Table 1. Summary of genetic toxicity STTs and rodent tests, positive and tested. Cochran-Armitage linear trend test, $P < 0.007$.

STTs positive/ tested	Rodent	
	Positive/ tested	Positive (%)
4/4	14/17	82.3
3/4	10/15	66.7
2/4	7/14	50.0
1/4	7/11	63.6
0/4	6/16	37.5
Total	44/73	60.3

Since a linear response fits the data better than a step function comparing "no STT positive" to "any STT positive," the data indicate that additional STTs provide additional information (as would be expected biologically). Since individual STTs are inexpensive relative to a long-term rodent test, the additional information is cost-effective (*5*).

All of this begs the question, "Are rodent tests predictive of humans?" Readers interested in that question might study (*6*) and (*7*) and reach their own conclusions.

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Response: Young (*1*) raises two issues: (i) the comparative performance of a battery of short-term tests (STTs) versus the *Salmonella* mutagenesis assay (SAL) for predicting rodent carcinogenicity and (ii) the false-positive rate associated with rodent carcinogenicity studies.

Regarding the first issue, we concluded that, for a set of 73 chemicals evaluated by the National Toxicology Program (NTP), a battery of four STTs was not significantly more predictive of the results of rodent carcinogenicity studies than was SAL alone (*2*). Young apparently questions this conclusion, asserting that, for the battery of four STTs (including SAL), a trend test shows that there is "a good correlation between the number of STT positives and the probability of a positive rodent result." This is misleading because the "good correlation" of the battery reflects primarily the high predictivity of SAL. When SAL is excluded from the battery and separate comparisons are made for SAL positive and SAL negative chemicals, Young's trend test analysis shows no significant association between the number of STT positives and rodent carcinogenicity, as indicated in Table 1.

To put this matter into perspective, one could consider a comparison of the predictivity and concordance of the two approaches. Young states that "when all four STTs were positive, the rodent test was positive about 80% of the time." However, the predictivity of a positive SAL is even greater (83%; see Table 1). Young further states that SAL "is 60% concordant [62% actually]" with the rodent test. However, the corresponding concordance of the battery of four STTs is essentially the same, that is, 55 to 66%, depending upon the decision rule employed (*2*). Thus, for the 73 NTP chemicals the predictivity and concordance of the battery of four STTs is similar to that of SAL alone.

Regarding the second issue, Young asserts that rodent carcinogenicity studies have a high statistical false-positive rate. His conclusion is based on what appears to be a misinterpretation of the results of Brown and Fears (*3*) and of Haseman *et al.* (*4*), who emphasized that such high false-positive rates (30 to 44%) would occur only if every statistically significant ($P < 0.05$) increase in tumor incidence were regarded as a biologically meaningful effect. This does not occur in practice because biological as well as statistical factors are taken into consideration in the overall evaluation of the data. Most investigators in this area are familiar with the multiple comparisons issue, and thus it is generally recognized that the actual false-positive rate is much lower than 30 to 44%.

What is the actual false-positive rate? The International Agency for Research on Cancer concludes that "rules which attempt to model the actual decision process indicate that false-positive rates are close to the nominal level" (*5*). The Office of Science and Technology Policy (*6*) reaches a similar conclusion. Moreover, one of us (J.K.H.) (*7*) has estimated that the false-positive rate associated with NTP carcinogenicity studies (such as those used by Tennant *et al.*) is no greater than 7 to 8%. Many NTP "nongenotoxic carcinogens" showed markedly increased tumor incidences at multiple sites and for multiple doses or in three to four sex-species groups, or both. It is extremely unlikely that these striking effects are statistical false-positives, as suggested by Young.

In summary, for the particular 73 chemicals considered by Tennant *et al.* (*2*), the evidence is compelling that the other three STTs did not improve significantly the performance of SAL for predicting rodent carcinogenicity. Additional studies are now in progress to determine whether these results also hold for a second set of chemicals recently evaluated by the NTP.

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Table 1. Performance of a battery of three STTs (excluding SAL) for predicting for carcinogenicity of 73 NTP chemicals.

Proportion of STTs positive	Chemicals positive in SAL [proportion of carcinogens (%)]	Chemicals negative in SAL [proportion of carcinogens (%)]
3/3	14/17 (82)	5/9 (56)
2/3	5/6 (83)	7/14 (50)
1/3	–	6/10 (60)
0/3	1/1 (100)	6/16 (38)
Total	20/24 (83)	24/49 (49)
Cochran-Armitage linear trend test	$P > 0.50$	$P > 0.20$

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