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LITTON BIONETICS, INC.

Interoffice Memorandum June 16, 1980

TO: Dr. David P. Martin

FROM: Dr. Richard H. Cardy RHC

SUBJECT: LBI Project No. 20771

I have reviewed Monsanto's suggestions for altering Dr. Seibold's grading system and I don't think that they are appropriate.

By arbitrarily assigning a value of 0.5 to ungraded lesions, Monsanto's scientists are saying that all such lesions are less than minimal, the level of severity represented by a value of 1 under Dr. Seibold's system. Any degree of change less than minimal, however, would not be detectable by light microscopy. In addition, certain ungraded lesions might well be quite severe but difficult to assign a number grade to without a basis for comparison. No lesion should be assigned a grade of this type unless pathologic criteria have been established by the pathologist.

I assume that the sponsor's objections are directed toward the grading of lesions attributable to the compound. Only a few of those lesions were graded for severity and as it happened those that were graded occurred only in the highest exposure levels examined histologically. It was thus impossible to make meaningful comparisons of specific graded lesions among dose groups.

Dr. Seibold has shown convincingly that more lesions occurred in the higher dose groups. In order to illustrate that graphically (without claiming statistical significance) he has, in effect, reduced each lesion to its minimal detectable level (grade 1) and, using that grade (1), counted how many detectable lesions occurred under the various circumstances defined by the study design. This numerical approach is statistically sound if one assumes that the individual lesions are related to a common stimulus but unrelated (causally) to each other. I believe that Dr. Seibold's approach is reasonable. Other, more detailed or complicated grading systems might be devised. One could even eliminate altogether the grading of those selected organs for severity, and the dose relationships among the various test groups would remain unchanged. However, I believe that there is value to the additional information regarding the degree of change that was perceived by the pathologist to be present in certain vital organ systems. Epithelial hyperplasia within duct systems of vital organs is of graver concern than squamous impaction of Meibomian gland ducts. It would seem to me to be important to the sponsor, not only that those kinds of changes were seen only in the highest exposure levels examined, but that the degree of such changes seen was not inconsequential.

To preserve the information in the report but to better define the roles of incidence and lesion severity, I propose to add the following

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paragraph to the report, page 31, insert after Table 2D:

> "During the course of the microscopic evaluation, selected lesions were graded as to their relative severity. A 1-5 grade was employed (see legend). The specific compound related lesions that were graded appeared only at the highest exposure levels of the groups examined histologically. Therefore, whereas the grading of any particular lesion for severity was not useful in making comparisons of dose effect, the presence or absence of lesions and the relative numbers of lesions encountered were of value."

I have discussed this response with Dr. Seibold and it is satisfactory to him.

RHC:ms

cc: Dr. Seibold

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