Upper airway inflammation and respiratory symptoms in domestic waste collectors

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Objectives: To compare respiratory symptoms and upper airway inflammation in domestic waste collectors and controls, and to find the association between measures of upper airway inflammation on the one hand and exposure concentrations of organic dust or respiratory symptoms on the other hand.

Methods: In a cross sectional study among 47 waste collectors and 15 controls, questionnaire data on respiratory symptoms were collected. Nasal lavage (NAL), to assess upper airway inflammation, was performed before and after a work shift at the beginning and at the end of the working week. In NAL fluid, cells were counted and concentrations of interleukin 6 (IL6), IL8, tumour necrosis factor-α (TNFα), and IL1β were measured. In collectors, inhalable dust samples were collected in which bacterial endotoxin and mould β(1→3)-glucan were assessed.

Results: Prevalence of respiratory symptoms was higher in waste collectors than in controls. Geometric mean exposure concentrations were 0.58 mg/m³ for dust, 39 EU/m³ for endotoxin, and 1.3 µg/m³ for β(1→3)-glucan. At the end of the week collectors had higher concentrations of total cells and IL8 in NAL before and after a shift than controls (cells, before 1,9-fold p<0.001, after 3,3-fold p<0.01; IL8, before and after 1,8-fold p<0.05), and after/before work shift ratios of total cells were also higher (2,3-fold p<0.06) in collectors than in controls. Cells in NAL fluid consisted predominantly of neutrophils and epithelial cells, whereas eosinophils and mononuclear cells were rarely found. Exposure to dust and endotoxin was associated with concentrations of IL8 after the shift (p<0.05). Increased concentrations of IL8 (p<0.05) and total cells (p<0.01) after the shift were associated with respiratory symptoms. Concentrations of IL6, TNFα, and IL1β were not associated with waste collecting, symptoms, or exposure.

Conclusions: Waste collectors show signs of increased upper airway inflammation and respiratory symptoms compared with controls. Exposure to organic dust probably underlies the inflammation mediated by neutrophils that result in respiratory symptoms.

Increased numbers of workers are involved in the household waste recycling industry, due to the recently introduced separate collection of organic and non-organic household waste in several European countries, as part of national or local environmental management policies. The health risks associated with this type of industry are, however, not yet clear. The few studies that assessed health risks showed that workers in waste handling, particularly workers collecting and processing domestic organic waste for composting, are at risk of developing various health effects—such as respiratory symptoms, systemic influenza-like symptoms, and gastrointestinal problems.

It is not clear which specific exposures and underlying mechanisms may induce these health effects. Waste workers are exposed to a heterogeneous mixture of bioaerosols, gases, and vapours—such as microbial and non-microbial volatile organic compounds. Moulds may induce allergic reactions, and case reports of hypersensitivity pneumonitis and allergic bronchopulmonary aspergillosis have been published. However, allergic diseases are rarely reported in surveys and are unlikely to explain the occurrence of most respiratory symptoms. Alternatively, non-allergic inflammatory reactions may be important, especially due to dust containing endotoxins and β(1→3)-glucans, two known proinflammatory cell wall components of gram negative bacteria and most fungi, respectively. The production of proinflammatory cytokines—such as interleukin-1β (IL1β), interleukin-6 (IL6), interleukin-8 (IL8), and tumour necrosis factor-α (TNFα)—plays a major role in these inflammatory processes.

Recently, two studies have specifically related exposure to bioaerosol to the presence of airway inflammation and subsequent symptoms in workers in the household waste collecting and organic waste composting industry. In these studies, airway inflammation seemed to be mainly mediated by neutrophils and was independent of specific antibodies, probably caused by direct interaction of inflammatory biological agents such as endotoxins or glucans with epithelial tissues and infiltrating white blood cells. As these studies were small and associations were weak, no firm conclusions could be drawn as to which agents and underlying mechanisms may be responsible for the symptoms. Furthermore, due to the small study populations, confounding variables—such as smoking, age, and atopy—could not be dealt with appropriately in these studies.

In the present study we therefore investigated prevalence of respiratory symptoms and upper airway inflammation in a larger population of domestic waste collectors and controls. In all subjects nasal lavage (NAL) was performed before and after the work shift, to assess acute across shift effects, and at the beginning and at the end of the week, to assess across week effects. We assessed differences between waste collectors and controls by comparing concentrations before and after the shift of NAL variables and after/before shift ratios of NAL variables. Associations between markers of upper airway inflammation and exposure concentrations of dust, endotoxin, and glucan, and prevalence of respiratory symptoms were also assessed.

Abbreviations: NAL, Nasal lavage; IL1β, interleukin-1β; IL6, interleukin-6; IL8, interleukin-8; TNFα, tumour necrosis factor-α; PR, prevalence ratio
Upper airway inflammation and respiratory symptoms in domestic waste collectors

Main messages
- Household waste collectors are exposed to microbial agents—such as bacterial endotoxins and β(1–3)-glucans irrespective of the type of rubbish they handle.
- Domestic waste collectors showed signs of increased prevalence of respiratory symptoms and showed increased concentrations of variables indicative of upper respiratory inflammation in nasal lavage compared with controls.
- The exposure to microbial agents is probably associated with the increased prevalence of respiratory symptoms and variables indicative of upper respiratory inflammation in nasal lavage fluid.
- Within the group of waste collectors a dose-response relation between exposure and increased concentrations of inflammatory variables in nasal lavage fluid was found.
- People with respiratory symptoms more often had increased concentrations of inflammatory mediators, especially IL8 and increased numbers of cells in nasal lavage fluid.

Implications
- Exposure of waste collectors to microbial agents is relatively low. Despite the low levels, a respiratory inflammatory response is measurable. The importance of this response for long term effects is not known but needs to be established.

METHODS
Subjects and process description
All domestic waste collectors of the municipal waste collecting facilities of four large Dutch cities (over 100,000 inhabitants) were approached to participate in the current study. Participants were approached by the facilities due to privacy regulations. As a result no information could be obtained on characteristics of non-responders. The medical ethics committee of Wageningen University approved the study and informed written consent was obtained.

Fieldwork was performed from June to September 1997. All domestic waste collectors of the municipal waste collecting facilities of four large Dutch cities (over 100,000 inhabitants) were approached to participate in the current study. Participants were approached by the facilities due to privacy regulations. As a result no information could be obtained on characteristics of non-responders. The medical ethics committee of Wageningen University approved the study and informed written consent was obtained.

Serology
Serum samples were collected by venipuncture. In the serum total IgE and specific IgE against common allergens (grass pollen mix, birch pollen, house dust mite, and cat dander) and specific IgE against mould allergens (Cladosporium species (mixed Cladosporium cladosporioides, Cladosporium cladosporioides, Cladosporium herbarum), Aspergillus species (mixed Aspergillus versicolor, Aspergillus fumigatus, Aspergillus amstelodami, Aspergillus nidulans), Penicillium species (mixed Penicillium brevicompactum, Penicillium expansum, Penicillium notatum, Penicillium commune), and Aspergillus fumigatus) were measured by an enzyme immunoassay as described previously by Doekes et al. All allergens were obtained as lyophilised extracts from ALK (Nieuwegein, The Netherlands).

Nasal lavage
Nasal lavage (NAL) was performed as described previously. Cells in the NAL fluid were counted and a cytospin was made for cell differentials. Interleukin-6, IL8, IL1β, and TNFα were measured in the fluid by enzyme immunoassays (BioSource, Biosource Europe SA, Fleurus, Belgium). The limits of detection were 45 pg/ml for TNFα, 6.2 pg/ml for IL1β, 0.5 pg/ml for IL6, and 2.5 pg/ml for IL8.

Exposure measurements
Full shift personal inhalable dust samples were collected with Gillian P5 portable constant flow pumps at a flow rate of 3.5 l/min in combination with GSP-samplers equipped with Whatman GF/A glass fibre filters (37 mm diameter). Dust, endotoxin, and β(1–3)-glucan concentrations were measured in the fluid by enzyme immunoassays (BioSource, Biosource Europe SA, Fleurus, Belgium). The limits of detection were 0.2 mg/m3 for dust, 4 EU/m3 (endotoxin units) for endotoxin, and 0.26 µg/m3 for glucan.

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Statistical analysis
Data were analysed with SAS statistical software (version 6.12; SAS institute, Cary, NC, USA). Concentrations that were below the limits of detection were assigned a value of two thirds of the detection limit. To assess acute (across shift) effects, after/before shift ratios of total cell, IL8, and IL6 concentrations were calculated. Levels of exposure, NAL variables, and NAL after/before shift ratios were natural log transformed before statistical analysis to ensure normality of the data. Because of high numbers of non-detectable concentrations of TNFα and IL1β in NAL measurements (both 74%), TNFα and IL1β data were dichotomised based on the limit of detection (detectable versus non-detectable), and acute effects were not studied.

A mixed effects models (an extension of multiple regression analysis for correlated observations) were used to analyse relations between NAL and being a collector or control, between NAL and exposure, and between exposure and exposure determinants correcting for first order autocorrelation between repeated measurements and with and without adjustment for potential confounding variables. By including an interaction term for exposure (collector v control) and day of the week (beginning v end of the week NAL) differences in across week changes were tested for. Also, we applied mixed models to obtain estimates of variance of the dependent variable within and between subjects. Mixed model linear
regression analyses were used for continuous variables and mixed model multiple logistic regression analyses for dichotomised variables.\(^a\)

Prevalence ratios (PR) for the respiratory symptoms were calculated by means of log binomial regression analyses\(^a\) to assess the association between health symptoms and outcomes of nasal lavage before and after the shift. As health symptoms were recorded only once per subject, NAL outcomes were first reduced to one value for before and after the work shift, by calculating the median value of repeated NAL measurements per subject. These median values were then dichotomised at the population median (based on the median value of each person): 1442 cells/ml, 190 pg/ml for IL8, 1.1 pg/ml for IL6, and detectable concentrations of TNF\(\alpha\) and IL1\(\beta\).

## RESULTS

Descriptive characteristics of the research population are listed in table 1. Waste collectors were not sensitised to moulds as no specific IgE against mould allergens was found in waste collectors, whereas three control subjects (27%) had increased IgE against mould allergens (all single allergen sensitisation to either Aspergillus species, Cladosporium species or Aspergillus fumigatus). Sensitisation to common allergens was found in both waste collectors and controls; IgE against grass pollen was 22% in collectors and 45% in controls, house dust mite 17% and 9%, birch pollen 0% and 27%, and cat dander 8% and 0%. Total IgE was increased (>100 kU/l) in 25% of the collectors and 0% of the controls. Total IgE was increased (>100 kU/l) in 25% of the collectors and 0% of the controls. Total IgE was increased (>100 kU/l) in 25% of the collectors and 0% of the controls. Total IgE was increased (>100 kU/l) in 25% of the collectors and 0% of the controls.

A total of 268 NAL fluids was collected from waste collectors and 57 from controls. The recovery of nasal lavage fluid was the same for waste collectors and controls both before and after the work shift. Average nasal lavage fluid recoveries were 5.8 ml (SD 1.5) and 5.8 ml (SD 1.4) before the work shift, and 6.2 ml (SD 1.4) and 6.0 ml (SD 1.1) after the work shift for waste collectors and controls, respectively. Cells in NAL fluid consisted predominantly of neutrophils (mean percentage 55% for collectors and 54% for controls) and epithelial cells (both 44%), whereas eosinophils (0.7% and 2.1%) and mononuclear cells (0.3% and 0.2%) were only occasionally present. Results from the regression analyses adjusted for autocorrelation are presented in figure 1. At the beginning of the week, no significant differences between waste collectors and controls in NAL inflammatory marker concentrations were found. Whereas, at the end of the week, waste collectors had higher concentrations of total cells (before shift 1.9-fold \(p=0.099\); and after shift 3.3-fold \(p=0.002\)), and higher concentrations of IL8 (before and after the shift 1.8-fold; \(p=0.016\)) controls. Significant \((p<0.10)\) different effects across the week in waste collectors versus controls were. No significant differences between collectors and controls were found in concentrations of IL6, TNF\(\alpha\), and IL1\(\beta\). Estimated variance components between and within person were 0.89 and 1.00 for total cells, 0.53 and 0.23 for IL8, and 0.79 and 0.39 for IL6. Analyses restricted to people who had worked in their present job for more than 6 months (excluding about 21% of collectors, table 1) gave similar results. Two other possible confounding variables, smoking and age, were not associated with any of the lavage variables, and analyses adjusting for smoking and age did not significantly change the results (regression coefficients that reflect the difference between collectors and controls changed with maximal −7% to +14%, data not shown). Atopic people had higher values for IL8 and lower number of cells, but the differences were not significant. Correction for atopy and a separate analyses for atopic and non-atopic people did not give any different results.

After/before work shift ratios, as a measure of acute effects of NAL inflammatory markers adjusted for autocorrelation are to technical measurement errors. No clear differences in exposure levels for different types of waste (organic versus non-organic or residual waste) were found. Highest dust, endotoxin, and glucan exposures \((p<0.05,\) table 2\) were found while loading waste. Estimated variance in components were 0.51 and 0.34 for dust, 1.08 and 0.22 for endotoxin, and 1.49 and 0.14 for glucan. Thus, day to day variability in exposure was large, relative to differences in exposure between people, especially for endotoxin and glucan.

### Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls</th>
<th>Waste collectors</th>
<th>(n)</th>
<th>(\bar{y}) (SD)</th>
<th>(\bar{y}) (SD)</th>
<th>(\alpha) &amp; (\beta) (months, median (25%–75%))</th>
<th>Median (25%–75%)</th>
<th>Male (%)</th>
<th>Current smoker (%)</th>
<th>Total smokers (%)</th>
<th>(\beta) (months, median (25%–75%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y, mean(SD))</td>
<td>36.4 (6.4)</td>
<td>34.0 (10.2)</td>
<td>16</td>
<td>1.5</td>
<td>47</td>
<td>Duration of employment() (months, median (25%–75%))</td>
<td>78 (49–128) 63 (6–155)</td>
<td>0.0</td>
<td>21.7*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment-duration()</td>
<td>0.0</td>
<td>1.1</td>
<td>0.0</td>
<td>21.7*</td>
<td>65.2</td>
<td>Employed 6 months (%)</td>
<td></td>
<td>86.7</td>
<td>100.0*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(\alpha\) *p<0.05 \(\) test waste collectors \(\) controls.

### Table 2

<table>
<thead>
<tr>
<th>Inhalable dust (mg/m(^3))</th>
<th>Endotoxin (EU/m(^3))</th>
<th>(\beta) (1→3)-Glucans (µg/m(^3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nd/N¶</td>
<td>GM (GSD)</td>
<td>Min–Max</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Job task:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driving</td>
<td>17/120</td>
<td>0.58 (2.6)</td>
</tr>
<tr>
<td>Driving or loading</td>
<td>8/33</td>
<td>0.41 (2.2)</td>
</tr>
<tr>
<td>Loading</td>
<td>6/32</td>
<td>0.52 (2.7)</td>
</tr>
<tr>
<td>Loading or driving</td>
<td>3/54</td>
<td>0.74 (2.7) †</td>
</tr>
<tr>
<td>Waste type:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic</td>
<td>13/44</td>
<td>0.49 (3.1)</td>
</tr>
<tr>
<td>Residual</td>
<td>3/53</td>
<td>0.59 (2.3)</td>
</tr>
<tr>
<td>Organic or residual†</td>
<td>0/16</td>
<td>0.89 (2.4) †</td>
</tr>
<tr>
<td>Other</td>
<td>1/5</td>
<td>0.42 (1.9)</td>
</tr>
</tbody>
</table>

\(\alpha\) \*p<0.05 \(\) driving in mixed effects analyses adjusted for auto correlation and type of collected waste; \(\beta\) \*p<0.01 \(\) driving in mixed effects analyses adjusted for auto correlation and type of collected waste; \(\beta\) \*p<0.05 \(\) driving or loading in mixed effects analyses adjusted for auto correlation and type of collected waste; \(\beta\) \*p<0.01 \(\) driving or loading in mixed effects analyses adjusted for auto correlation and type of collected waste; \(\beta\) \*p<0.05 \(\) organic waste in mixed effects analyses adjusted for auto correlation and job task; \(\alpha\) \*number of non-detectable samples/total number of samples; †predominantly organic (13/16) collection of separated organic and residual waste at the same time. GM, geometric mean; GSD, geometric SD.
upper airway inflammation and respiratory symptoms in domestic waste collectors

In this study, we showed signs of increased upper airway inflammation and respiratory symptoms in waste collectors compared with controls. The inflammation was shown at the end of the working week by higher concentrations of total cells and IL8—total cells and IL8 were higher in waste collectors compared with controls. Increased (above median) after shift IL8 concentrations were more common in subjects reporting respiratory symptoms, such as cough, cough with phlegm, wheezing, stuffy nose, and runny nose (PR range 1.6–7.7, p<0.05). Respiratory symptoms were also, but only weakly, associated with increased total cell concentrations after the shift (PR range 1.5–2.3, p<0.10). No associations were found between respiratory symptoms and dichotomised values of other inflammatory markers (IL6, TNFα, and IL1β). Analyses adjusting for collector/control status or current smoking and age showed similar results (data not shown). Separate analyses for collectors showed generally similar but slightly increased associations.

DISCUSSION

In this study, we showed signs of increased upper airway inflammation and respiratory symptoms in waste collectors compared with controls. The inflammation was shown at the end of the working week by higher concentrations of total cells and IL8 before and after the shift, and higher cross shift cell counts in NAL fluid. No differences between waste collectors and controls were found for IL6, TNFα, and IL1β in NAL fluid. The main types of cells found in the NAL fluid were neutrophils and epithelial cells, whereas eosinophils were only occasionally found, which is indicative of a non-immune response. Accumulation of IL8 and IL6 in NAL fluid was significantly associated with increased exposure concentrations of IL1α, IL8, and IL6 (p<0.05). Respiratory symptoms were also, but only weakly, associated with increased total cell concentrations after the shift (PR range 1.5–2.3, p<0.10). No associations were found between respiratory symptoms and dichotomised values of other inflammatory markers (IL6, TNFα, and IL1β). Analyses adjusting for collector/control status or current smoking and age showed similar results (data not shown). Separate analyses for collectors showed generally similar but slightly increased associations.

Figure 1 Geometric mean (95% CI) of concentrations in NAL fluid of total cells (cells/ml), IL8 (pg/ml), and IL6 (pg/ml), and the odds for detectable TNFα and IL1β, at the beginning (A) and at the end (B) of the week accounted for repeated measurements within subjects as estimated in mixed effects models.

Figure 2 Geometric mean (95% CI) of work shift ratios of NAL total cells, IL6, and IL8 at the beginning (A) and end (B) of the week accounted for repeated measurements within people as estimated in mixed effects models.
inflammation mediated by neutrophils as described previously in the waste industry. This was furthermore supported by the observed increased levels of IL8, a strong chemoattractant of neutrophils, and by the finding that IgE sensitisation against fungi was rarely found in either waste collectors and controls (data not shown), which has recently also been shown by others.

Although exposure concentrations of organic dust in waste collectors were lower than previously described for compost workers, signs of inflammatory responses were still found, but were less pronounced. Significant differences between waste collectors and controls in markers of upper airway inflammation (both before and after the shift) were found, but only at the end of the week, suggesting an across week effect. Concentrations of NAL variables in controls showed a strong decline during the week, probably due to a prolonged washout effect 2–3 days after the first NAL, which has been described previously in other studies. Assuming a comparable wash out effect in both groups, the less pronounced decline in NAL concentrations during the week for waste collectors can only be explained by an enhanced and probably subchronic inflammatory process in the nasal mucosa of collectors. Similar across week effects were not found in our previous study in more highly exposed compost workers, which might have been due to the design of that particular study as controls were only measured at the beginning of the week. However, in that study signs of subchronic inflammation were shown by increased concentrations of inflammatory markers in the NAL of the most highly exposed workers compared with controls before the work shift. No differences across waste collectors and controls were found for the proinflammatory cytokines IL6, TNFα, and IL1β in NAL fluid. Although those cytokines are thought to play a

Table 3  Relation in waste collectors between concentrations after a work shift of total cells, IL6, and IL8 in NAL fluid and personal exposure concentrations on the same day as NAL was performed (day of exposure) or a proxy for accumulated exposure for a week (sum of exposures) approximated by summing the exposures at the beginning and the end of the week.

<table>
<thead>
<tr>
<th>Exposure to</th>
<th>Total cells</th>
<th>IL8</th>
<th>IL6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of exposure at the beginning of the week: †</td>
<td>1.17 (0.25 to 5.39)</td>
<td>2.33 (0.84 to 6.55)</td>
<td>2.13 (0.51 to 8.89)</td>
</tr>
<tr>
<td>Endotoxin (EU/m³)</td>
<td>2.37 (0.40 to 14.04)</td>
<td>2.16 (0.62 to 7.59)</td>
<td>0.86 (0.16 to 4.68)</td>
</tr>
<tr>
<td>Glucans (µg/m³)</td>
<td>1.35 (0.28 to 6.50)</td>
<td>2.92 (1.09 to 7.84)</td>
<td>0.55 (0.09 to 3.46)</td>
</tr>
<tr>
<td>Sum of exposures during the week: ‡</td>
<td>1.88 (0.27 to 13.33)</td>
<td>3.31 (1.26 to 7.71)</td>
<td>2.66 (0.25 to 28.57)</td>
</tr>
</tbody>
</table>

*p<0.05; † association between concentration of marker in NAL and personal exposure measured on the day of NAL; ‡ association between concentration of marker in NAL and the sum of personal exposures measured on the day of NAL at the beginning and at the end of the week.

Results are expressed as relative increases (ratio (95% CI)) in NAL concentrations after a work shift associated with a difference of 2GSDs in exposure.

Table 4  Prevalence of respiratory symptoms and prevalence ratios (PR) of respiratory symptoms for above versus below median NAL concentrations of total cells and IL8 in waste collectors and controls.

<table>
<thead>
<tr>
<th>Chronic symptoms:</th>
<th>Prevalence (%)</th>
<th>Prevalence ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Collector</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Cough &gt;3 months in past 2 y</td>
<td>20.0</td>
<td>12.8</td>
</tr>
<tr>
<td>Cough with phlegm &gt;3 months in past 2 y</td>
<td>0.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Shortness of breath when walking with contemporaries on the flat</td>
<td>0.0</td>
<td>8.5</td>
</tr>
<tr>
<td>Wheeze ever</td>
<td>13.3</td>
<td>29.8</td>
</tr>
<tr>
<td>Wheeze &gt;1 week in past 2 y</td>
<td>6.7</td>
<td>14.9</td>
</tr>
<tr>
<td>Asthma attacks ever</td>
<td>6.7</td>
<td>12.8</td>
</tr>
<tr>
<td>Symptoms at any time during the past y: †</td>
<td>6.7</td>
<td>12.8</td>
</tr>
</tbody>
</table>

*Cough >3 months in past 2 y | 21.4 | 43.2 | 1.02 | 1.80† | 1.40 | 2.52** |
| Cough with phlegm | 14.3 | 37.8† | 1.78 | 2.00† | 2.80† | 2.36* |
| Wheeze in the chest | 14.2 | 21.6 | 1.39 | 1.33 | 1.31 | 4.28* |
| Shortness of breath | 7.1 | 16.2 | 1.48 | 0.80 | 1.61 | 2.44 |
| Dyspnoea | 7.1 | 10.8 | 2.37 | 3.00 | 2.58 | 2.75 |
| Chest tightness | 7.1 | 13.5 | 1.19 | 2.00 | 3.23 | 1.83 |
| Blocked nose | 42.9 | 62.2** | 0.95 | 1.47 | 1.45 | 1.15 |
| Runny nose | 50.0 | 56.8 | 1.25 | 1.50† | 1.16 | 1.59† |
| Itching nose or sneezing | 21.4 | 62.2** | 0.95 | 1.47 | 1.45 | 1.15 |
| Throat irritation | 14.3 | 29.7 | 1.34 | 2.33† | 1.03 | 2.14† |

*p<0.05; **p<0.01; †p<0.10; ‡symptoms at any time during the past 12 months, or when shorter, during the time working at the facility; †calculated by adding one person in the diseased group.
crucial part in the inflammatory processes, concentrations of
them in NAL fluid have been studied only rarely, showing no
consistent results.  
  Thus the reason for the lack in response of
those cytokines remains uncertain.
In the present study in waste collectors, concentrations of
inflammatory markers after the shift were positively associ-
ated with exposure concentrations. So far, associations
between inflammatory makers in NAL fluid and occupational
exposure concentrations have hardly been reported. The
response-exposure relation found was more pronounced for
total dust exposure than for endotoxin or glucan exposure
alone, suggesting that other currently unidentified agents—
for instance peptidoglycans—in the dust, besides endotoxin
and glucan, may also play a part.  

The availability of repeated exposure and NAL measure-
ments allowed calculation of variance components between
and within subjects, where the variance between subjects
reflects differences between people and the variance within
subjects the day to day variation within a person. Our data
showed that between and within subject variability was not
the same for each NAL marker, as the total variance for IL6
and total cell concentrations was larger than for IL8
showed that between and within subject variability was not
between people than within people, which has been described
previously.  

The variability of NAL inflammatory markers
between people and within subjects did not change after correction
for being a collector for a control or time of NAL or exposure
(data not shown), which has been reported previously by
Hauser et al.  

This suggests that differences between people in
responses exists independently of exposure, which may be due
to other undetermined factors—such as individual
susceptibility—that have been described for endotoxin related
airway responsiveness.  

In the present study, an association between respiratory
symptoms and NAL variables was shown by increased
concentrations of IL8 and total cells after the shift in subjects
reporting respiratory symptoms. An analysis including ex-
posed workers only did overall yield higher risk ratios,
suggesting that at least part of the association between NAL
outcomes and respiratory symptoms is related to occupational
exposure. To our knowledge, only one other small study in
bakers has reported increased concentrations of NAL variables
in the presence of nasal symptoms.  

In that study associations between symptoms and NAL were only found in bakers and
not in controls.

In conclusion, waste collectors showed signs of increased
upper airway inflammation and showed a slightly higher
prevalence of respiratory symptoms compared with controls.
Exposure to organic dust probably underlies the non-immune
inflammation characterised by attraction and infiltration of
neutrophils, resulting in respiratory symptoms.

ACKNOWLEDGEMENTS
We are indebted to the waste collectors and the waste collecting fac-
tilities for their participation and cooperation in the study. We also thank
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analyses, and Professor B Bruneekreef for reviewing the manuscript.
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Mortality from cardiovascular diseases and exposure to inorganic mercury

Paolo Boffetta and his coworkers presented a comprehensive cohort study comprising 6784 male and 265 female workers from four mercury mines and mills in Spain, Slovenia, Italy, and the Ukraine. The expected number of deaths were derived from the national rates specific for sex, age, and calender period. Slovenia was the only country with an increased mortality of ischaemic heart disease among men (SMR 1.66, 95% CI 1.35 to 2.02). In the Slovenian mine, dust measurements showed concentrations between 30 and 70 mg/m³ with 10–35% free silica in the 1960s, and about 40 mg/m³ in the 1970s. An increased mortality from pneumoconiosis was present in all countries. Mortality from ischaemic heart disease was positively correlated with duration of employment but not with cumulative exposure to mercury. Smoking habits was an unlikely confounder as smoking was not increased with cumulative exposure to mercury. Smoking was associated with an increase in plasma fibrinogen, particularly with another review, a significant difference (p = 0.049). Thus dust exposed workers (RR 1.16) were compared with low dust exposed workers (RR 0.65). Silicotics did not have an increased mortality due to IHD (RR 1.1, 95% CI 0.7 to 1.8).

A general hypothesis about exposure to inhaled particles and the occurrence of IHD can be expressed in the following way. Long term inhalation of particles retained in the lungs will create a low grade inflammation associated with an increase in plasma fibrinogen. The high concentration of fibrinogen will increase the likelihood for blood clotting and thereby the risk for myocardial infarction and IHD. A high concentration of fibrinogen in plasma is an established risk factor for IHD. An increased concentration of fibrinogen has been observed among tunnel construction workers after a workshift with a dust exposure of less than 2 mg/m³. Thus dust exposure in general and silica exposure in particular could be interesting to discuss in relation to ischaemic heart disease in this study by Boffetta and coworkers.

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Joint action of smoking and asbestos exposure on lung cancer

This subject has long been bedevilled by unwarranted circular argument. Why should there be only two possible hypotheses of interaction (additive and multiplicative)? Theory expects multiplicativity; epidemiology can seldom reject this hypothesis (so theory is “accepted”, and deviations from multiplicativity must be explained away). Resolution is made especially difficult because the nature of the data imposes very large errors. Also it has to be assumed that the exposed smoked as many cigarettes as the unexposed, and that smokers and non-smokers were exposed equally.

Thus the “comprehensive” review by Lee was to be welcomed. However, discrepancies, particularly with another review, demanded discussion: this letter is the result.

From almost 40 “results” in 23 reports, Lee makes two selections to confirm the well known facts that asbestos can increase lung cancer risk in non-smokers and that the additive effect of independent action does not explain many of the data. Then, for 16 results, Lee calculates a statistic V; for an observed multiplicative interaction, V = 1. The weighted average V = 0.90 (95% CI: 0.67 to 1.20) leads to Lee’s conclusion. Repair of (acknowledged) imperfections (one misquoted result, two incorrect omissions) reduced V only slightly, to 0.83 (95% CI: 0.63 to 1.08); for nine cohorts and nine case–referent studies, respectively, V = 0.63 and 1.08, a “significant” difference (p = 0.049). There are, however, other imperfections: two cohorts broke the rule of independence; in another, asbestos had a minuscule (protective) effect on lung cancer in both non-smokers and smokers (that is, no action, so no interaction); and in a Chinese cohort, risks from cigarette smoke were dramatically lower than in the West. After exclusion, the cohorts’ V = 0.54 (95% CI: 0.35–0.82), and the difference between types is much wider (p = 0.017).

Problems with case–referent designs are well known; here they are compounded by impute definitions of non-smokers and by retrospective assessment of exposure. It is clear from personal experience over five
decades that, unless obtained from employers’ records, job histories can be quite unreliable, even in basic facts, especially when reported by proxies. The assumption that the interactions between smoking and exposure to asbestos plus other carcinogens and between smoking and asbestos alone take the same form is untested and so indefensible. Thus, Lee’s grounds for his unprecedented incorporation of the Italian study in which all concerned were exposed to PAHs, neglected, unless exposed to PAHs, namely, that subjects in many studies would have been exposed to “other” carcinogens, far from justifying inclusion, provide strong additional reasons for excluding all such studies, the majority of the case–referent studies in particular. It becomes obvious that inferences from the latter cannot overthrow conclusions from the cohorts.

The potential risks from dusty coal reinforce the need to exclude the Chinese cohort. Undoubtedly, the North American insulation workers were not exposed only to 4–12 fibers/ml of chrysotile, since there is a good case for discarding this result, although it forms a cornerstone of the evidence for multiplicativity. On the other hand, the study of crocidolite miners might be taken into account, despite faults. The resultant is $V = 0.47$ (95% CI: 0.29 to 0.75). Lee proceeds from $V = 0.83$ (for 18 studies), noting that the significance of the difference between study types is not great, and “is removed” by an (admittedly dubious) adjustment of the lowest $V$. He “sides with other reviewers” and includes all data, concluding “that they do not clearly allow rejection of the simple multiplicative relationship”.

Despite some doubt about the “best” estimate of $V$ from cohort studies, most reasonable people would accept that it is $< 1$, as shown even by Lee’s $V = 0.63$, with $p = 0.018$. Therefore, the multiplicative hypothesis is not generally satisfactory. Nor, of course, is the additive hypothesis, although it does fit some data sets very well.

Evidently, interaction takes several forms.

### Table 1: Assessing the multiplicative relationship of smoking and asbestos in lung cancer risk

<table>
<thead>
<tr>
<th>Estimate*</th>
<th>Study type</th>
<th>$V$ (95% CI)</th>
<th>Heterogeneity $\chi^2$</th>
<th>Degrees of freedom</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. DeKlerk</td>
<td>CC</td>
<td>1.25 (0.19 to 8.08)</td>
<td>14.88</td>
<td>15</td>
</tr>
<tr>
<td>2. Marttunen</td>
<td>CC</td>
<td>2.89 (0.87 to 9.62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Pastorino, no PAH</td>
<td>CC</td>
<td>0.64 (0.10 to 4.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Pastorino, PAH</td>
<td>CC</td>
<td>1.01 (0.13 to 7.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Bovenzi</td>
<td>CC</td>
<td>0.86 (0.31 to 2.39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Kjuus</td>
<td>CC</td>
<td>1.52 (0.39 to 5.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Blot, Georgia</td>
<td>CC</td>
<td>1.26 (0.54 to 2.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Blot, Virginia</td>
<td>CC</td>
<td>0.81 (0.39 to 1.81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Blot, Florida</td>
<td>CC</td>
<td>0.72 (0.22 to 2.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. McDonald</td>
<td>P</td>
<td>0.61 (0.25 to 1.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Zhu</td>
<td>P</td>
<td>1.60 (0.43 to 5.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Meurman</td>
<td>P</td>
<td>1.19 (0.07 to 20.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Berry, 1960–70 M+F</td>
<td>P</td>
<td>0.61 (0.10 to 25.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Selikoff and Hammond</td>
<td>P</td>
<td>1.22 (0.32 to 10.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Selikoff</td>
<td>P</td>
<td>0.19 (0.07 to 0.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Hammond</td>
<td>P</td>
<td>0.95 (0.47 to 2.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Berry, 1971–80 M+F</td>
<td>P</td>
<td>0.33 (0.13 to 1.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. Liddell*</td>
<td>P</td>
<td>0.56 (0.20 to 1.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. Berry, 1960–70 F</td>
<td>P</td>
<td>1.47 (0.22 to 30.0)</td>
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Original analysis

Estimates 1–16

<table>
<thead>
<tr>
<th>Degree of freedom</th>
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<tbody>
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<tr>
<td>Revised analysis</td>
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Estimates 1–12, 14–19

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Estimates 1–9

<table>
<thead>
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<th>Degree of freedom</th>
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<tbody>
<tr>
<td>CC</td>
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</table>

Estimates 10–12, 14–19

<table>
<thead>
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<th>Degree of freedom</th>
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<tbody>
<tr>
<td>P</td>
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</table>

Revised analysis with exclusions

Estimates 1–3, 5–10, 15–19

<table>
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<th>Degree of freedom</th>
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<tbody>
<tr>
<td>All</td>
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Estimates 1–3, 5–9

<table>
<thead>
<tr>
<th>Degree of freedom</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
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</table>

Estimates 10, 15–19

<table>
<thead>
<tr>
<th>Degree of freedom</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
</tr>
</tbody>
</table>

*References and fuller details given elsewhere except where stated.

C, case–control; P, prospective.

$V$ is the ratio of the asbestos relative risk in smokers to that in non-smokers.

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observed results can cause bias. He would exclude estimate 14 as the study population is a subset of that for estimate 15. However, the follow up period was much longer for estimate 14 (1943–74) than for estimate 15 (1967–76), so omitting it would have lost data. Anyhow, omitting estimates 11, 12, and 14 only has a minor effect, V reducing to 0.79 (95% CI: 0.59 to 1.05) (table 1).

At face value, the combined data appear reasonably homogeneous and compatible with the multiplicative model. However, as Liddell notes, estimates for prospective and case–control studies differ. Using my revised analysis, prospective studies give \( V = 0.63 \) (95% CI: 0.43 to 0.92) and case–control stud- ies \( V = 1.08 \) (95% CI: 0.74 to 1.59), a statistically significant difference (\( p = 0.049 \)). With Liddell's four suggested exclusions, \( V = 0.54 \) (95% CI: 0.35 to 0.82) for prospective studies and \( V = 1.06 \) (95% CI: 0.74 to 1.60) for case–control studies, with \( p = 0.017 \).

He stresses this significant difference, re- jects the case–control data due to data unreliability, use of proxies, and inclusion of ex or ex-smokers, in the reference group and argues that inferences should be drawn only from the prospective studies. I regard these arguments as dubious. The significance of the difference is not great and is removed (p = 0.089 for the revised data) if the estimate of \( V \) for the one study (estimate 15) showing a very low value is revised based on “best available evidence” rather than on death certificate diagnosis (though this revision is itself questionable). Prospective studies may be limited by failure to record changes in smoking status after follow up starts. The Quebec prospective study obtained data from prospective studies while case–control studies did not. While data on accuracy of exposure is no doubt better in prospective studies, I side with other reviewers in considering the whole data.

The asbestos relative risk may be somewhat lower in smokers than non-smokers, but the available data do not clearly reject the simple multiplicative relation. More complex models of joint action might indeed fit the data better, but in view of the general problems with the data, it seems doubtful whether more detailed statistical analysis would shed any greater insight.

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**References**


**Occupational exposure to magnetic fields**

While Savitz’s point of view expressed in the editorial that epidemiological methodology faces its limits when the risk is small, exposure assessment is poor, and biological insight is lacking, must be reinforced, it is not so clear whether or not this view is applicable to the field of exposure to extremely low frequency electromagnetic fields (ELF EMF). Unfortunately some of the studies that could contribute to an evaluation of the relation between ELF EMF and brain cancer have serious deficits. This is apparently also the case for the paper by Sorahan and colleagues. First it has to be stressed that there is no such diagnostic entity as “brain tumour”. Brain tumours comprise a heterogeneous group of both malignant and benign neoplasms generating from different tissues, with different growth rates and other essentially different features (for an overview see Black). The authors do not even mention the number of cases of different tumour types, let alone discuss why they feel that all these completely different entities could be affected by a single cause.

Another crucial point is latency. The only essential criterion of causation in the assessment of epidemiological evidence is “temporo– causal relation”. It is crucial that provisions are made to allow for biologically reasonable latencies. Instead the authors report on estimates based on the most recent (1) five years of exposure plus choosing an exposure metric that has nothing to do with the vast majority of brain tumours that have latencies of at least five (but many 20 or more) years (for example, Strojan et al). Most of the brain tumours will have been already initiated before the point in time the exposure was accumulated to give the indicator the authors have chosen. At least the last 10 years prior to diagnosis of the tumour have to be truncated in computation of the exposure metric and all cases occurring earlier than 10 years after onset of exposure have to be omitted.

To choose Tesla-years as the exposure variable is also questionable because we do not know whether or not risk is cumulative. A more sophisticated exploitation of information on exposure could be expected from the authors. For example, time spent under peak exposures (e.g. exceeding 10% of the exposure limit) would be a meaningful surrogate. Tesla-years introduces an equivalence that has never shown to be meaningful: that exposure duration and intensity are commutative (that is, 10 years exposure to 1 µT is equivalent to one year exposure to 10 µT).

Overall the study in its presented form cannot be considered to contribute to the assessment of a relation between ELF EMF exposure and brain tumours.

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**Authors’ reply**

Professor Kundi implies that, in our analyses of brain tumour risks and magnetic field exposure, we only considered exposures occurring in the most recent five years. We did not. Analyses of total cumulative exposures to magnetic fields in relation to mortality risks from primary brain tumours were reported in table 3, and analyses of the potential role of recent exposures were reported in table 4. Confirmation of diagnosis had also been sought from cancer registration particulars. These analyses were planned in advance as tests of the main hypotheses of interest. These hypotheses had been derived from a review of the current literature, and for neither analysis was there any suggestion of magnetic field exposure being implicated in mortality risks for brain tumours. The ICD codes we used to define the health outcome and the use of micro-Tesla years as the unit of magnetic field exposure enabled our study findings to be compared to other reports. Their use appears, at least to us, to be eminently sensible. We remain open to the possibility that other exposure metrics may come to be appreciated as more biologically relevant but we doubt whether the pro- posal of Prof. Kundi is more reasonable than the arbitrary percentage of a contemporaneous exposure limit) which will gain favour.

We hope our study makes a useful contribu- tion to the practice of occupational health and that employees in the UK electricity supply and transmission industry treat the findings as good news.

---

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**Reference**

these ancient concepts and terminology have led many to consider Chinese medicine as primitive, ritualistic, and unchanging. Such negative connotations have deterred many from studying Chinese medicine. Even if they did so, they had to forgo its theories and use the Western scientific paradigm to explain their treatment.

Elisabeth Hsu and the other authors in this book aimed to challenge this stereotype of Chinese medicine. They did so using selected examples to explain how evolution occurred in different aspects of Chinese medicine over time and the factors which motivated these changes. They showed that such changes could be brought about by the prevailing cosmological theories at the time, such as the incorporation of the system of five circulatory phases and six seasonal influences around the tenth century. Some changes were brought about by the political ideology at the time, such as the development of the new acumoxa theory in early communist China. But many are down to individuals’ intuition, such as the new system of cataloguing natural pharmaceuticals by Li Shizhen in Bencao gangmu compiled in the sixteenth century. Many of the examples were chosen because they had far reaching consequences but some, notably one that was brought about for the sake of political correctness, did not have any sustainable influence.

The style of writing used in this book is one of its strengths. The reference text from which main arguments were based is cited both in Chinese and in English to avoid quoting out of context. Detailed footnote and extensive cross referencing underpin and expand the author’s line of argument. Readers with scientific and medical background will appreciate such “evidence based” approach.

Its method of translation deserves to be noted separately. Chinese medicine terms have been notoriously difficult to have a standard translation, partly because they represent abstract concepts and their meaning can be different, depending on the context. Hsu used the official transcription system pinyin and Chinese characters alongside the English translation. These minimise confusion and allow readers to cross reference these terms with texts from other sources.

As well as achieving the author’s objective, this book shows that Chinese medicine is not illusive and does not defy investigation. The author has shown how this could be done and her approach is different and innovative. The logical arguments in this book will appeal to professionals within the scientific community and can be a useful way to evaluate Chinese medicine.

Gilbert Shia

CORRECTIONS

We apologise for the following errors.

In the paper “Low level cadmium exposure and kidney damage—the OSCAR study” (Järup et al) published in 2000 (Occ Environ Med 2000;57:668–72) the following errors were made:

(1) In the second paragraph, page 670, and at the fourth row, page 671, the text reads “1.6 nmol/mmol creatinine”. It should read “1.0 nmol/mmol creatinine” at both places.

(2) In Table 1, “n” for age for the women should be 542 and not 544.

In the paper “Upper airway inflammation and respiratory symptoms in domestic waste collectors” (Wouters et al) published in February 2002 (Occ Environ Med 2002;59:106–12), the following errors were made:

(1) On page 108, right hand column, lines 5–7, part of the sentence was omitted. It should have read: “Estimated within and between subjects variance components of exposure concentrations were 0.51 and 0.34 for dust, 1.08 and 0.22 for endotoxin, and 1.49 and 0.14 for glucan.”

(2) Table 2 heading: “from microbial agents” should have been omitted.