Aromatic solvents: the not so sweet side

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In their published article, Alif *et al* report the findings from a carefully conducted longitudinal study showing the effects of occupational exposures on lung function decline between the ages of 45 and 50 years.[1] Data from 767 participants in the Tasmanian Longitudinal Health Study (TLHS) were examined: 'ever' exposure to aromatic solvents was associated with an excess decline in FEV_1 over that expected by ageing (15.5 mL/year (95% CI −24.8 to 6.3)) and in FVC (14.1 mL/year (95% CI −28.8 t0 −0.7)); as was 'ever' exposure to metals (FEV_1 (11.3 mL/year (95% CI −21.9 to −0.7)) and FVC (17.5 mL/year (95% CI −34.3 to −0.8))). This accelerated decline was also apparent for cumulative exposure to aromatic solvents, and interestingly, despite having lower overall exposures, the decline was greater in women than in men. The authors also found an excess decline in FEV_1 in those with ever exposure to gases and fumes and to chlorinated solvents and in FVC in those exposed to 'other' solvents.

Accelerated decline in spirometric measures is important. It may, of course, herald future development of respiratory disease but has been shown to be a predictor of all-cause mortality, independent of smoking.[2] As respiratory clinicians, we are often drawn towards trends in FEV_1, but there is also evidence suggesting the importance of FVC as an overall marker of lung health.[3] The TLHS cohort was recruited at the age of 7 years, and therefore, importantly (and unusually), the authors were able to adjust for childhood socioeconomic status, a potentially important predictor of lung function decline.

While associations between occupational exposures and lower lung function have been observed in a number of cross-sectional studies, there are only a limited number of published longitudinal studies which can provide stronger evidence to support a causal relationship.

Alif *et al* have previously reported cross-sectional studies from the TLHS and demonstrated associations between fixed airflow obstruction and exposure to biological dusts, pesticides and herbicides[4] and to metals and chlorinated solvents.[5] So it is intriguing that in this longitudinal study, the only persistent effect was for metals, and that an association with aromatic (but not chlorinated) solvents was apparent. This may be due to loss of power given the relatively small numbers exposed, particularly to pesticides. Of note, only 9% of the original cohort were included in this study; while this is a low response rate, it probably still allows for valid internal associations to be made.

As the authors explain, longitudinal studies often use the contemporaneous job to define exposure history. Any effects on respiratory health are likely to develop over years and pertinent exposures may have occurred many years ago. Using this approach makes assumptions about the stability of the individual's occupations and associated exposures, which increases the chance of misclassification. Thus, a major challenge in occupational epidemiology is how best to collect accurate data relating to lifetime exposures. Gathering data during individual interviews is expensive and subject to recall bias and differential misclassification; furthermore, it often requires narrative data to be synthesised into a structure appropriate for analysis. The use of a job exposure matrix (JEM) is, therefore, the most common method used to systematically collect lifetime occupational exposure histories and minimises these biases. But it still requires manual coding. A free web-based JEM entitled OSCAR (occupations self-coding automatic recording, www.oscar.com), where individuals can self-complete their job history, which is then coded using automated software, has recently become available and may be of interest to researchers planning future studies.[6]

While there are a few other reported longitudinal studies which used a JEM to investigate the effects of occupational exposures on lung function, this is the first to report the effect of solvents. de Jong *et al*[7] studied 2527 participants in a Dutch cohort for 25 years and found that both recent and cumulative exposures to pesticides were associated with an excess decline in FEV_1 with high exposure to pesticides, especially in ever-smokers, of −6.9 mL/year (95% CI −10.2 to −3.7). Sunyer *et al*[8] found no association with occupational exposure to vapours, gases, dusts and fumes in over 6000 young adults from the European Community Respiratory Health Study (ECRHS) followed for 9 years. A study of 4267 non-asthmatics from the Swiss Study on Air Pollution and Lung Diseases in Adults (SALPALDIA) cohort found, in adjusted analyses, an increased incident rate ratio of prebronchodilator airflow obstruction in those working with biological and mineral dusts, gases, fumes and vapours over a 10-year period.[9] A systematic review of the effects of welding found no effect on lung function.[10] It is intriguing that such variation in associations is seen not only in the cross-sectional studies of the TLHS referred to above, but also across these longitudinal studies. Indeed, the THLS study, which has the fewest participants and the shortest duration of follow-up (mean of just 5 years), shows the greatest decline in lung function. One question is whether these associations are due to chance, and it would have been interesting to see statistical adjustment made for multiple hypothesis testing. It will be intriguing to see if this accelerated decline is sustained in this population in future studies of the TLHS cohort.

Nonetheless, the observed size of effect for aromatic solvents was not insignificant and is similar in terms of both magnitude and gender difference to the results from a study of over 1000 Danish woodworkers reported by Jacobsen *et al*.[11] In this study, they found a dose–response relationship in female workers between cumulative wood dust exposure and FEV_1 decline over 6 years. In adjusted analyses, an additional decline of 14.5 and 28.0 mL/year for females in the medium and highest exposed groups, respectively, was observed compared with non-exposed or low-exposed females. However, other studies, including those described above, have shown occupational exposures to be associated with a much smaller excess decrease in FEV_1 of around 7-8 mL/year after adjusting for age and sex.[12] More recently, a study of the effects of cleaning products on 6235 participants, again from the ECRHS, found an excess decline in occupational cleaners in FEV_1 of 4.3 mL/year and in FVC of 7.1 mL/year over a 20-year follow-up.[13]

Solvents are volatile organic compounds and include a number of subgroups, including the aromatic solvents, such as benzene, naphtha, toluene, xylene and chlorinated solvents, containing a chlorine group and include, for example, carbon tetrachloride, trichloroethylene

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and methylene chloride. As the authors describe, they are widely used in very different industries and this may explain why the variation in the effect of different classes of solvents was seen.

If the association reported by Alif *et al* is real, what are the possible mechanisms? Only prebronchodilator spirometry was reported in the follow-up study, so an obvious explanation is that the lower lung function was due to asthma arising from concurrent exposure to asthmagens (eg, wood dusts, isocyanates contained in glues or welding stainless steel, which contains chromium). However, the authors carefully enquired about asthma status (both historical diagnosis and current symptoms) and adjusted accordingly in the analysis, making unrecognised asthma unlikely. Solvents can be highly irritant, so another explanation is that this is an irritant-induced mechanism due either to very high peaks of exposures (unlikely, given the industries involved) or chronic low-dose exposures leading to persistent changes in the airway mucous membrane and, in the longer term, remodelling of the airways with accelerated decline in spirometric values. Airflow obstruction was not the predominant change observed by Alif *et al* which makes occupational COPD an unlikely explanation but given the reduction in both FEV_1 and FVC other diagnoses, such as interstitial lung disease and solvent neuropathy, should also be considered.

The observed differential effects of aromatic solvents on FEV_1 decline by sex are intriguing and were not observed with any other exposures. It may be explained by differences in the occupation; of those exposed to aromatic solvents, women tended to work in art and woodwork and as life science technicians and men were most frequently painters, carpenters, plumbers, pipefitters and firefighters. Alternatively, it may be due to hormonal differences. While lung function is known to decline around the time of the menopause (which may have been relevant for some participants), the differential effects with solvent exposure may be attributable to hormonal effects on solvent metabolism.[14] Again, this may be a chance finding and it will be interesting to see if the results are replicated in future studies and if they remain unique to this particular group of solvents.

We know, surprisingly, little about the effects of occupational exposures on lung function, which makes this study very welcome. The results will be of interest not only to clinicians seeking alternative explanations for the presence of airflow obstruction in individual patients in clinic, but also to employers and regulators. How can we best use this knowledge? Undoubtedly, exposure to potentially hazardous agents should be reduced to the lowest reasonably practicable level using preventative measures in order of priority, the so-called 'hierarchy of controls'. This starts with the elimination of the substance, and if that is not possible then substitution of the product with a less hazardous one or use of engineering controls. Respiratory protection should only ever be used as a last resort. The study reported here provides cautious evidence to support an association between key agents and lung function decline but these associations will need to be confirmed in other studies and further work to understand possible mechanisms and pattern of disease are needed. Importantly, the deleterious effects on health from industrial exposures have not gone away and every effort should be made to minimise risks associated with these exposures and to prevent respiratory (and other) morbidity arising from people's jobs.

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