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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANC

MEMORANDUM

DATE: August 3, 1981

SUBJECT: PP#0F2413; Thiodicarb (Larvin); 6-Month Dog Study
CASWELL#900AA Accession#070153

FROM: William Dykstra, Toxicologist
Toxicology Branch, HED (TS-769)

WDD 8/3/81
DC 8/3/81

TO: Jay Ellenberger (12)
Registration Division (TS-767)
and
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

Recommendations:

1. The systemic NOEl for the 6-month dog feeding study with Thiodicarb is considered to be 15 mg/kg/day (Group 3).

   The cholinesterase NOEL is considered to be 15 mg/kg/day (Group 3).

   The study is acceptable as Core-Minimum Data.

Review:

1. Subchronic Toxicity Study in Dogs with Larvin Thiodicarb (Hazelton Project No. 400-626; Final Report; May 11, 1981)

   Forty-eight, healthy, young adult, purebred beagles (twenty-four per sex) were used in the study. The dogs ranged from twenty-six to thirty weeks of age at initiation of treatment and were individually housed in stainless steel cages with ground Wayne Lab Dog Diet and water (via an automated watering system) available ad libitum. The ambient temperature in the roon housing the dogs was recorded at least once daily. Each dog was uniquely identified by an ear tag.

The dogs selected for study use were stratified by body weight and randomly assigned to the following groups using a table of random permutations of nine:

Group	Number of Animals		Dose Level
	Males	Females	mg/kg/day
1 (control)	6	6	0
2 (low)	6	6	5
3 (mid)	6	6	15
4 (high)	6	6	45

All of the dogs were observed twice daily for mortality and moribundity and once daily for appearance, behavior, appetite, elimination, and signs of toxic and pharmacologic effects. These observations were recorded daily. Body weights and food consumptions were recorded weekly beginning one week prior to treatment.

The following clinical laboratory studies were performed on all dogs pretreatment (Week-3) and at weeks 4, 8, 13, 17, 21 and 26.

Hematology: hematocrit, hemoglobin, RBC, total and differential WBC counts, and platelet count.

Clinical Chemistry: total cholesterol, BUN, SGPT, SGOT, LDH, Alkaline phosphatase, total protein, albumin, albumin/globulin ratio, globulin, glucose, Na^+, K^+, Ca^{++}, Cl^-, direct bilirubin and total bilirubin.

Urinalysis: appearance, specific gravity, protein, pH, glucose, bilirubin, ketones, urobilinogen, reducing substances, and microscopic examination of the sediment.

In addition, plasma and red cell cholinesterase determinations were performed on all dogs twice pretreatment (Week-3 as fasted samples and Week-2 as unfasted samples). They were also performed on the day prior to the regularly scheduled bleeding (unfasted sample) and the regularly scheduled bleeding day (fasted samples) during weeks 8, 17, and 26. Brain cholinesterase determinations were performed on all dogs at the time of sacrifice.

Blood samples were collected from the jugular veins on dogs which had been food and water fasted overnight prior to collection. Urine samples were collected from cage-pan runoff.

Opthalmologic examinations were performed on all dogs prior to treatment and at termination using a slit lamp, an indirect opthalmoscope, and 1% tropicamide ophthalmic solution as a mydriatic.

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All surviving dogs were sacrificed after twenty-six weeks of treatment by exsanguination while under the effect of Surital anesthesia. Complete necropsies were performed on all dogs.

The terminal body weight and the weights of the following organs were recorded and the organ/body weight ratios determined: brain (including brainstem), pituitary, thyroid, heart, liver, kidneys, adrenals, and testes with epididymides (males) or ovaries (females).

The following tissues were preserved in 10% neutral buffered formalin: brain (three sections), pituitary, spinal cord (thoracic and lumbar), eyes, salivary glands (mandibular), thyroid with parathyroids, thymus, trachea, esophagus, lungs (two lobes), heart, aorta, liver (two lobes), gall bladder, spleen, kidneys, adrenals, stomach, pancreas, small intestine (duodendum), jejunum, and ileum), large intestine (cecum and colon), mesenteric lymph node, urinary bladder, prostate (males), ovaries and uterus (females), mammary gland, skin, bone (femur), bone marrow (femur), nerve with adjacent muscule, and any gross lesion.

The testes with epididymides from each male were preserved in Bouin's fixative.

All of the preserved tissues from all of the dogs were embedded in paraplast, sectioned, stained with hematoxylin and eosin, and examined microscopically.

Statistical analyses of the data were performed.

Results:

One high-dose (Group 4) female was sacrificed in a moribund condition at the end of Week 19.

There was a dose-related increase in the combined incidence of soft stools, mucoid stools and diarrhea for the treated males. This same finding was not apparent in the treated females. No other treatment related findings were noted.

Evaluation of the data shows no changes in either the body weights or the food consumptions which could be attributed to treatment.

The SGPT values of the Group 4 males and females were consistently higher than control at all compound-treatment intervals with the Week 4 value for the Group 4 males being significantly increased. The mean value for the Group 3 females at Week 8 was also significantly increased over the female control value.

The calcium values for the Group 4 males at Weeks 13, 17, 21, and 26 and the Group 4 females at Weeks 8 and 26 were decreased (significant for the females at Week 8 and males at Weeks 17 and 21). In addition, the calcium values for the Group 2 males and Group 3 females at Week 21 were decreased. The total protein values for the Group 4 males at Weeks 17, 21 and 26 were decreased (significant at Week 26). The same findings, although less pronounced, were noted for the Group 4 females at Weeks 13, 17 and 21.

The globulin levels of the Group 4 dogs were decreased at all intervals after initiation and, with the exception of the Week 17 value for the males, corresponding increases were noted for the albumin/globulin ratios. The albumin/globulin ratio increases for the Group 4 females at Weeks 8 and 13 were statistically significant.

The LDH values of all treated dogs were decreased at Week 4 when compared to the respective control values. With the exception of the Group 4 males, all of these changes were significant; however, it should be noted that the control values at this interval were higher than any values obtained during the study. Numerous instances of decreased mean values were noted for the compound-treated males and females beginning with Week 13 with the value for the Group 2 females at Week 13 being significant.

Evaluation of the plasma cholinesterase and RBC cholinesterase values revealed that seven of twelve plasma cholinesterase and nine of twelve RBC cholinesterase values for the Group 4 dogs were either significantly increased or greater than both the pretreatment and the control values. The mean plasma cholinesterase increases were significant for Group 4 females at Weeks 8 and 17. The mean RBC increased cholinesterase values for Group 4 female dogs at Weeks 8 and 26 were significant. In addition to the above, three of twelve plasma cholinesterase and five of twelve RBC cholinesterase values from the Group 3 dogs and one of twelve plasma cholinesterase and three of twelve RBC cholinesterase values from the Group 2 dogs were also elevated above the respective pretreatment and control values. When comparing unfasted to fasted values at the same intervals (samples obtained twenty-four hours apart) the control and test values from the fasted dogs were almost always elevated over the values from the unfasted dogs. The exceptions (fasted values equal to or lower than unfasted values) for the control males and females and the Group 2 males at Week 17 and RBC cholinesterase were for the Group 4 females at Week 8. All remaining values from the clinical laboratory studies were essentially normal.

Evaluation of urinalysis data revealed no changes which could be considered the result of treatment. No treatment-related ophthalmologic findings were noted in any of the compound-related treated dogs.

No treatment-related effects were noted with respect to terminal body weight and organ weight data, and gross and microscopic pathology.

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Conclusion:

The systemic NOEL is considered to be Group 3 (15 mg/kg/day). The cholinesterase NOEL is considered to be 15 mg/kg/day (Group 3). The systemic LEL is considered to be Group 4 (45 mg/kg/day) which demonstrated significant changes in hematological and clinical chemistry values.

Classification: Core-Minimum Data

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