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Some Tautologous Aspects of the Comparison of Carcinogenic Potency in Rats and Mice

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Some Tautologous Aspects of the Comparison of Carcinogenic Potency in Rats and Mice. BERNSTEIN, L., GOLD, L. S., AMES, B. N., PIKE, M. C., and HOEL, D. G. (1985). *Fundam. Appl. Toxicol.* **5**, 79–86. In risk estimation, the results of rodent carcinogenesis experiments are often used to quantitatively predict effects in man. The justification for this approach has in large part been dependent upon the good correlation of carcinogenic potency found between mice and rats over large numbers of test chemicals. Using the data base of chemicals tested by the NCI Bioassay Program, we observe that there is a very high correlation of the maximum doses tested (max-*d*) for rats and mice on a milligram per kilogram body weight per day basis. Next we show that the calculated carcinogenic potency (*b*—defined in the paper) is restricted to an approximately 30-fold range surrounding log(2)/max-*d*, which has a biological as well as a statistical basis. Since the max-*d*'s for the set of NCI test chemicals vary over many orders of magnitude, it necessarily follows statistically that the carcinogenic potencies will be highly correlated. This "artifact" of potency estimation does *not* imply that there is no basis for extrapolating animal results to man. It does suggest, however, that the interpretation of correlation studies of carcinogenic potency needs much further thought.

Long-term animal bioassays are currently the major source of information for assessing the carcinogenicity of the increasing numbers of chemicals in the environment. Qualitative evidence of the carcinogenicity of an agent is obtained from those experiments which show either an increase in tumor incidence or a decrease in the latency period for tumors. Recently, however, interest has focused on using the results of animal experiments to predict carcinogenic potency in man (NAS, 1977; Crouch and Wilson, 1979, 1981). To determine if this is a reasonable prospect, Crouch and Wilson and others (Gold *et al.*, 1984) have begun by comparing carcinogenic potency in rats and mice, since, if there is little correlation between these species, we could not hope to extrapolate animal experimental results to man. Crouch and Wilson (1979) demonstrated "good" interspecies correlation between the potencies in rats and mice for a number of chemicals (essentially those showing statistically significant carcinogenicity in both species) tested in the National Cancer Institute (NCI) series of carcinogenesis bioassays. Crouch (1981) argued further that "contradictory" results, i.e., chemicals found "positive" in one species and "negative" in the other, are very often actually compatible if the possible effects of chance are taken into account. Crouch and Wilson (1979) concluded that the results of the NCI series of bioassays are consistent with the possibility of extrapolation to humans.

The carcinogenic potency of a chemical as measured by a long-term animal bioassay is shown below to be reasonably represented

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by a single parameter, b. If $\hat{q}_0$ is the proportion of tumor-free animals in the control (zero-dose) group, and $\hat{q}$ is the proportion of tumor-free animals in the group exposed to the maximum dose (max-d) of chemical administered in the experiment, then the best estimate of b, i.e., $\hat{b}$, is approximately $[\log(\hat{q}_0/\hat{q})/\text{max-}d]$. The $\hat{b}$'s, i.e., carcinogenic potencies, of rats and mice must therefore be correlated if the range of values of max-d's is much greater than the range of values of $\log(\hat{q}_0/\hat{q})$'s and the max-d's of rats and mice are highly correlated. The max-d's of rats (and mice) used in the NCI experiments varied over many orders of magnitude. In theory, $\log(\hat{q}_0/\hat{q})$ can take an infinite range of values, since $\hat{q}$ is zero if all treated animals get tumors, but in practice, it has only an approximately 30-fold range. We demonstrate below that the max-d's of rats and mice are highly correlated. The major part of the observed "good" correlation between the carcinogenic potencies of chemicals in rats and mice can therefore be directly predicted from the conduct of the NCI experiments. Similar theoretical arguments show that truly "contradictory" results are in practice also effectively precluded by the conduct of the bioassays. These observations do *not* imply that there is no basis for extrapolating animal results to man, but rather that the grounds for such extrapolation must be sought in an understanding of the biological basis of the close relationship between "maximum tolerated doses" in different species, and of the reasons why there are so few experiments in which all the treated animals get tumors (or, either die or get tumors before any control animals develop tumors).

NCI BIOASSAYS

In the "standard NCI bioassay" as currently being carried out by the National Toxicology Program, the test agent is administered for most of the lifetime (assumed to be approximately 24 months) to both sexes of rats and mice. The doses of chemical to be administered in each sex–species experiment are determined in subchronic (3- to 6-month) studies of five dose levels with 10 animals per group, leading to an evaluation of the "maximum tolerated dose" (MTD) for each sex–species group. The MTD is defined in the NCI carcinogen bioassay guidelines as the maximum level of exposure "that can be predicted not to alter the animals' normal longevity from effects other than carcinogenicity" (Sontag *et al.*, 1975). It is the highest dose which causes "no more than a 10% weight decrement, . . . does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural life span" (Sontag *et al.*, 1975). In the "standard bioassay," for each sex–species studied there are three groups of 50 animals each: a control group, a group receiving one-half the MTD, and a group receiving the MTD.

The actual conduct of the NCI bioassays published prior to July 1980 varies from one experiment to another—a description may be found in Gold *et al.* (1984). In this paper we have chosen to refer to the dose given to the highest dose group simply as the "maximum dose tested" (max-d) rather than as the MTD.

AN "IDEAL-2-GROUP" EXPERIMENT AND THE MEASURE OF CARCINOGENIC POTENCY

It is sufficient for our purposes to consider the following hypothetical experiment situation:

(1) Two groups of n_0 and n_1 animals receive respective daily doses, d_0 (=0) and d_1 (=d) of a chemical (measured in mg/kg body wt) for the duration of the experiment:

(2) c_0 and c_1 animals respectively are diagnosed with "relevant" tumors during, or at the termination of, the experiment;

(3) no intercurrent deaths occur during the course of the experiment; and

(4) the relationship between dose and probability of tumor diagnosis is

p_i = probability animal at dose d_i is diagnosed with a tumor

$$= 1 - \exp[-(a + bd_i)],$$

where $a \geq 0$ and $b \geq 0$. This model is linear at low doses and is often referred to as the "one-hit model." The parameter a can best be described by the probability, q_0, that an animal at zero dose is *not* diagnosed with a tumor, i.e., $q_0 = 1\text{-}p_0 = \exp(-a)$ or $a = -\log(q_0)$. Similarly, b represents the increase in tumor occurrence with increasing dose of chemical, i.e., if we write the probability, q, that an animal at unit dose is *not* diagnosed with a tumor, then $q = \exp(-a-b)$, so that $b = \log(q_0/q)$.

In a previous paper (Peto *et al.*, 1984) we defined the TD50 of a chemical as the dose rate (in mg/kg body wt/day) which, if administered chronically for a standard period, would halve the probability of an animal remaining tumorless. In other words, TD50 is that daily dose which will induce tumors in half of the animals that would have remained tumor-free at zero dose. This measure is analogous to the well-known LD50, and is thus an appealing measure of carcinogenic potency.

For the "one-hit model" given above, this measure can be written

$$\text{TD50} = \log(2)/b,$$

and we note that TD50 does not involve the parameter a. The inverse of TD50, i.e., $b/\log(2)$, has better statistical properties than TD50 (Sawyer *et al.*, 1984), and $b/\log(2)$, or equivalently b, is generally to be preferred as a parameter, as when calculating correlations between the results of different experiments, since it tends to zero, not infinity, for low potency chemicals. The parameter b is estimated from the results of this experiment as

$$\hat{b} = \log(\hat{q}_0/\hat{q}_1)/d,$$

where

$$\hat{q}_0 = 1 - \hat{p}_0 = 1 - (c_0/n_0)$$

and

$$\hat{q}_1 = 1 - \hat{p}_1 = 1 - (c_1/n_1).$$

The statistical significance of the results of this experiment can be calculated using the one-sided Fisher–Irwin exact test.

RANGE OF STATISTICALLY SIGNIFICANT $\hat{b}$'s

Table 1 shows the possible results from an Ideal-2-Group experiment in which the control group is very large (n_0 = infinity) and $n_1 = 50$. We assume a 10% tumor incidence in the control group, in other words, $\hat{p}_0 = p_0 = 0.1$.

If we accept the conventional pairwise comparison rule that a one-sided P value must be less than or equal to 0.025 for the result to be statistically significant, then with $n_1 = 50$ and $\hat{p}_0 = 0.1$, the treated group must have at least 10 animals with tumors ($\hat{p}_1 = 0.20$), and the smallest statistically significant $\hat{b}$ is $0.118/d$ when $c_1 = 10$. The largest statistically significant $\hat{b}$ is infinity when $c_1 = 50$, so that the range of possible statistically significant estimates of b spans $0.118/d$ to infinity.

In actual long-term chronic experiments it is rare for the number of animals with tumors at a particular target site to equal the number of animals in the group, that is, c_1 is nearly always less than n_1. If we exclude the possibility that c_1 could be equal to n_1, then Table 1 shows that the statistically significant $\hat{b}$'s may vary over a 32-fold range from $0.118/d$ to $3.807/d$.

MAXIMUM DOSES USED IN NCI EXPERIMENTS

Figure 1 shows the pairs of different maximum doses (max-d) (expressed as average mg/kg body wt/day) used with female rats and female mice in the 186 NCI experiments for which results were published prior to July 1980, and in which both species were tested [see Gold *et al.* (1984) for method of calculating max-d in these units]. The maximum doses used are very highly correlated ($r^2 = 0.82$ on the logarithmic scale shown in the figure). A simple direct proportionality relationship between the maximum doses de-

TABLE 1

POSSIBLE RESULTS FROM AN IDEAL-2-GROUP EXPERIMENT

c_1	$\hat{p}_1$	$\hat{b}^a$	One-sided P value	95% Confidence limits for $\hat{b}^a$	
				Lower limit	Upper limit
5	0.10	0.000	0.569	0.000	0.141
6	0.12	0.022	0.384	0.000	0.173
7	0.14	0.045	0.230	0.000	0.206
8	0.16	0.069	0.122	0.000	0.239
9	0.18	0.093	0.058	0.000	0.272
10	0.20	0.118	0.025	0.000	0.306
11	0.22	0.143	0.009	0.017	0.340
12	0.24	0.169	0.003	0.035	0.375
13	0.26	0.196	0.001	0.053	0.411
14	0.28	0.223	0.000	0.072	0.448
15	0.30	0.251	0.000	0.091	0.485
20	0.40	0.405	0.000	0.201	0.689
25	0.50	0.588	0.000	0.334	0.930
30	0.60	0.811	0.000	0.496	1.226
35	0.70	1.099	0.000	0.702	1.617
40	0.80	1.504	0.000	0.982	2.194
45	0.90	2.197	0.000	1.417	3.298
48	0.96	3.114	0.000	1.881	5.217
49	0.98	3.807	0.000	2.135	7.484
50	1.00	∞	0.000	2.538	∞

Note. n_0 = Infinity, $n_1 = 50$, with 10% tumor incidence in the control group ($p_0 = 0.1$).
[a] $\hat{b}$ expressed per unit dose, i.e., $d = 1$.

scribes the data almost as well as the best fitting linear relationship (accounting for 97.6% of the variation accounted for by the best fitting linear relationship); the best fitting proportional relationship

$$\max\text{-}d_{\text{rats}} = 0.357 \max\text{-}d_{\text{mice}} \qquad (1)$$

is shown in the figure.[1]

A very similar relationship holds between the maximum doses used with male rats and male mice.

PLOTS OF SIGNIFICANT $\hat{b}_{\text{rats}}$ VERSUS SIGNIFICANT $\hat{b}_{\text{mice}}$

If Eq. (1) held absolutely and the NCI experiments were Ideal-2-Group Experiments with $n_1 = 50$, then we saw above that for any compound which is statistically significant in female rats the range of $\hat{b}_{\text{rats}}$ would be from 0.118/max-d_{rats} to 3.807/max-d_{rats}. Expressed in terms of max-d_{mice}, this range of $\hat{b}_{\text{rats}}$ would be 0.331/max-d_{mice} to 10.664/max-d_{mice}. If the compound was also statistically significant for female mice the range of $\hat{b}_{\text{mice}}$ would be 0.118/max-d_{mice} to 3.807/max-d_{mice}. Figure 2 shows these ranges of $\hat{b}_{\text{rats}}$ and $\hat{b}_{\text{mice}}$ for max-d_{mice} taking values (10^{-2}, 1, 10^2, 10^4) which cover the range shown in Fig. 1.

If the NCI experiments were Ideal-2-Group Experiments with n_0 = infinity and $n_1 = 50$ and if we only consider those experiments in which both $\hat{b}_{\text{rats}}$ and $\hat{b}_{\text{mice}}$ are statistically significant (taken as one-sided $P \leq 0.025$), then Fig. 2 suggests that $\hat{b}_{\text{rats}}$ will be highly correlated with $\hat{b}_{\text{mice}}$. This will be especially true if the range of max-d_{mice} (or equivalently max-d_{rats}) is wide (say four or more logs as shown in Fig. 1). Thus, the high correlation of $\hat{b}_{\text{rats}}$ and $\hat{b}_{\text{mice}}$ may be merely a function

[1] If we express dose on a mg/m^2 body surface area/day basis (Freireich *et al.*, 1966) then Eq. (1) would be max-$d_{\text{rats}} = 0.860$ max-d_{mice}.

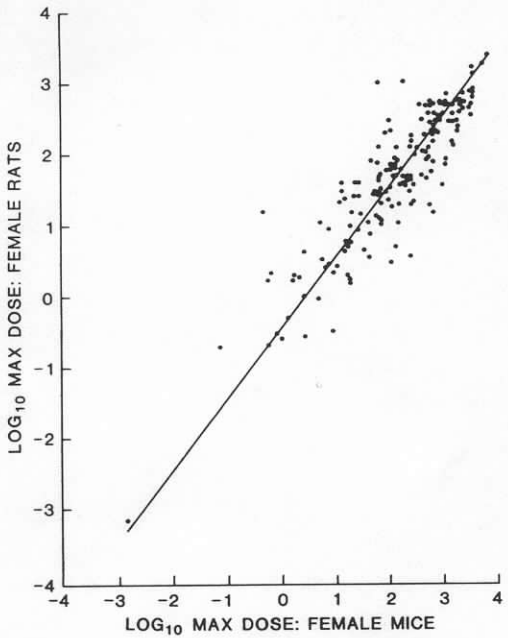

FIG. 1. Maximum doses used in 186 NCI experiments conducted in female rats and female mice.

of the high correlation between max-d_{rats} and max-d_{mice}.

If we take the 186 actual values of max-d_{rats} and max-d_{mice} from Fig. 1, and choose the values of $\hat{b}_{\text{rats}}$ and $\hat{b}_{\text{mice}}$ in the statistically significant range completely at random (on a logarithmic scale), then simulation shows that the expected correlation coefficient of $\hat{b}_{\text{rats}}$ and $\hat{b}_{\text{mice}}$ is 0.86. If we choose only those 49 values of max-d_{rats} and max-d_{mice} where $\hat{b}_{\text{rats}}$ and $\hat{b}_{\text{mice}}$ were statistically significant (Gold *et al.*, 1984), then simulation shows that the expected correlation coefficient is 0.90.

This extremely high correlation is not sensitive to "reasonable" departures from the Ideal-2-Group Experimental design. In particular, very similar results would be obtained if we vary n_0 and n_1 within the range of the conduct of actual experiments and/or if a third intermediate dose group is included. This extremely high correlation is also not particularly sensitive to the definition of what constitutes a "relevant" tumor or to the actual method of computing $\hat{b}$ including the method which allows for intercurrent deaths (see Crouch, 1981; Peto *et al.*, 1984; Sawyer *et al.*, 1984).

The "most potent" target site(s) (see Gold *et al.*, 1984) based on the statistical significance of $\hat{b}$ in each experiment was used as the basis for evaluating the observed relationship between carcinogenic potencies in female rats and mice. Figure 3 shows the actual values of the most potent $\hat{b}_{\text{rats}}$ and $\hat{b}_{\text{mice}}$ obtained from the 49 experiments in which both were statistically significant (one-sided $P \leqslant 0.025$). [These values of $\hat{b}_{\text{rats}}$ and $\hat{b}_{\text{mice}}$ were computed allowing for intercurrent deaths by the methods described in Peto *et al.* (1984) and Sawyer *et al.* (1984)]. The correlation coefficient of the data shown in Fig. 3 is 0.86, close to the expected "random" value we computed by simulation.

COMPARISON OF "POSITIVITY" IN RATS AND MICE

Some 30 to 40% of the 186 NCI chemicals tested in both rats and mice were found to be "positive" (one-sided $P \leqslant 0.025$) in one species and "negative" in the other, with a roughly equal split between mice-positive with rats-negative and rats-positive with mice-negative (Gold *et al.*, 1984). Crouch (1981)

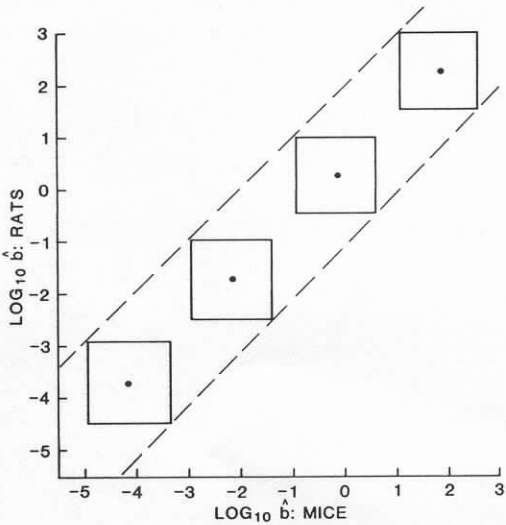

FIG. 2. Ranges of statistically significant $\hat{b}$'s for female rats and female mice in an Ideal-2-Group Experiment with maximum doses 10^{-2}, 1, 10^2, and 10^4.

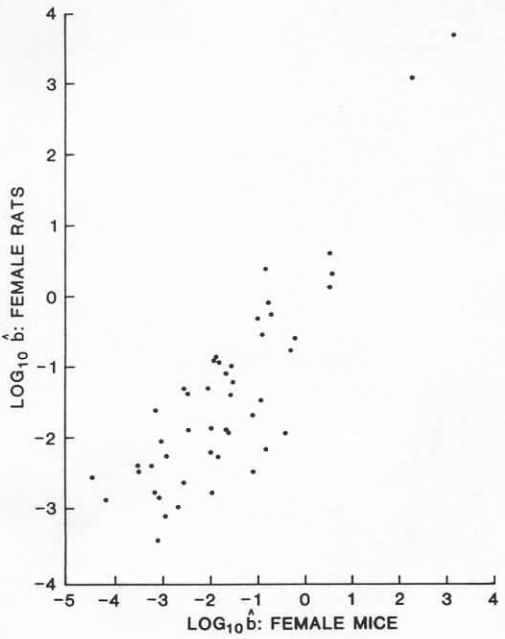

FIG. 3. Actual values of $\hat{b}$'s from 49 NCI experiments that were statistically significant (one-sided $P \leq 0.025$) in both female rats and female mice.

and others have argued that many of these "contradictory" results are only "naively" discrepant, that is, that many of the negative "contradictory" results are due solely to chance. They suggest that consideration of the upper confidence limit for b for the negative results will often show that the results in the two species are in fact compatible.

Unfortunately this argument suffers from a problem very similar to that discussed above when interpreting the correlation between actual values of $\hat{b}$'s from experiments with statistically significant results in both rats and mice. The last column of Table 1 shows the upper 97.5% confidence limit for the Ideal-2-Group Experiment with n_0 = infinity and $n_1 = 50$. We see that even with $\hat{b} = 0$ the upper confidence limit $(0.141/d)$ exceeds the lowest statistically significant $\hat{b}$ $(0.118/d)$. Thus, even if the results for rats and mice were *truly* discrepant, the upper confidence limit of the "negative" species would lie within the potency range of positive results, making the results appear compatible.

DISCUSSION

Figure 1 showed that the max-d's of rats and mice are very highly correlated. Because of the nature of the usual experimental design, the wide range of max-d's found in practice, and the experimental observation that a 100% tumor incidence in a treated group is only rarely seen, this *implies* that the carcinogenic potencies of chemicals that are positive in both rats and mice will also be very highly correlated.

Many of the 186 NCI experiments produced "discrepant" results when tested in rats and mice. It cannot usually be decided on the basis of the experimental results whether these represent true discrepancies between the two species, since the upper confidence limit of the negative results will, in most instances, be within the range of potencies that would have been judged positive if observed.

The small size of the usual experiment is responsible for the fact that the confidence intervals of the nonsignificant $\hat{b}$'s overlap with the range of the positive $\hat{b}$'s. The lack of 100% tumor incidence restricts the upper limit of $\hat{b}$'s. The reason for the rarity of the 100% tumor incidence may lie in part in the nature of the MTD, that is, the dose levels of a chemical necessary to produce a very high tumor yield may have to produce toxicity in the animals.

In certain experiments, the reason for not having a 100% tumor incidence in the treated group is that a few animals died early from unrelated causes; this effect can be allowed for by life-table analyses of the experiments (Peto *et al.*, 1984). Such analyses increase the upper limit of $\hat{b}$'s to some extent, but our analyses of the NCI experiments did not find this to be a major effect. Even with lifetable correction, $\hat{b}$ can only be very large if all animals in the treated group have either died or developed tumors before any animal developed a tumor in the control group—this does not occur very often. The reason for this may lie in the nature of tumor latent periods: for $\hat{b}$ to be very large, the shortest latent period in a control animal has to be

longer than the longest latent period in a treated animal.

Figure 1 suggested that the MTDs (expressed as mg/kg body wt/day) of female rats and mice may be related as

$$\mathrm{MTD}_{\mathrm{rats}} = 0.357\ \mathrm{MTD}_{\mathrm{mice}}.$$

If this relationship also holds true for carcinogenic potency then we would have

$$b_{\mathrm{mice}} = 0.357\ b_{\mathrm{rats}},$$

or defining "adjusted potencies," B_m and B_r as $B_m = b_{\mathrm{mice}}$ and $B_r = 0.357\ b_{\mathrm{rats}}$,

$$B_m = B_r.$$

We examined the relationship between the "adjusted potencies" $\hat{B}_m$ and $\hat{B}_r$ in the 122 (of 186) NCI experiments in female rats and mice which were "positive" in at least one species. To evaluate the compatibility of results for rats and mice in each bioassay, a series of statistical tests was performed to determine whether the ratio $\hat{B}_r/\hat{B}_m$ was statistically consistent with 1 or within factors of 2, 5, and 10. The percentages of tests which were statistically compatible at the 0.025 level of significance are presented in the first column of Table 2. (Details of the statistical test are given in the footnote to Table 2.) The observed ratio $\hat{B}_r/\hat{B}_m$ was also calculated and the percentages of bioassays for which this ratio was within a 2-fold, 5-fold, and 10-fold range are presented in the second column of Table 2.

TABLE 2

PERCENTAGE OF 122 NATIONAL CANCER INSTITUTE EXPERIMENTS IN FEMALE RATS AND MICE, POSITIVE IN AT LEAST ONE SPECIES, FOR WHICH THE PROPOSED "ADJUSTED POTENCY" RELATIONSHIP IS TRUE

"Adjusted potency" relationship	Statistically compatible[a] (%)	Observed (%)
$B_r = B_m$	65	—
$1/2 \leq B_r/B_m \leq 2$	76	20
$1/5 \leq B_r/B_m \leq 5$	93	41
$1/10 \leq B_r/B_m \leq 10$	96	57

[a] Based on the assumption that B is normally distributed (see Sawyer *et al.*, 1984), statistical compatibility within a factor k (k = 1, 2, 5, and 10) was tested at the 0.025 level of significance. For $\hat{B}_r > \hat{B}_m$ the hypothesis that $\hat{B}_r/\hat{B}_m < k$ was tested; for $\hat{B}_r < \hat{B}_m$ the hypothesis $\hat{B}_r/\hat{B}_m > 1/k$ was tested.

The first column of figures in Table 2 shows that 65% of the comparisons of $\hat{B}_r$ and $\hat{B}_m$ are statistically compatible with equality, and 96% of the comparisons are statistically compatible with $\hat{B}_r$ being within a factor of 10 of $\hat{B}_m$. This is the empirical counterpart of the above discussion of upper confidence limits of negative results. The second column of figures in Table 2 shows, however, that the observed "adjusted potency" in the more sensitive species is more than 10-fold greater than that of the other species in 43% of the experiments.

There were five experiments in which the "adjusted potencies" were not statistically compatible within a factor of 10, and 52 experiments in which the observed "adjusted potencies" differed by more than a factor of 10. In 38 of these 52 comparisons, the $\hat{b}$ for one species was zero.

Our arguments have shown that the strong correlation between MTDs and the experimental observation that a 100% tumor incidence in a treated group is only rarely seen necessarily imply a strong correlation between carcinogenic potencies as defined by the TD50 measure. Although we used a simple two-dose experiment with a 10% background tumor rate to show a 30-fold range for a TD50, this range seems to hold fairly generally for three-dose experiments with a variety of background rates and shapes of dose–response functions. Also, the (exponential) linear assumption for the dose–response function used in calculating the TD50 is not crucial. For example, assuming a purely (exponential) quadratic dose–response function, we found the actual TD50 to be within a factor of 5 of the linearly estimated TD50 for a selection of background rates and incidence rates at max-d.

Our arguments cannot be explained away by the shape of the dose–response function, nor can they be dismissed on the basis of a presumed saturation of the carcinogenic pro-

cess. If some compounds were highly carcinogenic compared with their MTDs, then we would expect to observe 100% (or at least very high) incidence rates at all of the experimental dose levels. This was not seen with the compounds under study. If the saturation of a metabolic activation process was involved, the dose response might plateau. From our data base we observed that approximately 10% of the dose–response functions were sublinear, indicating possible saturation. For the compounds in which this was observed, it was, however, generally not replicated in other target sites in the same experiment, in the other sex of the same species, or in other species.

Biologically it may indeed be the case that TD50 and the MTD are closely related (see Zeise *et al.*, 1984). Tissue damage with cell killing and consequent cell proliferation has been shown to be important in the promotion of liver tumors and possibly other tumors as well (Farber, 1984; Harris and Sun, 1984). Therefore, a single mutagenic compound given at tissue-damaging doses (near the MTD) can act as its own promoter as well as initiator. Thus, if cell killing shows an apparent threshold with dose, as is the case for several carcinogens in the liver (Farber, 1976), then the carcinogenic potency near the MTD might be expected to be much greater than at non-toxic doses.

Unfortunately, the study of potency correlations between species has not shed much light on this issue or on the issue of quantitative prediction across species based upon potency measures.

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