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Esfenvalerate 82-1a

These are Comments about the EXT Doc 004681

005341

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

AUG 12 1986

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ASANA Insecticide 1.9 EC (24.0% ai) - EPA File Symbol 201-URI and Technical ASANA Insecticide (75.0% ai) - EPA File Symbol 201-URO: Response to the Sponsor's Proposal to Raise the NOEL of 50 ppm to 150 ppm in the 13-Week Rat Feeding Study

Tox. Chem. No. ~~DIA~~ 268J

FROM: William B. Greear, M.P.H. William B. Greear, 7/31/86
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: George LaRocca, PM 15
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

THRU: Albin B. Kocialski, Ph.D., Supervisory Pharmacologist
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C) ABK 8/1/86

and

Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Under cover letters dated May 23 and July 21, 1986, the Shell Chemical Company has proposed that the no-observed-effect level (NOEL) observed in the 13-week rat feeding study be raised from 50 parts per million (ppm) to 150 ppm. The Shell Chemical Company provided the following rationale as to why the NOEL should be raised.

"During the course of the study, rat TP3M22 in the 150 ppm dose group was observed to have 'jerky leg movements' on week 11 of the study . . . this incident consisted of a mild prolonged flexion of the hindlimb

as the animal reentered his cage following examination. The sign was not observed during any subsequent examinations of the animal. Therefore, it was a unit event of a subjective observation which cannot be confirmed due to lack of reoccurrence of longer duration of the clinical sign. In fact, it is not unlikely for such an incident to occur if an animal's leg were to be temporarily caught in the wire floor of a cage. In addition to the fact that this sign is not clinically significant, since it was only observed in one animal at one time point, it is important to considered that pyrethroids have two distinctive actions - a short-term pharmacological effect which results in sparse axonal damage. The clinical signs, jerky leg movements, would be a reversible pharmacological action as opposed to a neurotoxic effect. Therefore, it can be concluded that the 'jerky leg movements,' which were barely detectable in one rat of 40, is not a significant toxicologic event. Based on the above reasoning, the no observable effect level is 150 ppm."

In addition, the Shell Chemical Company enclosed documentation from the veterinary pathologist at the contract laboratory that addresses the significance of the observations of "jerky leg movements" in rats in the study. The pathologist (W.A. Kelly) indicated that by the end of week 1 some of the animals in the 500 ppm group had abnormal forelimb and hindlimb movements and an abnormal gait which was recorded as "jerky leg movements" and "unsteady gait." By week 5 "jerky leg movements" were observed in some of the animals in the 300 ppm group. During week 11, prolonged flexion of the hindlimbs was noted in one rat in the 150 ppm group. This was the only time during the study that the rat in the 150 ppm group exhibited "jerky leg movements." The pathologist's summary was as follows:

"In summary, during weekly clinical examinations performed by the study director, group/treatment related clinical signs characterized by abnormal limb movements were noted for animals fed the 300 and 500 ppm MO 70616 diets. The presence of these signs was based on subjective evaluation and usually required close observation of limb movements during ambulation. The clinical signs were most

severe and observed early in the study in the 500 ppm MO 70616 group animals. Later in the study, some animals fed the 300 ppm MO 70616 diet had similar but milder clinical signs which were usually limited to a prolonged flexion of the hindlimbs observed as the animals entered their cages. On one occasion, prolonged flexion of the hindlimbs was noted for one of the 40 animals in the 150 ppm MO 70616 group. This mild clinical sign was not observed during subsequent weekly examinations of this animal."

The Toxicology Branch (TB) believes that neurological dysfunction as manifested by the "jerky leg movements" can be attributed to administration of the test material. There is a clear dose-response relationship as indicated by an increasing incidence of this pharmacotoxic sign in groups of animals as dosage increased, beginning at the 150 ppm dose level. In addition, the latency period for developing this pharmacotoxic sign was decreased as dosage increased. Also, the severity of the neurological signs observed increased as dosage increased. Although only one animal out of the 40 in the 150 ppm group displayed "jerky leg movements" it is believed that if the number of animals in the group was increased additional animals would probably have exhibited this clinical sign of toxicity. Considering that the one animal in the 150 ppm group exhibited mild clinical signs identical to the type observed in animals in the higher-dose groups, and the low number of animals per group, TB cannot discount the occurrence of the observation of "jerky leg movements" in the one animal even though it was only observed on one occasion.

The Shell Chemical Company also presents the argument that this abnormal clinical sign was a "reversible pharmacological action" and not a "significant toxicologic event." TB disagrees; the distinction between pharmacological and toxicological effects are difficult, if not impossible, to define. Therefore, TB considers the occurrence of "jerky leg movements" to be a pharmacotoxic effect, synonymous in a regulatory sense to an "adverse effect." In conclusion, the NOEL is still considered to be 50 ppm and will not be raised to 150 ppm.

Recommendation

Despite the arguments presented by the Shell Chemical Company concerning raising the NOEL from 50 ppm to 150 ppm, the TB maintains that the NOEL should be 50 ppm. TB cannot discount the observation of "jerky leg movements" in one

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animal in the 150 ppm group because the pharmacotoxic sign was observed with increasing frequency in other groups of animals as dosage increased.

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DATA EVALUATION RECORD

Subject: Subchronic (13-Week) Feeding Study of MO 70616 in the Rat for the Shell Development Company, Houston, Texas

Chemical: Fenvalerate (Pydrin) actually Es Fenvalerate

Accession No.: 257018, 257019, 257020

Laboratory: T.P.S., Inc., Mt. Vernon, Indiana

Study No./Report Date: 227A-101-030-84/December 20, 1984

Test Material/Purity: MO 70616 - WRC Tox Sample No. 730B/98.7% of the parent isomers of which 84% was the A-alpha isomer

Testing Period:: June 12, 1984 - September 17, 1984

Classification: Minimum Data

Materials and Methods:

Animals:

Thirty-four day-old male and female Sprague-Dawley rats were obtained from Camm Research, Wayne, New Jersey, and acclimated to the laboratory for a 28-day period prior to assignment to control and treatment groups. The rats placed on treatment were selected from a larger group of animals on the basis of body weight, body weight gain, and pretest physical examinations, including ophthalmoscopy. The rats were segregated by sex, assigned to test groups using a computer generated random list, and identified individually by ear punch. Additionally, 10 rats/sex were randomly selected to provide a pretest baseline reference for hematologic and serum chemistry values and assessment of pathogen burden prior to initiation of the study. Ten rats/sex were also randomly selected to provide clinical chemistry calibration values at the interim (5 rats/sex) and terminal (5 rats/sex) evaluations. Rats were assigned to groups as indicated below:

Group	Male Rats	Female Rats	Treatment
TP 1	30	30	Control
TP 2	30	30	50 ppm
TP 3	30	30	150 ppm
TP 4	30	30	300 ppm
TP 5	30	30	500 ppm

Environment:

All animals were caged in the same room. Rats were caged individually during the study in stainless steel cages with wire mesh bottoms and automatic watering systems. Cages were changed and the racks were rotated in position in the room at 2-week intervals. The flush pans under each cage were manually rinsed twice per day after observing whether feed had been spilled. The temperature was maintained at 23 ± 2 °C and humidity at 50 ± 10 percent. The lighting cycle was established at 12 hours on and 12 hours off. Room air was changed 10 to 15 times per hour. Water samples were taken prior to initiation of the study and shortly after termination and sent to Lancaster Laboratories, Lancaster, Pennsylvania, for chemical analysis for heavy metals, pesticides, and organic materials.

Test Diets:

The basal diet was Purina Certified Rodent Chow Meal #5002, which was analyzed by the Ralston Purina Company prior to initiation of the study for chlorinated and organophosphorus pesticides, heavy metals and PCB's. The test material (MO 70616) was kept refrigerated prior to incorporation into test diets. To prepare 90 kg of each test diet, the correct amount of the test material was dissolved in 150 ml of acetone and then mixed with 3 kg of basal diet in a 20 qt. Univex mixer until the acetone had evaporated. A premix weighing 10 kg was then made by mixing the contents of the Univex mixer with the appropriate amount of basal diet in a 60 qt. Hobart mixer for 20 minutes. The premix was later added to a Day ribbon mixer containing sufficient basal diet to make 90 kg of test diet and mixed for 60 minutes. Samples of each test diet were taken for analysis by the Shell Development Company for concentration of test material and for homogeneity. A second batch of test diets weighing 50 or 60 kg was similarly prepared. Test diets were stored at room temperature until used. Animals were provided their diets ad libitum. Each week the feeders were weighed, and were replaced with clean feeders containing the appropriate test diet.

Observations and Measurements:

Animals were observed twice daily and received weekly clinical examinations by a veterinarian. Blood from 10 rats/sex at pretest, 10 rats/sex/group at interim necropsy, 15 rats/sex/group at termination, and 5 rats/sex used for calibration at interim necropsy and at termination were evaluated. The hematologic evaluations included hematocrit, hemoglobin, erythrocyte count, erythrocyte indices (MCV, MCHC, MCH), total and differential leukocyte counts, erythrocyte morphology and platelet count. From the same animals cited above the following clinical chemistry determinations were made from their serum: sodium, phosphorus,

calcium, potassium, serum lactic dehydrogenase, serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), glucose, blood urea nitrogen, total bilirubin, total cholesterol, serum alkaline phosphatase, albumin, globulin, albumin/globulin ratio, and total protein. Prior to interim and terminal sacrifices, urine was collected from those animals scheduled for necropsy. The urine was examined for volume, gross appearance, glucose, ketones, pH, albumin, specific gravity, urobilinogen, bilirubin, and occult blood. After 7 weeks, 99 of the 100 male and female rats selected for the interim necropsy and, after 13 weeks, 144 of the 150 male and female rats selected for the terminal necropsy were sacrificed. (The difference between scheduled and actual number of animals sacrificed at these times was due to unexpected deaths and moribund sacrifices.)

Selection of animals for necropsy was based on random distribution lists. After an overnight fast, the animals were weighed and euthanatized with carbon dioxide gas. The external surface, all offices, the cranial cavity, carcass, the external and cut surfaces of the brain and spinal cord, the nasal cavity and paranasal sinuses, the thoracic, abdominal, and pelvic cavities with their associated organs and tissues, and the neck with its associated tissues and organs were examined grossly. The following organs were weighed: lungs, liver, kidneys, heart, testes with epididymides or uterus with cervix, and brain (including stem). The following tissues from all the control and high-dose animals were routinely processed, embedded in Paraplast, sectioned, stained with hematoxylin and eosin, and examined microscopically: brain (3 transverse sections - 1 section through the frontal cortex and basal ganglia, 1 section through the parietal cortex and thalamic area, and one section through the cerebellum and medulla oblongata), spinal cord (3 transverse sections - one section through the cervical area, thoracic area, and lumbar area), sciatic nerve (4 sections - proximal and distal areas of the left and right nerves), tibial nerves (2 sections), plantar nerves (2 sections), right median nerve, eyes, pituitary, adrenals, thyroid, parathyroid, parotid salivary gland, mandibular lymph node, mesenteric lymph node, external iliac lymph node, thymus, esophagus, trachea, aorta, heart, lungs with mainstem bronchi, liver (3 sections), kidneys (longitudinal section of left and transverse section of right, both through papillae), spleen, urinary bladder, testes, prostate, epididymis, ovaries, oviducts, uterus, cervix, stomach (a section from the fundus and pylorus), pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, skeletal muscle, skin, mammary gland (right inguinal from females only), femur (bone marrow), costochondral junction (right third rib), and other tissues with gross lesions. Sections from the pituitary, parotid salivary glands, lungs with mainstem bronchi, liver and kidneys were processed and evaluated for 25 male and 25 female animals in the 3 lower dose groups designated for the interim and terminal necropsies. Forty-nine of the 50

rats selected for electron microscopy were weighed, anesthetized with sodium pentobarbital, and then perfused with saline and 2 percent glutaraldehyde buffer solution. The brain, the right and left sciatic, tibial, and plantar nerves, a section of dorsal lumbar skin, and spinal cord were removed and fixed. The tissues were sectioned as follows: brain 1 to 2 mm sections through the frontal cortex and basal ganglia, one through the parietal cortex and thalamic area, and one through the cerebellum and medulla oblongata; spinal cord - 1 to 2 mm sections from the cervical, thoracic, and lumbar regions; sciatic, tibial and plantar nerves - 1 to 2 mm sections from right and left nerves; and dorsal lumbar skin - 1 to 2 mm sections. (It was not explained from which dose groups these animals came.) Electron microscopy was conducted on the tissues from one animal.

Statistics:

Weekly body weights were evaluated by analysis of covariance. Differences between control and treated group values for weekly body weights, estimated food consumption, hematologic and serum chemistry values, organ weights, and quantitative urinalysis data were analyzed for statistical significance by the method of Dunnett.

Results:

Clinical Signs:

One male in the 150 ppm group exhibited jerky leg movements during week 11 of the study. One female in the 150 ppm group developed alopecia on the forelimbs during week 6 and had spread to the thoracic area by week 13. In the 300 ppm group, 18 males and 24 females had jerky leg movements at some point in time during the study. One female rat in this group also had an unsteady gait from week 5 through 8. All rats in the 500 ppm had jerky leg movements and/or unsteady gait at some time during the course of the study. Additionally, 3 males and 1 female rat in the 500 ppm group had a scab-covered area at the base of the tail at the end of the study. One male rat in this group had hair loss of the forelimbs from weeks 2 through 6. One female in this group had stained hair in the urogenital area from weeks 4 to 6 and one female had a rough hair coat from weeks 8 to 11. Four female rats in this group appeared to be hypersensitive to sound during a portion of the study and one female rat appeared to be hyperactive from weeks 11 to 14. By the end of week 1, jerky leg movements and unsteady gaits were first detected in several animals in the 500 ppm group. When examined, animals with jerky leg movements shook their forepaws in a fanning motion as the forelimb was raised from the table surface. Flexion of the hind limbs was prolonged or exaggerated, and during ambulation the limb was momentarily suspended and held posteriorly. Return of the limb

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to the table surface was delayed. The gait was unsteady or uncoordinated in some affected animals. The severity of these signs appeared to be dose-related. The most severely affected animals in the 500 ppm group were hypersensitive to sound and had body tremors and/or convulsions eventually followed by death. Prior to death, nonspecific signs such as rough hair coat and scabs on the tail were observed in a few females in the 500 ppm group.

Body Weight and Food Consumption:

Male mean group body weight gain was decreased in animals fed 300 and 500 ppm in the diet from week 1 through week 6 when compared to the control group. Female mean group body weight gain was decreased in animals fed 500 ppm in the diet from week 1 through 5. Mean group food consumption was decreased in males in the 500 ppm group from week 1 through week 6. Mean group food consumption was decreased in females administered 500 ppm in the diet from week 1 through week 5. When food consumption was analyzed on a grams per kilogram body weight basis, males in the 500 ppm group exhibited an increase in relative food consumption from week 6 through week 13. In females, relative food consumption was increased in the group fed 500 ppm during weeks 6, 7, 8, 10, and 13.

Hematology:

There was a slight reduction in the erythrocyte count of females in the 500 ppm group at week 8. The remaining results obtained for test groups at week 8 compared favorably to those obtained for control animals. At termination of the study, there was a significant reduction in the hematocrit for all male test groups compared with the control group. However, when compared to mean hematocrit value obtained for the calibration group, no difference was apparent. Additionally, a dose-response relationship for the decrease in the hematocrit was not present. The erythrocyte count for males in the 300 ppm group and the mean hemoglobin levels for males in the 300 and 500 ppm groups were significantly lower than the values obtained for control males. However, when compared to males in the calibration group, no difference was discerned. These differences are sporadic and do not appear to be biologically significant.

Clinical Chemistry:

Males in the 500 ppm group exhibited a decrease in phosphorus levels when compared to all other groups of males at week 8. This is probably a spurious value since phosphorus levels were comparable among all groups at termination of the study. Females in the 500 ppm group had a decrease in potassium levels at week 8 which was attributed to slight hemolysis of the blood. When

compared to control males, all treated male groups exhibited slight decreases in glucose and total protein (primarily reflected as a decrease in globulin levels) at termination. However, when compared to values obtained for males in the calibration group, no differences were apparent. There was a very slight decrease in total protein (represented primarily as globulin levels) in females in the 500 ppm group. However, the level of total protein in females in this group was similar to females in the calibration group and was not considered to be biologically significant.

Urinalysis:

The specific gravity was increased in males and females in the 500 ppm group at weeks 7 and 13. The specific gravity was also increased in females in the 300 ppm group at week 13. Urobilinogen was slightly elevated in males and females in the 500 ppm group and in females in the 300 ppm group at week 7. Additionally, urobilinogen was increased in females in the 300 and 500 ppm groups at week 13. The above-mentioned findings are considered to be minor and are of questionable biological significance.

Necropsy:

At the interim sacrifice, 99 of the 100 selected animals for necropsy displayed no pattern of lesions that could be attributed to administration of the test material. One of the selected rats died prior to the interim sacrifice but had no lesions attributable to treatment. At terminal sacrifice, 6 of the 150 animals selected for necropsy died during the study. Five animals were females in the 500 ppm group of which 3 were reported to have died from self-inflicted trauma. The sixth animal in the 300 ppm group had accidentally fallen and succumbed to a skull fracture. Of the animals that survived to termination, 1 female in the 300 ppm group and 3 animals (2 males, 1 female) in the 500 group had scab-covered areas in the skin around the base of the tail. The other findings noted appeared not be related to treatment.

Organ Weights:

At the interim sacrifice, male and female rats in the 500 ppm group had a decrease in the absolute weight of the heart. Males in the 500 ppm group also exhibited a slight decrease in the absolute and relative weight of the liver. The relative weight of the brain was slightly increased in males in the 300 ppm group and was significantly increased in males in the 500 ppm group. The relative weight of the brain was also increased in females in the 300 and 500 ppm groups. Females in the 150, 300, and 500 ppm groups also had increases in the relative weight of the kidney. At termination, the absolute weight of the uterus

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was elevated in females in the 500 ppm group. The relative weight of the brain was increased in males and females in the 500 ppm group. Additionally, the relative weight of the kidneys was increased in males in the 300 and 500 ppm groups. These changes are minor, some do not show a dose-response relationship, and many reflect differences in body weights among the control and treated animals.

Histopathology:

At interim sacrifice, 2 of 10 male rats in the 500 ppm group had slight hypertrophy at the parenchymal cells in the pars intermedia of the pituitary gland. Slight hypertrophy of the parenchymal cells of the parotid salivary gland was observed in 4 of 10 males and 4 of 10 female rats in the 500 ppm group. One female with parotid salivary gland hypertrophy also exhibited slight hypertrophy of the submaxillary salivary glands. At terminal sacrifice, 3 of 15 male rats in the 500 ppm group had slight hypertrophy of the parenchymal cells in the pars intermedia of the pituitary gland. One of 15 male and 2 of 15 female rats in the 300 ppm group and 6 of 15 male and 4 of 15 females rats in the 500 ppm groups exhibited slight hypertrophy of the parenchymal cells of the parotid salivary gland. One male in the 500 ppm group with hypertrophy of the parotid salivary gland also had gross and microscopic evidence of hypertrophy of the submaxillary glands. Slight to moderate dermatitis was observed in 1 female rat in the 300 ppm group and in 3 rats (2 males, 1 female) in the 500 ppm group in the scab areas (noted at necropsy) near the back of the tail. The lesions mentioned above were not observed in animals **in the control, 50, or 150 ppm groups and are considered to be** related to treatment.

Discussion and Conclusions:

All animals in the 500 ppm group, several animals in the 300 ppm group, and one animal in the 150 ppm group had one or more clinical signs characteristic of neurological dysfunction. Several animals in the 500 ppm group had scabs around the base of the tail that were histologically identified as areas of dermatitis. Body weight gain was decreased in males and females in the 500 ppm group and in females in the 300 ppm group. Food consumption was decreased although relative food consumption was increased in animals in the 500 ppm group. At necropsy, male rats in the 500 ppm group exhibited slight hypertrophy of the parenchymal cells of the pars intermedia of the pituitary gland. Males and females in the 500 ppm group exhibited slight hypertrophy of the parenchymal cells of the parotid salivary gland and a few of these animals also had hypertrophy of the submaxillary salivary glands. A few animals in the 300 ppm group had hypertrophy of the parenchymal cells of the parotid salivary gland. The observations cited above are considered to be related to treatment.

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Note: Although sections of salivary gland were not examined in the low- and intermediate-dose groups, the occurrence of hypertrophy of the parenchymal cells of the submaxillary salivary glands was so low (1 male, 1 female) in the 500 ppm group, it is unexpected that the lesion would be observed in animals in the lower-dose groups.

LEL = 150 ppm (based on neurological signs)

NOEL = 50 ppm

Classification: Minimum Data

Recommendations: The sponsor should forward information to the Agency which describes the "self-inflicted trauma" which caused the deaths of 3 females in the 500 ppm group.