Calandra to Monsanto - Trying to present both sides of the issue. He is not to be quoted or published on this. HSB

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REVIEW OF THE TECHNICAL AND REGULATORY ASPECTS OF AROCLORS

On the basis of the results obtained in the chronic studies on the various PCB's at BIO-TEST, the conclusion has been reached that these materials are not carcinogenic. The slides have been reviewed three times by Drs. D. Gordon and W. Richter and their findings support this conclusion.

Certain liver changes occur in varying degree with the different Aroclors that are subject to several interpretations, as well as nomenclature and classification.

In the classical pathological sense the liver alterations seen with the Aroclors are benign in character. Lesions of this type have been shown to be reversible. Further, the benign features include lack of vascular invasion and lack of metastases as well as lack of transplantability.

The liver changes such as focal hyperplasia, hypertrophic nodules, and adenofibrosis may be induced by other chlorinated aromatic and aliphatic hydrocarbons. Some of the latter materials that may produce these lesions, such as dieldrin, aldrin, and carbon tetrachloride, are considered to be carcinogenic by the EPA and the National Cancer

Institute. In fact, these groups have redefined these terms as well as the concept of benign and malignant lesions as they have been used traditionally.

The view of these groups is that any tumor induced by a chemical is malignant despite the absence of the classical histological features of malignancy. The legal division of the EPA has enthusiastically embraced this approach and has used it successfully to cancel the registration of dieldrin and aldrin and are about to launch litigation against chlordane and heptachlor. It is expected that the registration of the latter materials will be in due course cancelled.

In the case of liver changes, the EPA and the National Cancer Institute have adopted the view that in the extreme any material which induces liver microsomal enzymes is a suspect carcinogen. In addition, focal hyperplasia of the liver produced by chemicals is being classified as a premalignant change and the chemicals involved are being classified as suspect carcinogens. Additional histological effects such as nodular hyperplasia are also considered to be premalignant. The philosophy that has been adopted by these agencies is that substances which cause the above liver changes are in fact carcinogenic. This philosophy permeates the extensive EPA brief in the legal proceedings to cancel the registration of dieldrin and aldrin as well as in its preliminary legal presentation on chlordane and heptachlor.

The EPA is supported by the National Cancer Institute as represented by Drs. U. Saffiotti, R. Squires, and W. Heston. In addition, non-government affiliated pathologists such as Drs. E. Farber, and M. Reuber, H. Popper and S. Epstein support the agencies' views.

On the other hand, a number of pathologists such as Drs. J. Newberne, W. Butler, G. Jones, A. Stein, G. Kent, D. Gordon, and W. Richter do not agree with the agency definitions or with the presumed end-point of the liver lesions - cancer. In this regard, it should be mentioned that the FDA had the BIO-TEST Aroclor slides for 3 years and to this date no adverse comments have been received.

Without question the Aroclors as well as other PCB-like materials are directly involved in this situation. The opinion of Drs. Gordon, Richter, Calandra, Keplinger and Kinoshita, on the basis of their own studies on Aroclor and on their experience, is that Aroclors are not carcinogenic. However, the attitudes and findings of others must be placed in perspective and weighed, each according to its own merits in accord with the data generated.

The findings of Ito,[1,2] Kimbrough and others are relevant in this context. Ito conducted a study in mice and found "hyperplastic nodules and well-differentiated hepatocellular carcinomas" at a dose level of 50 ppm of Kanechlor 500. However, hepatocellular carcinomas were not induced by Kanechlor 400 and Kanechlor 300. No specific information about the purity or composition of the products tested is

available. For example, were chlorinated dibenzofurans present? It has been shown by Vos[3] that certain biological changes can be induced by Kanechlors that do not occur with Aroclors.

Ito's work involved feeding levels of 500 ppm, 250 ppm and 100 ppm of each of the three test materials for 32 weeks to groups of 6-12 male mice. The article is sketchy and it is not possible to evaluate the significance of the findings. No histological descriptions are presented. The study obviously does not meet the scientific requirements for a meaningful bioassay for carcinogenesis as defined by the National Cancer Institute. The groups are much too small and only male mice were used. Surprisingly, the Kanechlor 500 material produced hepatomas and the Kanechlor 400 and Kanechlor 300 materials did not. It is not possible from the article to ascertain that the hepatomas are in fact hepatocarcinomas. In general, this study as presented is not acceptable and cannot be used to properly evaluate the carcinogenic activity of PCB's without additional information.

With reference to the use of the mouse in carcinogenicity testing, Grasso and Compton[4] have reviewed the value of this animal in testing for effects in the liver as well as other various organ systems. They note that a number of covariables significantly influence the incidence of hepatomas in mice. These include diet, presence or absence of "germs," sex, age and strain susceptibility. They state, "It thus appears that factors unconnected with the administration of the

test compound may have a considerable influence on the incidence of hepatomas in mice, so that other evidence is required if claims of carcinogenicity based on the induction of this type of tumor are to be seriously considered."

A study conducted by Kimura[5] on Kanechen 400 utilized 20 rats aged 10 weeks in the test group and 10 rats in the control group equally divided as to sex. The dietary level for the single test group varied from a low of 38.5 ppm to a high of 616 ppm. Liver changes included hypertrophy and fatty degeneration. "Multiple adenomatous nodules" were seen in 6 test female rats and in 2 control female rats. Male rats in either the test or control groups did not develop the nodules. The authors speculated that the nodules "in the presence of other stimuli may progress" to malignant changes. Once again, this study does not meet the technical criteria for chemical carcinogenesis bioassay procedures despite the negative results. The results confirmed the higher degree of susceptibility of females to the development of hyperplastic liver nodules. No specific conclusions, however, can be reached.

A short term study in mice (26 weeks) by Nishizumi[6] did not reveal liver changes consistent with either premalignant or malignant hepatocellular lesions.

A study by Kimbrough[7] in male and female Sherman rats fed Aroclor 1260 and 1254 at levels in the diet ranging from 0-1000 ppm for

8 months did not indicate the presence of hepatocellular carcinoma. Under light microscopy the changes seen were hypertrophy of the liver cells, inclusions in the cytoplasm, brown pigment in the Kupfer cells, lipid accumulation, and at the higher dietary levels, adenofibrosis.

Another study by Kimbrough[8] with Aroclor 1260 (Lot No. AK-3) in female Sherman rats at a dietary level of 100 ppm was conducted for 21 months. The results were strikingly different than those obtained earlier. In the latter study a high incidence of hepatocellular carcinoma was seen which is contrary to the findings of BIO-TEST. It is noteworthy that the incidence of hepatocellular carcinoma appears to be related to the new classification of liver lesions by NCI.

The results have some relevance in the resolution of the carcinogenic potential of PCB's; however, the study does not meet the criteria for a valid rat carcinogenicity bioassay. The evidence presented at this time is at best presumptive and does not take precedence over the chronic studies conducted in male and female rats at BIO-TEST. The liver slides from the latter study have been reviewed by a number of pathologists including Drs. Squires and Kimbrough, who agreed with the assessment that no hepatocellular carcinomas were present.

A number of questions can be raised about the Kimbrough study which raise serious doubt as to the value of the study as presently constituted. In and of itself, it is not the final answer and does not per se prove that PCB's are carcinogenic.

Kimbrough and Linder[9] conducted a study in BALB/cj male mice fed 300 ppm Aroclor 1254 for 11 and 6 months. The 6 months feeding group was maintained for an additional 5 month recovery period (transferred to control diet). The two significant histological findings were adenofibrosis of the liver and hepatomas. Adenofibrosis is not considered by experts in the field (Stewart and Snell[10]) to be a pre-canccrous lesion. The hepatomas were well differentiated and the authors (Kimbrough and Linder) are of the opinion that these are potentially carcinogenic; however, no direct evidence of malignancy was noted.

To further add to the confusion of the findings and relevance of the Kimbrough studies are the results obtained in still another experiment.[11] Fifty male Sherman strain rats were fed 500 ppm Aroclor 1254 for 6 months and at monthly intervals thereafter 5 rats were sacrificed and the livers examined by light and electron microscopy. Ten months after exposure 1192 ppm PCB was present in the adipose tissue and 22.65 ppm in the liver. In this study which used male Sherman rats only, no specific mention of focal hyperplasia or hyperplastic nodules is made. The principal lesion described is adenofibrosis. No evidence of hepatocellular carcinoma is presented.

Ito[12] confirmed this in a study in which male rats were fed Kanechlor 300, 400 and 500 for up to 52 weeks. These substances produced nodular hyperplasia but did not induce hepatocellular carcinomas in rats.

Norbeck and Allen[13] fed male rats 100 ppm of Aroclor 1248, 1254, or 1262 for up to 52 weeks and did not find evidence of hepatocellular carcinoma. However, hepatocellular hypertrophy associated with proliferation of the endoplasmic reticulum was seen. Mixed function oxidase microsomal enzymes were increased.

Additionally Makiura[14] fed rats PCB's alone and in conjunction with acetylaminofluorene, diethylnitrosamine and 3'methyl-4-dimethylaminozobenzene and found that "PCB's inhibited development of nodular hyperplasia, oval cell infiltration, and bile duct proliferation" (adenofibrosis).

Of special interest is the information that focal nodular hyperplasia is seen in the human being.[15] It is a rare benign tumor that has been studied and followed clinically in man without evidence of subsequent malignant transformation.

The issue of classification of the liver tumors and the presumption that focal hyperplasia and nodular hyperplasia are pre-malignant liver lesions and that these invariably lead to hepatocellular carcinoma needs to be discussed. A number of contrary opinions to this philosophy are available so that this consideration need not be decisive. However, it is important to note that the legal branch of EPA has clearly adopted these definitions.

When the question at issue is reviewed in the light of the regulatory agencies that may be involved, several points must be considered.

The EPA, based on the dieldrin and aldrin registration cancellations and the impending litigation on heptachlor and chlordane, are committed to the NCI philosophy of liver tumorigenesis and also that chemical agents which produce benign tumors are considered to be carcinogenic for the purposes of regulatory procedures.

In addition,[16] the following 9 principles are being followed at the present time by the EPA to evaluate the cancer hazard of environmental chemicals:

1. A carcinogen is any agent which increases tumor induction in man or animals.

2. Well-established criteria exist for distinguishing between benign and malignant tumors; however, even the induction of benign tumors is sufficient to characterize a chemical as a carcinogen.

3. The majority of human cancers are caused by avoidable exposure to carcinogens.

4. While chemicals can be carcinogenic agents, only a small percentage actually are.

5. Carcinogenesis is characterized by its irreversibility and long latency period following the initial exposure to the carcinogenic agent.

6. There is great variation in individual susceptibility to carcinogens.

7. The concept of a "threshold" exposure level for a carcinogenic agent has no practical significance because there is no valid method for establishing such a level.

8. A carcinogenic agent may be identified through analysis of tumor induction results with laboratory animals exposed to the agent, or on a post hoc basis by properly conducted epidemiological studies.

9. Any substance which produces tumors in animals must be considered a carcinogenic hazard to man if the results were achieved according to the established parameters of a valid carcinogenesis test.

In contrast to this, the FDA in a letter[17] written by the Associate Commissioner of Science to Senator Hart, indicated, "Although the Agency (EPA) stated that 'the above principles represent the most advanced research findings and policy of both national and international cancer experts and agencies,' it should be emphatically emphasized that there is by no means universal acceptance of many of the above principles as well as classification of tumors."

A review of the status of PCB's by L. L. Ramsey,[18] Associate Director of Regulatory Programs of the FDA, includes a number of important observations which have a bearing on the range of strategy and the possibilities that are available to resolve the issue of PCB.

1. The overall average of PCB's in all packaged food was 0.1 ppm.

2. This survey probably reflects samples of at least one year old and the industry has furnished us with data on more recent samples indicating that the corrective action they have taken is already effective: these PCB residue data appear to be significantly lower both in food and in its paper packaging.

3. In light of all available data including animal feeding studies, the human data from the Japanese Yusho incident and a history of use for about 40 years without deleterious effects in many being reported, the FDA has concluded that there is no immediate hazard

to the public health from the low level of environmental contamination leading to residues in food, but that it is prudent to reduce the long term exposure of man. Steps have been taken which will reduce the long term exposure of man and all evidence to date points to a successful outcome.

The most recent market basket survey by the FDA did not show PCB's to be present in any of the foods analyzed.

Another very important aspect of the regulatory question can be inferred from the recommendations[19] proposed by the EPA for dieldrin and aldrin which they have concluded is a carcinogen according to their criteria. The EPA has recommended the continued use of these materials for application directly to soil in materials buried in soil, e.g., termite control in foundations and seed treatments when properly applied.

On the basis of this attitude it is apparent that PCB's may continue to be used in controlled situations including supervised disposal where the benefit to risk is obvious despite the outcome of the questions raised about the liver changes. The recent additional evidence concerning biodegradability lends further support to this approach. For the present it is recommended that the FDA and EPA (if necessary) be provided with the final Aroclor reports on the chronic oral toxicity studies including the last addendum of the pathologists without additional comment.

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