

expected value of  $V$  with this approach also is negatively biased with

$$a = 2f_x f_y + f_x^2 (f_y/1 - f_x) + f_y^2 (f_x/1 - f_y)$$

$$b = 2f_x h + f_x^2 (h/1 - f_x) + \sum_{i=1}^s [f_i^2 (f_x/1 - f_i)]$$

$$c = 2f_y h + f_y^2 (h/1 - f_y) + \sum_{i=1}^s [f_i^2 (f_y/1 - f_i)]$$

and

$$d = h^2 - \sum_{i=1}^s [f_i^2 (f_x/1 - f_i)] - \sum_{i=1}^s [f_i^2 (f_y/1 - f_i)],$$

where  $f_i$  is  $n_i/N$  for each of the  $s$  species other than  $x$  and  $y$ . When I reanalysed my data, using the  $t$ -test as described above, the negative correlations I reported disappeared completely, as Harris predicted.

References 13–15, 18 and 19 in my initial Letter, as well as other sources<sup>2</sup>, can be consulted for abundant evidence justifying my assumption that the spatial arrangements of individuals in local areas may reveal the nature of interactions among them. Naturally, experimentation would be the next step.

I thank W. T. Starmer for taking me 'back to basics', showing me two of the possible ways of treating intraspecific nearest neighbours and pointing me in the direction of others.

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## Mutagenic effect of aromatic epoxy resins

ANDERSEN *ET AL.*<sup>1</sup> state that 'the demonstration of a mutagenic effect of aromatic epoxy resins (that is, those based on bisphenol acetone, BPA) indicates a genetic hazard, including a cancer risk, for humans exposed to these compounds'. We challenge the rationale for this rather definite conclusion. Epoxides as a class are reactive chemicals and in general are alkylating agents. However, in the extrapolation from direct alkylation of DNA to defining the risk of mammalian mutagenicity or carcinogenicity, other major factors must be considered, in particular the dose reaching target tissues/molecules and the importance of the detoxication or intoxication mechanisms which are only properly defined in the *in vivo* situation.

Such considerations are being included in a series of mutagenic assays to test for possible mammalian genotoxicity<sup>2–5</sup>. But at present, *in vivo* studies must be consi-

dered as giving more definitive data than work carried out *in vitro* or in non-mammalian systems.

It is surprising, therefore, when a BPA-based epoxy resin which has been tested several times for carcinogenic potential with negative results is now considered to be a potential carcinogen based on the results of a microbial mutagenicity assay (although it does indicate that *in vivo* mutagenicity studies are required). Andersen *et al.*<sup>1</sup> review some of the animal data, but we would summarise the available cancer studies as follows:

(1) Andersen *et al.* do not critically evaluate the paper by Kotin and Falk<sup>6</sup>. The latter do not provide sufficient experimental details, in particular the route and frequency of exposure, to enable any conclusion to be drawn from their work, but it can be stated that there was definitely more than one exposure to the test material.

(2) The results of Weil *et al.*<sup>7</sup> are not correctly interpreted by Andersen *et al.* They carried out two skin painting experiments. In the first, probably 30 mice were used and one papilloma was noted. In a repeat study, probably using 40 mice, no skin tumours occurred. The mortality of these mice was quite normal; there are no grounds for stating that the study was inadequate as the mice were dead in less than 24 months—the mice used by this laboratory lived their normal life span as evidenced by Weil's other data, and an average life span of about 18 months in mice is quite acceptable<sup>8</sup>.

(3) Hine *et al.*<sup>9</sup> carried out a skin painting study, not referred to by Andersen *et al.*, in which a typical BPA-based epoxy resin was tested in both mice and rabbits without any skin tumours developing. Further, reference by Andersen *et al.* to the injection site sarcoma data only must be questioned as these tumours are not generally accepted as providing any reasonable indication of carcinogenic hazard (for example, gold and hypertonic saline were shown to be carcinogenic by this route<sup>10,11</sup>).

In conclusion, the preponderance of available evidence indicates that currently used BPA-based resins present no carcinogenic hazard to man. This assessment is not changed by the evidence of Andersen *et al.*, although their findings should definitely stimulate further mutagenic studies.

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ANDERSEN *ET AL.* REPLY—Granville challenges our conclusions based on positive Ames tests with aromatic epoxy resins (AER). He claims that our conclusions are too definite and argues that tests in mammals would much better predict the risk for mutagenic and carcinogenic activity in humans. Conventional animal tests use only about 200 animals and are, therefore, rather insensitive. Only strong carcinogens will be identified by such tests<sup>1,2</sup>.

The animal tests that were made on AER in the 1950s and early 1960s are inconclusive. The tests which did not show tumours are faulty and insufficient. In several cases, exact information on the experimental details is lacking. Only about 100 mice and 50 rabbits were used<sup>3,4</sup>. The rabbit experiment was, according to the authors themselves, rather insensitive. Nevertheless, Granville claims that the experiments indicate that AER does not represent a cancer hazard, despite the experiment—albeit another one suffering from deficiencies in the description of the test conditions—in which tumours were produced by the resins<sup>5</sup>.

Thus our strong suspicions of dangerous effects of AER are in no way disproved by existing animal tests, nor will any new animal carcinogenicity test be able to give definite proof for non-carcinogenicity. It is our opinion that the doubt which might exist about the mutagenic or carcinogenic activity of a chemical substance should be used for the benefit of people who will come in contact with the substance. The only clear proof that AER is not dangerous to humans could come from experiments proving that AER cannot reach the relevant target molecules, namely DNA. As long as these experiments have not been made, AERs must be considered as mutagens and carcinogens.

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