Hazards of heavy metal contamination

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The main threats to human health from heavy metals are associated with exposure to lead, cadmium, mercury and arsenic. These metals have been extensively studied and their effects on human health regularly reviewed by international bodies such as the WHO. Heavy metals have been used by humans for thousands of years. Although several adverse health effects of heavy metals have been known for a long time, exposure to heavy metals continues, and is even increasing in some parts of the world, in particular in less developed countries, though emissions have declined in most developed countries over the last 100 years. Cadmium compounds are currently mainly used in re-chargeable nickel–cadmium batteries. Cadmium emissions have increased dramatically during the 20th century, one reason being that cadmium-containing products are rarely re-cycled, but often dumped together with household waste. Cigarette smoking is a major source of cadmium exposure. In non-smokers, food is the most important source of cadmium exposure. Recent data indicate that adverse health effects of cadmium exposure may occur at lower exposure levels than previously anticipated, primarily in the form of kidney damage but possibly also bone effects and fractures. Many individuals in Europe already exceed these exposure levels and the margin is very narrow for large groups. Therefore, measures should be taken to reduce cadmium exposure in the general population in order to minimize the risk of adverse health effects. The general population is primarily exposed to mercury *via* food, fish being a major source of methyl mercury exposure, and dental amalgam. The general population does not face a significant health risk from methyl mercury, although certain groups with high fish consumption may attain blood levels associated with a low risk of neurological damage to adults. Since there is a risk to the fetus in particular, pregnant women should avoid a high intake of certain fish, such as shark, swordfish and tuna; fish (such as pike, walleye and bass) taken from polluted fresh waters should especially be avoided. There has been a debate on the safety of dental amalgams and claims have been made that mercury from amalgam may cause a variety of diseases. However, there are no studies so far that have been able to show any associations between amalgam fillings and ill health. The general population is exposed to lead from air and food in roughly equal proportions. During the last century, lead emissions to ambient air have caused considerable pollution, mainly due to lead emissions from petrol. Children are particularly susceptible to lead exposure due to high gastrointestinal uptake and the permeable blood–brain barrier. Blood levels in children should be

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reduced below the levels so far considered acceptable, recent data indicating that there may be neurotoxic effects of lead at lower levels of exposure than previously anticipated. Although lead in petrol has dramatically decreased over the last decades, thereby reducing environmental exposure, phasing out any remaining uses of lead additives in motor fuels should be encouraged. The use of lead-based paints should be abandoned, and lead should not be used in food containers. In particular, the public should be aware of glazed food containers, which may leach lead into food. Exposure to arsenic is mainly *via* intake of food and drinking water, food being the most important source in most populations. Long-term exposure to arsenic in drinking-water is mainly related to increased risks of skin cancer, but also some other cancers, as well as other skin lesions such as hyperkeratosis and pigmentation changes. Occupational exposure to arsenic, primarily by inhalation, is causally associated with lung cancer. Clear exposure–response relationships and high risks have been observed.

Introduction

Although there is no clear definition of what a heavy metal is, density is in most cases taken to be the defining factor. Heavy metals are thus commonly defined as those having a specific density of more than 5 g/cm^3. The main threats to human health from heavy metals are associated with exposure to lead, cadmium, mercury and arsenic (arsenic is a metalloid, but is usually classified as a heavy metal).

Heavy metals have been used in many different areas for thousands of years. Lead has been used for at least 5000 years, early applications including building materials, pigments for glazing ceramics, and pipes for transporting water. In ancient Rome, lead acetate was used to sweeten old wine, and some Romans might have consumed as much as a gram of lead a day. Mercury was allegedly used by the Romans as a salve to alleviate teething pain in infants, and was later (from the 1300s to the late 1800s) employed as a remedy for syphilis. Claude Monet used cadmium pigments extensively in the mid 1800s, but the scarcity of the metal limited the use in artists' materials until the early 1900s.

Although adverse health effects of heavy metals have been known for a long time, exposure to heavy metals continues and is even increasing in some areas. For example, mercury is still used in gold mining in many parts of Latin America. Arsenic is still common in wood preservatives, and tetraethyl lead remains a common additive to petrol, although this use has decreased dramatically in the developed countries. Since the middle of the 19th century, production of heavy metals increased steeply for more than 100 years, with concomitant emissions to the environment (Fig. 1).

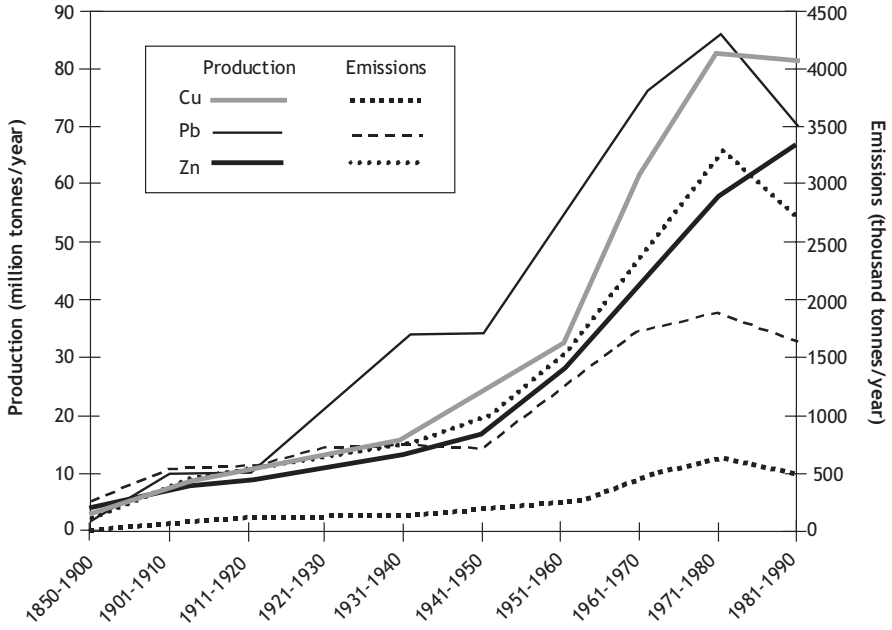

Fig. 1 Global production and consumption of selected toxic metals, 1850–1990. Source: Ref. 43.

At the end of the 20th century, however, emissions of heavy metals started to decrease in developed countries: in the UK, emissions of heavy metals fell by over 50% between 1990 and 2000[1].

Emissions of heavy metals to the environment occur *via* a wide range of processes and pathways, including to the air (*e.g.* during combustion, extraction and processing), to surface waters (*via* runoff and releases from storage and transport) and to the soil (and hence into groundwaters and crops) (see Chapter 1). Atmospheric emissions tend to be of greatest concern in terms of human health, both because of the quantities involved and the widespread dispersion and potential for exposure that often ensues. The spatial distributions of cadmium, lead and mercury emissions to the atmosphere in Europe can be found in the Meteorological Synthesizing Centre-East (MSC-E) website (http://www.msceast.org/hms/emission.html#Spatial). Lead emissions are mainly related to road transport and thus most uniformly distributed over space. Cadmium emissions are primarily associated with non-ferrous metallurgy and fuel combustion, whereas the spatial distribution of anthropogenic mercury emissions reflects mainly the level of coal consumption in different regions.

People may be exposed to potentially harmful chemical, physical and biological agents in air, food, water or soil. However, exposure does not result only from the presence of a harmful agent in the environment. The key

word in the definition of exposure is contact[2]. There must be contact between the agent and the outer boundary of the human body, such as the airways, the skin or the mouth. Exposure is often defined as a function of concentration and time: "an event that occurs when there is contact at a boundary between a human and the environment with a contaminant of a specific concentration for an interval of time"[3]. For exposure to happen, therefore, co-existence of heavy metals and people has to occur (see Chapter 1).

Cadmium

Occurrence, exposure and dose

Cadmium occurs naturally in ores together with zinc, lead and copper. Cadmium compounds are used as stabilizers in PVC products, colour pigment, several alloys and, now most commonly, in re-chargeable nickel–cadmium batteries. Metallic cadmium has mostly been used as an anti-corrosion agent (cadmiation). Cadmium is also present as a pollutant in phosphate fertilizers. EU cadmium usage has decreased considerably during the 1990s, mainly due to the gradual phase-out of cadmium products other than Ni-Cd batteries and the implementation of more stringent EU environmental legislation (Directive 91/338/ECC). Notwithstanding these reductions in Europe, however, cadmium production, consumption and emissions to the environment worldwide have increased dramatically during the 20th century. Cadmium containing products are rarely re-cycled, but frequently dumped together with household waste, thereby contaminating the environment, especially if the waste is incinerated.

Natural as well as anthropogenic sources of cadmium, including industrial emissions and the application of fertilizer and sewage sludge to farm land, may lead to contamination of soils, and to increased cadmium uptake by crops and vegetables, grown for human consumption. The uptake process of soil cadmium by plants is enhanced at low pH[4].

Cigarette smoking is a major source of cadmium exposure. Biological monitoring of cadmium in the general population has shown that cigarette smoking may cause significant increases in blood cadmium (B-Cd) levels, the concentrations in smokers being on average 4–5 times higher than those in non-smokers[4]. Despite evidence of exposure from environmental tobacco smoke[5], however, this is probably contributing little to total cadmium body burden.

Food is the most important source of cadmium exposure in the general non-smoking population in most countries[6]. Cadmium is present in most foodstuffs, but concentrations vary greatly, and individual intake also varies considerably due to differences in dietary habits[4]. Women usually have

lower daily cadmium intakes, because of lower energy consumption than men. Gastrointestinal absorption of cadmium may be influenced by nutritional factors, such as iron status[7].

B-Cd generally reflects current exposure, but partly also lifetime body burden[8]. The cadmium concentration in urine (U-Cd) is mainly influenced by the body burden, U-Cd being proportional to the kidney concentration. Smokers and people living in contaminated areas have higher urinary cadmium concentrations, smokers having about twice as high concentrations as non-smokers[4].

Health effects

Inhalation of cadmium fumes or particles can be life threatening, and although acute pulmonary effects and deaths are uncommon, sporadic cases still occur[9,10]. Cadmium exposure may cause kidney damage. The first sign of the renal lesion is usually a tubular dysfunction, evidenced by an increased excretion of low molecular weight proteins [such as β_2-microglobulin and α_1-microglobulin (protein HC)] or enzymes [such as N-Acetyl-β-D-glucosaminidase (NAG)][4,6]. It has been suggested that the tubular damage is reversible[11], but there is overwhelming evidence that the cadmium induced tubular damage is indeed irreversible[4].

WHO[6] estimated that a urinary excretion of 10 nmol/mmol creatinine (corresponding to *circa* 200 mg Cd/kg kidney cortex) would constitute a 'critical limit' below which kidney damage would not occur. However, WHO calculated that *circa* 10% of individuals with this kidney concentration would be affected by tubular damage. Several reports have since shown that kidney damage and/or bone effects are likely to occur at lower kidney cadmium levels. European studies have shown signs of cadmium induced kidney damage in the general population at urinary cadmium levels around 2–3 μg Cd/g creatinine[12,13].

The initial tubular damage may progress to more severe kidney damage, and already in 1950 it was reported that some cadmium exposed workers had developed decreased glomerular filtration rate (GFR)[14]. This has been confirmed in later studies of occupationally exposed workers[15,16]. An excess risk of kidney stones, possibly related to an increased excretion of calcium in urine following the tubular damage, has been shown in several studies[4].

Recently, an association between cadmium exposure and chronic renal failure [end stage renal disease (ESRD)] was shown[17]. Using a registry of patients, who had been treated for uraemia, the investigators found a double risk of ESRD in persons living close to (<2 km) industrial cadmium emitting plants as well as in occupationally exposed workers.

Long-term high cadmium exposure may cause skeletal damage, first reported from Japan, where the itai-itai (ouch-ouch) disease (a combination

of osteomalacia and osteoporosis) was discovered in the 1950s. The exposure was caused by cadmium-contaminated water used for irrigation of local rice fields. A few studies outside Japan have reported similar findings[4]. During recent years, new data have emerged suggesting that also relatively low cadmium exposure may give rise to skeletal damage, evidenced by low bone mineral density (osteoporosis) and fractures[18–20].

Animal experiments have suggested that cadmium may be a risk factor for cardiovascular disease, but studies of humans have not been able to confirm this[4]. However, a Japanese study showed an excess risk of cardiovascular mortality in cadmium-exposed persons with signs of tubular kidney damage compared to individuals without kidney damage[21].

Cancer

The IARC has classified cadmium as a human carcinogen (group I) on the basis of sufficient evidence in both humans and experimental animals[22]. IARC, however, noted that the assessment was based on few studies of lung cancer in occupationally exposed populations, often with imperfect exposure data, and without the capability to consider possible confounding by smoking and other associated exposures (such as nickel and arsenic). Cadmium has been associated with prostate cancer, but both positive and negative studies have been published. Early data indicated an association between cadmium exposure and kidney cancer[23]. Later studies have not been able clearly to confirm this, but a large multi-centre study showed a (borderline) significant over-all excess risk of renal-cell cancer, although a negative dose–response relationship did not support a causal relation[24]. Furthermore, a population-based multicentre-study of renal cell carcinoma found an excess risk in occupationally exposed persons[25]. In summary, the evidence for cadmium as a human carcinogen is rather weak, in particular after oral exposure. Therefore, a classification of cadmium as 'probably carcinogenic to humans' (IARC group 2A) would be more appropriate. This conclusion also complies with the EC classification of some cadmium compounds (Carcinogen Category 2; Annex 1 to the directive 67/548/EEC).

Mercury

Occurrence, exposure and dose

The mercury compound cinnabar (HgS), was used in pre-historic cave paintings for red colours, and metallic mercury was known in ancient Greece where it (as well as white lead) was used as a cosmetic to lighten the skin. In medicine, apart from the previously mentioned use of mercury as a cure for syphilis, mercury compounds have also been used as diuretics

[calomel (Hg_2Cl_2)], and mercury amalgam is still used for filling teeth in many countries[26].

Metallic mercury is used in thermometers, barometers and instruments for measuring blood pressure. A major use of mercury is in the chlor-alkali industry, in the electrochemical process of manufacturing chlorine, where mercury is used as an electrode.

The largest occupational group exposed to mercury is dental care staff. During the 1970s, air concentrations in some dental surgeries reached 20 $\mu g/m^3$, but since then levels have generally fallen to about one-tenth of those concentrations.

Inorganic mercury is converted to organic compounds, such as methyl mercury, which is very stable and accumulates in the food chain. Until the 1970s, methyl mercury was commonly used for control of fungi on seed grain.

The general population is primarily exposed to mercury *via* food, fish being a major source of methyl mercury exposure[27], and dental amalgam. Several experimental studies have shown that mercury vapour is released from amalgam fillings, and that the release rate may increase by chewing[28].

Mercury in urine is primarily related to (relatively recent) exposure to inorganic compounds, whereas blood mercury may be used to identify exposure to methyl mercury. A number of studies have correlated the number of dental amalgam fillings or amalgam surfaces with the mercury content in tissues from human autopsy, as well as in samples of blood, urine and plasma[26]. Mercury in hair may be used to estimate long-term exposure, but potential contamination may make interpretation difficult.

Health effects

Inorganic mercury

Acute mercury exposure may give rise to lung damage. Chronic poisoning is characterized by neurological and psychological symptoms, such as tremor, changes in personality, restlessness, anxiety, sleep disturbance and depression. The symptoms are reversible after cessation of exposure. Because of the blood–brain barrier there is no central nervous involvement related to inorganic mercury exposure. Metallic mercury may cause kidney damage, which is reversible after exposure has stopped. It has also been possible to detect proteinuria at relatively low levels of occupational exposure.

Metallic mercury is an allergen, which may cause contact eczema, and mercury from amalgam fillings may give rise to oral lichen. It has been feared that mercury in amalgam may cause a variety of symptoms. This so-called 'amalgam disease' is, however, controversial, and although some

authors claim proof of symptom relief after removal of dental amalgam fillings[29], there is no scientific evidence of this[30].

Organic mercury

Methyl mercury poisoning has a latency of 1 month or longer after acute exposure, and the main symptoms relate to nervous system damage[31]. The earliest symptoms are parestesias and numbness in the hands and feet. Later, coordination difficulties and concentric constriction of the visual field may develop as well as auditory symptoms. High doses may lead to death, usually 2–4 weeks after onset of symptoms. The Minamata catastrophe in Japan in the 1950s was caused by methyl mercury poisoning from fish contaminated by mercury discharges to the surrounding sea. In the early 1970s, more than 10,000 persons in Iraq were poisoned by eating bread baked from mercury-polluted grain, and several thousand people died as a consequence of the poisoning. However, the general population does not face significant health risks from methyl mercury exposure with the exception of certain groups with high fish consumption.

A high dietary intake of mercury from consumption of fish has been hypothesized to increase the risk of coronary heart disease[32]. In a recent case-control study, the joint association of mercury levels in toenail clippings and docosahexaenoic acid levels in adipose tissue with the risk of a first myocardial infarction in men was evaluated[33]. Mercury levels in the patients were 15% higher than those in controls (95% CI, 5–25%), and the adjusted odds ratio for myocardial infarction associated with the highest compared with the lowest quintile of mercury was 2.16 (95% CI, 1.09–4.29; P for trend = 0.006).

Another recent case-control study investigated the association between mercury levels in toenails and the risk of coronary heart disease among male health professionals with no previous history of cardiovascular disease. Mercury levels were significantly correlated with fish consumption, and the mean mercury level was higher in dentists than in non-dentists. When other risk factors for coronary heart disease had been controlled for, mercury levels were not significantly associated with the risk of coronary heart disease[34].

These intriguing contradictory findings need to be followed up by more studies of other similarly exposed populations.

Lead

Occurrence, exposure and dose

The general population is exposed to lead from air and food in roughly equal proportions. Earlier, lead in foodstuff originated from pots used

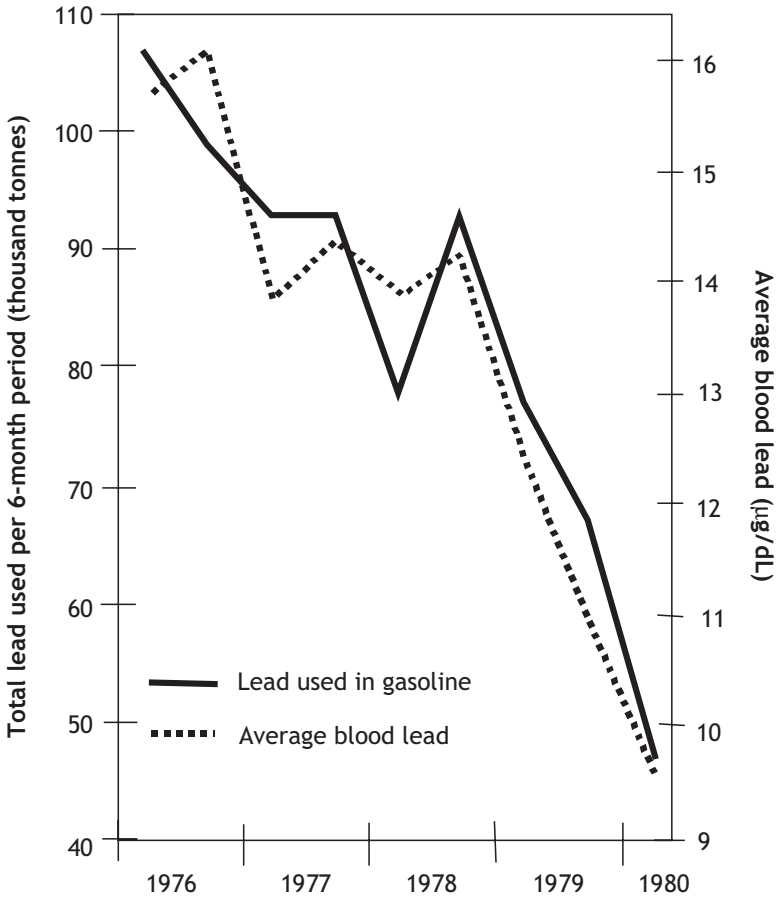

Fig. 2 Lead concentrations in petrol and children's blood (USA).
Source: redrawn from Annest (1983), as reproduced in National Academy of Sciences/National Research Council. Measuring Lead Exposure in Infants, Children, and Other Sensitive Populations. Washington, DC, USA: National Academy Press, 1993.

for cooking and storage, and lead acetate was previously used to sweeten port wine. During the last century, lead emissions to ambient air have further polluted our environment, over 50% of lead emissions originating from petrol. Over the last few decades, however, lead emissions in developed countries have decreased markedly due to the introduction of unleaded petrol. Subsequently blood lead levels in the general population have decreased (Fig. 2).

Occupational exposure to inorganic lead occurs in mines and smelters as well as welding of lead painted metal, and in battery plants. Low or moderate exposure may take place in the glass industry. High levels of air emissions may pollute areas near lead mines and smelters. Airborne lead can be deposited on soil and water, thus reaching humans *via* the food chain.

Up to 50% of inhaled inorganic lead may be absorbed in the lungs. Adults take up 10–15% of lead in food, whereas children may absorb up to 50% *via* the gastrointestinal tract. Lead in blood is bound to erythrocytes, and elimination is slow and principally *via* urine. Lead is accumulated in the skeleton, and is only slowly released from this body compartment. Half-life of lead in blood is about 1 month and in the skeleton 20–30 years[35].

In adults, inorganic lead does not penetrate the blood–brain barrier, whereas this barrier is less developed in children. The high gastrointestinal uptake and the permeable blood–brain barrier make children especially susceptible to lead exposure and subsequent brain damage. Organic lead compounds penetrate body and cell membranes. Tetramethyl lead and tetraethyl lead penetrate the skin easily. These compounds may also cross the blood–brain barrier in adults, and thus adults may suffer from lead encephalopathy related to acute poisoning by organic lead compounds.

Health effects

The symptoms of acute lead poisoning are headache, irritability, abdominal pain and various symptoms related to the nervous system. Lead encephalopathy is characterized by sleeplessness and restlessness. Children may be affected by behavioural disturbances, learning and concentration difficulties. In severe cases of lead encephalopathy, the affected person may suffer from acute psychosis, confusion and reduced consciousness. People who have been exposed to lead for a long time may suffer from memory deterioration, prolonged reaction time and reduced ability to understand. Individuals with average blood lead levels under 3 μmol/l may show signs of peripheral nerve symptoms with reduced nerve conduction velocity and reduced dermal sensibility. If the neuropathy is severe the lesion may be permanent. The classical picture includes a dark blue lead sulphide line at the gingival margin. In less serious cases, the most obvious sign of lead poisoning is disturbance of haemoglobin synthesis, and long-term lead exposure may lead to anaemia.

Recent research has shown that long-term low-level lead exposure in children may also lead to diminished intellectual capacity. Figure 3 shows a meta-analysis of four prospective studies using mean blood lead level over a number of years. The combined evidence suggests a weighted mean decrease in IQ of 2 points for a 0.48 μmol/l (10 μg/dl) increase in blood lead level (95% confidence interval from –0.3 points to –3.6 points)[35].

Acute exposure to lead is known to cause proximal renal tubular damage[35]. Long-term lead exposure may also give rise to kidney damage and, in a recent study of Egyptian policemen, urinary excretion of NAG

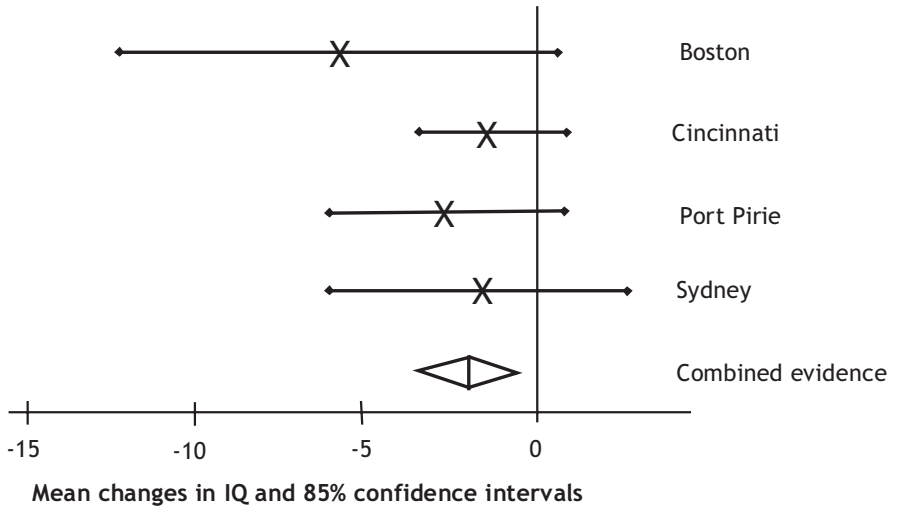

Fig. 3 Estimated mean change in IQ for an increase in blood lead level from 0.48 to 0.96 μmol/l (10–20 μg/dl) from a meta-analysis of four prospective studies[35].

was positively correlated with duration of exposure to lead from automobile exhaust, blood lead and nail lead[36].

Despite intensive efforts to define the relationship between body burden of lead and blood pressure or other effects on the cardiovascular system, no causal relationship has been demonstrated in humans[35].

Using routinely collected data on mortality (1981–96), hospital episode statistics data 1992–1995 and statutory returns to the Health and Safety Executive (RIDDOR), one death and 83 hospital cases were identified[37]. The authors found that mortality and hospital admission ascribed to lead poisoning in England were rare, but that cases continue to occur and that some seem to be associated with considerable morbidity.

Blood lead levels in children below 10 μg/dl have so far been considered acceptable, but recent data indicate that there may be toxicological effects of lead at lower levels of exposure than previously anticipated. There is also evidence that certain genetic and environmental factors can increase the detrimental effects of lead on neural development, thereby rendering certain children more vulnerable to lead neurotoxicity[38].

IARC classified lead as a 'possible human carcinogen' based on sufficient animal data and insufficient human data in 1987. Since then a few studies have been published, the overall evidence for lead as a carcinogen being only weak, the most likely candidates are lung cancer, stomach cancer and gliomas[39].

Arsenic

Occurrence, exposure and dose

Arsenic is a widely distributed metalloid, occurring in rock, soil, water and air. Inorganic arsenic is present in groundwater used for drinking in several countries all over the world (*e.g.* Bangladesh, Chile and China), whereas organic arsenic compounds (such as arsenobetaine) are primarily found in fish, which thus may give rise to human exposure[40].

Smelting of non-ferrous metals and the production of energy from fossil fuel are the two major industrial processes that lead to arsenic contamination of air, water and soil, smelting activities being the largest single anthropogenic source of atmospheric pollution[41]. Other sources of contamination are the manufacture and use of arsenical pesticides and wood preservatives.

The working group of the EU DG Environment concluded that there were large reductions in the emissions of arsenic to air in several member countries of the European Union in the 1980s. In 1990, the total emissions of arsenic to the air in the member states were estimated to be 575 tonnes. In 1996, the estimated total releases of arsenic to the air in the UK were 50 tonnes[42].

Concentrations in air in rural areas range from <1 to 4 ng/m^3, whereas concentrations in cities may be as high as 200 ng/m^3. Much higher concentrations (>1000 ng/m^3) have been measured near industrial sources. Water concentrations are usually <10 μg/l, although higher concentrations may occur near anthropogenic sources. Levels in soils usually range from 1 to 40 mg/kg, but pesticide application and waste disposal can result in much higher concentrations[40].

General population exposure to arsenic is mainly *via* intake of food and drinking water. Food is the most important source, but in some areas, arsenic in drinking water is a significant source of exposure to inorganic arsenic. Contaminated soils such as mine-tailings are also a potential source of arsenic exposure[40].

Absorption of arsenic in inhaled airborne particles is highly dependent on the solubility and the size of particles. Soluble arsenic compounds are easily absorbed from the gastrointestinal tract. However, inorganic arsenic is extensively methylated in humans and the metabolites are excreted in the urine[40].

Arsenic (or metabolites) concentrations in blood, hair, nails and urine have been used as biomarkers of exposure. Arsenic in hair and nails can be useful indicators of past arsenic exposure, if care is taken to avoid external arsenic contamination of the samples. Speciated metabolites in urine expressed as either inorganic arsenic or the sum of metabolites (inorganic arsenic + MMA + DMA) is generally the best estimate of recent arsenic dose. However, consumption of certain seafood may confound

estimation of inorganic arsenic exposure, and should thus be avoided before urine sampling[40].

Health effects

Inorganic arsenic is acutely toxic and intake of large quantities leads to gastrointestinal symptoms, severe disturbances of the cardiovascular and central nervous systems, and eventually death. In survivors, bone marrow depression, haemolysis, hepatomegaly, melanosis, polyneuropathy and encephalopathy may be observed. Ingestion of inorganic arsenic may induce peripheral vascular disease, which in its extreme form leads to gangrenous changes (black foot disease, only reported in Taiwan).

Populations exposed to arsenic *via* drinking water show excess risk of mortality from lung, bladder and kidney cancer, the risk increasing with increasing exposure. There is also an increased risk of skin cancer and other skin lesions, such as hyperkeratosis and pigmentation changes.

Studies on various populations exposed to arsenic by inhalation, such as smelter workers, pesticide manufacturers and miners in many different countries consistently demonstrate an excess lung cancer. Although all these groups are exposed to other chemicals in addition to arsenic, there is no other common factor that could explain the findings. The lung cancer risk increases with increasing arsenic exposure in all relevant studies, and confounding by smoking does not explain the findings.

The latest WHO evaluation[40] concludes that arsenic exposure *via* drinking water is causally related to cancer in the lungs, kidney, bladder and skin, the last of which is preceded by directly observable precancerous lesions. Uncertainties in the estimation of past exposures are important when assessing the exposure–response relationships, but it would seem that drinking water arsenic concentrations of approximately 100 μg/l have led to cancer at these sites, and that precursors of skin cancer have been associated with levels of 50–100 μg/l.

The relationships between arsenic exposure and other health effects are less clear. There is relatively strong evidence for hypertension and cardiovascular disease, but the evidence is only suggestive for diabetes and reproductive effects and weak for cerebrovascular disease, long-term neurological effects, and cancer at sites other than lung, bladder, kidney and skin[40].

Conclusions

Recent data indicate that adverse health effects of cadmium exposure, primarily in the form of renal tubular damage but possibly also effects on bone and fractures, may occur at lower exposure levels than previously

anticipated. Many individuals in Europe already exceed these exposure levels and the margin is very narrow for large groups. Therefore, measures should be taken to reduce cadmium exposure in the general population in order to minimize the risk of adverse health effects.

The general population does not face a significant health risk from methylmercury, although certain groups with high fish consumption may attain blood levels associated with a low risk of neurological damage to adults. Since there is a risk to the fetus in particular, pregnant women should avoid a high intake of certain fish, such as shark, swordfish and tuna. Fish, such as pike, walleye and bass, taken from polluted fresh waters should especially be avoided.

There has been a debate on the safety of dental amalgams and claims have been made that mercury from amalgam may cause a variety of diseases, but to date no studies have been able to show any associations between amalgam fillings and ill health.

Children are particularly vulnerable to lead exposure. Blood levels in children should be reduced below the levels so far considered acceptable, recent data indicating that there may be neurotoxic effects of lead at lower levels of exposure than previously anticipated. Although lead in petrol has dramatically declined over the last decades, thereby reducing environmental exposure, there is a need to phase out any remaining uses of lead additives in motor fuels. The use of lead-based paints should also be abandoned, and lead should not be used in food containers. In particular, the public should be aware of glazed food containers, which may leach lead into food.

Long-term exposure to arsenic in drinking water is mainly related to increased risks of skin cancer, but also some other cancers, and other skin lesions such as hyperkeratosis and pigmentation changes. Occupational exposure to arsenic, primarily by inhalation, is causally associated with lung cancer. Clear exposure–response relationships and high risks have been observed.

References

1 Department of the Environment, Transport and the Regions. *Statistics Release 184 1999 UK Air Emissions Estimates* (28 March 2001)

2 Berglund M, Elinder CG, Järup L. *Humans Exposure Assessment. An Introduction.* WHO/SDE/OEH/01.3, 2001

3 NRC. *Human Exposure Assessment for Airborne Pollutants. Advances and Opportunities.* Washington, DC: National Research Council, National Academy Press, 1991

4 Jarup L, Berglund M, Elinder CG, Nordberg G, Vahter M. Health effects of cadmium exposure—a review of the literature and a risk estimate. *Scand J Work Environ Health* 1998; **24** (**Suppl 1**): 1–51

5 Hossn E, Mokhtar G, El-Awady M, Ali I, Morsy M, Dawood A. Environmental exposure of the pediatric age groups in Cairo City and its suburbs to cadmium pollution. *Sci Total Environ* 2001; **273**: 135–46

6 WHO. *Cadmium*. Environmental Health Criteria, vol. 134. Geneva: World Health Organization, 1992
7 Flanagan PR, McLellan JS, Haist J, Cherian MG, Chamberlain MJ, Valberg LS. Increased dietary cadmium absorption in mice and human subjects with iron deficiency. *Gastroenterology* 1978; **74**: 841–6
8 Järup L, Rogenfelt A, Elinder CG, Nogawa K, Kjellström T. Biological half-time of cadmium in the blood of workers after cessation of exposure. *Scand J Work Environ Health* 1983; **9**: 327–31
9 Seidal K, Jorgensen N, Elinder CG, Sjogren B, Vahter M. Fatal cadmium-induced pneumonitis. *Scand J Work Environ Health* 1993; **19**: 429–31
10 Barbee Jr JY, Prince TS. Acute respiratory distress syndrome in a welder exposed to metal fumes. *South Med J* 1999; **92**: 510–2
11 Hotz P, Buchet JP, Bernard A, Lison D, Lauwerys R. Renal effects of low-level environmental cadmium exposure: 5-year follow-up of a subcohort from the Cadmibel study. *Lancet* 1999; **354**: 1508–13
12 Buchet JP, Lauwerys R, Roels H, Bernard A, Bruaux P, Claeys F, Ducoffre G, DePlaen P, Staessen J, Amery A, Lijnen P, Thijs L, Rondia D, Sartor F, Saint Remy A, Nick L. Renal effects of cadmium body burden of the general population. *Lancet* 1990; **336**: 699–702
13 Jarup L, Hellstrom L, Alfven T, Carlsson MD, Grubb A, Persson B *et al.* Low level exposure to cadmium and early kidney damage: the OSCAR study. *Occup Environ Med* 2000; **57**: 668–72
14 Friberg L. Health hazards in the manufacture of alkaline accumulators with special reference to chronic cadmium poisoning. *Acta Med Scand* 1950; **Suppl 240**: 1–124
15 Bernard A, Roels H, Buchet JP, Cardenas A, Lauwerys R. Cadmium and health: the Belgian experience. *IARC Scientific Publications* 1992; **118**: 15–33
16 Järup L, Persson B, Elinder C-G. Decreased glomerular filtration rate in cadmium exposed solderers. *Occup Environ Med* 1995; **52**: 818–22
17 Hellström L, Elinder CG, Dahlberg B, Lundberg M, Järup L, Persson B, Axelson O. Cadmium exposure and end-stage renal disease. *Am J Kidney Dis* 2001; **38**: 1001–8
18 Staessen JA, Roels HA, Emelianov D, Kuznetsova T, Thijs L, Vangronsveld J *et al.* Environmental exposure to cadmium, forearm bone density, and risk of fractures: prospective population study. Public Health and Environmental Exposure to Cadmium (PheeCad) Study Group. *Lancet* 1999; **353**: 1140–4
19 Alfven T, Elinder CG, Carlsson MD, Grubb A, Hellstrom L, Persson B *et al.* Low-level cadmium exposure and osteoporosis. *J Bone Miner Res* 2000; **15**: 1579–86
20 Nordberg G, Jin T, Bernard A, Fierens S, Buchet JP, Ye T, Kong Q, Wang H. Low bone density and renal dysfunction following environmental cadmium exposure in China. *Ambio* 2002; **6**: 478–81
21 Nishijo M, Nakagawa H, Morikawa Y, Tabata M, Senma M, Miura K *et al.* Mortality of inhabitants in an area polluted by cadmium: 15 year follow up. *Occup Environ Med* 1995; **52**: 181–4
22 IARC. Cadmium and cadmium compounds. In: *Beryllium, Cadmium, Mercury and Exposure in the Glass Manufacturing Industry*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. **58**. Lyon: International Agency for Research on Cancer, 1993; 119–237
23 Kolonel LN. Association of cadmium with renal cancer. *Cancer* 1976; **37**: 1782–7
24 Mandel JS, McLaughlin JK, Schlehofer B, Mellemgaard A, Helmert U, Lindblad P, McCredie M, Adami HO. International renal-cell cancer study. IV. Occupation. *Int J Cancer* 1995; **61**: 601–5
25 Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlagel B, Schill W. Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. MURC Study Group. Multicentre urothelial and renal cancer study. *Int J Epidemiol* 2000; **29**: 1014–24
26 WHO. *Inorganic Mercury*. Environmental Health Criteria, vol. **118**. Geneva: World Health Organization, 1991
27 WHO. *Methyl Mercury*. Environmental Health Criteria, vol. **101**. Geneva: World Health Organization, 1990
28 Sallsten G, Thoren J, Barregard L, Schutz A, Skarping G. Long-term use of nicotine chewing gum and mercury exposure from dental amalgam fillings. *J Dent Res* 1996; **75**: 594–8
29 Lindh U, Hudecek R, Danersund A, Eriksson S, Lindvall A. Removal of dental amalgam and other metal alloys supported by antioxidant therapy alleviates symptoms and improves quality of life in patients with amalgam-associated ill health. *Neuroendocrinol Lett* 2002; **23**: 459–82

30 Langworth S, Bjorkman L, Elinder CG, Jarup L, Savlin P. Multidisciplinary examination of patients with illness attributed to dental fillings. *J Oral Rehabil* 2002; **29**: 705–13
31 Weiss B, Clarkson TW, Simon W. Silent latency periods in methylmercury poisoning and in neurodegenerative disease. *Environ Health Perspect* 2002; **110** (**Suppl 5**): 851–4
32 Salonen JT, Seppanen K, Nyyssonen K, Korpela H, Kauhanen J, Kantola M, Tuomilehto J, Esterbauer H, Tatzber F, Salonen R. Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men. *Circulation* 1995; **91**: 645–55
33 Guallar E, Sanz-Gallardo MI, van't Veer P, Bode P, Aro A, Gomez-Aracena J, Kark JD, Riemersma RA, Martin-Moreno JM, Kok FJ; Heavy Metals and Myocardial Infarction Study Group. Mercury, fish oils, and the risk of myocardial infarction. *N Engl J Med* 2002; **347**: 1747–54
34 Yoshizawa K, Rimm EB, Morris JS, Spate VL, Hsieh CC, Spiegelman D, Stampfer MJ, Willett WC. Mercury and the risk of coronary heart disease in men. *N Engl J Med* 2002; **347**: 1755–60
35 WHO. *Lead*. Environmental Health Criteria, vol. **165**. Geneva: World Health Organization, 1995
36 Mortada WI, Sobh MA, El-Defrawy MM, Farahat SE. Study of lead exposure from automobile exhaust as a risk for nephrotoxicity among traffic policemen. *Am J Nephrol* 2001; **21**: 274–9
37 Elliott P, Arnold R, Barltrop D, Thornton I, House IM, Henry JA. Clinical lead poisoning in England: an analysis of routine sources of data. *Occup Environ Med* 1999; **56**: 820–4
38 Lidsky TI, Schneider JS. Lead neurotoxicity in children: basic mechanisms and clinical correlates. *Brain* 2003; **126**: 5–19
39 Steenland K, Boffetta P. Lead and cancer in humans: where are we now? *Am J Ind Med* 2000; **38**: 295–9
40 WHO. *Arsenic and Arsenic Compounds*. Environmental Health Criteria, vol. **224**. Geneva: World Health Organization, 2001
41 Chilvers DC, Peterson PJ. Global cycling of arsenic. In: Hutchinson TC, Meema KM (eds) *Lead, Mercury, Cadmium and Arsenic in the Environment*. Chichester: John Wiley & Sons, 1987; 279–303
42 DG Environment. Ambient air pollution by As, Cd and Ni compounds. Position paper, Final version, October 2000. Brussels: European Commission DG Environment
43 Nriagu JO. History of global metal pollution. *Science* 1996; **272**: 223–4
44 Annest JL. Trends in the blood level leads of the US population: The Second National Health and Nutrition Examination Survey(NHANES II) 1976–1980. In: Rutter M, Jones RR (eds) Lead Versus Health, John Wiley & Sons, New York, 1934; 33–58