Toxicity

From the desk of
W. B. PAPAGEORGE

5/5/75

Copies to:

H. S. Bergen
T. L. Gossage
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W. R. Richard
[redacted]

This is in response to Dr. Roush's request for a statement from Biotest Laboratori Dr. Roush wasn't satisfied and Biotest was requested to re-do.

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TOXICOLOGY
ENVIRONMENTAL SCIENCES
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April 18, 1975

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Dr. George Roush, Jr.
Monsanto Company
800 North Lindbergh Boulevard
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Dear George:

I fully appreciate that the meeting on PCB's today was not completely satisfactory and that many nagging questions remain. The enclosed is a brief summary of my personal views and I would appreciate any open and frank comments that you all may have.

Please let me know of any action that you contemplate in the way of seeking additional assistance in pathology or in contacting federal agencies. We will be pleased to be of help in any way that you may wish.

It is my feeling that we need to get together again within the next few weeks to continue our discussions.

Very truly yours,

J. C. Calandra
President

JCC:AR

cc - Dr. George Levinskas
Mr. Elmer Wheeler
Mr. William Papageorge

MONS 093307

REVIEW OF PCB MEETING

The central issue in question is whether the PCB's are carcinogens or not. The long term studies conducted at BIO-TEST indicate that the answer is no. Drs. Ward Richter and Donovan Gordon are of this opinion which is shared by M. L. Keplinger and J. C. Calandra.

On the other hand, a study conducted by Dr. Renata Kimbrough presents evidence that in female rats of the Sherman strain, liver carcinomas were found. This is the only study in which this finding is reported in rats. BIO-TEST has no basis for refuting the findings of Kimbrough except to take exception to the design of the experiment that used only female rats and to point out that to our knowledge no one else has reported similar results in rats. It should be noted that the earlier allegation by Kimbrough that bladder cancers developed in female rats fed PCB was successfully counteracted by BIO-TEST and Monsanto personnel.

Kimura[1] worked with Kanechlor-400, a commercial brand of PCB and in a rat study of 400 days' duration concluded that "PCB's induced a benign neoplastic change, though it seemed to be still short of malignancy, and that the change appeared exclusively in the females." The author expressed concern that the benign nodules in the liver may progress to carcinomas if "specific or non-specific stimuli are introduced into the animal."

Ito[2] conducted a study in mice and found "hyperplastic nodules and well-differentiated hepatocellular carcinomas" at a dose level of 500 ppm of Kanechlor 500. Hepatocellular carcinomas were not induced by Kanechlor 300 and Kanechlor 400.

The evidence to date indicates that male rats are more resistant than females to the formation of nodular hyperplasia as well as hepatocellular carcinoma. Rats also are more resistant to the induction of these lesions than mice.

To return to the BIO-TEST studies on PCB, it should be noted that the liver sections which were read by the pathologists and reported in IBT No. 641-06672 and dated March 24, 1975, were not the same slides or sections as those reported on originally. The preserved livers were reprocessed by taking 4 "cuts" from different areas to obtain as large a representative sample as possible. It is not surprising that under these circumstances a different tabulation of the various primary liver lesions was found. Studies on thyroid hyperplasia and by Richter's associate, Dr. Stanley Vesselinovitch, have shown that this procedure generally results in a different qualitative and quantitative line-up of lesions that are reported by the same pathologist.

Ideally one would like to be able to reaffirm the original findings by this procedure, but this is not always possible because of the additional variables introduced. Serial sections of the liver would

eliminate some of the covariants. The important point in the most recent study of the sections is the fact that no hepatocellular carcinomas were found which is in agreement with the earlier findings. It must be emphasized that the diagnosis of "hepatoma" by Gordon and Richter connotes a benign process and must not be confused with the classical definition of the term by "human" pathologists.

Further, Dr. Squires reviewed a number of the same slides on Aroclor 1260 with Drs. Gordon, Levinskas, Kimbrough and Richter and agreed with the BIO-TEST pathologists that liver carcinomas were not present in the slides. In addition, the original slides have been in the possession of FDA since June, 1973 and to date we have not been informed of any disagreement with BIO-TEST findings.

Dr. Squires has stated in a letter to Dr. Kimbrough dated November 12, 1974, that "I define 'discrete nodules' and 'trabecular (basophilic) hyperplasia' as precancerous lesions and thus indicative of carcinogenic response." This reflects a viewpoint which is not shared by all pathologists and there is nothing that BIO-TEST can do to change this definition except for its pathologists to accept or reject the view. Drs. Richter and Gordon do not accept Dr. Squire's definition.

Workers in the field have published extensively on the pathogenesis of hepatocellular carcinoma in recent years and the concepts have undergone considerable changes since the preparation

of the final BIO-TEST report on chronic oral toxicity studies. One must note that Popper[3] in his studies on Aramite in 1960 postulated that hyperplastic nodules were transformed into hepatocellular cancer; however, this concept was not generally accepted by the scientific community.

An excellent paper which describes "the highlights of some newer developments in our understanding of liver carcinogenesis" has been published by Farber.[4] If the concepts presented in this paper as well as those of Squires, Saffiotti and others are accepted, a number of substances would have to be reclassified as liver carcinogens. Carried to extreme, we could argue that any substance that results in stimulation of liver microsomal enzymes or possesses hepatocytoxic properties to any degree is a potential liver carcinogen.

BIO-TEST is unwilling to accept these concepts. The lesions seen in the livers of the rats in its PCB studies for Monsanto do not show vascular invasion, metasteses or anaplasia - all classical features of carcinoma. We continue to view the lesions seen to be benign.

Several additional things need to be done by BIO-TEST and these include:

(a) Re-examine the original liver slides.

(b) Cut new sections at different levels from original paraffin blocks and read slides.

(c) Tabulate liver findings separately in female and male rats.

(d) If possible, develop information on the reversibility of the liver changes.

It is important to point out the following:

1. The BIO-TEST position was and remains that the PCB's were not shown to be liver carcinogens in its studies. This conclusion is the opinion of its resident pathologists as well as its independent consultant.

2. The BIO-TEST results show that a no-effect level for the development of hyperplastic nodules was found in each of its studies.

3. BIO-TEST has no means at its disposal to dispute the findings of Kimbrough that Aroclor 1260 in female Sherman rats is a liver carcinogen except on the basis of experimental design.

4. BIO-TEST is not in agreement with the classification by Squires et al. that considers hyperplastic liver nodules to be pre-cancerous.

5. BIO-TEST studies on PCB's meet the scientific standards of Toxicology and Pathology and we are prepared to assist Monsanto in any adversary situation in or out of government.

J. C. Calandra

April 18, 1975

References

1 Kimura, N. T. Gann 64:105 (1973).
2 Ito, N. J. Nat. Cancer Inst. 51:1637 (1973).
3 Popper, H. Cancer 13:1035 (1960).
4 Farber, E. Arch. Path. 98:145 (1974).

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