*Industrial* BIO-TEST *Laboratories, Inc.*
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TOXICOLOGY
ENVIRONMENTAL SCIENCES
CHEMISTRY
PLANT SCIENCES
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March 24, 1975

AREA CODE 312
TELEPHONE 272-3030

George J. Levinskas, Ph.D.
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

I am enclosing the trip reports prepared by Dr. Richter and myself regarding our meeting at N.C.I. on January 31, 1975 with Drs. Kimbrough and Squire on Aroclor 1260 (IBT No. 622-07298).

The micro-slides of the liver sections from all these animals and those from Aroclor 1242 and 1254 will be forwarded today, under separate cover. We are also mailing the reports relevant to these studies today.

The charges for this additional work will be billed under a new Number (IBT No. 641-06672) instead of the previous number.

Sincerely,

D. E. Gordon, D.V.M., Ph.D.
Section Head, Pathology Dept.

DEG:hb
Enclosure

February 2, 1975

Trip Report

On January 31, 1975; Drs. Richter, Levinskas and myself met with Drs. Squire and Kimbrough at the National Cancer Institute in Bethesda, Maryland. The purpose of this meeting was to review the slides and data from a 23 month oral feeding study with Aroclor 1260 in rats that was conducted by Dr. Kimbrough while at the E.P.A. In her study, 200 female rats (Sherman strain) were fed 100 ppm of Aroclor 1260 in the diet for 21 months, while 200 female rats of the same strain served as controls and were fed Purina Rat Chow. The Sherman Rat is a random-bred animal derived from the Osborn Mendel Strain. The animals were 21-26 days of age when the study began, and were sacrificed after 23 months on the study. Therefore, there was a 2 month recovery period at the end of the study in which the test material was removed from the diet. The details of the experimental design, procedures and results that were forwarded to Dr. Levinskas are attached. In summary, Dr. Kimbrough found a rather high incidence of hyperplastic (nodular hyperplasia) and neoplastic (hepatomas, carcinomas) lesions in the liver of the test animals. The slides were subsequently reviewed by Dr. Robert Squire, Head of the Tumor Pathology Branch of The National Cancer Institute, who concurred with her findings, although, the terminology he used in classification of the lesions varied slightly from Dr. Kimbrough's. In this regard, it was his impression that all hyperplastic nodules should be regarded as "pre-cancerous lesions" and the term "hepatomas"

be deleted and re-classified as carcinomas or neoplastic nodules. This classification system was based on a Liver Tumor Workshop that was held on Dec. 11-13, 1974 in Silver Springs, Maryland which was attended by a small group of pathologists from the regulatory agencies, research laboratories and industry.

In view of Dr. Kimbrough's findings, additional sections of liver from a 2-Year Oral Feeding Study With Aroclor 1260, in rats, conducted at Industrial Bio-Test were processed and evaluated. In this study, there was a 3, 8 and 14 month interim sacrifice which enabled one to determine the approximate time of onset of the liver changes. No interim sacrifices were conducted in Dr. Kimbrough's study. The additional slides prepared at Bio-Test were examined by Dr. Richter and a tabulation of the liver findings are attached. These slides were reviewed by Drs. Kimbrough and Squire at our meeting. Although there was some disagreement on the terminology used in classification of the lesions, it was apparent that the incidence and severity of liver lesions (hyperplasia, nodular hyperplasia and neoplastic changes - carcinomas) was greater in Dr. Kimbrough's study when compared with the results of the Bio-Test Study, even though the same level of test material was administered in the diet. There are two possible explanations for this difference:

1.) The strain of rat. When questioned, Dr. Kimbrough had no information on the spontaneous incidence of hyperplastic or neoplastic liver lesions in the Sherman strain. However, the incidence of spontaneous liver cell hyperplasia would appear to be extremely low since this finding was reported in only 4 controls. The incidence of liver hyperplasia among control rats of the Bio-Test study was also very low. The incidence of spontaneous hyperplastic liver nodules reached 20% in the Fischer Rat

and in some of the other strains.

2.) Sex difference. On the basis of our studies and those of other investigators in rats and mice, it was found that the incidence of hyperplastic and neoplastic liver lesions are much higher in females.

The results of the liver tumor workshop are to be published in the near future and will include the participants. The views of this group, regarding classification of hyperplastic and neoplastic liver lesions is based on the pathogenesis of such lesions in rats that have been induced by known carcinogens such as the nitrosoamines and 2 - acetylaminoflorine (2-AAF). The adoption of this terminology and classification system by the scientific community will have widespread implications regarding assessment of safety of chemicals and drugs currently on test and those previously studied.

Attached are Dr. Richter's comments in regard to Dr. Kimbrough's findings.

D. E. Gordon

Donovan E. Gordon, D.V.M., Ph.D.
Dipl., Am. College Vet. Path.

February 3, 1975

Dr. Donovan Gordon
Industrial Bio-Test Laboratories

I wish to summarize my observations of the lesions seen in Dr. Kimbrough's study of Aroclor 1260 and the comparison of diagnoses with Dr. Kimbrough and Dr. Squire.

1.) The criteria that I used for diagnosis of the lesions are similar to what they used.

2.) My evaluation tends to be a little more conservative than theirs. For example: they would call some of my hepatomas carcinoma but with some question.

3.) Therefore, if we both read the same slides there might be a little variation in numbers of lesions in the different categories but no major difference.

4.) Dr. Squire and Dr. Kimbrough are using a new and revised terminology for the categories and list them as follows:

| My Terminology (Classical Use) | Dr. Squire's (Revised Terminology) |
|---|---|
| Focal Hypertrophy | Cellular Alteration |
| Nodular Hyperplasia } Hepatoma } | Nodular Neoplasia or Neoplastic Nodule |
| Carcinoma | Carcinoma |

5.) However, the lesions in Dr. Kimbrough's study were more severe than those in the Bio-Test study. The lesions that she and Dr. Squire are calling carcinoma are also carcinomas by my criteria. I would

conclude from an examination of their material that Dr. Kimbrough's study demonstrated carcinogenicity.

Ward R. Richter

Ward R. Richter, D.V.M.
Dipl. Am. College Vet. Path.