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Mr. Stanley Gross, Ph. D.
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Dear Stan:

Ter Haar, Sobel and I enjoyed our meeting with you and your team and we were all in agreement that the meeting was very rewarding and the time well spent.

Let me summarize for you the conclusions we have reached and indicate the priorities we would like you to observe. Much of what I write was part of our discussion, but as I indicated, I would put it in writing to be sure that we all understand the goals.

It would be very rewarding to have detailed biological models developed from the information you are compiling but Sobel's preliminary investigation indicates that such detail will probably be impossible because of the non-reproducible characteristics of the data. At any rate, any attempt to develop detailed biological models should be left for later.

The numbers we are particularly interested in are:

1) Equilibrium values of blood and urine lead as functions of dosage.
2) The shape of the closure curve after starting a change, hopefully as described by its 50% point.

In order to give us these values, you will have to fit the data to the model:

$$R = A - B_1 e^{-C_1 T}$$

If the data are good enough, you may be able to fit:

$$R = A - B_1 e^{-C_1 T} - B_2 e^{-C_2 T}$$

In these models, T is time, R is response while A, B, C as constants hopefully dependent on dose and route of administration of the dose.

We discussed the approaches to determine the model constants. One would be to use the non-linear regression model directly, the other to sequentially follow the BMD programs to equilibrium and then using as logarithmetic transform (also in the BMD). Both of these approaches appear adequate.

Ter Haar has made a priority list which I will repeat here.

For the diet portion of the experiments:

1. The equilibrium value for lead in blood and the time to equilibrium for each feeding study.

2. A plot of the lead fed daily vs. the equilibrium value and time to equilibrium.

3. A total balance of lead into the system and lead out.

4. Endogenous excretion.

5. The percent of lead absorbed from the gut.

6. Equilibrium values and time to equilibrium for lead in urine.

7. Equilibrium values and time to equilibrium for lead in feces.

For the inhalation portion of the experiments:

1. The equilibrium value for lead in blood from a given exposure to lead in air and the time to reach this equilibrium value.

2. As most of the experiments were run at more than 1 concentration of lead in air and several times of exposure, the data should be reduced to an average concentration of lead in air for a 24 hour exposure and plotted against the equilibrium values and time to equilibrium determined under priority one.

3. Percent of lead absorbed from the lung and the amount of lead cleared from the lung.

4. The percent of lead absorbed vs. the size of the inhaled particles.

5. The endogenous excretion: The investigators should be able to obtain this information from the fecal data on the diet portion of the experiments.

6. A total lead balance.

7. Person-to-person variations in percentage of lead absorbed and blood response.

8. Equilibrium values and time to equilibrium for lead in urine.

9. Equilibrium values and time to equilibrium for lead in feces.

Finally, if these several priorities can be met and the data sufficiently accurate, models can be set up to estimate the distribution of lead into the various compartments of the body. Especially valuable would be an estimate rate of the approach to equilibrium; that is is it linear or a curvilinear approach. Data on animals and other information on the ingestion and inhalation of trace materials indicates the curve should be curvilinear. This would be extremely valuable information to enable one to estimate the biological response of lead.

I will be keeping in close touch with you regarding the progress being made, but do not hesitate to call me, Ter Haar or Sobel at any time if you wish to discuss any aspect of the work.

Sincerely yours,

Mitchell R. Zavon, M.D.
Medical Director

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