The mortality of workers with occupational lead exposure: A research proposal

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LAY SUMMARY

Inorganic lead compounds are classified by the International Agency for Research on Cancer (IARC) as 'probably carcinogenic to humans', based on 'sufficient evidence of carcinogenicity in experimental animals' and 'limited evidence of carcinogenicity in humans'. Much of the epidemiological evidence for carcinogenic effects in humans comes from studies of lead workers. However, previous studies have often involved relatively small numbers of workers and suffered from methodological constraints such as limited information on co-exposures to other risk factors or poorly characterised exposure assessments.

We propose to study the mortality of approximately 10,000 UK workers who were participants in the Health and Safety Executive (HSE) Lead Mortality Study between 1975 and the early 1980s, and who had at least one blood lead measurement recorded during the study. The main focus of the research will be an investigation of the association between lead exposure and cancer mortality risk. In the first instance, mean blood lead levels will be used to categorise blood lead exposure. We will use information on factory and process codes for the study participants with information from the HSE National Exposure DataBase (NEDB) and HSE Visit Reports to assign likely exposure categories to lead compounds and to provide a qualitative assessment for other known or potential carcinogens. We will do some preliminary work to assess what additional information might be obtained for workers in the study from existing records, should it be decided that a follow-up nested case-control study is recommended.

Given the length of follow-up, the large size of the cohort and the relatively high exposures that they experienced (as documented by blood lead levels), the proposed study would make a significant contribution to the evidence on the carcinogenicity of lead exposure. This study will fill an important knowledge gap identified as a research priority by IARC.
MAIN PROPOSAL

1 WHAT IS THE WORK WE WOULD LIKE TO DO?

1.1 INTRODUCTION

We would like to test the hypothesis that occupational exposure to lead is associated with an increased risk of certain types of cancer mortality. During the 1970s the Health and Safety Executive (HSE) initiated a study to monitor blood lead levels (BLL) in a cohort of lead workers, tracking them as they moved around the industry. The study is referred to in the current document as the HSE Lead Mortality Study (LMS). Participants were flagged for mortality with the National Health Service Central Register (NHSCR). Cohort recruitment began in 1975, and continued until the early 1980s, with over 10,000 workers enrolled. Recruitment into the study stopped in the early 1980s, and no analysis of the cohort has ever been published. Around the same time, routine medical surveillance of blood lead levels in lead workers was introduced under the provisions of the 1980 Control of Lead at Work (CLAW) regulations.

HSE also have an extensive database of over 2,000 personal lead in air concentration measurements from at least 1985 until 2004 (the National Exposure Database [NEDB]) (Burns & Beaumont, 1989). These data are generally linked to a more extensive visit report containing details of the factory and processes where the measurements were made, and thus provide a potentially rich source of data to supplement the existing exposure data on BLL. HSE have agreed to allow the research team access to the cohort and would cooperate in providing access to data for the study – a supporting letter to this effect is in the process of being produced by HSE.

We propose to update the tracing information (vital status and cause of death) for participants in the HSE LMS in order to study the mortality patterns of the cohort.

1.2 SPECIFIC AIMS

- Compare the mortality patterns of lead exposed workers who participated in the LMS study with those of an external reference population - in this case the general population of England, Wales and Scotland. We will examine mortality including that from cancers of the lung, stomach, kidney and brain, and from ischaemic heart disease, stroke, kidney disease, and all causes. We will calculate standardised mortality ratios (SMRs) for the whole cohort, as well as for subgroups assessed as having low, medium and high levels of lead exposure.

- Use data from the HSE visit reports linked to the NEDB, or from other sources, and assess whether this can be used to refine the categorisation of lead exposure assessments based on the limited BLL data.

- Carry out a small feasibility study to assess what additional information on lead data and other factors potentially relevant for cancer risk, might be available in HSE records for workers in the study population.
2 WHY SHOULD THE WORK BE UNDERTAKEN?

In 2005, an estimated 8,023 (5%) cancer deaths were attributable to occupation in Great Britain (6,366 men; 1,657 women). Within these figures, 54 deaths were estimated to be due to occupational exposure to inorganic lead compounds, with most arising from work in: the manufacture of electrical machinery, apparatus, appliances, supplies; the manufacture of plastic products, not elsewhere classified; and in non-ferrous metals basic industries (Rushton et al, 2010). The number of workers under medical surveillance for lead in Great Britain in 2008/09 was just under 7,000 (HSE, 2010).

Acute effects of lead exposure at relatively high levels are well known, and include central and peripheral nervous system damage, kidney damage, inhibition of haemoglobin synthesis, and gastrointestinal symptoms (EPA, 2006). Historically such high exposures were most commonly encountered in occupational settings, and led to the widespread introduction of occupational safety standards and legislation to limit or prevent exposures at levels associated with acute effects (Schwartz & Hu, 2007). In recent decades, attention has turned to long-term health effects of subacute exposures, and a number of important reviews have been conducted. These include:

- the 2004 Report on Carcinogens, by the U.S. Department of Health and Human Services National Toxicology Program (NTP), and which included lead and lead compounds for the first time (NTP, 2004).

- the WHO International Agency for Research on Cancer (IARC) evaluation of lead and lead compounds (IARC, 2006). This review focused on associations between lead and specific cancers, and assessed evidence from epidemiological studies, animal studies and in vitro studies.

- a wide-ranging review of possible health effects of exposure to lead and lead compounds in ambient air, published in 2006 by the US Environmental Protection Agency (EPA, 2006).

For carcinogenicity, the epidemiological evidence is most consistent for stomach cancer, with lung cancer, kidney cancer and brain cancer showing elevations in some, but not all studies. The most recent evaluation of organic and inorganic lead compounds from IARC described the evidence in humans for the carcinogenicity of inorganic lead compounds as “limited” and for organic lead compounds as “inadequate”. IARC classified inorganic lead compounds as “possibly carcinogenic to humans” and organic lead compounds as “not classifiable as to their carcinogenicity” (IARC, 2006). In their 2006 report EPA reached a similar conclusion (EPA, 2006).

IARC have identified that further cohort studies to investigate the carcinogenicity of lead are of international importance in order to further clarify whether occupational exposure to lead and inorganic lead compounds is carcinogenic (Ward et al, 2010).
3 WHO IS DOING OR HAS DONE SIMILAR WORK, AND HOW WILL YOUR WORK ADD TO IT?

Other cohort studies to date have been relatively small and have had several methodological shortcomings. Prof. Kyle Steenland is carrying out a study of workers in the ABLES registry in the USA. The follow-up for this study only begins in 1990 and therefore we believe that our more mature cohort will add substantially to the evidence and will help fill the gap in knowledge and meet a research priority identified by IARC. We are not aware of any other large lead cohorts that are currently being studied.

4 HOW DO YOU INTEND TO CARRY OUT THE WORK, AND WHY DO YOU THINK THIS IS THE RIGHT APPROACH?

4.1 INTRODUCTION

The proposed study is a record-based retrospective cohort study. The hypothesis being tested is that workers occupationally exposed to high levels of lead and lead compounds, as evidenced by high blood lead measurements at the time of recruitment into the cohort, have increased rates of death from specific cancers, and deaths from cardiovascular disease and renal disease, compared to the general population of England, Wales and Scotland. We also hypothesise that workers with higher documented exposure levels will have higher mortality from these outcomes compared to workers in the cohort with lower blood lead levels.

Most cohort members had between one and five blood lead measurements during the study. In the first instance the mean BLL for each participant will be used to determine exposure category. It is recognised that this mean value may be a relatively poor proxy for cumulative lead dose received over the whole working life. We will analyse the available lead in air data from the NEDB and associated information from HSE Visit Reports to confirm that study participants have been assigned to the correct exposure category.

4.2 THE STUDY DATABASE

Enrolment and measurement of BLL began in 1975, and appears to have continued until the early 1980s. Participants were flagged for mortality with the UK National Health Service Central Register (NHSCR). As of 1995 the database held by the HSE Epidemiology and Medical Statistics Unit (EMSU) contained details of 10,921 individuals with at least one blood lead measurement, of whom 1,260 were deceased.

Study documentation and correspondence was filed in the UK National Archive after the study was halted. This file has now been retrieved and is held by the HSE. Full access to the study file will be possible once the relevant clearances have been obtained.

The study database is held at the HSE Epidemiology Unit at Bootle, UK. This contains details of participants including:

• personal identifiers
• date of birth
4.3 STUDY POWER

Using year of birth, and making a number of simplifying assumptions, we used a life table approach to estimate the total number of deaths (by age band, sex and calendar period) that would be expected in the LMS cohort were it to experience the same mortality rates as the general population of England and Wales. We then used age-, period- and sex-specific proportional mortality from the England and Wales population to estimate expected deaths from specific causes in the LMS cohort. These calculations exclude deaths in persons aged 90 and over, and deaths occurring before 1985, meaning that the estimates are likely to be slightly conservative. They are shown in Table 1.

<table>
<thead>
<tr>
<th>Cause of death*</th>
<th>Expected deaths Male</th>
<th>Expected deaths Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>2511</td>
<td>360</td>
<td>2871</td>
</tr>
<tr>
<td>All cancers</td>
<td>686</td>
<td>84</td>
<td>770</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>194</td>
<td>14</td>
<td>208</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>40</td>
<td>3</td>
<td>43</td>
</tr>
<tr>
<td>Brain cancer</td>
<td>15</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>CHD</td>
<td>652</td>
<td>68</td>
<td>720</td>
</tr>
<tr>
<td>Stroke</td>
<td>164</td>
<td>34</td>
<td>198</td>
</tr>
</tbody>
</table>

* Underlying cause

Calculations were not performed for kidney cancer and non-malignant kidney disease, but based on recent mortality statistics for England and Wales, numbers for each of these causes are likely to be similar to those for brain cancer (i.e. less than 20).

In terms of total cancer deaths, these projections position the LMS study as the second largest study to have been conducted in occupationally lead-exposed workers to date. The largest study to date involved 4518 lead acid battery workers and 2300 lead smelter workers with blood lead measurements taken between 1947 and 1972, with a total of 897 cancer deaths ascertained up to 1995 (Wong & Harris, 2000). The LMS is larger in terms of the number of participants, and only a study of 100,000 lead-exposed...
workers currently under way in 11 states in the US has the potential to provide substantially more deaths for analysis, although this study will have shorter follow-up (Steenland, personal communication).

Using the number of expected deaths (Table 1), we can calculate the power to detect an effect of specified size using the formula from Beaumont and Breslow (Beaumont & Breslow, 1981). Results are shown for selected causes, based on male deaths only, in Table 2.

The cohort has considerable power to detect even modest increases in risk (e.g. SMR=120) for lung cancer, heart disease and stroke.

Table 2  Power to detect a relative risk of given size, based on expected deaths for males only

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Expected Deaths (E)*</th>
<th>Power** (%) when Relative Risk (RR) =</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1.1</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>194</td>
<td>39</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>40</td>
<td>--</td>
</tr>
<tr>
<td>Brain cancer</td>
<td>15</td>
<td>--</td>
</tr>
<tr>
<td>CHD</td>
<td>652</td>
<td>80</td>
</tr>
<tr>
<td>Stroke</td>
<td>164</td>
<td>35</td>
</tr>
</tbody>
</table>

* Expected deaths are calculated under the null hypothesis that the cohort has the same age and period specific mortality rates as the England general population.

** Based on a one sided test, with a=0.05

Thus this study will have sufficient statistical power to detect modest increases in risk for the cancers of primary interest.

4.4 RESEARCH GOVERNANCE

Although full details are lacking, it is assumed that participants consented at the time of enrolment to being flagged at NHSCR. However, since that time, standards of ethical governance in health research have changed. In particular, provisions under the Data Protection Act 1998, and the NHS Act 2006 have led to more stringent requirements to document the consent process for participants of health research, and in some cases this can apply retrospectively. Section 251 of the NHS Act 2006 allows the common law duty of confidentiality to be set aside in specific circumstances, including the flagging and tracing of retrospective cohort studies with NHSCR for the purposes of medical research. Applications to carry out specific research projects under section 251 are now administered by the National Information Governance Board for Health and Social Care (NIGB), who took over this function from the Patient Information Advisory Group (PIAG) in 2009. The LMS is on the list of studies approved under Office for National Statistics (ONS) application (PIAG ref: 4-07(h)/2002), which allowed for the continuation of flagging on the NHS Central Register for certain historic studies, following the transfer of the NHS Central Register from the ONS to the Information Centre for Health and Social Care (IC) in April 2008. A register of approved studies is maintained by the NIGB, and for these studies section 251 of the NHS Act 2006 permits:
“disclosure of identifiers to the Information Centre for tracing and / or flagging and subsequent disclosure by the Information Centre to researchers of one or more of the following: death details, cancer registration, current health area and exits from the NHS”.

[http://www.nigb.nhs.uk/ecc/reg](http://www.nigb.nhs.uk/ecc/reg)

In order to resume the notification process, it will be necessary to inform the NIGB of our intentions, and register as the new data custodians for the study. In this respect it is worth noting that approval was recently obtained by one of the co-investigators, under very similar circumstances, for follow-up of a historic study of mortality in UK cotton workers.

We will also seek and obtain approval an appropriate ethics committee of Heriot Watt University (with which IOM is affiliated). If deemed necessary by NIGB, we would also seek approval of a relevant NHS ethics committee.

We will also obtain clearance from the HSE ethics committee, if required, to assess the feasibility of obtaining additional data on study subjects, should there be a recommendation that this study be followed up by a nested case-control study of one of the cancers of a priori primary interest.

4.5 TRACING SUBJECTS

The majority of participants in the HSE study were flagged for long-term follow-up with the UK National Health Service Central Register (NHSCR), which maintains an updated list of all persons registered with a GP in England, Wales and Scotland, as well as information about all deaths, cancer registrations, and embarkations. HSE continued to receive data on deaths in cohort members at least up to 2000, and the study remains 'live' at the NHSCR, although event notifications to HSE are suspended. We plan to reopen notifications to update the tracing returns for all cohort members, and obtain details of all deaths registered between the last update and the end of 2009.

An attempt was made by HSE in 1995 to reconcile the list of study participants with the NHSCR list of the flagged population. This exercise identified 9147 participants (or 84% of those with BLL measurements) who were either flagged or known to have died. Approximately 1500 participants had BLL measurements but did not appear to have been flagged (i.e. could not be identified from a members and postings list for the study, provided by NHSCR). If data permit, we will flag these participants for long-term follow-up, in order to maximise the number of events available for analysis. Information available to allow flagging includes forename, surname, and date of birth, and we will investigate whether additional information is available to improve the efficiency of the flagging process. Advice on this matter will be sought from the NHS Information Centre at Southport, which has responsibility for the NHSCR.

4.6 EXPOSURE ASSESSMENT

The LMS study allowed for the collection of multiple BLL measurements during the course of the study, but for 43% of the workers only a single blood lead measurement was taken. A further 38% of participants had between 2 and 5 measurements, while 19% had more than 5 measurements. The mean and maximum blood lead levels for each individual were recorded in the study database.
The distribution of blood lead levels in the LMS cohort are presented in Table 3. Blood lead levels were originally recorded in units of nmol/dl but are also presented in µg/dl for comparability with the majority of published studies.

Table 3 Distribution of mean blood lead levels in the LMS Cohort

<table>
<thead>
<tr>
<th>Blood lead level</th>
<th>µg/dl</th>
<th>Number of BLL measurements</th>
<th>% of results in category</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>&lt;24.8</td>
<td>2338</td>
<td>21.4</td>
</tr>
<tr>
<td>120 to &lt;240</td>
<td>24.8 to &lt;49.7</td>
<td>4512</td>
<td>41.3</td>
</tr>
<tr>
<td>&gt;=240</td>
<td>&gt;=49.7</td>
<td>4071</td>
<td>37.3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>10921</td>
<td>100</td>
</tr>
</tbody>
</table>

Fifteen participants had blood lead levels of less than 5 µg/dl, which is within the range commonly seen in individuals with environmental exposure only. Mean and median blood lead levels were 44µg/dl and 40µg/dl, respectively, which is consistent with levels reported in other contemporaneous occupational cohorts from the UK, USA, Sweden and Finland (Steenland & Boffetta, 2000). These levels are roughly twice as high as currently found in UK workers undergoing medical surveillance under the CLAW regulations (Morton et al, 2010), which is consistent with the reduction in occupational exposure levels which has occurred over time. The levels are also somewhat higher than reported for a major study of workers under blood lead surveillance programs between 1982 and 2005 in the United States, where action thresholds for blood lead levels have historically been more stringent than in the UK.

In addition, HSE has over 2,200 lead-in-air measurements in the National Exposure Database (NEDB), collected between 1985 and 2004. Earlier measurements may also be available. The mean level is 0.34 mg/m³, with the 90th percentile of the exposure distribution at 0.56 mg/m³. We will undertake a statistical analysis of the available data in relation to process, factory, date of measurement and other available descriptive information. These data can be analysed to assist in categorising subjects into High/Medium/Low exposure categories based on the process and job carried out. We will additionally explore the presence of any temporal trends in the exposure data, which may inform a discussion of possible changes in risk over time.

Subjects will be categorised into High, Medium or Low exposure groups based on the available blood lead data and the recorded process and job information. These categories will be used in the SMR analysis.

The main strength of the exposure data is that they present levels that are somewhat higher than commonly found currently in UK lead workers, and considerably higher than found in the general population, which will therefore provide a greater ability to detect a statistical association with increased risk of cancer and other diseases, if one truly exists. In addition the possibility of linking data from the NEDB and associated factory visit reports affords the opportunity to cross-validate the exposure measurements. Thus if there exist health consequences of occupational exposure to lead and lead compounds we have a good chance of detecting them with this study.

The industry and process codes will also be used to assess the likelihood of exposure to other occupational carcinogens such as arsenic and cadmium (ever/never). They will also be used to identify exposure as being to either inorganic or organic lead compounds. As part of our sensitivity analysis, we will examine the effect of excluding...
individuals with likely occupational exposure to known carcinogens and to different groups of lead compounds.

We will undertake appropriate data quality checks on both the NEDB air sampling data and the blood lead data to ensure as far as possible that it is reliable.

4.7 DATA ANALYSIS

We will compare the mortality experience of the entire cohort with that of the general population of England, Wales and Scotland, and present the results as standardised mortality ratios (SMRs), with appropriate 95% confidence intervals. The SMR compares the observed number of deaths from a specified cause, with the number expected if the cohort experienced the same age-, sex- and period-specific mortality rates as the reference population. Person-years will accrue from the date of enrolment in the study, until death or embarkation. SMRs will be calculated for all cancers, lung cancer, stomach cancer, kidney cancer, and brain cancer. We will also calculate SMRs for all causes, and for death from ischaemic heart disease, stroke, and non-malignant kidney disease. We will also look at SMRs by lead exposure category (including subdivision by organic and inorganic lead compounds, if this is practicable).

4.8 LIMITATIONS

There are a number of limitations inherent in the proposed study, and which are common to many studies of lead exposure in occupational cohorts. These are listed below along with suggestions for how their effects will be minimised.

Exposure assessment relies on the measurement of blood lead levels at a single point of time, or on a number of measurements taken over a relatively short time period. As lead has a half-life in blood of approximately 30 days, a single measurement may not be representative of the levels encountered at other times. Indeed, a finding of a high blood lead level may result in a worker being removed from work areas associated with high exposure levels. We will therefore use blood lead measurements to assign study subjects to categories of high, medium and low exposure (in the absence of knowledge of health outcomes) and to supplement this with knowledge obtained from NEDB data and from other sources, including the wider scientific literature. Should a follow-on nested case-control study be recommended we will carry out a feasibility study to assess whether additional blood lead measurements might be obtained from HSE field offices for members of the study cohort.

An inherent limitation of the LMS dataset is that information was not collected on potential confounders such as smoking and alcohol. Information on smoking may have been recorded for a subset of participants who subsequently came under medical surveillance as part of the CLAW legislation. In the event of a subsequent case-control study being recommended we will explore the extent of such information being available from additional records held by HSE.
5 WHAT RESOURCES WILL YOU NEED TO DO THE WORK, AND ARE THESE RESOURCES AVAILABLE?

The study will be jointly led by Dr John Cherrie and Prof. Damien McElvenny and statistical and analytical support will be supplied by Dr Laura MacCalman. Occupational hygiene expertise will be provided by Dr Martie van Tongeren and another occupational hygienist at IOM.

HSE’s epidemiology group will provide support to enable the documentation to be gathered together and will participate in study meetings, thus contributing to the direction of the project and to the writing up of the report and any scientific papers.

The SMR analyses will be carried out using the well-established computer program Genstat.

6 WHO WILL DO THE WORK, AND HOW MUCH TIME WILL EACH OF THE PEOPLE INVOLVED DEVOTE TO IT?

The project will be carried out by the IOM, with Prof McElvenny being employed part-time to work on this project.

<table>
<thead>
<tr>
<th>Task</th>
<th>Person</th>
<th>Person-days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project management</td>
<td>John Cherrie, Damien McElvenny</td>
<td>3 days each</td>
</tr>
<tr>
<td>Obtaining the necessary clearances to enable study to be undertaken</td>
<td>Damien McElvenny</td>
<td>7</td>
</tr>
<tr>
<td>Cataloguing study documentation, cleaning of study data in preparation for analysis</td>
<td>Damien McElvenny</td>
<td>26</td>
</tr>
<tr>
<td>Provision of occupational hygiene expertise</td>
<td>Martie van Tongeren plus Exposure Scientist</td>
<td>22</td>
</tr>
<tr>
<td>Setting up and running SMR analyses in OCMAP</td>
<td>Damien McElvenny</td>
<td>17</td>
</tr>
<tr>
<td>Data management and running SMR analyses</td>
<td>Laura MacCalman</td>
<td>20</td>
</tr>
<tr>
<td>Feasibility of obtaining extra data on study subjects from HSE records</td>
<td>Damien McElvenny (and HSE colleagues)</td>
<td>10</td>
</tr>
<tr>
<td>Attend progress meetings, write progress reports, final report and manuscripts</td>
<td>Damien McElvenny, Martie van Tongeren</td>
<td>3 days each</td>
</tr>
</tbody>
</table>
7 HOW LONG WILL THE WORK TAKE?

The work will take around 12 to 15 months to complete, from obtaining all the necessary clearances. Additional time will be required to enable scientific papers to be published.

The IOM has an established internal project management system developed and refined over many years of experience in the design, management and execution of funded multi-disciplinary research. The primary responsibility for the execution, completion and delivery of a project is vested in the project leader. The principal aim of the management system is to ensure adequate support and supervision for the project leader, to assist in their management of the project. A set of Research Guidance Notes gives help and advice, and describes the operation of the systems.

The procedures that help ensure the timely delivery of this project include:

- detailed project plans, updated throughout the project;
- regular project team meetings, fully documented;
- internal supervision and audit by senior IOM staff;
- internal peer review of all reports (and papers) arising from the work;
- archiving of all the documentation for a period of no less than six years.

As part of the project control and liaison, the project manager will prepare brief written progress reports at agreed intervals to be submitted to the Sponsor’s Representative.

8 HOW MUCH MONEY DO YOU NEED TO COMPLETE THE WORK?

[Details have been deliberately removed for this version.]

9 WHEN DO YOU PLAN TO START?

As soon as possible when funding is made available. Hopefully this will be in July 2011.

10 REFERENCES


APPENDIX 1: A BRIEF REVIEW OF THE RISKS ASSOCIATED WITH LEAD EXPOSURE

In 2005, an estimated 8,023 (5%) cancer deaths were attributable to occupation in Great Britain (6,366 men; 1,657 women). In the same year an estimated 13,694 (4%) cancer registrations were attributable to occupation in Great Britain (10,074 men; 3,620 women). Within these figures, 54 deaths and 67 cancer registrations were estimated to be due to occupational exposure to inorganic lead compounds, with most of these estimated to have occurred in: the manufacture of electrical machinery, apparatus, appliances, supplies; the manufacture of plastic products, not elsewhere classified; and in non-ferrous metals basic industries (Rushton et al, 2010). The number of workers under medical surveillance for lead in Great Britain in 2008/09 was just under 7,000 (HSE, 2010).

Acute effects of lead exposure at relatively high levels are well known, and include central and peripheral nervous system damage, kidney damage, inhibition of haemoglobin synthesis, and gastrointestinal symptoms (EPA, 2006). Historically such high exposures were most commonly encountered in occupational settings, and led to the widespread introduction of occupational safety standards and legislation to limit or prevent exposures at levels associated with acute effects (Schwartz & Hu, 2007). In children the developing nervous system appears particularly sensitive: neurological, cognitive and behavioural consequences of lead exposures in children are well documented, and occur at levels well below those needed to cause acute symptoms in adults (Schwartz & Hu, 2007). In recent decades, attention has turned to long-term health effects of subacute exposures, and a number of important reviews have been conducted. These include:

- the 2004 Report on Carcinogens, by the U.S. Department of Health and Human Services National Toxicology Program (NTP), and which included lead and lead compounds for the first time (NTP, 2004).
- the WHO International Agency for Research on Cancer (IARC) evaluation of lead and lead compounds (IARC, 2006). This review focused on associations between lead and specific cancers, and assessed evidence from epidemiological studies, animal studies and in vitro studies.
- a wide-ranging review of possible health effects of exposure to lead and lead compounds in ambient air, published in 2006 by the US Environmental Protection Agency (EPA, 2006).

For carcinogenicity, the epidemiological evidence is most consistent for stomach cancer, with lung cancer, kidney cancer and brain cancer showing elevation in some, but not all studies. The most recent evaluation of organic and inorganic lead compounds from the International Agency for Research on Cancer (IARC) described the evidence in humans for the carcinogenicity of inorganic lead compounds as limited and for organic lead compounds as inadequate. IARC classified inorganic lead compounds as possibly carcinogenic to humans and organic lead compounds as not classifiable as to their carcinogenicity (IARC, 2006a). In their 2006 report EPA reached a similar conclusion (EPA, 2006).

In laboratory animals (mainly rats and mice) lead is an established carcinogen. Carcinogenic effects have been demonstrated for a range of inorganic lead compounds
administered by different routes (e.g. orally in food or water, via subcutaneous or intraperitoneal injection). Kidney tumours are among the most consistently observed lesion in animal studies, but a number of other sites have been affected, including lung, brain and hematopoietic system. Importantly, a number of studies have demonstrated a dose-response effect. Lead does not appear to be strongly mutagenic in itself, and laboratory studies suggest that it may exert its effects indirectly, for example by inhibition of DNA repair and synthesis pathways, by interacting with various DNA-binding or tumour suppressor proteins, or by increasing oxidative stress. This is consistent with animal experiments showing for example that orally administered lead nitrate enhances the renal carcinogenicity of N-ethyl-N-hydroxyethylnitrosamine in rats (NTP, 2004).

The evidence for carcinogenicity in humans is less conclusive, and relies heavily on a small number of studies of highly exposed occupational cohorts, including lead smelters in the USA (Steenland et al, 1992; Wong & Harris, 2000), Italy (Cocco et al, 1997), and Sweden (Gerhardsson et al, 1995; Lundstrom et al, 1997), battery workers in the UK (Fanning, 1988), and lead exposed workers in a range of industries in Finland (Anttila et al, 1995). All worker studies had methodological limitations including lack of information on confounders (especially smoking, diet, and occupational exposure to other potential carcinogens), and limited exposure assessment (e.g. blood lead measurements taken at a single time point, or based on lead in air measurements, or based on job exposure matrices). Few studies have provided good data on dose-response relationships. The most relevant occupational studies were reviewed by Steenland and Boffetta in 2000, who conducted meta-analyses using data from 8 studies, for cancers of the lung, stomach, kidney and brain (Steenland & Boffetta, 2000). For lung cancer, a random effects model yielded a relative risk (RR) of 1.30 (95% confidence interval 1.15 to 1.46). However, excluding results from one study in which workers were also exposed to arsenic gave an RR=1.14 (1.04 to 1.25) in a fixed effects model. For stomach cancer, a fixed effects model gave a pooled RR=1.34 (1.14 to 1.57). For kidney cancer there was no evidence for an excess risk among lead exposed workers: pooled RR=1.01 (0.72 to 1.42). Similarly for brain cancer, there was little evidence of increased risk: pooled RR=1.06 (0.80 to 1.40).

A small number of occupational studies have been published since the IARC and EPA evaluations. These include an updated analysis of a case control study of 3730 men aged 35-70 and residing in Montreal (Canada) between 1979 and 1985 with newly diagnosed cancer (lung, stomach, kidney, oesophagus, colon, rectum, pancreas, prostate, bladder, melanoma) (Rousseau et al, 2007). Two control groups were used - general population controls (n=533), and cancer controls, which were selected from patients with non-lung cancers at sites other than the one of interest. Job histories were collected at interview and assessed for potential exposure to 3 groups of lead compounds (inorganic and inorganic lead compounds, and leaded gasoline emissions), and a 3 level exposure index (unexposed, non-substantial, and substantial exposure) was assigned for each group of compounds. Information collected on potential confounders included smoking, alcohol, diet, income and cultural origin (or place of birth), and likely occupational exposure to other carcinogens (arsenic, cadmium, chromium [VI], asbestos). Significant associations were reported for organic lead (which included non-combusted leaded gasoline) and stomach cancer using both population controls (adjusted OR 3.0 [1.2 to 7.3]) and cancer controls (adjusted OR 2.0 [1.1 to 3.8]), and also for organic lead and cancer of the rectum using population controls (adjusted OR 3.0 [1.2 to 7.5]), but not when using cancer controls (adjusted OR 1.5 [0.8 to 2.9]). Substantial exposure to leaded gasoline emissions was
associated with stomach cancer, but only when cancer controls were used (adjusted OR 2.9 [1.4 to 5.9]). As the authors note, these findings are based on small numbers of exposed cases (e.g. only 14 out of 136 cases of stomach cancer had substantial lead exposure), and are especially difficult to interpret when the results differ according to type of control group used.

Cancer risk in relation to lead exposure in men was explored in a study in New Jersey (USA) which linked data from the State Cancer Registry with an occupational lead surveillance database (the Adult Blood Lead Epidemiology and Surveillance System, or ABLES) (Lam et al, 2007). Standardised incidence ratios (SIR) were calculated using general population reference rates. This was a fairly young cohort and number of cancers at specific sites was small (85 in total, 22 lung, 4 stomach, 5 kidney). Overall there were significantly fewer cancers than expected (SIR = 0.51 [0.41 to 0.62]), and no significant excesses were noted for any site, although there were significantly fewer prostate cancers than expected (SIR = 0.35 [0.20 to 0.57]).

Data from the National Longitudinal Mortality Study (NLMS) was used to study brain cancer in relation to occupational lead exposures in a population based cohort of almost 318,000 individuals recruited between 1979 and 1981 (van Wijngaarden & Dosemeci, 2006). The probability and likely intensity of lead exposure (3 categories each) was estimated from details of current or most recent job (self-reported), using a job exposure matrix, and follow-up was continued up to 1989. The results of internal analyses (unexposed vs. exposed cohort members) were suggestive of an increased risk associated with any lead exposure (age and gender adjusted hazard ratio = 1.5 [0.9 to 2.3]), and there was some evidence of a dose response effect for both probability and likely intensity of exposure. Brain cancer risk was highest in the group with highest probability and highest likely intensity of exposure (HR=2.3 [1.3 to 4.2]).

A number of studies have tried to identify genetic variants that influence susceptibility to the effects of lead. One proposed candidate is a relatively common polymorphism in the δ-aminolevulinic acid dehydratase (ALAD) gene. The ALAD enzyme catalyzes the second step in the haem synthesis pathway, and strongly binds, and is inhibited by lead. A relatively common allele, ALAD2, results from a single point mutation (G to C at position 177, rs1800435), and the variant enzyme has a higher affinity for lead compared to the wild type (ALAD1). In a recent US case-control study of patients with glioma (n=489) and meningioma (n=197) the effect of lead on cancer risk was examined in relation to ALAD genotype (Rajaraman et al, 2006). Using self-reported job histories and a comprehensive job exposure matrix, cumulative lead exposure was estimated by integrating data on likely exposure intensity frequency and duration. There was a marginally significant trend (p=0.06) for meningioma risk with increasing cumulative lead exposure levels among carriers of the ALAD2 allele, but not among ALAD1 homoygotes. However the interaction term was not statistically significant, due at least in part to the small the number of cases among ALAD2 carriers. There was no detectable effect of lead exposure or ALAD genotype on glioma risk in this study.

The same case series was used by another group to investigate whether single nucleotide polymorphisms (SNPs) in genes related to oxidative stress may modify any effect of lead exposure on cancer risk (Bhatti et al, 2009). After adjustment for multiple comparisons, significant interactions were seen for a subset of patients with glioblastoma multiforme, with 2 (highly linked) polymorphisms in the GPX1 gene (rs1050450 and rs1800668), and one in the RAC2 gene (rs2239774). However, the
significant interaction term for the rs2239774 variant seems to be driven by a strong (though not statistically significant) protective effect of lead on cancer risk (OR = 0.3 [0.08 to 1.2] for each 100 µg/m³ y increase in cumulative lead dose) in carriers of the variant. This seems implausible, and given the limitations of the method for estimating cumulative lifetime lead exposure, these findings need to be replicated in a much larger study.

Cancer risk in relation to blood lead levels have also been studied in general population settings. In the US National Health and Nutrition Examination Survey II (NHANES II), 3,592 white participants were classified on the basis of a single blood lead measurement (taken between 1976-1980), and followed up for cause specific mortality to 1992 (an average of 13.3 years) (Jemal et al, 2002). After adjustment for age, alcohol and smoking, there was a non-significant trend in cancer mortality (all sites) with relative risks of 1.24 (0.66 to 2.33), 1.33 (0.57 to 3.09), and 1.50 (0.75 to 3.01) for the second, third, and fourth quartiles of blood lead exposure, compared to the lowest quartile. A second analysis of this NHANES II data was conducted which included non-white participants, with adjustment for a wider range of confounders, and excluding participants with blood lead levels greater than 30µg/dl (on the assumption that such high levels may reflect occupational rather than environmental exposures) (Lustberg & Silbergleid, 2002). Compared to the reference group (blood lead <10µg/dl), adjusted RRs for mortality from all cancers were 1.46 (0.87 to 2.48) for blood lead levels between 10-19µg/dl, and 1.68 (1.02 to 2.78) for blood lead levels between 20-29µg/dl.

Two analyses have been reported from the third National Health and Nutrition Examination Survey (NHANES III). Schober et al followed 9,757 participants aged 40 or over, classified according to blood lead levels in 3 groups: <5µg/dl, 5-9µg/dl, and 10 µg/dl or more (Schober et al, 2006). After adjustment for smoking, socioeconomic status, and other factors, a significant trend was observed (p<0.001) for all cancer mortality, with RRs for the two higher exposure categories of 1.24 (1.05 to 1.48) and 1.59 (1.28 to 1.98), respectively. Menke et al included participants aged 20 and over in their study of the NHANES III population, and used different cutpoints for blood lead levels (Menke et al, 2006). They found no convincing evidence for a dose response effect between lead and mortality from all cancers. Bone lead and blood lead levels were not associated with cancer mortality among 868 male veterans who were part of the Normative Aging Study (Weisskopf et al, 2009). Blood lead levels were not associated with cancer in prospective study of 533 women aged 65-87 who were enrolled in the US Study of Osteoporotic Fractures (Khalil et al, 2009).

Interest in the possible role of lead in the development of hypertension and cardiovascular disease stems in part from the ecological association between water hardness and cardiovascular disease rates observed in the UK in the 1980s. Lead is more soluble in softer acidic water, and soft water drinking supplies tend to coincide with areas having high rates of cardiovascular disease (Shaper & Pocock, 1985). The hypothesis was investigated in the British Regional Heart Survey, a community based sample of 7735 male participants living in 24 British towns, with inconclusive results (Pocock et al, 1984). In one of the earliest prospective studies of this association, blood lead was not consistently associated with blood pressure among a random population sample (n=728) in Belgium followed between 1985 to 1995 (Staessen et al, 1996). In contrast, significant positive associations between blood lead and both systolic and diastolic blood pressure were reported in the NHANES II study (Harlan et al, 1985). In the Normative Aging Study bone lead, but not blood lead levels were associated with baseline blood pressure and with development of hypertension among
The mortality of workers with occupational lead exposure: A research proposal

474 men who were normotensive at the baseline examination (Cheng et al, 2001). Further studies on this cohort demonstrated an interaction with self-reported stress such that the association between bone lead levels and hypertension was significantly stronger among participants with above median self-reported stress levels at baseline (Peters et al, 2007). Other findings from the Normative Aging Study include associations between bone lead and incident ischaemic heart disease (Jain et al, 2007); bone lead and heart rate variability (Park et al, 2006); and bone lead and pulse pressure (Perlstein et al, 2007).

A review and meta-analysis published in 2002, included 31 studies involving 58,818 participants and concluded that there was evidence for a modest effect such that a doubling of blood lead levels was associated with a modest increase in systolic blood pressure of 1.0 (0.5 to 1.4) mmHg, and an increase in diastolic blood pressure of 0.6 (0.4 to 0.8) mmHg (Nawrot et al, 2002). There is a good deal of experimental support from in vitro and animal studies (EPA, 2006), which taken with the epidemiological evidence, led the authors of a more recent systematic review to infer a causal association between lead exposure and blood pressure (Navas-Acien et al, 2007).

The same review concluded that the evidence was suggestive but insufficient to infer a causal association between lead exposure and clinical cardiovascular outcomes (Navas-Acien et al, 2007). Studies of highly exposed workers have tended to suffer from methodological limitations, including bias associated with the healthy worker effect, and limited information on confounders. Gerhardsson et al reported significantly elevated CHD mortality (SMR=172 [120 to 242]) among Swedish smelter workers compared to the general population (Gerhardsson et al, 1995). Cocco et al reported an elevated stroke risk in Italian smelter workers when using regional reference rates (SMR=122 [98 to 149]), but not when national reference rates were used (SMR=95 [77 to 115]) (Cocco et al, 1997). Steenland and colleagues found no overall elevated risk for stroke among US smelter workers (compared to the general population), except for a subgroup who had worked for 20 years or more in the industry (SMR 141 [92 to 207]) (Steenland et al, 1992).

Slightly more consistent results have come from community or population based studies. In the NHANESII study, 4190 participants with blood lead measurements taken between 1976 and 1980 were classified into 3 groups (<10, 10-19 and 20-29µg/dl), and followed up for mortality to the end of 1992. Relative risks for circulatory disease mortality among groups with intermediate and high blood lead levels were 1.10 (0.85 to 1.43) and 1.39 (1.02 to 2.78) respectively (Lustberg & Silbergeld, 2002). Similar results were obtained from the NHANESIII population (n=13,946): using tertiles of blood lead categories (corresponding to levels of <1.9, 1.9-3.6, and >3.6µg/dl), the RR for myocardial infarction in the intermediate and high blood lead tertiles were 1.02 (0.55–1.89) and 1.89 (1.04–3.43). For stroke mortality the corresponding RRs were 2.19 (0.87–5.53) and 2.51 (1.20–5.26), and for cardiovascular disease overall the RRs were 1.03 (0.69–1.55) and 1.55 (1.08–2.24) (Menke et al, 2006). For all three conditions, the trend was significant.

Acute lead intoxication is associated with nephrotoxicity in humans and in experimental animals (EPA, 2006). Occupational and community based studies have found evidence of an association between blood or bone lead measurements, and markers of impaired renal function (Ekong et al, 2006). Even relatively low lead levels may accelerate progressive loss of kidney function in some patients with underlying kidney disease (Lin et al, 2006; Tsaih et al, 2004; Weaver et al, 2009).
Hypertension is a major cause of kidney failure (end stage renal disease, or ESRD). Lead is thought to raise blood pressure, and may therefore exert some of its effects on the kidney through this mechanism. Impaired renal function may in itself be a cause of increased blood pressure, with the resulting feed-forward loop leading to accelerating renal failure.

Occupational studies have been a major source of epidemiological evidence on the potential health effects of lead. However they share a number of limitations, including limited ability to control for confounding. Smoking in the workplace is regarded as a potential confounder, since it may result in increased ingestion of lead containing particles, leading to higher blood lead levels in smokers (who have higher rates of lung and stomach cancer). Workers exposed to lead may also be exposed to a number of other compounds some of which are known to be carcinogenic. For example, co-exposure to arsenic is suggested to account for some of the elevated lung cancer rates in lead smelters (IARC, 2006).

Misclassification of exposure is a potential source of bias relevant to occupational studies of lead exposure. In many studies exposure classification has relied on job-exposure matrices devised by occupational hygienists, or a single blood lead measurement. Lead has a biological half-life of around 30 days in blood, and a single blood lead measurement therefore reflects recent exposure but may be a relatively crude indicator of cumulative lead dose (Hu et al, 1998; Hu et al, 2007). If this misclassification of exposure is non-differential, then it will bias effect estimates towards the null. However, categorisation of a continuous exposure variable which is measured with error can introduce differential misclassification (Flegal et al, 1991). The healthy worker effect will also lead to bias towards the null when the exposure of interest is associated with increased disease risk. An occupational cohort may differ from the reference population in other ways, resulting in bias (Pearce et al, 2007). For example, if an occupational cohort contains a higher proportion of migrant workers from areas with high prevalence of H-pylori infection, then stomach cancer rates may appear elevated relative to the reference population. This could explain at least part of the 50% excess risk stomach cancer reported in study of lead workers at battery plants and smelters in the USA. More than 20% of that cohort were first generation immigrants from Ireland and Italy, and a nested case-control study showed that this group had a 2-fold excess of stomach cancer (Wong & Harris, 2000).

A collaborative project between IARC and the US National Occupational Research Agenda (NORA) identified the research needs to resolve the carcinogenicity of the high-priority IARC carcinogens. It was pointed out that background rates of stomach cancer are highly variable and therefore epidemiological studies should consider local reference rates and internal dose-response analyses for this cancer. It was also suggested that additional studies of new cohorts with well-documented lead exposure, as well as further follow-up of existing cohorts would be useful (IARC/NORA, 2010; Ward et al, 2010).
References


Schober SE, Mirel LB, Graubard BI, Brody DJ, Flegal KM (2006) Blood lead levels and death from all causes, cardiovascular disease, and cancer: results from the NHANES III mortality study. Environmental Health Perspectives 114(10): 1538-1541


Schober SE, Mirel LB, Graubard BI, Brody DJ, Flegal KM (2006) Blood lead levels and death from all causes, cardiovascular disease, and cancer: results from the NHANES III mortality study. Environmental Health Perspectives 114(10): 1538-1541


APPENDIX 2: INSTITUTE OF OCCUPATIONAL MEDICINE

The Institute of Occupational Medicine (IOM) is a major independent centre of scientific excellence in the fields of occupational and environmental health, occupational hygiene and risk. We were founded as a charity in 1969 by the UK coal industry in conjunction with the University of Edinburgh and became fully independent in 1990, retaining our charitable status. Our mission is to benefit those at work and in the community by providing quality research, consultancy and training in health, hygiene and safety and by maintaining our independent, impartial position as an international centre of excellence. We aim to provide high quality research, consultancy and training to help to ensure that people's health is not damaged by conditions at work or in the environment. IOM currently employs about 120 staff based in Scotland and England.

Our first major research programme on Coal Miners' lung diseases began in the 1950s, and this was the basis for the formation of the IOM in 1969. Major themes were measurement of airborne dust concentrations underground in coal mines, characterisation of types and constituents of the dusts, measurement of health effects, relationships between exposure and disease, and proposals for prevention. This research became an international benchmark for epidemiological studies of occupational health, and was the primary scientific influence on dust control regulations in mines in the UK, US and other countries.

Our current work spans many industries and hazards including: construction, asbestos, man-made mineral fibres, pesticides, chemicals, energy, telecoms, metals, textiles, and agriculture, as well as the environment. While diseases of the respiratory tract remain a major interest, our scope now extends to many other health outcomes such as cardiovascular effects, cancer, musculo-skeletal disorders including back pain and upper-limb disorders, hearing loss, skin diseases, thermal and psychological stress. Our related work includes the development and application of measurement and control systems, mathematical models and survey methods. We are experienced in undertaking evaluations of occupational health and safety services, health promotion activities and environmental management projects.

IOM staff are skilled at working on high profile research projects with tight timescales. We have a system for managing the progress of our research and the financial costs associated with undertaking the work. We comply with appropriate ethical and professional standards in all our work.

We have extensive experience in the field of epidemiology. The early work we carried out into pneumoconiosis in the British coal industry was, we believe, the biggest integrated programme of occupational epidemiology ever undertaken, with a team-working approach combining all the IOM's skills in the necessary scientific disciplines and in project leadership. These skills have since been applied to investigate health effects of other hazards, including organic and inorganic dusts, fibres, volcanic ash, fumes, chemicals, noise and unsafe working practices. A constant theme has been reliable exposure estimation.
Some current and recent studies are given below:

- Pilot study of risks and long-term effects of carbon monoxide poisoning (UK Dept of Health)
- EDPHiS - Environmental Determinants of Public Health in Scotland (Scottish Government)
- Task-exposure matrix for pesticides in a study of Parkinson's disease (DEFRA)
- Mortality in coal workers exposed to respirable dust and quartz (BAuA, Germany)
- Pesticides and prostate cancer (DEFRA)

We believe that our research findings should be subject to the scrutiny of the international scientific community. We publish our findings in the peer reviewed scientific literature and through our own TM series of research reports. Access to all of IOMs past research reports is available through our online library at [http://www.iom-world.org/research/libraryentry.php](http://www.iom-world.org/research/libraryentry.php)
APPENDIX 3: CVS

John Cherrie
Institute of Occupational Medicine, Research Avenue North, Edinburgh, EH14 4AP, United Kingdom

Telephone +44 (0)131 449 8032
Fax +44 (0)131 449 8084
E-mail john.cherrie@iom-world.org
Website www.IOM-world.org

Nationality British
Date of birth 3rd September 1954
Gender Male

Work experience
2003 – Present
Position held Research Director
Honorary Reader at the University of Aberdeen
Main activities and responsibilities I am responsible for a team of 12 scientists who undertake research in occupational safety and health, and for the overall quality of all of IOMs research output. My own research interests include human exposure assessment, environmental and occupational epidemiology, natural and synthetic fibres – including asbestos, dermal exposure to chemicals and dermatitis, and particulate air pollution. I am a member of the IOM Board of Management, chair the Research Board and I contribute to a number of other IOM management initiatives. I manage or provide scientific contributions to several research projects within IOM and in collaboration with other research partners. I also prepare medico-legal reports in relation to dust and chemical exposures (further details at the end of this CV).

Name and address of employer Institute of Occupational Medicine, Research Avenue North, Riccarton, Edinburgh, EH14 4AP, UK

Position held Reader in Occupational Hygiene
Main activities and responsibilities I was responsible for organising and teaching a Master of Science degree course in Occupational Hygiene from 1991 to 2001. I carried out several research projects in collaboration with IOM and other organizations.
Name and address of employer
University of Aberdeen, Environmental & Occupational Medicine, Foresterhill, Aberdeen, UK

Position held
Section Head in Chemistry and Mineralogy

Main activities and responsibilities
I participated in consultancy and research in occupational hygiene.

Name and address of employer
Institute of Occupational Medicine, 8 Roxburgh Place, Edinburgh, EH8 9SU, UK

Education and training
1992 – 1996

Title of qualification awarded
PhD Occupational hygiene

Principal subjects/occupational skills covered

Name and type of organisation
University of Aberdeen

Dates
1972 - 1977
BSc (Hons) Physics 2.1
University of Edinburgh

Dates
1984
Diploma in Occupational Hygiene
Occupational hygiene
British Examining and Registration Board in Occupational Hygiene

Social skills and competences
Strong scientific leadership skills.
An able communicator, both in written materials and oral presentations.
Experienced university lecturer.

Organisational skills and competences
Well-organised and focussed on delivery of high quality on-time.
Ability to manage teams of scientists and to work collaboratively within a team.
Aptitude for problem solving.
Committed to improving the environment for the benefit of people at work and in the community.
Technical skills and competences | International expert in human exposure assessment for dust and chemicals.

Computer skills and competences | Competent in the use of Microsoft Office programs and other specialist software used for exposure assessment.


Government advisory committees | Department of Environment, Food and Rural Affairs
Member of the Advisory Committee on Pesticides (2002 – 2009)
Health and Safety Executive,
Member of the Committee on Fibre Measurement (1992 – date)
Department of Environment, Food and Rural Affairs
Member of the Expert Panel on Air Quality Standards (1994 – 2003)
Veterinary Medicines Directorate
Member of The Appraisal Panel For Human Suspected Adverse Reactions (1998 – 2002)

Additional information | References available on request.

Over 100 scientific publications in peer-reviewed journals and other scientific media.
A list of John Cherrie’s scientific publications can be found at…
Professor Damien Martin McElvenny

**Qualifications**

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<tr>
<td>2011</td>
<td>Nearing completion of PhD thesis “Meta-analysis in occupational epidemiology”, London School of Hygiene &amp; Tropical Medicine (due for submission Autumn 2011).</td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>MSc Statistics</td>
<td>University of Sheffield</td>
</tr>
<tr>
<td>1985</td>
<td>BSc (Hons) Statistics</td>
<td>University of Newcastle upon Tyne</td>
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**Professional Qualifications/Membership of Learned Societies**

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<tr>
<td>2008-</td>
<td>Member of International Epidemiology Association</td>
</tr>
<tr>
<td>2008-</td>
<td>Member of Society for Radiological Protection</td>
</tr>
<tr>
<td>2008-</td>
<td>Member of International Commission on Occupational Health (EPICOH)</td>
</tr>
<tr>
<td>1993-</td>
<td>Chartered Statistician and Fellow of the Royal Statistical Society</td>
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**Current Post**

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**Previous Appointments**

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<td>Professor of Epidemiology, University of Central Lancashire</td>
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<tr>
<td>1996-07</td>
<td>Statistician (Principal Scientific Officer), Health &amp; Safety Executive</td>
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<tr>
<td>1994-96</td>
<td>Senior Statistician, Northern and Yorkshire Clinical Trials and Research Unit</td>
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<td>1990-94</td>
<td>Senior Statistician, British Nuclear Fuels plc</td>
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<tr>
<td>1987-89</td>
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<tr>
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**Positions of responsibility**

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<tr>
<td>2008-10</td>
<td>Chair, Faculty of Health Ethics Committee</td>
</tr>
<tr>
<td>2008-10</td>
<td>Executive Director of Epidemiology and Genetics, Westlakes Scientific Consulting Limited</td>
</tr>
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**Current Research**

I am interested in all aspects of the causes and distribution of work-related ill-health, with particular focus on occupational cancers.

**Research grants and awards**

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<td>Epidemiological Studies of Exposed Southern Urals Populations (£716k – European Commission)</td>
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**Consultancy**

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<td>Canadian Nuclear Safety Commission ($1500)</td>
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<td>2008</td>
<td>Airbus UK (£1000)</td>
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<td>2008</td>
<td>Health &amp; Safety Executive (£2500)</td>
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The mortality of workers with occupational lead exposure: A research proposal

External Professional

- Peer-reviewer for Environmental Health Perspectives
- Peer-reviewer for MRC Grant Applications
- Peer-reviewer for BMC Public Health
- Peer-reviewer for International Journal of Cancer
- Member Industrial Injuries Advisory Council
- External examiner for MPhil/PhD upgrade, Imperial College
- Peer-reviewer for Journal of Radiological Protection
- Peer-reviewer for the Colt Foundation funding applications
- Peer-reviewer for Occupational and Environmental Medicine
- Peer-reviewer for Journal of Radiological Protection
- Peer-reviewer for the Colt Foundation funding applications
- Peer-reviewer for Occupational and Environmental Medicine
- Peer-reviewer for Environmental Health Perspectives
- Peer-reviewer for MRC Grant Applications
- Peer-reviewer for BMC Public Health
- Peer-reviewer for International Journal of Cancer
- Member Industrial Injuries Advisory Council
- External examiner for MPhil/PhD upgrade, Imperial College
- Peer-reviewer for Journal of Radiological Protection
- Peer-reviewer for the Colt Foundation funding applications
- Peer-reviewer for Occupational and Environmental Medicine
- Peer-reviewer for Journal of Radiological Protection
- Peer-reviewer for the Colt Foundation funding applications
- Peer-reviewer for Occupational and Environmental Medicine

Refereed Publications

Total publications to date: 20
Those published in the last 5 years:


Unrefereed Publications

Total publications to date: 6
Those published in the last 5 years:


| Presentations, conferences, workshops, exhibitions, performances, etc | 2010 | Oral Presentation, 21\textsuperscript{st} International Conference on Epidemiology in Occupational Health, Taipei, Taiwan. |
| | 2009 | Invited Lecture, Royal Society of Chemistry/British Nuclear Energy Society Cumbrian Branches, Seascale |
| | 2008 | Oral Presentation, 20\textsuperscript{th} International Conference on Epidemiology in Occupational Health, Heredia, Costa Rica |
| | 2007 | Oral Presentation, 19\textsuperscript{th} International Conference on Epidemiology in Occupational Health, Banff, Canada |

| Any other activities | 2010 | Co-organiser of 5\textsuperscript{th} UK & Ireland one day meeting on Occupational and Environmental Epidemiology, Manchester. |
| 2008 | Co-organiser of 4\textsuperscript{th} UK & Ireland one day meeting on Occupational and Environmental Epidemiology, London. |
Martie Josephus Arnoldus van Tongeren

Qualifications

2000  PhD in Occupational Health, University of Birmingham

1989  BSc and MSc in Environmental Science, Wageningen Agricultural University, The Netherlands

Professional Qualifications/ Membership of Learned Societies

Honorary Lecturer at the Department of Environmental and Occupational Medicine, University of Aberdeen.
Member of British Occupational Hygiene Society.
Assistant Editor of the Annals of Occupational Hygiene.
Chair of Conference Committee BOHS 2005.
Member of HSE's Working Group on Action to Control Chemicals (WATCH).

Current Post

Section Head Exposure Assessment Group, Director of Research Development Institute of Occupational Medicine Research Avenue North
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Previous Appointments

1989-91  Research Assistant, Wageningen Agricultural University, The Netherlands

1991-02  Research Assistant/Research Fellow/Senior Research Fellow, Institute of Occupational Health, University of Birmingham

2002-06  Senior Lecturer, Centre for Occupational and Environmental Health, University of Manchester

Publications


2010


2009


Carder M, McNamee R, Beverland I, Elton R, Cohen
GR, Boyd J, Van Tongeren M, Agius RM Does socio-economic status modify the effect of particulate air pollution on cardiopulmonary mortality? Accepted for publication by OEM.


McKinney PA, Raji OY, van Tongeren M, Feltbower RG. The UK childhood cancer study: Maternal occupational exposures and childhood leukaemia and lymphoma. Radiation Protection Dosimetry
The mortality of workers with occupational lead exposure: A research proposal


2007


The mortality of workers with occupational lead exposure: A research proposal

2004


2006


2003


2002


