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Letter to the Editor

Correspondence re: R. Peto *et al.*, Effects on 4080 Rats of Chronic Ingestion of *N*-Nitrosodiethylamine or *N*-Nitrosodimethylamine: A Detailed Dose-Response Study. Cancer Res., *51:* 6415–6451, 1991, and K. S. Crump *et al.*, Fundamental Carcinogenic Processes and Their Implications for Low Dose Risk Assessment. Cancer Res., *36:* 2973–2979, 1976.

Cancer risk forms the principal justification of the "Superfund" environmental legislation (1).[1] It is therefore a matter of concern to cancer researchers that this law and the cancer risk assessment, on which it is based, have descended into deepening regulatory chaos (2) and scientific controversy (3, 4). There is a need to reevaluate how science should be used in public policy, how scientific and regulatory responsibilities are to be divided, and the role scientific journals should play in this.

At the heart of the controversy lies a change in the definition of cancer risk first implied in the Delaney amendment (5). The changed definition extrapolates risk by many orders of magnitude beyond the observed evidence (6) and thus incorporates into risk assessment considerations of caution and uncertainty which were traditionally the responsibility of regulators. This changed risk definition blurs the distinction between scientific evidence and speculation and blurs the distinction between scientific and regulatory responsibility.

Cancer risk, thus exaggerated, has produced unacceptable scientific (7) and regulatory consequences that even the United States Environmental Protection Agency considers unacceptable. The EPA[2] Science Advisory Board (8), the United States Department of Health and Human Services (9), and the EPA Office of Drinking Water (2) have all rejected the exaggerated definition of risk of the Delaney Amendment.

The journal *Cancer Research* has unwittingly contributed to the risk assessment crisis by publishing, and thereby making scientifically respectable, two speculative articles. Crump *et al.* (10), a biostatistical model for low dose extrapolation, contains the unsupported assumption that cancer response is linear at doses below the observed range. A complicated mechanistic rationale, complicated mathematics, and publication in *Cancer Research* have effectively blurred the distinction between scientific evidence and unsupported assumption in this model. In the minds of lay persons and law makers this model has helped to turn into scientific fact what still is an unsupported assumption.

For years, this model has been used indiscriminately to regulate chemicals at low dose. When there was strong evidence for a classical threshold, as with the human carcinogen arsenic (11, 12), EPA used the Crump model to override that evidence (7) and was rebuffed by the EPA Science Advisory Board for that misinterpretation (8).

Recently, Peto, a coauthor in the earlier Crump *et al.* paper, again used the linear assumption to interpret a cancer bioassay beyond the experimental data, insisting in the abstract . . . . The linear relationship *observed* at low rates (below 1 ppm) suggests that under these experimental conditions . . . a dose of 1 ppm NDEA [nitrosodiethylamine] will cause about 25% liver neoplasms, 0.1 ppm will cause about 2.5% liver neoplasms, and 0.01 ppm will cause about 0.25% liver neoplasms *etc.*, *with no indications of any "threshold"* (13).

The data allow a different interpretation and Peto acknowledges as much on page 6441. Table 5A (in Peto *et al.*) shows a clear (zero) threshold at 0.26 ppm for esophagus neoplasms in NDEA treated male rats. All other data have non-zero control values, show a strong positive response above 0.5 ppm and a weak response between 0.26 and 0.5 ppm. Below 0.26 ppm, responses fall within the control range, lack a trend, and do not shorten the life of the animals (time to death). It is possible to interpret all data as indicating a common threshold below 0.26 ppm for cancerous and noncancerous lesions in all organs, roughly coinciding with the induction of indirect effects of diethylnitrosamine (15).

The results do not validate the cancer risk assumption in the Delaney Amendment or the Crump *et al.* model. Peto presents no evidence for cancer at doses below 0.03 ppm but clearly suggests in the abstract that cancer risk continues beyond the lowest data point.

Law makers in 1980 acted under the impression that linear cancer risk was a scientific fact, an impression partially based on publications like that of Crump *et al.* They believed that cancer risk left no moderate choice, that only extreme regulatory measures could protect public health and they legislated on that belief (1). The assessments by the EPA-Science Advisory Board and Health and Human Services show that this impression was mistaken, that the scientific evidence, at least for two specific substances (8, 9), is indeed compatible with moderate regulation.

The two assessments allow the interpretation that the scientific community is searching for a resolution of the risk assessment crisis and the long-running controversy about low-dose risk. The EPA-Science Advisory Board and Health and Human Services appear to have decided that risk assessment should be limited to the evaluation of the evidence and should not speculate beyond. It is also possible to conclude that both favor a clear distinction between scientific and regulatory responsibility and that the threshold of the observed evidence should mark the line between the two.

The journal *Cancer Research* can help this process of clarification by assuring a clear distinction between scientific evidence and speculation and by rejecting interpretations that would blur that distinction. In Peto *et al.*, this involves only a few words of interpretation in an otherwise fine study. In Crump *et al.*, it constitutes the essence of the statistical model.

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[1] Reproductive toxicity and neurotoxicity are also considered in Superfund but only cancer risk is claimed to extend to extremely low dose, literally to single molecules.

[2] The abbreviation used is: EPA, Environmental Protection Agency.

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Reply

If there is an appreciable background incidence of cancer that arises in untreated experimental animals by mechanisms similar to those of some carcinogen, then there are good general reasons to expect that, within the range of doses of that carcinogen that are low enough for the extra risk not to swamp this background risk, the extra risk will be approximately proportional to the dose of the test agent (1). Thus, when there is such a background one should expect "low-dose linearity" but, when there is no such background there may be no strong reason to do so. In nice conformity with these prior expectations, when we reported (2) the largest ever experimental study of nitrosamine carcinogenesis, the results indicated low-dose linearity only for liver tumors (where the background risk is easily demonstrable) and not for esophageal tumors (where it is not). When, as for liver tumors, both theory and experiment indicate approximate low-dose linearity, it is not good science for Stöhrer (3) to interpret (on grounds that appear to be partly political) the data as indicating a threshold.

On p. 6443 (2) we noted that, to determine whether or not a particular low dose had any carcinogenic effect, a standard significance test involving only that and lower doses may not be an appropriate statistical procedure, for if, as with liver neoplasms, there are highly significant carcinogenic effects of treatment that appear to show an approximately linear trend in risk over a range of doses that includes 0.5 and 1.0 ppm (of nitrosamines in the drinking water) and no suggestion of any divergence from this linear trend at any lower dose then the general theoretical arguments that lead one to expect linearity at low doses become even stronger. Such data therefore provide some evidence that, throughout the dose range below 1 ppm (*i.e.*, not only in the restricted range 0.1–1 ppm where hazards are indicated by conventional significance tests), there is approximate proportionality of the excess risk to the applied dose rate.

Those were our conclusions, and they remain valid. We followed these conclusions, however (p. 6445) with the statement that although the approximate linear trend that we observed at low doses provides us with "a reasonably reliable estimate (despite the practical impossibility of direct confirmation) of the effects of ppb nitrosamine concentrations *on rats* under these experimental circumstances, it does not provide reliable information as to the effects of ppb nitrosamine concentrations *on humans*, and it would be a serious distortion of these experimental results to suggest otherwise" (original italics). There are serious scientific objections (4, 5) to the common EPA practice of basing "risk assessment" chiefly on evidence from laboratory animals, but Dr. Stöhrer is wrong to include linear extrapolation (within one species) among them, as long as (*a*) there is an appreciable background cancer risk arising from mechanisms comparable to those of the action of the test agent, and (*b*) the induced cancer risk does not much exceed this background. Thus, for example, it could be reasonable to use linear extrapolation to assess the approximate effects of prolonged exposure to environmental tobacco smoke from the demonstrated hazards of active smoking.

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