CURRENT STATUS OF TOXICOLOGICAL ASPECTS OF PCB's

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The PCBs are manufactured in the USA as Aroclors and are also imported from other countries of manufacture in a variety of unknown products.

It is likely that PCBs have been getting into environmental circulation for a period of years, although such contamination on an environmental scale has only been recognized recently in the past few years.

Residues have been found in a variety of foods as a result of either direct contact with materials containing PCBs or as a result of biological uptake of PCBs circulating in the environment.

What is the toxicological significance of PCBs? I would like to briefly summarize data derived from animal experiments and from human intoxications.

While the oral LD^{50} in mammals varies from about 2 to 10 gms/kg, substantially smaller doses adversely affect egg production in birds. Chick embryo studies indicate that lethal effects decrease with increases in the chlorine content of the PCBs, and that a variety of birth defects can result from PCBs tested in this sensitive system.

Rats experience growth depression and increase in liver size when dosed with 1,000 ppm in the diet; however, induction of certain enzymes has been noted at levels as low as 25 ppm in the diet. Generally, enzyme induction increases with increases in chlorination of PCBs. Pathologically, monkeys given 1.4 to 16 mg/day PCBs in their diet showed liver cell enlargement, fatty degeneration, and an increase in the smooth endoplasmic reticulum of the liver cells indicating fibrotic changes. Reflecting alteration of liver metabolism, changes in hexabarbital sleeping time and other enzymatic related detoxification steps were noted,

largely related to induction of hepatic hydroxylating enzymes. Hydropericardial edema has been noted and may possibly in part be related to the contaminating presence of chlorinated dibenzofurans in PCBs of foreign manufacture.

At levels around 100 ppm in the diet, adverse reproductive effects with decreased litter size and survival have been noted in rats with increases noted in liver and thyroid weights. Obviously PCBs affect metabolism by inducing certain enzyme systems and undoubtedly inhibiting others. It is likely that such changes adversely affect the metabolism of hormones and pesticides, not to mention the relatively unexplored area of interactions with therapeutic drugs.

We know that PCB residues have been found in human fat and milk at levels of 60 ppb. However, little is known about the metabolism of the PCBs themselves in animals and humans.

Human intoxication with Kanechlor 400, a PCB manufactured in Japan with 48% chlorine, but unknown chemical characteristics as to the purity, was noted when a heat exchanger leaked into rice oil which was consumed by Japanese families in 1968. About 600 people were eventually affected. Exposure levels to the oil were calculated to approximate 15 gm/day. The oil itself was apparently contaminated at levels estimated to range from 200 to 2,300 ppm PCBs, but the origin of the lower figure is not given in the particular Japanese publication and is currently under FDA investigation. The higher figure is derived from the known organic chlorine content of rice oil related to the known organic chlorine content of Kanechlor 400.

The clinical problems associated with Japanese Yusho incident included chloracne, blindness, systemic neuro intestinal symptoms with jaundice, edema, and abdominal pains. Birth abnormalities were noted in that a few babies were born with decreased birth weights and skin discolorations usually Brown represented. Nothing is known as to whether or not these children have experienced permanent liver damage or alterations in liver function or metabolic detoxification of hormones, etc. Nothing was described in relation to thyroid function which you will remember was noted apparently to be affected in animals. Transplacental transmission of PCBs were noted by the presence of residues in fetal tissue.

To summarize what is presently known, the no-effect level in test animals may approximate 10 ppm in the diet. Based on this animal data with allowance for a 1,500 gm human dietary food intake, the ADI would permit a 100-fold margin of safety if set at 150 μgms PCBs per day.

From the observations available to us concerning Yusho, the lowest reported figures estimate a minimal positive effect level at 3 mg per day, even though the average doses to these Japanese may have been higher. Using a tenfold safety margin, we could roughly estimate that 300 μgms/day would be without overt effect although possibly subtle changes in liver function may still occur.

These animal and human data both point to 150 to 300 μgms/day as being in the range of consideration for establishing an acceptable daily intake for the period of time that we as a society are forced to tolerate the presence of these chemicals in our food supply, but I would like to emphasize that we know very little about the potential metabolic consequences to long-term PCB exposures even at these low levels.

In further consideration of low-level exposures, we can predict that since 2 ppm was reported to be the total dose necessary to cause an effect in the Japanese, then 200 ug would be an estimated total safe ingestion over an extended period of time. I emphasize that I am now talking total accumulated exposure and not a daily exposure.

Our previous lowest estimate of a safe dose was 150 ug/day based on animal data or 300 ug/day based on human data. With a total allowable ingestion of 200 mg we could estimate a safe period of intake of 44 months based on the 150 ug/day animal exposure data or 22 months at the 300 ug/day level based on human data.

If we can assume new regulatory approaches will bring the problem under better control within 6 months, this would permit 1.1 mg/day of PCB in the dietary intake for the next six-month period only as a temporary measure.

At a level of 5 ppm this allows total intake of 200 grams food.

At a level of 4 ppm this allows total intake of 250 grams food.

At a level of 3 ppm this allows total intake of 330 grams food.

At a level of 2 ppm this allows total intake of 500 grams food.

At a level of 1 ppm this allows total intake of 1 kilogram food.

Wed. AM 9-8

August 27, 1971

Ask Monsanto for a full list of (1) products that PCB's are used in, and, (2) full list of all customers receiving such products.

Taylor Quinn

TQuinn:mlf

PCBs in adhesives that may be used in food packaging?

Historical (10 to 20 yrs) what are major uses -

Categories of people we've said to Now for have we gone in Cutting off most exchange use in connection w/ feed.

Aug. 27, 1971
~~AugxxtexMonsantex~~
Questions to Monsanto

1. Is there any information on comparative analysis between Monsanto's PCB and those of competitors -- Europe, Japan.

2. Update of studies in progress or completed.

3. List of primary customers for PCBs and thier potential use.

4. List of uses of PCB known to Monsanto.

5. Do you know of human poisoning incidents with PCBs other than Yusho?

6. Does Monsanto manufacture other heat exchanger materials of potential use in the food industries? What are their contents?

NOTES OF MY MEETING WITH FDA

September 1, 1971

Re: PCB

As a result of my understanding that a large multi-Government Agency meeting was to be held at FDA yesterday, I dropped by Dr. Wodicka's office during the late afternoon. The PCB meeting had adjourned and Wodicka had gone into a budget meeting. While waiting for Wodicka, Dr. Albert Kolbye (Wodicka's deputy) asked me to come to his office. I explained that I was waiting for Wodicka to determine whether there would be any public release as a result of that afternoon's meeting. Kolbye said that there would no later than Friday be such a release and that the punch line was that the matter was too big for FDA handling it along. He suggested that our people be prepared to answer inquiries which may result from the release on the basis of suggesting the "good" uses -- the "essential" uses in order to place the subject in perspective. He understood why I would like to have a notice of the release a little in advance of it being given to the press. He telephoned Jack Walden, the public information officer, gave him my name and telephone number and instructions that Walden call me as soon as he felt he could give me the language of the release. Kolbye handed me a 4-page paper prepared by him and entitled Current Status of Toxilogical Effects of PCB. That material is being sent to you this morning on the DEX I machine with the understanding that it will be maintained confidentially and above all that it not be attributed to FDA. Kolbye found it necessary to ask Wodicka for permission to release this paper under those circumstances.

While waiting for Wodicka, Kolbye continued to discuss PCB and I continued to listen.

I was surprised to hear him say that imports of foreign PCB were suspect. He asked whether we had any estimates of the volumes of imports. He asked whether there were dioxins contained in the imports and particularly in Kanechlor 400; also whether they contained Dibenzol Furans or Chlorinated Napthalenes. He also stated that it was suspected that European products were very impure. You understand that I had heretofore advised Wodicka that the two year test result would probably be available during September---Kolbye was extremely interested. Kolbye asked whether other heat exchange fluids-Dowtherm-contained PCBs and whether "newer heat exchange fluids" were toxic. He asked whether lubricant manufacturers used Aroclors. He stated that it would be most helpful to know what our historical production figures and major uses had been and mentioned a 10 - 20 year time frame. I, of course, was unable to respond to any of his specific questions, but did advise him that the matter of furnishing production figures had been an issue for many months. I told him that Congressman Ryan had raised the matter and we had advised that under conditions of extreme confidentiality and agreement as to the receptacle, such figures might be furnished.

At that juncture Wodicka returned and we reconvened in his office. Deputy Commissioner Jim Grant was present as well as another gentleman whose name I did not get but who contributed nothing but silence to the meeting.

The long and short of this second meeting was that FDA hoped that the Monsanto PCB experts would be willing to discuss the subject with FDA -- and soon. A check of the calendar indicated that Wednesday morning, September 8 was the best date for such a meeting. It was suggested that probably the Commissioner, Dr. Edwards, would attend.

Dr. Wodicka handed me some questions which are likewise being Duxod this morning to you. The hand written notes at the bottom of the Quinn are mine and were propounded by Dr. Wodicka.

NCR was mentioned by name and carbonless carbon paper was referred to several times. I have the distinct feeling that there is perhaps little about this subject that is not known by FDA and if my feeling is correct, I see no reason not to meet on Wednesday (assuming that the proper people can be present) and several reasons why we should.

In my judgement Dr. Kelly and/or Elmer Wheeler and Bill Papageorge would be the likely attendees on behalf of Monsanto. Dr. Wodicak or Dr. Kolbye are the contacts and either can be called directly or we can handle the details through this office.

Kolbye and Wodicka's telephone number is:

Area Code 202 - 962-1431

Sam Pickard