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August 31, 1977

Dr. Donald C. Kennedy
Commissioner, U.S. Food & Drug Administration
U.S. Department of Health, Education & Welfare
5600 Fishers Lane
Rockville, Md. 20852

Dear Dr. Kennedy,

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 polychlorinated biphenyls (PCBs). I believe that this new information demands reconsideration of the temporary tolerances for PCBs proposed by FDA on April 1, 1977 (42 F.R. 17437 et seq.).

The significant new information is the recent and now widely reported finding by FDA and EPA that many toxicological tests conducted by Industrial Bio-Test Laboraties, Inc. (hereinafter "IBT") appear to be unreliable on the 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 were cited by FDA in its 1977 proposal for reduction in temporary tolerances and appear 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.

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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 F.R. 13006 et seq.) were based upon an estimated allowable daily intake of 175-210 ug/day (2.5-3 ug/kg/day) in man. This in turn was derived from experiments with rats and dogs which were accepted as showing no-effect levels at 10 ppm in the diet (38 F.R. 13003; 42 F.R. 17487). The experiments involved were conducted by IBT and were described in unpublished reports (refs. 207 and 212 in Attachment A to this letter).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 (42 F.R. 17847 et seq.) the proposed tolerances appear 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 of 10 ppm in rats and dogs, are cited at the outset of the section on Toxicity of PCBs (p. 17487). No qualification of this finding is made later in the notice. Although toxic effects of PCBs in mink and monkeys at dietary levels of 5 ppm and 2.5 ppm 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 ppm in rats and dogs are 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, 17491) the proposed reduction of the temporary tolerance in fish (the primary route of human exposure: p. 17489) was by a factor of only 2.5.

Clear evidence that FDA relied upon the IBT data in proposing the April 1, 1977, temporary tolerances is shown in response 3 on p. 17490. In this passage, FDA addressed the claim of the petitioners that "the rat and the dog, on which that tolerable daily intake was partially based, are 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 effects of PCBs from one kind of test animal to another or to humans. However, when

3. In the 1975 re-examination (ref. 416) the IBT pathologists reported pathological changes in the livers of treated rats at frequencies significantly higher than those in the controls in all 9 treated groups, including the 3 groups exposed to only 1 ppm (Table D2A). Lesions reported as "vacuolar change" and "focal hypertrophy" were reported in 20-26 percent and 7-12 percent of rats exposed to 1 ppm, versus 4 percent and 0 percent respectively in controls (Table D2A).

4. In the 1975 re-examination (ref 416) the IBT pathologists reported lesions diagnosed as "nodular hyperplasia" in 7-39 percent of animals exposed to 10 ppm PCBs, versus 4 percent 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 pathologists reported many liver tumors in rats exposed to 100 ppm (Table D2A).

5. Pituitary tumors were reported in 8 of the 9 treated groups of rats, including all 3 exposed to 1 ppm, but not in controls; the difference in incidence approached but did not reach statistical significance (Table D2A, p. D-10).

It is thus apparent that the IBT experiments do not support a finding that 10 ppm of any PCB mixture is a "no-effect" level in either rats or dogs. Indeed, at face value these reports indicate serious toxic effects in both species even at 1 ppm. 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 affected 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 of 1 and 10 ppm have been reviewed by the Administrator of EPA and were specifically accepted by him and incorporated in his Final Decision on Toxic Pollutant Effluent Standards for PCBs (42 F.R. 6537-8, February 2, 1977).

Conclusions and Recommendations

The reports summarized above and in Attachment A demonstrate:

1. That the IBT reports on toxicological studies with 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 *prima facie* evidence of toxic effects of PCBs in both rats and dogs at dietary levels as low as 1 ppm.

judgments regarding allowable intakes are made, all available data from all species are considered." (pp. 17490-1)

It is abundantly clear from this response that in proposing the reduced tolerances on April 1, 1977, FDA was continuing to rely upon the IBT data on rats and dogs, balancing the apparent insensitivity of these species against the apparent sensitivity 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 PCBs in water (EPA Report No. 440/9-76-021) and was incorporated as part of EPA's proposed Toxic Pollutant Effluent Standards for PCBs (41 F.R. 30468 et seq., July 23, 1976). Relevant sections of this Criteria Document, including the Technical 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 (refs. 212 and 207 to Attachment A, respectively). I noted and reported a number of discrepancies between data in these and subsequent reports by IBT and the summary statements on which FDA appears to have relied. In particular, the raw data in ref. 212 included listing of stomach nodules in many treated dogs, findings which were ignored in the summary; a subsequent oral presentation by an IBT toxicologist included a statement that re-examination of the slides in 1975 had shown evidence of "gastrointestinal inflammatory lesions and ulcerations which appeared similar to those reported by Allen in rhesus monkeys", but this key statement was deleted from the speaker's published paper (ref. 69: for details see pp. 197-199). In the case of rats, IBT pathologists re-evaluated 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 D2, D2A). In addition, there were substantial discrepancies between the total number of animals diagnosed in 1975 and the number listed as surviving to 24 months in the 1971 report (p. D-12).

Toxic effects in rats and dogs at levels below those reported as "no-effect" levels

Although the summaries of the 1971 IBT reports stated that 10 ppm was a "no-effect" level for rats and dogs, examination of the 1971 raw data and the 1975 re-evaluation do not support this conclusion.

1. "Pinpoint nodules" in the stomach, stated to have been "similar to those reported by Allen in rhesus monkeys" were listed for 22/66 of the dogs exposed to PCBs, including 5/24 of those exposed to 1 ppm, versus 0/8 in controls (Table III.9.6, p.193).

2. Leukocyte counts were elevated above those in controls in 9/9 groups of treated dogs; the difference was statistically significant in all 3 groups exposed to 10 ppm and in the group exposed to Aroclor 1254 at 1 ppm (Table III 9.6, p. 198).

Although the discrepancies in the reports can be resolved only by a thorough re-examination of the pathological material, the data are already sufficient to show that the assumption of no-effect levels at 10 ppm, 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 studies to include the 1971 reports on PCBs (refs. 207 and 212 in 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 re-open 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,

I.C.T. Nisbet

Ian C.T. Nisbet
Director, Scientific Staff

c.c. Douglas M. Costle, Administrator, U.S. Environmental Protection Agency

Attachment A: Criteria Document for PCBs (EPA 440/9-76-021): Technical data page and pp. 197-9, 251-253, D9-D13a, R7, R19-20, R38.

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