DRAFT

September 29
Joseph P. Hyle, Associate Comissioner for Compliance
to Dr. Ian C. T. Nisbet

Dr. Kennedy has asked me to respond to your letter of August 31, 1977 in which you requested reconsideration of the temporary tolerances for PCBs as proposed by FDA on April 1, 1977. We appreciate your interest in this very important issue and therefore will consider your thoughtful comments as part of the public record being established on this subject. Your comments, as well as those received by other interested persons, will be considered and addressed in the final order regarding the PCB tolerance. Your letter with the attachments will be placed on public display in our hearing clerk's office. If you have any questions concerning this matter, please let me know.

Letter
August 31, 1977
Massachusetts Audobon Society
Dr. Donald Kennedy
FDA
Letter is signed by Ian Nisbet
cc: Costell

This letter will confirm and amplify my telegram of

today's date. I wish to bring to your attention new information on the toxicity of PCBs. I believe that this new information demands reconsideration of the temporary tolerances for PCBs proposed by FDA on April 1 (and so forth.) The significant new information is the recent and now widely reported finding by FDA and EPA that many toxicological tests, conducted by IBT appear to be unreliable on a basis of internal inconsistencies and discrepancies in reporting. In this letter, I wish to point out to you the following related facts: 1) the temporary tolerances for PCBs established by FDA in 1973 were based primarily on data from tests carried out at IBT; 2) the same data from IBT recited by FDA in its 1977 proposal for reduction in temporary tolerances and appeared to be the primary toxicological basis for the proposed tolerances; 3) I have reviewed the IBT experiments with PCBs on behalf of EPA and found discrepancies similar to those reported to have been found in other IBT reports; 4) the raw data in the IBT reports show serious toxicological effects at dose levels at and below those reported as "no effect levels" and utilized as such by FDA in establishing temporary tolerances 5) these findings have been reviewed and accepted by the administrator of EPA.

The following paragraphs will amplify the above statements:

Dependence of 1973 Temporary Tolerances on IBT Data

The temporary tolerances for PCBs in animal feeds, foods, and food packaging established by FDA in 1973 (38 FR 18006 et. seq.) were based upon an estimated allowable daily intake of 175-210 micrograms per day (2.5 -3 micrograms per kilogram per day) in man. This, in turn, was derived from experiments with rats and dogs which were accepted as showing no effect levels at 10 parts per million in the diet. (38 FR 18008; 42 FR 17487). The experiments involved were conducted by IBT and were prescribed in unpublished reports (references 207 and 212 and attachment 8 of this letter).

Dependence of 1977 Temporary Tolerances on IBT Data

Although FDA proposed a reduction in the temporary tolerances for PCBs on April 1, 1977, the proposed tolerances are still to be based in large part on the same IBT reports. The results of the IBT tests, including the alleged establishment of a no effect level at 10 parts per million in rats and dogs, cited at the outset of the section on toxicity of PCBs.

No qualification of this finding is made later in the notice. Although toxic effects of PCBs in mink and monkeys ~~have~~ at dietary levels of 5 parts per million and 2.5 parts per million respectively are cited subsequently in this section of the notice (p. 17488) The relevance of the monkey data to establishment of human risk is questioned (p. 17489). At the end of this section (p. 17489) it is stated that "while the data does not support establishment of a new allowable daily intake of PCBs, especially in the light of the studies regarding carcinogenicity, the Commissioner concludes that the predicted level of exposure discussed below is tolerable." Although the April 1, 1977 notice thus does not explicitly relate the proposed tolerances to the IBT data (nor indeed to any other toxicological data cited in the notice) it is evident that FDA again relied on these data in 1977. The reported no effect levels of 10 parts per million in rats and dogs is cited on p. 17487 without qualification. Whereas effects in other species at lower levels are strongly qualified (p. 17488). Although the notice acknowledged that new data indicate that further reduction of PCB intake is desirable, (pp. 17489 and 17491) the proposed reduction of the temporary tolerance in fish (the primary ~~root~~ route of human exposure: p. 17489) was by a factor of only 2.5. Clear evidence that FDA relied on the IBT data in proposing the April 1, 1977 temporary tolerances is shown in response 3 on p. 17490. In

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this passage, FDA addressed the claim of the Petitioner as that "the rat ~~of~~ the dog in which that tolerable daily intake was partially based or relatively insensitive to many of the toxic effects of PCBs." FDA responded as follows "The Commissioner acknowledges that compared to the monkey, the rat and the dog may be relatively insensitive to PCBs. On the other hand, it is not known whether monkeys are unusually sensitive compared to humans. It is not yet possible to make a direct comparison of the facts of PCBs from one kind of test animal to another or to humans. However, when judgments regarding allowable intakes are made, all available data from all species are considered." (pp. 17490 and -1) It is abundantly clear from this response that in proposing the reduced tolerances on April 1, 1977 FDA was continuing to rely on the IBT data of rats and dogs, balancing the apparent insensitivity of these species against the apparent sensitivy of monkeys.

Discrepancies in the IBT Data on PCBs

In March 1976 under contract with EPA, I reviewed the scientific literature on PCBs and prepared a draft of a criteria document. My draft was adopted with only minor revisions as EPA's criteria document for PCB's in water. (EPA Report #440/9-76-021) and was incorporated as part of EPA's proposed toxic ~~bludentifolent~~ pollutant standards

(41 FR 30468 et. seq. July 23, 1976) relevant sections of this criteria document, including the toxicological report data sheet and relevant pages from the bibliography are attached to this letter as attachment A. As part of my review, I made a critical review of the IBT reports on dogs and rats which were relied upon by FDA in establishing temporary tolerances (references 212 and 207 to attachment A respectively). I noted and reported[a] number of discrepancies between data in these and subsequent reports by IBT in the summary statements on which FDA appears to have relied. In particular, the raw data in reference to 12 including listing of stomach nodules in many treated dogs. Findings which were ignored in the summary; a subsequent oral presentation by an IBT toxicologist concluded a statement that re-examination of slides in 1975 had shown evidence of "gastrointestinal inflammatory lesions and ulcerations which appeared similar to those reported by Alan in ~~Reese's~~ Rhesus monkeys". This key statement was deleted from the speaker's published paper (reference 69,for details see pp. 197-199). In the case of rats, IBT pathologists reevaluated the liver slides in 1975 and reported dramatically different lesions from those listed in the 1971 report (ref. 416 see pp.D-11,D-12 and Tables D-2 and D-2a) In addition, there were substantial discrepancies between the total number of animals diagnosed in 1975 and the number listed as surviving at 24 months in the 1971 report (p. D-12).

Toxic Effects in Rats and Dogs at Levels Below Those Reported at No Effect Levels

Although the summaries of the 1971 IBT reports stated that 10 parts per million was a no-effect level for rats and dogs, examination of the 1971 raw data and the 1975 re-evaluation did not support this conclusion. 1) Pinpoint nodules in the stomaches, stated to have been similar to those reported by Alan in Reese's monkeys, were listed for 22 out of 66 of the dogs exposed to PCBs including 5 out of 24 of those exposed to 1 part per million versus 0 out of 8 in controls (Table 3 9.6 p. 198). 2) ~~Lucosite~~ Leucocyte counts were elevated above those in controls in 9 out of 9 groups of treated dogs; the difference was statistically significant in all 3 groups exposed to 10 parts per million and the group exposed to ~~Clorofil~~ Aroclor 1254 at 1 parts per million. (Table III 9.6 p. 198). 3) In the 1975 reexamination (ref. 416) the IBT pathologist reported pathological changes in the livers of treated rats at frequencies significantly higher than those in the controls in all of the 9 treated groups, including the 3 groups exposed to only 1 part per million (Table D-2A). Lesions were reported as vacuolar change and focol hypertrophy were reported in 20-26% and 7-12% of rats exposed to 1 parts per million versus 4% and 0% respectively in controls (Table D2A). 4) In the 1975 reexamination reference 416, the IBT pathologist reported lesions diagnosed as nodular hyperplasia in 7-39% of animals exposed to 10 parts per million PCBs

versus 4% in controls (Table D2A). This finding is of great significance because nodular hyperplasia is often indicative of early stages in carcinogenesis (ref. 269) and because the IBT pathologist reported many liver tumors in rats exposed to 100 parts per million (Table D-2A) 5) Pituitary tumors were reported in 8 of the 9 treated groups of rats including all 3 exposed to 1 part per million but not in controls; the difference in incidence approached but did not reach statistical significance (Table D-2A p. D-10).

It us thus apparent that the IBT experiments do not support a finding of 10 parts per million of any PCB mixture as a no effect level in either rats or dogs. Indeed, at face value, these reports indicates serious toxic effects in both species even at 1 part per million. It is thus no longer necessary to speculate whether monkeys are more or less relevant than rats and dogs in predicting human risk: all three species are effected by exposure to PCBs well below the alleged no-effect levels reported in 1971.

Acceptance of Findings by Administrator of EPA

The above findings of toxic effects of PCBs in rats and dogs at dietary levels at 1 to 10 parts per million

have been reviewed by the Administrator of EPA and were specifically accepted by him and incorporated by him in his final decision on toxic pollutant effulent standards for PCBs (42FR637-8 Feb. 2, 1977).

Conclusions and Recommendations

The report summarized above in attachment A demonstrate 1) that the IBT reports on toxicological studies with the PCBs in rats and dogs contain discrepancies and inconsistencies which appear similar to those reported to have been identified by FDA and EPA in IBT reports on tests with other chemicals. 2) that the data in the IBT reports give primafacia evidence of toxic effects of PCBs in both rats and dogs at dietary levels as low as 1 part per million.

Although the discrepancies in the reports could be resolved only by a thorough reexamination of the pathological material, the data are already sufficient to show that the assumption of no effect levels at 10 parts per million on which FDA's proposed temporary tolerances were based in 1973 and 1977 is no longer tenable.

In the light of these findings, I therefore urge you 1) to extend FDA's audit of IBT's studies to include

the 1971 reports on PCBs(references 207 and 212 attachment A) 2) to reconsider the April 1, 1977 proposed temporary tolerances in the light of this new information and if judged necessary, to propose new tolerances or to reopen the matter for public comment.

I am sending a copy of this letter to the Administrator of EPA with recommendations for consistent action by that agency.

Yours sincerely,

Ian Nisbett

included is a telegram addressed to the commissioner

Ugently request FDA to reconsider the proposed tolerance level for PCBs in light of report on unreliability of industrial biotest reports which underlie proposals. Letter follows... Nisbett

(Attached is a criteria document for PCBs prepared by Nisbitt for EPA, Office of Water Planning and Standards. Report is many pages long. What is included here starts on page 197,as a considerable amount has been excerpted

by EPA. The entire file has been requested under the Freedom of Information Act by me on December 8 and will be copied and mailed to us in about 1 week. The file I am talking about is 77N-0080 Volume 5 and the specifics are comment 0088)

Monsanto

K. W. Easley - 1920

DATE: December 13, 1977

SUBJECT: PCBs

REFERENCE:

TO: G. J. Levinskas - A2SG

cc: R. C. Isham - B1NB
E. T. Mollica - B2SB
A. M. Navarro - A3NB
R. A. Stohr - B2SC
D. Wood - B2SD
C. Roush, Jr. - A2SA

In your memo of November 9, you asked that I chase down the Massachusetts Audobon Society letters which question the IBT data on PCBs and to seek confirmation of EPA's view that IBT's raw data is not being questioned. To get my hands on the letter, I had to go to the FDA Hearing Clerk's Office in Rockville. Attached is a rough transcription of my tape recording of the letter. The attachments referred to in the letter are not included, but should come along in a week or two and will include copies of the letters themselves. I requested them under the Freedom of Information Act, incidentally. The Audubon Society letter which was sent to EPA is identical to that which was sent to FDA. I do not plan to get a separate set from EPA. The EPA acknowledgment, like FDA's, doesn't really say anything, I'm told.

I had a long talk with John Wessel of FDA's Office of Compliance. As you know, he has been involved in this issue for some time. Incidentally, he is going to transfer to some other part of FDA and this work will be picked up by Betty Campbell in the Office of Compliance. Wessel does not know how FDA is going to react to the letter. He says that the Bio Research Monitoring group is examining it. The '73 PCB tolerances were established, according to John, primarily on the basis of Yusho data which, as he put it, is confirmed by the observations at IBT. If the IBT data turns out to be unreliable, they will still have the Yusho data to fall back on. He pointed out that it was after the 1973 tolerances were set that the cancer question arose. This got them into a box because no amount of PCBs in food could be considered safe, and they had to work toward getting the levels as low as possible considering analytical uncertainties, unavoidability of some contamination, and scientific judgments as to the levels people would consume over time. They could not fall back on a formula relating intake and toxicity. It follows then that even if the IBT data is discredited after their reassessment, there would still be no change in the final standard. Also, he noted, if FDA were to lower the standards, there would not be much of a reduction in PCB intake from foods. For

example, if they were to cut certain species of fish in the Great Lakes and the Hudson from 5 to 2, a change that looks significant on paper, it would, in practice, make no big difference. Asked when there might be something coming out of FDA, he said that they would probably be slow and that nothing will appear until 1980. The matter has a fairly low priority.

The person at EPA who is most responsible for this issue is Dr. Eugene Wallen. I have not talked to him about PCBs in connection with your memo, although I can do so if indicated. I have talked with George Wirth, Dave Downer, and Tom Kopp, all in the Office of Toxic Substances and all concerned with PCB. Kopp was the source of the report that EPA has no argument with the basic data that IBT developed, but probably does have some disagreement with IBT's conclusions. Kopp was giving us the opinion of others. He is not willing, of course, to put such an opinion in writing and it wouldn't mean anything if he did. I have no hesitancy about getting into a detailed conversation with Wallen on this, but before I do so, I would like for you to react to the material attached and the additional material you will be getting.

K. Warren Easley

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Attachment