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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Avermectin (Also Called Abamectin); PP #1G03930; Extension of Temporary Tolerances on Apples; Resubmission; Merck & Co.

Tox.Chem No.: 63AB
MRID No.: 426123-02
DP Barcode No.: D186636, D186629
Submission No.: S433378, S433370

TO: Adam Heyward, PM Team #13
Insecticde-Rodenticide Branch
Registration Division (H7505C)

FROM: William Dykstra, Ph.D., Toxicologist
Review Section I
Toxicology Branch I
Health Effects Division (H7509C)
William Dykstra 5/11/93

THRU: Roger Gardner, Section Head, Toxicologist
Review Section I
Toxicology Branch I
Health Effects Division (H7509C)
Roger Gardner 5-11-93 5/14/93

ACTION REQUESTED: The Registrant, Merck & Co., has submitted additional data in support of the request for temporary tolerances for abamectin and its delta -8,9 - metabolite on apples for fresh market only. The new studies consist of two subchronic oral (gavage) monkey studies and additional published and unpublished information on the comparative metabolism of ivermectin, an analog of abamectin, in humans and rats.

CONCLUSIONS: The extension of the temporary tolerances can be toxicologically supported based on the new studies and additional information submitted by the Registrant.

The new information and studies support the TB-I position that MOE's ≥ 100 for infants and children are considered adequate for tolerances for avermectin and its delta-8,9-isomer as determined in the DRES analyses.

Results from the additional studies indicated NOEL's of ≥ 0.1 and 1.2 mg/kg/day for infant and immature Rhesus monkies, respectively. The NOEL for infant monkies is similar to that for infant rats (0.12 mg/kg/day).

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I. Background

In an August 18, 1992 memorandum from W. Dykstra to G. Larocca regarding the original extension request, it was stated that the severity of effects of abamectin on pup survival in the reproduction study indicated that the margin of exposure (MOE) should be substantially greater than 100. Following a meeting with the Registrant on September 18, 1992, it was stated by R. Gardner in a memorandum dated Septemmber 24, 1992 to A. Heyward, that the new toxicology information may, after critical review, be sufficient to reduce the level of concern such that MOE's greater than 100 would probably be considered adequate.

A. Registrant's Comments

The Registrant indicated that the Agency was reevaluating the risks associated with exposure of children on the basis of results from the rat multigeneration reproduction study with avermectin (NOEL = 0.12 mg/kg/day). The Registrant further noted that, although the reproduction study would conventionally be used in assessment of chronic exposures, the Agency believed the study is appropriate for acute MOE calculations because:

(1) it is the only study where infant animals are directly exposed to the chemical,

(2) the cross-fostering component of a second study with ivermectin indicated that exposure was through the mothers' milk rather than transplacental, and

(3) the time period in which effects were noted represented a subacute exposure.

Merck agreed with the Agency that any assessment of avermectin should also include data on ivermectin. The two chemicals have nearly identical structures, pharmacology and toxicology which was recognized by the Agency in its assessment of potential avermectin risks in children.

Other points offered by the Registrant for the Agency's consideration in a risk assessment of the avermectin family of chemicals included:

(1) the blood-brain barrier is completed postnatally in rats, which is not the case in humans (Betz and Goidstein, 1981; Bohr and Mollgard, 1974; and Saunders, 1977);

(2) at the time of parturition, there is a greater use of fats in the rat than there is in humans (Amano, 1967; Snow *et al*, 1964; and Chiu *et al*, 1986) which, Merck suggests, would result in a release of ivermectin from adipose tissue into milk of nursing dams; and

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(3) the results from metabolism studies (Lankas and Gordon, 1989) with chronically treated rats allowed to bear and nurse their offspring indicated high concentrations of ivermectin in the milk compared with blood concentrations which could have caused the pup mortality observed in reproduction studies with avermectin and ivermectin.

Several published reports were submitted to support these points. In support of the first point, the Registrant summarized a study with ivermectin (also reviewed in Lankes and Gordon, 1989) as follows:

> In a metabolism study (Report #TT 79-711-0, not submitted for review)...female rats were administered tritium labelled drug (ivermectin) at a dosage of 2.5 mg/kg/day continuously for 61 days prior to mating and during mating, gestation, and lactation. Plasma and milk samples from dams and plasma and tissue samples from offspring were analyzed for total radioactivity on Days 1 (plasma and tissue only), 4, 6, and 10 postpartum.
>
> The increase in maternal plasma radioactivity at parturition relative to days 4 to 10 postpartum is likely due to increased utilization of fat at parturition in the rat resulting in the release of ivermectin from adipose tissue. The concentrations of ivermectin in milk were consistently 3 to 4-fold higher than those obtained from maternal plasma samples on comparable days postpartum. Plasma drug levels in F_1 offspring were relatively low on Day 1 postpartum but increased rapidly from Days 4 to 10 such that they equaled or exceeded the values in the dams...brain concentrations of ivermectin residues in offspring on Day 6 postpartum were approximately 10-fold greater than the maternal brain concentrations...

It was also noted that the plasma levels in the pups at day 10 were 40 times greater than the therapeutic levels achieved in humans.

The Registrant further indicated that ivermectin is used in the treatment of the parasitic disease known as river blindness that is found in human populations in tropical regions of the world. The therapeutic regimin involves treating a patient one to two times a year with 150-200 micrograms (mcg) ivermectin per kg body weight. Because mothers are likely to receive this treatment, and in common practice they may breast feed their infants, the secretion of ivermectin with human milk was evaluated. This study was discussed by the Registrant as follows:

> A single oral dose of 12 mg of ivermectin was administered to 12 lactating women who were not breast feeding and breast milk and blood was collected at 1, 4, and 12 hours post-treatment and daily thereafter for 14 days for milk and 3 days for blood. The peak mean concentration of ivermectin in breast milk occurred on day 1 at 4 hours post-treatment and was 7.6 ng/ml (range 1.0 to 13.0 ng/ml). The mean peak concentration of ivermectin in plasma occurred on day 1 at 4 hours post-treatment and was 23 ng/ml with a range of 5 to 63 ng/ml...the concentrations in human breast milk are 2 to 3 times lower than they are in human plasma at the corresponding time points.

In addition to the references submitted to support the Registrant's three points, Merck submitted detailed reports of two studies in ivermectin treated Rhesus monkeys (reviewed below, Data Evaluation Records attached). The first study with neonatal Rhesus monkeys was done to evaluate effects of ivermectin at low doses, and the second was done to assess potential risks to children requiring treatment with the drug. Merck noted:

> The results of this (second) study showed no adverse effects of ivermectin administration. Based on these results clinical trials were initiated in children aged 5-12 years to determine the safety and efficacy of ivermectin at a dose of 12 mg in the treatment of river blindness. The results of these studies showed that the drug was well tolerated in children as it was in adults, and that there were no specific ivermectin toxicities reported.

With respect to veterinary uses of ivermectin, Merck stated:

> The enormous veterinary experience with ivermectin confirms in a variety of species of livestock including swine, cattle, horses, dogs, and sheep, that administration of therapeutic doses of ivermectin (200-300 mcg/kg) with no restrictions on pregnancy status or nursing shows no evidence of adverse effects on mothers or offspring. More than 1.7 billion doses of ivermectin have been sold and administered to livestock...only 130 experiences have been reported,...These adverse experiences were not screened as to type and include any problem related to reproductive performance while on treatment with ivermectin...The majority of these adverse reports involve infectious diseases or trauma and are clearly not the result of ivermectin administration.

Merck concluded from the additional information they provided:

> ...the additional information on exposure of neonatal and immature monkeys to ivermectin provides strong support for the lack of any unique neonatal sensitivity in primates to toxicity from ivermectin or abamectin...the neonatal rat is not appropriate for the assessment of the safety of acute exposures of abamectin or ivermectin in human neonates. A more appropriate model is the result of studies in infant and immature monkeys which showed no adverse effects of ivermectin administration after 2 weeks of doses up to 0.1 mg/kg in neonates and 1.2 mg/kg in immature Rhesus monkeys.

The Registrant further stated:

> ...an adequate margin of safety exists for acute exposure based upon the 0.05 (mg/kg) no-effect level in the CF-1 mouse teratology study and a 100X safety factor to provide adequate margins of safety for acute dietary exposure to abamectin in either children or adults.

B. Review of Additional Published Information Submitted

Pertinant aspects of the toxicology of abamectin and ivermectin were summarized in Lankas and Gordon (1989). The family of chemicals was generally described as follows:

Abamectin and ivermectin increase calcium permeability by their interaction with GABA-gated chloride channels...The compounds' mechanism of toxicity in mammals is unknown, but GABA is a mammalian central nervous system neurotransmitter and effects on GABA may be relevant to their safety in mammals.

In general ivermectin is slightly less toxic than abamectin in laboratory animals. Clinical signs of toxicity for abamectin and ivermectin in laboratory animals are identical, depending on the species; mydriasis (pupillary dilatation) in dogs, emesis in monkeys, and convulsions and/or tremors and coma at higher doses in most species.

Tables 1 and 2 comparing acute toxicity for the two chemicals are exerpted from Lankas and Grodon (1989) as follows:

Table 1

Acute Oral Toxicity of Ivermectin
(Lankas and Gordon, 1989)

Species	LD_{50} (mg/kg)
Rat	50
Rat (infant)	2 to 3
Mouse	25
Dog	80
Rhesus Monkey	>24

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Table 2

Acute Toxicity and Plasma Concentrations of
in Rhesus Monkeys and Humans (from Lankas and Gordon, 1989)

	Monkeys		Humans
	Ivermectin	Abamectin	Ivermectin
Therapeutic dose Peak plasma levels	- -		0.2 mg/kg 20 ng/ml
Minimum effect level Peak plasma levels Signs	2 mg/kg 110 ng/ml emesis	2 mg/kg 76 ng/ml emesis	Not determined
Toxic effect level Peak plasma levels Signs	8 mg/kg 270 ng/ml emesis	8 mg/kg 150 ng/ml emesis	6.6-8.6 mg/kg unknown emesis, mydriasis, sedation
Toxic effect level Peak plasma levels Signs	24 mg/kg 680 ng/ml emesis, mydriasis, sedation	24 mg/kg 390 ng/ml emesis, mydriasis, sedation	Not determined
Fatalities	None	None	None

Results of multigeneration studies with ivermectin were also summarized in Lankas and Gordon (1989) as follows:

> Results of initial multigeneration studies of ivermectin in rats indicated increases in pup mortality several days after parturition and decreased pup weight at maternal doses as low as 0.4 mg/kg/day (lowest dose tested)...a multigeneration study was conducted in which ivermectin was administered to male and female rats orally daily throughout the production of 2 litters in each of 3 successive generations at dose levels of 0.05, 0.1, 0.2, and 0.4 mg/kg/day.
>
> There was no treatment-related mortality, nor were there physical signs of toxicity or effects on reproduction among parents or offspring in any dosage group throughout the production of 2 litters in each of the F0, F1b, and F2b generations. The body weights of offspring (F1a through F3b) during lactation (days 1 to 21 postpartum) were not adversely affected during drug administration. Treatment-related effects on body weight gain were limited to a slight but statistically significant ($p<0.05$) decrease in mean body weight gain among F1b females in the 0.4 mg/kg/day group in the postweaning period. Comparable effects were noted among weanling male and female rats at the same dose level in a previous ivermectin multigeneration study. On the basis of this study, and on other multigeneration studies at higher dosage levels, 0.4 mg/kg/day appears to be near the threshold dose in dams for producing neonatal toxicity. Doses ≤ 0.2 mg/kg/day produced no neonatal toxicity or other reproductive effects.

C. The Avermectin Multigeneration Study

The results of concern in establishing the NOEL of 0.12 mg/kg/day were from a multigeneration reproduction study in which avermectin B_1 was administered by gavage at dose levels of 0, 0.05, 0.12 and 0.40 mg/kg/day in sesame oil. The test substance reduced the lactation and viability indexes of pups (Table 3) as well as pup body weight at the 0.40 mg/kg/day dose level.

Table 3

Summary of pup survival during lactation in a 2-generation study with avermectin in rats.

Dose (mg/kg/day):	0	0.05	0.12	0.40
Data for F_0 to F_{1a} Generation				
Viability Indexes				
Days 1-4 (%)	94.2	97.0	97.6	96.0
Days 4-7 (%)	100.0	100.0	99.6	79.3**
Days 4-14 (%)	99.5	100.0	99.6	53.2**
Lactation Index (%)	99.5	100.0	99.2	52.7**
Selected Litter Data for F_0 to F_{1b} Generation				
Viability Indexes				
Days 1-4 (%)	99.6	99.2	96.7	100.0
Days 4-7 (%)	99.5	100.0	99.6	94.3
Days 4-14 (%)	98.0	98.5	99.2	62.1**
Lactation Index (%)	98.0	98.5	99.2	50.0**
Selected Litter Data for F_{1b} to F_{2a} Generation				
Viability Indexes				
Days 1-4 (%)	98.2	98.7	99.2	98.6
Days 4-7 (%)	100.0	100.0	100.0	98.9
Days 4-14 (%)	100.0	100.0	100.0	94.4**
Lactation Index (%)	100.0	100.0	99.5	93.9**
Selected Litter Data for F_{1b} to F_{2b} Generation				
Viability Indexes				
Days 1-4 (%)	95.8	99.2	99.0	97.5
Days 4-7 (%)	100.0	100.0	99.4	98.6
Days 4-14 (%)	100.0	100.0	99.4	93.5**
Lactation Index (%)	100.0	99.1	99.4	92.8**

*= statistically significant $p \leq 0.05$; **= statistically significant $p \leq 0.01$.

II. Response to the Registrant's Comments

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A. Review of Ivermectin Studies in Monkeys

1. 15-Day Study in Neonatal Monkeys

Doses of 0, 40 and 100 µg/kg/day were administered orally for 15 days to groups of 5 male and 3 female (a total of 8 monkeys in each group) neonatal Rhesus monkeys. Parameters measured were clinical signs, body weight, food consumption, clinical pathology data, organ weights, and macroscopic and microscopic evaluations.

There were no treatment related toxic signs or decreases in body weight and weight gain during the study. Treated animals gained more weight than the controls, but these changes were attributed to normal weight fluctuations in neonatal monkeys. There were also no compound-related effects on the incidences of mydriasis and pupillary light response, hematologic findings, clinical chemistry values, organ weights, or microscopic findings.

The NOEL for ivermectin in infant Rhesus monkeys is ≥100 µg/kg/day (HDT).

2. 16-Day Study in Immature Monkeys

Doses of 0, 0.3, 0.6, and 1.2 mg/kg/day were administered orally for 16 days to groups of 4 male and 4 femmale Rhesus monkeys.

There were no compound-related effects on body weight or body weight gain, hematology, clinical chemistry results, organ weights, or gross necropsy observations during the study. There were also no effects on pupillary response or the incidence of mydriasis in treated monkeys.

Hepatitis was indicated by elevated liver enzyme values and microscopic examination of liver tissues in one control female, one low-dose female, and two high-dose males and was not considered treatment-related, but due to a viral hepatitis A infection.

The NOEL for ivermectin in immature Rhesus monkeys is 1.2 mg/kg/day (HDT).

B. Discussion

According to the Registrant, avermectin and ivermectin increase calcium permeability by their interaction with GABA-gated chloride channels. The mechanism of toxicity for these compounds in mammals may be related to this interaction. Since GABA is a mammalian central nervous system (CNS) neurotransmitter, the effects of the avermectin family of chemicals in the CNS are a key part of the discussion that follows.

Data on pup survival in the multigeneration study with avermectin (Table 3) is similar to results summarized by Merck from multigeneration reproduction studies with ivermectin (discussed in Section I. B. above). The three studies showed that pup survival was affected at a dose level of 0.4 mg/kg/day in rats, but the NOEL's for decreased pup survival are 0.20 mg/kg/day for ivermectin and 0.12 mg/kg/day for avermectin. These similar results support use of ivermectin data in an assessment of potential hazards associated with avermectin.

Table 1 indicates that an acute oral LD_{50} for ivermectin in infant rats is 2 to 3 mg/kg. This estimate is 16 to 25 times less than the acute oral LD_{50} for adult rats (50 mg/kg) and 5- to 7.5-fold greater than the LOEL for decreased pup survival.

As indicated in Table 3 and the discussion of ivermectin reproduction studies in Section I. B., above, pup deaths were observed during days 4-10 after birth. According to the published information submitted by Merck, the pup deaths occurred after avermectin's release as the result of increased use of lipids during parturition and at a time when development of the blood-brain barrier is incomplete in rats.

Concentrations of ivermectin in milk from treated rats was low on day one of lactation, but it increased rapidly during days 4-10 when mortality was observed. The concentration of ivermectin in milk from treated lactating rats is 3- to 4-fold greater than that in the plasma, and the concentration of ivermectin in the brain of pups (3 ppm) was 10-fold greater than that found in the treated adult rat while plasma levels of the chemical in pups were reported to be equal to or exceeded maternal levels. These results, multigeneration studies in which the test material was administered by gavage and cross-fostering studies considered previously (see Section I. A. above) demonstrate that enhanced exposure through mother's milk and the incomplete development of the blood-brain barrier are important factors in the increased sensitivity of rat pups to avermectin toxicity.

In one of the monkey studies submitted for review, infant monkeys received ivermectin at levels up to 0.1 mg/kg/day for 15 days without showing signs of toxicity. The second study indicated that immature monkeys could tolerate doses as high as 1.2 mg/kg/day for 15 days without toxicity. Although these studies did not establish a lowest-effect level (LEL), data from Table 2 above show that doses as low as 2 mg/kg cause emesis in monkeys, and doses as high as 24 mg/kg cause mydriasis. There were no data available to suggest whether infant primates may be more sensitive to ivermectin toxicity than adults, but these studies demonstrated that infant monkeys were also unaffected at a dose level similar to that given to mothers of nursing rats (0.1 or 0.12 mg/kg/day for monkeys and rats, respectively).

The Registrant noted that the plasma levels in rat pups at day 10 were 40 times greater than the therapeutic levels in humans (0.8 ppm compared to 20 ng/ml). A therapeutic dose of ivermectin in humans was defined as 0.15 to 0.2 mg/kg administered one or two times per year. Another species difference noted by Merck was that the plasma levels of ivermectin in treated lactating women was 2 to 3 times that found in breast milk. But these differences should be considered carefully because:

(1) the plasma levels in rats were determined in pups and adults exposed to ivermectin at 2.5 mg/kg/day for 61 days, a dose level which is well above the 0.2 mg/kg/day NOEL for ivermectin, and

(2) the human plasma and milk levels were determined after administration of one therapeutic dose (0.15 to 0.2 mg/kg).

III. References

Amano, Y. 1967. Changes of the level of blood glucose during pregnancy in the rat. *Jap. J. Pharmacol.* 17:105-114.

Betz, L., and G. W. Goldstein. 1981. Developmental changes in metabolism and transport properties of capillaries isolated from rat brain. *J. Physiol.* 312:365-376.

Bohr, V., and K. Mollgard. 1974. Tight junctions in human fetal choroid plexus visualized by freeze etching. *Brain Res.* 81:314-318.

Chiu, S. H., E. Sestokas, R. Taub, *et al.* 1986. Metabolic disposition of ivermectin in tissues of cattle, sheep, and rats. *Drug Metabolism & Disposition.* 14:590-600.

Lankas, G. R., and L. R. Gordon. 1989. Toxicology, *In*: Ivermectin and Abamectin. W. C. Campbell, *ed.* Springer-Verlag. pp 89-112.

Saunders, N. R. 1977. Ontogeny of the blood-brain barrier. *Exper. Eye Res.* (Suppl.) pp 523-550.

Scow, R. O., S. S. Chernick, and M. S. Brinley. 1964. Hyperlipemia and ketosis in the pregnant rat. *Am. J. Physiol.* y206:796-804.

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Reviewed by: William Dykstra Ph.D., Toxicologist William Dykstra 5/11/93
Section I, Tox. Branch I
Secondary Reviewer: Roger Gardner, Section Head, Toxicologist
Section I, Tox. Branch I Roger Gardner 5-11-93

DATA EVALUATION REPORT

STUDY TYPE: 82-1 Subchronic Oral (By Gavage) Toxicity Study in Immature Rhesus Monkeys TOX. CHEM NO: 63AB

ACCESSION NUMBER: N/A MRID NO.: 426123-02

TEST MATERIAL: Ivermectin, MK-0933

SYNONYMS: Avermectin, Abamectin

STUDY NUMBER: Merck, TT #85-9033 and Hazleton Project #284-150

SPONSOR: Merck & Co.

TESTING FACILITY: Hazleton Laboratories, Inc., Vienna, VA

TITLE OF REPORT: 16-Day Oral Toxicity Study of MK-0933 in Immature Rhesus Monkeys

AUTHOR(S): D. W. Dalgard, D.V.M.

REPORT ISSUED: June 11, 1986

CONCLUSION: The NOEL is 1.2 mg/kg/day (HDT).

There were no compound-related effects in body weight or body weight gain during the study. Food consumption was not measured.

There were no compound-related ocular lesions observed in the study. One control male (#J00255) was reexamined in the second week by Nancy M. Bromberg, D.V.M., a board-certified veterinary ophthalmologist and found to have opaque vitreous humor rather than lens opacity. Other ocular lesions noted including persistent pupillary membrane and retinal degeneration were present pretest and were unrelated to treatment.

Daily examinations for mydriasis were conducted on all animals. All monkeys had normal pupillary responses (although no individual data were presented) with the excption of one control male (#J00252) and one high-dose male (#J00279) which had slightly delayed pupillary responses. The finding in the high-dose male was unaffected by treatment with MK-0933, and the occurrence of delayed pupillary response was considered to represent normal variation in monkeys.

There were no compound-related findings in hematological data and the differences observed were small and not dose-related.

There were no compound-related findings in clinical chemistry results. However, in week 2, control female #J00258, low-dose female #J00266, and high-dose male #J00279 had elevated AST and ALT values.

Based on these increases in liver function enzymes, testing for antibodies against hepatitus virus A (HAVAB) and IgM (HAVAB-M) was performed in the three animals with elevated transaminases, as well as in a random sample of the remaining animals from all groups.

The most likely explanation for the elevated transaminases is a recent hepatitis virus A infection. Histological evaluation of the livers showed hepatitis in each of the three seropositive animals, as well as high-dose male #J00276. However, this animal did not have elevated transaminases and there was no serum to evaluate for viral hepatitis A. There were no clincal signs of disease in any of the affected animals during the study.

Urine was not collected.

There were no compound-related effects in absolute organ weights. The small differences between control and treated groups reflected normal variation and were not dose-related, with the exception of female adrenal weights. The mean absolute weights were .54, .62 .62, and .66 grams for the control, low, mid, and high-dose groups, respectively. The 22% increase in absolute adrenal weight at the high-dose was also reflected in the 13% increase in relative (to body) adrenal weight, as well as the 14% increase in relative (to brain) adrenal weight.

Examination of all the adrenal weights from all dose groups shows the large random variation in normal distribution. Therefore, it is concluded that the slight increase in adrenal weight is not compound-related at the high-dose.

There were no compound-related gross necropsy findings. Alopecia was present in controls as well as treated animals and the incidence did not indicate a relationship to treatment.

Hepatitis was observed in one control female (#J00258), one low-dose female (#J00266), and two high-dose males (#J00276, #J00279) and was not considered treatment-related, but due to a viral hepatitis A infection. Other findings were incidental and unrelated to treatment.

Doses were 0, 0.3, 0.6, and 1.2 mg/kg/day for 16 days in 4/sex/dose Rhesus monkeys.

Classification: Supplementary

<u>Special Review Criteria</u> (40 CFR 154.7)

A. MATERIALS:

1. Test compound: . Description - MK-9033, Batch # - L-640,471-000W076, Purity - 97.3% by HPLC.; Vehicle: Sesame Oil, Lot - 746289

2. Test animals: Species: Monkey, Strain: Rhesus (Macaca mulatta), Age: 13 - 21 months , Weight: Males: 2.1 - 3.2 Kg; Females: 1.9 - 2.7 Kg, Source: Hazleton Research Animals, Texas Primate Center, oct. 30, 1985.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose by Gavage (mg/kg)	Main Study 16 Days male	Main Study 16 Days female	Interim Sac. None male	Interim Sac. None female
1 Cont	0	4	4		
2 Low (LDT)	0.3	4	4		
3 Mid (MDT)	0.6	4	4		
4 High (HDT)	1.2	4	4		

2. Dose preparation

The monkeys were dosed daily by nasogastric intubation at a volume of 1.0 ml/kg followed by a 2.0 ml. (changed to 0.5 ml on Day 3) flush of sesame oil. Gavage samples were prepared daily and reserve samples of the control and test solutions were taken on Dec. 4, 1985 (hand carried by the sponsor) and on Dec. 17, 1985 (shipped to sponsor) for analysis of the test solutions.

Results - Analyses of these samples showed concentrations ranging between 85-93% of nominal concentrations and were considered to be within acceptable limits of the assay. In addition, the sponsor has demonstrated the stability of MK-0933 in sesame oil for greater than 24 hours.

3. Animals were individually caged with the cages arranged in the room using the top tier only so as to provide more uniform exposure to light and thereby reduce variability in evaluating possible drug induce mydriasis. The monkeys received food (Purina Certified Monkey Chow™) twice a day with the first offering approximately 1-2 hours after

dosing and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data: means and standard deviations were calculated. Other statistical analyses were not performed.

5. A signed quality assurance statement was present and dated June 8, 1986.

C. METHODS AND RESULTS:

1. Observations:

Animals were inspected twice daily for signs of toxicity and mortality and once daily for appetite and changes in excreta. Observations for toxic and/or pharmacologic effects wer made prior to dosing and approximately 2-3 hours following dosing.

Results: No compound-related physical signs were observed in the study. Incidental findings were focal alopecia in both control and treated animals. Also, loose stool was increased in all groups during the first three days due to the sesame oil vehicle (2.0 ml rinse). When the rinse volume was lowered to 0.5 ml, the incidence of soft stool greatly diminished.

2. Body weight

Animals were weighed weekly during the pretest, then for twice weekly during the study.

Results: There were no compound-related effects in body weight or body weight gain during the study.

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	Weight (kg)					
Days	-1	1	6	8	13	15
			Males			
Dose (mg/kg)						
0	2.6	2.6	2.7	2.7	2.7	2.8
0.3	2.5	2.4	2.5	2.5	2.6	2.6
0.6	2.4	2.4	2.5	2.5	2.5	2.4
1.2	2.3	2.4	2.5	2.6	2.6	2.6
			Females			
Dose (mg/kg)						
0	2.2	2.2	2.2	2.2	2.2	2.3
0.3	2.3	2.3	2.4	2.4	2.5	2.5
0.6	2.3	2.4	2.4	2.4	2.4	2.5
1.2	2.2	2.3	2.4	2.4	2.4	2.4

3. Food consumption and compound intake

Food consumption was not measured.

4. Ophthalmological examination

Physical and ophthalmology exams were performed prior to initiation and during week 2. The monkeys were anesthetized prior to the examination. The ophthalmoscopic exams were performed using a slit lamp, direct and indirect ophthalmoscopes with 1% Mydriacyl™ as the mydriatic. The monkeys were also examined approximately four hours after each dose for changes in pupillary response to light and/or mydriasis. These observations were made once daily on all animals beginning approximately 1 week prior to initiation to obtain experience and baseline data in untreated animals.

Results: There were no compound-related ocular lesions observed in the study. One control male (#J00255) was reexamined in the second week by Nancy M. Bromberg, D.V.M., a board-certified veterinary ophthalmologist and found to have opaque vitreous humor rather than lens opacity. Other ocular lesions noted including persistent pupillary membrane and retinal degeneration were present pretest and were unrelated to treatment.

Daily examinations for mydriasis were conducted on all animals. All monkeys had normal pupillary responses (although no individual data were presented) with the excption of one control male (#J00252) and one high-dose male (#J00279) which had slightly delayed pupillary responses. The finding in the high-dose male was unaffected by treatment with MK-0933, and the occurrence of delayed pupillary response was considered to represent normal variation in monkeys.

5. Blood was collected before treatment and at week 2 for hematology and clinical analysis from all animals. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)
x	Platelet count*		Reticulocyte count
	Blood clotting measurements		
x	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)		

* Required for subchronic and chronic studies

Results - There were no compound-related findings in hematological data and the differences observed were small and not dose-related.

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b. Clinical Chemistry

X	Electrolytes:
	Calcium*
x	Chloride*
	Magnesium*
	Phosphorous*
x	Potassium*
x	Sodium*

	Enzymes
x	Alkaline phosphatase (ALK)
	Cholinesterase (ChE)#
	Creatinine phosphokinase*^
	Lactic acid dehydrogenase (LAD)
x	Serum alanine aminotransferase (also SGPT)*
x	Serum aspartate aminotransferase (also SGOT)*
	Gamma glutamyl transferase (GGT)
	Glutamate dehydrogenase

X	Other:
x	Albumin*
x	Blood creatinine*
x	Blood urea nitrogen*
x	Cholesterol*
	Globulins
x	Glucose*
	Total bilirubin
	Total serum Protein (TP)*
x	Triglycerides
	Serum protein electrophores

* Required for subchronic and chronic studies
\# Should be required for OP
^ Not required for subchronic studies

Results - There were no compound-related findings in clinical chemistry results. However, in week 2, control female #J00258, low-dose female #J00266, and high-dose male #J00279 had elevated AST and ALT values. The findings are shown below.

Animal Number	AST U/L	ALT U/L
J00258 - control female	83	254
J00266 - L.D. female	110	809
J00279 - H.D. male	69	167

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Based on these dramatic increases in liver function enzymes, testing for antibodies against hepatitus virus A (HAVAB) and IgM (HAVAB-M) was performed in the three animals with elevated transaminases, as well as in a random sample of the remaining animals from all groups. The results are shown below.

Animal Number	Sex	Dose Level mg/kg	AST U/L	ALT U/L	HAVAB	HAVAB-M
J00258	F	Control	83	254	+	-
J00266	F	0.3	110	809	+	+
J00279	M	1.2	69	167	+	+
J00252	M	Control	30	26	-	ND
J00262	M	0.3	30	20	-	ND
J00272	F	0.6	39	33	-	ND
J00282	F	1.2	30	26	-	ND
J00254	M	Control	28	21	-	ND
J00264	F	0.3	34	31	-	ND
J00274	F	0.6	28	23	-	ND

The most likely explanation for the elevated transaminases is a recent hepatitis virus A infection. Histological evaluation of the livers showed hepatitis in each of the three seropositive animals, as well as high-dose male #J00276. However, this animal did not have elevated transaminases and there was no serum to evaluate for viral hepatitis A. There were no clincal signs of disease in any of the affected animals during the study.

6. Urinalysis^

Urine was not collected. The CHECKED (X) parameters were examined.

X		X	
	Appearance*		Glucose*
	Volume*		Ketones*
	Specific gravity*		Bilirubin*
	pH		Blood*
	Sediment (microscopic)*		Nitrat.
	Protein*		Urobilinogen

^Not required for subchronic studies
* Required for chronic studies

Results - None

7. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
x	Tongue	x	Aorta*	xx	Brain*+
x	Salivary glands*	xx	Heart*	x	Periph. nerve*#
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*#
x	Stomach*	x	Lymph nodes*	xx	Pituitary*
x	Duodenum*	xx	Spleen	x	Eyes (optic n.)*#
x	Jejunum*	xx	Thymus*	Glandular	
x	Ileum*	Urogenital		xx	Adrenal gland*
x	Cecum*	xx	Kidneys*+		Lacrimal gland#
x	Colon*	x	Urinary bladder*	x	Mammary gland*#
x	Rectum*	xx	Testes*+	xx	Parathyroids*++
xx	Liver *+	x	Epididymides	xx	Thyroids*++
x	Gall bladder*	xx	Prostate	Other	
x	Pancreas*	x	Seminal vesicle	x	Bone*#
Respiratory		xx	Ovaries*+	x	Skeletal muscle*#
xx	Trachea*	xx	Uterus*	x	Skin*#
xx	Lung*			x	All gross lesions and masses*
	Nose^				
	Pharynx^				
x	Larynx^				

* Required for subchronic and chronic studies.
^ Required for chronic inhalation.
\# In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement.
\+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.

a. Organ weight - There were no compound-related effects in absolute organ weights. The small differences between control and treated groups reflected normal variation and were not dose-related, with the exception of female adrenal weights. The mean absolute weights were .54, .62, .62, and .66 grams for the control, low, mid, and high-dose groups, respectively. The 22% increase in absolute adrenal weight at the high-dose was also reflected in the 13% increase in relative (to body) adrenal weight, as well as the 14% increase in relative (to brain) adrenal weight. The individual adrenal weights for the various groups are shown below.

Dose (mg/kg)	Adrenal Weight (grams)
0	.40, .42, .61, .73
0.3	.56, .85, .50, .56
0.6	.43, .73, .69, .62
1.2	.68, .62, .51, .82

Examination of all the adrenal weights from all dose groups shows the large random variation in normal distribution. Therefore, it is concluded that the slight increase in adrenal weight is not compound-related at the high-dose.

b. Gross pathology - There were no compound-related gross necropsy findings. Alopecia was present in controls as well as treated animals and the incidence did not indicate a relationship to treatment.

c. Microscopic pathology - Hepatitis was observed in one control female (#J00258), one low-dose female (#J00266), and two high-dose males (#J00276, #J00279) and was not considered treatment-related, but due to a viral hepatitis A infection. Other findings were incidental and unrelated to treatment.

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D. DISCUSSION: The NOEL is 1.2 mg/kg/day (HDT).

There were no compound-related effects in body weight or body weight gain during the study. Food consumption was not measured.

There were no compound-related ocular lesions observed in the study. One control male (#J00255) was reexamined in the second week by Nancy M. Bromberg, D.V.M., a board-certified veterinary ophthalmologist and found to have opaque vitreous humor rather than lens opacity. Other ocular lesions noted including persistent pupillary membrane and retinal degeneration were present pretest and were unrelated to treatment.

Daily examinations for mydriasis were conducted on all animals. All monkeys had normal pupillary responses (although no individual data were presented) with the excption of one control male (#J00252) and one high-dose male (#J00279) which had slightly delayed pupillary responses. The finding in the high-dose male was unaffected by treatment with MK-0933, and the occurrence of delayed pupillary response was considered to represent normal variation in monkeys.

There were no compound-related findings in hematological data and the differences observed were small and not dose-related.

There were no compound-related findings in clinical chemistry results. However, in week 2, control female #J00258, low-dose female #J00266, and high-dose male #J00279 had elevated AST and ALT values.

Based on these increases in liver function enzymes, testing for antibodies against hepatitus virus A (HAVAB) and IgM (HAVAB-M) was performed in the three animals with elevated transaminases, as well as in a random sample of the remaining animals from all groups.

The most likely explanation for the elevated transaminases is a recent hepatitis virus A infection. Histological evaluation of the livers showed hepatitis in each of the three seropositive animals, as well as high-dose male #J00276. However, this animal did not have elevated transaminases and there was no serum to evaluate for viral hepatitis A. There were no clincal signs of disease in any of the affected animals during the study.

Urine was not collected.

There were no compound-related effects in absolute organ weights. The small differences between control and treated groups reflected normal variation and were not dose-related, with the exception of female adrenal weights. The mean absolute weights were .54, .62, .62, and .66 grams for the control, low, mid, and

high-dose groups, respectively. The 22% increase in absolute adrenal weight at the high-dose was also reflected in the 13% increase in relative (to body) adrenal weight, as well as the 14% increase in relative (to brain) adrenal weight.

Examination of all the adrenal weights from all dose groups shows the large random variation in normal distribution. Therefore, it is concluded that the slight increase in adrenal weight is not compound-related at the high-dose.

There were no compound-related gross necropsy findings. Alopecia was present in controls as well as treated animals and the incidence did not indicate a relationship to treatment.

Hepatitis was observed in one control female (#J00258), one low-dose female (#J00266), and two high-dose males (#J00276, #J00279) and was not considered treatment-related, but due to a viral hepatitis A infection. Other findings were incidental and unrelated to treatment.

Doses were 0, 0.3, 0.6, and 1.2 mg/kg/day for 16 days in 4/sex/dose Rhesus monkeys.

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Reviewed by: William Dykstra, Ph.D., Toxicologist William Dykstra 2/23/93
Section I, Tox. Branch I
Secondary Reviewer: Roger Gardner, Section Head, Toxicologist
Section I, Tox. Branch I Roger Gardner 3-11-93

DATA EVALUATION REPORT

STUDY TYPE: 82-1(c); Subchronic Oral-Monkey (Gavage); Toxicity Study in Neonatal Rhesus Monkeys

TOX. CHEM NO: 63AB

MRID NO.: 426123-02

TEST MATERIAL: Ivermectin, MK-0933

SYNONYMS: Abamectin, Avermectin

STUDY NUMBER: TT #86-9005, GLP-13

SPONSOR: Merck & Co.

TESTING FACILITY: California Primate Research Center, Davis, CA

TITLE OF REPORT: Fifteen-Day Toxicity Study of Orally Administered MK-0933 (Ivermectin) in Neonatal Rhesus Monkeys

AUTHOR(S): G. L. Lankas, D. L. Bokelman, E. M. Scolnick

REPORT ISSUED: December 12, 1986

CONCLUSION: The NOEL is 100 µg/kg/day (HDT).

There were no treatment related toxic signs. Incidental clincal signs involved 3 control animals and 2 100 µg/kg dose group and included weight loss, loose stools, dehydration and poor appetite. Two of the control animals were given fluids to relieve dehydration and to stimulate appetite.

There were no treatment related decreases in body weight or weight gain during the study. Treated animals gained more weight than the controls. The percent increase in body weight gain was 31% and 54% for the 40 µg/kg and 100 µg/kg groups, respectively. The report states "All weight changes were attributed to normal fluctuations often observed in neonatal monkeys".

There were no compound-related effects in the examinations carried out by the direct, indirect, and slit lamp methods. With respect to the daily post-treatment observations for mydriasis and pupillary light response, similar incidences of slow pupillary constriction and/or slight to moderate mydriasis were

observed in both the treated and control animals at a similar incidence.

Normal range of hematologic variations were observed between control and treated animals when comparisons were made between pre-treatment values and data collected on Day 12.
There were no compound-related effects in hematologic findings.

There were no compound-related effects in serum clinical chemistry values between control and treated animals. Occasionally, alkaline phosphatase values were significantly elevated in control as well as treated animals both during pretreatment as well as on Day 12. This random finding was attributed to rapid bone growth in the young animals.

Absolute pituitary weight was increased in the treated groups in comparison to controls. The mean values were 0.016, 0.019 and 0.020 grams for the 0, 40, and 100 µg/kg groups, respectively. The percent increases were 19% and 25% for the 40 and 100 µg/kg groups, respectively. Also, the absolute weight of the prostate was increased in treated males in comparison to controls. The means were 0.222, 0.337, and 0.323 grams for the control, 40, and 100 µg/kg groups, respectively. The percent increases in prostate glang were 52% and 46%, respectively, for the 40 and 100 µg/kg groups. In the absence of clinical chemistry findings and histopathological findings, and the fact that individual organ weights showed a large variation (control pituitary weights were .015, .013, .014, .019, .020, .019, .017, and .012 grams and high-dose weights were .018, .019, .026, .023, .016, .018, .019, and .018 grams; control prostate weights were .281, .269, .232, .236, and .092 grams and high-dose prostate weights were .338, .263, .352, .322, and .338 grams), these organ weight changes are considered to represent the normal variation in neonatal monkeys and are unrelated to treatment.

There were no compound-related microscopic findings. Moderate focal hepatitis was found in male monkey #022951 of the 40 µg/kg group, but since it was not dose-related, it was not considered compound-related. Other findings were of the type, incidence and severity normally seen in colony historical control monkeys and were unrelated to treatment.

Doses were 0, 40 and 100 µg/kg/day for 15 days in groups of 5 male and 3 female (a total of 8 monkeys in each group) neonatal Rhesus monkeys. Parameters measured were clinical signs, body weight, food consumption, clinical pathology data, organ weights, and macroscopic and microscopic evaluations.

<u>Core Classification</u>: Acceptable

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A. MATERIALS:

1. Test compound: . Description - MK-0933, Batch # - L-640, 471-000W076 was supplied in bulk form, Purity - 93.5% was verified by the Sponsor, Stored at Room Temperature in a light-free cabinet. Sesame Oil (Fisher Scientific), lot number 845766 and Sesame Oil (Sigma Chemical Co.), lot number 105F0584 were stored at Room Temperarure.

2. Test animals: Species: Monkey, Strain: Rhesus (Macaca mulatta), Age: 7-13 days, Weight: 400-600 grams, Source: CPRC, Davis, CA.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned based on the CPRC veterinarian's clincal judgement to the following test groups:

Test Group	Dose by gavage (mg/kg)	Main Study 15 days male	Main Study 15 days female	Interim Sac. none male	Interim Sac. none female
1 Cont	0	5	3		
2 Low (LDT)	0.04	5	3		
3 Mid (MDT)	-	-	-		
4 High (HDT)	0.10	5	3		

2. Diet preparation

Treated animals were administered a solution of MK-0933 and sesame oil in a dosing volume of 1 ml/kg via nasogastric intubation once each morning for 14 days. The control group recived sesame oil at a volume of 1 ml/kg each morning for 14 days. All 24 animals were fasted approximately 1.5 hours before and 30 minutes after dosing to avoid possible regurgitation of the dosing solution. At the initiation of the study, and once per month thereafter, two 5 ml. samples of the dosing solution from each prepared dosing concentration were collected. One set of these samples was shipped to the Sponsor in a light-free container for analysis of drug concentration by assay, and the duplicate was retained by the CPRC.

Results - No data were presented in the report, but the report states that the results of these assays by the

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Sponsor indicated that the concentration of the dosing solutions was within acceptable limits.

3. Animals received food (Enfamil with Iron™) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data: comparison of control and treated groups before, during, and after treatment for all variables by visual inspection of the data. Mean and standard deviations were calculated for all body weights, hematologic evaluations, and serum biochemical evaluations. Statistical analysis was not performed on other parameters.

5. A signed quality assurance statement was present and dated 11/6/86.

C. METHODS AND RESULTS:

1. Observations:

Animals were inspected daily for signs of toxicity and mortality.

Results: There were no treatment related toxic signs. Incidental clincal signs involved 3 control animals and 2 100 µg/kg dose group and included weight loss, loose stools, dehydration and poor appetite. Two of the control animals were given fluids to relieve dehydration and to stimulate appetite.

2. Body weight

Animals were weighed once per day for the study.

Results: There were no treatment related decreases in body weight or weight gain during the study. Treated animals gained more weight than the controls. The percent increase in body weight gain was 31% and 54% for the 40 µg/kg and 100 µg/kg groups, respectively. The report states "All weight changes were attributed to normal fluctuations often observed in neonatal monkeys". The following mean values for body weight present the changes during the study.

Days	P. T.*	3	7	10	12	W.G.**
		Weight (Kg)				
Dose µg/kg						
0	0.495	0.527	0.514	0.557	0.566	.071
40	0.563	0.596	0.618	0.644	0.656	.093
100	0.503	0.537	0.541	0.594	0.612	.109

* = pre-treatment

** = weight gain

3. Food consumption and compound intake

Food consumption was determined every 2 hours daily from approximately 7:00 a.m. to 10:00 p.m. per CPRC nursery SOP. Quantitative measurements of food consumption were not recorded during the study.

4. Ophthalmological examination

Animals were observed daily approximately 4 hours post-treatment for mydriasis and pupillary light response. 1 percent (1%) tropicamide (Mydriacyl™, Alcon) was applied to both eyes of all animals approximately 30 minutes prior to the examination to induce mydriasis. All animals had a complete ophthalmoscopic examination 3 days prior to initiation of treatment and at Day 12 ± 1 of treatment which included a Direct, Indirect, and Slit Lamp examination.

Results: There were no compound-related effects in the examinations carried out by the direct, indirect, and slit lamp methods. With respect to the daily post-treatment observations for mydriasis and pupillary light response, similar incidences of slow pupillary constriction and/or slight to moderate mydriasis were observed in both the treated and control animals at a similar incidence. The table below shows the number of animals with mydriasis tabulated over the 14 day treatment period.

Mydriasis

Dose µg/kg	0	40	100
	Number of Animals Affected One or More Days		
None	2	2	1
Slight	4	3	4
moderate	2	3	3

5. Blood was collected within 3 days before treatment and on Day 12 ± 1 of treatment on all nonfasted animals. The CHECKED (X) parameters were examined.

   a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)
x	Platelet count*		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies

Results - Normal range of variations were observed between control and treated animals when comparisons were made between pre-treatment values and data collected on Day 12. There were no compound-related effects in hematologic findings.

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b. Clinical Chemistry

X	Electrolytes:
	Calcium*
x	Chloride*
	Magnesium*
	Phosphorous*
x	Potassium*
x	Sodium*

	Enzymes
x	Alkaline phosphatase (ALK)
	Cholinesterase (ChE)#
	Creatinine phosphokinase*^
	Lactic acid dehydrogenase (LAD)
x	Serum alanine aminotransferase (also SGPT)*
x	Serum aspartate aminotransferase (also SGOT)*
	Gamma glutamyl transferase (GGT)
	Glutamate dehydrogenase

X	Other:
x	Albumin*
x	Blood creatinine*
x	Blood urea nitrogen*
x	Cholesterol*
x	Globulins
x	Glucose*
	Total bilirubin
x	Total serum Protein (TP)*
x	Triglycerides
	Serum protein electrophores

* Required for subchronic and chronic studies
\# Should be required for OP
^ Not required for subchronic studies

Results - There were no compound-related effects in serum clinical chemistry values between control and treated animals. Occasionally, alkaline phosphatase values were significantly elevated in control as well as treated animals both during pretreatment as well as on Day 12. This random finding was attributed to rapid bone growth in the young animals.

6. Urinalysis

Urinalysis was not performed. The CHECKED (X) parameters were examined.

X	
	Appearance*
	Volume*
	Specific gravity*
	pH
	Sediment (microscopic)*
	Protein*

X	
	Glucose*
	Ketones*
	Bilirubin*
	Blood*
	Nitrate
	Urobilinogen

^Not required for subchronic studies
* Required for chronic studies

Results - Not performed

7. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
x	Tongue		Aorta*	xx	Brain*+
x	Salivary glands*	xx	Heart*	x	Periph. nerve*#
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*#
x	Stomach*	x	Lymph nodes*	xx	Pituitary*
x	Duodenum*	xx	Spleen	x	Eyes (optic n.)*#
x	Jejunum*	xx	Thymus*	Glandular	
x	Ileum*	Urogenital		xx	Adrenal gland*
x	Cecum*	xx	Kidneys*+		Lacrimal gland#
x	Colon*	x	Urinary bladder*	x	Mammary gland*#
x	Rectum*	xx	Testes*+		Parathyroids*++
xx	Liver *+	x	Epididymides	xx	Thyroids*++
x	Gall bladder*	xx	Prostate	Other	
x	Pancreas*	x	Seminal vesicle	x	Bone*#
Respiratory		xx	Ovaries*+	x	Skeletal muscle*#
x	Trachea*	xx	Uterus*	x	Skin*#
xx	Lung*			x	All gross lesions and masses*
	Nose^				
	Pharynx^				
x	Larynx^				

* Required for subchronic and chronic studies.
^ Required for chronic inhalation.
\# In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement.
\+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.

a. Organ weight - Absolute pituitary weight was increased in the treated groups in comparison to controls. The mean values were 0.016, 0.019 and 0.020 grams for the 0, 40, and 100 µg/kg groups, respectively. The percent increases were 19% and 25% for the 40 and 100 µg/kg groups, respectively. Also, the absolute weight of the prostate was increased in treated males in comparison to controls. The means were 0.222, 0.337, and 0.323 grams for the control, 40, and 100 µg/kg groups, respectively. The percent increases in prostate glang were 52% and 46%, respectively, for the 40 and 100 µg/kg groups. In the absence of clinical chemistry findings and

151

histopathological findings, and the fact that individual organ weights showed a large variation (control pituitary weights were .015, .013, .014, .019, .020, .019, .017, and .012 grams and high-dose weights were .018, .019, .026, .023, .016, .018, .019, and .018 grams; control prostate weights were .281, .269, .232, .236, and .092 grams and high-dose prostate weights were .338, .263, .352, .322, and .338 grams), these organ weight changes are considered to represent the normal variation in neonatal monkeys and are unrelated to treatment.

b. Gross pathology - There were no compound-related gross necropsy findings.

c. Microscopic pathology - Control and high-dose animals were examined microscopically. There were no compound-related microscopic findings. Moderate focal hepatitis was found in male monkey #022951 of the 40 µg/kg group, but since it was not dose-related, it was not considered compound-related. Other findings were of the type, incidence and severity normally seen in colony historical control monkeys and were unrelated to treatment.

D. <u>DISCUSSION</u>: The NOEL is 100 µg/kg/day (HDT).

There were no treatment related toxic signs. Incidental clincal signs involved 3 control animals and 2 100 µg/kg dose group and included weight loss, loose stools, dehydration and poor appetite. Two of the control animals were given fluids to relieve dehydration and to stimulate appetite.

There were no treatment related decreases in body weight or weight gain during the study. Treated animals gained more weight than the controls. The percent increase in body weight gain was 31% and 54% for the 40 µg/kg and 100 µg/kg groups, respectively. The report states "All weight changes were attributed to normal fluctuations often observed in neonatal monkeys".

There were no compound-related effects in the examinations carried out by the direct, indirect, and slit lamp methods. With respect to the daily post-treatment observations for mydriasis and pupillary light response, similar incidences or slow pupillary constriction and/or slight to moderate mydriasis were observed in both the treated and control animals at a similar incidence.

Normal range of hematologic variations were observed between control and treated animals when comparisons were made between pre-treatment values and data collected on Day 12.

There were no compound-related effects in hematologic findings.

There were no compound-related effects in serum clinical chemistry values between control and treated animals. Occasionally, alkaline phosphatase values were significantly elevated in control as well as treated animals both during pretreatment as well as on Day 12. This random finding was attributed to rapid bone growth in the young animals.

Absolute pituitary weight was increased in the treated groups in comparison to controls. The mean values were 0.016, 0.019 and 0.020 grams for the 0, 40, and 100 µg/kg groups, respectively. The percent increases were 19% and 25% for the 40 and 100 µg/kg groups, respectively. Also, the absolute weight of the prostate was increased in treated males in comparison to controls. The means were 0.222, 0.337, and 0.323 grams for the control, 40, and 100 µg/kg groups, respectively. The percent increases in prostate glang were 52% and 46%, respectively, for the 40 and 100 µg/kg groups. In the absence of clinical chemistry findings and histopathological findings, and the fact that individual organ weights showed a large variation (control pituitary weights were .015, .013, .014, .019, .020, .019, .017, and .012 grams and high-dose weights were .018, .019, .026, .023, .016, .018, .019, and .018 grams; control prostate weights were .281, .269, .232, .236, and .092 grams and high-dose prostate weights were .338, .263, .352, .322, and .338 grams), these organ weight changes are considered to represent the normal variation in neonatal monkeys and are unrelated to treatment.

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Doses were 0, 40 and 100 µg/kg/day for 15 days in groups of 5 male and 3 female (a total of 8 monkeys in each group) neonatal Rhesus monkeys. Parameters measured were clinical signs, body weight, food consumption, clinical pathology data, organ weights, and macroscopic and microscopic evaluations.

Tof Review 010260

Page _____ is not included in this copy.

Pages 34 through 36 are not included in this copy.

The material not included contains the following type of information:

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Avermectin

Therapeutic doses of Ivermectin range from 200-300 µg/kg with no restrictions on pregnancy status or nursing.

Incidence of Adverse Pregnancy Outcome with Veterinary Use of Ivermectin*

Species	Doses Sold x 10^6	# Breeding with A.R.	% Total
Swine	36	29	0.0000805
Cattle	887	44	0.0000049
Horses	46	32	0.0000695
Dogs	178	5	0.0000028
Sheep	553	20	0.0000036
Totals	1700 x 10^6	130	0.0000076 (7.6×10^{-6})

* Animals reported to have any problem related to reproductive performance (abortion, stillbirth, congenital effects, decreased fertility) while on treatment with ivermectin. No preselection of data for known causes (i.e., infection, trauma, concurrent treatment with other agents, etc.)