

## CORRESPONDENCE

### 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.<sup>1</sup> With the exception of a weak significance for a raised incidence of pancreatic cancer the study arrived by and 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.<sup>2</sup> 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 carcinogenic potential of 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/m<sup>3</sup>.y. (We assume this to correspond to exposure of the whole factory staff to 0.25 mg/m<sup>3</sup> for 365 8 hour working days). At an alveolar ventilation rate of 0.2 l/kg.min this exposure would mean a cumulative uptake of about 9 mg acrylamide per kg body weight. This dose corresponds to a lifetime (70 years) uptake of 0.35 µg/kg.d. According to the estimate of the United States Environmental Protection Agency<sup>3</sup> this would correspond to a cancer risk of 1.6×10<sup>-3</sup>. An estimate based on the multiplicative model<sup>4</sup> would arrive at roughly a 3 times higher risk, 5×10<sup>-3</sup>. With a cancer mortality in the western world countries of 0.18, these figures correspond to a 1%–3% increase of the cancer mortality risk (RR)—that is, an RR of 1.01–1.03. As about one fifth of the workers were defined as exposed (at ≥10–3 mg/m<sup>3</sup>.y) the relative risk in the exposed group due to inhalation of acrylamide may have been about 1.05–1.15.

Although it is doubtful that these risk increments could be considered negligible, they would not be detectable in a study of the present kind. As uptake through the skin often occurs in addition to inhalation of acrylamide it is possible that the true risk increments are considerably higher. If we assume the total relative risk (from inhalation plus dermal uptake) to be in the range of 1.1–1.2, it is a pertinent question whether this risk increment is detectable within the large body of material studied by Marsh *et al.*<sup>1</sup>

Like many other materials of similar kinds the data are far from ideal for epidemiological analyses. The main reasons for this are the skewed distribution of duration of employment, 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 causes except cancers. 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.*<sup>1</sup> 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 carcinogens. It has been shown for a few mutagenic carcinogens including acrylamide that a linear multiplicative model,  $P_j = P_j^0 (1 + \beta D)$ , can be fitted to experimental cancer incidence data and, for radiation, to human data.<sup>5</sup>  $P_j$  and  $P_j^0$  are the total and background risks of tumour at site  $j$ ,  $D$  the dose and  $\beta$  a relative risk coefficient that is (at least approximately) the same for all tumour sites  $j$ .  $\beta$  is thus applicable to pooled data for groups of sites or for all (responding) sites. Although analysis of death risks associated with specific tumours has its indisputable value, a restriction of estimation of significance to individual sites leads as a main effect to a loss of statistical power. For related reasons the identification of certain sites as "interesting", with reference to response to acrylamide in animal experiments, is mostly a consequence of the pattern of background incidences  $P_j^0$  in the animal strain used.

The authors of the paper<sup>1</sup> possess information of extreme value in further efforts to clarify the carcinogenic potency of acrylamide. In view of the importance of this question we urge the authors of the paper to continue their work, particularly with analyses of regression on pooled data, primarily for all cancers, with and without exclusion of sites related to smoking.

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### Marsh *et al* reply

Granath *et al* take issue with our update of a cohort of acrylamide workers from three United States plants<sup>1</sup> 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 contention that we 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 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 extant epidemiological evidence such as in the case 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 of our study 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* as 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.<sup>1</sup> In each analysis, they found 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.<sup>1,2</sup> 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

Cumulative exposure (mg/m <sup>3</sup> .y)	Obs	Exp	SMR	95% CI
<0.001	30	37.50	0.80	0.54 to 1.14
0.001-0.29	5	3.82	1.31	0.35 to 3.05
>0.30	9	3.98	2.26	1.03 to 4.29

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."<sup>1</sup> Nevertheless, given the sufficient evidence in experimental animals for the carcinogenicity of acrylamide,<sup>3</sup> 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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### Amyotrophic lateral sclerosis and occupational exposure to 2,4-dichlorophenoxyacetic acid

Burns *et al*<sup>1</sup> report a significant excess of deaths due to amyotrophic lateral sclerosis (ALS) in a cohort of Dow employees potentially exposed to the herbicide 2,4-dichlorophenoxyacetic (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 relevant 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 rates of ALS," citing two studies,<sup>2,3</sup> 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,<sup>2</sup> 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 have shown no significant association in several studies" (emphasis added).<sup>1</sup>

In each of the three case-control studies cited, however, ALS was positively associated with pesticides or agricultural chemicals, with reported ORs of 1.4,<sup>4</sup> 2.0,<sup>5</sup> and 3.0,<sup>5</sup> although the associations do not reach significance. Finally, Burns *et al* refer to a case-control study,<sup>7</sup> which found a significant association between ALS and pesticides, but, they emphasise, "did not find a significant association of exposure to herbicides".<sup>1</sup> 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.

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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,<sup>1</sup> and 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 (ALS) compared with the weight placed upon controlled animal studies specific to the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D).

I agree with Freedman that undue reliance upon significance is ill advised. He is correct that the case-control studies cited in our paper showed increased odds ratios,<sup>2,5</sup> but there is no evidence that any subjects were actually exposed to 2,4-D as 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.<sup>6,7</sup> 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.<sup>1</sup>

Kavimaki *et al*<sup>1</sup> 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

Kivimaki *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.<sup>2</sup> 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.<sup>3</sup> 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.”<sup>4</sup> Emotional intelligence is considered

more important than intelligence quotient (IQ) in enabling people to function well in society.<sup>5</sup> We suggest that emotional intelligence, which can be taught, can be an important solution in reducing the incidence of bullying in the workplace.<sup>6</sup>

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