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WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Bayleton** - Validation of Reviews Recommended by RfD Committee on March 11, 1993

Tox. Chem. No. 109901
Caswell #: 862AA

FROM: Sheryl K. Reilly, Ph.D. Sheryl K Reilly 6/1/93
Review Section II, Toxicology Branch I
Health Effects Division (H7509C)

TO: The Files

THRU: Melba S. Morrow, D.V.M. Morrow 6/1/93 KB 6/4/93
Acting Section Head, Review Section II
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Health Effects Division (H7509C)

In an RfD meeting on March 11, 1993, the committee determined that five Bayleton studies needed to be reevaluated or changed. The studies that required revision were as follows:

1. **Two-year feeding/oncogenicity study in rats, MRID Nos. 41412001, 42153901, HED Doc. 009726.** The doses of Bayleton tested in this study were 0, 50 ppm (2.7 mg/kg/d ♂, 3.6 mg/kg/d ♀), 300 ppm (16.4 mg/kg/d ♂; 22.5 mg/kg/d ♀) or 1800 ppm (114.0 mg/kg/d ♂, 199.0 mg/kg/d ♀), and the species was the Wistar rat (♂/♀).

The RfD committee determined that the systemic NOEL in this study should be 300 ppm, and the systemic LOEL = 1800 ppm, based on decreased body weight and decreased body weight gain in both sexes; decreased RBC counts, HGB, HCT & MCHC, increased liver weight and cholesterol in females; increased lipopexia in hepatocytic plasma in both sexes, and thyroid follicular cell (TFC) hyperplasia. **These tox endpoints are the same as in the DER and the 1-liner files for this study, and thus do not need revision, as the committee had originally stipulated.**

The oncogenicity NOEL/LOEL for Bayleton cannot be determined from this study at this time. Although Bayleton induced a positive dose-related trend in the incidence of TFC adenomas/adenomas multiple in males, and a positive dose-related trend for combined incidence of TFC cystic hyperplasia and adenomas/adenomas multiple

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in both sexes (see table, below), these trends were not statistically significant.

In order to evaluate the oncogenicity of Bayleton in the rat, historical control data for thyroid tumors are needed because the incidence in the high-dose group of thyroid adenomas, adenomas multiple and TFC, though higher than the control animals in the study, may be within the normal variation for the test species. This information was requested in a memorandum dated 9/14/92 (HED Doc. # 009726). To date, this data has not been submitted by the sponsor. James Stone (PM-22) contacted the sponsor on April 21, 1993, and they verified that they had not complied with the request, and would do so in the near future.

	Concentration of Bayleton in Test Diet (ppm)			
	0	50	300	1800
Incidence of: Adenomas + Adenomas Multiple				
Males	0/50	0/50	1/50 (2%)	4/49 (8%)
Females	0/50	1/50 (2%)	0/50	2/50 (4%)
Adenomas + Adenomas Multiple + Cystic Hyperplasia				
Males	2/50 (4%)	3/50 (6%)	2/50 (4%)	7/49 (15%)
Females	2/50 (4%)	1/50 (2%)	1/50 (2%)	6/50 (12%)

2. Two-year feeding study in dogs, MRID Nos. 00032539, 00126261, 92188015, 92188016; HED Doc. Nos. 002008, 004695. The levels of Bayleton tested in this study were 0 (controls), 100 ppm (5.7 mg/kg/d), 330 ppm (11.4 mg/kg/d), and 1000 ppm (33.67 mg/kg/d) for the first 54 weeks; during weeks 55-104 of the study, the high-dose group was increased to 2000 ppm (60.42 mg/kg/d). Male and female beagle dogs were used in the study.

The RfD committee questioned the importance of the inflammation observed in the epididymides at 330 ppm, reported as the basis for the LOEL determination in the original DER. In the study, 1/4 contr ., 1/4 100 ppm, 3/4 330 ppm, and 4/4 1,000/2,000 ppm males exhibited minimal to moderate mononuclear cell infiltration into the epididymides. The RfD committee thought these observations were insignificant.

The NOEL for chronic toxicity in this study should be changed to 330 ppm (11.4 mg/kg/d), and the LOEL changed to 1000 ppm (33.67 mg/kg/d), based on the many changes that occurred in the high dose group after the dosage was increased, as stated in the original DER. These changes included: decreased food intake of

approximately 11% the first year in 4/4 female dogs at that dose level (this decrease in food consumption was more pronounced (approximately 15%) in 4/4 ♀ when the high dose group was increased to 2000 ppm the second year); depression in weight gain in both sexes (5/8 animals) after the dose was increased to 2000 ppm the second year (♂ = 20% less than controls; ♀ = 11% less than controls); significantly ($p<0.05$) increased alkaline phosphatase activity in both sexes; decreased glutamic pyruvate transaminase (GPT) activity and increased cholesterol (♀); decreased creatinine levels (♂); statistically significant increase in N-demethylase activity ($p<0.05$) in both sexes, indicative of microsomal enzyme induction; increased liver weights, and relative liver:body and heart:body weights; and the presence of bile duct concretions in 3/4 males.

In the study, the decreased food consumption observed in the high dose females was attributed to the relatively frequent number of weeks in which that group did not completely consume their food ration (74/104 weeks) compared with 3/104, 4/104, and 8/104 weeks for the control, low and mid-dose female groups, respectively. In all but one control and one low-dose group male, the male dogs always finished their food rations.

With the exception of alkaline phosphatase, the enzyme changes were not biologically significant, and the increased liver weight was probably adaptive in nature. The increased number of bile duct concretions observed support the increase of the alkaline phosphatase.

3. **Three-generation reproduction study. MRID No. 00032541, 92188019, 92188020, HED Doc. 004695.** The levels of Bayleton tested in this study were 0 (controls), 50 ppm (2.5 mg/kg/d), 300 ppm (15 mg/kg/d), and 1800 ppm (90 mg/kg/d). The purity was not specified, only that it was technical grade, batch number 16002/75. The test species was the SPF Wistar W. 74 rat (♂/♀).

See the attached addendum to the DER for this study.

This study was first reviewed in 1981 (HED Doc. #2008), and classified as "minimum". The study was independently reviewed again (by contractor) in 1985 (HED Doc. #4695); no reference was made to the first review. The study was classified as "supplementary" in the second review. The RfD committee suggested that this study be reviewed again, and if possible, upgraded to minimum. However, the classification will not be upgraded, as explained in the attached addendum to the DER. The results from this study, especially when considered together with the results from the two-generation study (see below), indicate that the test compound appears to cause severe developmental and reproductive toxicity at 1800 ppm. The NOEL is equivocal, and more data is needed from the sponsor in order to upgrade this study.

4. Two-generation reproduction study. MRID No. 00155075, 92188019, 02188020, HED Doc. 006563. The substance tested was Bayleton technical (92.6%). The doses tested were 0 (controls), 50 ppm (2.5 mg/kg/d) and 1800 ppm (90 mg/kg/d). The test species was the BOR:WISW (SPF/Cpb) rat (♂/♀).

See the attached addendum to this DER.

At this time, the classification of this study will not be upgraded to minimum, because only 2 doses of Bayleton were tested, and additional data were requested (in the DER) from the sponsor before the study can be upgraded to minimum. This data included food consumption, clinical observations, organ data for the 50 ppm group (F_1 and individual birth weights of the pups. This information has not been received from the sponsor. Further, the NOEL cannot be unequivocally established, even if this study is combined with the three-generation reproduction study. It appears that the NOEL for Bayleton could be less than 50 ppm, but lower doses were not tested. The quality of print in the study is so poor, much of the data cannot be read; thus, it is not possible to make an independent determination.

5. Developmental toxicity study in rats. MRID No. 00149336, 92188018, HED Doc. 006841. The levels of Bayleton tested were 0, 10, 30, and 90 mg/kg by gavage, in the CD-SD rat.

This study was erroneously classified as supplementary, and should be upgraded to minimum. The maternal and developmental NOEL was 30 mg/kg/d. The maternal and developmental LOEL was 90 mg/kg/d; the maternal endpoint was based on statistically significant decreases in weight gain, and the developmental endpoint was based on statistically significant increased rib abnormalities, and distended urinary bladders (HED Doc. # 004695).

Reviewed by: Cheryl K. Reilly, Ph.D. SKR 6/1/93
Section II, Toxicology Branch I (H7509C)
Secondary Reviewer: Melba S. Morrow, D.V.M
Section II, Toxicology Branch I (H7509C)

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Bayleton. Addendum to the Three-Generation Reproduction Study.

Tox. Chem. #: 109901

Caswell #: 862AA

MRID #: 00032541. (See also MRID # 92188019, 92188020, HED Docs. # 0002008 and # 004695, and Two-Generation Reproduction Study in the Rat, MRID # 00155075.)

Study #: MEB 6447

Title: MEB 6447 Multigeneration Reproduction Study on Rats

Author: Dr. E. Löser

Report Issued: April 12, 1979

Test Material: Bayleton Technical Grade (MEB 6447; batch #16002/75)

Doses Tested: 0 (controls), 50 ppm (2.5 mg/kg/d), 300 ppm (15 mg/kg/d), and 1800 ppm (90 mg/kg/d).

Test Species: SPF Wistar W. 74 Rats

DISCUSSION:

This study was first reviewed in 1981 (HED Doc. #2008), and classified as "minimum", with a NOEL of 50 ppm (2.5 mg/kg/d) and an LOEL of 300 ppm (15 mg/kg/d), based on significantly lower body weights in the F_{3b} pups (the time of this weight determination was not specified in the DER). The study was independently reviewed by a contractor in 1985 (HED Doc. #4695), and classified as supplementary. It was concluded in the second DER that the reproductive NOEL was 300 ppm, and the LOEL was 1800 ppm (90 mg/kg/d), based on decreased fertility, litter size, body weight of the adult females in the F_0 and adults of both sexes of the F_1 generation, decreased survival of the F_1 pups during lactation (90.7% v 97.8% in the controls of the F_{1a} litter, and 56.4% v. 84.2% in the controls, F_{1b} litter), and decreased fertility index (no. pregnant/no. mated ♀ = 1/20 v. 20/20 controls) in the first mating of the F_1 females. No litters were produced in the second mating of the high-dose F_1 females. The fetotoxic NOEL was 50 ppm, and the LOEL was 300 ppm, based on decreased weight gain in the F_{2b} and F_{3b} pups; this could not be confirmed, as the print quality of the

study was poor, and pup weight at weaning not legible.

The RfD committee suggested that this study be reviewed again, and upgraded to minimum, if possible. However, the classification will not be upgraded, for the following reasons.

The first DER contradicted the findings of the second, by stating that "there was no dose-related or statistically significant difference ($p>0.05$) between rats (weaned males and females) of the 50 and 300 ppm groups and the control of the F_{2b} generation." In addition, the quality of print in the study is so poor, much of the data (including the pup weight data) cannot be read and interpreted, and summary data on pup body weight is not provided. What is provided in the submission concerning pup and parental body weights are poorly visible graphs, which are difficult to read and interpret. It is not possible to make an independent determination of whether a significant difference exists between the controls, 50 and 300 mg/kg/d groups using these graphs, particularly since the control data is not included on most of the graph. Thus, the NOEL/LOEL and classification of this study is equivocal.

Further, no information or data were provided for how the range of doses tested were chosen, nor the incidence of stillborn or cannibalized pups. The results of the study indicate that the highest dose tested caused severe reproductive toxicity. At that dose, the test compound had significant inhibitory effects on fertility ($p<0.01$), litter size ($p<0.05$), and survival of the pups from birth to day 5 of lactation ($p < 0.01$; see tables below). The decreases in litter size and pup survival could be indicative of either developmental or reproductive toxicity (due to decreased lactation or direct toxicity to the pups) at the highest dose tested.

The mating scheme was not clearly defined in the submission. It appears that 2 females were mated with 1 male up to 20 days. The males were probably replaced after each estrus cycle, if mating had not occurred. However, there is no description of how mating success was determined, and thus it is unclear if the decrease in reproduction observed in the F_1 generation was due to reduced interest in mating or toxic effects of the test compound on fertility (e.g., spermatogenesis, ovulation, conception, or implantation).

In order for this study to be upgraded to "minimum", the registrants should submit individual and summary data tables on pup and paternal weight/weight-gain data, plus a description of how successful mating was determined, range-finding studies and data, incidence of stillbirths/cannibilizations, and an explanation of the numbers and types of tissues actually examined (an issue raised in HED Doc. # 4695). The study will remain classified as supplementary until receipt of these documents.

Bayleton - tox review

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Reviewed by: Sheryl K. Reilly, Ph.D. SKR 6/1/93
Section II, Toxicology Branch I (H7509C)
Secondary Reviewer: Melba S. Morrow, D.V.M
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010310

Bayleton. Addendum to the Two-Generation Reproduction study.

Tox. Chem. #: 109901

Caswell #: 862AA

MRID #: 00155075. (See also MRID # 92188019, 92188020, HED Doc. # 006563, and Three-Generation Reproduction Study, MRID # 00032541.)

Study #: MEB 6447

Title: MEB 6447 (Triadimefon) Multigeneration Reproduction Study with Rats (Supplementary Study)

Author: Dr. R. Eiben

Report Issued: 5/30/84

Test Material: Bayleton Technical (92.6%)

Doses Tested: 0 (controls), 50 ppm (2.5 mg/kg/d) and 1800 ppm (90 mg/kg/d).

Test Species: bor:wisw (SPF/Cpb) rats

DISCUSSION:

This study was submitted as a supplemental study to the three-generation study, presumably in response to the first DER, judging by the reporting date, and classified as supplementary. The study was reviewed by a contractor in 1988 (HED Doc. #6563), and classified as supplementary, but it never received a secondary review. The RfD committee requested a secondary review of the findings in the DER.

It was concluded in the DER that the reproductive NOEL was 50 ppm (2.5 mg/kg/d). This was based upon statistically significant ($p<0.01$) reductions in mean birth and lactational weights, and viability (survival from days 0-5 and 5-28) of the F_1 in the 1800 ppm group. Reduction in litter size and viability (days 0-5 and 5-28) also was significant ($p<0.01$), as were decreased mean birth and lactational weights ($p<0.05$) in the F_2 pups at this dose. (See attached tables, taken from the DER (HED Doc. 006563) for reproduction indices (Table 2), parturition data (Table 4), and viability (Table 5)).

It is important to note that the F_1 female adults exhibited significantly ($p<0.01$) reduced mean body weight (compared with body weight of controls) on days 1 (6.5% less than controls), 6 (6.6%) and 15 (6.3%) of gestation at 50 ppm. In addition, at the 50 ppm dose level, the absolute and relative ovarian weights in the F_0 females were significantly ($p<0.05$) greater than controls (10.5% greater absolute ovarian weight, and 10.4% greater relative ovarian weight). The organ weights and ratios were not determined for the 50 ppm F_1 adults.

The differences in body weights and ovarian absolute and relative weights indicate that the test compound may have a toxic effect at the 50 ppm level in the F_1 females; however, these differences are low (10.5% or less) and therefore may not be biologically significant. Thus the NOEL cannot be firmly established without further study of lower doses.

With regard to the effect of the highest dose on body weight, the adult male F_0 rats exhibited significant ($p<0.01$) reductions in body weights at weeks 4, 5, and 6, and females at weeks 1-16 and 21-26 of treatment. In addition, both sexes of F_1 adults exhibited statistically significant weight reduction at all weighing times between weeks 9-40 ($p<0.01$, except gestation day 20 and week 35 when $p<0.05$ in females) at the 1800 ppm level. (See Table 1, attached, for F_1 female weight data, from the DER, HED Doc. 006563).

A reduction in the number of litters produced was observed in the three-generation study. In the present study, the number of litters that the F_1 adults in the 1800 ppm group produced in this study were 7/20 matings, compared with 17/20 each in the control and 50 ppm group (Table 4, attached). The fertility index in the F1 rats in the 1800 ppm group was significantly ($p<0.01$) lower compared with control and 50 ppm groups (35% compared with 85% in control and 50 ppm groups). To determine if decreased fertility was due to lack of interest in mating or possible malformation or reduced number of sperm, male F_1 rats in this group were mated with control females, and 1800 ppm F_1 females were crossed with control males, 2 weeks after their first pups were weaned. The fertility index in the high-dose ♂ x control ♀ mating was 47.4%, but the high-dose ♀ x control ♂ fertility index was 80%. When the epididymides were examined at necropsy, no adverse effects were observed on sperm motility or morphology, thus the decreased fertility appears to be due to a decreased interest in sex in the males treated with 1800 ppm Bayleton. To support that conclusion, the study indicates that 6/10 males did not appear to copulate during the 3-week mating period with the control females. In the F_3 generation (from the matings between high dose and control animals), the high-dose females (x control males) had decreased ($p<0.05$) litter sizes with a mean of 8.4, compared with 11.8 pups/litter (1800 ppm ♂ x control ♀). However, viability increased in this group from days 5-28 ($p<0.05$ -- see Table 6, attached).

In the DER, a request was made for additional data from the sponsor in order for this study to be upgraded to minimum. This data included food consumption, clinical observations, organ data for the 50 ppm group (F_1) and individual birth weights of the pups. This information has not been received.

At this time, the classification of this study will not be upgraded, because the study only tested 2 doses of Bayleton, and the required information has not been received from the sponsor. Further, the NOEL cannot be unequivocally established, even if this study is combined with the three-generation reproduction study. It appears that the NOEL for Bayleton is less than 50 ppm, but lower doses were not tested. In addition, the quality of print in the study is so poor, much of the data cannot be read and interpreted, and it is not possible to make an independent determination.

Bayleton tox review

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