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Douglas J. Tomchuk
Emergency and Remedial Response Division
U. S. Environmental Protection Agency
26 Federal Plaza, Room 747
New York, NY 10278

RE: REEVALUATION OF PCB TOXICITY

Dear Mr. Tomchuk:

Enclosed is a paper recently accepted for publication in the Journal of Regulatory Toxicology and Pharmacology entitled: A Comparison of Liver Tumor Diagnoses From Seven PCB Studies in Rats. The General Electric Company (GE) has already submitted the results of the underlying research from this article on various comments on the Hudson River Reassessment RI/FS.

GE again requests, the U.S. EPA consider this significant information in developing the Hudson River risk assessment. The implication to the Hudson River project and other sites with PCBs with less than 60% chlorination are tremendous. The following statement from the research conclusion summarizes the issue:

> "These data indicate that continuation of a science policy of assuming that all PCBs are probable human carcinogens and possess a carcinogenic potency equivalent to the mixture that contains 60% chlorine has no scientific foundation and should be reconsidered."

GE again requests that the U.S. EPA incorporate this significant finding into the Hudson River reassessment risk assessment. Please place a copy of the enclosed report and this letter into the site administrative record. Please let me know if you have any questions or comments.

Yours truly,

John G. Haggard
Engineering Project Manager

Enclosure

cc: Paul Simon

A COMPARISON OF LIVER TUMOR DIAGNOSES FROM SEVEN PCB STUDIES IN RATS

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Comparison of PCB Liver Tumor Diagnoses

Moore et al., 1994

Abstract

Through a policy assumption, all PCBs are considered probable human carcinogens by most regulatory agencies based on experimental studies in rodents where an increased incidence of liver tumors have been observed. Recognizing that new consensus criteria for the diagnoses of liver tumors in rats had been promulgated a reevaluation of liver tumor diagnoses from seven PCB studies in rats was undertaken. These seven studies, in which rats were fed PCB mixtures containing either 42%, 54%, or 60% chlorine, were considered to be the best studies from which to evaluate the cancer potential of PCB mixtures. The reevaluation results, where consistent diagnoses now exist across all studies, clearly indicate major differences in carcinogenic potential based on degree of chlorination. Studies of mixtures with 60% chlorination consistently resulted in a high incidence of liver tumors whereas studies in which rats were fed mixtures with 54% or 42% chlorination showed no statistically significant increases in liver tumors. These data indicate that continuation of a science policy of assuming that all PCBs are probably human carcinogens with a potency equivalent to the mixture that contains 60% chlorine has no scientific foundation and should be reconsidered.

INTRODUCTION

Polychlorinated biphenyls (PCBs) are synthetic mixtures of congeners that vary as to the number and location of chlorines on the biphenyl ring. Extensive commercial production and use of PCBs occurred in electrical applications such as capacitors and transformers during the middle third of this century because of three desirable characteristics; PCBs do not support combustion or conduct electricity and can withstand high temperatures. PCBs were used for many other diverse applications such as heat transfer fluid, additives in wood and cement sealants, carbonless copying paper, plasticizers, and hydraulic fluids. The PCB mixtures varied as to the degree of chlorination depending on the specific commercial application. Their widespread penetration into and persistence in the environment, combined with laboratory toxicological data, led to significant concern as to potential adverse human and ecological effects. Because of these concerns, open-ended use of PCBs was discontinued in 1971 in the U.S. and a general ban on manufacture, processing, and commercial distribution was put in place in 1979. An excellent summary of the production, use, chemistry, and health effects is found in Kimbrough and Jensen (1989).

PCBs are primarily regulated in the United States under the Toxic Substances control Act that is administered by the Environmental Protection Agency (EPA). Levels in most commercial foods are regulated by the Food and Drug Administration under the Federal Food, Drug and Cosmetic Act. Through a policy assumption, EPA considers all PCBs to be a probable carcinogen in humans based on experimental studies in rodents where an increased incidence of liver tumors has been observed. Although there are a number of research reports on the carcinogenicity of PCBs in the literature, no systematic studies have been conducted on a variety of PCB mixtures that permit an assessment of dose response in group sizes adequate to assess carcinogenic potential. EPA originally derived quantitative estimates of cancer potency by using liver tumor response from a single dietary level of a 60% chlorine mixture (Aroclor 1260) in female Sherman rats (Kimbrough et al., 1975). In a subsequent action, EPA raised its upper bound estimate of cancer

risk by selecting liver tumor response data derived from the chronic toxicity and oncogenicity study of the same 60% chlorine containing PCB mixture (Aroclor 1260) in female Sprague-Dawley rats (Norback & Weltman, 1985). A third chronic study, in which Wistar rats were fed a German PCB mixture containing 60% chlorine (Clophen A60) has also been reported (Schaeffer et al., 1984). Chronic studies in which PCB mixtures containing 54% or 42% chlorine were given to F344 rats (NCI 1977) and to Wistar rats (Schaeffer et al., 1984), respectively, have also been evaluated by EPA 1987.

The criteria used for diagnosis and classification of hepatocellular changes in these studies were those published by Squire and Levitt (1975) or Stewart et al., (1980). The former publication summarized the conclusions of a Rat Liver Tumor Workshop sponsored by the National Cancer Institute in 1974. Subsequently, the National Toxicology Program (NTP) in the U.S. sponsored activities that led to a consensus revision of criteria and nomenclature for hepatoproliferative lesions of rats. The new criteria were based on an increased accumulation of data and a better understanding of the mechanism of toxicity and carcinogenesis (Maronpot et al., 1986). The nomenclature and diagnostic criteria differed from the previous classification schemes in that the terms, hepatocellular hyperplasia and hepatocellular adenoma, were recommended for lesions that were previously combined under the diagnosis of neoplastic nodule. To enhance the use of data in risk assessments that reflect current scientific knowledge, and to realize consistency in the classification of liver tumors, a reevaluation of the liver sections from these rat studies was undertaken. The studies selected for reevaluation had been used or discussed in previous EPA risk assessments and were considered to be the best studies from which to evaluate the cancer potential of PCB mixtures.

MATERIALS AND METHODS

The studies included in the reevaluation were originally published as three separate journal articles (Kimbrough et al., 1975); (Norback and Weltman, 1985); (Shaeffer et al., 1984); and one government report (NCI, 1977). An author from each study was apprised of the objectives and procedures to be employed in the reevaluation. Each agreed to permit their slides to be shipped to a single site to facilitate their review by a group of pathologists. Slides from the government study were reviewed at the National Toxicology Program (PWG) repository and released for use at a nearby site on the day of the Pathology Working Group review.

In general, the procedures developed by the National Toxicology Program were followed to conduct the review of these studies. The hematoxylin and eosin stained microscope slides and appropriate data from each of the studies to be reviewed were assembled. All slides within each individual study were randomized and coded to blind the reviewing pathologist. Dr. Deborah Banas, who has extensive experience in the study of rodent pathology, was the reviewing pathologist. She recorded all neoplastic and nonneoplastic lesions present in the liver sections. After microscopic examination, the data from each study were decoded and presented by treatment group for interpretation of the results and preparation for the PWG review.

The PWG consisted of a panel of five board-certified veterinary pathologists and a chairman, Dr. J. Hardisty, who organized and presented the material to them. Each member had extensive experience in the microscopic evaluation and interpretation of hepatic changes observed in rodent bioassay studies. The PWG was organized under the auspices of Experimental Pathology

Laboratories, Inc.[1] Each panelist examined the coded slides and recorded his diagnosis and comments on worksheets prepared by the chairman. Each lesion was discussed by the group, reexamined (if necessary), and the final opinions were recorded on the chairman's worksheets. The consensus diagnoses of the PWG were reached when at least three of five PWG participants were in agreement.

After the PWG completed the slide review for each of the PCB studies, the results were decoded by treatment group and the consensus diagnoses used to create histopathology incidence tables and summary tables for evaluation and interpretation by the PWG. The diagnostic criteria and nomenclature utilized for the evaluation of hepatoproliferative lesions were those developed by the National Toxicology Program (Maronpot et al., 1986) whose use was subsequently endorsed by the Environmental Protection Agency. The concurrent review of these five chronic PCB bioassay studies in rats provided a unique opportunity to compare the incidence, type and severity of hepatic lesions observed in each.

RESULTS

Seven separate studies were reviewed in which rats were fed PCB mixtures with either 60%, 54%, or 42% chlorination. For clarity and consistency of discussion we defined a study as a protocol that examined the pathological effects associated with the chronic dietary exposure to a PCB mixture in one sex of rat. Four studies had been conducted with a 60% chlorine PCB mixture: Aroclor 1260 (Monsanto Chemical Co., St. Louis, MO) was studied in female Sherman strain rats (Kimbrough et al., 1975) and in male and female Sprague-Dawley strain rats (Norback

[1] The members of the Pathology Working Group were: Dr. Jerry F. Hardisty (Chairperson), Dr. W. Ray Brown, Dr. Ernest E. McConnell, Dr. James A. Popp, Dr. Robert A. Squire, Dr. Jerrold M. Ward. The PWG review was performed on May 29-31, 1991, in the Research Triangle Park, North Carolina. Others who attended the work group meeting were: Dr. W. Goessner coauthor - Shaeffer et al., 1982; Dr. Renate Kimbrough, author Kimbrough et al., 1975; Dr. Diane Norback, coauthor Norback and Weltman, 1985; and the following observers: Dr. William M. Busey, EPL; Dr. Ronald Moch, FDA; Dr. Jack Moore, IEHR; Dr. D. Singh, EPA.

and Weltman 1985). Clophen A60 (Bayer, Leverkusen, FRG) was studied in male Wistar rats (Shaeffer et al., 1984). Two studies were conducted in male and female Fischer 344 rats (NCI, 1977) using a PCB mixture that contained 54% chlorine; Aroclor 1254 (Monsanto Chemical Co., St. Louis, MO). One study was conducted in male Wistar rats (Shaeffer et al., 1984) with a PCB mixture that contained 42% chlorine; Clophen A30 (Bayer, Leverkusen, FRG). The average molecular composition of the commercial PCB mixtures of U.S. and German manufacture used in these studies are listed in Table 1. A single dietary concentration of 100 ppm PCB was administered in 5 of the 7 studies. In two studies three dietary levels, 25, 50 or 100 ppm, were administered to separate groups of rats. The study durations ranged from 100 to 126 weeks when the rats were killed. They were necropsied, and tissues were prepared for microscopic examination. The number of rats tested in each study varied . Details of the various study designs are summarized in Table 2.

Tables 3 thru 6 permit a comparison of the original liver pathology diagnoses and the diagnoses of the PWG using the diagnostic criteria developed by the National Toxicology Program. The tables reveal that there are modest differences in the number of slides (rat livers) reevaluated by the PWG and the numbers reported in the original publications. Two factors account for these differences: reduced numbers reflect that some slides were either lost or misplaced in the intervening years since the studies were performed; increased numbers likely reflect slides from rats that were censored from the data based on criteria defined by the authors in their publications, for example, early death. In the latter instance written records or notes were not located that permitted the identification of these specific rats; therefore, no slides were censored from the reevaluation.

Table 3 provides the incidence data for female rats from the studies of a PCB mixture containing 60% chlorine by weight. The reevaluation resulted in a reduction of the combined incidence of benign and malignant hepatocellular tumors in Sherman strain rats from 170/184 (92%) to

138/189 (73%). The use of NTP criteria had the practical result of separating neoplastic nodules into one of two categories, hepatocellular adenoma or foci of cellular alteration. Under the new classification some hepatocellular carcinomas were diagnosed as hepatocellular adenomas reducing the number of hepatocellular carcinomas. This did not affect combined tumor incidence. In the study with Sprague-Dawley rats the combined incidence of hepatocellular neoplasms was reduced from 43/47 (91%) to 41/46 (89%). Three cholangiocarcinomas were also diagnosed by the PWG; however, each occurred in a liver that also contained a hepatocellular tumor thus the incidence of tumors in the liver remained unchanged.

Table 4 indicates that the reevaluation led to only a modest difference in the incidence of hepatocellular tumors in the study with Wistar rats fed a PCB mixture with 60% chlorination, 123/129 (95%) to 114/125 (91%). The majority of tumors (59%) were hepatocellular carcinomas, a modest increase from that reported by the original authors. The reevaluation supported the original authors' finding that hepatocellular tumors in male Sprague-Dawley rats occurred at a low incidence, 7/46 (15%) versus 5/40 (13%) in the reevaluation.

In Table 5, the pathology diagnoses of a study of male Wistar rats fed a PCB mixture containing 42% chlorine are presented. In this instance the reevaluation resulted in a significant decrease in the incidence of combined hepatocellular tumors from 42/130 (32%) to 16/128 (13%). Only a portion of the lesions originally diagnosed as neoplastic nodules, 38/130 (29%) were re-diagnosed as hepatocellular adenomas.

In Table 6, the data on male and female Fischer 344 rats in a study of a PCB mixture that contained 54% chlorine are summarized. The reevaluation diagnosed one hepatocellular adenoma in control and in the middle dose males where none had originally been reported. In females a hepatocellular adenoma was diagnosed in control rats where none were originally reported; an additional adenoma was also diagnosed in the mid dose and one less was diagnosed in the high

dose group. The lesions that were reported as nodular hyperplasia in the original report were diagnosed as foci of alteration by the PWG. The foci increased with increasing dose with greater than 60% of the male or female rats evidencing this change at the high dose.

DISCUSSION

Reevaluation of seven rat PCB studies by a panel of pathologists minimizes differences between studies that may be due to the diagnostic criteria used or individual variability among pathologists. Using the pathology diagnoses from the reevaluation tumor incidence and type can now be better analyzed to determine whether observed differences are associated with strain, sex, laboratory conditions, or differing levels of chlorination in the PCB mixtures. The majority of the liver lesions in all PCB studies were similar. Initially, enlarged hepatocytes were noted in the centrilobular portion of the hepatic lobule. Enlarged hepatocytes frequently formed round foci composed of large eosinophilic cells. With progression to hepatocellular adenomas, considerable growth occurred resulting in compression of the adjacent tissue and changes in the growth patterns of the hepatic cords. Some lesions progressed further with additional anaplastic features and distortion of the hepatic architecture resulting in the diagnosis of carcinoma. No metastases of hepatic neoplasia were reported.

In rats receiving the mixture with 54% chlorine, foci were similar although basophilic and mixed cell foci occurred in addition to eosinophilic foci. Only a few hepatic neoplasms occurred and these were not statistically significant.

The results show a basic consistency in diagnoses between the original reports and the reevaluation. However, there were a few key differences. The greatest change in incidence resulted from a change in some diagnoses, based upon current pathologic criteria, from neoplastic nodule to focus of cellular alteration. The latter term downgrades the finding to a non-neoplastic

lesion. For example, total incidence of hepatocellular neoplasms in rats fed 100 ppm of a PCB mixture with 42% chlorine decreased from 32% when carcinoma and neoplastic nodules are summed to 13% when carcinoma and adenoma are summed. The latter is a more accurate interpretation of the observed hepatic neoplasms. In this instance, pairwise comparison of the 13% response with a control incidence of close to 5% (Table 5) does not attain statistical significance. It is also interesting to note that the incidence of hepatocellular carcinoma in this study, based on current diagnostic criteria, was similar in treated and control rats.

Three of the four studies on the effects of exposure to a PCB mixture with 60% chlorine yielded similar results when total incidence of hepatocellular neoplasms was used as the basis of comparison. Rates of 73%, 89% and 91% were observed in female Sherman, female Sprague-Dawley and male Wistar rats, respectively. The dietary level tested was similar in each study, 100 ppm, although study duration varied from 100 to 126 weeks. The lower tumor incidence was observed in the study with the shorter duration. The incidence of hepatocellular carcinoma was lower in this same study, 15% versus 41 or 59%. The number of tumors in male Sprague-Dawley rats, a study conducted in parallel with the study in females of the same strain, were comparatively low with a combined liver neoplasm incidence of 13%. The difference in response cannot be readily dismissed due to strain or sex differences since female Sprague-Dawley and male Wistar rats had a liver tumor incidence of 89% and 91%, respectively.

A comparison of results from studies of PCBs with different levels of chlorination clearly indicate major differences in carcinogenic potential based on the degree of chlorination. Studies of mixtures with 60% chlorination consistently resulted in a high incidence of liver tumors whereas studies in which rats were fed mixtures with 54% or 42% chlorination showed no statistically significant increases in liver tumors. A degree of uncertainty exists as to the predictability of the study of PCBs with 54% chlorination since the number of rats per dose group were about half that specified in the NTP protocols or currently required by regulatory bodies such as the EPA.

Group size limitations not withstanding, the data strongly indicate that a tumor response associated with such a PCB mixture, if there is one, is likely to be low and will not approach the 70-90% response rates observed with the PCB mixtures containing 60% chlorine. Group size does not contribute to uncertainty about the non-significant increase in liver neoplastic response observed in rats fed a PCB mixture with 42% chlorine due. In this study 130 rats were exposed to the PCB mixture, a group size two and a half times larger than that required by current protocol. Furthermore, the study duration was about three months longer than current requirements stipulate. It should be noted that the laboratory performing this study also conducted parallel studies with a PCB mixture containing 60% chlorine in which 91% of the rats developed liver tumors.

The re-evaluations permit a more confident comparison of the carcinogenic responses observed in seven different studies with PCBs. The results highlight three issues: PCBs with a 60% chlorine content consistently provoke a high yield of liver tumors in rats; the liver tumor response observed in rats exposed to PCBs with lower levels of chlorine were not observed to have an increase in liver tumors; no clear sensitivity differences in tumor response were observed between males and females. These data indicate that continuation of a science policy of assuming that all PCBs are probable human carcinogens and possess a carcinogenic potency equivalent to the mixture that contains 60% chlorine has no scientific foundation and should be reconsidered.

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Table 1. Average Molecular Composition (wt. %) of Some Commercial PCB Mixtures

PCB Mixture (Wt. Percent Chlorine)	Number Chlorine per Biphenyl								
	1	2	3	4	5	6	7	8	9
40-42	1	13	45	31	10				
52-54			1	15	53	26	4		
60					12	42	38	7	1

*Adapted from Tables 1.12 and 1.13 (with permission) from deVoogt and Brinkman (1989).

Table 2. Experimental Design Summary of PCB Studies in Rats

Study	% Chlorine of PCB in Mixture	Strain	Sex	No. Rats Per Group[a]	Dosage Levels	Study Duration
Kimbrough et al., 1975	60%[b]	Sherman	F	200	0, 100 ppm	100 weeks
Norback & Weltman, 1985	60%[b]	Sprague-Dawley	F	63	0, 100 ppm for 16 months followed by 50 ppm for 8 months then control diet for 5 months	126 weeks
	60%[b]	Sprague-Dawley	M	70		
Schaeffer et al., 1984	60%[c]	Wistar	M	139, 141	0, 100 ppm	114-117 weeks
NCI, 1977	52-54%[d]	F344	M	24	0, 25 ppm, 50 ppm 100 ppm	104-105 weeks
		F344	F	24	(see above)	
Schaeffer et al., 1984	40-42%[e]	Wistar	M	139, 152	0, 100 ppm	114-117 weeks

[a]Number of rats when study began.
[b]Aroclor 1260.
[c]Clophen A60.
[d]Aroclor 1254.
[e]Clophen A30.

Table 3. Comparison of Liver Neoplasms in Female Rats Fed a PCB Mixture Containing 60% Chlorine

Strain:	Sherman[a]				Sprague-Dawley[b]			
Group:	Control		Treated		Control		Treated	
Pathology Diagnoses:	Orig.	Re-Eval	Orig.	Re-Eval	Orig.	Re-Eval	Orig.	Re-Eval
No. Examined	173	187	184	189	49	45	47	46
Benign Hepatic Tumors	0	0	144[c]	117[d]	1[c]	1[d]	2[c]	22[d]
Hepatocell. Carcinomas[e]	1	1	26	21	0	0	43	19
Benign + Carcinomas[f]	1	1	170	138	1	1	45	41[g]

[a]Kimbrough et al. (1975).
[b]Norback and Weltman (1985).
[c]Reported as neoplastic nodules.
[d]Reported as hepatocellular adenomas.
[e]Original study reported as trabecular carcinomas or hepatocellular carcinoma.
[f]Sum of benign hepatocellular tumor or hepatocellular carcinoma. If rat had both lesions counted only as carcinoma.
[g]Three cholangiocarcinomas were also diagnosed in rats that also had other liver tumors.

Table 4. Comparison of Liver Neoplasms in Male Rats Fed a PCB Mixture Containing 60% Chlorine

Strain:	Wistar[a]				Sprague-Dawley[b]			
Group:	Control		Treated		Control		Treated	
Pathology Diagnoses:	Orig.	Re-Eval	Orig.	Re-Eval	Orig.	Re-Eval	Orig.	Re-Eval
No. Examined	131	120	129	125	32	31	46	40
Benign Hepatic Tumors	5[c]	6[d]	62[c]	47[d]	0	0[d]	5[c]	4[d]
Hepatocell. Carcinomas	1	2	61	67	0	0	2[e]	1
Benign + Carcinomas[f]	6	8[g]	123	114	0	0	7	5

[a]Schaeffer et al. (1984).
[b]Norback and Weltman (1985).
[c]Reported as neoplastic nodules.
[d]Reported as hepatocellular adenomas.
[e]Original study reported as trabecular carcinomas.
[f]Sum of benign hepatocellular tumor or hepatocellular carcinoma. If rat had both lesions counted only as carcinoma.
[g]One cholangiocarcinoma also diagnosed in a rat with other liver tumors.

Table 5. Comparison of Liver Neoplasms in Male Rats Fed a PCB Mixture Containing 42% Chlorine

Strain:	Wistar[a]			
Group:	Control		Treated	
Pathology Diagnoses:	Orig.	Re-Eval	Orig.	Re-Eval
No. Examined	131	120	130	128
Benign Hepatic Tumors	5[b]	6[c]	38[b]	14[c]
Hepatocell. Carcinomas	1	2	4	2
Benign + Carcinomas[d]	6	8[e]	42	16

[a]Schaeffer et al. (1984).
[b]Reported as neoplastic nodules.
[c]Reported as hepatocellular adenomas.
[d]Sum of benign hepatocellular tumor or hepatocellular carcinoma. If rat had both lesions counted only as carcinoma.
[e]One cholangeiocarcinoma also diagnosed in a rat with other liver tumors.

Table 6. Comparison of Liver Neoplasms in Fisher 344 Rats Fed a PCB Mixture Containing 54% Chlorine[a]

Sex:	Male						Female					
Group:[b]	25		50		100		25		50		100	
Pathology Diagnoses:	Orig.	Re-Eval	Orig.	Re-Eval	Orig.	Re-Eval	Orig.	Re-Eval	Orig.	Re-Eval	Orig.	Re-Eval
No. Examined	24	24	24	24	24	23	24	24	22	24	24	24
Benign Hepatic Tumors	0	1[c]	0	1[d]	1[c]	1[d]	0	1[d]	1[c]	2[d]	2[c]	1[d]
Hepatocell. Carcinomas	0	0	1	0	2	2	0	0	0	0	0	0
Benign + Carcinomas	0	1	1	1	3	3	0	1	1	2	2	1

[a]NCI (1978).
[b]No neoplasms diagnosed in 24 male and 23 female control rats..
[c]Reported as adenoma NOS.
[d]Reported as hepatocellular adenomas.

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