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 large at 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 of this kind to detect moderate influences of specific causative factors on cancer mortality or incidence. The investigators state that they have carried out the most definitive study of the human cancer risk due to lifetime exposure to acrylamide conducted to date. The results, however, pose questions. Could unacceptable risks be detected? Which risks would have been expected? For the workers in the United States the average cumulative exposure is given as 0.25 mg/m³/year. (We assume this to correspond to exposure of the whole factory staff.) The results are far from ideal for epidemiological studies. The main reasons for this are: the incompleteness of data for smoking, and the healthy worker effect. The healthy worker effect leads to a deficit in death rates from all causes, in the present study by about 20% for all cancer except cancer of the lung. Deficits in SMR for all malignant neoplasms and for certain tumour types are also often significant, although with a disturbing influence of a significantly increased SMR for lung cancer in an earlier period. (The significant decrease in deaths from lung cancer as well as deaths from diseases of the circulatory system from 1925–83 to 1984–94 would be compatible with a drastic reduction in smoking, before 1984.) It is expected that the healthy worker effect comprises cancer, at least to some extent, as well as other causes of death.

A straightforward way of overcoming the healthy worker effect is a within cohort analysis of the regression of mortalities or incidences on the estimated dose. Marsh et al. have done this for each of a few selected tumour sites. Due to too few observed deaths in each dose interval the statistical power of this material is, however, too small to show anything.

This analysis of individual sites, avoiding a pooling of data that would increase the statistical power, illustrates the widespread dogma that different cancer types are affected specifically by different chemicals. It has been shown for a few mutagenic carcinogens including acrylamide that a linear multiplicative model, $P = P_0 (1 + \beta D)$, can be fitted to experimental cancer incidence data and, for radiation, to human data. It exemplifies the shortcomings of 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 improbable. Considerations of statistical power not only reduce the ability to evaluate the all important specificity to individual sites but also 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 aetiologial 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 occupational epidemiological data. 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 the one sided 5% significance level was in the excellent range (0.87), as would be the power to detect a similar excess of pancreatic cancer in a future update of this cohort.

Granath et al. take issue with our update of a cohort of acrylamide workers from three United States plants’ claiming that “it exemplifies the shortcomings of studies of this type to detect moderate influences of specific causative factors on cancer mortality or incidence.” To support their case they overlooked a small but “unacceptable” increase in cancer risk they performed a crude quantitative risk assessment. Granath et al. suggested that we perform a within cohort dose-response analysis with all malignant neoplasms as the end point as a means of attaining greater statistical power. They further contend that initial focus on specific cancer sites implicated in previous experimental animal studies is mostly a consequence of the pattern of background incidences in the animal strain used. Although choosing a generic health outcome such as all cancer sites combined will certainly increase statistical power, it also greatly reduces the ability to evaluate the all important specificity of an exposure-response relation. It is unlikely that even the most potent carcinogenic agent will increase the risks of all cancer sites to a level that can be detected with epidemiological methods.

F GRANATH
Department of Medical Epidemiology, Karolinska Institute, Stockholm, Sweden

L EHRENBERG
Department of Genetic and Cellular Toxicology, Stockholm University, Sweden

M TORNQVIST
Department of Environmental Chemistry, Stockholm University, Sweden

Correspondence to: M Tornqvist
margaret.tornqvist@mlu.ki.se


Marsh et al reply

Granath et al take issue with our update of a cohort of acrylamide workers from three United States plants’ claiming that “it exemplifies the shortcomings of studies of this type to detect moderate influences of specific causative factors on cancer mortality or incidence.” To support their case they overlooked a small but “unacceptable” increase in cancer risk they performed a crude quantitative risk assessment. Granath et al. suggested that we perform a within cohort dose-response analysis with all malignant neoplasms as the end point as a means of attaining greater statistical power. They further contend that initial focus on specific cancer sites implicated in previous experimental animal studies is mostly a consequence of the pattern of background incidences in the animal strain used. Although choosing a generic health outcome such as all cancer sites combined will certainly increase statistical power, it also greatly reduces the ability to evaluate the all important specificity of an exposure-response relation. It is unlikely that even the most potent carcinogenic agent 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 aetiologial 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 occupational epidemiological data. However, the power to detect a twofold or greater excess in lung cancer, the end point of primary concern, at the one sided 5% significance level was in the excellent range (0.87), as would be the power to detect a similar excess of pancreatic cancer in a future update of this cohort.

Granath 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.

G M MARSH
A O YOKU
L J LUCAS
L C SCHALL
Department of Biostatistics, Room A410 Crabtree Hall, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261, USA
Correspondence to: Professor G M Marsh
gmarsh@vms.cis.pitt.edu

E VAN WINGAARDEN
J C HERNANDEZ
Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7409, USA
L M BALL
Department of Environmental Sciences and Engineering
Correspondence to: Dr M R Schulz
mrs6388@email.unc.edu

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 a 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. Therefore, 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 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/m3 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>37.5</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 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.

M R SCHULZ
I HERTZ-PICCOTTO

Correspondence to: Dr M R Schulz
mrs6388@email.unc.edu

Amotrophic lateral sclerosis and occupational exposure to 2,4-dichlorophenoxyacetic acid

Burns et al report a significant excess of deaths due to amotrophic lateral sclerosis (ALS) in a cohort of Dow employees potentially exposed to the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D), but then argue against the plausibility of a causal association, concluding that the association “is not consistent with previous human or animal studies”. This conclusion and the authors’ characterisation of the results of the two epidemiological studies seem to rely entirely upon the significance of the statistics, which downplays the importance of their finding. Firstly, the authors state that “cohort studies of people with exposure to 2,4-D have not reported increased mortality of ALS,” citing two studies, both of which have limited power to detect the risk of ALS. One of the two studies assessed risk in a cohort that was quite young with a relatively short follow-up, and would therefore be unlikely to detect an increased risk for a disease such as ALS, which has a much older median age at onset. Burns et al then go on to state that “exposure to pesticides and agricultural chemicals, with reported ORs of 1.4, 2.0, and 3.0,” although the associations do not reach significance. Finally, Burns et al refer to a case-control study, which found a significant association between ALS and pesticide exposure, but, they emphasise, “did not find a significant association of exposure to herbicides.” The association between ALS and exposure to herbicide was increased, however, and the lack of significance reflected, at least in part, small numbers.

None of this is meant to say that the finding of a significant association between ALS and 2,4-D is conclusive. The finding is, however, consistent with several previous studies, and instead of being played down, warrants serious attention in future studies.

M FREEDMAN
Division of Cancer Epidemiology and Genetics,
National Cancer Institute, USA
Correspondence to: Dr M Freedman
mf101e@nih.gov

Correspondence to: Dr C J Burns
cburns@dow.com

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,1 the absence of sufficient evidence in others. A critical point in claiming causation is the weight of the evidence to be placed upon the non-significant increase of non-specific exposures found in human studies of amotrophic lateral sclerosis compared with the weight placed upon controlled animal studies specific to the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D).

In line with Freedman there is a need for reliance upon significance is ill advised. He is correct that the case-control studies cited in our paper showed increased odds ratios,2, 3 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.4 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.

C J BURNS
The Dow Chemical Company, 1803 Building, Midland, MI 48674, USA
Correspondence to: Dr C J Burns
cburns@dow.com
