KIDNEY DISEASE MORTALITY AND ENVIRONMENTAL EXPOSURE TO MERCURY

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ABSTRACT

Runcorn, North West England, has been a site of industrial activity for over 100 years. Preliminary investigations revealed excess risk of renal mortality in the population living closest to several sources of pollution. Though exposure to airborne mercury was highlighted as a possible cause, there is concomitant exposure to solvents and other heavy metals in this population. Validated air dispersion modelling was used to identify mercury and solvent exposed populations. Standardised mortality ratios (SMRs) for kidney disease were computed using the North West region as the reference. There was a significant exposure response relationship between modelled estimates of mercury exposure and risk of kidney mortality (test for trend p=0.02 for men and p=0.03 for women), which was more pronounced for estimated historical exposure (test for trend p=0.01 for men and p<0.001 for women). In the sub-population with concomitant exposures to mercury (>4ng/m^3) and solvents (>10µg/m^3) exposure, SMR was 241 (95% CI: 78, 562) in men and 156 (95% CI: 32, 455) in women. Little is known about the health effects of simultaneous exposure to several environmental pollutants, but our findings suggest that exposure to mercury and concomitant solvents exposure is a possible cause of the excess kidney disease mortality in this population.

Medical Subject Headings: Chemical industry, Environmental exposure, Kidney diseases, Mercury, Solvents

INTRODUCTION

A commentary published in the Lancet in January 1880 describes how the town of Runcorn 'is exposed to the irritating vapour cast off so freely by the large chemical works in its vicinity'(1). Mercury has been used for chlorine production at Weston Point, Runcorn, North West England, since 1897(2), and mercury cell technology is still used at the chlor alkali plant in Weston Point. In the year 2000 this plant released 1.24 tonnes of mercury to air (~15 percent of the UK total mercury release)(3).

In 1993 Imperial Chemical Industries initiated a voluntary assessment of the legacy of industrial activity in Runcorn, to establish whether there was any risk to health from two former quarries used as industrial waste disposal sites until the 1970s. Boreholes indicated the presence of hexachlorobutadiene (nephrotoxic in animals(4)) at levels which gave some cause for concern in 21 local houses. Health checks carried out on people living in contaminated homes found no overt renal disease, though renal function measured by sensitive urinary biomarkers was reported to have shown improvement after residents left their contaminated residences(5).

The UK Small Area Health Statistics Unit (SAHSU) reported excess mortality from renal disease in the Runcorn population living within 2km of 16 major point sources of pollution, while an excess risk of hospital admissions from renal disease in Runcorn was also reported, compared with other areas in North Cheshire(6). These studies indicated a higher than expected risk of renal disease throughout Runcorn, suggesting that this could not be attributed to localized hexachlorobutadiene contamination in Weston.

Exposure to inorganic mercury released to air from industry was highlighted as a possible cause of the adverse renal effects in the area due to the documented renal toxicity of this metal at relatively low exposure levels(7), and current health concerns over the release of this substance in Europe(8).

Air dispersion modeling was used to assess ambient mercury levels and to determine exposure. Mercury is well absorbed following inhalation exposure, with numerous occupational studies showing air levels to be correlated with internal dose (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.

As well as 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 processes based to the south west, and a large coal-fired power station to the north east. 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 pre-clinical 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.

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

MATERIALS AND METHODS

Exposure assessment

Atmospheric Dispersion Modeling System (ADMS)-Urban (version 2.0)(11), was used to model dispersion of mercury from three mercury emitting industries (a large chlor alkali plant, a multi-fuel 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, Warrington. Hourly meteorological data from Speke synoptic weather station were acquired for the years 1998-2001 from the British Atmospheric Data Centre(13). The ADMS output of estimated average ground level mercury concentrations (averaged over the period 1998-2001) were mapped using ArcView GIS 3.2 at a resolution of ~440 x 420m. The model was validated by environmental monitoring in nine representative sites, showing a good correlation between modeled levels and measured mercury concentrations (Pearson correlation coefficient between mean measured and modeled values at nine monitoring sites was 0.93, $p < 0.0001$).

Historical mercury exposure could not be modeled, as emissions data were not available prior to 1995. However historical monitoring data suggested that levels of mercury had fallen by a factor of approximately four 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; exposure to mercury across the area in the early 1990s was therefore estimated based on current dispersion modeling, and assuming a similar reduction in air levels of mercury across the Halton area over this period.

An ambient mercury concentration of (≤3ng/m^3) was defined as background level, which is slightly higher than the average background level in the UK (1.78 ng/m^3). Low (>3-<4ng/m^3), medium (4-10ng/m^3), and high (>10ng/m^3) ambient exposure contours were assigned. When historical exposures were investigated, an additional very high exposure contour (>20ng/m^3) was also used.

Data on mortality, population and socio-economic deprivation

The Office for National Statistics/SAHSU mortality database covers the period 1981 to 2001, and contains individual-level data geocoded by postcode. Each postcode was assigned to an enumeration district (the smallest geographical unit for which population and socio-economic deprivation data from Census were available) allowing mortality to be linked to the necessary demographic data. The International Classification of Disease (ICD) codes investigated covered the disease class 'Nephritis, nephrotic syndrome and nephrosis'; ICD9 codes 580-589; ICD10 codes N00-N06, N10-N12, N14-N15, N17-N19, N25-N27.

Population estimates and an indicator of socio-economic deprivation (quintiles of Carstairs' index which combine data on male unemployment, no car access, low social class and over crowding(14)) were available at enumeration district level for the years 1981 to 1999, derived from the 1981 and 1991 census data, with changes in population during the intervening years estimated using linear interpolation methods(15). At the time of study, the 2001 census population estimates were only available at district authority level; we therefore used 1991 geography, and used 1999 population estimates for the years 2000 and 2001.

Enumeration district population weighted centroids that fell within the modeled ambient mercury contours (based on the ADMS output over the period 1998-2001), historical ambient

mercury contours (estimated for the early 1990s) and solvents exposure contour (modeled over the year 2000) were identified and populations pooled by contour to give denominator data. Relevant deaths occurring over 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) were calculated stratified by gender, five-year age group and Carstairs quintile based on rates for the North West government region.

SMRs based on small numbers are difficult to interpret; furthermore the data provider (ONS) requests that reports suppress cells containing <5 cases for reasons of confidentiality. Therefore, where a cell contained <5 cases, the high and medium mercury exposure groups were combined to make one mercury exposed group (with ambient levels of >4ng/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

Overall there were 64 deaths from kidney disease among men and 82 among women from 1981-2001 (current exposure) and 480 and 622 respectively from 1981-2001 (historical exposure) (table 1). There were significant exposure response relationships between modeled estimates of mercury exposure and risk of kidney disease mortality in both men and women after adjustment for age and socio-economic deprivation (test for trend $p=0.02$ for men and $p=0.03$ for women) (table 1a). 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 1b).

It should be noted that the 95 percent confidence intervals for most of individual estimates are 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 relationship 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, exposure over several years or even decades would most likely need to be experienced to result in clinically overt kidney disease. 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.

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).

UK background mercury levels in ambient air are ~1.75 ng/m^3(22, 23), which is well below the suggested European Union limit value of 50ng/m^3 as an annual average(24). However, in the year 2000 the annual average mercury concentration near the chlor-alkali plant was 24.1ng/m^3, with weekly means up to 69ng/m^3(25). Ambient levels recorded by industry indicate levels were much higher in the past (industry monitoring data from 1990 onwards was available from the Integrated Pollution Control application and emissions data held at the EA Public Registry, Warrington, UK).

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 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, historical ambient levels were estimated from monitoring data close to the chlor alkali plant. However; these estimates could not be validated because of 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 the 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 of our findings.

Though 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 therefore unlikely to explain the trends in renal disease mortality observed. It is also recognized that people do not spend all 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 non-differential with respect to 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 likely unexposed to ambient mercury and solvents, while individuals migrating out of the area may lead to an underestimation of the number of exposure related cases. Taken together, the resultant exposure misclassification is likely to lead to underestimation of true risks.

The study design implies a possibility of ecological bias (28), but although we cannot infer that the observed relationship is causal, the dose response relationship between ambient mercury exposure and renal disease mortality is in the direction hypothesised.

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

In an attempt to explore the potential impact of concomitant mercury and solvents exposure, dispersion of a mixture of potentially nephrotoxic solvents (chloroform, 1,2 dichloroethane, chloromethane, dichloromethane, tetrachloroethene, trichloroethylene and chloroethene) from two industrial processes in the area (emitting >85% of the solvents of concern) was modeled for the year 2000(29), identifying a population exposed to more than 10$\mu g/m^3$ solvents (more than twice the background concentration) (figure 1).

There was a statistically non significant excess risk of kidney disease mortality in this population with exposure to more than 4ng/m^3 mercury and to more than twice the background level of solvents (>10μg/m^3) (SMR=241 (95 percent CI: 78, 562) in men and 156 (95 percent CI: 32, 455) in women). The similar pattern of exposure makes 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 also 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 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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TABLE 1. Mortality from nephritis, nephritic syndrome and nephrosis (1981 – 2001) in men and women adjusted for age and socio-economic deprivation in the study population compared to the population of North West England by a) current and b) historical estimated ambient mercury exposure contours.

a) Current exposures [*]					
Exposure (ng/m^3)	**Person years**	**Observed**	**Expected** [†]	**SMR** [‡]	**95% Confidence Interval**
Men					
North West	65,394,296			100	
Low (>3-<4)	556,499	31	28.04	111	75, 157
Medium (4-10)	361,245	27	18.94	143	94, 207
High (>10)	41,982	6	3.26	184	68, 400
	Chi^2 test for trend p=0.02				
Women					
North West	68,870,244			100	
Low (>3-<4)	582,619	52	34.62	150	112, 197
Medium & High (>4) [§]	419,192	30	25.62	117	79, 167
	Chi^2 test for trend p=0.03				

b) Historical exposures [#]					
Exposure (ng/m^3)	**Person years**	**Observed**	**Expected** [†]	**SMR** [‡]	**95% Confidence Interval**
Men					
North West	65,394,296			100	
Low (>3-<4)	5,382,075	345	326.96	106	95, 117
Medium (4-10)	1,782,323	101	91.45	110	90, 134
High (10-20)	3,11,521	21	15.71	134	83, 204
Very high (>20)	101,597	13	6.81	191	102, 326
	Chi^2 test for trend p=0.01				
Women					
North West	68,870,244			100	

Low (>3-<4)	5,719,964	444	428.16	104	94, 114
Medium (4-10)	1,856,263	154	112.39	137	116, 160
High (>10-20)	323,279	24	18.89	127	81, 189
Very high (>20)	105,832	10	7.06	142	68, 261
	Chi^2 test for trend $p<0.001$				

* Current exposure contours were based on modelled emissions over the period 1998-2001; deaths were included from 1981-2001.

† Expected numbers were based on rates derived from the North West government region by gender, five year age group and deprivation quintile (Carstairs index).

‡ SMR refers to the indirectly standardised mortality ratio, adjusted for age and socio-economic deprivation, using the population of the North West government region as the reference.

§ Due to small cell counts the high and medium mercury exposure groups were combined to make one mercury exposed group (with ambient levels of >4ng/m^3).

Historical exposure contours were a prediction of dispersion in the early 1990s based on historical industry monitoring records and current dispersion modelling; deaths were included from 1981-2001.

FIGURE 1: Estimate of mercury dispersion over the years 1998-2001 in the Runcorn area, UK; overlain solvent dispersion (>10μg/m^3 contour).