

Postscript

LETTERS

Methodological problems in a case-referent study based on a register of occupational asthma

Meredith *et al.*¹ performed a case-referent study to investigate asthma caused by isocyanates. They claimed that the results indicated that isocyanate asthma occurs at low 8 hour average exposure (around 1.5 ppb); for exposures above 1.125 ppb there was about a threefold increased risk, however, this was of limited significance (odds ratio (OR)=3.2, 95% confidence interval (95% CI) 0.96 to 10.6; $p=0.06$). They also concluded that their study, by contrast with other studies, had a higher risk of isocyanate asthma in smokers and people with atopy.

The study design is original as cases were recruited from a register of occupational asthma. A case-referent study based on a register of cases with both the disease and the exposure of interest is new. I think the design requires some discussion as it may introduce severe bias.

A typical case-referent study selects cases with a certain disease—for example, asthma—from a hospital register or in a population survey.² The referents should be selected to give an unbiased estimate of frequency of exposure in the study base.³ The study base of a register, including cases of occupational asthma, is the population that if the case had asthma would be reported to the register. Therefore, the authors of this study matched the referents to the cases by reporting doctor and factory or production area. Then they measured or estimated the exposure level for both cases and referents and found that the average 8 hour exposure was higher among cases. This design has certain weaknesses illustrated by the following hypothetical situations:

(1) Assume that the exposure in the production area is homogenous. Then both cases and referents would have the same exposure and the conclusion would be that the risk was independent of exposure level.

(2) Assume that the reporting doctor only knows a proportion of incident cases, a reasonable assumption. If seeing the doctor is dependent on exposure level, a bias is obvious.

(3) Assume that there was no increased risk at all in the workplaces at the current exposure but that there was exposure to irritants, which varied within the production area. Then cases with asthma would probably be more likely to report problems with their asthma to the occupational health physician. There would also be an association with all substances the concentration of which was correlated with the irritant.

(4) Assume that there was no causal association between the exposure and the occurrence of asthma at the current levels. As asthma is common among people with atopy, the study would certainly indicate that atopy was a risk factor in combination with the exposure.

Some of these biases could be avoided if there was some specific test that with certainty established the causal association

between asthma and the exposure among the cases. Asthma caused by isocyanates can with some certainty be established by provocation, but the study by Meredith *et al.* included no routine provocation test.

If it is presumed that all the reported cases really are caused by isocyanates, a rather improbable assumption according to the case definition, the conclusion by the authors that isocyanate asthma occurs also at very low exposures without any threshold could be made without doing any case-referent analysis. They could just simply measure the exposure of the cases and conclude that the lowest measured exposure obviously caused isocyanate asthma. It is obviously impossible to determine any other threshold.

Is there a proper design of a case-referent study based on cases identified through a register where the association between exposure and outcome is already established? If the disease is caused by short term high exposure a case cross over design seems possible.⁴ However, that design requires a very accurate determination of when the disease started, which rarely is possible for asthma. Another possibility is to estimate the study base from which the cases are recruited—for example, in the study by Meredith *et al.*¹ the number of person-years in the different production areas where the cases were detected should have been estimated. This requires that all or most incident cases from that area are known or there should at least not be any differential reporting of cases between the areas. Thus, the design of this study is interesting but includes many possibly biases of which a just a few were discussed in the paper. The conclusions that the risk of isocyanate asthma is increased at concentrations around 125 ppb, and is more common among people with atopy and smokers are questionable.

B Jarvholm

Department of Public Health and Clinical Medicine,
Umea University, SE-901 85 Umea, Sweden;
bengt.jarvholm@envmed.umu.se

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Authors' reply

We are grateful to Jarvholm for his comments on our paper. The specified aim of our study was to quantify the relation between the level of occupational isocyanate exposure and risk of developing asthma. The usual approach to this problem is a cohort study in an exposed workforce, possibly with a nested case-referent analysis. A register based case referent study of the type described by Jarvholm would be unsuitable for this purpose because the source population would be ill defined, selection of a appropriate referents difficult,

and reliable assessment of their exposure almost impossible. We used the SWORD reporting scheme, not as a register, but as a convenient means of identifying workplaces from which clusters of cases of asthma attributed to isocyanates have been reported, and in which exposure to isocyanate had been assessed by an occupational hygienist; we then investigated those sites. A few additional cases were identified during the course of the investigation and were included in the analysis. In company A, where most of our cases worked, all employees were subject to close respiratory supervision throughout their employment, including pre-employment assessment; in company B, the occurrence of the cluster of cases was recognised by the occupational health department and the workers in the relevant areas investigated. We are therefore reasonably confident that no cases were missed.

We were careful to select referents from workers who were exposed to isocyanates and were under the same level of surveillance as the cases to avoid some of the biases outlined by Jarvholm. We agree that the close matching of cases and referents probably reduced the sensitivity of the study, but we thought that it was more important to do that than to risk selection bias as described in his second hypothetical scenario. As we also acknowledged in the article, we cannot exclude the theoretical possibility that the cases of asthma were not caused by isocyanates, but by other chemicals present in the plants. Confounding is a risk in any observational study, although not necessarily a source of bias, but the other agent would have to be closely correlated with the isocyanate exposure to account for our findings.

The cases had work related asthma as diagnosed by an occupational physician. Nearly all had a history of symptoms associated with work that improved on days away from work and had had serial respiratory function tests that supported the diagnosis. Challenge tests are rarely used in the United Kingdom; very few centres undertake them, and without proper facilities are considered dangerous. However, as explained in the article, in company A people with respiratory symptoms were removed from exposure to isocyanates until they had recovered and then gradually returned to their previous work under very close supervision with serial respiratory function testing, which in practice was a form of challenge test.

The purpose of undertaking a case-referent study was not to establish that it is possible to develop isocyanate asthma at low exposures, but to examine the exposure-response relation. We do not conclude from our data that there is a threshold below which isocyanate exposure is safe. The concentration of 1.25 ppb was arbitrarily chosen because it was the median time weighted average exposure in the referent group in company A. Despite the fact that all estimated 8 hour time weighted average exposures were within the maximum exposure limits, those subjects whose estimated 8 hour time weighted average was greater than 1.25 ppb seemed to be at increased risk of occupational asthma. However, the data were also compatible with a linear exposure-response relation in which the odds of asthma increased by 1.08 for every 0.1

ppb. A much larger study would be needed to test these two possible exposure-response relations fully.

**S Meredith
J Bugler
R Clark**

MRC Clinical Trials Unit, 222 Euston Road, London
NW1 2DA, UK

Correspondence to: Dr S Meredith, Department of
Preventive Medicine, Vanderbilt University,
Nashville, Tennessee 37232-2637, USA;
sm@ctu.mrc.ac.uk

Response to a case of occupational asthma due to the enzymes phytase and β -glucanase

In their recent short report, O'Connor *et al*¹ describe a case of occupational asthma due to the enzymes phytase and β -glucanase. Their patient experienced asthma-like symptoms at work (wheezing and cough), had positive skin prick tests and specific IgE to both enzymes (by radioallergosorbent test), and reacted to both materials in separate inhalation challenge tests. None of 22 other employees in the same factory were reported to have experienced respiratory symptoms at work.¹

In a German language paper presented at the 38th Annual Meeting of the German Association of Occupational and Environmental Medicine in 1998,² we reported findings of a systematic clinical investigation of 49 research and development employees working with the enzymes phytase and xylanase. This investigation was undertaken after detecting airway sensitisation to dusts containing phytase in two analytical laboratory employees.

Forty nine employees with potential contact to the enzyme completed a questionnaire and underwent physical examination and lung function testing. Among 32 employees with findings of conjunctivitis, rhinitis, or bronchitis further immunological tests were undertaken on a voluntary basis (skin prick test, $n=17$; specific IgE by enzyme allergosorbent test (EAST), $n=31$). Also, nasal provocation challenge tests were performed in 13 employees, including all 11 with a positive skin prick test to phytase. Nine of these employees had a positive specific IgE test to phytase as well. All 11 had a positive nasal challenge response to phytase. The positive response rate was 62.5% among eight employees considered to have the highest potential exposure. Based on this investigation, it was concluded that phytase has a high sensitising potency. Our assessment of this is consistent with that of O'Connor *et al* and Doekes *et al*.^{1,3}

After implementation of extensive control measures to prevent enzyme exposure in this research and development facility, all employees now report being free of work related respiratory symptoms. This favourable experience agrees with the hypothesis that enzyme

related asthma can be avoided by implementing best practice procedures for health surveillance and environmental control when working with enzymes.⁴

**A Zober
K Strassburger**

Occupational Medicine and Health Protection
Department, BASF Aktiengesellschaft, D-67056
Ludwigshafen, Germany

X Baur
University of Hamburg 22083 Hamburg, Germany

Correspondence to: Professor A Zober
andreas.zober@basf-ag.de

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Nasal, eye, and skin irritation in dockyard painters

Chen *et al* report irritant symptoms experienced by dockyard painters in both Scotland and China.¹ In 1985, I reported² on painters involved in submarine refit work in one of Her Majesty's dockyards in England. I too found a high prevalence of symptoms of irritation. However, and possibly of more concern, the painters in my study also reported narcotic symptoms. In 106 painters, 74 (70%) reported episodes of light headedness. Some 28 (26%) reported that, on occasion, this had led them to stop painting and seek fresh air. A solvent taste in the mouth was reported by 75 (71%). Some reported that their partners complained of a solvent smell to their breath persisting into the evening after a day shift.

The full face air fed masks then meant to be in use as respiratory protective equipment were considered to be bulky, uncomfortable, and to restrict vision. They were almost universally disliked; instead, some painters preferred to wear half face masks and tolerate eye irritation from the paint vapours, and for "touch ups" sometimes used no respiratory protective equipment.

The messages were that painters, and perhaps their supervisors as well, needed to be reminded of the importance of narcotic symptoms; if a less potentially toxic paint system could not be found, additional consideration needed to be paid to ventilation and a search made for a more comfortable air fed mask.

My study predated both Control of Substances Hazardous to Health Regulations (COSHH)³ and Personal Protective Equipment at Work Regulations (PPE)⁴: one might have hoped that their principles and implementation would have led to fewer irritant symptoms than still apparently being experienced by the workers in the study of Chen *et al*. Finally, as well as the points in their paper, I would suggest occupational physicians with painters in their care remain vigilant for narcotic symptoms. There seems to remain scope for improved control.

G Woodroof

Occupational Health and Safety Unit, Derriford
Hospital, Plymouth PL6 8DH, UK;
gerard.woodroof@phnt.swest.nhs.uk

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CORRECTION

Environmental tobacco smoke and lung function in employees who never smoked: the Scottish MONICA study. R Chen, H Tunstall-Pedoe, R Tavendale. 2001;**58**:563-8.

In figures 1 and 2 the vertical axis in both of the lower graphs should be FVC.

NOTICE

**Environment and health:
regional decisions: global
impact. Environment and Health
Seminar. 17 April 2002.
University of Leicester, UK.**

The Institute for Environment and Health in Leicester, UK, are holding a 1 day open seminar to debate how public, special interest groups, scientific and policy concerns, and decisions made in developed countries can influence decision making and subsequent impacts on environment and health in developing countries.

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