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May 18, 1977

GENP 010318

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Dear Dr. Selikoff,

Before meeting with you next week, I would like to answer the five specific questions you raised in your letter of the 4th, and then list five key issues which I hope we can discuss on the 27th.

Question 1. Carcinogenicity of PCDF. To the best of my knowledge, there is not yet any specific evidence on the carcinogenicity of PCDF to equate with the recent reports on PCDD's, but I haven't asked around to find out what's in the pipeline. John Moore of NIEHS stated that they were planning to initiate a study of chronic PCDF effects more than a year ago. My rationale for implying that PCDF's should parallel PCDD's in carcinogenicity is that (a) in their non-carcinogenic toxic effects, both agents are toxic at doses that are orders of magnitude smaller than the activity levels of other simple organic molecules, implying relatively unusual mechanisms of pharmacological action; (b) the non-carcinogenic toxic effects exhibited by the PCDF's and PCDD are identical in all species of animals examined to date, implying that the mechanisms of non-carcinogenic pharmacological action are the same for both agents; (c) the reported carcinogenicity of PCDD at ppt levels implies a very unusual mechanism of pharmacological action; (d) it would be most implausible to assume that PCDD was capable of two different mechanisms of unusually potent pharmacological activity, one leading to carcinogenesis and the other to characteristic syndromes of non-carcinogenic effects (including teratogenesis); (e) accordingly, one must presume that PCDF, which mimics PCDD in its other toxic effects, will also be found to duplicate its carcinogenicity.

Question 2a. Range of PCDF Levels in Aroclors. You correctly point out that the available data indicate PCDF levels ranging from 2 to 12,000 ppm in Kanechlors (the high values being associated with PCB's from old heat exchangers) but only <0.001 to 2 ppm in Aroclors. No chemical data on PCDF levels in Aroclors from old heat exchangers have been reported, but Meigs et al. (1954) describe an incident of Yusho-like poisoning by exposure to vapors from an old Aroclor-filled

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heat exchanger under conditions where the cumulative exposure to PCB was apparently no greater than subsequently occurred with that 12,000 ppm PCDF Kanechlor 400 at Yusho. Evidently, the Aroclor being made up to 1954 at least (when substantial changes were made in Monsanto's manufacturing process) was just as susceptible as Kanechlor to developing impurities with PCDF-like toxicity patterns upon long heating.

Question 2b. PCDF Levels in Capacitor-Grade PCB. Monsanto claims that they do not use an oxygen catalyst (a likely source of PCDF's in the European and Japanese PCB's) in their current manufacturing process, and that they have been unable to detect any PCDF's in their Aroclors as manufactured. (The work on which this claim was based was done 4-5 years ago, however, and I think the analytical method then available was only sensitive to 0.5 ppm). Bowes' 1975 report on <0.001 ppm PCDF in Aroclor 1016 certainly confirms this, but was on only one specimen (of material made in 1972). We have never analysed any specimen of Aroclor 1016 for PCDF content, mainly because we didn't find out about Bowes' high sensitivity analytical procedure until the fall of 1975, when the decision was made to get out of PCB usage completely by mid-77. There is no reason to expect significant PCDF formation during the process of capacitor manufacture, since the rate of PCB flow through the plant is huge and the only heating the stuff gets is brief and in vacuum. However, your basic point is correct: unless we collect the PCB from the actual environment where the exposed employees work and analyse it, we will not know for sure that no PCDF formation has occurred somewhere along the line.

Question 3. Explaining Higher PCB Homologs in Sera. You state that Dr. Mary Wolff has been "regularly finding 1248's and 1254's, generally above 10 ppb, as well as lower PCB homologs." I don't know whether you mean 1248 and 1254 (e.g., tetrachloro and pentachloro-biphenyls, respectively) each above 10 ppb, or the sum above 10 ppb, nor what position in the range of observations is represented by the 10 ppb figure. However, in any case, the reported figures would not appear exceptional. Background levels of plasma PCB (essentially, 1254-like material) are reported as 3 ppb (range, 1-7 ppb) for Japan in 1972, and upstate New York, which (judging from acid rain levels) must represent the national trap for long-lived air pollutants, might easily exhibit comparable background levels. More importantly, the cumulative exposure of the capacitor plant workers to PCB's must have been massive. Until recently, sizeable portions of the plant were dripping wet with Aroclor, and I doubt whether the ambient air level was significantly below the occupational safety standard of 1 mg/m³

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(e.g., about 25% of saturation for Aroclor 1016 or 1242). I estimate that anyone working in there was probably absorbing 1 g. per year by inhalation plus substantial additional quantities through the skin. Since the 1242 (used 1954-71) contained 7-8% of 1254-like homologs, and the 1016 (used 1971-77) contained around 0.1%, and small additional quantities of 1254 itself were used up to the early 1970's, there is no problem explaining any modest increase in 1254 levels over background if one simply presumes it to be fairly persistent in the exposed individuals. The Aroclor 1248-like tetrachlorobiphenyls of course, represent 23-25% of the Aroclors 1242 and 1016 used in recent years, and hence their presence in the sera is to be expected.

Question 4. Dependence of Toxicity on Route of Absorption. As I've just indicated, I believe that PCB absorption in Hudson Falls plant employees occurs by both inhalation and dermal contact. Frankly, I don't believe that the route of administration really makes much difference in most cases, since all of the constituents appear to be efficiently absorbed by any route, to be readily transported around the body, and to produce their effects after long delays and at points distant from that of entry. The attribution of the slightly deviant pharmacological pattern seen at Yusho to a difference in the route of absorption is a somewhat lame explanation which I think I got from Leon Goldberg. A possibly less lame explanation has been advanced since I last wrote you by the FDA in the April 1 Federal Register, where they argue that much of the chlorinated contaminant in Yusho oil wasn't PCB at all. On the whole, however, the clinical patterns seen for the Yusho patients, who ingested their heat-aged or otherwise contaminated PCB's, and those of the American and Italian factory workers who got theirs by inhalation + skin contact, are pretty similar. Accordingly, I believe that the tabulation showing large toxicity differences between different specimens of PCB when ingested indicates that we should anticipate a similar range of toxicity differences for the occupational exposures. The only available data are in accord with this. The exposure levels (to heat-aged PCB) in the case reported by Meigs in 1954, which resulted in severe and obvious chloracne, were indicated as roughly 10% those existing at Hudson Falls since 1954.

Question 5. PCDF Levels in Hudson Falls PCB's. I've already covered the specific question in answering Question 2b. More generally, I found your reported observation of true chloracne in the plant population most interesting, since Dr. Feingold, the plant physician, told me 15-18 months ago that he'd never seen any. I wonder whether you've been able to correlate this chloracne incidence

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with the exposure history of the individuals, or with plasma PCB chromatographic pattern abnormalities like those reported by Masuda (through Kuratsune) for the Yusho patients.

Underlying your specific question of whether the PCDF levels in the actual PCB present in the plant environment be 0.000 or 0.01 or 1.0 ppm, of course, must be the more general one of whether the highly variable chloracne seen in both men and animals exposed to PCB/PCDF mixtures be due 99% or 99.9% or 100.0% to the PCDF content. There is one known PCB isomer (3,4,5,3',4',5'-hexachlorobiphenyl; fortunately, a species not present in commercial PCB products) that seems to be capable of undergoing metabolic conversion to a PCDF, and we certainly must maintain the suspicion that this might occur to some extent with other PCB's as well, implying a non-zero background level for PCDF-like effects due to the PCB's themselves. The only reason I harped so on the PCDF theme was my concern over the possible generation of programs involving theoretical calculations, specific therapeutic modalities, etc., directed at specific PCB components before they were established as toxicologically significant. The ambiguities in the case against the Aroclors remain very real, and I am far from alone in my concern over them. The FDA statement of April 1 justifying the tolerability of non-zero levels of PCB in food (Federal Register, 42, 17487-17494, (1977), for example, argues the uncertainties surrounding PCB toxicity at least as strongly as I did in my March 25 letter.

However, the real problem before us at the moment is not to re-argue the PCB case, but to figure out what is the best thing to do for the people at Hudson Falls who got those massive exposures over the past 29 years. Dr. Welch, the Group Executive in charge of the operation, is very much concerned with this question, and would like somebody - either your group, mine, Tom Casey's, or some combination of all of us - to come up with a convincing answer.

As I read the fragmentary descriptions of your findings that are presented in your May 4 letter, it seems to me that one way to tackle the overall problem might be to break it down into 4 or 5 specific issues that we might conceivably be able to generate answers to within a finite span of time. Accordingly, I'd like to suggest one such segmentation as a basis for our discussions on the 27th.

Issue 1. Persistence of the PCB's. One basic question is whether the PCB's in the capacitor workers will go away by themselves once the exposure is ended. Possible routes to answering this

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would include (a) surveying serum PCB levels in former employees who left at various times in the past, or (b) running longitudinal studies on previously-exposed workers, starting after PCB usage is discontinued. This is presumably a task that you're already set up to do, although I'd imagine that extra help would be required if it were to be done on a large scale.

Issue 2. Identification of Individuals at Risk. There was obviously a wide range of exposures of different people to the PCB's in the plant, and there is presumably also a considerable range in the abilities of different individuals to metabolize and eliminate the PCB they've absorbed. Before contemplating therapy, it would be desirable to know who had accumulated a PCB load that he was having trouble handling. Possible routes to doing this would include (a) conducting longitudinal studies of serum PCB's, to monitor individual levels and elimination rates; (b) looking for Masuda's characteristic patterns A and B in the chromatograms, to identify individuals who metabolize their PCB's like Yusho patients rather than like normals; (c) doing longitudinal studies on drug metabolizing enzyme activities; (d) assessing lymphocyte subpopulations and/or PHA responses; or (e) assessing PCDF levels in patient sera or biopsy specimens. Again, I presume that you'd already be in a position to do (a), (b), or (c) if given appropriate support. We could probably do the analytical work required to explain any abnormal pattern seen in (b), and conceivably also the major job in analytical method development required for (e). Approach (d) is one we could handle here relatively easily, if it appeared a worthwhile thing to do.

Issue 3. Identification of Chronic Health Effects. After 29 years of heavy exposure to capacitor grade PCB's, it certainly ought to be possible to say something about the chronic effects produced. I have heard very little about the nature of the epidemiological studies currently underway, or whether they need to be expanded to produce definitive results. Presumably, either you or Casey's people would be able to handle such an expansion if required.

Issue 4. Applicability of Existing Patient Management Procedures Once the nature of the risk is established and the people at risk identified, I would imagine that many opportunities to apply conventional treatments will present themselves. Thus, if excessive drug metabolizing enzyme levels are altering steroid balances, this is presumably correctable. If the elevation in cancer risk looks significant, the people involved could be given strong advice on the avoidance of synergistic risk factors, like tobacco or high fat diets. If an existing agent like cholestyramine really does lower the PCB

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level (I'd like to hear more about the data on this) it may be appropriate to prescribe it in some cases. In order to assess the anticipated efficacy of such procedures, it would possibly be desirable to do something like (a) looking for hormonal or other biochemical imbalances in patients showing elevated drug metabolism activities; (b) designing the epidemiological studies so as to pick up cross-products of risk factors; or (c) including patients already on cholesterol-reduction therapy in the longitudinal studies of serum PCB levels.

Issue 5. Need for New Therapeutic Procedures. As I indicated before, I think we're going to have a hard time justifying a program to develop totally new treatments unless we can (a) answer all the questions posed by Issues 1-4 and/or (b) generate a very convincing argument that a totally new approach may be beneficial. Along the latter lines, it occurs to me that if we really do have a PCDF-like pattern of toxicity, and if the analogies between PCDD's and PCDF's are valid, then there may be something in the more recent PCDD studies that could be applied to the PCB problem. Have you been following the PCDD story? Does anyone know yet how the stuff acts? Are there any specific therapies proposed for patients exposed to Agent Orange or polychlorinated phenols? Or can you think of some other reason for addressing Issue 5 even before the answers are in on No. 1-4?

As I indicated before, I have segregated the overall problem of figuring out how best to handle the PCB-exposed population into the above five "Issues" in hopes of providing a framework for our discussions on the 27th, and thereby enabling us to cover all aspects of the problem and arrive at some specific conclusions during the time allotted. If you think this particular list covers the subject adequately we could use it as an agenda for the meeting, following, of course, the usual round of self-introductions of participants. Otherwise, we could make additions or deletions as appropriate.

At the moment, it still looks as though our delegation will consist of Dr. Casey, our Corporate Medical Director, whom you know; Dr. John A. Bergeron, a physiologist who works for me as Manager - Diagnostic Projects; and myself, a long-time organic chemist retreaded a few years back by a post-doc in clinical pathology. We are all looking forward to meeting with you and your associates at 9:00 AM on the 27th.

Sincerely,

John F. Brown, Jr.
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cc: TR Casey, Fairfield
JA Bergeron
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