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1 - SEP 1978

Dursban (Chlorpyrifos)

PROPRIETARY

Caswell #219AA
Shaughnessy #059101

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Reference - The toxicology data found here is basically a presentation of previously summarized data on Dursban found in the files of Robert Coberly of the Toxicology Branch, Registration Division. The toxicology data was garnered from the following pesticide petitions: 817; 1306; 1370; 1445; and 1595. Additional data was also searched for using the Level III catalog and petitions in the Toxicology and Chemistry Branches. It was concluded that the summary data files fairly reflected the data available in EPA files on Dursban.

Animal Toxicology Data

Acute Oral LD₅₀'s

<u>Species</u>	<u>Sex</u>	<u>Vehicle</u>	<u>LD₅₀ - 95% C.L. (mg/kg)</u>
Mouse	M	Corn Oil	62.0
Rat	F	Corn Oil	137 (97-188) ✓
Rat	M	Corn Oil	163 (97-276) ✓
Guinea Pig	M	Corn Oil	504 (299-850) ✓
Rabbit	M and F	Corn Oil	1000-2000 (range)

Acute Dermal LD₅₀

Rats of unknown sex had an LD₅₀ of 202 (176-232) mg/kg.

Eye Irritation

Rabbits showed slight pain and irritation.

Acute Inhalation

Acute inhalation was determined on Dursban 24 E. The LC₅₀ was greater than 5.0 mg/liter after an exposure of one hour.

Neurotoxicity

Neurotoxicity was done in 23 Leg Horn laying hens. Doses of 40, 75, 100, 150 mg/kg were used. No evidence of delayed ataxia or paralysis up to 27 days post treatment. No microscopic pathology was reported. Ruelene was used as a positive control. This test however was found to

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be not sufficient and a second neurotoxicity study was requested. The second study has recently been reviewed and accepted by the toxicology branch. Dursban was found to be negative for neurotoxicity.

Subacute Inhalation

A twenty-one day inhalation study was conducted on rats. Exposure was 7 hrs./day at 0.007 micrograms per liter. No deaths were recorded and no cholinesterase effects were noted.

Subacute Dermal

Three to ten applications per rabbit produced slight hyperemia and slight burns. The areas healed in 21 days.

Subacute Feeding

Rats	20 Weeks	NEL. 0.03 mg/kg/day
Rats	90 Day	NEL. less than 10.0 ppm (ChE)
		NEL. systemic 100.0 ppm
Rats	6 Months	NEL. 0.15 mg/kg/day
Monkeys	6 Months	NEL. 0.08 mg/kg/day
Dogs	93 Days	Less than 0.08 mg/kg/day

Ninety-Day Dietary Feeding.

Ten rats per sex per dose were dosed at the following levels (expressed as percent) zero; 0.1; 0.03; 0.01; 0.003; 0.001 and 0.1. The 0.1% dose was removed because of high mortality and dramatic weight loss. Additional groups of 6 rats/sex/dose were fed the same diets for determination of interim ChE determinations. Microscopic examinations were performed on 19 organs per animal. The following determination were made:

Cholinesterase NEL equivalent to 10. ppm
Systemic NEL equivalent to 100 ppm

Twenty Week Rat Feeding (dietary)

This study was conducted in two phases.

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Ten rats per sex per dose of the Charles River strain were dosed with zero; 0.3; 1.0; 3.0 and 10.0 mg/kg/day (Phase I). The zero and 0.3 mg/kg/day rats were fed on the diet for 13 weeks. The animals on the 1.0; 3.0; and 10.0 mg/kg/day diet were fed at these levels for four weeks, then taken off their diet for three weeks and finally placed back on the diet at levels of zero 0.03 or 0.10 mg/kg day for 13 weeks (Phase II). The ChE no-effect-level for rats in this study was 0.03 mg/kg/day. There was apparently no gross or histopathology conducted.

Six Month Rat Dietary

Ten Sprague-Dawley rats per sex per dose were dosed at levels of zero; 0.03; 0.15 or 0.75 mg/kg/day. Animals were examined daily and body weights and food consumption were recorded weekly. Examination included clinical chemistry, gross and microscopic pathology. Red Blood cell and plasma cholinesterase was lowered at 0.75 mg/kg/day. Brain cholinesterase was unaltered. No other changes were noted in any of the other groups of animals. The cholinesterase NEL was determined to be 0.15 mg/kg/day.

Six Month Monkey Study (oral intubation)

Rhesus monkeys (*Macaca mulatta*) were orally intubated at three dose levels. Doses administered were; 0.08 mg/kg/day (2 males, 1 female); 0.40 mg/kg/day (2 males, 1 female); 2.0 mg/kg/day (2 males, 2 females) and controls (no dose) (2 males, 2 females).

Daily observations were made and weight recorded monthly. Clinical chemistry and hematology studies were conducted at 2, 4, and 6 months. One monkey per sex was necropsied from the control groups and the two high doses. Twenty-three organs of each animal were examined. In addition, the brain cerebellum and medulla oblongata were examined. RBC-C was depressed at doses of 0.4 and 2.0 mg/kg. The NEL level for cholinesterase inhibition was determined to be 0.08 mg/kg/day.

Ninety-Three Day Beagle (dietary) Study.

Four animals per sex were used as control. Two animals per sex were dosed with 0.006 and 0.002% of Dursban (equivalent to 1.8 and 0.8 mg/kg/day).

Due to adjustments of dose during the experiment a cholinesterase no-effect level was not determined. However the NEL would be less than 0.002% of the diet. Twenty-six organs were examined microscopically. No apparent adverse effects were noted.

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Chronic Toxicity - 2-Year Dietary Pat

Five rats per sex per dose were fed 3.0; 1.0; 0.1; 0.03 and 0.01 mg/kg/day of compound in feed. Supplementary groups were set up for interim pathological examinations and periodic cholinesterase determinations. Body weight and food consumption was monitored. Hematological examination and urine analysis were conducted; plasma and RBC cholinesterase were checked. BUN, SAP and SGPT levels were also determined. Gross pathology was conducted on 29 organs of each animal as well as any nodules or masses suggestive of tumor development, or other pathological process. Necropsies were conducted on the rats included in the study for that purpose as well as those which survived the two year study. Histopathological examinations were conducted on the tissues of rats of the controls, 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 other necropsies.

No alterations or deviations attributable to treatment were noted by the nine criteria used. The NEL was determined to be 0.1 mg/kg/day, equivalent to 2 ppm.

Oncogenicity

Dr. Reto Engler has been informed by a representative of Diamond Shamrock that Dursban will be classified as a carcinogen by NCI (Details unknown as of July 1978)

Chronic Toxicity - Beagle Dogs - 2-years Dietary

This study was conducted in two phases.

Phase A. - Groups of 3 dogs/sex/dose were fed at levels of zero; 3.0; 1.0; 0.03 or 0.01 mg/kg/day for 1 year and necropsied at 12 months or necropsied after a 3 month recovery period.

Phase B - Groups of 4 dogs/sex/dose (same doses as above) were fed for 2-years in Phase B. Weight and food consumption were monitored regularly. Hematology, blood chemistry and urinalysis were carried out. Thirty-nine organs from each animal were examined histologically. Animals in Phase A receiving zero; 3.0 and 1.0 mg/kg/day as well as animals in Phase B receiving doses of zero and 3.0 mg/kg/day were examined microscopically.

No treatment related signs were noted using 10 criteria.

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The RBC-ChE no-effect-level was determined to be 0.1 mg/kg/day equivalent to 4.0 ppm.

Reproduction/Teratology

Rats of the Sprague-Dawley strain (10M + 20F) of the P₁ generation were fed zero; 0.03; 0.1; 0.3 mg/kg/day of compound in their diet. Beginning with the P₂ generation rats were fed zero, 0.1; 0.3 and 1.0 mg/kg/day of compound in their diet.

The F₃A litter was weaned, the indices computed, gross and microscopic examinations conducted. Thirty-two organs of each animal were examined.

The F₃B generation was examined for terata. Two-thirds were examined for skeletal defects and one-third for internal anomalies.

The NEL for terata was determined to be "up to 1.0 mg/kg;" the NEL for reproduction was greater than 1.0 mg/kg; the NEL for ChE was 0.1 mg/kg based on RBC-ChE-inhibition.

Maximum Permissible Intake

MPI has been calculated at 0.6 mg/day. This value is based upon a two year rat feeding study showing a cholinesterase no effect level of 2.0 ppm and a cholinesterase no-effect-level (NEL) of 4.0 ppm in dogs.

Human Toxicity Data

Acute/Subacute Oral

Sixteen male volunteers were divided into four groups of four. Dowco 179 (Dursban-Technical) was administered orally in tablet form to three test groups. One group served as control. Tablets were administered daily according to the following doses and lengths of time.

Dose (mg/kg/day)	Time in Days
0.0	49
0.10	9
0.03	22
0.014	27

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Hematology and serum chemistry were done weekly, while RBC and plasma cholinesterase activity were determined twice a week. Urinalysis was determined weekly.

There were no treatment related effects for hematology, serum chemistry and urine. There was no effect on RBC-cholinesterase activity; however plasma cholinesterase was significantly depressed at 0.1 mg/kg/day and slightly (but not significantly) at 0.03 mg/kg/day.

Based upon RBC cholinesterase inhibition by Dowco 179 a NEL for humans was not determined. The NEL must therefore be stated as being equal to or greater than the highest level administered which was 0.10 mg/kg/day.

Acute/Subacute Dermal

Dursban 6 concentrate was applied to the skin of the back and abdominal areas to seven human volunteers. Exposure time was for 12 hours with a 12 hour non-exposure time between applications. Single applications were given at dose levels of 1.0; 1.5; 3.0; 5.0; or 7.5 mg/kg. Multiple applications were administered as follows:

- 2 to 3 applications at 25 mg/kg
- 4 applications at 10 mg/kg
- 20 applications at 5 mg/kg

A dose level of 25 mg/kg and three applications resulted in a decreased plasma cholinesterase level which was the only apparent effect of all dose levels. It is also noted that negative results were received from a lymphocyte tissue culture to determine whether morphological alteration had taken place in the chromosomes of the genetic material.

Addendum

Toxicology Branch files show a memorandum dated April 6, 1977 stating that a published study by T.B. Gaines (Ref.: Tox. and Appl. Pcol. 14: 515-534 (1969) suggested possible delayed neurotoxicity for Dursban.

Toxicology Branch reviews dated June 13 and September 30, 1977 requested the following studies be conducted:

1. A new neurotoxicity study (reviewed and accepted as of June 1977)
 2. A new teratology study (in progress)
 3. A second oncogenicity study (see oncogenicity paragraph)
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4. A mutagenic study (this request for a study was deferred until mutagenicity requirements were published).

Submitted By: Albin B. Kocialski, Ph.D.

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