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FROM
(NAME-LOCATION-PHONE)

G. J. Levinskas - G2WF (4-8809)

DATE

July 19, 1984

cc:

G. Roush - G2WG

SUBJECT

REFERENCE

TO

A. M. Ford - G3WD

W. J. McCarville - G3WG

I have read through the three volumes of Dr. Silbergeld's deposition which you provided on Monday. I have dictated comments relating to several sections of those depositions. These have been typed, and I presume you have received them by now.

In some places, she had made very specific statements about various compounds which I would question. However, I have not had time to go back and check specific sources to ascertain whether or not they are accurate. If you desire, I will proceed to do so in consort with other staff toxicologists. Kindly let me know whether this would be a worthwhile exercise or whether the need for such action has passed.

George J. Levinskas/STC
G. J. Levinskas

/dkr

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Page 399, line 12 - Cyanosis is not the accumulation of cyanides in the body because of lack of oxygen. Cyanosis is a blue coloration of the skin which results from an inability of tissue enzymes to obtain oxygen. The body has a fairly effective system for removing cyanide by converting it to phytol cyanate. That is a two detoxification mechanism since phytol cyanate is about 1/200th or 1/300th as toxic as cyanide itself. In acute cyanide intoxication, death results from anoxia because the body's mechanism for conversion of cyanide to phytol cyanate is exceeded. She compounds that error on line 20. The body does not overproduce metabolic cyanides in analine poisoning.

Page 446, line 20 - The implication is that despite the fact that \$30 million has been spent, dioxin is still present in Times Beach. While the commitment has been made to buy out Times Beach at a cost of over \$30 million, nothing like that sum has yet been spent. Certainly, that sum has not been spent on attempts at removal or cleanup of dioxin contaminated soil.

Page 465, line 11 - The references made to animal studies using pure 2,4,5-T. In the March 22 deposition on page 254, line 9, she questions whether any of these studies purported to have used pure 2,4,5-T actually were using pure material. One ought to declare and hold a consistent position. One should not accept the claim of purity, and then contest the claim of purity according to the points one wishes to make.

Page 468, line 1 - She is not convinced that TCDD is much of a mutagen. However, in the March 21 deposition, page 118, line 4, she is attempting to implicate TCDD in genetic damage. Mutagens damage genes. If TCDD is not much of a mutagen, how can it produce those transmittable, non-hereditary diseases, that she discusses on this and the following page.

Page 472, line 13 - The determination of causation is not a statistical exercise. Application of a chemical to skin or eye will determine whether the material is an irritant or corrosive. No statistics are necessary. If a chemical is fed to animals, and they all develop cancer, no statistics are necessary. The rigorous mathematical formula that she describes are used to determine whether observations are likely to have occurred by chance or not. Having determined the probability that these events may or may not have occurred by chance, the experimenter then makes a decision as to whether or not the observed effect was produced by the chemical. In other words, statistical analysis is an aid to making decisions. Decisions should not be made on the results of statistical analysis alone. Unfortunately, there is a current vogue, particularly with respect to risk assessment of carcinogens, to accept these statistical result as a final, definitive, invariably reliable conclusion.

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Page 473, line 13 - The approach she describes here is good. In arriving at a conclusion as to what may have caused an effect, every effort should be made to rule out all possible causes. Does she do this when she "critically reevaluates" data. As mentioned in earlier instances, does she apply that same rigid standard to everything she reviews, or does she selectively abstract those points which support her view or accept data she considers favorable without subjecting it to such scrutiny?

Page 509, line 16 - The catalog of differences and similarities in the responses of different species to dioxin can be compared to that appearing on page 333, line 1. There are some differences between those two sections.

Page 510, line 3 - A statement is made that it would be very difficult to generalize about neurologic effects because these have not been very systematically studied accross species. Since the majority of the dioxin work has been in rats and mice, the adequacy of testing accross species for the various effects could be explored.

Page 510, line 13 - She is greatly over simplifying the problem of extrapolating from animals to man. In fact, she make it sound more like a science than the art it is. After stating that the mechanism of the reactions is known and similar in all animals, including man, she states on line 19 that the only remaining issue is does dioxin get to those mechanisms in humans as it does in animals.

Page 512, line 1 - She states that the sensitivity of the guinea pig appears to be related to the distribution of dioxin. The question is how does one determine the distribution or, as she says on line 6 of this page, the "differences of internal dose" between animals and man. Earlier, on page 300, line 8, she notes that the biological half-life can be determined from toxical kinetics in a number of animal species. Those curves can be used for predicting effects in man. However, while the curves can be used to make the prediction, what is the mechanism by which one can test the validity of the predictions? In other words, while people do manipulate numbers, make extrapolations, etc., and they may even put faith in the conclusions that are reached from those manipulations, there should be some basis for testing or verifying in some fashion, the validity of the conclusions which have been drawn.

Page 512, line 18 - Guinea pigs are more sensitive to TCDD than mice or rats. They are at least one, possibly even two orders of magnitude more sensitive. I am surprised that she is not sure of that fact because the extreme sensitivity of the guinea pig to TCDD is frequently cited in the lay press as well as in technical journals.

Page 516 - line 8 - Parathion inhibits the enzyme acetylcholinesterase. That enzyme inhibits these cholinesterase which is the chemical messenger between nerve connections and nerve muscle connections. Thus, when cholinesterase is inhibited, the effect is similar to repetitive stimulation of a nerve. The net effect of this would be muscle tremors, and in severe cases, convulsions. It does not produce muscular paralysis.

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Page 516, line 20 - The effect on peripheral nerves will last as long as the parathion is present. In organic phosphate poisoning, such as parathion, the signs of intoxication, including the effect on nerves, appears relatively shortly after exposure. Depending on the dose, it may be rather rapid or it may be delayed as long as 24 hours. Upon removal from exposure to parathion, recovery will ensue in 24-48 hours. Any toxicologist familiar with organic phosphate pesticides could testify on this subject. Dr. Wayland Hayes at Vanderbilt would be an excellent choice for this.

Page 517, line 6 - Parathion does not produce a delayed neurotoxic action in the same sense as triorthocresyl phosphate, the classic example of this neurological condition.

Page 520, line 7 - If chlorinated phenols can denature membranes, then would they not denature the skin before they got into the body to denature nerve membranes? In other words, can one have serious systemic effects from chlorophenols without first having had severe, or at least detectable, external skin injury?

Page 521, line 6 - Halowax is a chlorinate naphthalene. I do not see how it can form dioxin. This a point which the chemists can describe better than I.

Page 533, line 10 - Just a reminder that she is expressing her "opinions on dioxin".

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1 yes.

2 Q. You can't take the amount, the dose with
3 these mice and in any fashion extrapolate that to man?

4 A. That's not what I'm saying, Mr. Love. That
5 one dose, that one experiment which we discussed, in a
6 totally different context I might state for the record,
7 by itself, has relatively little to contribute to what
8 we are presently talking about. People have done
9 specific studies to measure the toxicokinetics,
10 including the biological half-life which is a derived
11 number from toxicokinetics, of TCDD in a number of
12 animal species. Taking those curves, there are
13 methods for relating those on a predictive basis to
14 humans.

15 Q. But you have not done that.

16 A. That's not my interest in TCDD. Many people
17 have done it. It is contained at length in the EPA
18 document on TCDD, the Canadian government's document
19 on TCDD. There is no need for me to do it.

20 Q. Is there any reason why you cannot testify
21 about it?

22 A. I would be happy to testify about it. But

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