MEMORANDUM

SUBJECT: Avermectin B₁ (Also Called Abamectin) - PP#7F3500 (Avermectin B₁ in/on Cotton) - PP#7G3468, 7H5518 (Avermectin B₁ in/on Citrus, Temporary Tolerances); and PP#8F3592, 8H5550 (Avermectin B₁ in/on Citrus, Permanent Tolerances) - Additional Chronic Toxicology Data, Dog, Mouse, and Rat - Caswell No. 63AB; Project Nos. 8-0186, 8-0484 - Record Nos. 206650, 206652, 206653, and 215107, 215108, 215109; Accession Nos. 403755-01 Through -12; 405178-01, -02 (Volumes 1 and 2 for Each)

FROM: William Dykstra, Reviewer
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Requested Action

Review submitted chronic toxicology studies and/or addenda in dog, mouse, and rat in support of requested tolerances for abamectin.

Background

Toxicology Branch (TB) has previously reviewed the tolerance requests for avermectin B₁ and the Δ-8,9-isomer for citrus and cotton. In the review for citrus of April 23, 1987, TB concluded that for the 1-year dog study (MSDRL
TT#82-104-0; April 24, 1984), a NOEL could not be established based on the submitted data. TB required complete detailed results of the physical examinations of all dogs (control and treated) during the entire study to be submitted for evaluation. Additionally, TB required that the ophthalmoscopic examinations of all dogs at pretest and in weeks 12, 25, 40, and 52 be submitted for evaluation. The 1-year dog study was Core- Supplementary which could be upgraded pending review of the additional data.

In the review for cotton of May 14, 1987, TB concluded that for the final reports of the rat and mouse chronic feeding/oncogenicity studies, the following data were required:

1. A listing of all gross necropsy observations and palpable masses and corresponding microscopic findings for each animal;

2. Reformatted pathology reports of histopathology incidence tables and summary incidence tables; and 

3. Full reports of the ophthalmological examinations.

The registrant, Merck, has now submitted all the additional requested data for the 1-year dog study and the rat and mouse chronic feeding/oncogenicity studies.

Conclusions and Recommendations

1. The 1-year dog study can be upgraded to Core-Guideline and supports the registration. The NOEL for the study is 0.25 mg/kg/day. The LEL is 0.5 mg/kg/day, and the effect is mydriasis.

2. The chronic toxicity/oncogenicity study in mice is acceptable as Core-Minimum data. The oncogenic potential is negative up to 8 mg/kg/day (HDT). The high dose (8 mg/kg/day) is also the MTD, since in males at this level there was increased mortality and in females there was increased tremors and body weight gain (-22%). In addition, in a 12-week range-finding study in mice, decreased body weight gains of -25 and -32 percent were observed in male and female mice, respectively, at dosage levels of 11.8 and 13.1 mg/kg/day, respectively. The systemic NOEL for the study is 4 mg/kg/day, the mid dose. The LEL is 8 mg/kg/day (the high dose). At this level, there was an increased incidence in male mice of dermatitis, an increased incidence of extramedullary
hematopoiesis in the spleen of males, increased mortality in males, and tremors and body weight loss in females. A full DER for this study is attached.

3. The chronic toxicity/oncogenicity study in rats is acceptable as Core-Minimum data. The oncogenic potential was negative up to 2.0 mg/kg/day (HDT). The systemic NOEL is 1.5 mg/kg/day, the mid dose. The LEL is 2.0 mg/kg/day, the high dose. At this level, there were treatment-induced tremors in both sexes. An additional female in the mid-dose group also had tremors, but this animal consumed about 2.5 mg/kg/day of abamectin during this period (based on actual food consumption and body weight data). There were no compound-related pathological lesions to correlate with the tremors. The high dose (2.0 mg/kg/day) is considered to be the MTD for both sexes, since tremors were observed in both sexes at this level and particularly when the dose was temporarily raised to 2.5 mg/kg/day for 3 weeks during week 10 to 13 of the study. In addition, in an 8-week range-finding study in rats, decreased body weight gains, tremors, and death were observed in male and female rats at dosage levels of 4.1 to 5.8 mg/kg/day.

A full DER for this study is attached.

Review

- MK-0936: 53-Week Oral Toxicity Study in Dogs (Merck Sharp & Dohme Research Labs.; TT#82-104-0; Addendum; dated September 15, 1987; by L. Gordon (MRID No. 403755-10).

The registrant, Merck, has submitted the individual clinical signs of mydriasis for the 1-year dog study. Evaluation of the individual data shows a high incidence of mydriasis in dogs (both male and female) at 1.0 and 0.5 mg/kg/day during the 53-week study. At the 0.25 mg/kg/day dose level, two dogs (82-0496 and 82-0478) had mydriasis at week 10. Since there was no mydriasis before or after week 10, the finding of mydriasis at 0.25 mg/kg/day at week 10 is considered unrelated to treatment. The NOEL for mydriasis is considered to be 0.25 mg/kg/day.

Other toxic signs, which occurred at comparable frequencies in dogs of the control and treated groups, were swollen vulva, food emesis, and no stool. However, at the high-dose level (1.0 mg/kg/day), three dogs
exhibited salivation: dog 82-0476 (weeks 15 and 16), dog 82-0507 (week 33), and dog 82-0502 (week 38). This salivation finding may be compound-related, since these signs did not occur in controls or in the low- and mid-dose levels.

Additionally, the registrant has submitted the individual results of the ophthalmological examinations of all dogs at pretest and at weeks 12, 25, 40, and 52. Evaluation of of the individual data shows no compound-related eye effects.

Conclusions

The 1-year dog study can be upgraded to Core-Guideline and supports the registration. The NOEL for the study is 0.25 mg/kg/day. The LEL is 0.5 mg/kg/day and the effect is mydriasis.

Classification: Core-Guideline
Study Type: 83-5 - Combined Chronic Toxicity/Oncogenicity - Mouse

TOX Chem No.: 63AB

MRID Nos.: 400696-02,
Vol. 1-7; 405178-02,
Vol. 1 and 2; 403755-12

Accession No.: N/A

Test Material: Abamectin

Synonyms: Avermectin B₁, MK-0936

Study Number(s): TT#83-002-0, -1, -2, -3

Sponsor: Merck and Company

Testing Facility: Merck Sharp and Dohme Research Labs

Title of Report: Ninety-Four Week Dietary Carcinogenicity and Toxicity Study in Mice.

Author: L. Gordon

Report Issued: August 27, 1985

Conclusions:

The oncogenic potential was negative up to 8 mg/kg/day (HDT). The high-dose (8 mg/kg/day) is also considered the MTD. The systemic no-observed-effect level is 4 mg/kg/day. The lowest-effect level is 8 mg/kg/day and the effects are increased incidence of skin dermatitis in males, an increased incidence of extra-medullary hematopoiesis in the spleen of males, increased mortality in males, and tremors and body weight decrease in females.

Classification: Core-Minimum

Special Review Criteria (40 CFR 154.7): N/A
Review:

- MK-0936: Ninety-Four-Week Dietary Carcinogenicity and Toxicity Study in Mice; Merck Sharp & Dohme Research Labs.; TT#83-002-0, -1, -2, -3; August 27, 1985; by L. Gordon (MRID Nos. 400696-02, Vol. 1-7; 405178-02, Vol. 1 and 2; 403755-12).

Test Material - MK-0936; abamectin; Lot No. L-676, 863-00V54; Purity 91.1 percent.

Animals - CrL:CD-1 (ICR) BR mice, approximately 6 weeks old at study initiation, were used in the study. The mice were obtained from Charles River Breeding Laboratories, Kingston, NY, and weighed 15.5 to 33.2 g (males) and 15.8 to 22.1 g (females). The mice were housed in plastic cages, by sex and dosage group, at 1 to 3 mice per cage. Purina Certified Rodent Chow and water were available ad libitum.

Two control groups, each identical, were used in the study.

Methods:

Randomized groups of 74 male and 74 female CD-1 mice were fed test material in the Rodent Chow diet at levels of 0 (control I), 0 (control II), 2.0, 4.0, and 8.0 mg/kg/day of abamectin. The levels of abamectin the feed were adjusted and mixed biweekly to attain the targeted dose levels. The vehicle used was acetone, which was subsequently dried off. At 25/26 weeks and at 52 weeks, 12 mice/sex/group were sacrificed for blood examinations (see below). Due to increase in mortality in high-dose group males, dosing of this group and sex only was discontinued beginning in Drug Week 90 when survival had reached 40 percent.

The total number of days on test for the males was 655 to 657 (93.5 to 93.8 weeks). The total number of days on test for the females was 652 to 654 (93.1 to 93.4 weeks).

Test diets were prepared every 2 weeks and were used up within 4 weeks. Stability of test material in diets was determined to be satisfactory over a period of 1 month at room temperature. Homogeneity of samples from the top, middle, and bottom of each dietary mix was acceptable. Concentrations of test material were determined in samples from each biweekly dietary batch. Test material consumed by the mice (on a mg/kg/day basis) was generally within 20 percent of targeted levels (see p. 9 of this review).

Animals were observed twice daily for morbidity and toxic signs, and were examined in detail weekly for physical ailments and palpable masses.
Body weights were recorded weekly for all mice throughout the study. Food consumption was measured weekly over a 6-day interval for 12 boxes/sex/group.

Ophthalmological examination was performed on all mice at pretest and all control and high-dose mice in weeks 51 (or 53) and 91.

Hematological and biochemical examinations were conducted on approximately 12 mice/sex/group at interim sacrifice in weeks 25 (or 26) and 52. No organ weights or histological examinations were done on these interim sacrificed mice.

In addition, vena cava blood samples were taken from all moribund animals at unscheduled sacrifice beginning in week 70 and from all mice at terminal sacrifice.

The following hematological parameters were determined - Hg, RBC, WBC, Differential WBC, MCV, platelets*, hematocrit, MCH, and MCHC.

The following biochemical parameters were determined - Total protein, albumin, glucose*, BUN, creatinine, cholesterol*, triglycerides*, Na*, K*, Cl*, SAP, alanine aminotransferase*, and aspartate aminotransferase.**

All animals that died during the study, or were sacrificed moribund, and all terminally sacrificed animals were given a complete necropsy. Routine tissue samples were fixed in 10 percent neutral buffered formalin or Bouin's fixative.

At terminal necropsy, weights of brain, spleen, heart, kidneys, liver, adrenals, lungs, thyroid, pituitary, testes, prostate, ovaries, and uterus were taken. In addition, terminal body weight of each animal was also taken for the purpose of calculation of relative organ weights.

Hematoxylin and eosin-stained sections from the following tissues were examined microscopically: salivary gland, stomach, small intestine, large intestine, liver, gallbladder, pancreas, adrenals, parathyroid (when present in thyroid section), pituitary, thyroid, kidneys, urinary bladder, epididymides, prostate, seminal vesicles, skin, mammary gland (when present in skin section), lung, heart, spleen, lymph nodes, thymus (when present in section from the area), bone with bone marrow, joint, skeletal muscle, brain, spinal cord, sciatic nerve, and eye including optic nerve.

*Parameters measured at terminal bleeding only in week 94 and in moribund animals at sacrifice.
**Parameters not measured at terminal bleeding in week 94.
All gross lesions from all animals including all palpated masses were also examined microscopically. Statistical analyses of the data were performed with p < 0.05 being significant.

Results:

Raw data or summary tables for toxic signs were not provided by the registrant. However, the report states that treatment-related tremors were observed in several female animals in each MK-0936 treated group after day 1 of treatment. In addition, seven females in the high-dose group and three females in the mid-dose group were found dead the next day. These 10 female animals were replaced with spare animals from the same animal shipment, and the study was restarted the following week.

After restart of the study, treatment-related tremors were again observed in several females in each of the groups receiving MK-0936. No explanation could be found for the sensitivity of the female mice to test material.

Since the male mice were not affected, they remained on study, while the females were terminated and a new group of animals restarted 4 weeks later (TT#83-002, -2, -3).

Following the start with the new group of females, no tremors were observed until a female animal of the mid-dose had tremors 1 day prior to being found dead in week 49.

This female mouse had a metastatic lymphoma of the pituitary, and the tremors were considered secondary to the tumor rather than related to treatment.

Two high-dose females had tremors in weeks 89 and 91, and were killed at terminal necropsy at week 94. There were no gross or microscopic findings associated with the tremors. Since tremors did not occur in controls, the tremors in the high-dose females were considered compound-related.

In the males, tremors were seen in three moribund animals (1 control and 2 high-dose) 1 day prior to sacrifice in weeks 50, 61, and 68. Since these animals were moribund, the tremors were considered secondary and unrelated to treatment.

"Other toxic signs noted during the study included alopecia, swollen ears, lethargy, abdominal swelling, and pale extremities. These signs occurred at comparable incidences in control and treated groups."

Two mice escaped from the study; male mouse 0216 of the low-dose group and female mouse 1763 of the mid-dose.
The most common causes of death were amyloidosis and lymphoma. The tables below show the distribution of mortality for male and female mice.

### Males

<table>
<thead>
<tr>
<th></th>
<th>Control I</th>
<th>Control II</th>
<th>Low</th>
<th>Mid</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Starting</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
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<tr>
<td>No. Escaped</td>
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<td>1</td>
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<tr>
<td>No. Found Dead</td>
<td>15</td>
<td>12</td>
<td>13</td>
<td>12</td>
<td>15</td>
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<tr>
<td>No. Sacrificed</td>
<td>10</td>
<td>13</td>
<td>11</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>No. Terminal Kill</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>26</td>
<td>16</td>
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<td>Totals</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
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</tr>
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</table>

### Females

<table>
<thead>
<tr>
<th></th>
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<th>Control II</th>
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<th>Mid</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Starting</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
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<tr>
<td>No. Found Dead</td>
<td>9</td>
<td>6</td>
<td>10</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>No. Sacrificed</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>No. Terminal Kill</td>
<td>36</td>
<td>34</td>
<td>30</td>
<td>29</td>
<td>34</td>
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<tr>
<td>Totals</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Due to increased mortality in high-dose male mice, dosing of this sex and group only was discontinued beginning in week 90 when survival had reached 40 percent (20 survivors/50 started).

Sacrifice of survivors in all groups occurred at terminal kill at week 94. The increased mortality in the high-dose male group was statistically significant (p < 0.05) in comparison to male controls and is considered to be possibly compound-related (see attached graph). Mortality in females was comparable in all control and test groups.

Body weight gain was statistically significantly decreased (-22%) in high-dose females in comparison to controls at termination of the study. Similar decreases were also consistently observed throughout the study. This decreased body weight gain was considered compound-related. Body weight gains in the mid- and low-dose female mice were comparable to controls. In male mice, the mid- and high-dose group body weight gains were slightly decreased (-7%) in comparison to control group I, but were increased in comparison to control group II.
* Statistically significant difference (P=0.012) for 8.0 mg/Kg/day group when compared to combined controls
The following tables show the body weight gain (difference in average body weight [grams] between pretest period and weight obtained in week 94) of male and female mice.

<table>
<thead>
<tr>
<th></th>
<th>Control I</th>
<th>Control II</th>
<th>Low</th>
<th>Mid</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males (Body Weight Gain, g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.8</td>
<td>12.7</td>
<td>14.9</td>
<td>13.2</td>
<td>13.1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Control I</th>
<th>Control II</th>
<th>Low</th>
<th>Mid</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females (Body Weight Gain, g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.9</td>
<td>18.3</td>
<td>18.4</td>
<td>17.5</td>
<td>14.1*</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05.

The decreased body weight gains in mid- and high-dose male mice were not considered compound-related.

Food consumption in males was comparable between control and treated groups. The total mean food consumption (g/kg bwt) in males was 124.2, 119.0, 118.4, 121.3, and 125.5 in control I, control II, low-, mid-, and high-dose groups, respectively. In female mice, food consumption showed a slightly dose-related increase (2 to 8%) in treated groups in comparison to both control groups. The total mean food consumption (g/kg bwt) was 133.4, 133.2, 136.2, 142.28, and 144.7 for control I, control II, low-, mid-, and high-dose groups, respectively.

Compound intake averaged 2.0, 4.1, and 8.1 for male mice and 2.1, 4.2, and 8.3 for female mice of the low-, mid-, and high-dose groups, respectively.

Feed efficiency was comparable between controls and treated male mice. Feed efficiency was decreased 20 percent in high-dose female mice in comparison to controls. This decrease in feed efficiency in high-dose females correlates with the 22 percent decrease in body weight gain observed in this group.

Ophthalmoscopic examination of males and females at weeks 51 (or 53) and week 91 did not reveal any compound-related ocular effects.

There were no compound-related effects in average hematology values for male mice at weeks 25, 52, and 94.

At week 52, the average leukocyte value for mid-dose male mice was 12.6 (1000/mm³) as compared to 5.3, 3.5, 3.4, and 3.1 for the control I, control II, low-, and high-dose groups,
respectively. The finding was not dose-related and did not occur at week 94. The increased average value was due to an anemic mid-dose male mouse (83-0658) which had a fortyfold increase in total leukocytes due to leukemia. Other values of male mice in the mid-dose group were comparable to controls at week 52.

At week 94, the average leukocyte value for low-dose male mice was 9.6 (1000/mm$^3$) as compared to 4.3, 4.5, 3.8, and 5.2 for control I, control II, mid-, and high-dose groups, respectively. This finding was not dose-related and was due to male mouse 83-0214, which had a thirtyfold increase in total WBC counts due to leukemia [141.9 leukocytes (1000/mm$^3$)].

There were no compound-related effects in average hematology values for female mice at weeks 25, 52, and 94.

At week 52, the average value for nonsegmented neutrophils for control I female mice was 367 (cells /mm$^3$) as compared to 0, 0, 5, and 0 for control II, low-, mid-, and high-dose groups, respectively. This finding was due to female mouse 83-1919, which had 4032 nonsegmented neutrophils/mm$^3$ due to leukemia.

There were no compound-related effects in average serum biochemical values for male mice at weeks 25, 52, and 94. At week 52, the average AST value for male mice at the mid-dose level was elevated in comparison to controls and other treated groups. This finding was considered unrelated to treatment since it was not dose-related.

There were no compound-related effects in average serum biochemical values for female mice at weeks 25, 52, and 94.

There were no compound-related effects in gross lesions in male and female treated mice in comparison to controls. Two of the most commonly found gross lesions were discolored foci of the liver and pale and granular areas of the kidneys. The incidences in treated males and females were comparable to their respective controls. The incidence of whole body autolysis, listed under gross lesions, was 4, 5, 4, 6, and 3 in males and 11, 9, 7, 7, and 7 in females of the control I, control II, low-, mid-, and high-dose groups, respectively. Evaluation of individual gross and microscopic data indicated that histopathological evaluation of tissues of these animals was performed.

Absolute organ weights, as well as relative organ weights (both body and brain), did not demonstrate any compound-related effects in male or female mice. Statistical analyses of the increased mean spleen and adrenal weights in high-dose males did not reveal any significance.

Evaluation of individual male organ weight data showed that the liver weight as percent of body weight was 14.30 percent for
control male 83-0076, 13.19 percent for 2-mg/kg male 83-0226, and 12.37 percent for 8-mg/kg male 83-0406. Each of these three male animals had a hepatocellular adenoma or carcinoma at week 94.

In female mice, the ovarian weight as percent of body weight was 2.85 percent for control female 83-1531, 1.07 percent for 2-mg/kg female 83-1621, and 2.35 percent for 4 mg/kg female 83-1789. Animal 83-1789 had an ovarian cyst adenoma, animal 83-1621 had a uterus polyp, and animal 83-1531 (control) had no uterine or ovarian lesion.

There was good correlation between gross masses and lesions and corresponding histological lesions. The registrant provided individual pathology sheets for each animal which included ante-mortem observations and antemortem tissue masses, and a correlation between gross masses and lesions and corresponding microscopic findings.

The most common histological lesion was amyloidosis in both sexes. The occurrence of amyloidosis was not compound-related.

There may be a compound-related increase in extramedullary hematopoiesis of the spleen in the high-dosage level male mice. The incidence of this lesion among male groups is shown below:

<table>
<thead>
<tr>
<th>Dose mg/kg/day</th>
<th>0</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Examined</td>
<td>50</td>
<td>49</td>
<td>49</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Extramedullary Hematopoiesis</td>
<td>5</td>
<td>4</td>
<td>8</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>(Percent)</td>
<td>10%</td>
<td>8%</td>
<td>16%</td>
<td>16%</td>
<td>30%</td>
</tr>
<tr>
<td>Grades of Lesion</td>
<td>1,2,2, 2,2,2, 2,3,2, 2,3,2, 2,2,2, 2,2,2, 2,3,3, 2,1,2, 2,2,3</td>
<td></td>
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</tbody>
</table>

The incidence of extramedullary hematopoiesis in the spleen of males was increased three-fold above the control level at 8 mg/kg/day. Also at 8 mg/kg/day, there was a slightly increased incidence of myeloid hyperplasia of the bone marrow in males, which although not statistically significant and not directly
attributable to the test material (see bottom of this page), nevertheless tended to support the likelihood that the increased incidence of extramedullary hematopoiesis in the spleen of males observed at the high dosage level may be related to the test material. At lower dosage levels, although extramedullary hematopoiesis of the spleen was increased somewhat above the control level, there was no supportive evidence in males of increased myeloid hyperplasia in the bone marrow or of additional extramedullary hematopoiesis in any other organ, such as the liver or lymph nodes. Furthermore, analysis of the hematological data in males did not indicate any effect at any dosage level that might suggest possible stimulation of a compensatory response in blood cell forming organs. The NOEL for extramedullary hematopoiesis in the spleen of male mice in this study is considered to be 4 mg/kg/day.

Extramedullary hematopoiesis in female mice did not occur in a compound-related manner.

In male mice, there was a substantially increased incidence (22%) as compared to the control level (4-6%) of dermatitis of the skin at the high dosage level of 8 mg/kg/day. The incidences of this lesion in the male mice in this study are presented below:

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>0</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Examined</td>
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<td>50</td>
<td>49</td>
<td>50</td>
<td>50</td>
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<tr>
<td>Dermatitis</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>(Percent)</td>
<td>4%</td>
<td>6%</td>
<td>6%</td>
<td>12%</td>
<td>22%</td>
</tr>
<tr>
<td>Grades of Lesion</td>
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<td>3,4,2</td>
<td>1,4,3</td>
<td>4,4,3,3</td>
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<td>2,3,2</td>
<td></td>
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<td>3,2,4,</td>
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<td></td>
<td></td>
<td>4,3,3,3</td>
</tr>
</tbody>
</table>

The lesion in the high dose males may be related to the test material. At the mid dosage level of 4 mg/kg/day, there was also a slightly increased incidence of dermatitis of the skin in males (12%), but the potential relationship of this lesion to the test material at this dosage level is much more equivocal. Since there were no other data supporting an effect on the skin in this study in males or in females, the NOEL for dermatitis in males is considered to be 4 mg/kg/day.

A third lesion occurring in males at slightly increased incidences in the high-dose treated group was myeloid hyperplasia of the bone marrow. The incidences were 5, 9, 4, 4, and 11 for the 0, 0, 2, 4, and 8 mg/kg/day groups, respectively. The grades of the lesion were comparable among groups. This lesion was not regarded as compound-related, except possibly at the HDT.
There were no compound-related neoplastic lesions in male and female mice in the study. The most frequently occurring tumors in male mice were liver and lung adenomas as shown below:

<table>
<thead>
<tr>
<th>Males</th>
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<td>7</td>
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<tr>
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</tr>
</tbody>
</table>

*HC = Hepatocellular

In females, the most frequently occurring tumors were lung adenomas and malignant lymphomas.

<table>
<thead>
<tr>
<th>Females</th>
<th>Dose mg/kg/day</th>
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<th>2</th>
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<tbody>
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<tr>
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<td>1</td>
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<tr>
<td>Malignant lymphoma (Primary site undetermined)</td>
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<td>18</td>
<td>11</td>
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</table>

Conclusion:

The doses for the chronic study were selected on the basis of a range-finding study (TT#82-082-0, -1, -2). Doses in the range-finding study were dietary levels of 2, 5, 10, 20, 40, and 60 ppm.

In this 12-week range-finding study, although there were no deaths or treatment-related toxic signs at any dose, there were moderate decreases in body weight gains in males and females (25 and 32 percent, respectively) at the highest-dose level of 60 ppm. The intake of abamectin at this level was 11.8 and 13.1 mg/kg/day for males and females, respectively. Based on the
results of this range-finding study and the results (see below) of the chronic feeding study in mice, the HDT of 8 mg/kg/day in the chronic study is considered an MTD.

The oncogenic potential for abamectin in CD-1 mice is negative up to 8 mg/kg/day (HDT). The high dose (8 mg/kg/day) is also considered the MTD, since in high-dose males there was possibly increased mortality, and in high-dose females there were tremors and body weight loss (~22%).

The systemic NOEL for the study is 4 mg/kg/day (the mid dose). The LEL is 8 mg/kg/day (the high dose).

At the LEL, there was an increased incidence of skin dermatitis in male mice, an increased incidence of extramedullary hematopoiesis in the spleen of males, increased mortality in males, and tremors and body weight loss in females.

Classification: Core-Minimum
DATA EVALUATION REPORT

Study Type: 83-5 - Combined Chronic Toxicity/Oncogenicity - Rat

TOX Chem No.: 63AB

MRID Nos.: 400696-01,
Vol. I-II; 405178-01,
Vol. 1 and 2; 403755-11

Accession No.: N/A

Test Material: Abamectin

Synonyms: Avermectin B1, MK-0936

Study Number(s): TT#82-099-0

Sponsor: Merck and Company

Testing Facility: Merck Sharp and Dohme Research Labs

Title of Report: One-Hundred and Five-Week Dietary Carcinogenicity and Toxicity Study in Rats.

Author: L. Gordon

Report Issued: August 27, 1985

Conclusions:

The oncogenic potential was negative up to 2.0 mg/kg/day (HDT). The high-dose is also considered to be the MTD. The systemic no-observed-effect level is 1.5 mg/kg/day, the mid-dose. The lowest-effect level is 2.0 mg/kg/day and the effects were treatment-induced tremors in both sexes. An additional female in the mid-dose group also had tremors, but this animal consumed about 2.5 mg/kg/day of abamectin during this period (based on actual food consumption and body weight data). There were no compound-related pathological lesions to correlate with the tremors.

Classification: Core-Minimum

Special Review Criteria (40 CFR 154.7): N/A
Review:

- One-Hundred-and-Five-Week Dietary Carcinogenicity and Toxicity Study in Rats with MK-0936; Final Report; Merck Sharp & Dohme Research Labs.; TT#82-099-0; August 27, 1985 by L. Gordon (MRID No. 400696-01, Vol. 1-11; 405178-01, Vol. 1 and 2; 403755-11).

Test Material - MK-0936, abamectin, Lot No. L-676, 863-00054; purity: 91.1 percent.

Animals - Outbred albino rats, CrI:CD (SD) BR, approximately 5 weeks old at initiation, were used in the study. The rats were obtained from Charles River Laboratories, Wilmington, MA. At initiation, males weighed 115 to 191 gm, and females weighed 93 to 154 gm.

The rats were housed in individual cages and were fed Purina Certified Rodent Chow and water ad libitum. Food was withheld approximately 17 hours prior to bleedings and interim and final necropsies.

Methods:

Randomized groups of 65 male and 65 female Sprague-Dawley rats were fed test diets containing 0 (control I), 0 (control II), 0.75, 1.5, and 2.0 mg/kg/day of abamectin. The levels of abamectin in the feed were adjusted and mixed biweekly to attain the targeted dose levels. The vehicle used was acetone which was subsequently dried off. Doses were selected on the basis of results of a range-finding study (TT#82-075-0, -1).

In the 8-week range finding study, the dietary doses were 5, 10, 15, 20, 40, and 60 ppm. Tremors and death were observed in the 40 and 60 ppm groups, as were dose-related decreases in body weight. The tremors began on day 2 and on day 5 the 60 ppm group was terminated. Tremors persisted in the 40 ppm group. Ten animals of the 40 ppm group died by days 3 to 5. The body weight decreases ranged from 5 to 15 percent in the 15 to 40 ppm groups. The intake of abamectin at 40 ppm, ranged from 4.1 to 5.8 mg/kg/day for both sexes. Based on the results of this range-finding study and the results (see below) of the chronic rat feeding study, the HDT of 2.0 mg/kg/day in the chronic rat study is considered the MTD.

Since no effects attributable to test material were observed after 10 weeks, the high-dosage level was increased to 2.5 mg/kg/day to establish a maximum tolerated dose (MTD). However, due to the appearance of severe signs of CNS toxicity (tremors and death) following the increase in dosage, the dose level for the high-dose group was decreased back to 2.0 mg/kg/day in week 13 for the remainder of the study.
Fifteen animals/sex/group were selected for the 53-week interim sacrifice prior to study initiation.

The total number of days on test was 729 to 733 for males and 729 to 731 for females.

Test diets were prepared every 2 weeks and were used up within 4 weeks. Stability of test material in diets was determined to be satisfactory over a period of 4 weeks at room temperature. Homogeneity of samples from the top, middle, and bottom of each batch was acceptable. Concentrations of test material were determined in duplicate samples from each biweekly dietary batch. Test material consumed by the rats (on a mg/kg/day basis) was generally within 10 percent of targeted levels.

All animals were observed daily for toxic signs and were given detailed physical examinations weekly.

Body weights were recorded at pretest and weekly for all animals throughout the study. Food consumption was measured weekly over a 6-day interval for 12 animals/sex/group.

Ophthalmic examinations were done on all animals at pretest; high-dose and control animals only in weeks 26, 52 (males), or 53 (females), 76 and 102 (males), or 103 (females).

Hematologic examinations were conducted on 10 animals/sex/group at weeks 12, 25, 38, 51, 78, and 105. Beginning in week 89, all early sacrifice animals were bled for hematological examination.

The following hematological parameters were measured - Hg, RBC, WBC, differential WBC, MCV, clotting time, platelet count, erythrocyte sedimentation rate, hematocrit, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

The following biochemical parameters were measured - Glucose, BUN, albumin, total protein, creatinine, SGPT, SGOT, bilirubin (direct and total), SAP, cholesterol, triglycerides, Na, K, Ca, and Cl.

Urinalyses were conducted on 10 animals/sex/group at weeks 12, 25, 38, 40, 51, 78, and 103. Urine was collected overnight from rats placed in metabolism cages. Animals did not have access to feed during the urine collection interval. The parameters measured were microscopic examination of sediment, glucose, protein, bilirubin, and occult blood.

For all early deaths or early sacrifices of moribund animals, all rats had a complete necropsy examination. Terminal body weights but not organ weights were recorded. All tissues,
except testes from early sacrifice males which were fixed in Bouin's fixative, were fixed in neutral buffered formalin.

All remaining rats at the time of scheduled sacrifice were killed by exsanguination after ether anesthesia. All rats had a complete necropsy examination. All tissues were fixed in neutral buffered formalin except for the testes, which were fixed in Bouin's fixative.

Terminal body weights and the following organ weights were recorded: heart, liver, brain, adrenals, kidneys, spleen, and testes. In addition, the following organ weights were recorded at the final sacrifice (at 105 weeks) salivary glands, lungs, thyroid, pituitary, prostate, seminal vesicles, ovaries, and uterus.

Histopathology - Hematoxylin and eosin-stained sections of the left eye (including optic nerve), heart, liver, kidneys, spleen, mesenteric and cervical lymph nodes, pancreas, stomach, small and large intestines, pituitary, adrenals, urinary bladder, thyroid and parathyroid (if present in the section), lung, thymus, salivary gland, bone including joint and bone marrow, brain (3 levels), spinal cord (2 levels), sciatic nerve, testes including epididymides, prostate or ovaries, uterus, skeletal muscle, skin and mammary gland (if present in the skin section) from: (1) the 53-week group: 15 males and 15 females from the control I group and 15 males and 15 females from the highest dosage level and all early death rats in the control II, middle-, and low-dose groups, and (2) all rats in all groups assigned to the 105-week part of the study. Gross lesions were examined from rats in all dosage groups. Statistical analyses of the data were performed.

Results:

Compound-related whole body tremors and overall unthrifty appearance were observed in a few rats in the 2.0 mg/kg/day group.

This effect (tremors) appeared in animals #82-7741F, 82-7742M, and 82-7692M in week 12, which correlated with the increase in dosage from 2.0 to 2.5 mg/kg/day in weeks 11 and 12. The tremors persisted intermittently until the time of sacrifice, despite the reduction in the high-dose level back to 2.0 mg/kg/day in week 13. Additional instances of tremors were observed in animals #82-7691F, 82-7667F, and 82-7713F, all of the high-dose group, beginning in weeks 9, 98, and 65, respectively. The tremors persisted for several weeks until the animals were sacrificed or found dead.

In the mid-dose group, animal #82-7491F developed tremors in week 62 which persisted until the animal was found dead at week 100. Analysis of the food consumption and body weight data
for this animal indicated that this female generally consumed about 2.5 mg/kg/day of abamectin during the interval the tremors were observed. Therefore, tremors were not considered to be an effect of the test material at a dose level of 1.5 mg/kg/day.

The following summary shows the time period between the appearance of tremors and the death of the rats:

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Dose</th>
<th>Week of Tremors</th>
<th>Week of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>7691F</td>
<td>High</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>7741F</td>
<td>High</td>
<td>12</td>
<td>53</td>
</tr>
<tr>
<td>7742M</td>
<td>High</td>
<td>12</td>
<td>98</td>
</tr>
<tr>
<td>7692M</td>
<td>High</td>
<td>12</td>
<td>42</td>
</tr>
<tr>
<td>7667F</td>
<td>High</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>7713F</td>
<td>High</td>
<td>65</td>
<td>69</td>
</tr>
<tr>
<td>7491F</td>
<td>Mid</td>
<td>62</td>
<td>100</td>
</tr>
</tbody>
</table>

Additionally, there were no gross or histopathological lesions in examined nervous tissue or muscle of the rats which could be associated with the tremors. The testing laboratory noted that tremors had also been observed in other species, also without pathological lesions.

The tremors observed in the high-dose group (2.0 mg/kg/day) were considered compound-related. The NOEL for tremors in this study was 1.5 mg/kg/day.

No compound-related effects on survival were noted. Although survival in female control group II was higher than in the treated groups, the survival of females in control group I and the treated groups was similar (see table below).

In male rats, although survival was slightly lower in the high-dose group, the group mean survival times were comparable in the controls and treated groups. The slight decrease in survival in the high-dose group was not considered compound-related.

The table below, as presented in the report, shows the summary of survival in the study.

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>Control I</th>
<th>Control II</th>
<th>0.75</th>
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<tr>
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</tr>
<tr>
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<td>15 14</td>
<td>14 15</td>
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<td>No. Found Dead</td>
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<td>3 11</td>
<td>11 17</td>
<td>12 8</td>
<td>12 13</td>
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<tr>
<td>No. Sacrificed</td>
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<td>21 15</td>
<td>23 14</td>
<td>21 13</td>
<td>20 21</td>
</tr>
<tr>
<td>No. Survivors</td>
<td>19 24</td>
<td>26 25</td>
<td>17 19</td>
<td>17 30</td>
<td>18 17</td>
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<tr>
<td>Group Survival</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Weeks) Mean</td>
<td>82.1 83.0</td>
<td>83.3 84.8</td>
<td>81.0 82.6</td>
<td>80.5 84.9</td>
<td>80.4 79.4</td>
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</tbody>
</table>
Body weight was increased for both male and female treated rats in all treated groups in comparison to controls.

This effect (increased body weight) has been observed in other studies with abamectin and is considered to be a compound-related effect. Graphs presenting the body weight data in this study are attached.

For the first 76 weeks of the study, body weight of treated female rats exceeded those of the control. The greatest increases occurred at week 60 and were 23, 10, and 9 percent for the low-, mid-, and high-dose groups, respectively, in comparison to the combined controls. Beginning at week 77, the control groups exceeded the treated groups in weight gain, so that at week 104, the average body weights of female rats were 507, 550, 532, 510, and 531 g for the control I, control II, low-, mid-, and high-dose levels, respectively. The overall weight gains for the entire study were comparable for control and treated female rats. These gains were 388, 429, 413, 390, and 409 g for the control I, control II, low-, mid-, and high-dose groups, respectively.

In male rats, the body weight of treated rats exceeded the controls during the entire study. At week 104, the average body weights of male rats were 762, 768, 893, 825, and 797 in control I, control II, low-, mid-, and high-dose groups, respectively. These increases were 21, 9 and 6 percent for the low-, mid-, and high-dose groups, respectively, in comparison to the combined controls. The overall weight gains for the entire study were 610, 614, 742, 668, and 647 g for control I, control II, low-, mid-, and high-dose groups, respectively.

Although these increases in body weight for the male and female rats at all treatment levels are considered to be a compound-related effect, they are not considered to be an adverse toxicological effect and will not be used for the purpose of determining the NOEL for this study or for determining an ADI for abamectin.

Food consumption (gm/day) was comparable between control and treated groups of both sexes during the study. The total mean food consumption for female rats was 22.8, 22.6, 23.4, 23.2, and 23.6 gm/day for control I, control II, low-, mid-, and high-dose groups, respectively. For male rats, the total mean food consumption was 28.0, 27.7, 29.4, 29.2, and 29.0 gm/day for the control I, control II, low-, mid-, and high-dose groups, respectively.

Food consumption, expressed as gm/kg bwt, was comparable between control and treated rats of both sexes during the study.
FIGURE 1: 105-WEEK DIETARY CARCINOGENICITY AND TOXICITY STUDY IN RATS WITH A 53-WEEK INTERIM NECROPSY.

AVERAGE BODY WEIGHTS (GRAMS) FOR FEMALE RATS.

- F-CONTROL
- F-CONTROL II
- F-8 1/25 MG/KG/DAY
- F-1 5 MG/KG/DAY
- F-2 0 MG/KG/DAY

Averages for treated females are significantly different (P<.05) when compared to combined control group.
Figure 9: 105-Week Dietary Carcinogenicity and Toxicity Study in Rats with a 53-Week Intermittent Necropsy.

Average Body Weights (Grams) for Male Rats

- M-Control I
- M-Control II
- M 0.75 mg/kg/day
- M 1.5 mg/kg/day
- M 2.0 mg/kg/day

*Statistically significant (P<0.05) when compared to combined control values.
Feed efficiency (body weight gain/amount of food consumed) was slightly increased for low-dose females during the first half of the study in comparison to controls and other treated groups. Thereafter, the feed efficiency declined in the low-dose group to levels comparable to all female groups. The total mean percent of feed efficiency for female rats for the entire study was 2.7, 2.4, 2.3, 2.2, and 2.3 percent for the control I, control II, low-, mid-, and high-dose groups, respectively.

Feed efficiency for male rats was comparable between control and treated groups during the study. The total mean feed efficiency for male rats was 3.0, 3.0, 2.8, 3.0, and 2.7 percent for the control I, control II, low-, mid-, and high-dose levels, respectively.

Average consumption values of MK-0936 for female rats varied during the study between 0.5 to 0.9, 1.2 to 1.7, and 1.6 to 2.5 mg/kg/day for low-, mid-, and high-dose groups, respectively. The mean intake for the entire study was 0.8, 1.5, and 2.1 mg/kg/day for the female rats in low-, mid-, and high-dose groups, respectively.

In male rats, average consumption values for MK-0936 varied during the study between 0.6 to 0.9, 1.4 to 1.7, and 1.8 to 2.8 mg/kg/day for low-, mid-, and high-dose groups, respectively. The mean intake for the entire study in male rats was 0.7, 1.5, and 2.0 for low-, mid-, and high-dose groups, respectively.

Ophthalmological examinations of controls and high-dose male and female rats in weeks 26, 52 (males), or 53 (females), 76 and 102 (males), or 103 (females) did not reveal any compound-related lesions. The most commonly observed lesions which occurred at comparable incidences in control and treated rats included conjunctivitis, corneal scar, anterior and posterior synechiae of the iris, posterior subcapsular cataracts, focal retinopathy, and retinal degeneration.

There were no compound-related effects in hematological parameters measured at weeks 12, 25, 38, 51, 78, and 105 weeks in male and female rats. Average values for hematologic parameters in control and treated females were within normal ranges and there were no significant dose-related decreases or increases with time. Similarly, in male rats, most average values for hematological parameters for control and treated rats were within normal ranges and there were no significant dose-related decreases or increases with time. A slight exception to this finding was the average absolute value of 466 nonsegmented neutrophils/mm³ for the males of the 1.5 mg/kg/day group at week 78. Usually, individual values varied from 0 to 400 for nonsegmented neutrophils in control and treated male rats during the study. However, male rat #82-7574 of the 1.5 mg/kg/day group at week 78 had a value
of 4116 cells/mm³. This rat had metastatic granulocytic leukemia
(primary site undetermined) and was killed moribund in week 92.
The tumor was not considered compound-related. Additionally, the
increase in average nonsegmented neutrophils was not dose-related
and did not occur at week 105 in the remaining rats.

There were no treatment-related effects in serum biochemical
parameters measured at weeks 12, 25, 38, 51, 78, and 105 in male
and female rats. However, average BUN and creatinine values were
increased for low- and high-dose females in week 78, low-dose
females in week 105, and high-dose males in week 105. Evaluation
of individual animal data showed that in females at week 78,
animals #82-7457 (low dose), #82-7571 (mid-dose), and #82-7705
and #82-7711 (high dose) had fourto elevenfold increases in BUN
and creatinine elevenfold as compared to controls (58 to 145 mg/100
mL for BUN and 2.2 to 4.4 mg/100 mL for creatinine as compared
to normal values for BUN of 10 to 20 mg/100 mL and creatinine of
0.6 to 1.0 mg/100 mL). All these female animals had chronic
nephritis (severe), which is a common finding in aged rats.

Additionally, the increases in average BUN and creatinine
values in low-dose females and high-dose males at week 105 were
due to two females and one male. Females #82-7407 and #82-7409
of the low dose had BUN values of 65 and 63 mg/100 mL and creati-
nine values of 2.0 and 4.0 mg/100 mL, respectively. High-dose
male animal #82-7632 had a BUN value of 370 mg/100 mL and a
creatine value of 8.9 mg/100 mL. Histopathological examination
of these animals showed that the low-dose females had marked
chronic nephritis and the high-dose male had moderate
pyelonephritis.

At week 78, average glucose, protein, cholesterol, and
triglyceride values of low-dose females were elevated. These
increases were due to female animal #82-7441, which had a glucose
value of 645 mg/100 mL, a protein value of 19.40 gm/100 mL, a
triglyceride value of 9400 mg/100 mL, and a cholesterol value of
695 mg/100 mL. The blood chemistries were repeated within 7 days
for this animal and the values were still elevated. Animal
#82-7441 was an unscheduled death at week 92 and had a partially
necrotic stomach and liver and a mammary fibroadenoma.

Urinalyses did not reveal any compound-related effects in
male and female rats during the study.

There were no compound-related effects in organ weights,
gross necropsy findings, or histopathology in male or female
rats.

At the 53-week interim sacrifice, focal necrosis of the
liver was observed in females at incidences of 1, 0, 0, 3 and
in males at 1, 1, 1, 0 in the control, low-, mid-, and high-dose
groups, respectively. The grade of the lesion was very slight or
slight in all cases and was not considered compound-related. No indication of compound-related focal hepatocyte necrosis was evident in rats of the 2-year main study.

There were no compound-related effects in organ weights or gross lesions in males and females of the main 2-year study.

There were no compound-related nonneoplastic lesions. Focal myocardial fibrosis was increased in treated females in comparison to controls. The incidences of this lesion were 5, 4, 8, 8, and 11 in control I, control II, low-, mid-, and high-dose females. The grades of the lesion were very slight to slight and were comparable among groups. Additionally, the occurrence of this lesion was primarily in the early deaths and early sacrificed animals. The earliest occurrence of the lesion was recorded at days 420, 465, 310, 442, and 449 in control I, control II, low-, mid-, and high-dose groups. There was no relationship to treatment.

There were no compound-related benign or malignant neoplasms in male or female rats. Additionally, there were no decreases in latency.

The most common tumors in male rats were in the pituitary, liver, pancreas, and thyroid.

The type and incidences of the commonly occurring tumors in male rats are shown below.

<table>
<thead>
<tr>
<th>Males</th>
<th>mg/kg/day</th>
<th>0</th>
<th>0.75</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Examined</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>HC* Adenoma</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>HC* Carcinoma</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Thyroid C-Cell Adenoma</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Pancreas, Islet - Adenoma</td>
<td>3</td>
<td>8</td>
<td>3</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Pituitary - Adenoma</td>
<td>17</td>
<td>21</td>
<td>18</td>
<td>24</td>
<td>18</td>
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<tr>
<td>Pituitary - Adenocarcinoma</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

*Hepatocellular
The most commonly occurring tumors in female rats were in the mammary gland and pituitary. The types and incidences of these tumors are shown below.

<table>
<thead>
<tr>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/kg/day</td>
</tr>
<tr>
<td>No. Examined</td>
</tr>
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**Mammary Gland**

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<tr>
<td>Adenocarcinoma</td>
<td>8</td>
<td>11</td>
<td>9</td>
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</tr>
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<td>Adenoma</td>
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<td>8</td>
<td>7</td>
<td>5</td>
</tr>
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</table>

**Pituitary**

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<th>37</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>15</td>
<td>10</td>
<td>7</td>
<td>5</td>
<td>10</td>
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</tbody>
</table>

**Conclusion:**

The oncogenic potential is negative. The systemic NOEL is 1.5 mg/kg/day, the mid dose. The LEL is 2.0 mg/kg/day, the high dose. At this level, there were four females and two males with treatment-induced tremors. An additional female in the mid-dose group also had tremors, but this animal consumed about 2.5 mg/kg/day of abamectin during this period (based on actual food consumption and body weight data). There were no compound-related pathological lesions to correlate with the tremors. The high dose is also the MTD for both sexes, since tremors were observed in both sexes.

**Classification:** Core-Minimum