

US EPA ARCHIVE DOCUMENT

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE MAY 16 1980

CASWELL#219AA

SUBJECT EPA Reg.#464-448. -449, -343, -360; Results of a two-year toxicity and oncogenic study of chlorpyrifos administered to CD-mice in the diet. Acc.#242059

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

WWD 4/29/80

TO Charles Mitchell
Product Manager#12
Registration Division (TS-767)

WMB

Recommendations:

- 1) Chlorpyrifos was not oncogenic in this mouse feeding study. The study is acceptable as Core-Minimum Data.

Review:

- 1) Results of a two-year toxicity and oncogenic study of chlorpyrifos administered to CD-mice in the diet (Dow Chemical Co., Warner, S.D. et al, March 4, 1980)

Test Material: Chlorpyrifos, 99.6 ± 0.9%

Four week old CD-1 mice (Charles River, Portage, MI) were assigned to a control and three treatment groups each consisting of 56 animals/sex and were placed on diets providing chlorpyrifos as shown below:

<u>Treatment</u>		<u>Animal Numbers</u>	
<u>ppm of diet</u>	<u>% of diet</u>	<u>Male</u>	<u>Female</u>
0	0	5001-5056	5057-5112
0.5	0.00005	5113-5168	5169-5224
5.0	0.0005	5225-5280	5281-5336
15.0	0.0015	5337-5392	5393-5442

Each animal in a cage (4/sex/cage) was identified by ear notching and by a card attached to the cage showing the animal number which corresponded to the respective ear notches. The animals were maintained in a separate room which was controlled for temperature and humidity. Food and water were supplied ad libitum.

The animals were observed daily for abnormalities in behavior and physical condition. The onset, location and extent of external lesions or palpable masses were recorded as observed while handling mice during routine animal care procedures. Mean body weights were recorded monthly throughout the study. Mean daily food consumption was recorded over a 3 or 4-day interval during each month.

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(2)

Moribund animals were killed and necropsied when death was imminent to minimize autolysis for purposes of gross and microscopic tissue examinations.

A complete gross examination was made and findings recorded for all mice that died spontaneously, for moribund-sacrificed animals and for survivors at termination of the study. All mice were killed by CO₂ inhalation and exsanguination from the several axillary blood vessels. The weight of the brain, testes, heart, kidneys and liver was recorded on survivors at termination of the study. Representative samples of the weighed organs as well as of the following organs or tissues were collected and fixed in 10 per cent buffered formalin: adrenals, pituitary, eyes, lacrimal gland, spleen, pancreas, salivary glands, trachea, esophagus, thyroids, parathyroids, thymus, skeletal muscle, sciatic nerve, ovaries, uterus, urinary bladder, testes, epididymides, prostate and/or accessory sex glands, preputial or clitoral gland, lung, stomach, small and large intestines, mammary gland, skin, vertebrae with spinal cord in situ, tibial/femoral bone, sternbrae, rib, gall bladder and cervical, mediastinal, mesenteric and/or somatic lymph nodes.

All of the above tissues including those weighed at terminal sacrifice were collected from animals which died or were moribund sacrificed. Specimens of gross lesions were collected and preserved from all animals.

Peripheral blood smears were prepared from tail blood from all survivors at terminal sacrifice. The smears were stained with Wright's stain and examined microscopically.

A routine set of hematoxylin and eosin stained tissue sections were prepared for microscopic examined from each animal necropsied.

Statistical evaluation of the data was performed.

Dietary treatment with chlorpyrifos was initiated on November 9, 1976 and continued until animals were sacrificed terminally. The final sacrifice date was November 16, 1978, thus groups of animals were treated with chlorpyrifos for approximately 105 weeks.

Results:

No statistically significant differences were observed between the mean body weights of the control and treated groups of animals during the course of the study.

Statistically significant decreases in mean daily food consumption were observed on study day 168 in males given 5 ppm and on study days 504 and 588 in males given 0.5 ppm. In female mice, a statistically significant decrease in food consumption occurred on study day 476 in females given 5 ppm and on study day 504 females given 15 ppm (it should be noted that the mean food consumption of control females showed a disproportionate increase at these same intervals). Food consumption of female mice given 0.5 ppm showed a statistically significant increase over the mean control value on day 28.

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In summary, the few sporadic instances in which there was a statistical decrease or increase in food consumption between the control and various treatment groups showed no consistent trend and were, therefore, considered of no toxicological significance.

Treated males had higher survival rates than their control counterparts; 46% of the high dose (15 ppm) males lived to the termination of the study at 105 weeks whereas only 39% of male controls survived.

In females, the survival rate of groups of mice given 0.5 or 5 ppm of chlorpyrifos was greater (59%) or equivalent (46%), respectively, to their control counterparts. The poorest survival rate was shown by females given 15 ppm in which 38% of the animals survived to termination of the study as compared to 46% of female control animals. In neither sex was there a statistically significant difference between the control and treated groups in survival rate.

There were no changes in behavior or physical appearance during the course of the study that could be attributed to ingestion of chlorpyrifos in the diet.

A variety of non-neoplastic lesions of a degenerative, chronic inflammatory, or proliferative nature were observed with approximately equal frequency and severity in treated and control animals.

A statistically significant decrease occurred in the absolute weight of the heart and kidneys of males of the low dose level (0.5 ppm) only. In females, a statistically significant decrease occurred in the absolute weight of the liver at the low (0.5 ppm) and intermediate (5.0 ppm) dose levels of chlorpyrifos; the relative weight of the liver was statistically as well at the low dose level only. The differences in heart, kidney and liver weights were not considered to be of toxicological significance due to the absence of a dose-response relationship and lack of gross or microscopic lesions.

The incidence of tumors and tumor-like lesions were most frequent in the lung, liver, lacrimal gland (Harderian gland), skin and organs of the lymphoreticular system in both treated and control mice.

There was no statistically significant differences observed in the incidence rate of tumors between animals of the treated and control groups except for a statistically significant but non-dose related increase in adenomas of the lung in males of the intermediate dose level.

However, when the incidence rates of adenomas and carcinomas of the lungs were combined and analyzed (an acceptable practice due to their biological behavior - oral communication 4/24/80 with Dr. L. Kasza, TOX Branch pathologist), there were no statistical differences in tumors of the lung between any of the treated and control groups of animals.

A statistical increase in the incidence of hyperplasia nodules in males of the intermediate dose level only was considered fortuitous and not the result of treatment due to (1) the lack of spontaneous hyperplastic nodules in the absence of other parenchymal nodules in control males as compared to control females, (2) the absence of dose-response and (3) the absence of an increase of other nodular lesions of the liver parenchyma at this dose level.

Conclusion:

Chlorpyrifos was not oncogenic in this mouse feeding study.

Classification: Core-Minimum Data

3