UNITED STATES GOVERNMENT

Memorandum

001592

TO : Dr. A. J. Lehman

DATE: July 19, 1965

FROM Dr. Kent J. Davis

Collaborators: Mr. Walter Hansen
Dr. O. G. Fitzhugh

SUBJECT: Pathology Report on Mice Fed Aldrin, Dieldrin, Heptachlor or Heptachlor Epoxide for Two Years

One thousand individually caged C3Heb/Fe/J mice were divided into five groups of 100 males and 100 females each and started on a 2-year pesticide feeding study. The two hundred control mice were given Purina laboratory chow ad libitum and test groups received chow diets to which had been added 10 ppm of either aldrin, dieldrin, heptachlor, or heptachlor epoxide.

As the mice died during the experiment or were killed at the end of the test period, they were autopsied and viscera were fixed in formalin solution. Four to twelve mice from each of the five groups were either lost or discarded. In addition, in a cooperative hepatic tumor transplant study with Dr. Andervont, four males and four females each from the aldrin and dieldrin groups and eight males from the control group were taken to N.I.H. for autopsy, hence part of the liver from each of these twenty-four mice which completed the 2-year study was not available for re-examination after fixation. Both Dr. Dunn at N.I.H. and I prepared some liver sections on these twenty-four mice. Other tissues from these mice were returned to us and re-examined along with the other mouse tissues from this experiment.

At a later date an additional ten control mice were killed at N.I.H. for liver tissue and no liver was available to us for examination on these ten mice. N.I.H. prepared liver sections on these ten but mouse identity was not maintained on these slides. These inconsistencies in tissue examination naturally bias any attempted statistical conclusions on the data from this 2-year study. With exceptions as noted above, viscera from all mice were re-examined after fixation and hematoxylin-eosin stained paraffin sections of all gross lesions from all mice, and of heart, lung, liver, kidney, spleen, testis and occasionally other tissues from all mice killed at the end of the 2-year test period were prepared and examined microscopically. Lung sections were examined for possible metastases on all mice with gross liver lesions. Survival and pathology observed in this experiment are summarized in Table I.

TABLE I: Summarized Observations in Mice Fed 10 Ppm Aldrin, Dieldrin, Heptachlor or Heptachlor Epoxide for 2 Years

Observation	Control	Aldrin	Dieldrin	Hepta-chlor	Hepta-chlor Epoxide
Survivors at 52 weeks	188	152	169	172	160
Survivors at 78 weeks	150	121	117	135	109
Survivors killed at 2 years	62	31	39	60	19
Hepatic hyperplasia	38	72	71	108	65
Benign hepatoma	27	65	69	47	85
Hepatic carcinoma	4	3	5	4	9
Enlarged mesenteric lymph nodes	35	23	22	35	23
Pulmonary adenoma	4	1	6	2	4
Pulmonary adenocarcinoma	2	2	--	2	2
Lymphosarcoma	2	2	1	1	1
Fibrosarcoma	6	1	3	--	--
Adrenal adenoma	--	--	--	2	--
Adrenal adenocarcinoma	2	--	--	--	--
Mammary adenoma	--	--	--	1	--
Mammary adenocarcinoma	3	--	--	2	--
Ovarian adenoma	--	--	--	1	--
Ovarian adenocarcinoma	--	1	--	1	--
Epidermoid carcinoma	--	--	--	--	1
Squamous cell carcinoma of stomach	--	--	1	--	--
Renal carcinoma	1	--	--	--	--
Thyroid adenoma	1	--	--	1	--
Pancreatic adenocarcinoma	1	--	--	--	--
Interstitial cell tumor of testis	1	--	--	--	--
Atrial thrombosis	1	4	4	--	3
Uterine polyp	3	--	--	--	--
Mice with benign tumor only	30	61	71	51	85
Mice with malignant tumor	21	9	9	10	13

DISCUSSION

We have now failed for the third time, to prove that either aldrin or dieldrin are carcinogenic for inbred C3lleb/Fe/J mice when fed at near toxic levels for 2 years. As shown in Table I, the increased incidence of both hepatic hyperplasia and benign hepatic tumors in test groups attests to the hepatic stressor effects of these pesticides. While toxic and/or pathologic trends are evident from the data presented in the foregoing table, there is no call for carrying out statistical evaluation of these results to either the second or third decimal place or thousandths of a mouse. Probabilities still do not accurately predict winners of horse races or losers in toxicologic experiments. Added points of statistical bias in this case are in completeness of data due to transfer of some tissues to N.I.H. (more control than other tissue) and arbitrariness of microscopic diagnoses which are the basis for incidence figures given in the table. For example, the criteria used for malignant hepatic lesions were either metastases or invasion outside the liver. Practically all hepatic lesions listed as malignant tumors in this study had metastasized to the lungs. In some cases there were both tumor emboli (which had not taken root and grown) and metastatic liver cells (those growing lumps) in the same lung sections. Lesser criteria of malignancy (anaplasia, etc.) are uncalled for in evaluations of this type of test data because all lesions examined were from dead mice, hence there was little possibility for further development or metastasizing by these tumors. Stated another way, these tumors had either metastasized or were not going to in these dead mice, hence tumor nomenclature and classification in Table I is descriptive rather than prognostic. Attempts were made to maintain relative consistency of diagnostic criteria throughout the examination and evaluation of the approximately 1800 histologic slides on this study by the periodic spot re-checking of diagnoses.

We have received copies of some of the tumor transplant results from N.I.H. but we have not yet received their final evaluation of any significance they may attach to these results.

SUMMARY

One thousand individually caged C3lleb/Fe/J mice were divided into five groups of 100 males and 100 females and for 2 years test groups were fed laboratory chow diets containing 10 ppm added amounts of either aldrin, dieldrin, heptachlor or heptachlor epoxide. These feeding levels were somewhat toxic for this strain of inbred mice as shown by the decreased survival in all test groups. Incidence of both hepatic hyperplasia and of benign hepatomas were approximately doubled in test groups. These pesticides had no significant effect on the incidence of malignant liver tumors. While there was a 2 to 3 fold increase in overall incidence of benign tumors in all test groups, there were only approximately half as many mice with malignant tumors in each of the test groups as were noted in the control group.

Path. Nos. 30413-613
30681-880
30933-31332
31866-32065

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