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

006841

MAR 10 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Registration No. 3125-320 - Bayleton
Accession Nos. 254694 and 254697

Caswell No. 862AA

FROM: George Z. Ghali, Ph.D. G. Ghali 3.2.88
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Lois A. Rossi, PM 21
Fungicide-Herbicide Branch
Registration Division (TS-767C)

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

REGISTRANT: Mobay Chemical Corporation
Kansas City, MO 64120

Action Requested

Review and evaluation of human safety data including:

1. Mihail, F., and Kaliner, G. (1979) Subacute oral cumulative toxicity study on rats. Mobay Report No. 69477.

2. Hixson, E.J. (1982) Alteration of excretion of of ^{14}C-Bayleton by several therapeutic regimens. Mobay Report No. 80263.

3. Nakasato, Y., and Iyatomi, A. (1977) Acute toxicity studies. Mobay Report No. 63081.

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4. Knaak, J.B., Yee, K., Ackerman, C.R., Zweig, G., and Wilson, B.W. (1982) Development and validation of an animal model to study the dermal absorption of pesticides. Mobay Report No. 80981.

5. Polacek, I. (1983) Safety pharmacology Study with MEB 6447 on oral administration. Mobay Report No. 85867.

6. Negata, T., Armaki, Y., Sato, M., and Enomoto, M. (?) Subacute toxicity on rats. Mobay Report No. 69700.

7. Watanabe, M. Iyatomi, A., and Enomoto, M. (1979) Triadimeform; 7-day treatment and 14-day recovery tests on rats. Mobay Report No. 82525

8. Roetz, R. (1982) Study of embryotoxic and teratogenic effects on rabbits after oral administration. Mobay Report No. 82236.

9. Unger, T.M., Goethem, D.V., and Shellenberger, T.E. (1982) A teratological evaluation of Bayleton in mated female rats. Mobay Report No. 82270.

10. Thyssen, J. and Groning, P. (1978) Reproduction study [the title and the text of the study are in German]. Mobay Report No. 67070.

11. Machemer, L. (1977) Micronucleus test on mice to evaluate MEB 6447 for mutagenic effects. Mobay Report No. 52724.

12. Hixson, E.J. (1982) Therapy of eye irritation of Bayleton 50% W.P. Mobay Report No. 80686.

13. Inkmann-Koch, A., and Stegh, R. (1982) Studies on the determination of applicator exposure in the application of Bayleton. Mobay Report No. 82584.

14. Sangha, G.K. (1984) Acute inhalation study with Bayleton 50% W.P. in rats. Mabay Report No. 86398.

15. Mihail, F. (1980) Acute toxicity studies. Mobay Report No. 68922.

16. Mihail, F. and Kaliner, G. (1979) Subacute oral cumulative toxicity on rats. Mobay Report No. 254694.

Conclusions and Recommendations

For conclusions, recommendation, and Core-classification of each study, please see the data evaluation records (DERs) for individual studies.

The following is a brief summary and the highlights of each study report:

1. Mihail, F., and Kaliner, G. (1979) Subacute oral cumulative toxicity study on rats. Mobay Report No. 69477.

   No data evaluation records were prepared for this study. Parts of the data tables are in German. The study is unacceptable as presented.

2. Hixson, E.J., (1982) Alteration of excretion of of ^{14}C-Bayleton by several therapeutic regimens. Mobay Report No. 80263.

   Based on the data included in the report, none of the therapeutic regimens tested, such as sodium carbonate, ammonium chloride, lasix diuretic, activated charcoal, or magnesium sulfate resulted in any alteration in the excretory pattern of Bayleton.

   The study is considered as supplemental information.

3. Nakasato, Y., and Iyatomi, A. (1977) Acute toxicity studies. Mobay Report Nos. 63081 and 66922.

   No DERs were prepared. The data requirements for acute toxicity on Bayleton have been fulfilled. The newly submitted data did not provide any new information that may affect the toxicity category of Bayleton. However, the data have been made a part of the permanent file on Bayleton for future reference.

4. Knaak, J.B., Yee, K., Ackerman, C.R., Zweig, G., and Wilson, B.W. (1982) Development and validation of an animal model to study the dermal absorption of pesticides. Mobay Report No. 80981.

This report had been previously submitted to the Agency in 1982. A copy of the report is attached to this memorandum.

^{14}C-triademeform was applied to the skin of female rats as an acetone solution and as a wettable powder. In the first case, 39.6 and 39.3 percent of the dose was excreted in the urine and feces, respectively, in 192 hours. In addition, 3.9, 5.7, and 4.5 percent was recovered in the cage washings, skin, and carcass, respectively. In the case of the wettable powder, 8.2 percent was excreted in each of the urine and feces at the first 72 hours. About 41.5% remained in/on the skin, 8.8 percent was recovered in the carcass, and 12 percent of the dose was recovered in the cage washings. The study is acceptable.

5. Polacek, I. (1983) Safety pharmacology Study with MEB 6447 on oral administration. Mobay Report No. 85867.

No DERs were prepared for this study. Parts of the data tables were in German. A summary provided by the author stated that "MEB 6447 at doses of 0.3, 1.0 and 3.0 mg/kg, oral, stimulated spontaneous motility in mice, but the effect was not dose-dependent.

"In these doses the compound had no analgesic, anti-convulsive, muscle relaxant and cataleptic properties, and did not affect central co-ordination, orientation motility and hexobarbital anaesthesia."

The study is considered as supplemental information.

6. Negata, T., Armaki, Y., Sato, M., and Enomoto, M. (?) Subacute toxicity on rats. Mobay Report No. 69700.

No DERs were prepared for this study. The study report consisted of only a 3-page summary. The study is unacceptable as presented.

7. Watanabe, M. Iyatomi, A., and Enomoto, M. (1979) Triadimeform; 7-day treatment and 14-day recovery test on rats. Mobay Report No. 82525

Oral administration of Bayleton to rats for 7 days was associated with decrease in body weight gain and food consumption, decrease in the urine pH, fatty degeneration of the liver hepatocytes, increased

fatty contents, BUN and potassium in the serum, atrophy of testes in males and alteration of the absolute and relative organ weights.

A NOEL could not be established under the conditions of the study. The LEL was considered to be 1500 ppm. The study was classified as <u>supplemental information</u>.

8. Roetz, R. (1982) Study of embryotoxic and teratogenic effects on rabbits after oral administration. Mobay Report No. 82236.

Administration of Bayleton to Himalayan rabbits on day 6 through day 18 of gestation resulted in maternal toxicity at the 100 mg/kg/day level. Symptoms of toxicity at this level included reduced body weight gain during the treatment period ($p < 0.01$), an increase in digestive disturbances, inflammation of the external vagina, and a statistically significant increase in resorptions in the 100 mg/kg/day group ($p < 0.05$). None of these symptoms were observed in the 300 mg/kg/day groups except a marked reduction in body weight gain for the treatment period and for the entire gestational period. While these reductions were not statistically significant, they do follow the trend set by the high-dose group. The 17.2% of resorptions at this level is also part of a dose-related trend and reinforces signs of toxicity in the middle-dose group. No maternal toxicity was observed in the 10 mg/kg/day group. It can be concluded that, under the conditions of this study, a maternal NOEL in rabbits can be set at 10 mg/kg/day. The maternal LOEL in this study is 30 mg/kg/day based on an observed reduction in body weight gain during the treatment period and during the entire gestation.

An embryolethal effect was observed at the 100 mg/kg/day dose level. A statistically significant increase in fetal resorptions was observed in this high-dose group. Surviving fetuses at this dose level exhibited normal weight and no embryotoxic effects. The fetuses at the 10 and 30 mg/kg/day dose level exhibited no embryotoxic effects. From the information available in this report, it can be concluded that a Developmental Toxicity NOEL can be set at 30 mg/kg/day. The Development Toxicity LOEL is set at 100 mg/kg/day based on embryolethal effects at this level.

The report on the effect of Bayleton on pregnant

rabbits was very brief. Important data elements missing were:

a. Information on how often the animals were observed for signs of toxicity.

b. Exact weights of individual does at each weighing.

c. Individual weights of fetuses.

d. Number of corpora lutea.

e. Details on signs of toxicity - time of onset, degree, and duration.

f. Food consumption data.

g. pathological information on the dose (evidently no autopsy was performed).

h. Was dosing based on pre-pregnancy weights or on the last weighing?

i. Parity of the does.

j. Age of the does other than that they were sexually mature.

k. Historical control data.

The study was classified as Core-supplementary data.

9. Unger, T.M., Goethem, D.V., and Shellenberger, T.E. (1982) A teratological evaluation of Bayleton in mated female rats. Mobay Report No. 82270.

Administration of Bayleton at doses of 0, 10, 30, and 90 mg/kg/day to CD-SD rats on day 6 through day 15 of gestation resulted in maternal toxicity at the 90 mg/kg/day dose level. This toxicity was expressed by a statistically significant ($p < 0.05$) decreased in the body weight gain during the dosing period. The maternal weight gains of the 10 and 30 mg/kg/day groups are similar to those of the control group. Another sign of probable maternal toxicity was a non-statistically significant increase in late fetal resorptions found in the high-dose group. The only maternal data usually found in teratology studies which are absent from this report are those on maternal food consumption. There was no evidence

at any dose level of a statistically significant adverse effect of Bayleton on maternal reproduction parameters. It can be concluded that a maternal NOEL in rats can be set at 30 mg/kg/day. The maternal LOEL in this study is 90 mg/kg/day based on a statistically significant decrease in weight gain during the dosing period.

There was an increase in urogenital irregularities in the high-dose group of this study. The Charles River CD strain of rats has a tendency toward anomalies in this system. Banerjee and Durloo encountered a 1.38 percent incidence of hydroureter in 725 fetuses of untreated mothers. Woo and Hoar found that the normal renal development late in gestation in CD rats involves a transient variation in growth rates, resulting in an enlarged renal pelvis which disappears shortly after birth. This condition, "apparent hydronephrosis," is considered by them to be a normal aspect of development which should not be mistaken for a congenital malformation. The rats treated with 90 mg/kg/day of Bayleton produced a significantly increased number of fetuses with distended urinary bladders when compared to those in the controls. This may not be extraordinary when one considers the frequency of anomalies in this system and the basic statistical principle that a value of $p = 0.05$ means that the differences can occur by chance one time in 20. Grouping all urogenital anomalies together, the incidence of 13.6 percent in the high-dose group was not increased statistically over the 4.2 percent in the controls.

The occurrence of a statistically significant increase in rib anomalies in the 90 mg/kg/day group was striking with 86.4 percent of the litters affected compared to 4.5 percent of the control litters. While Kimmel and Wilson, in a frequently cited article, state that skeletal variations in themselves should not be considered as malformations, they suggest that extra 14th ribs could be regarded as indicators of teratogenic potency of a drug at some higher dosage. The extent of damage caused by rib variations may be debatable, but there is no doubt that Bayleton produced an effect on the fetuses at the high-dose level.

Under the conditions of this study, the developmental toxicity LOEL of Bayleton in rats is 90 mg/kg/day, based on statistically significant increases in rib anomalies and in distended urinary bladders. The developmental NOEL is 30 mg/kg/day.

The study was classified as Core-supplementary.

10. Thyssen, J. and Groning, P. (1978). Reproduction study. Mobay Report No. 67070.

The study report was in German. However, the author included an English summary. The English summary stated "Groups of 10 female White Leghorn hens, which were mated with one cock per group, were maintained for 4 weeks on a diet containing MEB 6447 (90.0 - 92.7% purity) at concentrations of 0, 10, and 100 ppm. A secondary study to determine possible hematological effects was conducted in groups of chickens receiving identical treatment. Data were recorded for each group beginning with a 2-week pretreatment period and continuing for the 4-week treatment period and a 4-week observation period.

"Appearance, behavior and feed intake were assessed daily and body weights were determined weekly. The size, weight and thickness of eggshell was determined for all eggs laid. Eggs were placed in an incubator and the fertilization rate was determined on days 7, 14, and 21 after egg laying. The appearance and behavior of chicks were assessed for the first 3 or 4 days of their life. Neither the main study nor the hematological study gave any indication of a treatment-related effect. The behavior, appearance, body weight gain (Table 1), and food intake (Table 2) of treated hens was normal. Hematological tests (Table 12), gross pathological examinations, and histopathological examinations revealed no treatment-related effects. The number of eggs, egg quality, egg weight and egg size were unaffected by treatment (Table 4). No effect on fertility rate or hatch rate was detected (Table 7). The incidence of chicks with anomalies (Table 8) and the type of anomalies found did not indicate a treatment-related effect. Under the conditions of this study, the no-observable effect level was 100 ppm for hens and their offspring."

The study is unacceptable as presented.

11. Machemer, L. (1977) Micronucleus test on mice to evaluate MEB 6447 for mutagenic effects. Mobay Report No. 52724.

This study was submitted to the Agency by Mobay Chemical Corporation and had been evaluated by the Toxicology Branch (Tox Br. Doc. No. 002003).

However, the study was evaluated again by Dr. Kerry

L. Dearfield (memorandum dated February 16, 1988, attached). The recent evaluation further confirmed that the study is deficient in certain parameters, and th..fore is considered unacceptable.

12. Hixson, E.J. (1982) Therapy of eye irritation of Bayleton 50% W.P. Mobay Report No. 80686.

According to the author, "Bayleton 50 WP is a positive eye irritant with lesions spontaneously reversed in eight days. Washing the eyes offers an improvement in severity and duration of the responses. Therapy of the eyes with ophthalmologic ointment containing antibiotics and steriod was not superior to washing with water in alleviating the irritation." The study was not Core-classified. The study was considered supplemental information.

13. Inkmann-Koch, A., and Stegh, R. (1982) Studies on the determination of applicator exposure in the application of Bayleton. Mobay Report No. 82584.

This study has not been reviewed by the Toxicology Branch. Worker exposure data are normally evaluated by the Exposure Assessment Branch of the Hazard Evaluation Division.

14. Sangha, G.K. (1984) Acute inhalation study with Bayleton 50% W.P. in rats. Mabay Report No. 86398.

The 4-hours LC_{50} of Bayleton 50% W.P. to male and female rats is greater than 3.532 mg/L. The study is classified as supplementary information.

15. Mihail, F. (1980) Acute toxicity studies. Mobay Report No. 68922.

No DER's were prepared. The data requirements for acute toxicity on MEB 6447 (Bayleton) has been satisfied. The new data do not provide any additional information in this area, nor do they affect the toxicity category.

16. Mihail, F. and Kaliner, G. (1979) Subacute oral cumulative toxicity on rats. Mobay Report No. 254694.

This study was not reviewed since most of the data table are in German.

Attachment.

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DATA EVALUATION RECORD

Subacute Oral Toxicity in Rats

Accession Number: 254694

Mihail, F. and Kaliner, G. (1979) Subacute oral cumulative toxicity study on rats. An unpublished report prepared by Bayer AG, Institute for Toxicology, Wuppertal-Elberfeld. Report No. 8195, dated February 20, 1979.

Test Chemical: MEB 6447*, pure technical grade 97.0% purity, Batch No. 16002175, received April 1975.

Experimental Protocol:

Male and female SPF Wistar albino rats weighing 130 to 145 g (males) and 130 to 140 g (females) were used in this study. The rats were acclimatized for 7 days prior to the commencement of the experiment. Animals were randomized into 4 groups each consisted of 20 males and 20 females.

The test chemical was emulsified in acetone and groundnut oil DAB 7 (1:10), and administered to the rats by gavage at 1.0, 5.0, or 25.0 mg/kg. The concentration was adjusted for each rat to receive a constant volume of 1.0 mL/100 g body weight. A control group was included and animals of this group were given the solvent only. The daily dose and volume of the emulsion given to each animal was based on the body weights measured at the beginning of each week. The animals were fed Altromin 1324 pellets and allowed access to tap water ad libitum.

The rats were observed daily for any changes of physical appearance and behavioral patterns and posture. The animals were weighed at the beginning of each week and at termination. At the end of the 28 days of the test chemical administration, the animals were kept alive for another 28 days of observation. After that, laboratory tests were conducted on blood samples, liver (N and O demethylase and Cytochrome P450), and feces (blood). The laboratory tests were performed on 10 males and 10 females of each group.

Blood samples required for testing were taken at sacrifice from the etheranesthetized animals by cardiac puncture. The following tests were performed: hemoglobin, blood in feces, aspavtate aminotransferase (GOT), alanine aminotransferase (GPT), N-demethylase, O-demethylase, and liver cytochrome P-450.

* known as triadimefon and as Bayleton.

Necropsy was performed and organ weights were determined on half of the males and females at termination. The other half of the animals were killed at the end of the postadministration observation period. Animals were killed by exsanguination after being narcotized with ether.

Histopathological examinations were performed on all animals and included liver, oesophagus, stomach, and small and large intestines. The heart of one female from the middle dose group was also examined histopathologically.

Statistical comparison of the mean values was performed by the Wilcoxon nonparameter ranking test.

Results:

Parts of the data table are in German language. This precluded a meaningful and complete evaluation of the study.

Conclusions:

Unacceptable since parts of the data table are in German.

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DATA EVALUATION RECORD

Alteration of Excretion of ^{14}C-Bayleton
by Several Therapcutic Regimens

Hixson, E.J. (1982) Alteration of excretion by several therapeutic reagents. Study No. 81-912-01, Report No. 223, dated January 15, 1982. Prepared by Mobay Chemical Corporation, Stanley Research Laboratory, Stilwell, Kansas. EPA Accession No. 254694.

Test Chemical: Bayleton technical with 93.2% purity (unlabeled), described as white powder. Batch No. 80-R-159-92

Testing Laboratory: Stanley Research Laboratory, Mobay Chemical Corporation, Stilwell, Kansas

Experimental Protocol:

Adult male and female Sprague-Dawley rats were orally dosed with 1000 mg/kg of ^{14}C-labeled Bayleton. One hour later they were treated with a dose of sodium carbonate, ammonium chloride, lasix diuretic, activated charcoal, or magnesium sulfate. Animals were observed for mortality and toxicity signs twice a day for 14 days posttreatment. Animals were weighed on the day 1, day 7, and day 14 of the treatment. Urine was collected at 4, 8, 24, 48, and 72 hours after treatment. Urine volume and pH were measured. Blood samples were collected and weighed in at 2, 24, 48, and 72 hours. Feces were collected at 8, 24, 48, and 72 hours. Aliquots of blood and excreta were taken for total radioactivity count. Rats were sacrificed at termination. No gross necropsies were performed.

Results:

According to the authors "none of the regimens appeared to exert any clear beneficial effects based on body weights, mortality, duration of toxicity in either sex." The treatment did not affect the rate of excretion and clearance of Bayleton.

Conclusion:

None of the therapeutic regimens altered the excretory pattern of Bayleton.

Core Classification: Supplemental information

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DATA EVALUATION RECORD

Dermal Absorption

Knaak, J.B.; Yee, K.; Ackerman, C.R.; Zweig, G.; and Wilson, B.W. Development and validation of an animal model to study the dermal absorption of pesticides, phase I: dermal absorption of triadimefon using the back skin of the female rat. EPA Accession No. 254697.

Toxicology Branch Comments:

This report had been previously submitted to the Agency in 1982. A copy of the report is attached to this DER.

^{14}C-triademeform was applied to the skin of female rats as an acetone solution and as a wettable powder. In the first case, 39.6 and 39.3 percent of the dose was excreted in the urine and feces, respectively, in 192 hours. In addition, 3.9, 5.7, and 4.5 percent was recovered in the cage washings, skin, and carcass, respectively. In the case of the wettable powder, 8.2 percent was excreted in each of the urine and feces at the first 72 hours. About 41.5 percent remained in/on the skin, 8.8 percent was recovered in the carcass, and 12 percent of the dose was recovered in the cage washings. The study is acceptable.

Attachment

RIN 5711-93

TRIADIMEFON TOX REVIEWS

Page_____ is not included in this copy.

Pages 16 through 28 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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DATA EVALUATION RECORD

Pharmacological Effects of MEB 6447

Polacek, I. (1983) Safety: Pharmacology study with MEB 6447 on oral administration. Unpublished report prepared by Bayer, A.G. EPA Accession No. 254697.

No DER was prepared for this study since parts of the data tables were presented in German.

A summary provided by the registrant stated "MEB 6447 at doses of 0.3, 1.0 and 3.0 mg/kg, oral, stimulated spontaneous mortility in mice, but the effect was not dose-dependent.

"In these doses the compound had no analgesic, anti-convulsive, muscle relaxant and cataleptic properties, and did not affect central co-ordination, orientation motility and hexobarbital anaesthesia."

DATA EVALUATION RECORD

7-Day Treatment and 14-Day Recovery in Rats

Watanabe, M.; Iyama, A.; and Enomoto, M. (1979) 7-day treatment and 14-day recovery tests on rats. A report prepared by the Medical Science Institute, Tokyo University. Report No. 134.

Test Chemical: Triadimeton technical with a purity of 94.6%.

Experimental Protocol: Attached.

Results:

1. General Observation - the author(s) stated that "Hyperkinesia and sterotyped sniffing were observed in some rats of 4500 ppm group after 6 hours of the administration and 1500 ppm group after one day. In some rats of 4500 ppm group, moreover, the biting against the cages was observed 1 to 3 days after the administration. On the other hand, in 100 mg/kg/day group, hyperkinesia and sniffing appeared in all rats within 30 minutes after the oral application and observed for several hours afterwards. However, most of them distinguished on the day after the administration. Moreover, increase of sensitivity to sound was found in many rats of each treated group.

"After the treatment period, these abnormal behaviors in each treated group disappeared relatively fast.

"No dead rats due to the administration was observed. However, each one rat of 4500 ppm and 100 mg/kg/day groups died because of our mistake in handling technique."

2. Body Weight - The body weight of the high-dose group (4500 ppm) was significantly reduced when compared to the control from the fourth day of the administration of the compound. This effect on body weight was reversed in the recovery period.

3. Food Consumption - Food consumption was significantly decreased in the high dose group. This effect was reversed in the recovery period.

4. Urinalysis - Results of semiquantitative analysis indicated that the pH was within the normal physiological range for the low-dose group. The pH was on the acidic side for the 1500 ppm group in day 1 and the 4500 ppm group in days 1, 3, and 7. This effect was reversed in the recovery period. Increases in cell and crystal components were sporadically seen in some rats but not in a dose-related manner.

5. Liver Weight and Liver Function - Liver weight was significantly increased in all groups. The activity of ALP was increased in the 1500 ppm, and GOT, GPT, and ALP activities significantly increased in the 4500 ppm group. These effects reversed after the recovery period.

6. Fatty Metabolism - Treatment was associated with increased cholesterol and decreased triglycerides levels in the serum of the high-dose groups.

7. Kidney Function - Treatment caused elevation of the serum BUN level in all treated groups. Potassium was significantly increased in the high-dose group.

8. Autopsy - The treatment caused liver enlargement in animals of treated groups. Atrophy of thymus and testes was also observed.

9. Organ Weight - Significant decreases in the absolute weight of the thymus and lungs, and in the relative weight of thymus, and significant increases in the relative weight of brain were observed in the first week in the high-dose group. After the 14 day recovery period, decreases in the absolute weight of heart and increases in the relative weights of brain, testes and pituitary were observed in the same group.

10. Histopathological Examination - A dose-related fatty degeneration of the hepatocytes was observed and was severe in the high-dose group. This effect was less severe in all dose groups after the 14-day recovery period.

According to the author, pneumonia, cystic dilatation of the pituitary, atrophy and hemorrhage of thymus, erosion of mucosal epithelium in the urinary bladder, and atrophy in testes were observed in a few rats.

Conclusion:

The treatment caused decreases in body weight gain and food consumption, decreases in the pH of urine, fatty degeneration of liver hepatocytes, increased fatty contents, BUN and potassium in the blood, atrophy of testes, and effects on the relative and absolute organ weights. A NOEL could not be established under the conditions of this study. An LEL is considered to be 1500 ppm.

Core Classification: Supplemental data.

RID 5711-93

TRIADIMEFON TOX REVIEWS

Page_____ is not included in this copy.

Pages 32 through 36 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

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STUDY REVIEW

Chemical: Bayleton
Test Material: Triadimefon - 93.2%
Study/Action Type: Teratology Study

STUDY IDENTIFICATION:

"A Teratological Evaluation of Bayleton in Mated Female Rats"

Testing Facility: Midwest Research Institute, Kansas City, Missouri
Project No.: 7272-8
Report Date: 8-31-82
Study Director: Timothy M. Unger
EPA Accession No.: 254697

Study Reviewed by: Helene B. Morgan, B.A.
Geraldine S. Danford, B.A.

BACKGROUND

The Midwest Research Institute, Kansas City, Missouri, conducted this teratology study of Bayleton in CD-SD rats. The study was initiated on September 23, 1981, and the experimental work was completed on March 1, 1982.

CONCLUSION

It is concluded that the teratology study of Bayleton in rats (Midwest Reseach Institute, # 7272-8) demonstrates the following:

Maternal No Observed Effect Level (NOEL): 30 mg/kg/day
Maternal Lowest Observed Effect Level (LOEL): 90 mg/kg/day

These values are based on a statistically significant ($P<0.05$) decrease in body weight gain during the dosing period of the 90 mg/kg/day dams. A non-statistically significant increase in late fetal resorptions was also found in this group. No maternal toxicity was observed in the 30 mg/kg/day treatment group.

Developmental Toxicity NOEL: 30 mg/kg/day
Developmental Toxicity LOEL: 90 mg/kg/day

These values are based on a statistically significant ($P<0.05$) increase in abnormal ribs, especially extra ribs, in fetuses from the 90 mg/kg/day treated dams. A statistically significant ($P<0.05$) increase in distended urinary bladders was also observed in these fetuses. No developmental toxicity was observed at the 30 mg/kg/day dose level.

93.2% active ingredient

PROCEDURES

Test material:	Bayleton (Technical Grade)
Vehicle:	0.5% Cremophor EL Emulsion (10 ml/kg)
Dosage levels:	0, 10, 30, 90 mg/kg/day by gavage
Period of administration:	Days 6-15 of gestation
Species:	CD-SD rats

The protocol used in this study was in compliance with those recommended in the Standard Evaluation Procedure (SEP), Teratology Studies (EPA-540/9-85-018, June 1985).

Sexually mature, primigravid CD-SD rats, approximately 3 months of age, were used in this study. Females were mated following a 12-day quarantine period. Two females were caged with one male and the mating was checked by vaginal smear. The day sperm were found was identified as day 0 of gestation. Upon mating, each rat was weighed and this weight was used in a randomized assignment of the female to one of four experimental groups.

Bayleton, technical grade, (93.2% active ingredient) was formulated as a 0.5% Cremophor EL emulsion in water for use as a dosing solution.

Identification of individual rats, housing, food, water, environment, quarantine time and group assignments were of standard experimental design. Dosing was performed as indicated in Table 1.

Table 1.

Dosing Schedule

Group number	Number of females	Days of treatment	Dose (mg/kg/day)
1 (control)	26	6-15	0
2	26	6-15	10
3	26	6-15	30
4	26	6-15	90

The test suspension was administered orally by gastric intubation using 16 gauge dosing needles. The volume administered was 10 ml/kg based upon the body weight of the rat at the start of treatment. The treatment period, days 6-15, was chosen to correspond to the post-implantation period of major organogenesis in rats.

Each female was observed in the morning and afternoon each day for adverse reaction or toxicological responses to the test substance. Maternal body weights were taken on days 0, 6, 13, 15, and at the time of sacrifice. On day 20 of pregnancy , the dams were weighed and sacrificed and their viscera examined grossly. Detailed examinations and recordings were made of the uterine contents. The ovaries were examined and the number of corpora lutea were counted.

One female in the 10 mg/kg/day group (dam AP-237) delivered seven full-term pups on what was considered gestation day 17 and was sacrificed at that time. Data obtained from this animal have been omitted from the summary tables but can be found in the appendix tables of the report.

The positions of the fetuses in the uterus were recorded. Resorption sites were noted as "early" or "late". All fetuses were counted, numbered, weighed, and checked for viability. Live fetuses were examined for external abnormalities. One half of the viable fetuses from each litter were dissected and examined for visceral anomalies. The other half of the fetuses from each litter were processed for skeletal examination.

RESULTS

A. MATERNAL EVALUATION

Maternal Mortality

None of the females in any of the groups died or had to be sacrificed due to morbidity during the experiment.

Clinical and Pathological Observation

The slight clinical signs of maternal toxicity observed in this experiment appeared to occur randomly without relation to dose level. These signs included hair loss in one control rat and blood by the eye of one high dose female.

At necropsy, hydronephrosis involving one or both kidneys was observed in 3 control, 2 low dose (10 mg/kg/day) and 2 middle dose (30 mg/kg/day) females. Since hydronephrosis occurred in greatest incidence among control dams, this abnormality cannot be associated with treatment with Bayleton.

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Pregnancy Rates

The pregnancy rates for the 0, 10, 30, and 90 mg/kg/day groups were, respectively, 84.6%, 84.0% (does not include dam AP-237), 80.8% and 88.5%. The pregnancy rates given are within acceptable ranges for rats. Woo and Hoar reported a 90% pregnancy rate for pooled data on 2452 Charles River CD rats in control studies.[1]

Maternal Body Weight Data

Individual maternal body weights were recorded on days 0, 6, 13, 15, and 20 of presumed gestation (Table 2).

Prior to the dosing period, no differences in body weight gain were noted in any group. During the dosing the body weight gains in the 10 and 30 mg/kg/day groups were similar to those of the control group. The high dose group (90 mg/kg/day) showed a statistically significant decrease in body weight gain ($p<0.05$) during the dosing period. During the post-dosing period the high dose group showed an increase in weight gain which resulted in total weight gain which was only slightly less than that of the control group.

Maternal Food Consumption

No data were given in the report concerning the maternal food consumption.

Reproduction Data at C-Section

The results of cesarean section, including ovarian, uterine, and litter data, are presented in Table 3.

The mean number of corpora lutea, uterine implantations, nonviable implants, and viable fetuses were comparable for all groups examined. An increase in the number of late resorptions was found in the high dose group; however, this increase was not statistically significant. The mean number of live fetuses per litter was 13.2 (control), 13.4 (10 mg/kg), 13.0 (30 mg/kg), and 13.3 (90 mg/kg). This reproduction data compares favorably with the mean litter size of 11 found in control data of Charles River CD rats compiled by Woo and Hoar.[1]

[1] Woo, D.C. and R.M. Hoar, Reproductive performance and spontaneous malformations in control Charles River CD rats: a joint study by MARTA, Teratology 19: 54A, 1979.

TABLE 2.
EFFECTS OF BAYLETON UPON BODY WEIGHT OF PREGNANT RATS IN A TERATOLOGY STUDY

	Dose level (mg/kg/day)			
	0	10	30	90
Number of pregnant animals	22	21[a]	21	23
Dam body weight				
Day 0	242 ± 2[b]	243 ± 3	247 ± 3	249 ± 3
6	267 ± 2	265 ± 4	269 ± 3	272 ± 4
13	294 ± 3	290 ± 5	294 ± 3	289 ± 4
15	306 ± 3	302 ± 5	305 ± 3	301 ± 4
20	371 ± 4	366 ± 6	373 ± 5	373 ± 7
Corrected terminal body weight[c]	294 ± 3	290 ± 5[f]	298 ± 4	294 ± 4
Body weight change				
Day 0–6[d]	25 ± 2	22 ± 2	22 ± 2	23 ± 2
6–15	38 ± 2	37 ± 2	36 ± 2	29 ± 3[e]
15–20	65 ± 2	64 ± 3	67 ± 2	73 ± 3
Total weight gain	128 ± 4	122 ± 5	126 ± 4	124 ± 5
Corrected[c]	52 ± 3	47 ± 3[f]	51 ± 3	45 ± 3

a Does not include AP-237, sacrificed after premature delivery of full-term pups. It is assumed that this dam mated prior to designation of day 0.
b Mean ± S.E. in grams.
c Corrected by subtraction of weight of reproductive tract and fetuses.
d Day 0 to 6, pretreatment period; day 6 to 15, treatment period; day 15 to 20, post-treatment period.
e Significantly different from controls; Dunnett's Procedure, $p<0.05$.
f AP-021 omitted from calculations as weight of reproductive tract was recorded incorrectly.

TABLE 3.
EFFECTS OF BAYLETON ON REPRODUCTION PARAMETERS OF FEMALE RATS IN A TERATOLOGY STUDY[a]

	Dose level (mg/kg/day)			
	0	10	30	90
No. of animals	22	21	21	23
Corpora lutea/dam	14.6 ± 0.4[b]	14.8 ± 0.6	14.8 ± 0.8	14.9 ± 0.5
Implants/dam	14.2 ± 0.4	14.3 ± 0.6	13.8 ± 0.6	14.4 ± 0.7
Viable fetuses (%)	93 ± 2	93 ± 2	95 ± 2	91 ± 3
Dead fetuses (%)	0	0	0	0
Early resorptions (%)	6.7 ± 2.4	6.6 ± 1.6	5.0 ± 1.6	5.7 ± 1.7
Late resorptions (%)	0	0	0	3.0 ± 2.2
No. of nonviable implants/dam[c]	1.0 ± 0.4	0.9 ± 0.2	0.7 ± 0.2	1.0 ± 0.3
Live litters	22	21	21	23
Dams with complete resorptions	0	0	0	0
Fetuses/dam	13.2 ± 0.4	13.4 ± 0.6	13.0 ± 0.6	13.3 ± 0.7
Males/litter (%)	51 ± 3	46 ± 3	49 ± 3	45 ± 3
Average fetal weight	3.64 ± 0.07	3.59 ± 0.06	3.61 ± 0.07	3.68 ± 0.05

a Test of significance was Dunnett's Procedure, $p<0.05$.
b Mean ± S.E.
c Includes dead fetuses and early and late resorption sites.

8. DEVELOPMENTAL TOXICITY EVALUATION

Fetal Data

The fetal data collected at cesarean section are summarized in Table 3.

As noted earlier, no significant change in the litter size was observed. No dead fetuses were recorded for any group. Also, the sex ratio was similar for all groups.

Table 3 shows clearly that no observable differences were found in any of the mean fetal weights. The average fetal weights were 3.64 grams for the controls, 3.59 grams for the 10 mg/kg group, 3.61 grams for the 30 mg/kg group, and 3.68 grams for the 90 mg/kg group. The mean body weight of 20-day CD fetuses in Woo and Hoar's study was 3.8 grams.[2] Since the litters in this Bayleton study were larger than those reported by Woo and Hoar, a lower fetal weight is expected. A careful examination of individual fetal body weights shows that Bayleton caused no increase in the number of runts or in the number of litters containing runts.

~ definition of runt

Malformations and Variations

In this study, gross anomalies occurred in control fetuses at an incidence rate greater than or equal to the rate in treated litters and thus cannot be related to treatment with Bayleton.

Soft tissue anomalies are summarized in Table 4. An extensive variety of endpoints were examined, and 25 malformations appear in the table because they occurred at least once. Frequency of various aberrations was unremarkable in systems other than the urogenital system. Distended urinary bladders were found in 2.6% of the fetuses from the group treated with 90 mg Bayleton/kg/day. This is the mean of the percent of fetuses with the anomaly calculated on a litter basis, and it is a statistically significant increase over the controls ($P<0.05$). Four litters were affected in this high-dose group, while no litters were affected in the controls. Hydronephrosis was increased in fetuses of rats at the 30 and 90 mg/kg/day levels. This anomaly occurred at the rate of approximately 11% in these 2 groups while the rate in the control group was 4.2%, but this was not statistically significant. The incidence of all urogenital anomalies considered together as one lesion was 4.2%, 4.1%, 12.6%, and 13.6% at the 0, 10, 30, and 90 mg/kg/day dose levels, respectively. The differences were not statistically significant at $P=0.05$.

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[2] Woo and Hoar, op. cit.

TABLE 4.
SOFT TISSUE ANOMALIES IN LITTERS FROM DAMS TREATED DURING GESTATION WITH BAYLETON

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	Dose Level (mg/kg/day)			
	0	10	30	90
Number of				
Litters affected/examined (%)	12/22 (55)	6/21 (29)	12/21 (57)	14/23 (61)
Fetuses affected/examined (%)	14/141 (10)	9/137 (7)	20/133 (15)	29/149 (19)
Soft Tissue Anomalies				
Fourth ventricle of brain enlarged	0.8 (1)[a]	0 (0)	0 (0)	0 (0)
Aplasia of cerebrum	0.8 (1)	0 (0)	0 (0)	0 (0)
Exencephaly[b]	0.6 (1)	0 (0)	0 (0)	0.6 (1)
Hemorrhage in occipital region of brain	0.6 (1)	0 (0)	0 (0)	0 (0)
Subarachnoid space enlarged	0 (0)	0.8 (1)	0 (0)	0 (0)
Displacement of brain	0.8 (1)	0 (0)	0 (0)	0 (0)
Blood in nasal passage	0.6 (1)	0 (0)	0 (0)	0 (0)
Blood in tissue by nasal passage	0.6 (1)	0.5 (1)	0 (0)	0 (0)
Eyelids open or absent[b]	0.6 (1)	0 (0)	0 (0)	0 (0)
Microphthalmia	0 (0)	0 (0)	0 (0)	0.6 (1)
Displaced lung	0 (0)	0 (0)	0.6 (7)	0 (0)
Right sided arch of aorta	0 (0)	0 (0)	0 (0)	0.5 (1)
Interventricular septum abnormally thin	0.9 (1)	0 (0)	0 (0)	0 (0)
Diaphragmatic hernia	0 (0)	0.7 (1)	0 (0)	0 (0)
Hemmorhage in liver	0 (0)	0.8 (1)	0 (0)	1.2 (2)
Hemorrhage in abdominal cavity	0.6 (1)	0 (0)	0.6 (1)	1.2 (2)
Blood in stomach	0.6 (1)	0 (0)	0 (0)	0 (0)
Hydroureter	0 (0)	0 (0)	1.0 (1)	2.2 (1)
Hydronephrosis	4.2 (5)	4.1 (5)	11.4 (9)	11.1 (9)
Marked	0.8 (1)	2.3 (3)	6.5 (7)	5.5 (7)
Slight	3.5 (4)	1.9 (2)	4.9 (6)	5.6 (4)
Urinary bladder not visibly present	0 (0)	0 (0)	0 (0)	0.6 (1)
Urinary bladder distended	0 (0)	0 (0)	0.6 (1)	2.6 (4)[c]
Malplaced testicle	0 (0)	0 (0)	1.3 (2)	0.5 (1)
Short snout	0.6 (1)	0 (0)	0 (0)	0 (0)
Subdermal hemorrhage	0.6 (1)	0 (0)	0.6 (1)	1.8 (3)
Stubby digits on paws	0 (0)	0 (0)	0 (0)	0.6 (1)

a Mean of the percent of fetuses with the indicated anomaly calculated on a litter basis. The number in the parenthesis is the number of affected litters.

b The incidence of these anomalies were calculated based upon the number of pups examined for soft anomalies, or roughly one-half the total pups in a litter.

c Significantly different from controls: two-sample rank test, $p<0.05$.

Skeletal anomaly data are summarized in Table 5. Some of the individual end points given in the report have not been included in this review because their rate of incidence was not unusual, but details on the skull and ribs appear on the table. A statistically significant increase in the occurrence of extra ribs was observed at 90 mg/kg/day ($P<0.05$). The fetal incidence was 33.1%, and 86.4% of litters were affected. Fetal incidence in the control group was 0.6% with 4.5% of the litters affected. Extra ribs were also slightly raised at 10 and 30 mg/kg/day levels. Grouping all rib anomalies together, the total incidence was 0.6%, 10.6%, 8.9% and 35.7% for control, 10, 30, and 90 mg/kg/day groups, respectively. This was statistically significant only at the high dose group ($P<0.05$). The occurrence of ossification irregularities in the hyoid apparatus of the skull was higher in the controls than in the dosed groups. Therefore it is not related to treatment with Bayleton.

DISCUSSION

This report was carefully written to include pertinent details. Excellent tables provide data on specific dams and their individual fetuses.

Administration of Bayleton at doses of 0, 10, 30, and 90 mg/kg/day to CD-SD rats on day 6 through day 15 of gestation resulted in maternal toxicity at the 90 mg/kg/day dose level. This toxicity was expressed by a statistically significant ($P<0.05$) decrease in the body weight gain during the dosing period. The maternal weight gains of the 10 and 30 mg/kg/day groups are similar to those of the control group. Another sign of probable maternal toxicity was a non-statistically significant increase in late fetal resorptions found in the high dose group. The only maternal data usually found in teratology studies which are absent from this report are those on maternal food consumption. There was no evidence at any dose level of a statistically significant adverse effect of Bayleton on maternal reproduction parameters. It can be concluded that a maternal NOEL in rabbits can be set at 30 mg/kg/day. The maternal LOEL in this study is 90 mg/kg/day based on a statistically significant decrease in weight gain during the dosing period.

There was an increase in urogenital irregularities in the high-dose group of this study. The Charles River CD strain of rats has a tendency toward anomalies in this system. Banerjee and Durloo encountered a 1.38% incidence of hydroureter in 725 fetuses of untreated mothers.[3] Woo and Hoar found that the normal renal development late in gestation in CD rats involves a transient variation in growth rates, resulting in an enlarged

[3] Banerjee, B.N. and R.S. Durloo, Incidence of teratological anomalies in control Charles River C-D strain rats, Toxicology 1: 151-154, 1973.

TABLE 5.
SKELETAL ANOMALIES IN LITTERS FROM DAMS TREATED DURING GESTATION WITH BAYLETON

	Dose Level (mg/kg/day)			
	0	10	30	90
Litters - Affected/Total	22/22	21/21	21/21	22/22[a]
Fetuses - Affected/Total	121/149	128/144	120/141	135/158
Skull				
Litters Affected	15	11	12	7
Fetuses Affected	28	16	19	16
Abnormal skull - Total	17.8 (15)[b]	10.6 (11)	13.9 (12)	9.8 (7)
Skull collapsed	0	1.9 (2)	1.6 (1)	0
Tympanic annulus incompletely ossified	0.6 (1)	0	0	0
Squamosal split	2.6 (3)	0	0	1.3 (1)
Squamosal incompletely ossified	0	0	0	0.6 (1)
Zygomatic incompletely ossified	0	0	0	0.6 (1)
Zygomatic malformed	0	0	0	0.8 (1)
Hyoid abnormal - Total	15.4 (13)	4.5 (6)[c]	9.3 (9)	5.6 (5)[c]
Hyoid unossified	8.2 (8)	3.1 (5)	6.4 (8)	1.3 (2)[c]
Hyoid incompletely ossified	6.1 (6)	1.4 (2)	2.9 (3)	4.3 (5)
Hyoid split	0.9 (1)	0	0	0
Mandible malaligned	0	0.8 (1)	0	0
Frontal fontanel enlarged	1.8 (2)	0.7 (1)	0	0.6 (1)
Occipital fontanel enlarged	1.3 (2)	2.2 (3)	2.2 (2)	2.5 (2)
Parietal incompletely ossified	1.3 (2)	0.5 (1)	3.1 (3)	3.1 (3)
Interparietal incompletely ossified	2.6 (4)	1.4 (2)	4.5 (4)	4.9 (4)
Interparietal medially curved	0	0	1.2 (1)	0
Supraoccipital incompletely ossified	5.7 (4)	1.4 (2)	1.5 (2)	3.8 (3)
Centra				
Litters Affected	13	10	14	16
Fetuses Affected	32	22	26	29
Sternebrae				
Litters Affected	21	21	21	22
Fetuses Affected	110	115	112	116
Ribs				
Litters Affected	1	10	10	19
Fetuses Affected	1	16	13	57
Abnormal Ribs - Total	0.6 (1)	10.6 (10)	8.9 (10)	35.7 (19)[c]
Incompletely ossified	0	5.1 (4)	1.3 (2)	1.9 (2)
Wavy	0	0	1.7 (2)	1.3 (2)
Extra Ribs - Total	0.6 (1)	5.5 (6)	6.8 (7)	33.1 (18)[c]
Full	0	0	0	3.0 (3)[c]
Rib bud	0.6 (1)	5.5 (6)	6.8 (7)	30.2 (18)[c]
Pelvic Girdle				
Litters Affected	3	0	1	2
Fetuses Affected	5	0	1	3
Limbs				
Litters Affected	14	9	11	11
Fetuses Affected	32	28	30	28

a Animal AP-095 had only one pup which was examined for soft tissue anomalies.
b Mean of the percent of fetuses with the indicated anomaly calculated on a litter basis. The number in parenthesis is the number of affected litters.
c Significantly different from controls: nonparametric rank test.

renal pelvis which disappears shortly after birth.[4] This condition, "apparent hydronephrosis", is considered by them to be a normal aspect of development which should not be mistaken for a congenital malformation. The rats treated with 90 mg/kg/day of Bayleton produced a significantly increased number of fetuses with distended urinary bladders when compared to those in the controls. This may not be extraordinary when one considers the frequency of anomalies in this system and the basic statistical principle that a value of P=0.05 means that the differences can occur by chance one time in 20. Grouping all urogenital anomalies together, the incidence of 13.6% in the high-dose group was not increased statistically over the 4.2% in the controls.

The occurrence of a statistically significant increase in rib anomalies in the 90 mg/kg/day group was striking with 86.4% of the litters affected compared to 4.5% of the control litters. While Kimmel and Wilson, in a frequently cited article, state that skeletal variations in themselves should not be considered as malformations, they suggest that extra 14th ribs could be regarded as indicators of teratogenic potency of a drug at some higher dosage.[5] The extent of damage caused by rib variations may be debatable, but there is no doubt that Bayleton produced an effect on the fetuses at the high-dose level.

Under the conditions of this study, the developmental toxicity LOEL of Bayleton in rats is 90 mg/kg/day, based on statistically significant increases in rib anomalies and in distended urinary bladders. The developmental NOEL is 30 mg/kg/day.

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[4] Woo, O.C and R.M. Hoar, "Apparent hydronephrosis" as a normal aspect of renal development in late gestation of rats: the effect of methyl salicylate, Teratology 6:191-196, 1972.

[5] Kimmel, C.A, and J.G. Wilson, Skeletal deviations in rats: malformations or variations? Teratology 8:309-316, 1973.

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STUDY REVIEW

Chemical: Bayleton
Test Material: Triadimefon - 93.5%
Study/Action Type: Teratology study

STUDY IDENTIFICATION:

"Study of Embryotoxic (and Teratogenic) Effects on Rabbits after Oral Administration of Bayleton"

Testing Facility: Laboratory for Reproduction Toxicology, Institute of Toxicology, BAYER AG, Wuppertal-Elberfeld, FRG
Project No.: T 300 3938
Report Date: 4-21-82
Study Director: Dr R. Roetz
EPA Acession No.: 254697

Study Reviewed by: Geraldine S. Danford, B.A.
Helene B. Morgan, B.A.

BACKGROUND

The teratogenic potential of Bayleton in Himalayan rabbits was investigated in a study conducted at the Laboratory for Reproduction Toxicology, Institute of Toxicology, BAYER AG, Wuppertal-Elberfeld, FRG. The experiment was conducted from August to November 1981.

CONCLUSION

It is concluded that the teratology study of Bayleton in rabbits (Institute of Toxicology, BAYER-AG, # T 300 3938) demonstrates the following:

Maternal No Observed Effect Level (NOEL): 10 mg/kg/day
Maternal Lowest Observed Effect Level (LOEL): 30 mg/kg/day

These values are based on a marked decrease in mean weight gain during the treatment period and also for the entire gestational period in the 30 mg/kg/day group. While these decreases were not statistically significant they followed a trend that was statistically significant ($P<0.01$) at the 100 mg/kg level.

Developmental Toxicity NOEL: 30 mg/kg/day
Developmental Toxicity LOEL: 100 mg/kg/day

These values are based on a statistically significant increase in the number of fetal resorptions in the 100 mg/kg/day group. No developmental toxicity was observed at the 30 mg/kg/day dose level.

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PROCEDURES

Test material:	Bayleton - 93.5% active ingredient
Vehicle:	0.5% Cremophor EL emulsion (5 ml/kg)
Dosage levels:	0, 10, 30, or 100 mg/kg/day by gavage
Period of administration:	Days 6-18 of gestation
Species:	Himalayan (CHBB:HM) rabbits

The experiments were performed on Himalayan rabbits (CHBB:HM strain). This strain has proven to be sensitive for teratology tests. The females were caged singly, except during the mating period. Standard laboratory procedures were followed during the study.

One female was caged with one male in a perforated sheet metal cage. Copulation was verified by observation. After approximately one hour, the animals were mated again and then separated. The day on which mating occurred was designated Gestation Day 0.

The inseminated females were divided into 4 treatment groups of 12 females each by a randomization program. Doses of Bayleton, 0, 10, 30, or 100 mg/kg/day, were administered by gavage on days 6-18 of gestation. The Standard Evaluation Procedure (SEP), Teratology Studies (EPA-540/9-85-018, June 1985) states if gestation day 0 is the day of mating, treatment should be on days 7-19 of gestation for rabbits. The dosing schedule is shown in Table 1.

Table 1: Dosing schedule

Group number	Number of females	Days of treatment	Dose (mg/kg/day)
Control	12	6-18	0
1	12	6-18	10
2	12	6-18	30
3	12	6-18	100

Doses of Bayleton, dispersed in aqueous 0.5% Cremophor EL emulsion, were administered to the does per os with an oral intubation tube. The volume administered was 5 ml/kg body weight/day and was the same for all groups including controls.

The females were observed for changes in appearance, behavior, and other toxicity end points. Their weight gains during treatment and during the entire gestation were recorded. On gestation day 29, the does were sacrificed and cesarean sections were immediately performed.

At cesarean section the number of pregnant females was determined. The number of corpora lutea were not determined and an autopsy was not mentioned. The fetuses were examined for external malformations, weights of litters were determined, stunted fetuses were recorded, placentas were weighed, and the sex of all fetuses was determined by external features. A necropsy of all fetuses and gross evaluation of the organs was performed. The brains were examined for malformations. Following these procedures the fetuses were prepared for skeletal examination using Dawson's method.

RESULTS

A. MATERNAL EVALUATION

Maternal Mortality

None of the does in the control or any of the treatment groups died during the study prior to sacrifice.

Clinical Observations

Bayleton administered at the 10 mg/kg/day and 30 mg/kg/day levels caused no changes in the appearance or behavior of these does.

At the highest dose, 100 mg/kg/day, 10 of 12 animals exhibited disturbed digestion characterized by hard feces, reduced fecal output, reduced feed consumption, or diarrhea. In addition, edema/inflammation of the external vagina was observed in 4 does of this group. None of the above data was recorded in the tables which were included with the report, so it is not possible to associate these symptoms of toxicity with individual animals. The time of onset of these symptoms was not reported.

No autopsy of does or pathological observations from an autopsy were mentioned in this report.

Pregnancy Rates

The pregnancy rate (females pregnant/females mated) was 100% for the controls and for each of the treated groups. The percentages of rabbits with living fetuses were 91.6% (controls), 100% (10 mg/kg), 100% (30 mg/kg), and 75.0% (100 mg/kg). One of the does in the control group and 3 of the does in the high dose group had total resorption of their implantations.

Maternal Body Weight Data

The only weight data provided are weight gains based on 4 weighings: start of gestation, start of treatment, end of treatment, and day of sacrifice. None of the individual weights or mean weights have been included in the report. Maternal body weight gains were recorded for the treatment period (gestation days 6-18) and for the entire period of gestation (Table 2). In the 10 mg/kg/day group no changes in mean weight gain were observed. The 30 mg/kg/day females had a decided reduction in weight gain for both the treatment period and the entire gestation as compared to the controls. While neither of these reductions was statistically significant, they appear to be biologically significant because they support a dose-related trend.

The weight gains during treatment for the high dose group, 100 mg/kg/day, were reduced by a statistically significant amount ($P<0.01$). This group actually had a weight loss during the treatment period. The weight gain for the entire gestation was also reduced for this group, but not in a statistically significant manner.

Maternal Food Consumption Data

No data was given on maternal food consumption, except that the does in the high dose group exhibited reduced food consumption.

Abortion

No data was given to indicate that abortion occurred.

Reproduction Data at C-Section

The results of the cesarean section, including uterine and litter data, are presented in Table 3.

The mean number of implantations was similar in all groups, 7.6 (controls), 7.4 (10 mg/kg), 7.3 (30 mg/kg), and 7.6 (100 mg/kg). These rates compare favorably with Froberg's Laboratory Standard Value for implantation frequency in CH88:HM rabbits, which is a mean of 7.1 per doe.[1] The increase in mean number of uterine losses (3.2), which are referred to as resorptions in the text, are statistically significant for the high dose (100 mg/kg) group ($P<0.05$). Uterine losses for the other treated groups are similar to those of the controls, 0.9 (controls), 1.0 (10 mg/kg),

[1] Frohberg, Harald. 1977. An introduction to research in teratology. In: Methods in prenatal toxicology. Neubert D, Merker HJ, Kwasigroch TE, eds. Stuttgart: Georg Thieme, pp. 1-13.

TABLE 2.

EFFECT OF BAYLETON ON PREGNANT RABBITS

Mean Weight Gains of the Pregnant Rabbits

Dose Level mg/kg/day	Treatment Period Days 6-18 (Grams)	Entire Gestation Period Days 0-29 (Grams)
0	39.1	251.8
10	47.5	253.3
30	4.6	165.8
100	-64.3	202.2

TABLE 3.

EFFECT OF BAYLETON ON PREGNANT RABBITS AND THEIR FETUSES

13 Daily Doses per os from Gestation Day 6 through 18

-- M E A N S --

Number of:					Mean Weight in grams of the:		Fetuses with:		
Impl.	Fetuses Male	Fetuses Female	Fetuses Total	Losses	Fetuses	Placentas	Slight Bone Changes	Malformations	Stunted Fetuses < 25 g
7.6	4.2	2.5	6.7	0.9	36.43	4.02	0.00	0.27	0.18
7.4	3.7	2.8	6.4	1.0	38.98	4.58	0.00	0.00	0.00
7.3	3.0	3.0	6.0	1.3	35.55	4.15	0.00	0.00	0.58
7.6	1.9*	2.5	4.4	3.2*	35.86	4.18	0.00	0.11	0.00

fferences from control are significant (P<0.05)

and 1.3 (30 mg/kg). The percentages of resorptions related to implantations, were 12.1% (controls), 13.5% (10 mg/kg), 17.2% (30 mg/kg), and 41.8% (100 mg/kg). The Laboratory Standard Value for resorptions in this strain of rabbit is 4.9%.[2]

The mean number of live fetuses per litter was 6.7 (controls), 6.4 (10 mg/kg), 6.0 (30 mg/kg), and 4.4 (100 mg/kg). The high dose group had a reduced number of fetuses; however, this difference was not statistically significant. The Laboratory Standard Value for CH88:HM rabbits is 6.7 live fetuses per doe.[2]

8. DEVELOPMENTAL TOXICITY EVALUATION

Fetal Data

The fetal data collected at cesarean section are summarized in Table 3.

As noted above, the high dose group had a reduction in the number of fetuses which was not statistically significant. A statistically significant difference was found in the sex ratio (male/female) of the high dose group (1.68) when compared to that of the control group (0.76). This significant difference ($P<0.05$) may be due as much to the very low male/female sex ratio of the controls as to the high sex ratio of the high dose group. The researcher states that this deceptive finding is of no biological relevance and the reviewers agree with this statement.

No observable differences were seen in the mean fetal body weights or placental weights for any of the treated groups as compared to those of the control group. The number of runts, living fetuses with a body weight less than 25 grams, were 2 (in 1 litter) in the control group and 7 (in 3 litters) in the 30 mg/kg group. An influence of treatment is improbable, since stunted fetuses were found only in the control group and the intermediate dose group and not in the high dose group.

Malformations and Variations

Bayleton did not exhibit teratogenic potential at the tested levels (Table 4). There were more malformed fetuses and more litters with malformations in the control group than in any of the 3 treated groups. The case of multiple deformities in one fetus of the 100 mg/kg dose group is a malformation that occasionally occurs spontaneously in this rabbit strain and is not considered dose-related. Table 3 shows the incidence of "slight bone changes" as zero in all 282 fetuses produced by this study.

[2] Frohberg, op. cit.

TABLE 4.

EFFECT OF BAYLETON ON RABBIT FETUSES

Fetal Malformations

Dose mg/kg/day	Doe No.	Number of Malformed Fetuses	Types of Malformations
0	2077	2	1 x arthrogryposis 1 x general edema
	2111	1	arthrogryposis
10	-	0	-
30	-	0	-
100	2117	1	multiple malformations, including gastroschesis, dysplasia of the extremities, and multiple skeletal changes

DISCUSSION

The report on the effect of Bayleton on pregnant rabbits was very brief. Important data elements missing were:

1. Information on how often the animals were observed for signs of toxicity
2. Exact weights of individual does at each weighing
3. Individual weights of fetuses
4. Number of corpora lutea
5. Details on signs of toxicity - time of onset, degree, and duration
6. Food consumption data
7. Pathological information on the does (Evidently no autopsy was performed.)
8. Was dosing based on pre-pregnancy weights or on the last weighing?
9. Parity of the does
10. Age of the does other than that they were sexually mature
11. Historical control data

Administration of Bayleton to Himalayan rabbits on day 6 through day 18 of gestation resulted in maternal toxicity at the 100 mg/kg/day level. Symptoms of toxcity at this level included reduced body weight gain during the treatment period ($P<0.01$), an increase in digestive disturbances, inflammation of the external vagina, and a statistically significant increase in resorptions in the 100 mg/kg/day group ($P<0.05$). None of these symptoms were observed in the 30 mg/kg/day group except a marked reduction in body weight gain for the treatment period and for the entire gestational period. While these reductions were not statistically significant, they do follow the trend set by the high dose group. The 17.2% of resorptions at this level is also part of a dose-related trend and reinforces signs of toxicity in the middle-dose group. No maternal toxicity was observed in the 10 mg/kg/day group. It can be concluded that, under the conditions of this study, a maternal NOEL in rabbits can be set at 10 mg/kg/day. The maternal LOEL in this study is 30 mg/kg/day based on an observed reduction in body weight gain during the treatment period and during the entire gestation.

An embryolethal effect was observed at the 100 mg/kg/day dose level. A statistically significant increase in fetal resorptions was observed in this high dose group. Surviving fetuses at this dose level exhibited normal weight and no embryotoxic effects. The fetuses at the 10 and 30 mg/kg/day dose level exhibited no embryotoxic effects. From the information available in this report, it can be concluded that a Developmental Toxicity NOEL can be set at 30 mg/kg/day. The Developmental Toxicity LOEL is set at 100 mg/kg/day based on embryolethal effects at this level.

DATA EVALUATION RECORD

Micronucleus Test on Mice

Machemer, L. (1977) Micronucleus test on mice to evaluate MEB 6447 for mutagenic potential. An unpublished report prepared by Bayer, A.G. Institute for Toxicology, Wuppertal-Elberfeld, West Germany, Report No. 6622, dated February 23, 1977, submitted to the Agency by Mobay Chemical Corporation, EPA Accession No. 254697.

Test Chemical: MEB 6447 (Bayleton), Batch No. 16002/75, with unspecified purity.

Experimental Protocol: Attached.

Results:

The results of this study are shown in tables 1 through 4. These tables were taken from the registrant's report.

Conclusions and Recommendations:

This study was submitted to the Agency before and evaluated by the Toxicology Branch (Document No. 02003). The study was not acceptable.

Further evaluation of the study did not change the Agency's position. The study is classified as unacceptable. See attached memorandum by G. Dearfield, dated February 16, 1988.

Attachment

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

FEB 16 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Bayleton - Mouse Micronucleus Assay

FROM: Kerry L. Dearfield, Ph.D.
Geneticist
Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: George Ghali, Ph.D.
Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

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

A mouse micronucleus assay with Triadimefon, Bayleton active ingredient has been submitted to OPP. It is report no. 6622 and was reported on February 23, 1977. The EPA document number is 52724. The following are comments regarding this assay.

The test substance was administered to male and female NMRI strain mice (5 mice/sex) in two oral applications, 24 hours apart. Six hours after the second dosing, the mice were sacrificed to obtain bone marrow for analysis. Only one dose level was used in this assay, 2 X 200 mg/kg; a solvent control and a Thiotepa (2 X 10 mg/kg subcutaneous) positive control were also used.

The results indicated no increased frequency of micronuclei in test substance treated animals compared to solvent control. The Thiotepa control produced an appropriate increased frequency of micronuclei. The ratio of polychromatic erythrocytes (PCE) to normochromatic erythrocytes (NCE) was slightly increased in relation to solvent control; the Thiotepa control decreased this ratio, indicating bone marrow depression.

This assay should be classified as unacceptable. This assay was performed by the Schmid protocol (Schmid, 1976), which is not the recommended protocol by today's standards. Most guidelines currently recommend that sampling times begin not earlier than 12

hours after the second treatment and at appropriate intervals up to 72 hours (e.g. see OTS and OECD guidelines). The primary support for these sampling times is reviewed in Heddle et al. (1983). It has been found that enucleation of the erythrocyte takes place about 6-8 hours after the final mitosis of the cell. Therefore, sampling intervals at this time or earlier do not provide a reasonable time frame for micronucleus formation in PCE. Also, more than one sampling time may be necessary to detect the optimal time for maximum micronucleus formation frequency in PCE (if no other data are available to suggest a single appropriate sampling time). Furthermore, to obtain dose response information, at least three doses should be examined.

Supporting this unacceptable classification for this assay is the apparent lack of toxicity to the test animals. No preliminary toxicity testing was reported to allow proper selection of doses that would provide some signs of toxicity. In the report itself, nothing was reported to indicate any signs of toxicity, thus indicating that higher dose levels may have been appropriate. Also, there was no depression of the PCE/NCE ratio by the test substance, which usually indicates some sign of cytotoxicity. In this case, there was actually an elevation of this ratio; the significance is unclear. Overall, it appears that higher dose levels should have been used to obtain a better indication of micronucleus induction potential.

References

Heddle J, Hite M, Kirkhart B, Mavournin K, MacGregor J, Newell G, Salamone M. 1983. The induction of micronuclei as a measure of genotoxicity. A report of the U.S. Environmental Protection Agency Gene-Tox Program. Mutat Res 123: 61-118.

Schmid W. 1976. In: Chemical Mutagens: Principles and Methods for their Detection, A. Hollaender (ed.), Vol. 4, Plenum, New York, pp. 31-43.

RID 5711-93

TRIADIMEFON TOX REVIEWS

Page_____ is not included in this copy.

Pages 60 through 71 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

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____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

DATA EVALUATION RECORD

Therapy of Eye Irritation

Hixson, E.J. (1982) Therapy of eye irritation of Bayleton 50% W.P. Unpublished report prepared by Stanley Research Center, Stilwell, Kansas. Report No. 267 submitted by Mobay Chemical Corporation under No. 80686. EPA Accession No. 254697.

Test Chemical: Bayleton 50% wettable powder.

Experimental Protocol: Attached.

Results:

1. Eye Irritation

According to the author, in the washed group "Very slight corneal opacity was observed in one of the three rabbits on day 1 only. Very slight iritis was also observed in this rabbit on day 2 only. Slight to moderate erythema was observed in all three rabbits and cleared by day 4 or 7. Chemosis was observed in two rabbits and cleared by day 3. Slight to moderate discharge was observed in all three rabbits; discharge cleared by day 2 or 4."

In the nonwashed group "Very slight to severe corneal opacity was observed in two rabbits and cleared by day 3 or 8. Iritis was not observed. Moderate erythema, observed in all three rabbits, cleared by day 8 or 9. Slight to severe chemosis was observed in all three rabbits and cleared by day 2, 3, or 4. Moderate to severe discharge was observed in all three rabbits and cleared by day 7."

2. Therapy

"Ophthocort®. Neither corneal opacity nor iritis was observed in any of the three rabbits. Moderate to severe erythema was observed in all three rabbits and cleared by day 8, 9 or 10. Chemosis was observed sporadically in all three rabbits and cleared by day 2, 8 or 9. Slight to moderate discharge was observed in all three rabbits and cleared by day 2, 4 or 7.

"BPNHA. Very slight corneal opacity was observed in only one rabbit on day 1 only. Iritis was not observed. Slight to moderate erythema was observed in all three rabbits and cleared by day 8 or 9. Slight chemosis was observed in all three rabbits on day 1 only. Slight to moderate discharge was observed in all three rabbits and cleared by day 3, 4 or 7."

A comparison made by the author indicated that "Washing the eyes with water offered some improvement in response over eyes that were not washed, particularly in the incidence and severity of corneal opacity. The severity and duration of erythema was slightly reduced by washing, as were the severity of chemosis and discharge. A slight decrease in the duration of the discharge was also observed. Results after therapy with Ophthocort® or BPNHA were similar to those obtained after washing the eyes. However, both therapeutic regimens increased the severity and duration of erythema."

Conclusion:

According to the author, "Bayleton 50% Wettable Powder is a positive eye irritant with lesions spontaneously reversed in eight days. Washing the eyes offers an improvement in the severity and duration of the responses. Therapy of the eyes with ophthalmologic ointments containing antibiotics and steroid was not superior to washing with water in alleviating the irritation."

Core Classification: Supplemental information

Attachment

RID 5711-93

TRIADIMEFON TOX REVIEWS

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DATA EVALUATION RECORD

Acute Inhalation Toxicity Study With
Bayleton 50% WP in Rats

Sangha, G.K. (1984) Acute inhalation toxicity study with Bayleton 50% W.P. in rats. Unpublished report prepared by Mobay Chemical Corporation, Environmental Health Research. Report No. 86389, dated March 7, 1984, Study No. 84-041-01. EPA Accession No. 254697.

Test Chemical: Bayleton 50% W.P.

Experimental Protocol: Attached.

Results:

Temperature and Humidity - The temperature ranged between 22 and 24 °C. The humidity was kept at about 26 percent at all times except in the last hour in the treatment chamber, where it increased to about 68 percent due to the clogging of the filter. In the control chamber the humidity increased to 96 percent for the first 15 minutes then stayed around 40 percent for the duration of the study.

Particle Size: According to the author "the average mass medium diameter was 4.2 Um. The data indicated that about 50 percent of the particles sampled was below 4.2 Um."

Chamber Concentration - The author indicated that "the nominal gravimetric concentrations was about 33% of the nominal value. A higher nominal concentration during the last hour of exposure might have occurred due to lower airflow through the chamber."

General Observations - All compound-exposed animals exhibited lacrimation and nasal ocular irritation during exposure and up to 1.5 hours postexposure. One male showed salivation on day 3 and appeared normal on day 4. One female died on day 9. Hair loss around the eyes was observed in some females. Statistically significant decreases in body weights of exposed animals were observed in treated animals.

The control animals also showed nasal and ocular discharge during exposure and up to 1.5 hours postexposure. The results are shown in table 1.

Conclusions:

The 4-hour LC_{50} of Bayleton 50% W.P. to male and female rats is greater than 3.532 mg/L.

Core Classification: Supplementary.

Attachment

Table I . Summary of Data of Acute Inhalation Toxicity Study with BAYLETON 50% Wettable Powder in Rats

Animal Number	Conc mg/m³	Initial Body Weight Range (g)	Mean Body Weights (g) Day 0	Day 3	Day 7	Day 14	Observations No. Dead/ Signs/ Exposed	Begin (Hour)	End Within (Day)	Time of Death (Day)
Males										
11-20	3532	198-228	217	211*	252*	300	0/10/10	DE	5	-
		SD	10	12	15	20				
1-10	Control	197-225	213	222	258	299	0/08/10	DE	1	-
		SD	9	8	11	12				
Females										
76-85	3532	183-199	190	182	203	220	1/10/10	DE	14	9
		SD	5	12	12	13				
66-75	Control	184-211	199	194	210	226	0/05/10	DE	1	-
		SD	8	12	13	16				

SD = Standard Deviation
DE = During Exposure
* = Significantly different from controls

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006841

DATA EVALUATION RECORD

Acute Toxicity Studies

Mihail, F. (1980) Acute toxicity studies. Unpublished report prepared by Bayer, A.G. Institute for Toxicology. Report No. 9277, Mobay Report No. 68922, dated June 27, 1980. EPA Accession No. 254697.

Test Chemical: MEB 6447, purity 92.6%.

Complete DERs were not prepared. The data requirements for acute toxicity on MEB 6447 (Bayleton) has been satisfied. The newly submitted data do not provide any new information in this area, nor do they affect the toxicity category.

A summary of the findings provided by the registrant is attached.

Attachment

RID 5711-93

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006841

DATA EVALUATION RECORD

Subacute Oral Cumulative Toxicity Study in Rats

Mihail, F. and Kaliner, G. (1979) Subacute oral cumulative toxicity study on rats. An unpublished report prepared by Bayer, A.G. Institute of Toxicology. Report No. B195 dated February 20, 1979. Mobay Report No. 69477, EPA Accession No. 254694.

Test Chemical: MEB 6447, pure technical grade (purity 97.0%), Batch No. 16002/75.

Testing Laboratory: Bayer, A.G. Institute of Toxicology.

This study was not reviewed since most of the result tables are in German and are illegible.

However, since the data base for Bayleton is complete, the registrant is not required to submit an English translation for this study unless the data indicate adverse effects that have never been reported before on Bayleton.

006841

DATA EVALUATION RECORD

Primary Dermal Irritation

Report Sheet No. 25

Mobay Chemical Report No. 80329, dated May 15, 1981

This is a summary sheet. The information included is inadequate for evaluation.

006841

DATA EVALUATION RECORD

Reproduction Study

Thyssen, J. and Groning, P. (1978) MEB 6447 Futterungsversuche mit Huhnern Unter Resonderer Beruck-Sightigung Einer Moglichen Beeinflussung der Fortpflanzung. An unpublished report, No. 67070 prepared by Bayer, A.G. Institute of Toxicology, dated November 15, 1978, submitted to the Agency by Mobay Chemical Corporation. EPA Accession No. 254697.

No DER was prepared; the study report is in German. Data requirements for reproduction have been previously satisfied on Bayleton. The registrant is not required to submit an English translation unless the new study includes adverse effects that were not included in the earlier reports.

RID 5711-93

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006841

DATA EVALUATION RECORD

Acute Toxicity Studies in Rats and Mice

Nakazato, Y.; and Iyatomi, A. (1977) MEB 6447 (Bayleton) acute toxicity studies. An unpublished report prepared by Nitokuno, Agricultural Chemical Institute, Laboratory of Toxicology. Report No. 88, dated December 14, 1987, submitted to the Agency by Mobay Chemical Corporation. EPA Accession No. 254697.

Test Chemical: MEB 6447 with 97.0% purity.

No DERs were prepared. The data requirements for acute toxicity on Bayleton have been satisfied. The current data did not provide any new information, nor did they affect the toxicity category.

A summary of the findings provided by the registrant is attached.

Attachment

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