CORRESPONDENCE

Exposure to asphalt or bitumen fume and renal disease

EDITOR,—The correspondence from Dittmer and Armitage provides further support for a causal association between exposure to various hydrocarbons and the development of renal disease. Since 1912, some case reports, cross-sectional studies, and animal experiments have provided compelling evidence for a causative role for hydrocarbon exposure in the development of both tubular and glomerular lesions.

We now report the case of a road worker exposed to asphalt and bitumen fumes who presented in 1990 at the age of 36 with nephrotic syndrome. He was then normotensive, had proteinuria with 24-hour urinary protein excretion of 5.0 g/day. However, he currently is hypertensive with serum creatinine 170 µmol/l, urea 10.4 mmol/l, serum albumin 30 mmol/l, and 24-hour urinary creatinine excretion of 5.0 g.

Searches of the scientific literature in 1990 and subsequently have not found any specific references to exposure to asphalt or bitumen and renal disease. We therefore investigated the issue further by means of (a) detailed fume analyses, and (b) a study of the renal health of road workers exposed to asphalt or bitumen.

It was clear from the fume analyses that exposures in this industry include a wide range of aromatic and aliphatic hydrocarbons. Time weighted average exposures ranged from 0.4 to 8.9 mg/m³ measured as total organic fume (not including inorganic particulates), but short term or peak fume exposures were as high as 300-900 mg/m³. During all his years exposed to these fumes, the patient had never been provided with or worn respiratory protective equipment.

The study of renal health included 92 people regularly exposed to asphalt or bitumen fumes as road workers, 38 hard rock quarry workers not occupationally exposed to hydrocarbons, and 43 office workers also not exposed to hydrocarbons.

Each participant was given a questionnaire which included questions about occupational and recreational exposures and medical history including renal disease. Urine and blood samples were collected for urinary chemistry, blood biochemistry, and microscopic analyses. Any person with an abnormal finding on blood or urine analyses were tested and examined by a nephrologist to assess the presence or otherwise of renal disease.

The criteria which determined an abnormal test result were as follows: (a) persistently raised serum creatinine >120 µmol/l; (b) persistently raised serum urea >7.5 mmol/l; (c) persistent microscopic haematuria or pyuria; (d) 24-hour urinary protein >150 mg/day; or (e) corrected creatinine clearance <90 ml/min.

Table 1 Age and blood pressure

<table>
<thead>
<tr>
<th></th>
<th>No exposure</th>
<th>Quarry</th>
<th>Exposure to bitumen or asphalt</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>People (n)</strong></td>
<td>43</td>
<td>38</td>
<td>92</td>
<td>173</td>
</tr>
<tr>
<td><strong>Age (mean)</strong></td>
<td>39</td>
<td>32</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td><strong>BP (mean systolic)</strong></td>
<td>133</td>
<td>131</td>
<td>133</td>
<td>133</td>
</tr>
<tr>
<td><strong>BP (mean diastolic)</strong></td>
<td>86</td>
<td>83</td>
<td>83</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 2 Renal disease

<table>
<thead>
<tr>
<th>Number of people</th>
<th>No exposure</th>
<th>Quarry</th>
<th>Exposure to bitumen or asphalt</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-existing renal disease (%)</strong></td>
<td>43</td>
<td>38</td>
<td>92</td>
<td>173</td>
</tr>
<tr>
<td><strong>Idiopathic renal disease (%)</strong></td>
<td>4 (9.3)</td>
<td>2 (5.3)</td>
<td>1 (1.1)</td>
<td>7 (4.0)</td>
</tr>
<tr>
<td><strong>Haematuria</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>12 (13.0)</td>
<td>12 (6.9)</td>
</tr>
</tbody>
</table>

Table 3 Renal function

<table>
<thead>
<tr>
<th>People (n)</th>
<th>No exposure</th>
<th>Quarry</th>
<th>Exposure to bitumen or asphalt</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematuria</strong></td>
<td>43</td>
<td>38</td>
<td>92</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>4</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td><strong>Rapid decrease in creatinine</strong></td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td><strong>At least one abnormality (%)</strong></td>
<td>4 (9.3)</td>
<td>2 (5.3)</td>
<td>24 (26.1)</td>
</tr>
</tbody>
</table>

**p<0.01.

We think that chronic glomerulonephritis and chronic tubulointerstitial nephritis are renal diseases which may result from exposure to hydrocarbons—as such as those experienced from asphalt or bitumen fumes generated during road making.

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Authors’ reply.—The report of Douglas and Carney of a further case of renal disease associated with hydrocarbon exposure, together with their cross-sectional study of those with prolonged exposure to bitumen and asphalt further strengthens the case for an association between renal disease and hydrocarbon exposure. Yaqoob et al have also convincingly shown, that in particular, proteinuria may be associated with hydrocarbon exposure.7

This highlights the need for a careful occupational and social history to be taken at the time of presentation. This case also highlights the need for performing a renal biopsy in adults presenting with unexplained proteinuria. If interstitial nephritis is found then a short course of steroids may result in a dramatic improvement in renal function.8

The presence of renal disease was determined as pre-existing or idiopathic according to the following criteria. Pre-existing renal disease: (a) family history or history of renal disease; (b) normal renal ultrasound. Idiopathic renal disease: (a) no known cause for abnormalities; (b) abnormal creatinine, urea, and creatinine clearance; (c) abnormal proteinuria; or (d) abnormal urinalysis—haematuria or pyuria.

The findings of the study are summarised in tables 1–3.

We concluded from this study that: (a) workers regularly exposed to asphalt or bitumen fumes were far more likely to have evidence of early stage renal disease than those working in a quarry or office; (b) workers regularly exposed to asphalt or bitumen fumes were far more likely to have at least one abnormal renal function test than those working in a quarry or office; and (c) the renal dysfunction was non-specific, but the overall findings were consistent with previous findings—such as those from the similar study done by Yaqoob et al.8


epoxy resin fumes. If there was evidence of significant renal damage then it may also be wise to counsel the patient to avoid further contact with the substance. Indeed in our case, the patient found that his general health improved dramatically when direct contact with the material was avoided. Evidence of general industrial health and possible compensation or litigation also need to be considered.

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Cancer risk in the rubber industry: a review of recent epidemiological evidence

EDITOR—Although the comprehensive review of the rubber industry reported by Kogevinas et al only considers papers published after 1982, several of these studies relate to groups of workers from much earlier eras—for example, 1910 for the German study, 1946 for the British Rubber Manufacturers' Association (BRMA) study—and Veyes studies.1,2 By considering the findings of these earlier rubber workers along with studies of more recent groups of workers we are getting a picture of 80 years of cancer experience in the industry, which is not the same as the situation that exists today.

It should also be borne in mind that the very large cohort studies—such as the 34 000 workers in the BRMA study—have a much greater statistical power than those of the smaller studies, in which confounding factors and the role of chance are more difficult to evaluate. This does not seem to have been taken into account and indeed Kogevinas et al tell us that they have not "paid much attention to statistical significance". This is disappointing, however, looking at the overall picture (see figure 1 of our review) is a small consistent picture (see figure 1 of our review) is a small but consistent excess risk for bladder cancer even in studies conducted in relatively late periods. There is a lack of detailed exposure information in most studies but it is probable that β-naphthylamine was not used in these late periods. We agree with Straughan that it is difficult to conclude that the observed small excess risk is due to a late effect of early exposures.

The findings of the large BRMA study are, indeed, more stable (statistically) than those of studies in the Nordic or other countries, but they are not necessarily either more or less confounded than those of other studies. We understand Straughan's plea for a full meta-analysis in which large studies are not given the same weight as small studies. The variability of exposures over time, geography, and process argue against performing a meta-analysis which presumes homogeneity of exposure.

It is commendable that the BRMA has been and continues to be actively involved in examining risk of cancer among workers in the rubber industry. Whatever the outcome, the BRMA study initiated by the BRMA will do justice to the concluding sentence of our paper: "The preventive measures taken in the rubber industry in recent years may decrease risks, but this has not been documented yet in epidemiological studies"

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2 Veyes studies1 (4 140 000 workers) followed up for 40 years. The relatively large size of this domestic epidemiology enable us to conclude, with considerable confidence, that in the United Kingdom occupational leukaemia was never a factor and that the problems of bladder cancer were due to the use from the 1940s with the discontinued use of chemicals contaminated with β-naphthylamine. These studies also showed a small but nevertheless significant excess of stomach, lung, pharyngeal, and oesophageal cancers. With more detailed analysis, however, and consideration of confounding and socioeconomic factors, the occupational importance of these excesses seems to be less clear as time goes on. Geographical and confounding factors and a lack of a clear time-dose response also lessen the possibility of occupational causes.

Having expressed our confidence in the United Kingdom findings, I re-emphasise that they are largely based on results from an earlier generation of rubber workers and that their experience may not be the same as the currently employed in a modern day rubber factory.

So that we may investigate more recent experience, the BRMA initiated a further collaborative project with Birmingham University, to carry out a new study of its members' employees. The collection of data for this study was completed last year and it includes nearly 10 000 male and female workers with at least 12 months of employment and who were first employed between 1982 and 1991. This study involves 42 rubber factories engaged in manufacturing the full range of rubber goods. This cohort study will look at both cancer incidence and mortality and make full use of all available occupational hygiene and exposure data. Examination of the health experience generated by the study to date will take place later this year to see if there is sufficient information for a full analysis to be carried out or whether it would be appropriate to delay this until more data are available. Kogevinas et al have given an interesting and important overview of health hazards observed in rubber worker employed during the past 80 years and I agree with him that even more relevant, modern, and comprehensive epidemiology is necessary if we are to obtain a true picture of the situation today.

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Authors’ reply—We thank Straughan for his comments. We agree that some of the studies we reviewed provide a picture of 80 years of cancer experience in the industry, which is not the situation existing today (in industrialised countries). We tried to identify and report separately results for studies examining workers first employed in the 1980s. These studies did not clearly indicate the absence of an excess risk of cancer. Unfortunately the number of subjects and cancer deaths or cases in these studies is small and does not allow definite conclusions to be drawn yet.

Considerable heterogeneity exists between and within countries in exposure circumstances in the rubber industry. What we did in our review was to give a picture of the risks in this industry. This overall picture does not apply to all countries, nor to all periods. However, an overall picture may highlight conditions that are not easily recognised at a local level. One example is the identification of an increased risk for laryngeal cancer, which had not been previously reported although it seemed consistent between centres. Another example is the bladder cancer risk by Straughan (and others), that the British studies do not indicate an excess risk for bladder cancer after the discontinuation of use of β-naphthylamine. What is usually meant is that there was no significant excess risk, which is correct. What can be distinguished, however, looking at the overall picture (see figure 1 of our review) is a small but consistent excess risk for bladder cancer even in studies conducted in relatively late periods.

There is a lack of detailed exposure information in most studies but it is probable that β-naphthylamine was not used in these late periods. We agree with Straughan that it is difficult to exclude the possibility that the observed small excess risk is due to a late effect of early exposures.

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Inhalation of ammonium nitrate fuel oil explosive (ANFO): and possible concomitant exposure

Editor,—Donoghue1 reports on respiratory symptoms and rhonchi in a miner after exposure to ammonium nitrate fuel oil explosive (ANFO). As diesel fuel is the most commonly used fuel in ANFO the vapour he refers to might be components of diesel fuel. He excludes concomitant exposure to nitrogen dioxide because the inhalation occurred before any explosion took place. Although diesel powered machines are commonly used in underground work he does not discuss possible exposure to diesel exhaust. I have measured up to 15 ppm nitrogen dioxide during construction of a tunnel where the only known source was diesel exhaust. Exposure to such high concentration may contribute to respiratory symptoms and rhonchi. Therefore nitrogen dioxide should not be excluded as a concomitant causative factor.

In a study of the contribution of gases from diesel exhaust and from the blasting cloud caused by ANFO explosive during excavation of a tunnel, diesel exhaust contributed most to the total amounts of nitrogen dioxide in the tunnel.2


1. Hendrick DJ, Landsberg AS, Elston RS, Dowling J, Neely Kazeroni S, Sheliahoar-Hahn S, et al. Propensity to cause proteolytic effects varies between different enzymes, but the data available suggest that many enzymes, including those involved in production of chronic respiratory disease, are more likely to be due to allergy. In considering this, Roman et al.1 have developed a questionnaire based method for collecting data on reproductive outcome and child health which has been applied to a study population comprising (predominantly female) members of the College of Radiographers. We have recently had cause to revisit their report of this work in more detail and have several comments.

The study relies on postal questionnaires for details of adverse outcomes, many congenital abnormalities, and malignancies, but only reports of cancer were validated by reference to national registration schemes and medical records. Comparisons with national cancer registration rates for England and Wales and congenital malformation rates derived from data compiled by the Liverpool Congenital Malformation Registry showed little evidence to suggest an increased risk for cancer or for major congenital malformations. Within specific systems no excess relative risk was found—for example, ‘other musculoskeletal’ malformations and for ‘chromosomal anomalies other than Down’s syndrome’—both dominated by adverse outcomes reported by female radiographers. My particular interest is with the group of six cases of chromosome anomalies other than Down’s syndrome.

Four cases of Turner’s syndrome were reported by female radiographers diagnosed before birth and the pregnancies terminated. The Turner phenotype, recognised in live born infants, is characterised by monosomy X and has a birth incidence in females of 1/2000–1/5000.2 However, the frequency of monosomy X at conception is much higher, occurring in 1–2% of all clinically recognised pregnancies.2 Over 99% abort spontaneously, 70% of these between 11 and 14 weeks gestation.3 The incidence of Turner’s syndrome will vary considerably with different stages of pregnancy and this has implications for the calculation of expected numbers of cases. When evaluating Turner’s syndrome in relation to aetiological influence it is important to have accurate information on the timing and method of diagnosis, and comparisons must be made with appropriate registry data. In around 80% of cases the X chromosome present is maternal, and therefore, by contrast with most cases of Down’s syndrome, an error in meiotic disjunction cannot be attributed to the mother. Of those diagnosed after birth, some are mosaics with a normal cell line and a cell line with one normal and one abnormal X chromosome, and it has been suggested that mosaicism increases the likelihood of survival during pregnancy.4 Such mosaics are assumed to have arisen post-zygotically. Turner’s syndrome is, therefore, most likely to occur due to an error in non-disjunction arising either during spermatogenesis or after fertilisation, and the origin of the error can often be determined by undertaking cytogenetic studies. Consequently, it is unlikely that maternal preconceptional exposure is relevant to the occurrence of the cases of Turner’s syndrome reported to Roman et al.1 although it is possible that events immediately after conception could be implicated in the origin of any with a mosaic karyotype. It is unfortunate that Roman et al.2 provide no karyotypic data nor information on whether the mothers were working as radiographers when they conceived as this would have assisted in the interpretation of this association.

Two further pregnancies with chromosomal abnormalities were described—45,X and X0. Although the possibility of the gross chromosomal anomaly being the result of a familial rearrangement could then have been explored. Trisomy 17 is rather a surprise as this is considered incompatible with embryo development and has not, to my knowledge, been detected by antenatal diagnosis. There must be a possibility that this information is incorrect.

Aetiological mechanisms must be considered when assessing the biological plausibility
The authors deeply regret these errors, which do not alter the conclusions of the cross sectional study. The reprints of the articles should read:


5. ZSCHENDERLEIN, U DANIEL, S SCHUBERTH, TM D ROTHENBACHER, H BRENNER, E FRAISSE, B...
This book, one of a series of reviews produced by the World Health Organization, Environment and Health, provides a useful summary of the current understanding of the risks associated with both asbestos and more importantly, and less well-known, man-made mineral fibres. It provides useful background information on the many types of fibre produced and used in industry and documents comprehensively the amount and types of fibre to be found in materials and in buildings in the United Kingdom. After assessing the difficulties of measuring tiny respirable fibres, it summarises the scientific literature on fibre concentrations to be found in the general and domestic environment and makes estimates of the exposure of the United Kingdom population that might expect over a lifetime. In parenthesis the sort of figures provided show nicely how protagonists in the polarised fibres debate can use figures to strengthen their case. For example, our back-ground exposures to fibres in the environment average between 0.000001 and 0.0001 fibres per ml, a figure that might not unreasonably be reassuring. However, calculating up a total lifetime exposure over 70 years can give a figure as high as almost 30 million fibres in total to which the unsophisticated sounds rather a lot. Those, however, who know something of the lung's anatomy and physiology can take comfort from the fact that we have some 300 million alveoli for these fibres to be shared out among even after a lifetime of exposure so much of them are deposited (which they are not!).

The book summarises the known health effects of asbestos and the, as yet, incomplete but reassuring literature on the epidemiology of workers exposed to other fibres. It then discusses the experimental animal and in vitro evidence with respect to man-made fibres. There is useful discussion of fibre deposition, clearance, and solubility leading to conclusions which in my view are wholly sensible. For asbestos, the authors argue against a general policy of removal and for management in situ unless the material is releasing unacceptable amounts of dust. For man-made mineral fibres, they express caution about the production of fine diameter fibres but point out that almost all the material used commercially is not respirable and that there is no reason to suppose that current levels of exposure pose any risk to the public. All in all this is a remarkably informative book containing much information on mineral fibres that is not readily available elsewhere. The debate about the harmfulness of fibres needs to shift back to the protection of exposed workers and away from theoretical risks to the general population.

ANTHONY SEATON


“Every 10 seconds, another person dies as a result of tobacco use”. This is the stark introductory sentence to this reference book compiled by the World Health Organisation as a source of standardised baseline information on tobacco production, trade, consumption, health effects, and control in WHO member states. The book is divided into two parts: the first, comprising 60 pages, attempts to summarise the global situation in the late 1980s and early 1990s. The second and larger part provides a series of “country profiles” for each of the member states, typically of one or two pages. These list the latest available information on demographic and general health indicators, tobacco production, trade and industry, tobacco consumption, and smoking prevalence by age and sex, and national tobacco control policies and programmes.

Designed as a reference text, this is not a book to be read from cover to cover. Its strength is the near comprehensive coverage of national statistics on tobacco production and use, which are usefully summarised in part one. These may suffice for readers with an epidemiological background, among whom the adverse health effects of smoking are taken for granted. For a more general readership, however, a notable weakness of this book is the paucity of information on health consequences of tobacco use. The relevant chapter in the first part runs to only five pages, including four tables, and is supported by only two references, one of which is yet to be published (although it was cited as a recent article in the Lancet). The discussion of health effects is entirely focused on mortality, mainly from broad groups of causes, such as total mortality, and cancer deaths. Remarkably, there is no mention of the disability and loss of productivity related to cardiovascular and respiratory diseases, nor of the consequences of environmental tobacco smoke. Where the health effects are assessed for individual countries in part two, figures are provided mainly for developed countries and relate principally to estimates of tobacco related deaths and trends in mortality.

This volume provides a powerful reminder, if such is needed, that tobacco use is a global phenomenon, with one third of adults now smoking, and two thirds of these residing in developing countries. The premise upon which the report is that widespread tobacco consumption and public health are mutually incompatible, but readers seeking a comprehensive collation and consideration of the epidemiological evidence will find it rewarding. The WHO intends these data to be a baseline for a global programme of surveillance of smoking habits and tobacco control trends and it is hoped that the book will serve as an inventory of national statistics on tobacco production, trade and consumption, and on smoking prevalence by age and sex, and national tobacco control policies and programmes.

DAVID P STRACHAN


This monograph gives full details of a study conducted to test the Gardner hypothesis—namely, that childhood leukaemia and non-Hodgkin’s lymphoma result from the father’s...
exposures to ionising irradiation before conception. This study has also been published as a paper in the *BMJ*, but this volume goes into far greater details than is available elsewhere. This is very much a book for the concerned specialist reader who wants the technical background to the *BMJ* article.

This study is essentially a record linkage exercise. The exposed fathers (and mothers) were defined as having records with the National Registry for Radiation Workers (NRRW) held by the NRPB. This is a database of over 120,000 people and it was linked with the national register of childhood tumours, a database of over 50,000 children with all types of cancers. Two other data sources on childhood cancers were also included.

For the three sources of data on childhood tumours, controls were found in various ways to ascertain if these children had a father in the NRRW. The parental estimated doses were created from the NRRW. In all a total of 200 fathers and mothers were linked to children with cancer. Eighty two children with leukaemia or lymphoma were linked to fathers’ records at the NRRW, as were 79 control fathers. The corresponding numbers for mothers were 15 and three.

The cases in the original Gardner paper were excluded and the results for fathers showed that case fathers had a 1.77 significant excess risk over control fathers for having a child with leukaemia or lymphoma. However, the risk was associated with the lowest dosages and there were no dose responses in any of the comparisons. In this sense the Gardner hypothesis is refuted!

Furthermore, the risk in mothers was also significantly and greater in magnitude than the fathers. However, the small numbers make this result unreliable and difficult to use to extrapolate risk.

The explanation of the association found in these NRRW members exposed to low doses is not known. It could be chance, it could also be due to misuse of film badges by those in high risk industries. This explanation is unlikely in that the cancers were distributed widely across industries in the United Kingdom and were not confined, by any means, to the nuclear reprocessing or related industries. It may be due to other exposures associated with the wider radiation industries where many other hazardous substances exist as well as ionising irradiation. Finally, it could be some other, more subtle aspect, of wearing a film badge. The authors speculate that this might be associated with the mobility of the parents, thereby linking these results with the Kinlen hypothesis which is based on ideas of infectivity associated with population mixing. They do not produce evidence to suggest that film badge wearers are more mobile than other professions but the differences in behaviour may be more complex.

Further light might be shed on this association when the nuclear industry family study (NIFS) is analysed shortly. This study will answer some criticisms of the present study. For example, it is known that there are differences in behaviour of people within the nuclear industry and those outside it. The NIFS uses internal comparisons and so such differences can be accounted for.

Despite the lack of any explanation of this observation attention is now bound to be focused on other preconceptional and periconceptional exposures in both sexes and their possible links with childhood malignancies.

R A CARTWRIGHT

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Occupational asthma due to amylase.

M L Flindt

*Occup Environ Med* 1998 55: 647

doi: 10.1136/oem.55.9.647b

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