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Carcinogenesis Bioassay Data: Correlation by Species and Sex*

FREDERICK J. DI CARLO
Consultant, U.S. Environmental Protection Agency
P.O. Box 361
Denville, New Jersey 07834

Ad nauseum, it has been truculently emphasized that it is extremely difficult to extrapolate carcinogenesis bioassay data from rodent species to humans. This paper addresses a matter which apparently is comparatively simple. Specifically, the present question is: What is the present capability for extrapolating carcinogenesis bioassay data between rodent species? Response to this question was generated by reviewing the entire *Handbook of Summaries of the National Cancer Institute/National Toxicology Program Carcinogenesis Bioassay Technical Reports* [2].

The summaries cover 230 carcinogenesis bioassays on 221 substances. By far the largest group, 178 bioassays, involved feeding as the route of administering test substances (Table 1). Seven feeding tests were conducted in only one species. Of the remaining

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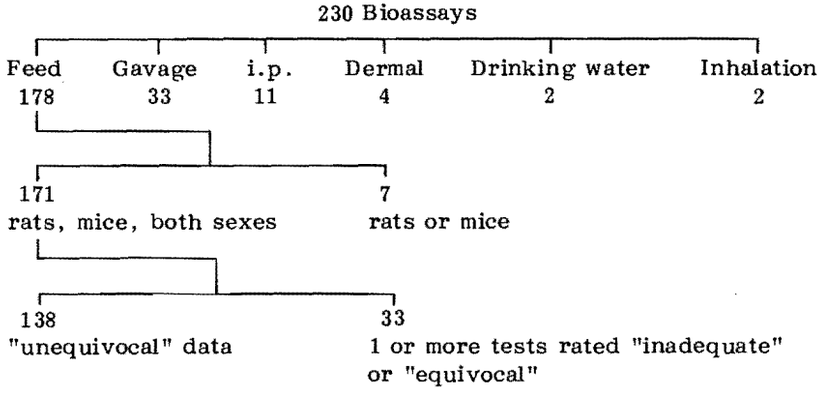
TABLE 1

Routes of Test Compound Administration Employed in NCI/NTP Carcinogenesis Bioassays



171 bioassays, 33 yielded results that preclude correlation because the data were classified as "inadequate" or "equivocal" for one or more groups of animals. For the present purpose, the other 138 bioassays are regarded as having yielded "unequivocal" results; this data set comprises 60% of the total.

Table 2 shows that the unequivocal results present 14 different conformations of positive and negative data. The most frequent conformation consists of totally negative findings, indicating that the test substances demonstrated no carcinogenicity in male or female rats or mice. Since it is possible to identify thousands of such substances, this data set can be neglected when seeking correlation between species and sexes.

Table 3 allows an examination of species and sex correlations from NCI bioassay data after excluding test substances that gave uniformly negative results. This table shows that only 21% of the test substances were positive in both sexes of both species, 32% were species specific, and 46% demonstrated neither species nor sex correlation. Until this area of mouse/rat response is understood, it is illusory to support (or not support) any given extrapolation of carcinogenesis bioassay data from rodents to humans.

TABLE 2

Conformations of "Unequivocal" NCI/NTP Carcinogenesis Bioassay Results of Feeding Studies and Correlations by Species and Sex

Rat		Mouse			Correlation		
m	f	m	f	n	Species	Sex	%
-	-	-	-	75[a]	+	+	63.8
+	+	+	+	13	+	+	
+	+	-	-	10[b]	+	-	14.5
-	-	+	+	10[c]	+	-	
+	-	+	-	1	-	+	0.7
+	-	-	-	4	-	-	21.0
-	+	-	-	2	-	-	
-	-	+	-	7	-	-	
-	-	-	+	2	-	-	
+	+	-	+	7	-	-	
+	-	+	+	3	-	-	
+	-	-	+	2	-	-	
-	+	+	-	1	-	-	
-	+	+	+	1	-	-	
				138			100.0

[a] 54.3%.
[b] Five are azo compounds.
[c] No azo compound found positive.

It has been proposed that the human population must be divided into subsets relative to susceptibility to carcinogenesis, and this viewpoint is acceptable. In this regard, one interpretation of the NCI bioassay data is that the rat and mouse strains employed were not members of comparable subsets of their species. If this is true, how should appropriate subsets be selected?

One approach is to use metabolism and pharmacokinetics, as broadly defined [3], as the basis for selections. Following this avenue is not likely to lead to single strains of rats and mice applicable to evaluation of the universe of chemical substances. This view is suggested by the observation that five azo compounds are

TABLE 3

Correlation of Positive "Unequivocal" NCI/NTP Carcinogenesis Data by Species and Sex

n	Correlation		%
	Species	Sex	
13	+	+	20.6
20	+	-	31.7
1	-	+	1.6
29	-	-	46.0
63			99.9

positive in both sexes of rats and negative in both sexes of mice (Table 2). It appears reasonable to assume that this sharp difference is due to azo reductase levels. Since mice tend to have higher, not lower, levels of azo reductase than rats [4], the bioassay findings may be attributable to azo reductase differences in intestinal microflora of the rodents. Calabrese [5] summarized many interesting differences in microorganisms present in the intestine of mammals and concluded that "biotransformations by intestinal microflora may have profound toxicological implications," but he did not find any report of mammalian species differences related to azo reduction by intestinal bacteria [6].

It is painfully clear that carcinogenesis in the mouse cannot now be predicted from positive bioassay data obtained from the rat, and vice versa. The preceding considerations lead to the conclusion that metabolism/pharmacokinetics studies should precede toxicologic testing, especially when long-term testing is involved and it is desirable to generate mechanistic interpretations of data. It was emphasized earlier [7] that anomalies in short-term mutagenesis testing results are also attributable to the lack of metabolism data. In my view, whether the problem concerns expensive chronic animal bioassays or inexpensive short-term bacterial tests, the solution is qualitatively identical. Without metabolism/pharmacokinetics information on test compounds, toxicologic data will continue to defy explanation. And without explanation, many interspecies extrapolations of toxicity data will remain unscientific.

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