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Histopathological examinations were conducted on the tissues of rats of the control, 3.0, and 1.0 mg/kg/day doses at 12 months and from rats of the control and 3.0 mg/kg/day groups at the other necropsies. Tissues of all rats with gross evidence of tumor development were also subjected to histopathologic evaluation.

2. Results

No alterations or deviations attributable to treatment were noted by any of the following criteria:

| | |
|---|---|
| appearance and demeanor | mortality |
| body weight | food consumption |
| hematology | urinalyses |
| clinical chemistry | organ weight |
| gross pathology | histopathology |

The plasma and RBC ChE activity was consistently reduced in the 3.0 and 1.0 mg/kg/day rats of both sexes. The brain ChE was inhibited in the 3.0 mg/kg/day rats. The RBC ChE of the 0.1 mg/kg/day F was inhibited at 2 of the 8 test periods (30 and 365 days). The remaining 6 determinations were normal.

3. Conclusion

Based upon RBC ChE activity, the NEL for rats fed Dursban for 2 years is 0.1 mg/kg/day. (2 ppm)

B. Results of Two-Year Dietary Feeding Studies on Dowco 179 in Beagle Dogs (Dow; December 10, 1971)

1. Procedure

Dowco 179 mixed with ground Purina chow was fed to Beagle Dogs for up to 2 years at levels of 0, 3.0, 1.0, 0.03, or 0.01 mg/kg/day. Groups of 3 dogs/sex/dosage level were fed for 1 year and necropsied immediately or after a 3 month recovery period in Phase A. Groups of 4 dogs/sex/dosage level were fed for 2 years in Phase B. All dogs were observed daily for changes in demeanor. Body weights were recorded weekly the first 6 months and bi-weekly thereafter. Food intake was measured weekly

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during months 1-3 and 1 week/month thereafter.

Hematologic studies (PCV, Hgb, RBC, total and differential WBC, prothrombin) were conducted on all the 0, 3.0, and 1.0 mg/kg/day dogs twice pre-test and at 1, 3 (A), 6 (B), 12, and 24 (B) months. Urinalyses (specific gravity, pH, sugar, albumin, microscopic sediment exam) were performed on the same dogs at pre-test 1, 12, and 24 (B) months. BUN, SAP, SGOT, and SGPT were measured on all Phase A dogs twice pre-test and after 1, 3, 6, and 12 months. All Phase B dogs were tested for these compounds twice pre-test and after 1 and 24 months. The 0, 3.0, and 1.0 dogs were also sampled after 6, 12, and 18 months. BSP was measured on all Phase B dogs twice pre-test and terminally and on the 0, 3.0, and 1.0 dogs after 12 months.

ChE activity in the plasma and RBC of all dogs was determined 2(B) to 3(A) times prior to feeding the test diets, and after 1 week and 1, 3, 6, 9(A), 12, 15(B), 18(B), and 24(B) months. RBC and plasma ChE was measured on all dogs (A) placed on the recovery diet and RBC ChE was measured on the 0, 3.0, 1.0, and 0.1 dogs at 6 weeks and the 0, 3.0, and 1.0 dogs after 3 months on control feed. Brain ChE was measured on all dogs necropsied after 1 and 2 years and on the 0, 3.0, and 1.0 mg/kg/day dogs placed on recovery for 3 months. A modification of the pH Stat method was used for all ChE determinations.

The Phase B dogs were given complete physical examinations prior to termination including routine neurologic and ophthalmoscopic evaluations. Following gross necropsy examinations, the heart, liver, brain, kidneys, spleen, and testes were removed and weighed. Microscopic examinations were conducted on the following tissues from the 0, 3.0, and 1.0 mg/kg/day dogs from Phase A and from 0 and 3.0 Phase B dogs (H&E stain):

| | | | |
|---|---|---|---|
| heart | pituitary gland | esophagus | sciatic nerve |
| liver | thyroid gland | lungs | spinal cord |
| brain | parathyroid gland | aorta | sternum |
| kidneys | small intestine | stomach | sternal bone marrow |
| spleen | mesenteric lymph nodes | pancreas | adrenal gland |
| testes | urinary bladder | colon | |
| eye | accessory sex glands | ovaries | |
| trachea | skeletal muscle | uterus | |

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2. Results

No treatment-related signs were noted by the following criteria:

| | |
|---|---|
| Appearance and demeanor | Body weight |
| Food consumption | Hematology |
| Urinalyses | Clinical Chemistry |

Ante-mortem physical examination (Phase B only)
Gross and microscopic post-mortem examination

The mean liver/body weight ratio in male dogs receiving 3.0 mg/kg/day Dowco 179 was increased. The plasma ChE was significantly depressed at dosages of 0.1 mg/kg/day for 1 year in the Phase A dogs and 541 days in the Phase B dogs. The plasma ChE of the 3.0 and 1.0 mg/kg/day dogs was depressed throughout the study period. The 0.03 mg/kg/day dogs exhibited a depression in plasma ChE at some sampling times. Plasma ChE returned to normal within 2 weeks after being fed control diet. The ChE activities of RBC of dogs receiving 3.0 and 1.0 mg/kg/day were depressed. RBC ChE activity returned to pre-test levels in male and female dogs maintained on control feed for 3 months subsequent to receiving doses of 3.0 and 1.0 mg/kg/day Dowco 179 for 1 year. Brain ChE activity was slightly depressed in dogs receiving 3.0 mg/kg/day for 2 years.

3. Conclusions

The ChE NEL in dogs fed Dowco 179 for 2 years based upon RBC and plasma ChE inhibition is 0.1 mg/kg/day. (4 ppm).

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