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How Tautological Are Interspecies Correlations of Carcinogenic Potencies?

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Crouch and Wilson demonstrated a strong correlation between carcinogenic potencies in rats and mice, supporting the extrapolation from mouse to man. Bernstein *et al.*, however, show that the observed correlation is mainly a statistical artifact of bioassay design. Crouch *et al.* have a comeback. This paper will review the arguments and present some new data. The correlation is largely (but not totally) tautological, confirming results in Bernstein *et al.*

KEY WORDS: Carcinogenic potency; TD_{50}; interspecies correlation; one-hit model; animal cancer tests.

1. INTRODUCTION

Crouch and Wilson[1] suggest that there is a strong correlation between carcinogenic potencies in mice and rats. However, Bernstein *et al.*[2,3] show that this correlation is largely a statistical artifact of bioassay design—and Crouch and Wilson's choice of test set, namely, chemicals with a statistically significant potency estimate in both species.

Bernstein *et al.*[2] introduce a somewhat simplified model bioassay, in which the control group is very large and has a 10% tumor incidence. The treatment group has 50 animals, which are given the MTD (maximum tolerated dose); not all the animals develop tumors. Under these conditions, if the estimate of potency is statistically significant (i.e., exceeds 0 by an amount that is statistically significant), it must be on the order of 1/MTD. The MTDs for rats and mice are strongly correlated, and range over many orders of magnitude. The potency correlation follows.

To put this a bit more algebraically, let β denote the estimated carcinogenic potency of a chemical. The analysis in Crouch and Wilson[1] and in Bernstein *et al.*[2,3] is based on the "one hit" model. To state the model, let $P(d)$ be the probability of a response at dose d. Then

$$P(d) = P(0) + [1 - P(0)][1 - e^{-\beta d}] \quad (1)$$

Given the constraints of bioassay design, if β is statistically significant, and not all dosed animals develop tumors, then $\beta \times$ MTD must be nearly 1, as shown by Bernstein *et al.*[2] It will be useful to define

$$\delta = \log \beta + \log \text{MTD} \quad (2)$$

This quantity can be viewed as a measure of tumor yield when the dose is the MTD: see Eq. (1). In short, if β is statistically significant, Bernstein *et al.*[2,3] show that

$$\delta \approx 0 \quad (3)$$

We will have to consider mice and rats; thus, we use β-mice for estimated potency in the mouse, and β-rats for estimated potency in the rat. Later, we use δ for mice:

$$\delta = \log \beta\text{-mice} + \log \text{MTD-mice} \quad (4)$$

Similarly,

$$\epsilon = \log \beta\text{-rats} + \log \text{MTD-rats} \quad (5)$$

From Bernstein *et al.*[2,3]

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$$\epsilon \approx 0 \qquad (6)$$

Since log MTD-mice and log MTD-rats are highly correlated, log β-mice and log β-rats must be highly correlated: indeed, log β-mice $\approx -$log MTD-mice and log β-rats $\approx -$log MTD rats, by Eqs. (3) and (6).

In the simplified bioassay designs considered by Bernstein *et al.*,[2] with significance at the .025 level (one-sided), the range of log (β × MTD) is about 1.5. The range in real bioassays is more like 2.5, but the range of log MTD is nearly 8. (Logs are to base 10, so a range of 2.5 corresponds to a factor of about 300; a range of 8 corresponds to a factor of 100,000,000.) Real bioassays in the NCI/NTP series have two dose groups, variable response rates in the control group, and life-table estimates are used for β, all of which widen the range in log (β × MTD) by comparison with the simplified bioassay design in Bernstein *et al.*[2] However, in the NCI/NTP bioassays as in the simplified bioassays, log (β × MTD) shows much less variability than log (MTD), and that is what generates the artifact. As Bernstein *et al.*[2] say, "it necessarily follows statistically that the carcinogenic potencies [in rats and mice] will be highly correlated."

Crouch *et al.*[4] seem to deny that the interspecies correlation in log potencies is artifactual; they "conclude that the correlations between carcinogenic potency are valid" (p. 1). Also see Zeise *et al.*[5] Goodman and Wilson[6] say "That there is a good correlation between the carcinogenic potency at the most sensitive site in rats with that in mice is now firmly established" (p. 211), and argue that Bernstein *et al.*[2] "have biased the outcome" (p. 212).

One object of the present paper is to review the argument: how much of the observed correlation between carcinogenic potencies in rats and mice is artifactual, and what is the source of the artifact? We take the second question first, illustrating our answer with data from the NCI/NTP bioassays. See Gold *et al.*[7–11]; potencies are computed using a lifetable analysis[12,13]; the site with highest potency is used. We begin with female mice and rats. There were 87 NCI/NTP bioassays where the chemical on test was carcinogenic at the .025 level (one-sided) in female mice and rats, that is, the estimated potency was positive by a "statistically significant" amount in both species. These 87 chemicals will be our test set.

The data are shown in Fig. 1. Each dot represents one chemical in the test set. The top left panel shows log β-mice on the horizontal axis and log β-rats on the vertical. There is a strong interspecies correlation—as observed in Crouch & Wilson.[1] However, at least in our opinion, this correlation is largely artifactual. The source of the artifact may be described as follows:

1. The test set consists of chemicals with estimated potencies that are statistically significant: selection procedures have a profound impact on results. [Crouch and Wilson[1] used chemicals "that were considered statistically significant in the original reports," plus some additional chemicals where the potency was statistically significant by a criterion of their own (p. 1109).]
2. There is a very strong correlation between toxicity in rats and mice. This correlation is, we believe, a fact of biology. The data are plotted in the top right panel of Fig. 1: log (1/MTD-mice) is shown on the horizontal axis, and log (1/MTD-rats) is shown on the vertical, with one dot for each chemical in the test set.
3. Due to constraints of bioassay design, log (potency-mice) and log (1/MTD-mice) are highly correlated—if the potency estimate is statistically significant. This fact of mathematical statistics is the basic finding in Bernstein *et al.*[2]: see Eq. (3). The data are shown at the bottom left in Fig. 1, with log (1/MTD-mice) on the horizontal axis and log (potency-mice) on the vertical. The picture for rats is similar and is omitted.

Ordinarily, applying mathematical statistics to biological facts should lead to good results. In the present case, however, the result is an artifact. More specifically, the interspecies correlation in potencies (Fig. 1, top left) is largely—but not completely—driven by the correlation in toxicities (Fig. 1, top right, biology) and the correlation between log potency and log MTD (bottom left, mathematical statistics applied to bioassay designs). The interspecies correlation observed by Crouch and Wilson[1] is largely artifactual because it is driven by these more primitive correlations.

We also have some modest new empirical findings to report: δ and ϵ are correlated. For females, $N = 87$, $r \approx 0.52$, $p \approx 1/10^4$; for males, $N = 96$, $r \approx .32$, $p \approx 1/10^3$. This correlation seems to be independent of the artifact identified in Bernstein *et al.*[2] The new correlation (in females) is shown at the bottom right of Fig. 1, which plots $\delta =$ log (β × MTD-mice) on the horizontal axis and $\epsilon =$ log (β × MTD-rats) on the vertical.

The next objective is to quantify, roughly, the artifactual component of the correlation between mouse and rat log potencies. This involves two statistical models, where the impacts of various assumptions can be cal-

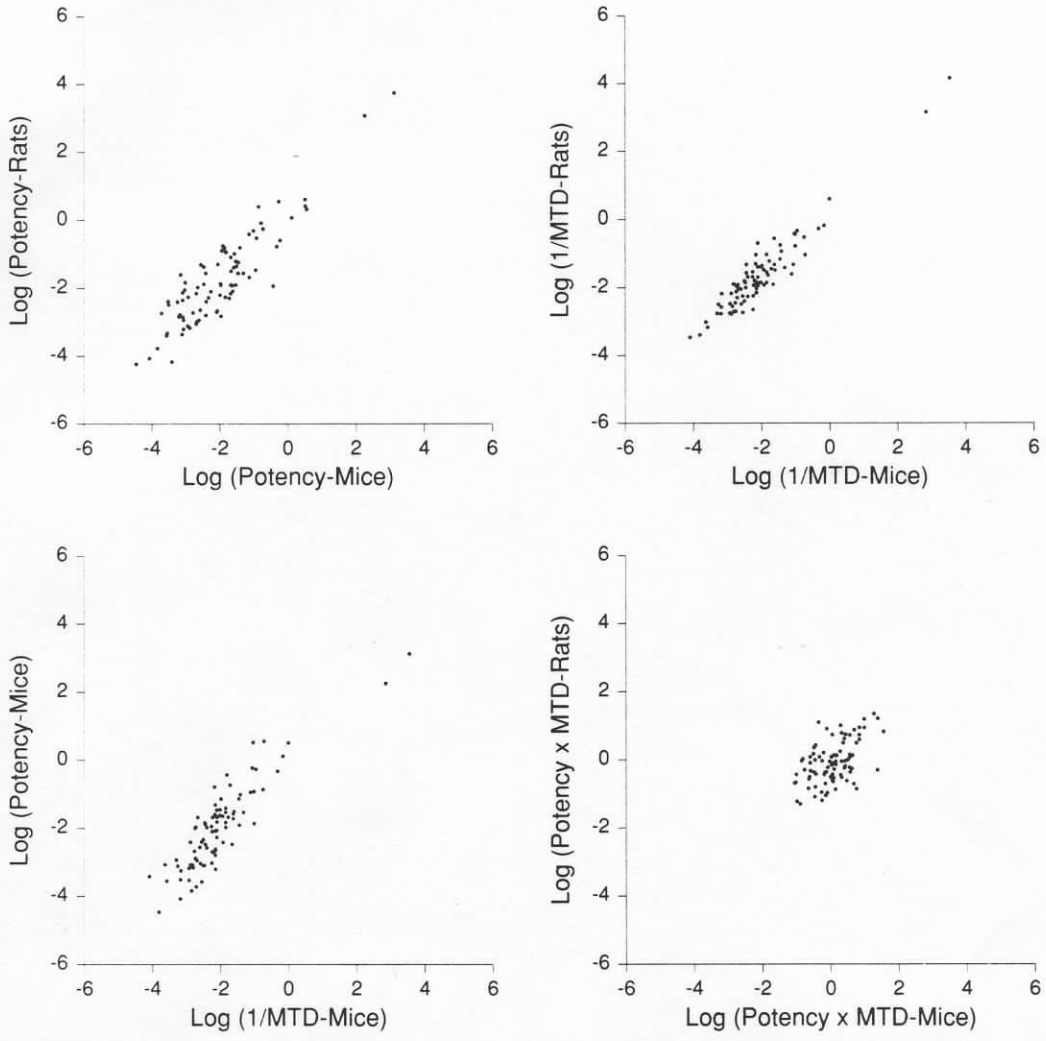

Fig. 1. Top left: The strong inter-species correlation of carcinogenic potencies; the horizontal axis shows log β-mice, while the vertical shows log β-rats. Top right: the horizontal axis shows log (1/MTD-mice), while the vertical shows log (1/MTD-rats); this correlation is believed to be real. Lower left: A statistical artifact which drives the inter-species correlation of carcinogenic potencies; the horizontal axis shows log (1/MTD-mice), while the vertical axis shows log β-mice. Lower right: A weak inter-species correlation which seems to be real; the horizontal axis shows log (β × MTD)-mice, while the vertical shows log (β × MTD)-rats. Each dot represents one of the 87 NCI/NTP bioassays where the chemical on test was significant at the .025 level (one-sided) in female mice and in female rats. Data are for females only. Logs are to base 10.

culated. In effect, the first model assumes that interspecies correlation of potencies is purely artifactual: it ignores the correlation between δ and ϵ. The second model incorporates the correlation between δ and ϵ, which says that part of the interspecies correlation in potencies is real. A comparison of the models and data suggests that over 80% of the interspecies correlation in carcinogenic potencies observed by Crouch and Wilson[1] can be explained as follows:

1. selecting chemicals with statistically significant potencies in both species;
2. the interspecies correlation in toxicity;
3. the correlation between log potency and log MTD.

In brief, our two models can be described as follows. Each chemical in the test set is characterized by two numbers: its MTD in mice and its MTD in rats. Across the 87 chemicals, Model I randomly couples β × MTD with MTD, separately in mice and rats.

Model II randomly couples the pair ($\beta \times$MTD-mice, $\beta \times$MTD-rats) with the pair (MTD-mice, MTD-rats).

2. DECOMPOSING THE CORRELATIONS

We consider two models for decomposing correlations. Model variables are denoted by primes, and correspond to variables in the real data which are "unprimed." For instance, X' denotes a model entity corresponding to the log potency in the real data, denoted by X. The notation is laid out in Table I.

Both models share Eqs. (7)–(8):

$$X' = U' + \delta' \tag{7}$$

$$Y' = V' + \epsilon' \tag{8}$$

The SDs of U' and V', as well as the correlation $r(U', V')$, are chosen to match the real data. Likewise, the SDs of δ' and ϵ' match the real SDs. Both models assume, as is almost true:

The pair (δ', ϵ') is independent of the pair (U', V') (9)

We begin with females, taking up data for males later. Then SD $X' = \sqrt{(\text{SD } U')^2 + (\text{SD } \delta')^2} \approx 1.27$, a bit lower than the observed 1.29 (Table I); the difference is due to the small positive correlation between U and δ (Table II). Likewise, SD $Y' = \sqrt{(\text{SD } V')^2 + (\text{SD } \epsilon')^2} \approx 1.28$, a bit lower than the observed 1.35. This completes the presentation of elements common to both models.

Table I. Summary of Data for Female Mice and Rats: Means and SDs[a]

	Female Mice		
	X log β	U log 1/MTD	δ log ($\beta \times$MTD)
Average	−1.98	−2.04	.07
SD	1.29	1.12	.59
	Female Rats		
	Y log β	V log 1/MTD	ϵ log ($\beta \times$MTD)
Averge	−1.73	−1.65	−.08
SD	1.35	1.12	.62

[a] 87 NCI/NTP bioassays where the chemical on test was significant at the .025 level (one-sided) in both species. Logs to base 10. Dose in mg/kg bw/day.

2.1. Model I: Interspecies Correlation Is Purely Artifactual

This model makes the additional assumption

$$\delta' \text{ and } \epsilon' \text{ are independent} \tag{10}$$

In Model I, the correlation between X' and Y' is purely artifactual, being driven by the correlation between U' and V' in Eqs. (7) and (8). To make Model I more concrete, index the chemicals in the test set by i. For each chemical, compute δ_i. For the mouse MTDs, let $U_i' = U_i$, the real value. The log potency in the mouse for chemical i is $X_i = U_i + \delta_i$, in the real data, by definition (4). But to construct X_i' in Model I, pick a random index j and add δ_j to U_i. That is, let $X_i' = U_i + \delta_j$, where j is chosen at random. Likewise for the rat variables (Y', V', and ϵ').

Thus, Model I links log potencies for mice and rats only through log 1/MTD-mice and log 1/MTD-rats. The links between δ and ϵ have been broken by randomization. Model I captures the idea that the correlation between log β-mice and log β-rats is purely artifactual—that is, due solely to the correlation between log MTD-mice and log MTD-rats.

In model I,

$$\text{cov}(X', Y') = \text{cov}(U', V')$$

And the correlation between X' and Y' is

$$\begin{aligned} r(X', Y') &= \frac{\text{cov}(X', Y')}{(\text{SD } X') \times (\text{SD } Y')} \\ &= \frac{(\text{SD } U') \times (\text{SD } V')}{(\text{SD } X') \times (\text{SD } Y')} \times r(U', V') \\ &= \frac{1.12 \times 1.12}{1.27 \times 1.28} \times .95 \\ &\approx 0.73 \end{aligned}$$

2.2. Model II: Interspecies Correlation Has Real Component

We replace Eq. (10) by the assumption that, as in the real data (Table II),

$$r(\delta', \epsilon') = 0.52 \tag{11}$$

Equation (11) gives a "real component" to the correlation between log potencies. To make this more vivid, we can use a similar randomization. Again, we index the chemicals in the test set by i. For each chemical, compute δ_i and ϵ_i. For the MTDs, Model II uses the real

Table II. Summary of Data for Female Mice and Rats: Correlations[a]

		X	U	δ	Y	V	ϵ
Log β-mice	X	1	.89	.49	.90	.86	.40
Log 1/MTD-mice	U	.89	1	.035	.87	.95	.19
Log (β × MTD)-mice	δ	.49	.035	1	.30	.074	.52
Log β-rats	Y	.90	.87	.30	1	.89	.57
Log 1/MTD-rats	V	.86	.95	.074	.89	1	.14
Log (β × MTD)-rats	ϵ	.40	.19	.52	.57	.14	1

[a] 87 NCI/NTP bioassays where the chemical on test was significant at the .025 level (one-sided) in both species. Logs to base 10. Dose in mg/kg bw/day.

values as Model I did: $U_i' = U_i$ and $V_i' = V_i$. The log potencies for chemical i are $X_i = U_i + \delta_i$ for the mouse and $Y_i = V_i + \epsilon_i$ for the rat, in the real data, by definitions (4) and (5). However, to construct X_i' and Y_i' in Model II, pick a random index j; then let $X_i' = U_i + \delta_j$ and $Y_i' = V_i + \epsilon_j$. In effect, Model II restores the link between δ and ϵ by operating on pairs (δ,ϵ), not on individual δ's and ϵ's. However, the pair (δ,ϵ) still cannot be linked to the pair (U,V), due to the randomization.

To compute the impact on the correlation, begin with the covariance:

$$\text{cov}(X',Y') = \text{cov}(U',V') + \text{cov}(\delta',\epsilon')$$

Then

$$r(X',Y') = \frac{\text{cov}(X',Y')}{(\text{SD } X') \times (\text{SD } Y')} = \frac{(\text{SD } U') \times (\text{SD } V') \times r(U',V') + (\text{SD } \delta') \times (\text{SD } \epsilon') \times r(\delta',\epsilon')}{(\text{SD } X') \times (\text{SD } Y')} = \frac{(1.12 \times 1.12 \times .95) + (0.59 \times 0.62 \times 0.52)}{1.27 \times 1.28} \approx 0.85$$

Thus, the correlation in Model I is 0.73/0.85 ≈ 86% of the correlation in Model II. The correlation in Model I is due to bioassay design only, and has nothing to do with biology—apart from the correlation between MTD-mice and MTD-rats.

The observed correlation between log potencies in female mice and rats is 0.90; see Table II. Thus, Model I already produces 0.73/0.90 ≈ 81% of the real correlation in log potency. Put another way, the artifact identified in Bernstein *et al.*[2] accounts for most of the observed correlation between log potency in female rats and mice.

Models I and II are only intended to quantify the impact of the artifact on the interspecies correlation. Model I does not fit the data because it sets to 0 the correlation in the lower right panel of Fig. 1. Model II provides quite a reasonable description of the data; discrepancies are generally within the appropriate margins of error. For example, in Table II, $r(\delta,U) = 0.035$ rather than the expected 0.0, but the standard error with 87 observations is about 0.11.

In the real data, the correlation between log β-mice and log β-rats is 0.90. The difference between this 0.90 and the 0.85 for Model II reflects the impact of small correlations in the real data that are set to 0 in the model. This difference seems to be small in practical terms, but it is statistically significant by simulation; the standard error for the difference is about 0.018. This completes our discussion of the data for female rodents.

We turn now to the male rodents, where the situation is very similar. The data are summarized in Tables III and IV, and the results are indicated below:

$$\begin{aligned} \text{SD of } X' &\approx \text{SD of } Y' \approx 1.26 \\ r(X',Y') &\approx .73 \text{ in Model I} \\ r(X',Y') &\approx .80 \text{ in Model II} \\ r(X,Y) &\approx .85 \text{ in the real data} \\ .73/.80 &\approx 91\% \quad .73/.85 \approx 86\% \end{aligned}$$

For male rodents, Model I produces 91% of the correlation in Model II, and 86% of the real correlation. The artifact accounts for even more of the observed interspecies correlation, because $r(\delta,\epsilon)$ is smaller in the males: 0.32 compared to 0.52 for females. See Tables II and IV.

DISCUSSION

The interspecies correlation observed by Crouch and Wilson[1] is often used to justify extrapolation from rodents to humans (see, e.g., Goodman and Wilson[6]). However, most of this correlation is an artifact of bioassay design, and selecting "statistically significant" potencies. Of course, the extrapolation from rodents to humans may still be valid—but the justification in Crouch and Wilson[1] is not.

Table III. Summary of Data for Male Mice and Rats: Means and SDs[a]

	Male Mice		
	X log β	U log 1/MTD	δ log (β × MTD)
Average	−2.14	−2.06	−.08
SD	1.27	1.14	.54
	Male Rats		
	Y log β	V log 1/MTD	ϵ log (β × MTD)
Average	−1.70	−1.68	−.02
SD	1.29	1.11	.61

[a] 96 NCI/NTP bioassays where the chemical on test was significant at the .025 level (one-sided) in both species. Logs to base 10. Dose in mg/kg bw/day.

It may be conjectured that changing the selection rule for the test set will solve the problem. However, that is not so easy. Indeed, the artifactual correlation will be only slightly weakened if the test set consists of chemicals where the estimated values of β-mice and β-rats are both positive numbers rather than zero, ignoring statistical significance. A very similar artifact will be observed if the test set consists of all chemicals—but β's which are estimated as zero are replaced by upper confidence limits. [Compare Crouch[14] (p. 323).]

Some readers have asked why we consider the interspecies correlation of toxicity to be real. That correlation seems almost axiomatic in the field of toxicology, and statistical analysis of the NCI/NTP data can add little new insight. Still, there are two comments to make:

1. There is little difference between the correlations in MTDs for the selected chemicals and the remaining chemicals, making it harder to explain the correlation in toxicities as an artifact of selection bias.
2. The interspecies correlation between potencies is weaker than the correlation between MTDs. That is consistent with the correlation between potencies being driven by the correlation between MTDs. However, the difference in correlations is small.

4. COUNTERARGUMENTS

Crouch *et al.*[4,5] seek to rehabilitate Crouch and Wilson[1] by answering Bernstein *et al.*[2,3] There are two arguments:

1. β and MTD are related, as demonstrated by a permutation test that randomly pairs β and MTD; and,
2. bioassays seldom show 100% response, a point discussed in considerable detail by Bernstein *et al.*[2]

Point 1 is certainly true, but does not refute Bernstein *et al.*[2] To explain the issue in slightly more detail, we summarize the procedure used by Crouch *et al.* Index the chemicals by i. Take, for instance, the female mouse. Let β_i be the potency of chemical i in the female mouse, and MTD_i the maximally tolerated dose. Let π be a random permutation of i's.

Crouch *et al.* observe that a histogram for $\beta_{\pi(i)} \times MTD_i$—where potency and dose have been paired at random—looks nothing like a histogram for $\beta_i \times MTD_i$, with potency and dose paired as they are in reality. But this is just the basic observation in Bernstein *et al.*[2,3]: $\beta_i \times MTD_i$ is practically 1. Pairing potency and dose at random across chemicals produces an enormous range

Table IV. Summary of Data for Male Mice and Rats: Correlations[a]

		X	U	δ	Y	V	ϵ
Log β-mice	X	1	.91	.44	.85	.86	.23
Log 1/MTD-mice	U	.91	1	.020	.84	.93	.10
Log (β × MTD)-mice	δ	.44	.020	1	.21	.069	.32
Log β-rats	Y	.85	.84	.21	1	.88	.52
Log 1/MTD-rats	V	.86	.93	.069	.88	1	.049
Log (β × MTD)-rats	ϵ	.23	.10	.32	.52	.049	1

[a] 96 NCI/NTP bioassays where the chemical on test was significant at the .025 level (one-sided) in both species. Logs to base 10. Dose in mg/kg bw/day.

for the product $\beta \times$ MTD, instead of the very narrow range forced in the real data by the artifact.

Crouch *et al.*[4] say they "have demonstrated that the correlation between the carcinogenic potency β and the maximum tolerated dose (MTD) ... is not solely an artifact" (p. 7). This seems to be a considerable overstatement. Indeed, so far as we can see, Crouch *et al.*[4,5] have in effect rediscovered the artifact identified by Bernstein *et al.*[2,3]

What is the precise difference between our models and the permutation test in Crouch *et al.*[4]? In our models, the link for each chemical between β and MTD is always there—as it is in the real data; Crouch *et al.*[4] break that link. Our randomization in Models I and II only breaks the link between the disturbance terms (δ,ϵ) and the carcinogens, each chemical on test being characterized by the MTD in mice and in rats. Model II preserves the link between δ and ϵ, while Model I breaks that link too. In short, Crouch *et al.* couple the MTD with a random β, violating the constraint documented in Bernstein *et al.*[2] Our Model I, for instance, couples the MTD with a random product $\beta \times$ MTD, which respects the constraint.

Point 2 in Crouch *et al.*[4,5]— that 100% response is rare—is also true, but its bearing on the debate is unclear. For a brief statement of the issues, see Whipple[15]; also see Bernstein *et al.*[2,3] Few known chemicals induce tumors in 100% of test animals at the MTD. That may tell us something interesting about the biology of cancer, for instance, that mitogenesis is an important factor in carcinogenesis. Indeed, if mitogenesis at near-toxic doses were not important, then dose–response curves might be expected to plateau before the MTD; and all animals might develop tumors. For a review of evidence on the role of mitogenesis, see Ames and Gold[16–18] and Ames *et al.*[19] However, there are viable alternative explanations for the absence of 100% tumor yields, including classification error in the pathology and dependent competing risks. Genetic variability plays some role. So do other failures in the one-hit model and its generalizations.[20–22] On this score, more research is needed.

Whether toxicity is or is not a primary cause of carcinogenicity in bioassays, the artifact identified in Bernstein *et al.*[2] still obtains: the range of potency $\times$ MTD is severely restricted. That restriction must be recognized, when using bioassay data to investigate relationships between toxicity and carcinogenicity, or interspecies correlations in potency. As Bernstein *et al.*[2] say, "the interpretation of correlation studies of carcinogenic potency needs much further thought."

5. OTHER LITERATURE

Shlyakhter *et al.*[23] use Monte Carlo techniques to consider various possible joint distributions for true potency and MTD and some implications for the observed distribution of estimated potency and dose. They conclude, "At least some fraction of [the interspecies] correlation is attributable to the biological similarity of the two species" (p. 74). That seems right, although our data suggest that the nonartifactual component of the correlation in log potencies is rather small.

For another discussion of these issues, see Krewski *et al.*,[24] who show among other things that the artifactual correlation between potency and dose holds even in the multistage and Weibull models; compare Kodell *et al.*[25] Previous work along these lines is reported by Rieth and Starr.[26] (They give smaller values for the correlations between δ and ϵ, in the "normalized" lines of their Table 1; we do not know the source of the discrepancy.) For other work on qualitative interspecies correlations, see Piegorsch *et al.*,[27] Gold *et al.*[28,29]

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REFERENCES

1. E. Crouch and R. Wilson, "Interspecies Comparison of Carcinogenic Potency," *J Toxicol Environ Health* **5,** 1095–1118 (1979).
2. L. Bernstein, L. S. Gold, B. N. Ames, M. C. Pike, and D. G. Hoel, "Some Tautologous Aspects of the Comparison of Carcinogenic Potency in Rats and Mice," *Fund Appl. Toxicol.* **5,** 79–86 (1985).
3. L. Bernstein, L. S. Gold, B. N. Ames, M. C. Pike, and D. G. Hoel, "Toxicity and Carcinogenic Potency," *Risk Analysis* **5,** 263–264 (1985).
4. E. Crouch, R. Wilson, and L. Zeise, "Tautology or Not Tautology?" *J. Toxicol. Environ. Health* **20,** 1–10 (1987).
5. L. Zeise, E. Crouch, and R. Wilson, "Reply to Comments: On the Relationship of Toxicity and Carcinogenicity," *Risk Analysis* **5,** 265–270 (1985).
6. G. Goodman and R. Wilson, "Predicting the Carcinogenicity of Chemicals in Humans from Rodent Bioassay Data," *Environ. Health Perspect.* **94,** 195–218 (1991).
7. L. S. Gold, C. B. Sawyer, R. Magaw, G. M. Backman, M. de Veciana, R. Levinson, N. K. Hooper, W. R. Havender, L. Bernstein, R. Peto, M. C. Pike, and B. N. Ames, "A Carcinogenic Potency Database of the Standardized Results of Animal Bioassays," *Environ. Health Perspect.* **58,** 9–319 (1984).
8. L. S. Gold, M. de Veciana, G. M. Backman, R. Magaw, P. Lopipero, M. Smith, M. Blumenthal, R. Levinson, L. Bernstein, and B. N. Ames, "Chronological Supplement to the Carcinogenic

Potency Database: Standardized Results of Animal Bioassays Published Through December 1982," *Environ. Health Perspect.* **67,** 161–200 (1986).
9. L. S. Gold, T. H. Slone, G. M. Backman, R. Magaw, M. Da Costa, P. Lopipero, M. Blumenthal, and B. N. Ames, "Second Chronological Supplement to the Carcinogenic Potency Database: Standardized Results of Animal Bioassays Published Through December 1984 and by the National Toxicology Program Through May 1986," *Environ. Health Perspect.* **74,** 237–329 (1987).
10. L. S. Gold, T. H. Slone, G. M. Backman, S. Eisenberg, M. Da Costa, M. Wong, N. B. Manley, L. Rohrbach, and B. N. Ames, "Third Chronological Supplement to the Carcinogenic Potency Database: Standardized Results of Animal Bioassays Published Through December 1986 and by the National Toxicology Program Through June 1987," *Environ. Health Perspect.* **84,** 215–286 (1990).
11. L. S. Gold, N. B. Manley, T. H. Slone, G. B. Garfinkel, L. Rohrbach, and B. N. Ames, "The Fifth Plot of the Carcinogenic Potency Database: Results of Animal Bioassays Published in the General Literature Through 1988 and by the National Toxicology Program Through 1989," *Environ. Health Perspect.* **100,** (1993).
12. R. Peto, M. C. Pike, L. Bernstein, L. S. Gold, and B. N. Ames, The TD_{50}: A Proposed General Convention for the Numerical Description of the Carcinogenic Potency of Chemicals in Chronic-Exposure Animal Experiments," *Environ. Health Perspect.* **58,** 1–8 (1984).
13. L. S. Gold, L. Bernstein, J. Kaldor, G. Backman, and D. Hoel, "An Empirical Comparison of Methods Used to Estimate Carcinogenic Potency in Long-Term Animal Bioassays: Lifetable vs. Summary Incidence Data," *Fund Appl. Toxicol.* **6,** 236–269 (1986).
14. E. A. C. Crouch, "Uncertainties in Interspecies Extrapolations of Carcinogenicity," *Environ. Health Perspect.* **50,** 321–327 (1983).
15. C. Whipple, "Toxicity and Carcinogenicity," *Risk Analysis* **5,** 261–264 (1985).
16. B. N. Ames and L. S. Gold, "Too Many Rodent Carcinogens: Mitogenesis Increases Mutagenesis," *Science* **249,** 970–971 (1990); *Letters* **250;** 1498 (1990); **250;** 1645–1646 (1990); **251;** 12–13 (1991); **251;** 607–608 (1991); **252;** 902 (1991).
17. B. N. Ames and L. S. Gold, "Chemical Carcinogenesis: Too Many Rodent Carcinogens," *Proc. Nat. Acad. Sci. USA* **87,** 7772–7776 (1990).
18. B. N. Ames and L. S. Gold, "Endogenous Mutagens and the Causes of Aging and Cancer," *Mutation Research* **250,** 3–16 (1991).
19. B. N. Ames and M. K. Shigenaga, and L. S. Gold, "DNA Lesions, Inducible DNA Repair, and Cell Division: Three Key Factors in Mutagenesis and Carcinogenesis," *Environ. Health Perspect.* **101,** Supp. 4 (1993).
20. D. Freedman and H. Ziesel, "From Mouse to Man: The quantitative Assessment of Cancer Risks," *Statistical Sci.* **3,** 3–56 (1988).
21. D. Freedman and W. Navidi, "On the Multistage Model for Carcinogenesis," *Environ. Health Perspect.* **81,** 169–88 (1989).
22. D. Freedman and W. Navidi, "Ex-smokers and the Multistage Model for Lung Cancer," *Epidemiology* **1,** 21–29 (1990).
23. A. Shlyakhter, G. Goodman and R. Wilson, "Monte Carlo Simulation of Rodent Carcinogenicity Bioassays," *Risk Analysis* **12,** 73–82 (1992).
24. D. Krewski, D. W. Gaylor, A. P. Soms, and M. Szyszkowicz, "Correlation Between Carcinogenic Potency and the Maximum Tolerated Dose: Implication for Risk Assessment" (Washington, D.C., September 6, 1990).
25. R. L. Kodell, D. W. Gaylor, and J. J. Chen, "Carcinogenic Potency Correlations: Real or Artifactual? *Journal of Toxicology and Industrial Health* **32,** 1–9 (1991).
26. J. P. Rieth and T. B. Starr, "Experimental Design Constraints on Carcinogenic Potency Estimates," *J. Toxicol. Environ. Health* **27,** 187–296 (1989).
27. W. W. Piegorsch, G. J. Carr, C. J. Portier, and D. G. Hoel, "Concordance of Carcinogenic Response Between Rodent Species: Potency Dependence and Potential Underestimation," *Risk Analysis* **12,** 115–121 (1992).
28. L. S. Gold, L. Bernstein, R. Magaw, and T. H. Slone, "Interspecies Extrapolation in Carcinogenesis: Prediction Between Rats and Mice," *Environ. Health Perspect.* **81,** 211–219 (1989).
29. L. S. Gold, N. B. Manley, and B. N. Ames, "Extrapolation of Carcinogenicity Between Species: Qualitative and Quantitative Factors," *Risk Analysis* **12,** 579–588 (1992).