: Acute Oral Toxicity to Fasted Male Rabbits

Dose mg/kg	Death
50	0/5
100	1/5
250	3/5
500	1/5

Table 4: Acute Oral Toxicity to Fasted Mice

Dose mg/kg	Death	
	Males	Females
250	0/15	0/15
350	1/15	-
500	4/15	0/15
750	9/15	1/15
1000	10/15	5/15
1500	13/15	12/15
2500	15/15	-

Conclusions:

The acute oral LD_{50}'s were determined by the authors as follows:

Fasted rats, oral LD_{50} (males) = 1855 (1399 to 2460) mg/kg.
Fasted rats, oral LD_{50} (females) = 1020 (756 to 1377) mg/kg.

Nonfasted rats, oral LD_{50} (males) = 1245 (992 to 1562 mg/kg.
Nonfasted rats, oral LD_{50} (females) = 793 (602 to 1045) mg/kg.

Fasted rabbits, oral LD_{50} (males) = ~ 250 to 500.

Fasted mice, oral LD_{50} (males) = 732 (562 to 952) mg/kg.
Fasted mice, oral LD_{50} (females) = 1158 (993 to 1350) mg/kg.

Core Classification: Supplementary.

DATA EVALUATION RECORD

005849

Study Type: Acute Dermal Toxicity In Rats

This is a summary of a published study. No DER was prepared. The following is an excerpt taken from the registrant's submission:

"These experiments were performed on groups of five male and five female rats using the method reported by Noakes and Sanderson (Brit. J. Ind. Med. 26, 59, 1969). The test compound dose of 5000 mg/kg was pasted up with 10 drops of 0.9% NaCl solution, and applied for a contact time of 24 hours to the intact dorsal skin that had been shaved the day before. The treated skin areas were covered with aluminium foil and wrapped in an adhesive plaster sleeve. Upon removal of the occlusive dressings, the treated skin areas were washed with soap and water. The rats were kept under observation for 14 days posttreatment.

"Dermal application of MEB 6447 was tolerated without causing any symptoms. None of the rats died either during the contact time or during the postexposure observation period.

"Gross pathology performed on the rats sacrificed at the end of the postexposure observation period did not reveal any tissue alterations constituting variations from the physiological norm. The acute dermal toxicity of MEB 6447 is thus higher than 5000 mg/kg."

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DATA EVALUATION RECORD

Study Type: Intraperitoneal Toxicity in Rats

Study ID: Mihail, F. (1980) Acute Toxicity Studies. An Unpublished Report Prepared by Bayer, A.G. Institute of Toxicology. Report No. 9277, Dated June 27, 1980, Mobay Report No. 68922. EPA Accession No. 261904.

Test Chemical: Bayleton technical, 92.6% purity

Experimental Protocol:

According to the authors "the test compound was dissolved polyethylene glycol 400, and injected into the abdominal cavity of male and female rats. The test compound concentrations were adjusted for rats to receive injections of constant volume of 0.5 mL of the dilution per 100 g body weight. The rats were kept under observation for 14 days postinjection."

Results:

According to the authors, poisoning symptoms observed in this study were similar to those in the oral administration studies. Gross pathology performed at the end of the study revealed adhesion of the liver with surrounding organs such as stomach, spleen, and diaphragm, or encapsulation of one lobe or more of the liver in connective tissue-like capsules. Results are shown in table 1.

Table 1: Intraperitoneal Toxicity in Rats

Dose mg/kg	Death	
	Males	Females
100		0/15
150	0/15	1/15
175	1/15	-
200	7/15	4/15
225	-	9/15
250	12/15	12/15
300	-	15/15

Conclusions:

The acute intraperitoneal LD_{50} for Bayleton in male rats is 214 (195 to 235) mg/kg, and in female rats is 213 (197 to 230) mg/kg.

Core Classification: Supplemental information.

Study Type: Dermal Sensitization

Study ID: Flucke, W. (1981) KWG 0599, Evaluation for Sensitization in Guinea Pigs: Maximization Test after Magnussen and Kligman. (An Unpublished Report Prepared by Bayer, A.G. Institute for Toxicology, Wuppertal. Elberfeld, Study No. T2003027, Report No. 9934, Dated May 4, 1981.) EPA Accession No. 261904.

Test Chemical: KWG 0599 (Bayleton Technical), Batch No. 16010/77, with unspecified purity

Experimental Protocol:

According to the authors, the test was conducted according to the "Maximization Test" developed by B. Magnusson and A.M. Kligman (1969) J. Invest. Dermat. 52, 268, and "Identification of Contact Allergens" (1970) in: Allergic Contact Dermatitis in the Guinea Pig," Ed. C.C. Thomas, p. 102 to 103.

Two groups of 10 male and 10 female guinea pigs were used. One group was considered a control group. Three intradermal injections of 0.1 mL were made simultaneously on each longitudinal side at 1 to 2 cm from each other after the skin of the animal was shaved.

The skin of two groups of 10 male and 10 female guinea pigs was shaved 24 hours prior to injection. Three intradermal injections of 0.1 mL were made simultaneously on each longitudinal side at 1.2 cm from each other. One of the two groups served as a control group. According to the authors, the animals of the two groups were treated in the following manner:

"a) Test compound group

1st Injection site pair (cranial)
Freund's Complete Adjuvant (Difco Lab.) diluted 1:1 with 0.9% physiological saline solution

2nd Injection site pair
KWG 0599 applied as a 1% emulsion (5 drops of Cremophor EL® per 10 mL physiological saline)

3rd Injection site pair (caudal)
KWG 0599 applied as a 1% emulsion (5 drops of Cremophor EL® per 10 mL physiological saline) incorporated in a 1:1 dilution of Freund's Complete Adjuvant in physiological saline.

"b) Control group

The guinea pigs in the control group were treated in the same way as those in the test compound group except that the emulsions applied to the injection site pairs 2 and 3 did not contain any test compound.

"Topical application (1 week after intradermal injection)

Saturated filter papers (2 x 2 cm) were placed between or on the injection sites, covered with aluminum foil and firmly secured by adhesive bandage wound around the torso of the animal; this dressing was left in place for 48 hours. Twenty-four hours before the application, the application sites were depilated and treated with 10% sodium lauryl sulphate vaseline massaged into the skin.

"The filter papers were saturated as follows:

a) Test compound group
25% emulsion of KWG 0599 (5 drops of Cremophor EL® per 10 mL distilled water).

b) Control group

Emulsion as in a) but containing no test compound.

"After removal of the bandages and filter papers, all the guinea pigs were treated again. The test compound and control emulsions were applied respectively in 0.2-mL amounts to the skin between the injection sites and spread over each area.

"Challenge test (performed 3 weeks after intradermal induction resp. 2 weeks after topical induction)

"Challenge procedure

A filter paper saturated with a 25% test compound emulsion was placed for 24 hours on the left depilated flank of each of the guinea pigs in both the test compound group and the control group, in the same fashion as for topical induction described above.

For comparison, a similar control filter paper saturated only with the formulating aids was placed on the right flank of each guinea pig.

"Reading of challenge reactions

The challenge sites were macroscopically evaluated at 24 hours and again at 48 hours after removal of the patches from the guinea pigs. The reactions were scored on the following scale:

0 = no reaction
0.5 = scattered mild redness (slightly mottled)
1.0 = slightly mottled, partly confluent redness
2.0 = moderate and diffuse redness
3.0 = intense diffuse redness and swelling"

Results:

According to the authors, only a few cases of scattered mild redness were observed. These were not considered to be treatment-related since they were not dose dependent. These cases of redness may be accidental since they were also observed in both control and treated animals.

Conclusion:

The data as submitted did not provide any evidence that Bayleton (KWG 0599) is a skin sensitizer under the testing conditions.

Core Classification:

Supplementary.

89883:Ghali:HED-11:KENCO:4/2/87:7/14/87:LIZ:VO:EK:LIZ
R:91524:Ghali:HED-11:KENCO:4/7/87:7/17/87:dej:lf:de