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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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