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CASWELL FILE

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Supplement to Two-Year Chronic Feeding Study in Dogs With Chlorpyrifos.
EPA ID No. 464-558 CASWELL #219AA

TO: Jay Ellenberger (12)
Registration Division (TS-767)

FROM: D. Stephen Saunders Jr., Ph.D.
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TOX/HED (TS-769)

DSS 10-4-85

THRU: Laurence D. Chitlik, DABT
Head, Section V
TOX/HED (TS-769)
and
Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-679)

10/8/85

Action Requested

Review the supplement to the chlorpyrifos chronic feeding study in dogs, submitted in response to the chlorpyrifos registration standard.

Recommendations

The submitted addendum resolves the questions raised by the review of the two-year chronic feeding study in dogs (study #T35, 12-44793-18, reviewed by Dr. J. Quest in the chlorpyrifos registration standard, memo Rurin to Ellenberger, 5-25-84).

It is recommended that the study be upgraded to Core-Minimum status. The conclusions of the original review are unchanged by the submitted addendum. The NOEL for inhibition of plasma cholinesterase activity is 0.01 mg/kg/day (LEL = 0.03 mg/kg/day), and the NOEL for systemic effects is 1.0 mg/kg/day (LEL = 3.0 mg/kg/day) based on alterations in absolute and relative liver weights.

Data Evaluation Record

Study Type: Addendum to the dog chronc feeding study.

Study Identification: "SUPPLEMENT TO ORIGINAL REPORT ENTITLED Results of Two-Year Dietary Feeding Studies on DOWCO 179 in Beagle Dogs."

Lab. performing study:	Mammalian and Environmental Toxicology Research Labs. Dow Chemical Co.
Sponsor:	Dow Chemical USA
Study no.:	NRT 3512-44793-18
Accession no.:	257601
Report date:	3/26/85
Submitted to EPA:	4/10/85
Study authors:	Kociba, R.J., McCollister, S.B., Keyes, D.G. and Dittenber, D.A.
Reviewed By:	D. Stephen Saunders Jr., Ph.D. Toxicologist, Section V TOX/HED (TS-769)
Approved By:	Laurence D. Chitlik, DABT Head, Section V TOX/HED (TS-769)

Conclusions: No additional treatment-related findings were presented in this addendum. The submitted data resolve the issues raised in the chlorpyrifos registration standard concerning this study.

Classification: Core-Minimum When considered with the data from the dog chronic feeding study (#T35, 12-44793-18).

Background

This addendum was submitted in response to the chlorpyrifos registration standard (memo G. Burin to J. Ellenberger, 5-25-84), in which the chronic dog study (MRID #00064933) was reviewed by Dr. J. Ouest. That study was found deficient because "data was not available at the intervals specified in the protocol for several of the parameters that were monitored (e.g. body weight, ophthalmology, etc.)" and because "histology data was not submitted for each of the individual tissues examined". The study was classified as Core-Supplementary data.

Included in the present submission were:

1) Individual animal body weights.

2) Individual animal pre-test and pre-terminal physical examinations.

3) Summary clinical examinations which provided data only for animals that were not normal.

4) Individual animal pretest ophthalmoscopic examinations.

(con't)

Background (con't)

5) A list of ophthalmoscopic observations and procedures performed in the course of the study.

6) The trade names and suppliers of veterinary medicines used during the study.

7) An inventory of tissues examined histologically in treated dogs.

Materials and Methods

This study consisted of two phases: Phase I- 3 dogs/sex/dose were exposed to dietary concentrations of 0, 0.01, 0.03, 0.1, 1.0 or 3.0 mg/kg/day of chlorpyrifos for 1 year. One dog/group was sacrificed at one year, and the remaining 2 dogs/group were sacrificed after a 3 month recovery period. Phase II- 4 dogs/sex/dose were exposed to the same dietary concentrations of chlorpyrifos as in Phase I for a total of 2 years, at which time all dogs were sacrificed.

The protocol for this study was previously reviewed in the chlorpyrifos registration standard (see "Background" of this review).

Results

A. Body Weights- Data were submitted for individual animal body weights, taken at approximately weekly intervals for the first 7 months of treatment, and at biweekly intervals thereafter.

The submitted data demonstrate that the test article had little effect on weight gain. No toxicologically significant difference in body weight between control and treated animals was apparent at any of the intervals reported.

B. Physical Examinations: (1) Pre-test examinations indicated that most dogs were in generally good health before initiation of Phase I or II. Some animals were treated for infections or other ailments, however apparently none were considered sufficiently serious by the examining veterinarian to warrant replacement of test animals.

(2) Pre-terminal examinations of Phase II dogs did not reveal any apparent treatment-related findings. Common findings in most animals without relation to treatment were "accumulation of debris" in the ears and dental tartar.

(3) Clinical observations were reported for Phase I dogs weekly for the first month, biweekly for the next 3 months, and then at approximately monthly intervals until 1 year. Data consisted of a summary table which noted only animals with significant findings. Most entries stated "All dogs appear normal". No treatment-related findings were apparent. One high dose male (#457) had a small tumor removed from his left front paw after approximately one-month of treatment. This tumor was diagnosed as a histiocytoma. One male from the 0.03 mg/kg/day group (#473) was treated for an abcess of the neck after 4 months of treatment. One high dose female was treated for an abcess below the right eye after about 10 months of treatment, and two 0.1 mg/kg/day females were treated in the fourth month for wounds sustained from fighting.

(4) Clinical observations of Phase II animals were recorded at approximately biweekly intervals for the first three months of treatment, and at approximately monthly intervals thereafter. Data consisted of summary tables which noted only those animals with significant findings.

No treatment-related findings were apparent. Control male #20353 was treated for a salivary cyst after 3 months of treatment, and control male #489 was treated for "milky eye" after about 18 months of treatment. High dose male #511 was reported to have "sore feet" or possible "hind-quarter lameness" at several of the reported intervals. After x-rays and blood examinations, no apparent cause was found. This animal was also treated for "ulcerative otitis externa" and "cloudy eye". The remaining high dose males were apparently normal. Males treated with 1.0 mg/kg were normal, with the exceptions of #496 who was treated for an apparent eye infection in month 5, and #501 who was treated for injuries sustained in a fight during month 12. Male #496 from the 1.0 mg/kg/day group was treated from month 18 through month 23 with daily "Cytomel" tablets and occasional baths in "Weladol" shampoo due to an apparent skin ailment. No other remarkable findings were noted in males.

One control female (#487) was noted to have "sore feet" from month 7 through month 12. Two high dose females (#516 and 486) were treated in month 13 for wounds sustained in a fight. No other notable findings were reported for the remaining treated females.

C. Ophthalmoscopic Examinations: (1) Pretest examinations of Phase I dogs revealed that most animals were "within normal limits", with the exceptions of:

#465 (control male)- removal of glandular tissue of nictating membrane.
#472 (0.01 mg/kg male)- optic disc of left eye misshapen, not considered pathological.
#462 (0.01 mg/kg male)- depression in center of optic disc; glandular tissue of nictating membrane surgically removed.

(2) Pretest examinations of Phase II dogs similarly revealed that all dogs were "within normal limits" with the exception of #485 (0.01 mg/kg male) who was reported to have "mild entropion- left eye".

(3) The only ophthalmoscopic observation reported for dogs during the treatment period was for dog #496 (male, 1.0 mg/kg), who during month 5 was reported to have "slight conjunctivitis of the left eye, right cornea opaque", and was treated with Neo-Polycin ointment.

(4) Preterminal examinations of Phase II dogs revealed that all animals were "within normal limits", with the following exceptions:

#511 (high dose male)- mature cataract, left eye.
#490 (male, 0.01 mg/kg)- 1mm circular posterior capsular opacity, right eye.
#487 (female, control)- corneal opacity, left eye.
#507 (female, 0.03 mg/kg)- 2mm pannus, right corneal surface.

D. Inventory of Tissues Examined Histologically- (1) Phase I- This inventory indicated that tissues were examined from 3/3 males and females from the control, high dose and 1.0 mg/kg/day groups, 1/3 males of the 0.01 mg/kg/day groups, and 1/3 females from the 0.03 mg/kg/day group. Apparently, no tissues from the remaining treated males or females were examined microscopically.

Tabulation of the tissue inventory (by the reviewer) indicated that the same number of tissues was not examined in all animals (see attached inventory). Missing tissues included liver (1/3 control and high dose males), gall bladder (1/3 control and high dose males, 1/3 high dose females), stomach (1/3 control females), thyroid (2/3 control males); and other tissues too numerous to specify. However, the majority of major tissues and organs were examined in most animals. Although the conduct of histopathological examinations in this study certainly cannot be considered exemplary, in the opinion of this reviewer an adequate number of tissues was examined.

When the tissue inventory is considered with the individual animal findings presented in the original study report, the minimal amount of data necessary for review of the study is provided. The more desirable manner of reporting histopathological data in a chronic feeding study is to provide findings (both positive and negative) by individual animal for each tissue examined.

(2) Phase II- The inventory indicated that tissues were examined from 4/4 control and high dose males and females, and 1/4 males from the 1.0 mg/kg/day group. Apparently, no tissues from the remaining treated males and females were examined for microscopic changes.

As was noted for Phase I animals, the tissue inventory (tabulated by the reviewer) indicated that an equal number of tissues was not examined in all animals (see attached inventory). Similar to Phase I, although numerous tissues were missing from control and treated dogs, a majority of major organs in most animals was examined, with the exception of 3/4 hearts from control females which were not examined. Since no potential treatment-related findings were identified in this tissue, the lack of examination of control tissues does not compromise the interpretation of the study. Other missing tissues included spleen (1/4 control females, 1/4 high dose males and females), stomach (1/4 high dose males and control females), gall bladder (2/4 high dose males, 1/4 control and high dose females), urinary bladder (1/4 control, 2/4 high dose males, 1/4 high dose females), ovary (1/4 control and high dose females) and uterus (1/4 high dose females), and other tissues too numerous to specify.

For the reasons presented above, the minimal amount of data necessary for review of the study is provided by the tissue inventory and the individual animal findings in the original study report.

Discussion

The data submitted in this addendum to the 2-year dog feeding study did not reveal any additional treatment-related effects. The original review of this study (reviewed by J. Ouest as part of the chlorpyrifos registration standard) found that the major effects of treatment were inhibition of plasma and erythrocyte cholinesterase activities, with a NOEL of 0.01 mg/kg/day for plasma inhibition, and an increase in absolute and relative liver weights in high dose (3.0 mg/kg/day) males. The study was considered deficient because individual animal data were not submitted for body weights or ophthalmoscopic examinations, nor were the results of histological examinations presented for each tissue examined.

In the present submission, individual animal data for body weights and eye examinations were submitted along with an inventory of tissues examined for histopathological changes. When considered with the data reported in the original study report, the minimal amount of data necessary for review of the study is provided. The questions raised by the registration standard regarding the dog study are therefore resolved.

Phase I { 1 yr; * 3 mo recovery

	MALE										FEMALE									
	control			3 mg/kg			1 mg/kg			0.01 mg/kg	control			.3 mg/kg			1 mg/kg			0.03 mg/kg
Tissue	465	444*	445*	457	469*	448*	453	437*	464*	452*	475	478*	481*	474	450*	483*	461	455*	482*	447*
spleen	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
liver	✓	✓		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
bile duct	✓																			
stomach	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓
lg intest	✓	✓	✓	✓	✓	✓			✓	✓	✓		✓	✓	✓	✓	✓	✓		✓
sm intest	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
gall bladder		✓	✓		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
pancreas	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
aorta	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	
heart	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
thyroid			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
parathyroid				✓									✓	✓		✓				
trachea	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
lung	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
bronchi	✓			✓			✓													
prostate	✓	✓	✓	✓	✓	✓	✓		✓	✓										
testes	✓	✓	✓	✓	✓		✓	✓	✓	✓										
ovary											✓	✓	✓	✓	✓	✓	✓	✓		✓
uterus											✓			✓	✓	✓	✓	✓		✓
mammary														✓						
adrenal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
kidney	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
u. bladder	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
urethra																				
sk muscle	✓	✓	✓		✓	✓	✓			✓		✓	✓	✓	✓	✓	✓	✓		
bone (rib)	✓	✓		✓		✓	✓			✓	✓			✓		✓	✓	✓	✓	✓
bone marrow	✓	✓				✓				✓						✓		✓	✓	✓
sternum	✓																			
cartilage				✓																
integument											✓			✓						
spinal cord	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
pituitary	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓				✓	✓		✓	✓	✓
per. nerve	✓	✓		✓	✓	✓	✓		✓	✓	✓		✓			✓		✓	✓	
brain stem	✓			✓			✓				✓			✓			✓			
cerebellum	✓			✓			✓				✓			✓			✓			
cerebrum	✓			✓			✓				✓			✓			✓			
lymph node	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
tonsils																				
tongue																				
epiglottis																				
oral mucosa	✓																			
salivary		✓	✓		✓	✓		✓	✓	✓		✓	✓		✓	✓		✓	✓	✓
nasopharynx																				
lens																				
eye		✓	✓		✓	✓		✓	✓	✓		✓	✓		✓	✓		✓	✓	
optic nerve		✓	✓																	
Forepaw				✓																
Brain		✓	✓		✓	✓		✓		✓		✓	✓		✓	✓		✓	✓	
duodenum		✓																		
esophagus		✓																		

Phase 2yr II

MALE

FEMALE

Tissue	Control 20353	Control 522	Control 489	Control 509	3mg/kg 20352	3mg/kg 488	3mg/kg 511	3mg/kg 503	1mg/kg 496	Control 20382	Control 20359	Control 487	Control 506	3mg/kg 486	3mg/kg 498	3mg/kg 20398	3mg/kg 516
spleen	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	
liver	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
bile duct																	
stomach	✓	✓	✓	✓	✓		✓	✓		✓		✓	✓	✓	✓	✓	✓
lg intest	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
sm intest	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
gall bladder	✓	✓	✓	✓	✓		✓			✓		✓	✓	✓	✓		✓
pancreas	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
aorta	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
heart	✓	✓		✓	✓	✓	✓	✓					✓	✓	✓	✓	✓
thyroid	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
parathyroid	✓	✓	✓		✓		✓	✓	✓	✓					✓	✓	
trachea	✓		✓	✓		✓	✓	✓			✓	✓	✓	✓	✓	✓	✓
lung	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
bronchi																	
prostate	✓	✓	✓	✓	✓	✓	✓	✓									
testes	✓	✓	✓	✓	✓	✓		✓	✓								
ovary											✓	✓	✓	✓	✓	✓	
uterus										✓	✓	✓	✓	✓	✓		✓
mammary																	
adrenal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
kidney	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
u. bladder	✓		✓	✓	✓	✓			✓	✓	✓	✓	✓	✓		✓	✓
urethra	✓	✓						✓									
sk muscle	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓		✓	✓	✓	
bone	✓		✓	✓	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
bone marrow	✓		✓	✓	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
sternum																	
cartilage																	
integument																	
spinal cord	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓
pituitary	✓	✓		✓		✓		✓	✓		✓	✓	✓	✓	✓	✓	✓
per. nerve	✓	✓		✓	✓	✓	✓	✓		✓		✓		✓		✓	
brain stem																	
cerebellum																	
cerebrum																	
lymph node	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
tonsils	✓		✓	✓	✓	✓		✓		✓	✓	✓		✓	✓	✓	✓
tongue						✓											
epiglottis		✓	✓	✓	✓	✓	✓	✓		✓		✓		✓	✓	✓	✓
oral mucosa																	
salivary	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
nasopharynx																	
lens	✓	✓															
eye	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
optic nerve																	
LARYNX	✓																
BRAIN	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Acc. Sex Glands									✓								
Skin									✓								
Bronchioles									✓								