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CHAPTER 24

Options for Aggregation of Incidence Data and Reevaluation of Pathology Data in Regulatory Decision Process

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The consensus of the audience seemed to be that the stance taken by National Toxicology Program (NTP) in relation to the aggregation of data for neoplasms in the evaluation of rodent carcinogenicity studies (McConnell EE, Solleveld HA, Swenberg JA, Boorman GA [1986], J Natl Cancer Inst, 76: 283–289) was, in general, a sensible one. The guidelines for combining or not combining data for hyperplasia, benign neoplasia, and malignant neoplasia of the same cell type were not seriously questioned although Dr. Iversen pointed out that benign neoplasia in some tissues does not lie in the sequence of hyperplasia to dysplasia to carcinoma in situ to invasive cancer. In other words, in some tissues benign tumors are *qualitatively* different from malignant ones with progression from benign to malignant being rare as compared with de novo malignancy.

The move toward a weight-of-evidence approach and away from condemning chemicals on the basis of single adverse findings of differences significant at the 5 or 1% levels was met with the very obvious approval of many participants. Indeed the collective sigh of relief was deafening!

Dr. McConnell's view that "percentage of animals with one or more neoplasms of any site" usually is fairly meaningless was not challenged seriously. Nevertheless, those at the sharp end of adverse regulatory decisions are bound to question the banning of chemicals which clearly reduce the overall incidence of tumors while increasing the incidence of just one kind of tumor to an extent which sparks off the regulatory decision. Another comment on the present NTP stance is the failure to consider multiplicity of tumors of the same kind and site in individual animals and the failure to take tumor size into account in the analyses of data. It is clear that in some instances a consideration of such additional data can change an equivocal response to a clear-cut negative or a clear-cut positive one.

Dr. Salsburg's controversial paper achieved his objective of stimulating furious discussion. However, it was clear that the army of toxicologists involved in carcinogenesis bioassay research is not well attuned to the idea that such assays have yet to be validated and that such tests may be doing no more than detecting nonspecific biological activity in a dose-related fashion. Dr.

Salsburg's specific suggestion that any chemical that disturbs physiological status might in the long run change the risk of development of one or other form of cancer in either direction found more credence with some of the participants, particularly since it agreed with conclusions drawn from Mr. Conybeare's earlier presentation. On the other hand, Dr. Salsburg's speculation that one may learn as much about cancer risks from rodent studies of 1-year's duration as from lifetime studies or studies of 2-year's duration found few takers, particularly because it is easy to identify chemicals, such as asbestos, for which validated carcinogenicity in animals would not be evident after only one year. In the end, the consensus feeling seemed to be that whereas Dr. Salsburg had overstated his case, his analysis of the present situation brought to the surface several very disturbing grains of truth. As an example of such a grain of truth is Dr. Salsburg's claim that if one cannot define a noncarcinogen then one cannot define a carcinogen. The logic of this is impeccable. Nevertheless, members of the audience seemed more prepared to accept human common sense and judgment, rather than cold logic, as their guide.

Dr. Moch's detailed justification of the decision by the FDA's Center for Food Safety and Applied Nutrition (CFSAN) in relation to the results of carcinogenesis bioassays of various food colors and on irradiated chicken showed the toxicological problems which regulators face. The main audience comment was a second huge collective sign of relief that common sense and weight-of-evidence approaches are presently being effectively brought to bear in at least one U.S. regulatory agency. Dr. Moch's comment that data are often submitted to the CFSAN without meaningful or sensible interpretive comment by the sponsors of tests was accepted as meriting the serious attention of those who commission such tests.

Dr. S. Stanley Young presented data from an experiment conducted at Lilly Research Laboratories (Table 24.1). The numbers of cages with 0, 1, 2, or 3 animals with malignant lymphoma are given for the males of each dose group. Also in Table 24.1 is a chi-square test that examines whether the distribution

Table 24.1. Animals with malignant lymphomas

Cage incidence	Numbers of cages with 0, 1, 2, or 3 animals with malignant lymphoma			
	Dose group			
	0	1	2	3
0/3	20	13	18	16
1/3	10	10	8	9
2/3	7	2	0	1
3/3	3	1	0	0
Chi-square test	10.19	2.34	1.23	0.29
P value	.017	NS	NS	NS

of the number of animals in a cage with malignant lymphoma follows a binomial distribution independent of caging. It is clear that the binomial distribution does not fit in the control group in which there are three cages where all three animals developed malignant lymphoma. It is also clear in the treated groups that animals within a cage appear independent. A beta-binomial analysis also supports the position that the animals are not independent in the control group but are independent in the treated groups. These results imply that the cage is the statistical sampling unit and that treatment reduced the incidence of malignant lymphoma, by preventing animal-to-animal transfer within the cage. If the cage is the statistical sampling unit then the sample sizes in this experiment are 40, 26, 26, and 26 and not 120, 80, 80, 80, and 80.

When asked whether cage-dependence or independence is usual for malignant lymphoma, Dr. Young replied that cage dependence is the usual situation, and that the independence seen in the treated groups in the study referred to was exceptional. Someone else in the audience added that he had observed a clustering of hepatic tumors in mice.