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September 2, 1983

Dr. George Rousch
Building G
Monsanto Company
800 N. Lindberg Boulevard
St. Louis, MO 63167

Dear George:

I am trying to further clarify the issues of systemic response to AO and/or dioxin insult and the questions of potential for circulating antigens and antibodies associated with this.

It would appear that there is some evidence that chloracne may be a sequela to internal ingestion of dioxin. Do you agree? Is there a skin response to internal administration of this material?

If there is a skin response to internal administration then how is this mediated? Do you see a circulating hapten without a protein complex which is not recognized by the body as an antigen? Is it possible, assuming a skin response to an internal insult, that there is a circulating antigen? Could we detect this?

Further, according to Poland it would appear that a dioxin/messenger complex forms and this provides the transport for dioxin into the cell. Poland appears to assume that this complex is with a protein. This permits the practically insoluble dioxin to enter the intracellular milieu and, indeed, a second complex may be formed to permit transport of the dioxin into the nucleus. If such complexes form would not you anticipate that these could be recognized as antigens promoting antibody reactions?

Finally, assuming that the dioxin does not form a complex then does it not bind to the cell surface as the first step for transport into the cell. Would not this possibly be recognized as a surface antigen?

Initially, I am in the possibility of antibody formation as a possible approach to diagnosis of dioxin exposure. It appears that we now have proof that the vast majority of Americans have been exposed to and have absorbed dioxin into the system. Such a test might show that there is no difference between the AO plaintiffs and the average American. I am interested in this latter because I am trying to demonstrate that the AO plaintiffs were not "at unusual risk" by AO use. A test showing equal amounts of exposure in this group as the average stay-at-home would be useful.

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MONSANTO POLYMER PRODUCTS CO.
800 N. Lindbergh Boulevard
St. Louis, Missouri 63167
Phone: (314) 894-1000

August 19, 1983

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Dr. Myron Weinberg
Weinberg Consulting Group, Inc.
Suite 301
2828 Pennsylvania Avenue, N.W.
Washington, DC 20007

Dear Myron:

I have enclosed the items you requested last week and added a few that I thought might be of some help to you. They include:

A) Toxicology

These papers are copies of those I prepared for Dr. Roush for use in discussing subacute effects with Dr. Davey next week. Subacute effects other than immune depression have been alleged to have been caused by 2,3,7,8-TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin), so I am not suffering the puerile belief that the subject has been covered, but rather that the immune response issue may not be resolvable through current scientific understanding.

While not explicitly stated in any of the literature, the dioxin-like toxicity would seem to be a function of both the two adjacent chlorine atoms in the 2,3, positions (or 7,8) and molar concentration. If both are considered, the variation in toxicity within species, but among isomers and homologs, tends to smooth out. It would be nice if toxicity comparisons were made in molar quantities.

B) Nonindustrial Source

I have enclosed a few key articles on the nonindustrial source argument. It has been unfortunate that this issue has been referred to as the "Dow argument" by the media since the Dow researchers were by no means the first to publish on it nor have they been the most prolific in the area. The most prominent name at the moment would

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seem to be Otto Hutzinger of the Netherlands equivalent of the EPA who considers low temperature combustion processes a serious problem in Europe.

The point is often made that 2,3,7,8-TCDD is not the major dioxin produced in low temperature combustion processes. Chlorine or chloride is common enough in the environment to give various chlorobenzene isomers during low temperature combustion which couple to give a broad distribution of chlorinated dibenzo-p-dioxin and analogous dibenzofurans. It would seem to me that the two issues of major importance are not the isomer distribution or the concentration of the various isomers and homologs, but first the amount of material with 2,3,7,8-TCDD-like toxicity, and secondly the mass transfer rates of that material. Hutzinger has indicated in several papers that his work suggests a "dioxin-like" toxicity 40 to 50 times greater than would be expected from the 2,3,7,8-TCDD content alone. It is interesting to do a loose calculation of the magnitude of the problem using wood-fired stoves and fireplaces, disregarding incineration of trash for the moment. Referring to enclosed papers by author:

1) Amount of TCDD in firewood - all tetra isomers =

0.05 $\frac{\text{mg}}{\text{metric ton}}$ (Jennsen)

2) 2,3,7,8-TCDD averages 7% of total TCDD's (Cavallaro)

3) U.S. burns 16.6 metric tons/yr of firewood. (Lipfert)

4) Toxicity ~40 times greater than 2,3,7,8-TCDD suggests

$$(16.6 \times 10^6 \frac{\text{ton}}{\text{yr}}) (0.05 \frac{\text{mg}}{\text{ton}}) (0.07 \frac{\text{mg}}{\text{mg}}) = 58 \frac{\text{kg}}{\text{yr.}} \text{ of 2,3,7,8-TCDD}$$

$$(58 \frac{\text{kg}}{\text{yr.}}) (40) = 2320 \frac{\text{kg}}{\text{yr.}} \text{ of 2,3,7,8-TCDD equivalent (Hutzinger)}$$

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This estimate suggests that emissions from firewood are of the same magnitude as the amount of 2,3,7,8-TCDD sprayed on Vietnam. Of course, this is on an ongoing annual basis but Vietnam was only sprayed intermittently for a brief period. In addition, I do not have much domestic incinerator data which I suspect is as much of a problem as wood burning.

In any event, it does not take much approximation to question whether or not industry is, or has been, the major supplier of dioxin to the environment.

C) Reviews

I have enclosed copies of several reviews. The AMA review has had considerable publicity, and I feel it sticks to the technical issues. The others were handy today and no better or worse than many.

D) Analytical

One of the issues that clouds much of the older literature is the inability to analyze specifically and unambiguously for 2,3,7,8-TCDD prior to 1979. I am not sure if many authors were making toxicity measurements upon 2,3,7,8-TCDD as indicated in their work. Of course, if toxicology was done on materials obtained from isomer specific synthetic routes, the data is probably good, but it is often hard to tell where some investigators got their samples.

I have enclosed a review of the analytical technique by Warren Crummett which I think covers the difficulties of the technique very well.

E) Federal Regulations

I have enclosed a copy of the EPA proposed regulations. A final copy may be out but I do not have it yet. The pseudoscience in this document is frightening.

F) Computerized Literature

We expect the software for our literature file system to be complete the week of the Washington ACS meeting. We will begin coding the following week. This will be done on RAMIS software.

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I will send you a separate discussion of what we have done in terms of literature searching the past few years.

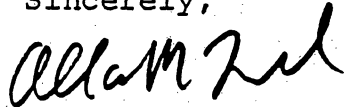
G) ACS Extended Abstracts

The ACS Division of Environmental Chemistry has issued extended abstracts on the papers to be presented at the Washington symposium August 28-30. I have enclosed a xerox copy.

Finally, I will be staying at the River Inn in Washington from Friday evening, August 26 through Wednesday, August 31. I hope we can get together and discuss some of the events at the ACS symposium if you do desire. In any event, I will be available on the weekend if you have time.

I look forward to seeing you in Washington.

Sincerely,



Allan M. Ford, Ph.D.

/dkr
Enclosures

cc: *Mr. D. R. Bishop - F3EE
*Mr. T. M. Bistline - E2ND
*Mr. G. H. Griffin - E2NC
*Mr. D. S. Frazer - 1670
*Mr. M. C. Throdahl - D1D
*Mr. W. B. Papageorge - B3NA
*Mr. R. L. Pfleiderer - E3SB
*Dr. J. D. Wilson - G3WG
*Dr. W. J. McCarville - G3WG
*Dr. G. Roush, Jr. - G2WG
*Mr. F. E. Kearney - E3NA

*w/o Enclosures

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