Kidney Disease Mortality and Environmental Exposure to Mercury

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Runcorn, North West England, has been a site of industrial activity for over 100 years. Preliminary investigations have revealed excess risk of renal mortality in the population living closest to several sources of pollution. Exposure to airborne mercury has been highlighted as a possible cause, although there is also concomitant exposure to solvents and other heavy metals in this population. The authors used validated air dispersion modeling to identify mercury-exposed populations. Standardized mortality ratios for kidney disease were computed using the North West government region as the reference. There was a significant exposure-response relation between modeled estimates of mercury exposure and risk of kidney disease mortality (test for trend: $p = 0.02$ for men and $p = 0.03$ for women), and this relation was more pronounced for estimated historical exposure (test for trend: $p = 0.01$ for men and $p < 0.001$ for women). These findings suggest that exposure to mercury is a possible cause of the excess kidney disease mortality in this population, indicating that there might still be a health legacy of the historically high levels of industrial activity in the Runcorn area.

chemical industry; environmental exposure; kidney diseases; mercury; mortality; solvents

Abbreviations: ADMS, Atmospheric Dispersion Modeling System; SMR, standardized mortality ratio.
Exposure to inorganic mercury released into the air from industrial activity was highlighted as a possible cause of the adverse renal effects in the area, because of the documented renal toxicity of this metal at relatively low exposure levels (7) and current health concerns about the release of this substance in Europe (8).

Air dispersion modeling was used to assess ambient mercury levels and to determine exposures. Mercury is well absorbed by the body following inhalation, with numerous occupational studies showing air levels to be correlated with internal doses (estimated by urinary mercury excretion) (9). Inhalation exposure was the main route of interest; however, the modeled ambient levels would also be a proxy for exposure from consumption of locally grown vegetables.

In addition to the chlor-alkali plant and associated processes at Weston Point, there are several other industries located along the banks of the Mersey Estuary—including petrochemical processing based to the southwest and a large coal-fired power station to the northeast. These industries release significant quantities of nephrotoxic heavy metals and solvents, exposing the local population to a mixture of toxic substances, the combined effects of which are largely unknown.

Low-level exposures to heavy metals and solvents have been shown to have an adverse effect on the kidneys (often evidenced by an increased prevalence of tubular proteinuria/ enzymuria (10)). While the kidneys are able to compensate for these preclinical changes, relatively minor alterations in renal function can lead to more major changes, which beyond a certain point will be irreversible and ultimately require medical intervention.

Our aim in this study was to investigate the occurrence of renal disease in this population in relation to mercury exposure.

**MATERIALS AND METHODS**

**Exposure assessment**

The Atmospheric Dispersion Modeling System (ADMS)–Urban, version 2.0 (Cambridge Environmental Research Consultants Ltd., Cambridge, United Kingdom) (11), was used to model the dispersion of mercury from three mercury-emitting industries (a large chlor-alkali plant, a multifuel power station, and a coal-fired power station (figure 1)). Full details can be found elsewhere (12). In summary, point-source characteristics and emissions data were obtained from Integrated Pollution Control applications data held at the Environment Agency Public Registry in Warrington. Hourly meteorologic data recorded at the Speke synoptic weather station were acquired for the years 1998–2001 from the British Atmospheric Data Centre (13). The ADMS–Urban output of estimated average ground-level mercury concentrations (averaged over the period 1998–2001) was mapped using
ArcView GIS 3.2 (ESRI, Redlands, California) at a resolution of approximately 440 × 420 m. The model was validated by environmental monitoring at nine representative sites, showing a good correlation between modeled levels and measured mercury concentrations (for correlation between mean measured and modeled values at the nine monitoring sites, the Pearson correlation coefficient was 0.93; \( p < 0.0001 \)).

Historical mercury exposure could not be modeled, since emissions data were not available prior to 1995. However, historical monitoring data suggested that levels of mercury had fallen by a factor of approximately 4 in close proximity to the chlor-alkali plant over the period 1990–2003. No historical monitoring data were available for locations further from the chlor-alkali plant; therefore, exposure to mercury across the area in the early 1990s was estimated on the basis of current dispersion modeling, assuming a similar reduction in air levels of mercury across the Runcorn area over this period.

An ambient mercury concentration of \( \leq 3 \text{ ng/m}^3 \) was defined as the background level; this is slightly higher than the average background level in the United Kingdom (1.78 ng/m\(^3\)). Low (\( > 3 < 4 \text{ ng/m}^3 \)), medium (\( 4 – 10 \text{ ng/m}^3 \)), and high (\( > 10 \text{ ng/m}^3 \)) ambient exposure contours were assigned. When historical exposures were investigated, an additional very high exposure contour (\( > 20 \text{ ng/m}^3 \)) was also used.

Data on mortality, population, and socioeconomic deprivation

The Office for National Statistics/Small Area Health Statistics Unit mortality database covers the period 1981–2001 and contains individual-level data geocoded by postcode. Each postcode was assigned to an enumeration district (the smallest geographic unit for which population and socioeconomic deprivation data from the United Kingdom Census were available), allowing mortality data to be linked to the necessary demographic data. The *International Classification of Diseases* codes investigated covered the disease class “Nephritis, nephrotic syndrome and nephrosis” (*International Classification of Diseases*, Ninth Revision, codes 580–589; *International Classification of Diseases*, Tenth Revision, codes N00–N06, N10–N12, N14–N15, N17–N19, and N25–N27).

Population estimates and an indicator of socioeconomic deprivation were available at the enumeration district level for the years 1981–1999, derived from the 1981 and 1991 census data, with changes in population during the intervening years being estimated using linear interpolation methods (14). At the time of study, the 2001 census population estimates were only available at the district authority level; therefore, we used 1991 geography and used 1999 population estimates for the years 2000 and 2001. We adjusted for socioeconomic deprivation using quintiles of the Carstairs index, a small-area deprivation measure that has been widely used in the United Kingdom and has been shown to be strongly predictive of mortality and cancer incidence (15). This index is a standardized combination of four 1991 census variables—percentage of persons with no car, percentage of persons living in overcrowded housing, percentage of persons with a household head in social class IV or V, and percentage of men unemployed—and is calculated on the enumeration district level (15).

Population-weighted centroids of enumeration districts that fell within the modeled ambient mercury contours (based on the ADMS–Urban output over the period 1998–2001) and historical ambient mercury contours (estimated for the early 1990s) were identified, and populations were pooled by contour to obtain denominator data. Relevant deaths occurring during the period 1981–2001 among residents in each contour area (for both current and historical exposures) were linked to the underlying populations at risk. Indirectly standardized mortality ratios (SMRs) adjusted for 5-year age group and Carstairs quintile were calculated on the basis of rates for the North West government region. SMRs were calculated separately for males and females to avoid the domination of the results by any occupational effects (anticipated in males) and to increase interpretability. SMRs based on small numbers are difficult to interpret; furthermore, the data provider (Office for National Statistics) requests that investigators suppress cells containing fewer than five cases for reasons of confidentiality. Therefore, where a cell contained fewer than five cases, the high and medium mercury exposure groups were combined to form one mercury exposure group (with ambient levels of \( > 4 \text{ ng/m}^3 \)).

Confidence intervals were calculated using the exact Poisson method when the number of expected events was below 100. The global null hypothesis (chi-squared test for homogeneity) was applied (and rejected) before the chi-squared trend statistic was used to assess relative risks across exposure contours (16, 17).

RESULTS

Using current exposure, there were 64 deaths from kidney disease among men and 82 deaths among women from 1981 to 2001 (table 1). Using historical exposure, there were 480 and 632 deaths among men and women, respectively, from 1981 to 2001. There were significant exposure-response relations between modeled estimates of mercury exposure and risk of kidney disease mortality in both men and women after adjustment for age and socioeconomic deprivation (test for trend: \( p = 0.02 \) for men and \( p = 0.03 \) for women) (table 1). When historical exposure data were used, based on estimated mercury levels in the early 1990s, the exposure-response trends were more pronounced (test for trend: \( p = 0.01 \) and \( p < 0.001 \) for men and women, respectively) (table 1).

The 95 percent confidence intervals for most of the individual estimates were not statistically significant. However, these point estimates do not provide an appropriate test of the null hypothesis (no exposure-response effect); this is provided by the trend statistic.

DISCUSSION

We found an exposure-response relation between ambient mercury levels (a proxy for mercury exposure) and risk of kidney disease mortality. Latency periods between nephrotoxin exposure and clinically evident kidney disease are not
well characterized, but it is likely that renal damage following low-level exposure to nephrotoxic substances will initially result in subtle changes that are compensated for until a significant degree of renal function is lost (18–20). Therefore, a person would most likely need to experience exposure over several years or even decades in order for clinically overt kidney disease to result. The exposure-response trends for risk of kidney disease mortality were more pronounced for estimated historical exposure levels, suggesting that higher exposures in the past are more important for kidney disease risk than current exposure.

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* Expected numbers of cases were based on rates derived from the North West government region by gender, 5-year age group, and deprivation quintile (Carstairs index (15)).
† Indirectly standardized mortality ratio, adjusted for age and socioeconomic deprivation; calculated using the population of the North West government region as the reference group.
‡ Current exposure contours were based on modeled emissions over the period 1998–2001; deaths from 1981–2001 were included.
§ Because of small cell counts, the high and medium mercury exposure groups were combined to form one group with ambient exposure levels of ＞4 ng/m³.
# Historical exposure contours were a prediction of dispersion in the early 1990s based on historical industry monitoring records and current dispersion modeling; deaths from 1981–2001 were included.

The role of the kidneys in the excretion of toxic substances from the body means that the kidneys are a target organ for many toxic substances (10), and renal effects have been used as an early indicator of environmental exposure to many heavy metals and solvents, most notably following cadmium exposure (21).

United Kingdom background mercury levels in ambient air are approximately 1.75 ng/m³ (22, 23), which is well below the suggested European Union limit value of 50 ng/m³ as an annual average (24). However, in the year 2000, the annual average mercury concentration near the Runcorn
chlor-alkali plant was 24.1 ng/m³, with weekly means ranging up to 69 ng/m³ (25). Ambient levels recorded by industry indicate that levels were much higher in the past (industry monitoring data from 1990 onwards were available from the Integrated Pollution Control application and emissions data held at the Environment Agency Public Registry).

A number of factors need to be considered in interpreting these findings. Assuming a latency period between environmental mercury exposure and clinical renal disease of years to decades, exposure during 1970–1990 would be relevant for renal mortality over the period 1981–2001, for which health data were available. The current modeled ambient mercury levels are likely to underestimate exposure during the 1970–1990 period; however, available data on emissions only allowed current ambient levels to be modeled and validated by air monitoring data. In an attempt to assess the “true” exposure for the relevant time period, we estimated historical ambient levels from monitoring data close to the chlor-alkali plant. However, these estimates could not be validated because of a lack of historical monitoring data further from the plant.

The higher risk found in men in this study might be due to occupational exposure, since anecdotal evidence from local industry indicates that men are more likely to be employed in the chemical industry. However, we found significant exposure-response trends for both genders, indicating that occupation is not a likely explanation for our findings.

Although the dispersion model correlated well with monitored ambient mercury levels, it is acknowledged that these ambient exposure contours do not take account of additional exposure of the general population to mercury from other sources, especially dental amalgam (26). However, exposure from dental amalgam is unlikely to be correlated with environmental exposure and is therefore unlikely to explain the trends in renal disease mortality observed. It is also recognized that people do not spend the entire day outdoors in the vicinity of their homes (27), and therefore an exposure estimate based only on ambient levels related to place of residence will result in exposure misclassification. This misclassification is most likely nondifferential with respect to the study outcome (kidney disease mortality), and thus observed risks are likely to underestimate the true risks.

Furthermore, migration into the area will increase the denominator population (though with people who were probably unexposed to ambient mercury and solvents), while migration of some persons out of the area may lead to underestimation of the number of exposure-related cases. Altogether, the resultant exposure misclassification is likely to lead to underestimation of true risks.

The study design implies a possibility of ecologic bias (28). Although we cannot infer that the observed relation was causal, the dose-response relation between ambient mercury exposure and renal disease mortality pointed in the direction hypothesized.

In addition to mercury, this study population was exposed to various other nephrotoxic substances, including other heavy metals and solvents. These substances are all emitted from point sources in the immediate area and, in the case of solvents, follow a pattern of dispersion similar to that of mercury.

In an attempt to explore the potential impact of concomitant exposure to mercury and solvents, we modeled dispersion of a mixture of potentially nephrotoxic solvents (chloroform, 1,2-dichloroethane, chloromethane, dichloromethane, tetrachloroethene, trichloroethylene, and chloroethylene) from two industrial processes in the area (emitting >85 percent of the solvents of concern) for the year 2000 (29), identifying a population exposed to solvents at a concentration of more than 10 µg/m³ (more than twice the background concentration) (figure 1). There was a statistically nonsignificant excess risk of kidney disease mortality in this population with exposure to more than 4 ng/m³ of mercury and more than twice the background level of solvents (>10 µg/m³) (SMR = 241 (95 percent confidence interval: 78, 562) in men and SMR = 156 (95 percent confidence interval: 32, 455) in women). The similar patterns of exposure make it difficult to assess the effects of specific exposures. Little is known about exposure to mixtures of nephrotoxicants, but it is plausible that simultaneous exposure to several nephrotoxic substances would increase risks, and our findings could be the result of simultaneous exposure to several nephrotoxicants.

Future work should include analyzing biomarkers of dose (urinary mercury) and early renal effect (proteinuria/enzymuria) to further elucidate the contribution of mercury to the renal disease burden in this population. In addition, a case-control study on renal disease risk in relation to past exposures (environmental and occupational) would allow collection of detailed individual information on potential confounders (such as dental amalgam).

In summary, in an area with more than a century of high levels of industrial emissions, we found a trend of higher renal disease mortality risk with higher estimated exposures to renal toxicants. Although pollution levels today are much lower than in the past, it would appear that there might still be a legacy of the historically high levels of industrial activity in the Runcorn area.

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REFERENCES