Cancer risk from exposure to occupational acrylamide

Recently the results of a comprehensive epidemiological follow up study of cancer mortality in cohorts with occupational exposure to acrylamide was published. With the exception of a weak significance for a raised incidence of pancreatic cancer the study arrived at conclusions similar to the conclusion that there is “little evidence for a causal relation between exposure to acrylamide and mortality from any cancer sites”. The study updates and confirms an investigation 10 years earlier of the same cohorts. The analysis was based on standardised mortality ratios (SMRs) in comparison with United States national or relevant county mortality statistics. It exemplifies the shortcomings of epidemiological studies to formulate initial testable aetiological hypotheses for human studies is an effective, accepted method commonly used in occupational epidemiological research. Animal studies can be particularly helpful when investigators are faced with a paucity of extrapolation from animal data to human epidemiological data, especially having in mind the recognized carcinogenic potential of acrylamide. This practice does not preclude, however, the exploratory investigation of other non-implicated sites as long as the related findings are interpreted in the light of their hypothesis generating nature.

We agree that for many of the initial cancer sites examined in our study, the statistical power to detect a moderate excess in mortality (1.5 to twofold or greater) was low, a point considered in the discussion section of our paper. However, the power to detect a twofold or greater excess in lung cancer, the end point of primary concern, at least in part, to one or more carcinogenic agents will increase the risks of all cancer sites to a level that can be detected with epidemiological methods.

We were fully justified in using cancer site specific findings as the focus of our epidemiological investigation. The use of cancer site specific findings from experimental animal studies to formulate initial testable aetiological hypotheses for human studies is an effective, accepted method commonly used in occupational epidemiological research. Animal studies can be particularly helpful when investigators are faced with a paucity of extrapolation from animal data to human epidemiological data, especially having in mind the recognized carcinogenic potential of acrylamide. This practice does not preclude, however, the exploratory investigation of other non-implicated sites as long as the related findings are interpreted in the light of their hypothesis generating nature.

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Graham et al overlook a fundamental point—occupational cohort studies of the type we used to evaluate cancer mortality risks among workers exposed to acrylamide are neither designed nor necessarily well suited for quantitative risk assessment. Occupational cohort studies are purposely not designed to detect small excesses in the range of 5%–15% deemed by Granath et al unacceptable. The primary reason for this is that excesses of this magnitude could easily be due, at least in part, to one or more confounding factors. Observational epidemiological studies usually cannot discriminate among such small mixed effects, and are generally most useful for detecting increases in risk that exceed 50%–100% as these are unlikely to be due to uncontrolled confounding. Considerations of statistical power notwithstanding, the fact remains that our study is the largest and most comprehensive study of exposure to acrylamide conducted to date,
and will continue to provide useful epidemiological information through future updates and analysis.

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Dose-response relation between acrylamide and pancreatic cancer

In their 1999 study of workers exposed to acrylamide, Marsh et al conducted an SMR analysis, and fitted several relative risk regression models to the data. In each analysis, they found the risk of pancreatic cancer increased by about twofold for workers in the highest cumulative exposure group, but risk of pancreatic cancer did not increase monotonically with cumulative exposure in any of their analyses. Duration of exposure was monotonically related and mean intensity showed a nearly monotonic relation with risk of pancreatic cancer.

The cut-off points Marsh et al chose for the cumulative exposure groups are based on multiples of current and proposed regulated levels of exposure intensity. Because these cut off points resulted in small numbers of expected deaths in the low and intermediate exposure groups, 1.08 and 2.74 respectively, we have regrouped the data to attempt to obtain more stable standardised mortality ratios (SMRs). These results are presented in table 1 and indicate a monotonic dose-response pattern with the SMRs increasing from 0.80 to 1.31 to 2.26.

Table 1 Observed deaths, expected deaths, and SMRs for cancer of the pancreas, all United States workers, 1950–94, local county comparisons, two lowest exposure groups combined

<table>
<thead>
<tr>
<th>Cumulative exposure (mg/m²·y)</th>
<th>Obs</th>
<th>Exp</th>
<th>SMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.001</td>
<td>30</td>
<td>37.50</td>
<td>0.80</td>
<td>0.54 to 1.14</td>
</tr>
<tr>
<td>0.001–0.29</td>
<td>5</td>
<td>3.82</td>
<td>1.31</td>
<td>0.35 to 3.05</td>
</tr>
<tr>
<td>&gt;0.30</td>
<td>9</td>
<td>3.98</td>
<td>2.26</td>
<td>1.03 to 4.29</td>
</tr>
</tbody>
</table>

In part based on the absence of a pattern of monotonically increasing risk with increased cumulative exposure, Marsh et al argue that “our findings for cancer of the pancreas should be interpreted with caution, in the context of an exploratory analysis to generate hypotheses.” Nevertheless, given the sufficient evidence in experimental animals for the carcinogenicity of acrylamide, this study plays an important part in the evaluation of safety for occupational exposures to acrylamide.

When data are sparse, it is not always clear how best to choose cut-off points; the grouping we have shown results in a finding that is more compatible with the findings for duration and for intensity of exposure. It would be interesting to see if a regrouping of the exposure categories alters the results of the analyses based on internal comparisons.

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Burns replies

We appreciate the interest taken in our study by Freedman. At the heart of the discussion are the interpretation of the significance of the statistics in our study, the lack of significance in others. A critical point in valuing causation is the weight of the evidence to be placed upon the non-significant increase of non-specific exposures found in human studies of amyotrophic lateral sclerosis compared with the weight placed upon controlled animal studies specific to the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D).

In free with Freedman the undue reliance upon significance is ill advised. He is correct that the case-control studies cited in our paper showed increased odds ratios, but there is no evidence that any subjects were actually exposed to 2,4-D. The exposures were limited to pesticides, agricultural chemicals, and herbicides. The cohort studies examined workers who were definitely exposed to 2,4-D and thus provide a more valid assessment of risk even though they are less powerful than the case-control studies.

The cohort studies of 2,4-D do not consistently show increased risk of ALS.

The associations found in the case-control studies are clearly unsupported by the experimental studies that have been conducted on 2,4-D. Environmental causes of ALS remain unknown. If future epidemiological studies investigate the neurotoxicity of herbicides such as 2,4-D, the researchers must improve upon the status quo of surrogate exposure information used in case-control studies or perform further studies of the 2,4-D workers. Epidemiologists must make a commitment to quality exposure assessment of individual pesticides, perhaps coupled with biomonitoring, to assess the putative health concerns associated with pesticides.

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Bullying in hospitals

As victims of bullying and proponents of emotional intelligence in the health profession we read with interest the article on workplace bullying.  

Kavimaki et al did not mention whether the responses were anonymous. Identified responses may underestimate the incidence of bullying in the cohort. Given that previous studies (mentioned by the authors in the discussion) have shown a considerable percentage of victims deciding to resign as a result of bullying, it is a pity that the article by Kavimaki et al did not contain similar data. The other two issues that should have been included were the duration of the bullying, and how many bullies are actually aware that they are bullies. These can be answered by asking the question: Have you subjected your colleagues to such bullying behaviour? With doctors and nurses constituting 58% of the victims, we wonder whether the authors could reanalyse their data to see whether there is a higher incidence of bullying in the high stress specialties—such as adult intensive care and neonatal intensive care. We would also like to know whether the victims in their study were offered any counselling by their institutions, and if so, the nature and impact of the counselling.  

Emotional intelligence is defined by the five emotional quotients of self awareness of feelings, emotional self regulation, self monitoring and goal setting, empathy, social skills, and communication skills. According to Goleman, “The rules for work are changing, we’re being judged by a new yardstick: not just how smart we are, or our expertise, but also how well we handle ourselves and each other.” Emotional intelligence is considered more important than intelligence quotient (IQ) in enabling people to function well in society. We suggest that emotional intelligence, which can be taught, can be an important solution in reducing the incidence of bullying in the workplace.

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