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The Honorable Donald Clay
Assistant Administrator
Office of Solid Waste & Emergency Response
Environmental Protection Agency
401 M Street SW
Washington, DC 20460

Dear Don:

The Institute for Evaluating Health Risks has just completed a project in which the pathological diagnoses in five key rat PCB studies were reassessed.[1] Based on the results of this reassessment, a copy of which is enclosed, these studies could then be analyzed for consistency of result and it could be determined whether the differences in tumor incidence and type were due to the differing levels of chlorination in the tested PCB mixtures. The analysis clearly indicates that a reconsideration of the Agency's traditional cancer risk policy is warranted.

In the studies that were reviewed in this project rats were chronically exposed to commercial PCB formulations with three different levels of chlorination. The results of the pathology reassessment are briefly summarized as follows:

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[1] The project, which was funded by General Electric, was managed by the Institute for Evaluating Health Risks; coordination of the pathology reassessment was performed by Experimental Pathology Laboratories Inc.

These specific studies were selected because they were utilized or discussed in previous EPA risk assessments and they represent the best studies for evaluating the cancer potential of these mixtures of chemicals.

reaffirmed that chronic dietary exposure of rats, in three different studies, to 60% chlorinated PCB formulations resulted in the development of benign and malignant liver tumors;

reaffirmed that chronic exposure of rats to a PCB formulation that was 54% chlorinated did not yield a statistically significant increase of either benign or malignant tumors;

revealed that rats chronically exposed to a PCB formulation that was 42% chlorinated did not develop any increase in malignant tumors or a statistically significant increase in benign tumors.

These reassessment results indicate that the following two traditional EPA PCB policy positions be reconsidered: 1) an assumption that all PCB formulations are probable human carcinogens; 2) the assumption that all PCB formulations have the same quantitative potency to cause cancer.

Both of these positions were initially established years ago when our knowledge base from which to determine the cancer potential of PCBs was meager. They represent the use of conservative default assumptions. However, since then new data and knowledge have accrued that have not been effectively incorporated into the PCB risk assessment.[2]

I believe that a revised PCB cancer risk assessment should reflect the following:

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[2] Because of insufficient data default assumptions commonly are a necessary component of a risk assessment. However, there is another policy position which should guide the decision that determines the use of defaults; that overarching policy should establish a clear bias for the use of data whenever it is available. In other words the operant policy position is to use data, the burden should lie on the risk assessor to clearly establish why available data should not be used before it can be replaced by a default assumption.

Develop separate risk assessments for each of the major PCB formulations.

The reassessed data underscore that there are major differences in carcinogenic potential based on the degree of chlorination of the PCB mixture. While the results from studies of mixtures with 60% chlorination consistently report a high incidence of liver tumors studies in rats which were fed mixtures with 54% or 42% chlorination did not detect statistically significant elevations of liver tumors. It is not proper to continue a policy which does not consider data, developed subsequent to the initial judgement, that demonstrates other formulations are either not carcinogens or at best, weak carcinogens. There is precedent for such action; several years ago the Science Advisory Panel, which advises the State of California on cancer designations under Proposition 65, voted to recommend Aroclor 1260 as a carcinogen rather that list all PCBs.

The tissue diagnoses of the expert group of pathologists should be used for risk assessment.

There are three factors that support the use of these consensus diagnoses:

1) it reflects the use of current pathology conventions that are endorsed by the National Toxicology Program and the Environmental Protection Agency;

2) it represents the consensus opinion of pathologists that are experienced in the evaluation of rodent bioassays; specifically liver tumors.

3) the results of the present review permits greater confidence that observed differences in tumor incidence and type in each study are due to differences in the test substances.

Utilize all available data when calculating cancer potency for PCB mixtures that have 60% chlorination.

There is no logical basis to continue the current practice of only using the results obtained in female Sprague Dawley rats. A comparison of the results of each of these studies[3] shows a striking similarity in the nature of the tumor response. It should be noted that three separate strains of rats were used and that the similarity of response is apparent when one compares female Sherman rats, male Wistar rats, and female Sprague Dawley rats. Male Sprague Dawley rats, while developing the same type of liver tumors, did so at a lower incidence. To assume that this reduced response reflects a generic tendency of male rats not to develop tumors is not supported by the data. The greatest incidence of liver tumors (91.2%) was observed in male Wistar rats. The results in male Wistar rats also do not support continuing the practice of censoring the male Sprague Dawley results from the calculation of a cancer slope factor.

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[3] Induction of Liver Tumors in Sherman Strain Rats By Polychlorinated Biphenyl Aroclor 1260. Kimbrough, R.D. et al, JNCI (1975) 55:6, 1453-1459.

Polychlorinated Biphenyl Induction of Hepatocellular Carcinoma in the Sprague Dawley Rat. Norback, D.H. & Weltman, R.H., Env Hlth Perspect (1985) 60:, 97-105.

Pathology of Chronic Polychlorinated Biphenyl (PCB) Feeding in Rats. Schaeffer, E., Greim, H., & Goessner, W., Tox & Applied Pharm. (1984) 75:, 272-288.

When using the results from each of these studies one should apply a consistent decision rule to the censoring of animals from studies; each author used a different convention in their publications. Observing the convention employed by the National Toxicology Program may be more appropriate and consistent for all studies.[4] The group size in several of these studies would increase if this recommendation were adopted.

Employing the geometric mean of the cancer potency factors of the four study groups, female Sherman, male Wistar, male Sprague Dawley, and female Sprague Dawley rats would reflect a less arbitrary use of all existing data. There is ample precedent for this approach in a number of Agency decisions. The geometric mean, using the re-evaluation results, would yield a cancer potency factor of approximately 1.9. The current value calculated by EPA is 7.7 using only the female Sprague Dawley rat.

<u>The reassessment of the NCI study[5] clarifies the significance of "nodular hyperplasia"</u>

This study which evaluated a PCB mixture with 54% chlorination, essentially reaffirmed the original findings that the bioassay did not show a carcinogenic response in either male or female F344/N rats. The group size at each treatment level was 24 rats.

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[4] Censor all rats that died during the first year of the study or censor rats that died prior to the diagnosis of the first tumor in a target organ; whichever date is earlier.

[5] Bioassay of Aroclor 1254 for Possible Carcinogenicity. NCI Carcinogenisis Technical Report Series, Number 38, 1978.

Utilizing the current pathology nomenclature the consensus diagnoses by the expert panel classified "nodular hyperplasia" lesions, a designation used in the original report, as nonneoplastic. Therefore, continuing to incorporate the incidence of nodular hyperplasia in a cancer potency calculation, as was done in the most recent Water Quality Criteria Document[6] would fail to have a supportable scientific basis.

Rather than exclusively focus on how to estimate a cancer potency factor for the 54% chlorination PCB mixture I would urge consideration of a more fundamental question; namely, the estimation of cancer potency from any negative study.

<u>The reassessment of the pathology diagnoses of lesions in the liver of rats fed a PCB mixture containing 42% chlorination reveals that there is no statistically significant increase in tumors.</u>[7]

This study, which was performed in parallel with a PCB mixture with 60% chlorination, has not been accorded the attention that it deserves from a risk assessment perspective.[8]

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[6] Drinking Water Criteria Document for Polychlorinated Biphenyls, April 1988, (PB89-192256) pp VIII-32 to VIII-35.

[7] Liver tumor incidence in controls 8/120 (hepatocellular adenoma 6/120, hepatocellular carcinoma 2/120). Liver tumor incidence in treated group 16/128 (hepatocellular adenoma 14/128, hepatocellular carcinoma 2/128). Fisher exact test, one tailed, p =.098). It is arguable that a two tailed test should be used given that a decrease in pituitary tumors and endocrine tumors was reported in several of these studies. A two tailed test would further erode the p value.

[8] Pathology of Chronic Polychlorinated Biphenyl Feeding in Rats. Schaeffer, E., Greim, H., & Goessner, W., Tox. & Applied Pharm. (1984) 75:, 272-288

Factors which underscore the value of this study include:

1) it is the only major study of a PCB mixture with this level of chlorination.

2) it has far better statistical power to detect an effect than do most bioassays, e.g., the number of animals studied were about two and a half times greater than required by EPA or used by the National Toxicology Program.

3) the selection of male rats as the test subject would not appear to be a limitation. A parallel group of male rats, fed a PCB mixture containing 60% chlorine, yielded a liver tumor incidence of 91%, the highest incidence reported in any of the studies that were reassessed.

4) the study duration was approximately 118 weeks, this is three months longer than the protocol requirements of either EPA or the National Toxicology Program. It is generally held that studies of longer duration favor the detection of tumors, particularly with these types of chemicals.

I am not asking you to focus on an issue that is only of arcane scientific interest. The current cancer policy is clearly overstating the cancer risks associated with many exposures to PCBs in the environment. In a number of instances it is driving regulatory decisions that, by any standard are a major economic impact for, at best, trivial public health gain. As an illustration, mixtures with 60% or greater chlorination were about 12% of total PCB sales in this country; current policy calculates <u>all</u> PCB exposure as if it were equivalent to Aroclor 1260.

While PCBs in the environment undergo changes in composition they do not develop into the chemical "fingerprint" that identifies Aroclor 1260. Therefore, 88% of the PCB that was used is being treated as if it were a potent carcinogen when the data indicate that these lower chlorinated mixtures are either of markedly diminished potency or not carcinogenic at all!

A request to develop a risk assessment utilizing all pertinent data, I believe, is consistent with the Agency's stated goals of focusing on risks which represent true public health or environmental concern and of reducing the uncertainties in risk assessment by applying sound scientific knowledge.

I would be pleased to work with the Agency in explaining the results of this project and discussing alternative approaches to estimating PCB risks.

Sincerely,

John A. Moore