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HSL contribution to the investigation of the Rutherford Laboratories at Manchester University

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In addition to Dr Todd’s work, the documents assembled by him and John Churcher and Don O’Boyle in “Possible Health risks due to ionising radiation in the Rutherford Building (Formerly Coupland 1) at the University of Manchester.” have provided a further invaluable resource.

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EXECUTIVE SUMMARY

The University of Manchester asked Professor David Coggon to conduct an independent review into issues raised in a report "Possible health risks due to ionising radiation in the Rutherford Building (formerly Coupland Building 1) at the University of Manchester" (Authors: John Churcher; Don O'Boyle and Neil Todd). To underpin the review the University commissioned the Health Protection Agency to look into radiological hazards and the Health & Safety Laboratory to look at the toxicity of elemental mercury, past and present exposures and likely health consequences.

Objectives

The scope of the work agreed with Professor Coggon was to address the following questions:

1. What are the health consequences reported in the peer reviewed literature following exposure to mercury vapour? In particular:
   - Assess the evidence regarding health effects of mercury vapour, and any associated contaminants.
   - Review the relationship between risk and adverse outcomes to exposure levels in air or biological materials (urine, blood, hair etc).
   - Consider issues relating to time to clear any toxic products from the body.

2. Could the levels of exposure to mercury vapour reported in the Rutherford Buildings lead to health consequences? In particular, we will:
   - Collate the evidence available regarding exposure to mercury and related toxic compounds in the affected areas of the Rutherford Buildings.
   - Make an assessment of risks to health past and present of these exposures (using a "worst case scenario" model).
   - Consider any uncertainties and/or gaps in the information available.
   - Recommend additional testing (as appropriate) to address any gaps identified above.

3. What remedial actions might be required?

Main Findings

This review focused on the toxicity of elemental mercury in humans following chronic, low-level exposures. It is based on key authoritative, review documents by international groups of experts that have comprehensively examined the toxicity of elemental mercury (e.g. Scientific Committee on Occupational Exposure Limits; Deutsche Forschungsgemeinschaft; International Programme on Chemical Safety; Health and Safety Commission's Advisory Committee on Toxic Substances, Agency for Toxic Substances and Disease Registry, United States Environmental Protection Agency, United Kingdom Health and Safety Executive, International Agency for Research on Cancer (IARC)). Toxicological endpoints addressed include neurotoxicity, renal toxicity, respiratory, cardiovascular, gastrointestinal, haematological and reproductive effects, genotoxicity and carcinogenicity.

After acute and chronic inhalation exposures in occupational and non-occupational settings the kidneys and central nervous system are the main target organs for mercury toxicity, whereas gastrointestinal, respiratory and reproductive effects have been seen after exposure to high concentrations. Studies of populations chronically exposed to mercury have reported a wide range of neurological effects including effects on cognitive, sensory, personality and motor

function. While many of these effects have been found to subside when exposures to mercury cease, persistent tremor and cognitive effects can remain for up to 20 years. Psychomotor effects indicative of central nervous system toxicity are associated with mercury levels in urine greater than 35 μg Hg/g creatinine. The same urinary concentrations are associated with elevated enzyme and protein levels in the urine; the elevations seen at higher mercury concentrations are suggested to be early indicators of kidney toxicity. Reversal of renal changes (e.g. proteinuria) associated with mercury-mediated renal disease has been observed following cessation of exposure.

There is no conclusive evidence that chronic, inhalation exposures give rise to genotoxic effects in humans. Several studies have explored the relationship between cancer incidence and exposures to mercury including occupational studies involving exposures to mercury at four-times the old United Kingdom Workplace Exposure Limit (WEL) of 0.025 mg/m^3). Taking findings from studies of cancer incidence in the nuclear weapons industry, in chloralkali workers, in mercury miners and in case-control studies of various exposed populations into account, expert reviewers, including IARC have reached a consensus view that clear conclusions about the carcinogenic potential of elemental mercury in humans cannot be drawn. They conclude that studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations.

There is broad agreement in the various International expert groups that if airborne concentrations of mercury are kept below 20 – 25 μg/m^{3}and urine mercury concentrations below 25 –35 μg Hg/g creatinine nearly all workers may be repeatedly exposed, day after day, over a working lifetime without adverse effects from mercury.

The exposure assessment for the Rutherford buildings shows that inhalation exposures immediately before 2004 and from 2006 onwards were well below these exposure limits and are therefore unlikely to have caused any ill-health effects. Biological monitoring results from 10 urine samples analysed between January and June 2009 show levels of mercury in the background range and are indicative of no significant recent exposure.

Prediction of the levels of mercury over 20 years ago is complicated by the uncertainty about the form of mercury in the waste flock material removed from under floor boards. If the mercury compound(s) were formed as a result of chemical reaction with spilled mercury then it is possible that larger quantities of mercury, and therefore higher levels of mercury vapour, were present in the distant past. However, if the mercury compound(s) were applied to the flock material during manufacture or installation to prevent decay and damage, then mercury vapour levels may have remained at the same low level for many years.

Recommendations

The Control of Substances Hazardous to Health Regulations (COSHH) oblige dutyholders to prevent exposure to substances hazardous to health or, where not reasonably practicable, control exposures "adequately." Although current exposure levels are well below Occupational Exposure Limits it is clearly desirable to minimise exposures and further reductions should be sought if practicable.

It is understood that work to confirm and address the principal remaining source of mercury vapour in the Rutherford Building is now under way.

For the other locations with mercury vapour concentrations significantly above background it would be desirable to establish whether they are consistently at those levels, or whether there are seasonal variations. A suitable threshold for 'significant' might be 20% of the exposure limit (i.e. 4 μg/m^3), to ensure that areas with temporarily low levels are not overlooked.

This would be best if it covered all four seasons until it is established that there was an adequate margin of safety below the exposure limit.

The propensity for the vapour to move between rooms in under-floor air currents has been established. Besides measuring the background concentrations of mercury in apparently-affected rooms it might therefore also be appropriate to measure in those immediately adjacent.

If continuing elevated concentrations are found, mitigation measures might be justified in some cases. Where remediation is performed, monitoring can usefully demonstrate the effectiveness of the work.

Biological monitoring is an alternative means of measuring exposure and could be offered to those staff willing to participate or who have particular concerns, but appropriate support will need to be arranged to discuss the results.

Analysis of the waste material from under the floorboards to determine the type of mercury compounds may help explain their origin and with assessing historical exposures.

1 TOXICITY OF ELEMENTAL MERCURY

1.1 INTRODUCTION

This review has focused primarily on the toxicity of elemental (metallic) mercury (e.g. in valency state 0) in humans following chronic inhalation, low-dose exposures. Organic mercury compounds have not been considered in the review as there is no suggestion that they have been used in the building. Effects following acute inhalation exposure have been summarised briefly for completeness.

Since literature on mercury is extensive, this review has focused on key authoritative, review documents on the risk assessment of chemicals, compiled by international groups of experts that have comprehensively examined the toxicity of elemental mercury and its inorganic compounds. The sources of key review documents consulted are (most recent first):

- ***Scientific Committee on Occupational Exposure Limits (SCOEL)*** – In the most recent review, SCOEL evaluated the toxicity of elemental mercury and inorganic divalent mercury compounds to establish occupational exposure limits and a biological limit value for the European Union, according to the Chemical Agents Directive (SCOEL, 2007).
- ***Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)*** - The Senate Commission of the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) on the Investigation of Health Hazards of Chemical Compounds in the Work Area has presented Maximum Allowable Concentrations (Maximale Arbeitsplatzkonzentrationen – MAK) and Biological Tolerance Values (Biologische Arbeitsstofftoleranzwerte – DFG) values for mercury and its inorganic compounds in a list submitted it to the German Federal Minister of Economics and Labour (DFG, 2005).
- ***International Programme on Chemical Safety (IPCS)*** – IPCS provide an evaluation of the human health aspects of elemental mercury and its inorganic compounds in the Concise International Chemical Assessment Documents (CICAD), prepared as part of a cooperative programme of the World Health Organisation (WHO), the International Labour Organisation (ILO) and the United National Environment Programme (UNEP) (IPCS, 2003).
- ***Health and Safety Commissio***n's ***Advisory Committee on Toxic Substances (ACTS)*** – ACTS summarised available data on elemental mercury when making recommendations on occupational exposure limits. EH64 contains a summary for mercury and it inorganic divalent comounds reflecting the basis on which the occupational limit listed in EH40 was established. This is based on HSE's review of mercury in 1995 (HSE, 2002).
- ***Agency for Toxic Substances and Disease Registry (ATSDR)*** – The ATSDR evaluated the toxicity of metallic mercury as part of the toxicological profile on mercury developed in response to United States public law: the Superfund Amendments and Reauthorization Act of 1986 (ATSDR, 1999).
- ***United States Environmental Protection Agency (US EPA)*** – the US EPA evaluated the health effects of mercury as part of a comprehensive study on atmospheric emissions of mercury submitted to congress (EPA, 1997).
- ***United Kingdom Health and Safety Executive (HSE)*** – the HSE critically evaluated literature on elemental mercury and it inorganic divalent comounds for the purpose of establishing an occupational exposure limit for this substance (HSE, 1995).

- ***International Agency for Research on Cancer (IARC) –*** On behalf of the World Health Organisation, a Working Group of IARC evaluated the potential carcinogenic risks to humans of elemental mercury as part of the monograph programme (IARC, 1993).

Studies evaluated in older review documents (e.g. Environmental Health Criteria) were found to be included in the more recent reviews listed above and were therefore not consulted in this review. Primary papers cited in the reviews listed above have not, in the most part been consulted in this review but references to these relevant studies and their corresponding review have been included for information[1].

Searches of primary literature were also carried out to identify additional papers not evaluated in these reviews. Only a few, more recent, papers to those evaluated in the reviews listed above were identified that addressed the topic of mercury toxicity.

1.2 GENERAL EXPOSURE

Mercury occurs at low concentrations in the Earth's crust, mainly in sulphide ores from which it has been extracted for a variety of uses for many centuries. Metallic mercury has commonly been used as a cathode in the electrolytic production of chlorine, in dental amalgams, in the extraction of gold from ore concentrate, in electrical equipment and in devices for measuring temperature and pressure (IARC, 1993).

Occupational exposures occur by inhalation, primarily to metallic mercury vapour. Occupations in which the highest exposures occur include mercury mining, work in chloralkali and alkaline battery plants and production of devices for measuring temperature and pressure. Lower exposures to mercury have been observed in workers in hospital laboratories and dental clinics. Exposures have been measured by ambient air and biological monitoring. Non-occupational exposure to metallic mercury occurs primarily from dental amalgam fillings, although exposure levels are typically much lower than those encountered in occupational settings (IARC, 1993).

Following inhalation, some metallic vapour condenses into droplets that are more likely to be ingested than inhaled, resulting in a lower absorbed dose than would be expected for a given air concentration (ATSDR, 1999). Airborne concentrations of mercury in the general work environment may be lower than in the microenvironment immediately surrounding workers, and estimates of mercury levels in air in occupational studies should be carefully evaluated for bias towards a level that may be lower than actual exposure levels (ATSDR, 1999). Mercury vapour from amalgam fillings may dissolve in saliva and be ingested (ATSDR, 1999).

Regulatory agencies of many countries have derived occupational exposure limits and guideline values for mercury. A selection of these, including associated biological monitoring guidance values is shown in Appendix 1. Workplace exposure limits are usually based on a concentration at which harm is not likely when exposure occurs over a lifetime for 40 hours per week, 48 weeks of the year.

[1] *The following convention was adopted when citing studies from authoritative reviews; the review was cited first, followed by the primary study (e.g. IARC, 1993; Buiatti* et al*, 1985)*

1.3 TOXICOKINETICS

1.3.1 Absorption

Inhalation is the primary route of exposure in the body for elemental mercury. Elemental mercury vapours are readily absorbed through the lungs (WHO, 2003). Studies in volunteers suggest 75-85% of the inhaled dose of elemental mercury vapour is absorbed by rapid diffusion (EPA, 1997; WHO, 2003). The high lipid solubility of elemental mercury vapour relative to its vapour pressure favours its rapid diffusion across the alveolar membranes and dissolution in blood lipids (EPA, 2007). Liquid metallic mercury is very poorly absorbed from the gastrointestinal (GI) tract (EPA, 2007). In contrast to the inhalation route, only 0.01% of elemental mercury is absorbed through the GI tract (WHO, 2003). The release of vapour from liquid mercury in the GI tract and its subsequent absorption is limited by its reaction with sulphur to form mercuric sulphide. Elemental mercury vapour is absorbed through human skin at the rate of 0.024 ng mercury / cm^2 (skin) per 1 mg/m^3 in the air. This rate of absorption accounts for less than 3% of the total systemic dose during exposures to elemental mercury vapour, with greater that 97% of the dose arising from absorption of the inhaled vapour (EPA, 1997). Although absorption of elemental mercury vapour via olfactory nerves has been proposed, no relationship has been shown between mercury concentrations in the lower part of the brain and the amount of amalgam fillings in the mouth (WHO, 2003).

The absorption, blood levels and excretion of mercury has been investigated in nine healthy volunteers after inhalation exposure to elemental mercury vapour in air at 400 $\mu g/m^3$ for 15 minutes (corresponding to a dose of 5.5 nmol mercury/kg bodyweight). Samples of exhaled air, blood and urine were collected for 30 days after exposure. The mean retention of elemental mercury after 30 days was 69% of the inhaled dose. This corresponds to an estimated half-life of 60 days for elemental mercury (WHO, 2003).

1.3.2 Distribution

Once absorbed, due to its high lipophilicity, elemental mercury is readily distributed throughout the body and can traverse the placental and blood-brain barriers (EPA, 1997, WHO, 2003). Elemental mercury dissolves in the blood upon inhalation and some remains unchanged (WHO, 2003). Elemental mercury in red blood cells is oxidised to inorganic divalent mercury cations by the hydrogen peroxidase-catalase pathway, a pathway present in most tissues (EPA, 1997, WHO 2003). Divalent mercury cations can exist as either diffusible or a non-diffusible forms. The non-diffusible form occurs when mercuric ions bind to proteins and are held in high-molecular weight complexes in cells. Mercury cations held in these complexes exist in equilibrium with the mercury cations in the diffusible form. In the plasma, the mercury cations are predominantly in the non-diffusible form, and, as such, can bind to albumin and globulins (WHO, 2003). The distribution of absorbed elemental mercury is therefore limited primarily by its oxidation to the inorganic mercuric cation. Inorganic mercuric ions have low lipophilicity and therefore have limited ability to cross the placental and blood-brain barrier. Once elemental mercury has traversed the blood-brain barrier and has been oxidised to mercuric ion, its return to the general circulation is impeded; and mercury can be retained in the brain tissue (WHO, 2003).

Elemental mercury distributes to all tissues and reaches peak levels within 24 hours, except in the brain, where peak levels are achieved within 23 days. The longest retention of elemental mercury after inhalation of mercury vapour occurs in the brain. A study of Japanese workers

who died 10 years after their last exposure to elemental mercury still had high residual levels of mercury in their brains (WHO, 2003).

In a study of volunteers who inhaled a tracer dose of elemental mercury vapour for 20 minutes, approximately 2% of the absorbed dose was found per litre of whole blood after the initial distribution was complete. Although distribution to the red blood cells was complete after 2 hours, distribution to the plasma was not complete until 24 hours. The concentration of elemental mercury in red blood cells was twice that measured in the plasma. This ratio persisted for at least 6 days after exposure (WHO, 2003).

Animal studies indicate that the brain and kidney are the primary organs of mercury deposition following inhalation of elemental mercury vapour. The extent of deposition in these organs is dependent on the concentration and duration of exposure. In rats exposed to elemental mercury vapour at concentrations ranging from 10 to 100 $\mu g/m^3$ (6 hours/day, 5 days/week), the highest concentration of mercury, relative to other organs, was found in the kidney cortex. Exposure to mercury stimulates the production of metallothionein in the kidney, which in turn increases the amount of mercuric ion binding (WHO, 2003). In contrast, in a study of mice exposed to elemental mercury vapour for 4 hours, the highest mercury retention, relative to other organs was found in the brain. In a study of rats exposed to elemental mercury vapour at 1 mg/m^3 (24 hours/day, 5 weeks or 6 hours/day, 3 days/week for 5 weeks), mercury was found primarily in the neocortex, basal nuclei, and cerebellar Purkinje cells. In mice exposed to elemental mercury vapour at 8 mg/m^3 for 6 hours/day for 10 days, higher mercury levels were found in the grey brain matter than in the white brain matter. In primates exposed to mercury through amalgam in dental fillings or maxillary bone, mercury accumulation in the brain was found in several cells types populating the dorsal root ganglia (e.g. ganglion cells, satellite cells, fibroblasts and macrophages) and dorsal root neurons and satellite cells (WHO, 2003).

1.3.3 Metabolism

Once inhaled into the lungs, elemental mercury vapour rapidly enters the blood stream. The dissolved vapour can undergo rapid oxidation, primarily in the red blood cells, to its inorganic divalent form by the hydrogen peroxide catalase pathway. The rate of oxidation depends on (1) the concentration of catalase in the tissue (2) endogenous production of hydrogen peroxide and (3) availability of mercury vapour at the oxidation site. Stimulation of hydrogen peroxide production in red blood cells has been found to increase the uptake of mercury vapour in red blood cells. The mercury content in the blood is proportionally higher after a low dose than after a high dose indicating that a higher proportion of the lower dose is oxidised. At higher dose levels, the hydrogen peroxide catalase pathway may become saturated. The oxidation of elemental mercury is inhibited by ethanol. Ethanol is a competitive substrate for the hydrogen peroxide catalase and can therefore block the uptake of mercury by red blood cells. Deficiencies in the activity of this enzyme could potentially result in subpopulations that are more susceptible to mercury toxicity (WHO, 2003).

The oxidation of elemental mercury can occur in the brain, liver and other tissues. In the brain, unoxidised elemental mercury can be oxidised and become trapped in the brain because it is more difficult for the divalent forms to exit the brain via the blood-brain barrier. (WHO, 2003)

1.3.4 Elimination

The elimination of elemental mercury occurs primarily via urine and faeces with exhaled air, sweat and saliva contributing to a lesser extent (WHO, 2003). The pattern of excretion

depends on the extent to which elemental mercury has been oxidised to mercuric mercury (EPA, 1997).

The urine and faeces are the main excretory pathways of elemental mercury in humans with an absorbed dose half-life of approximately 1-2 months. Whilst urinary excretion in humans accounts for 13 % of the total body burden after short-term high level mercury exposure, it increases to 58% after long term exposure. In a sample of 1107 individuals from 15 countries with no known occupational, environmental, or medicinal exposures to mercury, urinary samples in 95% of these individuals were < 20 μg mercury/l urine (WHO, 2003).

Elimination of mercury from the blood and brain is thought to be a biphasic process, with an initial phase in which the decline in the body burden is associated with high levels of mercury being cleared from tissues followed by a slower phase of mercury clearance from tissues. An even longer terminal elimination phase of mercury is also possible because of the persistence of mercury, primarily in the brain (WHO, 2003).

In a study of former chloralkali workers exposed to elemental mercury vapour for 2-18 years, the elimination of mercury in urine was found to be well characterised by a one-compartment model with an estimated half-life of 55 days (WHO, 2003). In volunteers, the half-life of mercury in urine varied between 12.8 and 98.9 days with a median of 63.2 days (DFG, 2005).

1.4 BIOMARKERS OF EXPOSURE

Biological monitoring of mercury exposure by un-timed, random urine measurements is well established. Urine levels of mercury reflect average exposure over the previous few months in chronically exposed individuals and urine sampling is considered to be the best determinant of the body burden of elemental mercury from long-term, low-level exposure (WHO, 2003; SCOEL, 2007). Urinary mercury concentrations in the literature are reported either as simple concentrations (μg/l) or as a concentration of mercury adjusted for the concentration of creatinine (μg Hg/g creatinine or μg/g) to compensate for urine dilution. Urine mercury concentrations can vary within an individual on a day to day basis and to minimise the variation it is recommended that samples be collected at the same time each day and that results should be adjusted for creatinine and reported as μg/g (DFG 2005, Mason et al). In this review, to avoid confusing units and for ease of reading, results are expressed as μg/g. Where appropriate reported values in μg/l have been converted to μg/g assuming a nominal urinary creatinine concentration of 1 g creatinine/l.

Whilst blood mercury measurements are useful for determining short-term exposures, these are less reliable when long-term exposures are of interest and are less frequently used due to their invasive nature (WHO, 2003; SCOEL, 2007).

Although several studies have reported a correlation between airborne mercury and levels of mercury in the urine and blood, results have been found to vary and it is not known whether the ratio between concentrations in urine and blood is constant at different exposure levels. In studies in which exposures had been assessed using personal breathing zone mercury measurements, it was estimated that in continuous 8 hour/day occupational exposure, an airborne mercury concentration of 1 $\mu g/m^3$ leads to an average urinary mercury of 1.4 μg / g urine (measurements across studies ranged from 0.7-2.3 mg/g urine; n = 7) and to average blood mercury concentrations of 0.48 mg/l. (ranging from 0.17- 0.81 mg/l; n=6) (WHO, 2003, SCOEL 2007).

Background levels of urinary mercury, adjusted for creatinine, in an unexposed population are generally expected to be <5 μg Hg/g creatinine (WHO, 2003, Becker et al 2003).

1.5 HEALTH EFFECTS

Inhalation of sufficient levels of metallic mercury vapour has been associated with systemic toxicity in both animals and humans (ATSDR, 1999). Since literature on the health effects of mercury is extensive, this section has focused primarily on human studies. Considerable evidence from acute and repeated exposure studies in animals and from epidemiology suggests that the kidney and nervous system are the most sensitive toxicological endpoints following exposure to elemental mercury. Generally however, neurological effects are observed at lower mercury exposure levels than those that induce kidney or pulmonary effects (EPA 1997). Although the major target organs of metallic mercury-induced toxicity following inhalation exposure in humans are the kidneys and central nervous system, respiratory, cardiovascular and gastrointestinal effects have been reported at high exposure levels (ATSDR, 1999). The sensitivity of the kidneys to mercury toxicity may, in part, be due to the relatively high accumulation of mercury in these organs (ATSDR, 1999).

1.5.1 SINGLE AND SHORT-TERM EXPOSURE

1.5.1.1 Mortality

Several studies have reported death in humans following accidental acute exposure to high, but unspecified concentrations of mercury vapour generated by volatilising metallic mercury by heating. Death in all cases was due to respiratory failure (ATSDR, 1999).

1.5.1.2 Irritation and Sensitisation

No studies are available investigating skin or eye irritation, or the skin sensitisation potential of elemental mercury in animals or humans (SCOEL, 2007). There have been some reports that exposure to elemental mercury vapour produces both non-allergic and allergic dermatitis reactions in exposed humans (SCOEL, 2007). Erythematous, pruritic skin rashes, heavy perspiration and reddened, peeling skin on the palms of the hands and soles of the feet (e.g. acrodynia) have been reported after inhalation exposure to elemental mercury vapour (IPCS, 2003, ATSDR, 1999). Red and burning eyes and conjunctivitis have been observed in subjects exposed to high concentrations of elemental mercury vapour (IPCS, 2003).

There have been no reports of respiratory sensitisation following exposure to elemental mercury (SCOEL, 2007).

1.5.1.3 Neurotoxicity

The central nervous system is a sensitive target organ for metallic mercury vapour exposures, giving rise to consistent and pronounced effects. Acute-, intermediate- and chronic- (see repeated exposures section) duration exposures elicit similar neurological effects. Symptoms intensify and may become irreversible as exposure duration and/or concentration increases (ATSDR, 2003). In humans, several case reports have reported adverse neurological effects following acute, accidental inhalation exposures of high concentrations of mercury vapour. A wide variety of cognitive, sensory, personality and motor functions have been reported; the most prominent symptoms include tremors, emotional lability, insomnia, memory loss,

neuromuscular changes, headaches, polyneuropathy and performance deficits in tests of cognitive function (ATSDR, 2003).

1.5.1.4 Respiratory Effects

Respiratory symptoms are prominent effects of short-term, high level exposure to metallic mercury vapour. Commonly reported symptoms include cough, dyspnoea and tightness or burning pains in the chest (IPCS, 2003; ATSDR, 1999). Workers accidentally exposed to metallic mercury vapours at concentration up to 44.3 mg/m^3 for between 4 and 8 hours experienced chest pains, dyspnoea, cough, haemoptysis, impairment of pulmonary function (e.g. reduced vital capacity), diffuse pulmonary infiltrates and interstitial pneumonia (IPCS, 2003). Decreased vital capacity has been reported to persist for up to one year after acute exposure (IPCS, 2003).

1.5.1.5 Cardiovascular Effects

Increased blood pressure and heart rate have been reported in subjects after short-term inhalation exposure to high concentrations of metallic mercury vapour (IPCS, 2003, ATSDR, 1999).

1.5.1.6 Gastrointestinal Effects

A variety of gastrointestinal effects have been reported in humans following short-term inhalation exposure to high concentrations of metallic mercury. Effects include stomatitis (inflammation of the oral mucosa), occasionally accompanied by excessive salivation and difficulty swallowing, abdominal pain, nausea and diarrhoea (IPCS, 2003; ATSDR, 1999). Anorexia, intermittent abdominal cramps, mild diarrhoea, painful mouth and bleeding gingival were reported in a teenage girl 2 weeks after a spill of mercury occurred in the home. Air levels measured 6 months after the spill ranged from 0.02 to 1 mg mercury/m^3.

1.5.1.7 Haematological Effects

Exposures to high concentrations of metallic mercury vapours produce a syndrome similar to "metal fume fever", characterised by fatigue, fever, chills and elevated leukocyte counts (ATSDR, 1999). Leukocytosis and neutrophilia have been reported following acute inhalation exposures to metallic mercury vapour (ATSDR, 1999). Elevated white cell counts reported in a 12 year old girl following 6 months of exposure to mercury vapour after a spill at her home (ATSDR, 1999: Fagala and Wigg, 1992). Thrombocytopenia and frequent nosebleeds were reported in members of a family exposed to a mercury vapour after a spill at the home, an effect considered to be unique to mercury exposure (ATSDR, 1999: Schwartz *et al*, 1992).

1.5.1.8 Hepatic effects

Hepatocellular effects characterised by biochemical changes, hepatomegaly and central lobular vacuolation have been reported following acute inhalation of metallic mercury vapour (IPCS, 2003, ATSDR, 1999).

1.5.1.9 Renal Effects

Renal effects observed following short-term exposure to high concentrations of mercury vapour range from mild transient proteinuria or slight changes in urinary acid excretion to frank proteinuria, haematuria, to acute renal failure with degeneration or necrosis of the proximal convoluted tubules (IPCS, 2003, ATSDR, 1999). Although the actual exposure concentrations associated with these effects are not known, urinary excretion ranging from 59-193 µg mercury/hour has been reported (ATSDR, 1999: Blum *et al,* 1992).

1.5.2 REPEATED AND LONG-TERM EXPOSURE

The effects of repeated exposure to metallic mercury in humans have been thoroughly investigated (SCOEL, 2007). The majority of studies have attempted to correlate observations of health status with mercury levels in blood and urine and do not therefore present reliable personal airborne exposure data.

1.5.2.1 Neurotoxicity

Several studies are available of chronically exposed populations, that report a wide variety of neurological effects on cognitive, sensory, personality and motor functions. Not all the effects of mercury are reversible; although symptoms generally subside when exposure to mercury ceases, persistent tremor and cognitive effects can remain for up to 20 years after exposure has ceased.

The symptoms of mercury vapour-induced neurotoxicity include (EPA, 1997):

- Tremors, initially affecting the hands, sometimes spreading to other parts of the body.
- Emotional lability, such as irritability, loss of confidence and nervousness.
- Insomnia.
- Neuromuscular changes including weakness, muscle atrophy and twitching.
- Headaches.
- Polyneuropathy including paresthesias, stocking-glove sensory loss and slowed neuronal conduction velocities.
- Memory loss and cognitive deficits.

Neurotoxicity has been observed in workers exposed to levels as low as 25 µg/m^3, with symptoms including both self-reported effects and objective measures of neurological changes (EPA, 1997). The largest study of 567 workers employed in chloralkali plants proposed No-observed-adverse-effect-levels (NOAEL) and Lowest-observed-adverse-effects-levels (LOAEL) of 100 µg/m^3 and 180 µg/m^3 respectively. However many of the studies that have tried to correlate health effects with urine or blood levels of mercury do not provide reliable estimates of inhalation exposure levels (SCOEL, 2007).

The summary provided here is largely based on the most recent reviews carried out by HSE (1995), EPA (1997), DFG (2005) and SCOEL (2007).

Case studies

The available case studies of individuals exposed to elemental mercury are summarised in Table 2 (see Appendix 2).

Cross-sectional studies

In studies of mercury use in dentistry, no correlation was found between a urinary mercury concentration of 1.7 μg/g creatinine and neuropsychological test results in 550 adults with mercury amalgam fillings (DFG, 2005: Factor-Litvak *et al*, 2003).

DFG (2005) summarised six studies of the neurotoxicity of mercury in dental personnel (Table 3, Appendix 2). The current mercury urine levels in the workers varied between 0.89 – 25 μg/g. However, DFG notes that these results are problematic, for two reasons: (i) exposure in dentists have decreased over time with introduction of improved practices, so that it is difficult to separate effects due to past high exposures and current lower levels, and (ii) many of the neurological effects were recorded at doses within the current range for the general population (<5 μg/g). Two further studies of dentists were identified by HSE (1995). Finger tremor was diagnosed in two dentists, exposed to mercury levels in the air of 2-8 $\mu g/m^3$, but who had high concentrations on their hands (150 and 300 $\mu g/m^3$) suggesting that absorption from skin was potentially a contributing factor (HSE 1995: Symington *et al*, 1980). There was significant impairment in several peripheral nerve functions in 23 dentists with elevated tissue mercury levels (detected by X-ray fluorescence technique) compared to controls, with 30% of the exposed dentists having polyneuropathy (HSE, 1995: Shapiro *et al*, 1982).

EPA (1997) and DFG (2005) provided the most comprehensive overviews of the available studies on the neurotoxicity of mercury. EPA identified eleven critical studies in their analysis (EPA, 1997), with further non-key studies, many of which had limited exposure data, described in Table 4 (Appendix 2). These key studies are summarised here.

Workers (26 males) who had been exposed occupationally to metallic mercury vapours for an average of 15.3 years showed a statistically significant increase in "intention" tremors occurring upon initiation of voluntary movements compared to unexposed workers (EPA, 1997: Fawer *et al* 1983). The effects were related to the duration of exposure and age of the subjects. The concentration of mercury in the air was measured and a time-weighted average (TWA) of 26 $\mu g/m^3$ was derived. Little detail was presented of the measurement of exposure levels and it was assumed that exposure levels remained constant for the duration of employment, which may be unlikely. Mean mercury levels in urine were 20 μg/g compared to 6 μg/g in controls. The tremors may have resulted from intermittent exposure to concentrations higher than the TWA (EPA 1997).

Chloralkali workers used to be exposed to significant levels of mercury during production of chlorine using mercury cells. Several studies have reported the effects of long-term exposure to metallic mercury vapours in cohorts of these workers. Abnormalities in electroencephalograms were noted in 15% of a group of 41 male workers exposed for 15.6 ± 8.9 years, who had mean blood mercury levels of 12 μg/L and mean urine levels of 20 μg/g (EPA, 1997: Piikivi & Tolonen, 1989). The changes seemed to correlate with mercury content of the cortex. Extrapolation of the blood concentrations suggested an exposure level of 25 $\mu g/m^3$, but shift work was a confounding factor (HSE, 1995). In another study apparently of the same cohort, the exposed workers reported increased heart palpitations, but all the other subjective symptoms of autonomic function did not reach significance (EPA, 1997: Piikivi, 1989).

In a group of 60 male chloralkali workers exposed to metallic mercury vapours for a mean of 13.7 ± 5.5 years, who had mean blood levels of 10 μg/L and mean urine levels of 17 μg/g, there were significant increases in a range of symptoms, including memory disturbances, sleep disorders and fatigue (EPA, 1997: Piikivi & Hanninen, 1989). HSE (1995) point out however that the results of a battery of computerised psychological tests showed no differences between exposed workers and controls. Extrapolation of the blood concentrations suggested an exposure level of 25 μg/m^3.

Exposure to elemental mercury has also been associated with preclinical evidence of peripheral neurotoxicity. Motor and sensory nerve conduction velocities correlated with time-integrated urine mercury levels in asymptomatic workers with urinary mercury levels exceeding 25μg/g (EPA, 1997: Levine, 1982).

Whilst some neurological changes (e.g. in forearm tremor frequency, eye-hand coordination) increased in 142 exposed workers, whose urine mercury levels exceeded 50 μg/g, other changes (e.g. eyelid fasciculation) did not correlate with urine levels (EPA 1997: Miller *et al*, 1975). The effects appeared reversible (HSE, 1995).

Although subjective central nervous system (CNS) symptoms were elevated in exposed workers, there was no direct correlation between symptoms and urinary mercury levels in a study of male (131) and female (54) workers exposed to mercury vapour for an average of 4.8 years; they had mercury urinary levels of 52 / 37 μg/g creatinine (male/female) and blood mercury levels of 14 / 9 μg/L (male/female) (EPA 1997: Roels *et al*, 1985). However male workers who had urinary mercury levels of > 50 μg/g creatinine showed preclinical signs of hand tremor that were not seen in females or other male workers with lower exposure levels. In a companion study, air mercury levels were related to blood and urinary mercury concentrations in 10 workers in a chloralkali plant (EPA, 1997: Roels *et al*, 1987). Based on these two studies, Roels *et al* suggested that mercury-related effects may occur when urinary levels exceed 50 μg/g creatinine, which corresponds to a mercury TWA of ~ 40 μg/m^3.

A larger study of 567 workers in 21 chloralkali plants was carried out by Smith *et al* (1970; EPA 1997). The exposure levels varied up to 270 μg/m^3 and duration of employment was 1-10 years. Workers were also exposed to chlorine (0.1-0.3 ppm). Strong positive correlations were reported between mercury TWAs and subjective and objective neurological symptoms including insomnia, tremors, weight and appetite loss, and between exposure levels and urinary and blood mercury levels. A NOAEL and LOAEL were proposed of 100 μg/m^3 and 180 μg/m^3 respectively.

In a study of 79 workers exposed to metallic mercury vapour, neurological effects (e.g. tremors, short-term memory loss) were only noted in 10 workers who had mercury levels of over 500 μg/g urine, although performance in the neurological tests improved after lowering of the mercury exposure levels (EPA 1997: Langolf *et al*, 1978). No functionally significant effects in the other exposed workers (average urinary mercury 240 μg/g were noted (HSE, 1995). Smith *et al* also assessed this group of workers, reporting a significant correlation between short-term memory loss and increasing urinary mercury levels (HSE, 1995: Smith *et al*, 1983). Workers with urinary mercury levels over 100 μg/g had impaired performance in mechanical, visual memory and psychomotor tasks (EPA 1997: Forzi *et al*, 1978).

Preclinical psychomotor dysfunction has been seen in 43 workers (mean exposure duration 5 years) with urinary mercury levels of 50 μg/g (EPA 1997: Roels *et al*, 1982), and tremors seen in 54 workers (mean exposure duration 7.7 years) with urinary mercury levels of 63 μg/g (EPA 1997: Roels *et al*, 1982). Verbreck *et al* (1986; EPA 1997) proposed a LOAEL for tremors of 35 μg/g creatinine on the basis of increasing effects with increasing urinary excretion of mercury in 21 workers exposed to mercury vapour for 0.5 – 19 years.

In its evaluation of literature to inform the derivation of a biological monitoring value for mercury, DFG (2005) summarised five studies of industrial workers currently working with mercury and four studies of workers whose current exposure levels were comparable to

controls, but who had previously been exposed to high levels of mercury. The main study described by DFG (2005) of workers currently working with mercury was carried out by Ellingsen *et al* (2001), who reported no significant neurological changes in 47 chloralkali workers. Workers had urinary mercury levels of 16 μg/g, with a range of 7 – 35 μg/g. However multiple linear regression analyses incorporating potential confounding factors revealed a correlation between reduced attention and memory performance with current blood mercury levels, and between attention with average exposure over the preceding years, but the effects were described as slight. Biological monitoring data had been gathered since 1949. Maximum mercury levels were obtained in 1983 and were around 19 μg/g with a 95% CI up to 24 μg/g. Current mercury levels were 10 μg/g (range 4 – 30 μg/g)

The other four studies of workers currently working with mercury were not considered suitable by DFG (2005) for deriving a DFG level and therefore they are summarised here in Table 5 (Appendix 1). These studies are more recent than those cited by EPA (1997) or HSE (1995).

The reversibility of the neurological effects of mercury was studied in subjects who had urinary levels of mercury comparable to non-exposed people at the time of study but who had had much higher urinary levels of mercury on account of past exposures to mercury in the chloralkali industry. Average urinary concentrations in 147 chloralkali workers employed in the industry for durations ranging from several months to 35 years were measured at 72 μg/g urine (range 13.0-172.7 μg/g urine) during employment. Mercury urinary concentrations at the time of the study were not different to those in 132 controls (e.g. 3.42 ± 2.54 μg/g versus 3.12 ± 2.48 μg/g) (DFG, 2005: Frumkin *et al*, 2001a). However, a range of self-reported symptoms and sensitivity to vibration, tremor, motor responses, motor coordination and memory were significantly altered in the group of chloroalkai workers compared to the controls. Although some of the effects correlated with exposure levels, many did not; this is explained as due to the low statistical power of the study (e.g. only 4 workers had the highest exposure levels). However, DFG (2005) concludes that the maintenance of some of the symptoms in the formerly exposed group suggests that long-term mercury-induced effects are involved.

Mathiesen *et al* (1999), Kishi *et al* (1994) and Letz *et al* (2000) (DFG, 2005) all reported similar findings. Neuropsychological changes such as attentiveness, concentration, motor functions and memory, with dose-response relationships were observed for former chloralkali workers whose exposure 12.7 ± 11.7 years previously had given rise to 108 ± 93 μg/g but had urinary mercury levels comparable to those in unexposed people at the time of the study (DFG, 2005: Mathiesen *et al*, 1999). Workers exposed previously to mercury and had urinary mercury concentrations in the range 500-2000 μg mercury/g urine at the time, still showed changes in attentiveness/concentration, motor skills, perception and constructive performance parameters, with dose-response relationships in motor coordination, motor rapidity and perception 18 years after exposures had ceased (DFG, 2005: Kishi *et al*, 1994). Some of the workers had suffered acute mercury poisoning, and the acute symptoms had subsided with time. In 104 former workers, relationships still existed between the previous mercury exposures (giving up to 635 μg/g) and nerve conduction velocity, tremor and motor performance, with a close association demonstrated for cumulative levels of mercury (DFG, 2005: Letz *et al*, 2000).

Further investigations of the long-term effects of mercury were carried out by Albers *et al* (1988; EPA, 1997 & HSE, 1995) and Kishi *et al* (1993; EPA, 1997). A group of 247 workers who were exposed to mercury 20-35 years previously (and 255 unexposed controls) were studied for delayed neurological effects (EPA, 1997 & HSE, 1995: Albers *et al*, 1988). In subjects who had peak urinary mercury levels of more than 600 μg/g (n=112), decreased coordination and sensation, abnormally increased Babinksi reflexes and tremor were observed, and in subjects with peak levels above 850 μg/g, clinical neuropathy was more prevalent. In a study of 117 mercury miners (and 76 controls), tested 18 years after closure of

the mine, effects on motor coordination, reaction time and short-term memory were observed, although the effects had decreased over time (EPA, 1997: Kishi *et al*, 1993).

All of these studies therefore suggest that the effects of earlier exposures to mercury are not fully reversible, even decades later. However, the longevity of the effects may be symptom-specific since Cavalleri & Gobba (1998; DFG, 2005) showed that changes in colour discrimination in 21 workers with mean urinary mercury levels of 115 μg/g were reversible after a year when occupational exposures to mercury had decreased and urinary mercury concentrations had fallen to 10 μg/g.

Longitudinal studies

DFG (2005) highlights two longitudinal studies. Gunther *et al* (1996) tested 50 workers in a chloralkali plant four times over the course of 7 years, and observed significant correlation between urinary mercury levels (21-152 μg/g urine) and personality traits, attentiveness, memory and motor performance. Although there was an increase in motor effects with urinary mercury levels between 50 – 150 μg/g, there was not a clear dose-response relationship.

Dietz *et al* (1997) tested 16 renovation workers four times over 2 years. Neuropsychological effects were noted in some individuals with mean urinary concentrations of 21.5 μg/g, but there was no control group and no dose-response relationship could be established.

In an earlier study (HSE, 1995: Bunn *et al*, 1986) of workers at two chloralkali plants, who were studied for 21 and 3.5 years, neurological effects were only observed for subjects with urinary mercury levels exceeding 500 μg/g.

Meta-analysis of studies

One meta-analysis of 12 studies published between 1980 and 1999 has been carried out (Meyer-Baron *et al*, 2002) and is described by EPA (1997) and DFG (2005). The analysis is based on 686 exposed individuals and 579 controls. Significant effects were found for 9 psychological parameters from 6 tests in individuals with urinary mercury concentrations ranging from between 18 μg/g (tests for attention) and 34 μg/g (tests for visual memory and fine motor coordination). The results of 6 further tests gave significant differences between control groups (e.g individuals with background urinary mercury concentrations) and exposed groups (e.g. individuals with urinary mercury concentrations ranging from 18 to 34 μg/g . On this basis, DFG (2005) proposed a LOAEL of between 18-34 μg/g. Significant dose-response relationships were observed between urinary mercury concentrations and attention, memory and psychomotor effects. The authors note however that high past exposures could have contributed to the effects observed. DFG (2005) address this by estimating the differences between previous and current levels of exposure in 5 of the 12 studies used for the meta-analysis. They estimated that past exposure levels were 1.09-2.06 fold higher than current levels, suggesting a mean ratio of 1.5 (assuming equivalence of the studies). They do not however use this factor in their final analysis and determination of a MAK value since the ratio cannot be generalised across all 12 studies.

Further analysis of 18 studies carried out between 1980 and 2002 found reduced test responses that correlated with mercury exposure. The strongest correlation was for motor performance; a significant though weaker correlation was for memory, whilst the effects of mercury on attention did not reach statistical significance (DFG, 2005: Meyer-Baron *et al*, 2004).

Summary of neurological effects

Neurological effects have consistently been observed in independent studies using different measurement methods.

Overall the data support the conclusion that urinary mercury levels above 35 μg/g correspond with adverse effects on the CNS (SCOEL, 2007). DFG (2005) conclude that no clinically relevant neurotoxicological effects occur at maximum mercury concentrations of 30 μg/g. HSE in turn conclude that CNS toxicity occurs above a threshold of mercury levels of 35 μg/g in the urine and 9 μg/l in the blood (HSE, 1995; EH64, 1994). These levels are based on mercury levels in the urine or blood rather than personal airborne exposure values, but it can be estimated that an exposure level giving of 35 μg/g in the urine correlates with an airborne mercury level of 0.025 mg/m^3 (EH64, 1994).

The irreversibility of effects was demonstrated in four studies of individuals previously exposed to mercury, who had urinary mercury concentrations between 100-2000 μg/g urine at the time. It is suggested that these workers previously exposed to high levels of mercury demonstrate symptoms that are comparable to workers with more recent exposures to mercury at lower levels, with corresponding urinary concentrations in the range 20-30 μg/g creatinine, after a long period of no exposure. This argues against a complete reversibility of the neurological effects of mercury exposure. DFG (2005) discusses how analogies can be drawn between the effects of mercury on memory span in exposed individuals and age-related changes in performance observed following exposures to lead. In a meta-analysis of eight studies, individuals with urinary mercury concentrations of 26 μg/g did not perform in the Digit Span and Benton Visual Retention test (measures of attention and memory respectively), as was expected for their age group when compared with controls (e.g. individuals with background urinary mercury concentrations). The mercury exposed individuals achieved scores in the tests that were comparable to those achieved by unexposed individuals who were 10 years older. In a further study of the concomitant effects of alcohol and mercury exposure, following intake of 500 ml of 5% beer (giving a blood alcohol level of 0.3%) individuals with urinary concentrations of 26 μg/g urine displayed reduced reaction times (e.g. 5-7% lower) compared to unexposed individuals.

1.5.2.2 Renal Toxicity

All forms of mercury, including metallic mercury vapours are neprotoxic, with the *pars recta* of the proximal tubuli constituting the most sensitive part of the kidney (DFG, 2005). Within the kidneys, mercury ions interact with thiol groups of proteins, peptides and amino acids. Interactions between mercury ions and albumin, metallothionein, glutathione and cysteine are particularly important in the onset of nephrotoxic effects, resulting in damage to kidney cells and the release of cellular enzymes and proteins into the tubular lumen which are subsequently released into the urine (DFG, 2005).

A nephritic syndrome, characterised by edema and proteinuria with albumin and hyaline casts in the urine, was reported in subjects in two independent reports relating to exposure after a spill in the home and after occupational exposures of intermediate duration respectively (ATSDR, 1999: Agner and Jans, 1978, Friberg *et al,* 1953). The syndrome abated within a few months after exposure had ceased.

A number of studies have examined renal toxicity in workers chronically exposed to mercury vapour (ATSDR 1999: Barregard *et al* 1998, Bernard *et al* 1987, Buchet *et al* 1980, Cardenas

et al 1993, Danziger and Possick 1973, Ehrenberg *et al* 1991, Kazantzis *et al*, 1962, Langworth *et al* 1992, Piikivi and Ruokonen 1989, Roels *et al*, 1982, Stewart *et al* 1977, Stonard *et al*, 1983, Sunderman 1978, Tubbs *et al*, 1982). These studies reported a number of renal effects associated with exposures to mercury vapour ranging from no effects to increases in urinary proteins, the specific gravity of urine and urinary levels of the lysosomal enzyme: *N*-acetyl-β-glucosaminidase (NAG, ATSDR, 1999).

Several occupational studies have reported renal effects associated with different urinary concentrations of mercury. Whilst no signs of renal dysfunction were observed among 62 workers at a chloralkali or at a zinc-mercury amalgam factory with mean urinary mercury concentrations of 56 μg/g (IPCS, 2003: Lauwerys *et al*, 1983), slight renal changes linked to tubular dysfunction have been reported in workers with mean urinary mercury concentrations of 30 μg/g (IPCS, 2003: Roels *et al*, 1985). In a cohort study of 50 workers exposed to metallic mercury with mean duration of 11 years and 50 controls (IPCS, 2003: Cardenas *et al*, 1993), exposed workers excreted an average of 22 μg/g. Renal effects were mainly found in workers excreting in excess of 50 μg/g and included cytotoxicity (e.g. increased breakage or tubular antigens and enzymes in urine) and biochemical alterations (e.g. decreased urinary excretion of eicosanoids and glycosamininoglycans and lowering of pH). Concentrations of anti-DNA antibodies and total immunoglobulin E in the serum of workers were found to be positively associated with mercury in the urine and blood respectively.

Several studies have indicated that occupational inhalation exposures to metallic mercury vapour giving rise to urinary concentrations above certain levels, causes increased urinary excretion of a number of proteins including β-galactoside, *N*-acetyl-β-glucosaminidase (NAG), transferrin, β2-microglobulin and albumin (IPCS, 2003). No differences could be found in the kidney parameters investigated in 122 workers with mean urinary mercury concentrations of 8.1 μg/g or in 38 workers with mean urinary concentrations of 11.9 μg/g when compared to kidney parameters in 197 and 47 controls respectively (DFG, 2002: Alinovi *et al*, 2002, Camerino *et al*, 2002). In a detailed analysis of markers for urinary dysfunction associated with inhalation exposures to mercury vapour, urinary excretion of Tamm-Horsfall glycoprotein (THG), and tubular antigens was found to be increased in exposed workers, whereas urinary pH, excretion of glycoaminoglycans, prostaglandin E_2 (PGE_2) and $F_2\alpha$ (PGF_2), and thromboxane B2 (TXB_2) were decreased (ATSDR, 1999: Cardenas *et al* 1993). No changes in kidney parameters were observed at urinary mercury concentrations below 5 μg/g. The first changes in parameters (prostaglandin PGE_2, PGF_2, and TXB_2) were observed at urinary mercury concentrations between 5 and 50 μg/g (DFG 2005: Price *et al*, 1996). Significantly reduced eicosanoid concentrations, especially PGE_2, have been reported at urinary mercury concentrations of 35 μg/g (DFG 2005: Roels 2002, Roels *et al*, 1999). Brush border antigens BB50, BBA, HF5 and intestinal alkaline phosphatase were increased at urinary mercury concentrations over 50 μg/g. Although levels of THG, NAG, BB50, HF5 and intestinal alkaline phosphate have been found to correlate positively with the mercury concentration in urine, no correlation with exposure duration has been found (DFG, 2005: Price *et al*, 1996). High numbers of workers with proteinuria (14.6 – 39%) were found in two groups of workers with urinary mercury concentrations of 29.3 ± 23.2 μg/g and 138 ± 80.9 μg/g (DFG, 2005: Abdennour *et al*. 2002). The urinary pH in workers was frequently below 6.5, especially in workers of the high exposure group. Other studies confirm that no changes in albumin or NAG levels were found in the urine of workers with mean mercury urinary concentrations of 16.9 μg/g and a maximum of 52 μg/g (DFG, 2005: Piikivi and Ruokonen 1989).

Elevated levels of β-galactoside were observed in workers with urinary levels of mercury in excess 20 μg/g (IPCS, 2003: Buchet *et al*, 1980). Although, a small, statistically significant difference in NAG activity was reported in 47 workers with mean urinary mercury concentrations of 12.5 (2.3-35.7) μg/g when compared to controls, no other changes in kidney parameters in the urine or in serum where observed in the study (DFG, 2005: Ellingsen *et al.,*

2000a). In its evaluation of this study, DFG conclude that the biological relevance of such minor changes in kidney parameters may be questionable (DFG, 2005). In a cross-sectional study, changes in five different kidney parameters (total protein, retinol-binding protein, leucine aminopeptidase, glutathione transferase, NAG) were observed in a group of 20 non-smoking workers occupationally exposed to mercury vapour for 11 years and showing urinary mercury concentrations of 21.4 ± 15.9 μg/ and in a group of 27 non-smoking workers with exposures of up to 10 years and urinary mercury concentrations of 25.6 ± 19.3 μg/g DFG, 2005: El-Safty *et al*, 2003).

A wide range of parameters including low and high molecular weight proteins; lysosomal enzymes; brush border enzymes distal tubular proteins; globular structural proteins; protagloadins and Kallikreins, have been regarded as biomarkers of renal damage induced by exposure to mercury (DFG, 2005). However, the evidence of biomarkers in urine is not a sufficiently reliable indicator of chronic renal damage (DFG, 2005). Studies have indicated that specific patterns of biomarkers rather than individual biomarkers show greater specificity towards neprotoxicity whereas intestinal alkaline phophatase, retinol-binding protein and brush-border-specific antigens are regarded as more sensitive markers of toxicity (DFG, 2005). Since inter- and intra- individual variability in biomarkers associated with renal damage can be quite considerable, judgements over whether changes in biomarker levels truly indicate adverse affects should be made with caution (DFG, 2005).

Attempts to define threshold levels for renal toxicity associated with chronic exposures to mercury vapour based on urinary biomarkers, have produced mixed results (ATSDR, 1999). A no-effect level of 72 μg/g was determined for urinary excretion of albumin, β_2-microglobulin, or retinol-binding protein (ATSDR, 1999: Bernard *et al*, 1987). Several studies have reported consistent changes in different mercury-relevant kidney parameters at urinary mercury concentrations above 50 μg/g (DFG, 2005: Barregard *et al*., 1988, Buchet *et al*, 1980, Ehrenberg *et al* 1991, Himeno *et al*, 1986) or above 100 μg/g (DFG 2005: Kolenic *et al*, 1995, 1997, Marek and Wocka-Marek, 1994). Elevated levels of NAG and albumin have been reported in chloroalkali workers with urinary levels of mercury in excess of 50 μg/g whereas elevated levels of β-galactoside were observed in workers with urinary levels of mercury in excess 20 μg/g (IPCS, 2003, ATSDR, 1999: Buchet *et al*, 1980). Although a transient increase in NAG was observed after exposure to mercury giving urinary levels below 35 μg mercury/g creatinine, no correlation with duration of exposure was found. This increase was not considered to be an early indicator of developing renal dysfunction (ATSDR, 1999: Boogard *et al*, 1996). In other studies, no clear effects on kidney parameters were measured in workers found to have urinary mercury concentrations up to 35 μg/g (DFG, 2005: Ellingsen *et al* 200a) or up to 42 μg/g (DFG, 2005: Alinovi *et al*, 2002, Camerino *et al*, 2002).

In their evaluation of available data to establish an occupational exposure limits and a biological limit value for the EU, SCOEL noted that urinary mercury concentration has been regarded as a No Observed Adverse Effects Level (NOAEL) for renal toxicity indicated by elevated levels of these protein markers in urine (SCOEL, 2007). Elevated levels of protein markers seen at higher mercury concentrations (e.g. 50 μg/g and above) indicate the onset of renal toxicity (SCOEL, 2007).

When making a recommendation on the occupational exposure limit for mercury, the UK Health and Safety Commissions's (HSC's) Advisory Committee on Toxic Substances (ACTS) considered that a urinary mercury concentration of 35 μg/g appears to be a NOAEL for elevated enzyme and protein levels in urine, given that elevations seen at higher mercury concentrations are suggested to be early indicators of kidney toxicity (HSE, 2002; 1995). Given that human data suggest indications of CNS effects also appear with urinary mercury levels above 35 μg/g (HSE, 1995), this urinary concentration has been established as the

biological monitoring health guidance value associated with the occupational exposure standard (OES) for mercury of 0.025 mg/m^3 (HSE, 2002).

The DFG adopted a different approach to setting a biological tolerance value (DFG, 2005) for exposures to mercury, principally regarding the findings from the study by El-Safty *et al* (2003) in which no nephrotoxic changes were found in two groups of non-smoking workers with urinary mercury concentrations of 26 ± 19 µg/g and 31 ± 23 µg/g respectively and exposure of duration 11 and 10 years respectively (DFG, 2005). Based on the indication from available data that no relevant mercury-related nephrotoxic effects (and no clinically relevant neurotoxic changes) are to be expected at a concentration of 25 µg/g, when taking the 95th percentile into account, the DFG established a DFG value of 25 µg/g.

No indications of renal dysfunction have been observed in studies of volunteers with amalgam fillings, as compared with controls, in which NAG was used as a protein marker for renal damage (IPCS, 2003: Eti *et al*, 1995; Herrstrom *et al*, 1995). Although no signs of renal toxicity were found in 10 healthy volunteers with an average 18 dental amalgam fillings before and after their removal, plasma mercury levels were significantly increased one day later (ATSDR, 1999: Sandborgh-Englund and Nygren, 1996). A decreased ability to concentrate urine and elevated urinary albumin was observed in 10 individuals who reported adverse affects associated with dental amalgam (ATSDR, 1999: Anneroth *et al*, 1992). Removal of dental amalgam was found to significantly reduce urinary albumin in one patient.

The spontaneous resolution of proteinuria associated with mercury-mediated renal disease has been observed in humans following cessation of exposure to mercury. Treatment of chronic kidney disease caused by exposure to mercury therefore involves the removal of affected individuals from possible sources of exposure (Balmes *et al*, 2006)

1.5.2.3 Respiratory Effects

Chronic cough has been reported in subjects exposed to metallic mercury vapour for several weeks (IPCS, 2003; ATSDR, 1999).

1.5.2.4 Cardiovascular Effects

Increased blood pressure and heart rate have been reported in workers after accidental spills or longer-term occupational exposures to metallic mercury vapour (IPCS, 2003; ATSDR, 1999).

Studies of chronic occupational exposures to metallic mercury vapour have reported contrasting findings of cardiovascular effects. No effects on blood pressure or electrocardiography were observed in two studies of workers exposed to mercury via inhalation with average values of 0.048 mg/m^3 and 0.075 mg/m^3 respectively for around 7 years (ATSDR, 1999: Schuckman 1979; Smith *et al*, 1970). In contrast, increased incidence of palpitations and reduced cardiovascular reflex responses were reported in workers exposed to mercury vapour estimated at 0.03 mg/m^3 when compared to unexposed controls (ATSDR, 1999: Piikivi, 1989). Reports of a higher incidence of hypertension in workers at a thermometer plant (ATSDR, 1999: Vroom and Greer, 1972) and an increased likelihood of death from ischemic heart and cerebrovascular disease in chloralkali workers (ATSDR, 1999: Barregard *et al*., 1990) should be cautiously interpreted since the underlying studies were limited (ATSDR, 1999).

Statistically significant increases of around 5 mmHg (0.7 kPa) in both systolic and diastolic blood pressure, increased mean corpuscular haemoglobin and decreased haemoglobin and haematocrit were reported in 50 volunteers with mercury dental amalgam when compared with an age- and sex- matched control group without amalgam fillings (IPCS, 2003, ATSDR, 1999: Siblerud, 1990). Potential confounding factors such as lifestyle and body mass were not discussed.

1.5.2.5 Gastrointestinal Effects

There is limited information available regarding gastrointestinal effects after chronic exposure to metallic mercury vapour. Stomatitis (inflammation of the oral mucosa) has been reported in occupational settings in workers exposed to metallic mercury vapour for prolonged periods (IPCS, 2003). Stomatitis was observed in 22 or 72 workers exposed to mercury vapour in the manufacture of thermometers in the 1940s (ATSDR, 1999: Bucknell *et al*, 1993). Drooling, sore gums, ulcerations of the oral mucosa and/or diarrhoea were observed in 5 out of 9 workers in a thermometer-manufacturing plant (ATDSR, 1999: Vroom and Greer, 1972). Patients with hypersensitivity to mercury (indicated by positive patch tests) developed stomatitis at the sites of contact with amalgam fillings that faded once the fillings had been removed (IPCS, 2003).

1.5.2.6 Hematological Effects

Decreased activity of δ-aminolevulinic acid dehydratase in the erythrocytes, correlating with increases in urinary mercury was found in workers exposed to metallic mercury vapour in the manufacture of tungsten rods (ATSRD, 1999: Wada *et al*, 1969). Exposure to mercury vapour at the plant was estimated to be < 0.1 mg/m^3. Significant increases in α_2-macroglobulin and ceruloplasmin levels were reported in workers exposed to mercury vapour ranging from 0.106-0.783 mg/m^3 compared to controls (ATSDR, 1999: Bencko *et al*, 1990)

Significantly decreased haemoglobin and hematrocrit levels and increased mean corpuscular haemoglobin concentrations have been reported in a study of volunteers with dental amalgam compared to controls (ATSDR, 1999: Siblerud, 1990).

1.5.2.7 Reproductive Effects

Several studies found no effects on fertility following long-term occupational inhalation exposure to metallic mercury in humans (IPCS, 2003). No effects on fertility were reported in a retrospective cohort study of male workers exposed for at least 4 months to mercury vapour at a nuclear plant who had urinary mercury concentrations ranging from 2144 to 8572 µg/g (IPCS, 2003: Alcser *et al*, 1989). In a questionnaire study to assess male fertility, no statistically significant difference was observed in the number of children born to mercury exposed versus unexposed workers from various industries with urinary mercury concentrations ranging from 5.1 to 272.1 µg/g (e.g. chloroalkali, zinc-mercury, manufacturers of electrical equipment; IPCS, 2003: Lauwerys *et al*., 1985). Studies of reproductive hormones in workers occupationally exposed to metallic mercury vapour did not find any correlation between blood or urinary mercury levels and levels of prolactin, testosterone,

luteinising hormone or follicle stimulating hormone (IPCS, 2003: Erfurth *et al*, 1990; McGregor and Mason, 1991).

Although increased complications in parturition (including toxicosis, abortions, prolonged parturition and haemorrhagic parturition) were reported in a study of 349 women workers occupationally exposed to mercury vapour when compared to 215 unexposed controls, the methods used in the study were unclear (IPCS, 2003: Mishonova *et al*, 1980). In contrast, no increases in spontaneous abortions or congenital abnormalities have been reported in a number of studies of dental workers with potential exposures to mercury (IPCS, 2003: Heidam, 1984; Brodsky *et al*., 1985; Ericsson and Kallen, 1989)

Menstrual cycle disorders were more frequently reported in a study of women workers in a mercury vapour lamp factory, who had historically received exposures giving rise to urinary mercury concentrations in excess of > 50 μg/g, decreasing to < 10 μg/g at the time of the study (IPCS, 2003: De Rosis *et al*, 1985). The authors reported a higher prevalence of primary subfecundity and of dislocations of the hip in newborns in married females at the factory but noted that the frequency of this anomaly varied between different regions of Italy. Increased rates of spontaneous abortions were not observed (IPCS, 2003).

A case study of a woman chronically exposed to an undetermined concentration of mercury vapour reported that the first pregnancy resulted in spontaneous abortion and the second pregnancy resulted in the death of the child soon after birth (ATSDR, 1999: Derobert and Tara, 1950). It is unclear whether these effects were due to mercury exposure and the woman went on to have a healthy child after recovery from overt mercury toxicity (ATSDR, 1999). Another woman exposed to mercury vapour for 2 years prior to pregnancy and throughout pregnancy gave birth to a healthy child at term (ATSDR, 1999: Melkonian and Baker, 1988). At 15 weeks of pregnancy the woman had a urinary mercury level of 875 μg/g compared to normal levels of approximately 4 μg/g. A normal child, meeting all developmental milestones was also delivered by a woman exposed to mercury vapour at home for the first 17 weeks of pregnancy (ATSDR, 1999: Thorpe *et al*, 1992). Although the mercury exposure concentrations were not known, the child had hair levels of mercury of 3mg/kg; a comparable level to that observed in the general population consuming fish once a week (ATSDR, 1999).

1.5.2.8 Genotoxicity

There is little information concerning the potential genotoxicity or mutagenicity of metallic mercury. In their evaluation of cytogenetic monitoring studies of workers occupationally exposed to metallic mercury by inhalation (Verschaeve *et al* 1976, 1979; Popescu *et al*., 1979; Mabille *et al*., 1984; Barrregard *et al* 1991; Mottironi *et al*, 1985*)*, IPCS, ATSDR and the HSE did not consider that there was any convincing evidence that mercury adversely affects the number or structure of chromosomes in human somatic cells. Studies reporting positive results were compromised by technical problems, a lack of consideration of confounding factors or a failure to demonstrate a relationship between mercury exposure and induced aberrations (IPCS, 2003; HSE, 1995; ATSDR; 1999).

Increased aneuploidy was reported in a study by Verschaeve *et al* (1976) of workers exposed to metallic mercury; the incidence of aneuploid cells in whole blood lymphocytes was found to be 32.5% ($p<0.001$) and 31.1% ($p<0.05$) for workers exposed to metallic mercury and mercury amalgam respectively compared to 24.6% for controls (HSE, 1995). Mean urinary mercury levels of 39.6 ± 38.3 μg/g and 10.7 ± 2.6 μg/g were found for metallic mercury and mercury amalgam workers respectively (HSE, 1995). The frequency of chromosome aberrations was not significantly altered in these two exposed groups (HSE, 1995). ATSDR did not regard this study to be well controlled with respect to sex, smoking habits or sample size (ATSDR, 1999). In a subsequent study by the same researchers, no increase in

chromosome abnormalities was reported in lymphocytes from whole blood samples collected from 28 chloralkali workers exposed to metallic mercury for between 1 and eleven years at air concentrations below 50 μg mercury/m^3 compared to 12 unexposed workers (ATSDR, 1999, HSE, 1995: Verschaeve *et al*, 1979). Urinary mercury levels only exceeded 50 μg/g in 4 subjects (HSE, 1995). The authors concluded that the results of the 1976 study in which an association between increased chromosomal aberrations and occupational exposure to metallic mercury may have been affected by factors other than exposure to mercury (ATSDR, 1999).

Whilst a statistically significant increase in aneuploidy, but no increase in chromosome aberrations was reported in a cytogenic investigation of 10 dental workers exposed to metallic mercury in dental amalgam (HSE, 1995: Verschaeve and Susanne, 1979), no increase in chromosome aberrations in peripheral lymphocytes was reported in 22 workers from a chloralkali plant exposed to mercury vapour for a mean duration of 4 years or in 10 workers from a mercury-zinc amalgam plant (HSE 1995, ATSDR 1999: Mabille *et al*, 1984). Mean levels of mercury in the urine and blood of exposed workers were 117 μg/g (range 8.2 – 286 μg/g) and 3.06 μg mercury/100 ml (range 0.75-10.52 μg mercury/100 ml) respectively. Another cytogenetic study also failed to demonstrate an increase in chromosome aberrations or the incidence of sister chromatid exchange in 20 workers at a caustic soda/copper foil production plant exposed to mercury for between 0.8 and 34.8 years (HSE, 1995: Mottironi *et al*, 1985). Exposed workers had mean blood mercury levels of 26.9 ng mercury/ml, with a range 6.7 – 89.1 ng mercury/ml (HSE, 1995).

Although a significant increase in the frequency of chromosome breaks (e.g. acentric fragments) occurred in 4 workers exposed to high concentrations of metallic mercury vapour in the range 0.15 to 0.44 mg/m^3 (ATSDR, 1999: Popescu *et al*, 1979), ATSDR regarded the findings of this study to be suspect since the control group was not matched for sex, smoking habits or sample size. No increase in the incidence of aneuploidy was found in the exposed workers (ATSDR, 1999).

In a more recent study, an investigation of micronucleus induction in peripheral lymphocytes was carried out in samples from 26 male chloralkali workers exposed to mercury vapour in the range 25 – 50 μg/m^3, for a mean exposure time of 10 years and in comparison with 26 unexposed workers (ATSDR 1999: Barregard *et al*, 1991). Exposed and unexposed groups were matched for age and smoking habits and plasma, erythrocyte and urinary mercury levels were determined. Parallel lymphocyte cultures from mercury exposed and unexposed groups were incubated in the presence of pokeweed mitogen, a stimulator of B- and T-lymphocytes and phytohemagglutinin, a primary activator of T-cells. No significant increase in the frequency or the size of micronuclei was observed in either the exposed or unexposed groups and no correlation was found between micronuclei induction and the levels of mercury in plasma, erythrocytes or urine. However, a significant correlation was found in the exposed group between micronuclei induction in the phytohemagglutinin-stimulated lymphocytes and cumulative exposure (e.g. whole-blood mercury over employment time), suggesting a genotoxic effect on T-lymphocytes. These findings were considered to be unusual, since there is evidence that B-lymphocytes may be more sensitive indicators or chemically-induced clastogenesis that T-lymphocytes (ATSDR, 1999). The authors stated that evidence of a genotoxic response confined to T-lymphocytes may have been a random finding but may also suggest that long-term exposure to mercury may cause accumulation of cytogenic effects (ATSDR, 1999).

1.5.2.9 Carcinogenicity

The potential carcinogenicity of mercury has been comprehensively examined by a Working Group of the International Agency for Research on Cancer (IARC) of the World Health Organisation (WHO) as part of a long-established programme of work to evaluate the carcinogenic risk of chemicals to humans and to produce monographs on individual chemicals. The outcome of IARC's evaluation of mercury has been presented in the IARC Monograph 58 (IARC, 1993). This section principally summarises the findings of the IARC evaluation but conclusions reached by other expert reviewers (e.g. EPA, ATSDR, and HSE) have also been highlighted. Follow-on studies to the occupational epidemiological studies evaluated by IARC and published subsequently to the monograph have been additionally summarised. No more recent primary studies since IARC's evaluation published in 1993 on the potential carcinogenic risk of chronic, low level inhalation exposed to mercury vapour have been identified.

IARC's evaluation of the carcinogenic risks to humans of metallic mercury

Acknowledging that many populations have low-grade or infrequent exposure to metallic mercury or mercury compounds, the IARC Working Group restricted their review to studies specific to these substances and to groups known to have considerable exposure.

Occupational mortality studies

In a study of occupational mortality in the United States during the period 1950 to 1971 on the basis of death certificates, the proportionate mortality ratio (PMR) for male dentists for all malignant neoplasms was 1.05 (127 cases [95% confidence interval (CI), 0.88-1.25]; IARC 1993: Milham, 1976). When cancer sites with more than five cases were considered, the PMR was 1.53 for pancreatic cancer based on 12 cases [95% CI, 0.79-2.69]; 1.32 for prostatic cases based on 20 cases [95% CI, 0.8-2.03] and 1.45 for neoplasms of the lymphatic and haemotopoietic tissues based on 17 cases [95% CI, 0.84-2.33]. Cancer mortality in male dentists was also reported in a study of occupational mortality in Canada during 1951 to 1961 (IARC 1993: Gallagher *et al*, 1985). Among dentists there were 4 cases of kidney cancer (PMR, 1.94; 95% CI, 0.52-4.96) and 5 tumours of the brain and central nervous system (PMR, 2.36; 95% CI, 0.76-5.52; IARC 1993).

Cohort studies

In their evaluation of the carcinogenic risks to humans posed by metallic mercury, the IARC working group considered data from occupational cohort studies of nuclear weapons industry workers (Cragle *et al*, 1984), dentists (Ahlbom *et al*, 1986 and Hrubec *et al*, 1992), chloralkali workers (Barregard *et al*, 1990 and Ellingsen *et al*, 1993) and mercury miners (Amandus and Costello, 1991). The findings from these studies are summarised below and in Table 6 (Appendix 1).

In a study of nuclear weapons industry workers from Oak Ridge Y-12 plant, Tennessee, USA, mortality was investigated in cohorts of 2133 white workers exposed to metallic mercury and 3260 unexposed white workers in comparison with national mortality rates for white men (IARC, 1993; Cragle *et al*, 1984). Exposure to mercury had occurred during lithium production in a nuclear weapons plant that had previously produced a fissionable isotope of uranium. Any worker with detectable levels of urinary mercury was assumed to have been

exposed to mercury from these processes. A mercury monitoring programme began in 1953 and cohorts were followed-up from 1953 to 1979. An examination of mercury air monitoring data revealed that the highest air concentrations of mercury occurred in 1955 and 1956, with between 12 and 87.2% of air samples exceeding 0.1 mg mercury/m^3 (IARC, 1993: Cragle *et al*, 1994). Between 1957 and 1960, only between 1.3 and 10.3 % of air samples exceeded 0.1 mg mercury/m^3. A mercury urinalysis programme was started at the plant in 1953 which included all workers in processes involving mercury. The "plant action value" (PAV) was set at 300 μg/g (10x current guidance values). Any workers with urinary mercury concentrations exceeding 2 x PAV were removed from the process until their urinary mercury concentrations had fallen to below the PAV.

Total mortality was lower than expected, when compared with the national rate, for both the exposed and unexposed worker cohorts. There was no excess of any non-cancer deaths, possibly related to mercury exposure (e.g. target organs being regarded as: liver, lung, brain and central nervous system and kidney). Whilst the overall cancer mortality ratio for the exposed cohort was lower than expected, a higher that expected cancer mortality ratio was observed for the unexposed worker cohort. A statistically significant excess of death from lung cancer was seen in both the exposed (SMR, 1.34 [95% CI 0.97-1.81], n= 42) and unexposed cohorts (SMR, 1.34 [95% CI 1.05-1.69], n=71). Although an excess of cancers of the brain, central nervous system and kidney were observed in the exposed cohort, this was not statistically significant. A statistically significant excess in deaths from brain cancer was observed in workers in the plant not involved in the mercury process. No clear increase in cancer mortality rates was observed in worker subgroups with urinary mercury levels exceeding 300 μg/g (e.g. the PAV) at least once or with more than one year of exposure. In their evaluation of this study, the IARC working group could not determine the basis for the excess of lung cancer observed in both the exposed and unexposed cohorts, but indicated that lifestyle factors or some factor other than exposure to mercury at the plant may be important.

IARC considered cancer mortality data from other occupational sectors. A two-fold increased risk of brain tumours was found in cohorts of 3454 male and 1154 female dentists and 4662 dental nurses in a Swedish cancer mortality study from 1961 to 1979 (IARC 1993: Ahlbom *et al*, 1986). The overall standardised incidence ratio (SIR) for glioblastoma (astrocytoma III-IV) observed overall in the group of dental workers was 2.1 (95% CI, 1.3–3.4, n= 18) in comparison with national incidence rates. For the individual cohorts, SIRs of 2.0, 2.5 and 2.2 were found for male dentists, female dentists and dental nurses respectively. No excess of glioblastomas were found in a comparative study in physicians and female nurses. The authors proposed that amalgam, chloroform and X-radiation may be possible occupational factors. An excess risk of intracranial gliomas (subtypes not specified) was also found in another analysis of the same cohorts (IARC 1993: McLaughlin *et al*, 1987). SIR values of 2.1 ($p < 0.05$; 12 cases) and 2.1 ($p < 0.09$; 9 cases) were reported for male dentists and female dental assistants respectively. Comparative analysis of male chemists, physicists, veterinary surgeons, agricultural research scientists and pharmacists and female physicians indicated a two-fold or greater risk of brain cancer for these groups also, suggesting that factors other than exposure to mercury may be of importance in these occupational groups (IARC 1993: McLaughlin *et al*, 1987).

Mortality risks by occupation were assessed among 300,000 veterans who served in the US Armed Forces between 1917 and 1940. Occupation and smoking status were assessed through questionnaires in 1954 and 1957 and follow-on to 1980 was carried out using insurance and pensions systems (IARC, 1993; Hrubec *et al*, 1992). The smoking-adjusted relative risk (RR) for each occupation was estimated by using all other occupations as the standard and Poison regression modelling. An increased risk of brain or kidney cancer was not found in a sub-cohort of 2498 dentists with a total of 1740 deaths in the study . Although this group had an excess risk of pancreatic cancer (RR, 1.4; 90% CI, 0.98-1.86, 27 deaths), this was not

statistically significant. The relative risk (RR) of death from all cancers was 0.9 (90% CI, 0.8-0.97). In the same study, an excess risk of colon cancer (RR, 1.9; 90% CI, 1.01 –3.53; 7 deaths) was found in a cohort of 267 medical and dental technicians. Whilst the risk of death from all cancers was elevated in non-smokers in this group, this risk was only slightly elevated when smokers and non-smokers were considered collectively. Although the risks of brain (RR, 1.5, 1 case) and kidney (RR, 2.8, 2 cases) cancer were found to be elevated in this group, confidence intervals were not reported and the significance of these findings is therefore unclear.

A cohort study of 1190 male Swedish chloralkali workers identified a two-fold, significant excess risk for lung cancer and some non-significant excess risks for cancers at other sites (IARC, 1993: Barregard *et al*, 1990). The authors note that occupational exposures to mercury in the chloralkali workers were likely to be 5-10 times higher that those in dental workers. Mercury levels in the blood and urine of these workers had been measured for at least one year between 1958 and 1984. The mean level of mercury excreted in the urine by workers had been about 200 μg/g in the 1950s, 150 μg/g in the 1960s and <50 μg/g in the 1980s. Whilst it was estimated that around 26% of workers had accumulated urinary mercury doses of 1000 years x μg/g, 457 workers in the cohort had known exposures to low grade asbestos or static magnetic fields. Although the overall mortality and mortality from all types of cancer were not increased in the cohort, lung cancer mortality (with a latency of 10 years) was in clear excess (RR, 2.0, 95% CI 1.0 – 3.8; 10 cases versus 4.9 expected). Non-significant excesses in brain (RR 2.7; 95% CI, 05-7.7, 3 cases versus 1 expected), kidney (RR 1.6, 95% CI 0.3-4.7, 3 cases versus 1.9 expected), bladder (RR 1.7, 95% CI 0.6 –4.1, 5 cases versus 2.9 expected), and prostate (RR 1.2, 95% CI 0.6 – 2.1, 10 cases versus 8.6 expected) cancers were observed in the cohort.

A two-fold excess in lung cancer (SIR 1.66; 95% CI 1.00-2.59; 19 cases versus 11.5 expected) was also found in a cohort study of 674 male Norwegian chloralkali workers between 1953 and 1989 exposed to mercury for more than one year prior to 1980 who had mean cumulative urinary concentrations of 740 μg/g (IARC 1993; Ellingsen *et al*, 1993). An excess in the overall mortality and mortality from all types of cancer was not found in the cohort and the number of brain and kidney cancers were close to expected numbers.

In both these studies, exposure to asbestos was judged to be an important determinant of the excess lung cancer risk as cases of mesothelioma were found. Smoking was also considered to be an important contributing factor (IARC, 1993).

The risk for lung cancer was found to be higher among workers with silicosis in a study of US mine workers from 1959 to 1975 than in non-silicotic mercury mine workers and other individuals with silicosis who worked elsewhere (IARC, 1993; Amandus and Costello, 1991). The SMR for 11 silicotic mercury mine workers was 14 (95% CI, 2.89-41.0) based on three lung cancer deaths compared 2.66 (95% CI, 1.15 –5.24) based on eight cases for 263 non-silicotic mine workers and 1.39 (95% CI, 0.70-2.49) based on eleven silicotic lung cancers in 110 workers from other mines (e.g. copper, lead-zinc, iron). These findings were based on small numbers and confidence limits overlapped.

Case-control studies

In their evaluation of the carcinogenic risks to humans posed by metallic mercury, the IARC working group considered data from case-control studies of the incidences of lung, prostatic, bladder and brain cancers in hospital and population-based groups (Buiatti *et al*, 1985; Siemiatycki, 1991; Carpenter *et al*, 1988 and Ryan *et al,* 1992). The findings from these studies are summarised below and in Table 7 (Appendix 2).

A case-control study in Italy indicated an excess risk for lung cancer (p=0.01, 6 cases) among women in the felt-hat industry who had heavy exposure to mercury but also to arsenic (IARC, 1993; Buiatii *et al*,1985).

Carpenter *et al* (1988) conducted a nested case-control study of cancers of the central nervous system among workers employed at two nuclear facilities at Oak Ridge in US, between 1973 and 1977. Seventy-two and 17 cases of mortality from cancer of the central nervous system in white male and female workers respectively were each matched to 4 controls with respect to race, sex, employment history and year of birth. Each case was evaluated for potential exposure to 26 different chemicals, including mercury. The authors concluded that their study did not support the hypothesis that occupational exposure to any of the 26 chemicals studies appreciably increased the risk for cancers of the central nervous system (IARC, 1993).

In a Canadian population-based case-control study, risk for prostatic cancer was associated with exposure to mercury compounds in general and the risk for lung cancer with exposure to metallic mercury (IARC, 1993; Siemiatycki, 1991). A broad range of chemical exposures, including metallic mercury and mercury compounds were investigated in the study that involved all major cancer forms and hospital-based and population-based controls. The prevalence of exposure to metallic mercury among cancer cases for which exposures had been successfully assessed (533 cases) was 0.6%. For prostatic cancer, 5 of 449 cases were exposed to metallic mercury, giving an odds ratio of 6.2 (90% CI, 1.2-33.2) whereas for lung cancer, 4 of the 857 cases had been exposed to metallic mercury (odds ratio 4; 905 CI, 1.2-13.0). In their evaluation of this study, the IARC working group noted that not all possible occupational confounding factors had been addressed.

In an Australian case-control study of brain tumours and amalgam fillings, there was a decreased risk for gliomas but no effect was seen with regard to meningiomas (IARC, 1993; Ryan *et al*, 1992). In the study, the relationship between incidence of brain tumours and exposure to amalgam fillings and diagnostic dental X-rays was investigated in an Australian case-control study. A total of 110 glioma cases, 60 meningioma cases and 417 controls were included in the analysis. Decreased odds ratios for glioma associated with self-reported amalgam fillings (odds ratio 0.47, 95% CI, 0.24-0.76) and with diagnostic X-rays (odds ratio 0.42, 95% CI, 0.24-0.76) were observed in the study. Non significantly increased odds ratios for meningioma associated with amalgam fillings (odds ratio 1.04, 95% CI, 0.43-2.47) and with diagnostic X-rays (odds ratio 1.37, 95% CI, 0.68-2.73) were observed.

Conclusions drawn by IARC on the carcinogenic potential of exposures to mercury in humans.

IARC summarised their evaluation of the human carcinogenicity data as follows (IARC, 1993) :

"A cohort study in a nuclear weapons factory in the USA on exposure to metallic mercury showed no difference in risk for lung cancer in exposed and unexposed subcohorts from the same factory. In a nested case-control study at nuclear facilities in the USA, the risk for cancers of the central nervous system was not associated with estimated levels of exposure to mercury.

A cohort study of chloralkali workers in Sweden identified a two-fold, significant excess risk for lung cancer and some nonsignificant excess risks for cancers of the brain and kidney. Lung cancers also occurred in an almost two-fold excess in Norwegian chloralkali workers. In both studies, asbestos and smoking were judged to be the main determinants of the excess risk for lung cancer.

In a study of male and female dentists and female dental nurses in Sweden, a two-fold risk for brain tumours was found in each of the three cohorts. No such risk appeared among dentists

or medical and dental technicians in a US study of military veterans; these groups had excess risks for pancreatic and colon cancer, respectively. In an Australian case-control study of brain tumours and amalgam fillings, there was a decreased risk for gliomas and no effect was seen with regards to meningiomas.

The risk for lung cancer was found to be higher among individuals with silicosis who had been working in US mercury mines than in subjects with silicosis who had worked elsewhere. This finding was based on small numbers, however, and the confidence limits overlapped.

A case-control study in Italy indicated an excess risk for lung cancer among women in the felt-hat industry who had heavy exposure to mercury but also to arsenic.

In a population-based case-control study from Canada, risk for prostatic cancer was associated with exposure to mercury compounds in general and the risk for lung cancer with exposure to metallic mercury".

Animal carcinogenicity data

In their evaluation of studies of cancer associated with exposure to metallic mercury in animals, the IARC working group considered only one study of intraperitoneal exposure in rats (IARC, 1993; Druckrey *et al*, 1957). A group of 39 male and female rats (3 months old) were given two intraperitoneal injections of 0.05ml metallic mercury over 14 days. Only gross lesions were investigated histopathologically. At 22 months, of the 12/39 treated rats that were still alive, 5 rats (3 female, 2 male) developed spindle-cell sarcomas in the abdominal cavity. IARC regarded that the study had been incompletely reported and the lesions seen were possibly due to a solid-state effect.

Overall evaluation of the carcinogenic risk of metallic mercury by IARC

On the basis of their evaluation, the IARC working group concluded that there is inadequate evidence in humans and experimental animals for the carcinogenicity of metallic mercury (and inorganic mercury compounds). Metallic mercury and inorganic mercury compounds are therefore regarded by IARC as *'not classifiable as to their carcinogenicity to humans (Group 3)'* (IARC, 1993).

Cancer mortality of workers at Oak Ridge nuclear plants, Tennessee.

The conclusion by Cragle *et al* (1984) that exposures to mercury vapour at the Oak Ridge Y-12 plant was not related to any excess of deaths from cancer motivated a number of studies to further investigate the basis of these findings. The relationship between cancer mortality and exposure to alpha and gamma radiation emanating from insoluble uranium compounds was later investigated in a historical cohort mortality study of 6781 white male workers from the Oak Ridge Y-12 plant, employed during the period 1947 to 1979 (Checkoway *et al*., 1988). The study did not however, differentiate workers on the basis of exposures to mercury. In concordance with the findings of Cragle *et al*, the authors reported excesses of lung cancer and brain and other central nervous system (CNS) cancer mortality in the worker groups compared to the US and Tennessee referent populations groups. SMR values of 1.36 [95% CI 1.09-1.67] and 1.18 [95% CI 0.95-1.45] for lung cancer and SMR values of 1.8 [95% CI 0.98-3.02] and 1.31 [95% CI 0.48-2.85] for brain and other CNS cancers compared respectively with the US and Tennessee reference populations (Checkoway *et al*., 1988). Although the

statistical significance of these findings was not discussed, an SMR value is generally not regarded as statistically significant if the 95% confidence interval includes the null value. Whereas further analysis of dose-response trends indicated potential carcinogenic effects to the lung of relatively low-dose radiation, no dose-response trend for mortality from brain and other CNS cancers was observed. Given that the study by Cragle *et al* had indicated that the excess cases of brain and other CNS cancers and lung cases at the Oak Ridge plant were unrelated to exposure to mercury, together with the generally obscure aetiology of occupational-related brain cancers, the authors proposed that chemical exposures, more so than radioactive substances, were likely causal factors.

The influence of occupational exposure to 26 different chemicals, including mercury, on the risk of death from primary malignant neoplasms of the CNS was examined in a nested case-control study of workers employed between 1943 and 1997 at two nuclear plants at Oak Ridge Tennessee: Y-12 and the Oak Ridge National Laboratory (ORNL; Carpenter *et al*, 1988). Seventy-two white male and 17 white female workers who had died from primary CNS cancers as identified from death certificates were identified as cases. The study investigated possible links between CNS cancers and potential exposures to a range of chemicals including: carbon dusts, welding fumes, metals (mercury, lead, beryllium, chromium), cutting oils, solvents, asbestos, lubricants, benzene, and chlorinated and fluorinated compounds. Independent of their case-control status, an industrial hygienist subjectively evaluated each subject to determine potential chemical exposure history using semi-quantitative exposure scores taking into account: duration of employment, review of information about processes carried out, on-site visits, interviews with other staff and urinalysis and air monitoring data. The results of the study did not support the hypothesis that occupational exposures to the 26 chemicals or chemical groups appreciably increased the risk of development of CNS cancers in the subjects studied, but confidence intervals around the risk estimates obtained were large so that modest effects could not be ruled out (Carpenter *et al*, 1988). In a comparison of cancer risks between exposed and unexposed workers, the authors reported a matched odds ratio of 1.8 [95% CI 0.5-5.8] was obtained for mercury.

Mortality of workers at the Oak Ridge Y-12 plant over the period 1947 to 1990 was further explored in a follow-on study of 6049 workers including 4806 white males, 373 non-white males and 870 females (Loomis and Wolf, 1996). In agreement with findings from studies by Cragle *et al* and Checkoway *et al*, the authors reported statistically non-significant excesses in death rates in the cohort relative to a US reference population of lung, brain and other CNS cancers, pancreas, prostate, kidney and breast cancers. The authors concurred with Carpenter *et al* (1988) that an excess in brain cancer mortality may be linked to chemical exposures and suggested that, since metal-machining, involving oils, solvents and metal dusts was one of the principal activities at Y-12, any further investigation of brain cancer should focus on these agents (Loomis and Wolf, 1996).

Conclusions drawn by other expert reviews on the carcinogenic potential of exposures to mercury.

ATSDR

The Agency for Toxic Substances and Disease Registry (ATSDR) reviewed a number of occupational epidemiological studies (Kazantziz, 1981; Cragle *et al*, 1984; Ellingsen *et al*, 1993; Barregard *et al*, 1990; Ahlbom *et al*, 1986; McLaughlin *et al*, 1987; Hrubec *et al*, 1992) to determine whether chronic exposures to metallic mercury were linked to cancers. ATSDR concludes in CICAD 58 (WHO, 2003):

"There is no sound evidence from epidemiological studies indicating that inhalation of metallic mercury produces cancer in humans. Although an increased incidence of lung, brain, and kidney cancers has been reported within an exposed cohort when compared with the general population, these incidences were not elevated in comparison with the reference cohort. An increased incidence of cancer was not reported in a study of workers exposed to a variety of metals including mercury. No excess of cancers of the kidney or nervous system was found among a cohort of 674 Norwegian men exposed to mercury vapour for more than one year in two chloroalkali plants. Although an excess of lung cancer (type unspecified) was found in Swedish chloroalkali workers, co-exposure to asbestos had occurred. An excess of brain cancer was observed among Swedish dentists and dental nurses. In a separate study, no excess risk of overall cancer mortality was observed among dentists who were US armed forces veterans"

HSE

In their evaluation of the carcinogenicity of elemental mercury, the HSE appraised three occupational cancer incidence studies: Cragle *et al*, 1984, Ahlbom *et al*, 1996 and Barregard *et al* 1990 (HSE, 1995). The HSE considered that all these studies suffered from a lack of power to detect excess risks of cancer incidence in the brain, kidney and the liver.

EPA

In their evaluation of the carcinogenicity of metallic mercury, the EPA outlined that human epidemiological studies failed to show a correlation between exposure to mercury vapour and increased cancer incidence and were limited by compounding factors. Only one, incompletely reported study has investigated the carcinogenicity of metallic mercury in animals (Druckrey *et al*, 1957) in which tumours were found only at contact sites. (EPA, 1997)

1.6 SUMMARY OF THE TOXICITY OF ELEMENTAL MERCURY

The toxicity of metallic mercury following acute and chronic inhalation exposures has been broadly studied across occupational and non-occupational scenarios. The kidneys and central nervous system are the main target organs for mercury toxicity, whereas gastrointestinal, respiratory and reproductive effects have been seen after exposure to high concentrations. Studies of populations chronically exposed to mercury have reported a wide range of neurological effects including effects on cognitive, sensory, personality and motor function. While many of these effects have been found to subside when exposures to mercury cease, persistent tremor and cognitive effects can remain for up to 20 years. Psychomotor effects indicative of central nervous system toxicity are associated with mercury levels of 35 μg/g in the urine and 10 μg/l in the blood. The same urinary concentrations are associated with elevated enzyme and protein levels in the urine; the elevations seen at higher mercury concentrations are suggested to be early indicators of kidney toxicity. Reversal of renal changes (e.g. proteinuria) associated with mercury-mediated renal disease has been observed following cessation of exposure.

There is no conclusive evidence that chronic, inhalation exposures give rise to genotoxic effects in humans. In its evaluation of the carcinogenicity of mercury the IARC working group concluded that there was inadequate evidence that exposure to mercury vapour is carcinogenic to humans. In reaching this conclusion, the IARC working group had considered

evidence from a number of occupational studies. This included an evaluation of cancer mortality at the Oak Ridge Y-12, Nuclear Plant in which 2133 workers were exposed to mercury at high air concentrations, up to four times the American Threshold Limit Value of 25 μg/m^3, for several years. Whilst an excess of cancers at a number of sites, including the brain and pancreas was found in studies at the Oak Ridge site, IARC and expert reviews that evaluated these findings have considered that the study lacked the statistical power to detect excess risks of these cancers. Furthermore, statistically significant excesses of deaths from cancers of the lung, brain and other CNS tissues were observed among the plant workers who were not involved in the mercury processes. Exposure to mercury vapours at the plant was therefore not regarded to be related to any excess of deaths from cancers of organs determined to be target organs for mercury. Other factors at the site or lifestyle factors, other than exposure to mercury were thought to give rise to these excess cancers.

Taking findings from studies of cancer incidence in the nuclear weapons industry, in chloralkali workers, in mercury miners and in case-control studies of various exposed populations into account, expert reviewers have reached a consensus view that clear conclusions about the carcinogenic potential of elemental mercury in humans cannot be drawn.

There is broad agreement in the various International expert groups that if airborne concentrations of mercury are kept below 20 – 25 μg/$m^3$and urine mercury concentrations below 25 –35 μg Hg/g creatinine nearly all workers may be repeatedly exposed, day after day, over a working lifetime without adverse effects from mercury. (Appendix 1 Table 1)

2 EXPOSURE TO MERCURY AT MANCHESTER UNIVERSITY

2.1 INTRODUCTION

This assessment is intended to assist the University of Manchester's understanding of and to quantify the potential exposure to mercury vapour of occupants of the Rutherford building at the University of Manchester over the period 1976 to 2004. The building has also been named "Coupland" or "Coupland 1" over the course of the years. The task of constructing a retrospective mercury exposure assessment is made difficult by the fact that there is no clear picture of the physical condition of the building through its occupation, nor is there a coherent record of what alterations or remediations have been applied. Most of the decontamination that has been undertaken has focused principally on radiological contamination and where records refer to mercury only one set includes records of vapour concentrations in room air prior to 2004.

Information has been gathered from a variety of sources and is not limited to documents referring to the Rutherford Building. A large number of the documents drawn on are among those collected in Churcher et al (2008,) and a further 50 or so have been supplied directly or indirectly by the University. One set of documents (from November 2001) refers to a Bragg Building, otherwise Coupland 2, which seems to be the annexe building still occupied by the Psychology department. The majority of the information refers exclusively or principally to radiological contamination, but inferences may be drawn on either the presence of mercury from work with the radioisotopes or the effects of the remediations on building structure and hence on mercury vapour release.

The building was occupied as the Schuster Laboratory by Rutherford and his co-workers between 1903 and 1919 and continued to house the Department of Physics, initially under W L Bragg. The building was occupied by the Psychology Department from 1976 until it was vacated and thoroughly refurbished between 2004 and 2006. Understanding the occupancy of the building is complex for a number of reasons, not least that the cluster of buildings dating from the early 20th century have both been added to and had extensions demolished, and have also housed a variety of departments, including a dental hospital and the Museum. The boundaries of the various departments have moved within the buildings and also differ from floor to floor.

This exposure assessment is limited to inorganic mercury, as there is no suggestion that organic mercury compounds have been used in the building and it is unlikely that they would have been formed after the spillage of metallic mercury.

2.2 REASONS FOR THE PRESENCE OF MERCURY VAPOUR IN ROOM AIR

The discovery of liquid mercury under the floor of an occupied building is naturally of concern as the inhalation of mercury vapour is recognised as a cause of disease. However the presence of contamination does not inevitably lead to the inhalation of a harmful concentration of vapour. There are many factors that influence the resulting concentration in room air and hence the likelihood of inhalation, including:

- physical factors affecting the source (e.g. mass and temperature),
- the transport mechanisms between the source and the occupied space (such as the effectiveness of the floor as a seal and the airflows within the building structure,

which themselves depend on building height and aspect, wind loading, etc.,) in short, a combination of the structure and the weather

- Office ventilation rates (affected by the opening of doors and windows)

These aspects are covered in the following sections.

2.2.1 Uses of mercury and consequent distribution

Mercury has been used for a variety of purposes in the buildings and thus contamination has become widespread. When Rutherford worked in the Department of Physics mercury was used for two significant purposes in the investigation of the properties of "radium emanation", which was ultimately discovered to be radon gas. Radon was collected from a solution of a radium salt by reducing the pressure by means of a simple pump (a Toepler pump) which took advantage of the density of liquid mercury. An open reservoir of mercury was connected by flexible tube to an intermediate gas reservoir and then to the radium vessel: when the vessel of mercury was lowered to induce a partial vacuum the radon gas was drawn from solution. The line to the solution of radium was then isolated and the mercury was raised to force the gas in the reservoir into an inverted tube over mercury, in the same way as other gases can be collected in a gas jar over water. (This apparatus is illustrated and its use described in more detail in Todd 2008, section I.3.2.2). The other stages in the purification of radon and compressing it into tubes to hold it for experimentation involved similar gas transfers by the raising or lowering of mercury reservoirs. This clearly presented repeated opportunities for the spillage of mercury.

Todd (2008) states that radon was transferred to other apparatus over a container of mercury, which is also described in other descriptions of Rutherford's work as a "crucible of mercury". This implies the transport of open-topped containers of mercury around the laboratory as a matter of routine: it had been found that to minimise contamination by radon daughter isotopes in experimental rooms it was necessary to minimise the release of radon and hence locate the source elsewhere. Over the course of years accidental spillages of mercury are likely to have occurred in the radon collection room, anywhere the radon was used and in any corridor, lift or stair that was traversed when moving the tubes of gas. There have undoubtedly been many other uses of mercury in the physics department.

Mercury is very dense and consequently acquires a proportionate kinetic energy when dropped. After impact the momentum gained is then able to propel the resulting beads of mercury a considerable distance horizontally, particularly as it does not wet surfaces and suffers little drag. The significance of this is that besides expecting to find mercury below floorboards where a vertical penetration route is available, we should also anticipate its presence below the edges of rooms where there has been any gap between the floorboards and the bottom of the skirting boards.

The University **Dental Hospital** of Manchester occupied the building at the north-east corner of the site (on the corner of Bridgeford St. and Oxford Rd.) from 1908 until 1939. The dental hospital will have seen the use of substantial quantities of amalgam in fillings in the course of its existence. Powdered silver is mixed with mercury to make the amalgam immediately before use and the probability of spillage of liquid mercury, combined with the mobility of the liquid will have led to under-floor contamination as described above, although probably to a much lesser degree. Dental surgeries have been the subject of research on exposure to mercury vapour.

The **museum** might have held scientific or meteorological instruments containing liquid mercury, but it is less likely that spillage has occurred in the course of curatorial activities than it has from the use of volumes of mercury in the Physics department. The collections of textiles and animal specimens would also undoubtedly have been treated with preservatives

containing mercury salts, in addition to any contamination that might exist as a consequence of the museum moving into rooms formerly occupied by the Department of Physics.

Mercury vapour is of concern at workplace concentrations of around 20 $\mu g/m^3$ and the metal is exceptionally dense, with a specific gravity of 13.6 at room temperatures. Thus a small volume of mercury can release vapour to generate a concentration of interest, even if below exposure limits, for a very long period. (1 cm^3 of liquid mercury, or 13.6 g, could create a concentration of 10 $\mu g/m^3$ in a room of 80 m^3 with 3 air changes per hour for 236 days.) The converse is important: the release of mercury vapour from an area of contamination is not likely to significantly reduce the mass over time, with the significance that the vapour concentrations found during the 2004 survey (Shaw 2004) will represent concentrations that probably will not have been affected by any significant reduction in mercury mass over recent years.

2.2.2 Building structure etc.

The construction of the Coupland 1 building has been revealed to a limited extent by some of the declarations of the waste removed in the course of the remediations, but mostly by a detailed illustrated description of the process adopted in 2004 to 2006 dated 17 July 2009. This was supplied to the University by Mr Frith of IRAS Ltd, the radiological consultancy which was retained by the University to supervise the decontamination work, and showed that below the floor boards a layer of dark fibrous material (presumed to be sound insulation) rested on the upper surface of the ceiling of the room below. (A picture from this letter is shown below.) It would seem that most of the sub-floor radioactive contamination was held in this material, described as "flock" in some other documents, together with some of the mercury. The floorboards themselves were apparently simply butt-jointed rather than being tongued and grooved.

During the major remediation all the floorboards were removed, the floor joists and the ceiling upper surface were vacuum-cleaned to remove loose radiological and mercury contamination after which any adherent residues were addressed. The 2009 letter refers to "the wire mesh / plaster surface which was the upper side of the ceiling of the room beneath." The value of this statement is that it illustrates the robustness of the construction and tells us that the plaster of the ceiling is applied to a very resilient reinforcing foundation, with the consequence that cracks which would otherwise penetrate the ceiling plaster, not uncommon in buildings of Victorian construction, are unlikely to have occurred. There is therefore unlikely to have been any downward migration of liquid mercury into a room below an area of contamination. The ceiling surfaces can be presumed to be of plaster trowelled smooth, which has the effect of increasing the density and reducing the porosity of the material. The layers of paint which will have been added over the years will also have contributed to the effectiveness of the barrier, but this material would not be expected to provide an absolute barrier to the movement of mercury vapour, however.

Air movements in buildings are usually complex and variable, due to the variety of ways in which the air spaces are connected, both underfloor-to-room and between adjacent rooms above- and under-floor. It is not generally appreciated how many crevices allow air to enter or leave buildings under the influence of wind loading or convection. These would include the joins between waste pipes and the masonry of a building wall, around window frames and simple settlement cracks or gaps in mortar dating from construction. These air movements vary with wind loading, both direction and strength. Within this building one boundary that looks more air-tight than average is between a lath-and plaster ceiling in good condition and the joists to which it is fixed. The photographs in Mr Frith's 2009 letter show this, together with solid bracing timbers at right-angles between the joists. These would impede airflows along the spaces. Opened windows and doors naturally dominate the routes by which air

enters and leaves rooms; beyond this the main routes for stray air currents is probably from underfloor spaces via the gaps beneath skirting boards.

There has been no suggestion that forced ventilation has ever been installed in the building, and neither is there any reference to fume cupboards or other equipment that would extract air. The absence of extraction is important as it removes a permanent source of a negative pressure that would tend to draw air into occupied rooms from other parts of the building structure.

2.2.3 Data

The information on mercury vapour concentrations used for this review of potential exposures is principally drawn from the two records of measurements that precede the 2004 to 2006 building alterations:

- 2004 measurements of underfloor concentrations together with room air mercury concentrations, reported in "Survey of the presence of mercury residues within the Coupland Building, Manchester University", by M Shaw of Casella (Shaw 2004)

- a 2000 Mercury contamination survey at Manchester Museum which is limited to measurements underfloor. ("Mercury contamination survey at Manchester Museum" G Watkiss of Diamond Environmental (Watkiss 2000)

Many other documents (referenced in the tables below and in appendix 1) have been examined as a source of information on the factors which would affect the ultimate exposures, i.e. amounts of mercury or removals and air movement, etc.

There is some uncertainty about the form of mercury under floorboards. The first reference to mercury in the Rutherford building was in Dr Churcher's Feb 2003 email referring to an observation of liquid metal in the previous summer (Churcher et al 2008, Appendix B5.) This would fit with the descriptions of the quantities of the metal used and an easily-understandable contamination mechanism. However some preparatory work on the treatment of the under-floor 'flock' wastes removed during the major remediation of Rutherford noted "a significant proportion of the mercury is present as mercury compounds". This was based on an inability to remove the mercury by dissolving it in dilute nitric acid (Design Services Group Project 4097 note dated 26/03/2007). The average concentration of 40 000 mg/kg mercury or compounds is widely spread through the 120 samples analysed. In contrast, the Casella (Shaw 2004) survey showed a wide range of under-floor mercury concentrations suggesting that liquid mercury was *not* present under all floors to the same extent but instead was far from evenly distributed. (In fact underfloor mercury-in-air measurements averaged less than 10 $\mu g/m^3$ in 21 (two thirds) of the rooms, above 20$\mu g/m^3$ in 7 and above 100 $\mu g/m^3$ in only 3 rooms. These figures are shown in the table in section 2.3.4 below.)

This conflict could be explained if the "flock" under the floor (an organic fibrous material) had been treated with a non-volatile mercurial compound, during manufacture or when the floors were laid, to prevent either rodent attack or degradation by insects or fungi. If so, the quantities of "mercury" in the wastes have little relevance to potential historical emissions of mercury vapour. The flock material has presumably been stable and such vapour releases as have occurred are related to a limited amount of liquid mercury in a (relatively) small number of rooms. In this case the Casella survey (Shaw 2004) probably represents conditions for many of the preceding years.

If the mercury compound(s) in the flock resulted from chemical reactions with liquid mercury then, unless the reaction to form them was rapid, the levels of liquid mercury and mercury vapour would have been higher in the past. In this case, the Casella 2004 survey would still

be indicative of exposures in the recent past but would be less representative of exposures many years ago.

2.2.4 History

The need of the University today is to find useful data on concentrations of mercury in air which can be used to

- link the status of the location when the mercury measurements were made, and then to
- see whether those measurements can provide information to help extrapolate backwards in time to create a picture of the exposures which might have occurred before the remediation works started,

i.e. to create a retrospective assessment of exposure between 1976 and 2004.

This task is made difficult because the majority of reports or descriptions of work seem to refer only to above-floor (radiological) surveys and remediations. Most fail to note the presence of mercury and one report explicitly states "Hazardous materials [and] special waste not present" (Quality plan for the disposal of LLW to BNFL, ref UOM/Coupland1, Wastestream characterisation, 04/09/2001). The principal events and data generated are shown in the table below, and more fully in appendix.1.

Mercury has been recognised as toxic for many centuries. It has had to be treated as "special waste" since disposal legislation was introduced and it is therefore unlikely that recognisably- or heavily-contaminated material removed from the building would have passed without comment. The possibility remains, however, that the level of containment applied to ensure radiological safety led people to assume no other contaminants needed declaration. This is not particularly plausible as the documented "Quality plan for the disposal of LLW to BNFL, ref UOM/Coupland 1, Waste-stream characterisation" (Churcher Appendix C21) clearly shows a declaration of the absence of both hazardous materials and Special wastes.

Significant events that have been documented or inferred from documents are summarised in the table below. A fuller list is shown in Appendix 1 Table 8.

Table: significant events and measurements

Date	Event	Author	Churcher ref	Monitoring/report	Inference
1960s	"in the early 60s E.B. Paul discovered that he had been exposed to radiation in his offices in the Schuster Building, which were then vacated until they had been replastered and repainted	Todd 2008 p65		Todd 2008–p 65	No work on or under floors
Sept 2000	***Residual*** **[radiological]** contamination survey of Coupland 1 building etc (Coupland 1 and Museum)	S M Adams		Refers to/includes an earlier University survey. Although no reference to decontamination, mentions "analysis on radioactive waste originating from Coupland 1"…	…which hints at some earlier decontamination, although "residual" could mean remaining from research in the building.
Sept 2000	"Mercury contamination survey at Manchester Museum"	G Watkiss (2000) Diamond Environmental		Two *underfloor* measurements $> 25\mu g/m^3$, two circa $10\mu g/m^3$, rest $5\mu g/m^3$ or less.	room concentrations could have been 2% of underfloor (based on ratios from 2004 Shaw/Casella Coupland 1 data).
04/09/2001	Quality plan for the disposal of LLW to BNFL, ref UOM/Coupland1, Wastestream characterisation	S Adams	C21	"floorboards…wrapped in polythene… Refers to "Initial work in room C1.10"… then 31x200-litre drums, Rubble… ***Hazardous materials not present, Special wastes not present"*** (p4 of 7)	Implies no mercury removed, so only effect on above-floor concentrations will be if replacement of floor changed airflow patterns ***mentions earlier phase, BNFL doc refers, possibly the work below

Date	Event	Author	Churcher ref	Monitoring/report	Inference
November 2001	Remediation work…in the basement of Coupland 2 - No mention of mercury	Stephanie Adams, NIRAS Ltd		Final Report on the Remediation work carried out in the basement of Coupland 2	"Room B10…The walls are to be removed… the University RPS will be in attendance… Presumably all from solid floors (woodblocks and bitumen mentioned.).
Jan 2004	Casella Winton mercury survey following observation of liquid Hg	M Shaw		Survey of the presence of mercury residues within the Coupland Building, Manchester University. Underfloor and room mercury-in-air measurements throughout Coupland 1. Highest room underfloor average concentrations of 157, 111& 109 ug/m^3 correlate with room air at 4.9, 1.6 and 4.9 µg/m^3	
	Major decontamination and refurbishment of Coupland 1 Inferred 2004 to 2006				Apparently under the supervision of iras Ltd (Radiological consultants to University)
24 May 2006		A Frith, iras Ltd.		Radiological Clearance certificate for whole of Coupland 1	
26 March 2007	Design Services Group Project 4097 Coupland 1 decontamination			Project 4097C note: "Disposal of contaminated flock containing…mercury"	Removed during 2004-2006 remediation
Aug 2008 – March 2009	University of Manchester Surveys of mercury vapour, validation by parallel HSL measurement			General room Hg concentrations (all post 2006 re-occupation) show concentrations below exposure limits.	

Date	Event	Author	Churcher ref	Monitoring/report	Inference
7 Jan 2009	Sealing of floor in 2.057			Rise in concentrations in 2.058 (UoM monitoring)	Some residual mercury somewhere, underfloor airflows diverted into 2.058
May 2009	Passive atmospheric monitoring survey of Museum, Coupland 1 and Annexe undertaken by HSL			Max 12 µg/m^3 (the only result >10 µg/m^3) 17 results $1<x<10$ µg/m^3 40 results 0.2 - 0.9 µg/m^3 56 < lld of 0.2 µg/m^3 (lld) Geometric mean 0.28 µg/m^3 using 0.1 (half lld of 0.2) where values lld.	

Note on results of recent (2009) monitoring: lld – Lower limit of detection, 0.2µ $g.m^{-3}$.

2.3 DISCUSSION

2.3.1 Applicability of key pieces of information

One of the key pieces of information for use in a retrospective exposure assessment is the survey of mercury vapour concentrations in Shaw (2004.) The applicability of this study, which measured below-floor and room ("background") mercury vapour concentrations is discussed below in conjunction with documents included in Churcher et al (2008) which shed light on the building structure or work that has been undertaken.

2.3.2 State of building structure during 2004 mercury survey (prior to remediation)

The state of the building when the 2004 mercury survey (Shaw 2004) was undertaken seems to have been "as built" apart from in the rooms where the specific remediation works had been undertaken. The indications in the various reports of work are that only limited areas had been addressed. In one instance some remedial work on walls is reported (Todd 2008 p65) but in general usually it would seem that action has been limited to replacing contaminated lengths of floorboard at various times. This has been made easier by the absence of tongue-and-grooved boards, so the damage usually associated with disturbance does not occur. When the major remediation was undertaken the process was to remove contamination by "cutting [out] in uncontaminated sections, pass to contractor who de-nailed and stored …for re-use or disposal." It is not possible to guess whether floorboards replaced during the remediations before 2004 are likely to have increased the air exchange between the underfloor spaces and the rooms. If they shrank more after installation than the original Victorian timber had, then more air movement could have ensued, allowing more mercury vapour out into the occupied space. Plywood might have reduced underfloor-to-room vapour migration. However unaltered rooms (probably the majority) would be expected to have a wider differential between an underfloor mercury measurement and the room air due to accumulated debris forming a partial seal between floorboards, and if carpets were present they would have further reduced airflows between the underfloor voids and the rooms.

The report states that in the majority of cases 8mm holes were drilled for sampling access to the underfloor spaces, implying that only a small minority of rooms had access holes available (such as a removable floorboard) which would have allowed air movements to carry mercury vapour into the room. In compromising the usual barrier to air movement during the monitoring an opening would reduce the normal differential that would have been found in mercury concentrations between the underfloor and the room prior to the 2004 remediation.

2.3.3 Weather

It is important to consider how typical the weather was during the survey period and how it might have affected the concentrations of mercury in air. The survey report was submitted on 29th Jan 2004 after an undated interim report. The actual measurements may therefore have been made some time between the 22nd and the 28th January. The weather conditions in that week compared to the average annual conditions are discussed below.

Summary of temperature and windspeed at Manchester Airport, derived from data in appendix 2 table 9

Period	Ave temp, degrees C	Average wind velocity, km/hr
Whole year 2003	10.48	14.28

Average 22nd to 28th Jan 2004	3.9	13.4

This suggests below annual average temperature and near average windspeed outdoors during the period when the 2004 measurements were made. However the temperature inside the building would have been maintained by central heating and the actual temperatures of the materials forming most of the building's structure would probably not have been very much lower during the survey than at other times of the year.

Mercury vapour pressures (origin also in appendix 2):

Temperature, degrees C	Vapour pressure, mm Hg
5	0.0005
10	0.000775

Although mercury vapourisation rises with temperature, the rate of release during the measurement period would probably not have fallen below the figure for 10 deg. C due to the heating of the building. The windspeed during that week was very little below the average for the whole of the previous year. This suggests that the mercury vapour generation and air movement which would move mercury vapour from the underfloor voids into rooms may have been normal, and the measurements could therefore reflect the normal mercury concentrations in the building reasonably well. The higher ambient temperatures that would be expected in the summer could cause more rapid evaporation of mercury, possibly by a factor of two. However this would probably be balanced by the tendency of occupants to open windows, substantially increasing the ventilation and reducing the potential concentration increase.

There are many references to carpeted offices in the radiological surveys (as the thickness of a carpet would prevent the detection of alpha particles emitted from contaminated areas on the floorboards immediately beneath.) The presence of carpet would also tend to reduce the airflows from beneath floorboards into rooms, especially if carpets were well-sealed at the edges of rooms.

2.3.4 Room air and underfloor mercury-in-air measurements in Coupland 1, 2004

The results of the background, i.e. room air concentrations of mercury in Coupland 1 are shown in the table below, ranked by concentration. The method of collection of these background results is not described in the survey report, but can be assumed to represent concentration at waist height, which is where one carries an instrument in reasonable comfort and also (conveniently) represents the head height of a seated person. It is probable that in measuring the background concentrations of mercury the operative would have noted the highest concentrations seen in the room, rather than recording a mentally calculated average. Notwithstanding this potential for (positive) bias, these data do provide information on what exposures might have occurred, rather than showing the highest or mean sub-floor concentrations of mercury vapour (which are the values shown in table II.5 of Todd 2008).

Room mercury concentrations measured in 2004, ranked, with underfloor averages for comparison are shown below:

Room	(Background) Room Hg, μg/m3	Average underfloor Hg, μg/m3
2.52, extreme SE corner of bldg	10.7	67
2.62 (bay window)	6.0	46.3
2.52(a)	4.9	157
2.63	4.9	109.2
2.53(RHS)	3.9	18.3
2.53LHS)	3.3	4.9
1.52 (Main)	1.9	23.3
1.52 (Cupboard)	1.8	7.1
G53	1.6	111.4
1.53	1.6	5.8
Postgraduate	1.4	15.7
1.56	1.1	1.3
2.54	1.0	6.4
2.58	1.0	6.6
(2. 61)	0.9	5.5
1.52 (kitchen)	0.7	6
1.55	0.7	3
2.57	0.7	0.3
2.64	0.6	0.6
G54	0.5	1.3
1.54	0.4	1.9
2.55	0.4	1.2
2.6	0.4	10.4
1.57	0.3	1.2
2.56	0.3	2.8
2.59	0.3	1.2
G56	0.2	0.8
G51	0.1	0.6
G52	0.1	1
(G55)	0.1	20.5
Beekeepers	0.1	0.2

It can be seen that a measurement above 10 $\mu g/m^3$ occurred in only one room. This figure was less than half of the former UK exposure limit (which was 25 $\mu g/m^3$, now withdrawn) and is approximately half of the value of 20 $\mu g/m^3$ which is likely to be introduced (SCOEL 2007). The mercury vapour concentrations around 5$\mu g/m^3$ in the next-most contaminated group of rooms are approximately 20% of the old UK exposure limit and 25% of the limit likely to be introduced. Workplace exposure limits are usually based on a concentration at which harm is not likely when exposure occurs over a lifetime for 40 hours per week, 48 weeks of the year. It has to be acknowledged that they apply to adults (not juveniles or the elderly) and that we are told that some academics work much more than a 40-hour week. Balancing this, however, is the likelihood that fieldwork or vacations would be likely to take occupants out of their offices for more than 4 weeks of the year.

The implication of the consideration of building structure and the weather during the sampling is that for measurements in most rooms the above-floor (and underfloor) mercury concentrations found in 2004 would have been representative of conditions during the post-Physics occupancy.

2.3.5 Data from 2000 Museum underfloor survey

The under-floor concentrations of mercury in the museum were typically an order of magnitude less than those measured in Coupland 1, ranging from not detected (<5 μg/m^3) to 38 μg/m^3. If the 2004 Coupland 1 background and under-floor average data (from Shaw 2004) are plotted against each other a correlation factor of approximately 0.05 can be derived. This would suggest that the room air mercury concentrations in the museum would probably all have been undetectable, <5 μg/m^3 (and is not surprising given the relative quantities of mercury in dental amalgam compared with the operations described in the physics department.)

2.3.6 Data from HSL monitoring, June 2009

In June 2009 HSL undertook monitoring of mercury in room air in a total of 114 rooms in Rutherford building, the Psychology Annexe and in the non-public areas of the Museum by passive (sorbent) sampling over approximately 2 weeks. The ambient concentrations of mercury vapour were all below half of the previous UK exposure limit and 103 of the measurements were below 10% of the limit proposed by SCOEL (20 μg/m^3.) The measurements above this figure are shown in the following table.

Building	Room	Concentration of Mercury in air (μg/m^3)
Museum	B58	12.1
Psychology Annex	1.39	9.3
Museum	B56	7.5
Rutherford	2.058	6.3
Museum	B62	5.4
Museum	G54	4.0
Psychology Annex	1.41B	3.8
Psychology Annex	1.31	2.5
Psychology Annex	1.41A	2.2
Psychology Annex	1.41	2.2
Rutherford	2.052A	2.0

Museum (basement storage) room B58 contains a dense set of vertical racks to which hand weapons are fixed. The room might be used occasionally to examine an item but in general specimens are removed from the stores for study. These results would seem show that potential exposures should not be a cause of concern; they will also help the University identify whether any further investigatory work is needed.

2.4 SUMMARY

Before 2004 there is no reference to the removal of mercury from Coupland 1. None of the documents discussing waste indicate the presence of (or the removal of) mercury before March 2007, when 40 000 mg/kg in waste was mentioned, unless talking specifically about arisings from the contaminated drainage system.

The floors in the building were probably substantially in as-built condition at the time of the Casella 2004 survey, so air movement patterns probably had not changed much over the preceding decades.

The ceilings of rooms have apparently not been altered and have probably provided a barrier to air movement similar to or better than the floors in the building. Ventilation of rooms is likely to have ensured that the air in a room below a contaminated under-floor space is less contaminated than in the room above it.

At the time of the Casella 2004 survey the weather was such that the measurements would have been comparable with conditions over the preceding year, and probably give a reasonable picture of room and under-floor mercury concentrations over the preceding 10 - 20 years.

The background concentrations of mercury found in rooms were generally 25% or less of the most restrictive workplace exposure limit with the highest measurement approximately 50% of that limit.

Biological monitoring results from 10 urine samples analysed between January and June 2009 show levels of mercury in the background range and are indicative of no significant recent exposure.

There is some uncertainty about possible levels of mercury in the distant past. If the widespread presence of mercury compounds in the remediation wastes is the result of treatment of under-floor materials with a non-volatile mercurial compound during manufacture or before the floors were laid then the total amount of mercury compounds in the remediation arisings has relatively little relevance to potential mercury vapour exposures in the building. Any measurements of mercury vapour have been the consequence of the presence of (relatively) small amounts of liquid mercury, and in this case the Casella survey (Shaw 2004) probably represents conditions for many of the preceding years.

If the mercury compound(s) in the flock resulted from chemical reactions with liquid mercury then, unless the reaction to form them was rapid, the levels of liquid mercury and mercury vapour could have been higher in the intermediate past. In this case, the Casella 2004 survey would still be indicative of exposures in the recent past but would be less representative of exposures in the preceding years.

2.5 CONCLUSIONS

Records suggest that little or no removal of mercury took place before 2004

Vapour concentrations found during the 2004 survey by Casella probably indicate concentrations over the last 10 – 20 years.

The structure of the building does not seem to have been altered to any great extent in ways that would be expected to change the relationship between the underfloor mercury (and vapour) and vapour in the rooms. Exposures have therefore probably remained relatively stable.

The Casella survey probably gives a reasonable picture of “historical” exposures for some years before the major 2006-2008 remediation. It found a single measurement of room air just below half the former UK exposure limit, air in four rooms was approximately one quarter of the limit and the rest were 10% of the limit or less. No health effects would be expected at these concentrations. How far back the Casella report can be extrapolated depends, in part, on the form and origin of mercury in the flock waste.

None of the new data suggests that future exposures might exceed half of the SCOEL proposed value of 20 $\mu g/m^3$, even if no further remediation occurs.

3 RISK ASSESSMENT

The toxicology of mercury has been comprehensively evaluated by international expert groups. Based on these assessments, there is broad agreement in the various International expert groups that if airborne concentrations of mercury are kept below 20 – 25 μg/$m^3$and urine mercury concentrations below 25 –35 μg Hg/g creatinine nearly all workers may be repeatedly exposed, day after day, over a working lifetime without adverse effects from mercury.

At the University of Manchester Rutherford building based on

1) the background concentrations of mercury found in rooms during the 2004 survey and

2) consideration of the probable state of the structure of the building deduced from a variety of other reports

it is probable that past exposures were generally 25% or less of the workplace exposure limit and the highest was approximately 50% of the workplace exposure limit.

Workplace exposure limits are intended to prevent adverse health effects in nearly all workers exposed at the exposure limit for 40 hours per week for a working lifetime and on that basis it is unlikely that exposure to mercury in the Rutherford and adjacent buildings over the last 10 – 20 years will have caused any ill-health or other effects.

4 SUGGESTIONS FOR FURTHER WORK

The Control of Substances Hazardous to Health Regulations (COSHH) oblige dutyholders to prevent exposure to substances hazardous to health or, where not reasonably practicable, control exposures "adequately." Although current exposure levels are well below Occupational Exposure Limits it is clearly desirable to minimise exposures and further reductions should be sought if practicable.

It is understood that work to confirm and address the principal remaining source of mercury vapour in the Rutherford Building is now under way.

For the other locations with mercury vapour concentrations significantly above background it would be desirable to establish whether they are consistently at those levels, or whether there are seasonal variations. A suitable threshold for 'significant' might be 20% of the probable exposure limit (i.e. 4μg/m^3), to ensure that areas with temporarily low levels are not overlooked. This would be best if it covered all four seasons until it is established that there was an adequate margin of safety below the exposure limit.

The propensity for the vapour to move between rooms in under-floor air currents has been established. Besides measuring the background concentrations of mercury in apparently-affected rooms it might therefore also be appropriate to measure in those immediately adjacent.

If continuing elevated concentrations are found, mitigation measures might be justified in some cases. Where remediation is performed, monitoring can usefully demonstrate the effectiveness of the work.

Biological monitoring is an alternative means of measuring exposure and could be offered to those staff willing to participate or who have particular concerns, but appropriate support will need to be arranged to discuss the results.

Further work to determine the form and origin of the mercury compounds in the flock waste would help resolve some of the uncertainties in historic exposures.

5 APPENDICES

APPENDIX 1

Table 1: Occupational exposure limits and guidelines for mercury

Regulatory authority (country/region)	Year	Air concentration (mg/m^3)	Comments	Biological monitoring guidance value	Comments	Reference
Health and Safety Executive (UK)	1995	0.025	8-hr TWA	*Urinary: 20 μmol Hg /mol creatinine = 35 μg Hg/g creatinine*	*Biological monitoring health guidance value*	*HSE (2002)*
SCOEL (European Union)	2007	0.02	8-hr TWA	Blood: 10 μg Hg/l blood Urinary: 30 μg Hg/g creatinine	Biological limit value	SCOEL (2007)
DFG (Germany)	2005	0.1		Urinary: 25 μg Hg/g creatinine		DFG (2005)
OSHA (USA)	1992	0.05	8-hr PEL TWA Skin notation : 'absorption through the skin may be significant'			IARC (1993)
NIOSH (USA)	1990	0.05	8-hr REL TWA Skin notation : 'absorption through the skin may be significant'			IARC (1993)
ACGIH (USA)		0.025	8-hr TWA, Skin notation: 'absorption through the skin may be significant'	Urinary : 35 μg Hg/g creatinine Blood: 15 μg Hg/l blood	Total inorganic mercury in urine prior to shift Total inorganic mercury in blood end of shift at end of workweek	ACGIH (2009)

Key

SCOEL – Scientific Committee on Occupational Exposure Limits
DFG – Deuttsche Forschungsgemeinschaft
OSHA – Occupational Health and Safety Administration
NIOSH – National Institute for Occupational Safety and Health
TWA – Time weighted average
PEL – Permissible exposure limit
REL – recommended exposure limit

APPENDIX 1

Table 2: Case studies of human exposures to mercury (from EPA, 1997; HSE, 1995)

No. per sex	**Exposure duration**	**Dose (mg/m^3)**	**Effects** **Limitations** **BML**	**Reference** (from EPA, 1997 & HSE, 1995)
1 male (adult)	8-9 months (occupational)	0.02-0.45	Fatigue, irritability. Small sample size; co-exposure to chlorine; limited data.	Friburg *et al*, 1953
6 males	< 8 hr	44.3 (estimate)	Tremor, irritability, visual & hearing abnormalities. Small sample size; limited data. BML range: 1060-3280 μg/24hr urine.	McFarland & Reigel, 1978
5 males 6 females 12 controls (adults + children)	51 – 176 days	0.1 – 1.0	Nervousness, insomnia, inattentiveness more common in exposed than controls. Personality changes and altered EEGs noted. Small sample size. BML: 183-620 μg/L in blood (1^{st} measure)	Sexton *et al*, 1978
2 males 2 females (adults)	3 days	Not stated.	Headache, slow speech. Small sample size; limited exposure data. BML range: 82-5700 μg/24hr urine.	Snodgrass *et al*, 1981
1 male (adult)	2 days	Not stated.	Delayed neurotoxicity, paresthesias, muscle fasciculations, hyperactive deep muscle reflexes, fatigue, weight loss. Small sample size; limited exposure data. BML range: 99 μg/g urine 3.5 months after exposure.	Adams *et al*, 1983
1 female (8 month old)	~ 1 day	Not stated.	Seizures, weakness, short-term hearing deficit, cortical atrophy. Limited exposure data. BML range: 16-43 μg/24hr urine.	Jaffe *et al*, 1983

No. per sex	**Exposure duration**	**Dose (mg/m^3)**	**Effects** **Limitations** **BML**	**Reference** (from EPA, 1997 & HSE, 1995)
1 male	~ 2 hours	Not stated.	Dizziness, weakness. Small sample size; limited exposure data. BML range: 1900 μg/g urine (1^{st} day)	Lilis *et al*, 1985
1 female (child)	2 months	Not stated.	Lethargy, irritability. Small sample size; limited exposure data and reporting of symptoms. BML range: 214μg/24hr urine.	Foulds *et al*, 1987
1 male (child)	2 weeks	Not stated.	Tremor, sleep disturbance, anxiety, cold hands and feet. Small sample size; limited exposure data. BML range: 130 μg/24hr urine.	Karpathios *et al*, 1991
17-26 males	< 16 hours	Not stated.	Fatigue, headaches, irritability, depression, anxiety, tremor, impaired visual-motor skills following accidental exposure (welders). Chronic exposure to other metals; limited exposure data. BML range: 60 μg/L (blood) 20 days after exposure.	Bluhm *et al*, 1992a
1 female (child)	6 months	Not stated.	Peripheral neuropathy, erethism, dizziness, depression, irritability. Small sample size; limited exposure data. BML range: 686 μg/24hr urine.	Fagala *et al*, 1992
2 females (children)	Several months	0.01-0.04 (several months after spill)	Numbness in fingers and toes, absence of deep tendon reflexes, visual field effects. BML not described.	Taueg *et al*, 1992

APPENDIX 1

Table 3: Longitudinal studies of human exposures to mercury within dentistry (from DFG, 2005).

No. per sex	**Mean *current* urinary mercury levels (in exposed individuals)**	**Effects**	**Reference** (from DFG, 2005)
48	0.89 – 1.07 μg/g	Attentiveness, motor performance & mood scores correlated with current exposures; symptom and memory scores correlated with previous exposures.	Echeverria *et al*, 1998
43 exposed (43 controls)	1.17 nmol/mol creatinine 2.1 μg/g	Reduced performance in memory test	Aydin *et al*, 2003
162 exposed (163 controls)	5.5 μg/g	Reduced ability to concentrate; lower scores in attentiveness and memory tests compared to controls. No relationship with mercury exposure in regression analysis.	Ritchie *et al*, 2002
44	3.0 nmol/mol creatinine 65.3 μg/g	Weak correlation between symptoms and mood scores with mercury levels, but exposure to amalgam only lasted 24 mins/day (although employment in dentistry for 8-35 years)	Langworth *et al*, 1997
36 dentists (46 controls)	13.2 μg/24 hour 0.8 μg/24 hour (controls)	Amplitudes of visual evoked potentials changed in dentists.	Urban *et al*, 1999
230 dentists (from 6 studies)	3 μg/g (half of group) versus 25 μg/g (half of group)	Significant association between intentional hand steadiness and urinary mercury levels (log-transformed).	Bittner *et al*, 1998

APPENDIX 1

Table 4: Studies of human exposures to mercury[2] (from HSE, 1995; EPA, 1997)

No. per sex	**Exposure duration**	**Airborne levels (mg/m^3)**	**Effects** **BML**	**Reference** (from HSE, 1995 & EPA, 1997)
39 males	Mean 15.4 years	Mean air value: 75.1; peaks of 300-500	No significant effects. BML: 99 nM (blood); 108/166 μg/g (urine)	HSE, 1995: Schuckmann 1979
28 (sex not specified)	At least 7 years employment at chloralkali plant.	NS	No significant effects on memory. BML: 53 ± 34 μg/g urine	HSE, 1995: Schuckmann 1981
36 males 36 controls	Average 16.9 years	0.022-0.028 (estimates)	Memory impairment, decreased verbal intelligence compared to controls. BML: >15 μg/L (blood); >56 μg/g (urine)	EPA, 1997: Piikivi *et al*, 1984
192 females 207 males	*Not specified.*	Group 1: 0.005-0.044 (n=160) Group 2: 0.001-0.006 (n=170) Group 3: none (n=62)	Asthenia reported but no correlation with mercury exposure.	HSE, 1995: Franco *et al*, 1981
21 males	*0.5-19 years*	NS	Increase in tremor with increasing urinary mercury levels. No controls. BML: 35.5 ± 18.6 μmol/mol creatinine	HSE, 1995: Verbeck *et al*, 1986

[2] *Non-key studies, not discussed in the preceding text.*

No. per sex	**Exposure duration**	**Airborne levels (mg/m^3)**	**Effects** **BML**	**Reference** (from HSE, 1995 & EPA, 1997)
50 (sex not specified) 22 controls	*10.3-12.5 years*	0.006-0.073	Significant difference between Group 1 and others in one behavioural test. No changes in other more sensitive tests. Inconsistent pattern of results due to individual variations not related to mercury. BML: 9.5-215 μg/L urine (Group 1: n=8) Group 2: occasional exposures, urinary levels < Group 1 (n=20)	HSE, 1995: Soleo *et al*, 1990
9 males 9 females	*Mean 3.5 years*	0.11-0.40	Nerve conduction velocities significantly reduced, but no relationship between effects and blood or urinary mercury levels. BML: 123 μg/L urine; 126 μg/g creatinine; 30 μg/L blood.	HSE, 1995; Triebig & Scholler, 1982
72 females, 12 males (exposed) 9 males, 60 female (controls)	*Average 5.4 years*	0.076 (average) 0.03-0.27 (range)	Abnormal neurological results: significant difficulty with heel-to-toe walk, but no association with urinary mercury levels. Average BML: 73.2 μg/g creatinine.	EPA, 1997: Ehrenberg *et al*, 1991
25 (sex not specified)	*4-9 months*	1-2 (estimated)	7 subjects had severe symptoms: tremor, speech disturbances, vertigo, lack of coordination, depression, anorexia, vomiting & sleeplessness. Most reversible. BML: 103-212 μg/g urine	HSE, 1995: Tamir *et al*, 1964
43 males 47 controls	*≥6 months (mean 5.3 years)*	NS	Eye-hand coordination test: no significant differences with controls, except in one test. BML: 29.2 μg/L blood; 95.5 μg/g creatinine.	EPA 1997: Roels *et al*, 1982.

No. per sex	**Exposure duration**	**Airborne levels (mg/m^3)**	**Effects** **BML**	**Reference** (from HSE, 1995 & EPA, 1997)
12 (sex not specified)	*3 months – 8 years*	NS	Poor performance in tests of motor control, visual-motor skills and short-term memory. BML: <10-670 μg/g urine	EPA 1997: Williamson *et al*, 1982.
54 males 48 controls	*Average 7.7 years*	NS	Significant differences in eye-hand coordination tests but changes in hand tremor did not reach significance. BML: 24 μg/L blood; 63 μg/g creatinine.	EPA 1997: Roels *et al*, 1989.
52 (sex not specified) 29 controls	*7.6-15.5 years*	Workers divided into 4 exposure groups; highest exposures were "higher than TLV"	Reduced performance in visual-motor skills, short-term memory and reasoning, related to urinary mercury levels so that differences with controls were significant for all workers with peak mercury levels >50 μg/L urine. BML: 38, 98 and 192 μg/g urine	HSE, 1995: Camerino *et al*, 1981
27 (sex not specified)	*3 months – 39 years*	0-1.67 (estimated)	Tremor, irritability, visual impairment. Concomitant exposure to other chemicals likely. BML: 1495-7950 μg/24 hour urine	EPA, 1997: Bidstrup *et al*, 1951
3 males, 6 females 10 male, 30 female controls	*NS*	NS	Irritability, tremor, memory loss, poor coordination, visual impairment, altered electrophysiology. BML: 4-1101 μg/24 hour urine	EPA, 1997: Vroom & Greer, 1972
89 (sex not specified) 75 controls	*> 1 year*	0.025	Increased tiredness & memory disturbance. No effects on psychometric test results. BML: 11 μg/L blood; 25 μg/g creatinine	EPA, 1997: Langworth *et al*, 1992a

No. per sex	**Exposure duration**	**Airborne levels (mg/m^3)**	**Effects** **BML**	**Reference** (from HSE, 1995 & EPA, 1997)
60 male, 38 female 27 each sex controls	*10 hour/day, 6 days/week* *0.7-24 years*	0.014 (TWA)	Impaired neurobehavioural test results in dentists; severity correlated with exposure. Confounding factors (physical vibration load, folk medicines). BML: 9.8 μg/L blood.	EPA, 1997: Ngim *et al*, 1992
77 males 53 male controls	*Average 7.9 years*	0.059	Sensory nerve conduction velocity and visual evoked responses correlated with mercury exposure. BML: 3190 μg/g creatinine (current); 106 μg/g urine (during exposure)	EPA, 1997: Ellingson *et al*, 1993
19 male, 69 female 97 controls	*Average 10.4 years*	0.033 (average) 0.008-0.085 (range)	Increased fatigue and confusion; impaired performance in neurobehavioural tests. BML: 25 μg/g urine	EPA, 1997: Liang *et al*, 1993

APPENDIX 1

Table 5: Epidemiological studies of human exposures currently working with mercury[3] (from DFG, 2005)

No. per sex	**Exposure duration**	**Mean *current* urinary mercury levels (in exposed individuals)**	**Effects** **Limitations** **BML**	**Reference** (from DFG, 2005)
122 workers (196 controls)	Average 14.6 years	10 ± 6.9 µg/g g; 12.5 ± 8.3 µg/L Controls: 5.4 µg/g g;	Significant effects: reduced motor coordination, tremor, reduced prolactin correlated with mercury exposures. No details on earlier exposures.	DFG, 2005: Lucchini *et al*, 2002, 2003.
24 workers (24 controls)	14.7 ± 9.7 years	20.5 ± 19.3 µg/g creatinine;	Increased colour confusion index (1.15 compared to 1.04 in controls). Increase not assessed to be adverse effect.	DFG, 2005: Urban *et al*, 2003b
24 workers (24 controls)	15 ± 9.7 years	Mercury flushed out with administration of chelating agent: 64.3 ± 59.9 µg/24 hours	Significant differences in EEG as result of light stimulation that correlated with cumulative exposure. Chelating agent increased mercury excretion.	DFG, 2005: Urban *et al*, 2003a
36 dentists 36 chloralkali workers 77 mercury ore workers (46 controls)	Not stated.	13.2 µg/24 hours 129 µg/24 hours 840 µg/24 hours 0.8 µg/24 hours	In all groups: changed amplitude of visual evoked potentials compared with controls, but not between groups. Correlation between effects and flushed out mercury levels (as measure of previous exposures). Lack of dose-response between groups.	DFG, 2005: Urban *et al*, 1999

[3] *Non-key studies, not discussed in the preceding text. Current exposure levels comparable to controls, but workers had previously been exposed to high levels of mercury.*

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Table 6: Cohort studies of cancer in workers exposed to metallic mercury (from IARC, 1993)

Study population **Period of follow-up**	**End-point**	**Site**	**No of cases**	**Standard mortality ratio (SMR)**	**95% Confidence Interval**	**Reference**
Nuclear weapons industry workers						
	Mortality (exposed)	All	85	0.94	0.75-1.16	Cragle *et al*. (1984)
2133 mercury exposed,		Lung	42	1.34	1.0-1.8	
3260 unexposed male workers		Kidney	4	1.65	0.4-4.2	
(USA, 1953-79)		Brain	4	1.22	0.3-3.1	
	Mortality (unexposed)	All	175	1.10	0.94-1.28	
		Lung	71	1.34	1.0-1.7	
		Kidney	3	0.72	0.1-2.1	
		Brain	13	2.30	1.2-3.9	
Dentists						
9201 Dentists and dental nurses	Incidence	Glioblastoma	18	2.1	1.3-3.4	Ahlbom *et al* (1986)
(Sweden, 1961-79)		Glioma	4	1.8	0.5-4.7	
		Meningioma	6	1.3	0.5-2.8	
2498 Dentists	Mortality	Pancreas	27	1.4	0.96-1.86	Hrubec *et al* (1992)
(US veterans, 1954-80)		Brain	6	0.9	0.45-1.74	
		Kidney	6	0.8	0.39-1.50	
267 Medical and dental assistants	Mortality	Colon	7	1.9	0.01-3.53	Hrubec *et al* (1992)

Study population **Period of follow-up**	**End-point**	**Site**	**No of cases**	**Standard mortality ratio (SMR)**	**95% Confidence Interval**	**Reference**
(US veterans, 1954-80)		Brain	1	1.5	Not reported	
		Kidney	2	2.8	Not reported	
Chloralkali workers						
1190 Males (Sweden, 1946-82)	Incidence	Lung	13	1.8	0.9-3.0	Barregard *et al* (1990)
		Kidney	4	1.3	0.4-3.4	
		Brain	4	1.8	0.5-4.7	
674 Males (Norway, 1953-89)	Incidence	Lung	19	1.66	1.0-2.59	Ellingsen *et al* (1993)
		Kidney	3	0.95	0.2-2.8	
		Brain	2	0.8	0.1-3.0	
Mercury miners						
274 Males (USA, 1959/61-75)	Mortality (11 Silicotics)	Lung	3	14.0	2.89-41.0	Amandus & Costello (1991)
	Mortality (263 Non-silicotics)	Lung	8	2.66	1.15-5.24	

APPENDIX 1

Table 7: Case-control studies of populations exposed to mercury (from IARC, 1993)

Study population	End-point	Exposure	Sex	No. of exposed cases	Odds ratio	95% Confidence Interval	Reference
Lung cancer							
Hospital based (Italy)	Incidence	Hat makers	F	6		P=0.01	Buiatti *et al* (1985)
Population-based (Canada)	Incidence	mercury, metallic	M	4	4.0	1.2-13.0 (90% CI)	Siemiatycki (1991)
Prostate cancer							
Population-based (Canada)	Incidence	mercury, metallic	M	5	6.2	1.2-33.2 (90% CI)	Siemiatycki (1991)
		mercury & mercury compounds	M	14	1.7	1.0-3.0	
Bladder cancer							
Population-based (Canada)	Incidence	mercury & mercury compounds	M	14	1.5	0.9-2.6 (90% CI)	Siemiatycki (1991)

Study population	End-point	Exposure	Sex	No. of exposed cases	Odds ratio	95% Confidence Interval	Reference
Brain cancer							
Population-based (USA)	Mortality	Nuclear facilities	Central nervous system	29	1.77	0.5-5.8	Carpenter *et al* (1988)
Population-based (Australia)	Incidence	Amalgam fillings	Glioma		0.47	0.25-0.91	Ryan *et al* (1992)
			Meningioma		1.04	0.43-2.47	

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Table 8: Table of document sources - Principal documents relating to Mercury status in Coupland 1

EVENT	Document/Title	Author	Date	Churcher ref	Building/floor/room	Mercury data:	Relevance
Wastestream characterisation, LLW from Coupland 1	Quality plan for the disposal of LLW to BNFL, ref UOM/Coupland1, Wastestream characterisation UOM/COUPLAND1, wastestream WS074	S Adams	April 2000	C21		31x200-litre drums, "floorboards…wrapped in polythene" "**Special wastes not present" (p4 of 7)** refers back to "Initial work in room C1.10 was carried out by NNC Harwell, waste assessed, MTC/01/026"	implies no mercury recognised in decontamination arisings - so remediation had no effect on mercury available for release, floor structure replaced in places.
Preparatory for "work" and disposal of arisings	**Residual** contamination survey of Coupland 1 building, Annexe and old dental hospital.	S M Adams	Sept 2000	C14	Coupland 1 and Museum	none - radiological only	implies preparatory survey preparation for remediation or building work
	Mercury contamination survey at the Manchester Museum	G Watkiss, Diamond Environmental	12 Sept 2000		museum/old dental hospital.	Underfloor mercury vapour measurements, entirely within museum/old dental hospital. No above-floor measurements.	No help.
	Manchester Museum analysis of mercury in drains	G Watkiss, Diamond Environmental	22 N0v 2000		museum/old dental hospital, Coupland drains marked	mercury concentrations in 5 samples of museum drain sediment, highest 508 mg/kg dried sediment	none to room air concentrations or Coupland..
	The Manchester Museum phase 2b mercury contamination	C MacKeith for Ian Simpson Architects	28 Nov 2000		Museum, 3 floors	uses data from MMu1556	Work precautions based on earlier underfloor mercury measurements only.
Post remediation survey	Final report for the decommissioning of Coupland 1 Building. C5952/0008 MTC/01/005	B Frith	January 2001	C17			
	The Manchester Museum phase 2b existing drainage decontamination/removal	B M Chadwick, area manager	1 Feb 2001			contamination of drains only.	
1999/2000 decontamination	Final report for the decommissioning of rooms 2.62 & 2.63, Coupland 1…		5 April 2001	C20	Rooms 2.62 & 2.63, Coupland 1…	no reference to mercury	
Disposal of waste from NIRAS/NNC	Estimation of drum activity of waste removed from Coupland 1 building MTC/01/026	S M Adams	9 April 2001	C19	Mostly brickwork. Rms 2.52 & 2.53:Floorboards: Rms 2..62 & 2.63: lagging between joists,	no reference to mercury in detailed description of arisings refers back to arisings from initial NNC activity	
	Coupland 1 Temporary refurbishment project	Kevin Robson, cc. J Duffy Estates Department	20 May 2002	C22	Throughout Coupland 1: G22 bare plywood floor…since ..Extensive remedial work. Second floor toilet: the floor is the original floor."	None. Planning for temporary project, mentions covering areas with plywood, re-carpeting over new plywood *leaving existing carpets in place*	Suggests G22 floor has been replaced. Unlikely that this suggestion would be adopted.

EVENT	Document/Title	Author	Date	Churcher ref	Building/floor/room	Mercury data:	Relevance
	Appendix to meeting notes…2?.8.02(?)			C23	NOTES: "Rooms 2-52 and 2-54 have had no remedial work carried out ,2-62 and 2-63 remedial work carried out by NNC (NIRAS)		
	John Churcher's email of 24.2.2003		24.2.2003	B5	Coupland 2nd floor	Mercury was first noticed/recorded in 2.62 Coupland in Summer 2002	Some flooring has been removed. [not all as floorboards are visible under plywood at the room threshold in 2009.] it is stated that mercury " had not been removed" by Feb 2003.
	Casella/Winton/Stanger	M Shaw	Feb 2004		Coupland survey	**Correlations between underfloor and room concentrations, in all rooms - gives distribution**	
Blanket radiological clearance	Radiological conditions upon completion of decommissioning of Coupland 1	Andrew Frith, IRAS	24 May 2006		Apparently whole of University-occupied Coupland 1	None. No radiological data either.	Blanket radiological clearance
	Design Services Group Project 4097 Coupland 1 decontamination	?	26 Mar 2007		disposal of final material	Mercury contamination of removed flock…on average 40 000 mg / kg	
	Summary of work done in Coupland 1 and adjacent buildings	A Frith, IRAS Ltd	2 July 2008		Coupland	None	
	RADIOLOGICAL CONDITIONS IN COUPLAND 1 ROOMS 2.62, 2.63 AND 1.55	A Frith, IRAS Ltd	17 July 2009		COUPLAND 1 ROOMS 2.62, 2.63 AND 1.55	Detailed description of 2004 - 2006 decontamination methods	

APPENDIX 1

Table 9 Manchester weather, 2003 and Jan 2004 and Mercury volatility.

2003 Month	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Average 2003
Ave temp, degrees C	4.8	4.4	7.7	10.1	11.9	15.9	17.2	17.6	14.1	9.1	8	5	**10.48**
Average wind velocity, km/hr	16.4	14.5	14.2	16.1	16.6	13.8	14.2	10.6	10.8	14.4	16.3	13.5	**14.28**

Jan 2004	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Average 22nd to 28th Jan
Ave temp, degrees C	4.7	2.2	2.1	8.6	8.9	7.6	7.3	8.1	5.3	3.1	2.7	1.3	-0.2	1.6	4.3	8.7	**3.9**
Average wind velocity, km/hr	16.5	8.9	11.5	22	17.4	10	17.6	16.7	12.8	8.1	11.7	10.7	16.5	12.4	23.9	25	**13.4**

The record of weather conditions at Manchester airport are available at ttp://www.tutiempo.net/en/Climate/Manchester_Airport/01-2004/33340.htm. During the 7 days ending 28th January temperatures and windspeeds averaged 3.9 deg C and 13.4 km/hr.

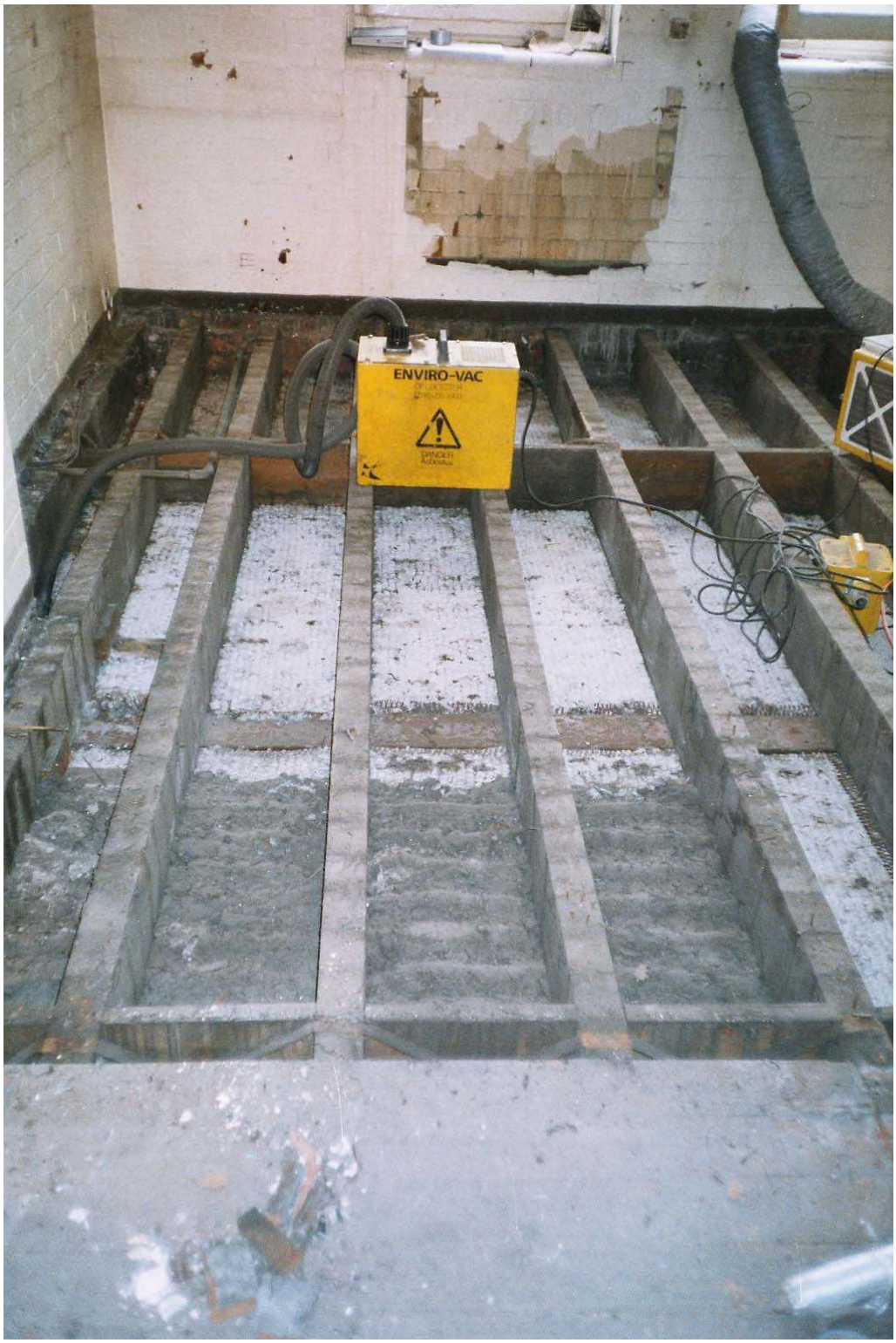
The averages for the previous year were 10.5 deg C and 14.3km/hr.

Volatility of Mercury

The vapour pressure of mercury rises from approximately 0.0005 mm. of Hg at 5 deg C to 0.000775 mm Hg at 10 deg C and 0.00125 at 15 deg C. (Measurement of Mercury Vapor Pressure by Means of the Knudsen Pressure Gauge, Phys. Rev. 20, issue 3 pp 259 - 266 (1922))

Vapour pressure of mercuric chloride: 1 mm Hg at 136.2 deg C.

6 PHOTOGRAPH



Photograph showing the removal of floorboards and insulating material with vacuum cleaning in progress, Coupland 1

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