Metals and Women’s Health

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Received July 31, 2001

There is a lack of information concerning whether environmental-related health effects are more or less prevalent or manifested differently in women compared to men. Previously, most research in the area of toxicology and environmental and occupational health involved male subjects. The present work aims at reviewing exposure and health effects of cadmium, nickel, lead, mercury, and arsenic manifested differently in women than in men. The gender difference in exposure to nickel results in a much higher prevalence of nickel allergy and hand eczema in women than in men. The internal cadmium dose is generally higher in women than in men, due to a higher gastro-intestinal absorption at low iron stores. This was probably one major reason why Itai-itai disease was mainly a woman’s disease. Yet, data are sparse regarding the risk for women relative to men to develop cadmium-induced kidney damage in populations exposed to low levels of cadmium. Lead is accumulated mainly in bone and increased endogenous lead exposure has been demonstrated in women during periods of increased bone turnover, e.g., menopause. Both lead and mercury exposure in pregnant women has to be kept low in order to prevent neurodevelopment effects in the developing fetus and child. Limited data indicate that women are more affected than men following exposure to methylmercury at adult age, while males seem to be more sensitive to exposure during early development. Regarding arsenic, some data indicate gender differences in the biotransformation by methylation, possibly also in susceptibility to certain arsenic-related cancers. Obviously, gender-related differences in exposure and health effects caused by metals are highly neglected research areas, which need considerable focus in the future. © 2002 Elsevier Science (USA)

INTRODUCTION

There is a lack of information on whether environmental-related health effects are more prevalent in women or manifested differently in women compared to men. A number of research priorities on causes for gender differences in susceptibility to environmental factors have been listed, including exposure situations, and basic research on genetics and physiology (Setlow et al., 1998). The research boom in toxicology and environmental health effects during the past decades mainly involved occupationally exposed men. Still, the results were in most cases used as being representative of the general population, including women, children, and elderly. Often, words like subjects, humans, or workers were used in the presentation of results, even if only men were included in the studies, or information on the number of men and women included were not even given. In other circumstances, results were given for women and men separately, but not properly evaluated according to gender differences. Toxicological studies on animals have almost exclusively used males. An exception is skin sensitization studies, where female guinea pigs or mice are used, as they cause fewer skin injuries to each other. Also, tissue and cell cultures are in most cases derived from male animals.

Both biological events and nonbiological gender factors in women’s lives can affect the exposure to and kinetics and toxicity of chemicals. Biological factors that may influence kinetics and toxicity of chemicals within a woman’s body include changes in relation to menarche, pregnancy, lactation, and menopause (Roberts and Silbergeld, 1995; Silbergeld and Flaws, 1999). It may be emphasized that the
TABLE 1
Main Toxic Effects of Metals in Relation to Female Exposure

<table>
<thead>
<tr>
<th>Metal</th>
<th>Critical health effects</th>
<th>Main sources of exposure</th>
<th>Critical concentration/exposure</th>
<th>Female risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cd</td>
<td>Kidney damage, osteoporosis</td>
<td>Diet, smoking</td>
<td>(Järup et al., 1998) 50 µg/g kidney cortex</td>
<td>Increased absorption, skeletal changes associated with pregnancy, lactation and menopause</td>
</tr>
<tr>
<td>Ni</td>
<td>Allergic contact dermatitis</td>
<td>Objects with skin contact</td>
<td>EU: nickel release limit 0.5 µg/cm²/week</td>
<td>Higher exposure</td>
</tr>
<tr>
<td>Pb</td>
<td>Neurotoxicity</td>
<td>Diet, air</td>
<td>CDC: ≥ 100 µg/L blood children</td>
<td>Endogenous exposure from bone fetal exposure</td>
</tr>
<tr>
<td>Hg⁰</td>
<td>Neurodevelopment</td>
<td>Dental amalgam</td>
<td>Unknown in women</td>
<td>Fetal exposure</td>
</tr>
<tr>
<td>Methyl-Hg</td>
<td>Neurodevelopment</td>
<td>Fish</td>
<td>NRC: reference dose 0.1 µg/kg/day</td>
<td>Fetal exposure</td>
</tr>
<tr>
<td>Inorganic As</td>
<td>Cancer</td>
<td>Water</td>
<td>WHO: 10 µg/L water</td>
<td>Fetal exposure</td>
</tr>
</tbody>
</table>


Effects of chronic exposure may become apparent much later than the causative exposure and sometimes as a result of interaction with other factors. There may also be later physiological changes that alter body deposition and/or progression of disease. Therefore, the causal relationship may be difficult to detect.

Nonbiological factors that affect toxicity differently in men and women include exposure situations in the working or general environment and lifestyle factors such as smoking, dietary factors, physical activity, cosmetics, fashion, as well as stress factors. One aspect of women’s exposure to toxic chemicals that have been somewhat more extensively studied concerns the effects in the fetus and breast-fed child. There is increasing evidence that exposure to environmental agents early in life may give rise to different toxic effects than adult exposure. Often, the effects occur in childhood, but sometimes the effects of exposure during early development are not apparent until adult age. A well-known example is the development of vaginal cancer in women who were exposed to the anti-miscarriage drug diethylstilbestrol (DES) during fetal development (Newbold, 1995). This review focuses on the effects of exposure to the highly toxic metals lead, cadmium, mercury, arsenic, and nickel (Table 1) with specific emphasis on women. It serves to provide examples showing the necessity of evaluating gender differences in the exposure to and toxicity of chemicals and pollutants.

**CADMIUM**

Besides tobacco smoking, which results in four to five times higher blood cadmium and two to three times higher kidney cadmium concentrations in smokers than in nonsmokers, the diet is the main source of environmental cadmium exposure. Cadmium concentrations in food vary considerably, but generally fiber-rich foods like cereals, vegetables, and potatoes contribute the major exposure (Järup et al., 1998).

Cadmium accumulates in kidney cortex and the concentration increases with increasing age. The concentrations of cadmium in blood, urine, and kidneys are generally higher in women than in men (Baecklund et al., 1999; Järup et al., 1998). However, the reason behind this has neither been studied nor considered in the risk assessment until recently. A likely explanation for the higher levels in women is that the absorption of cadmium, which in general is a few percentage points, increases substantially at low iron stores, suggesting a common mechanism of uptake for iron and cadmium. Indeed, the duodenal metal transporter (DMT1), which is responsible for the uptake of iron into the mucosa cell and upregulated by iron deficiency, has affinity for cadmium (Gunshin et al., 1997). Increased concentrations of cadmium at decreasing iron stores has been shown in different groups of pregnant and non-pregnant women and in children (Staessen et al., 1992; Åkesson et al., 2002; Berglund et al., 1994;
Osman et al., 1998). Thus, it can be concluded that depleted iron stores and iron deficiency, which is prevalent in women of childbearing age worldwide, leads to increased cadmium uptake and increased cadmium accumulation. As shown in Fig. 1, studies on twins revealed that 65% of the variation in blood cadmium was governed by genetic factors in women, compared to only 13% in men (Björkman et al., 2000). This may be attributed to the fact that iron stores to a large extent are determined by blood loss via menstruation. Homozygous female twins have more similar blood losses via menstruation, causing similarly increased iron and cadmium absorption, than heterozygous twins. This is further supported by the fact that the difference in blood cadmium between men and women is less obvious or nonexistent after menopause (Baecklund et al., 1999).

Pregnancy may also affect cadmium accumulation and toxicity. Iron absorption is gradually increased during pregnancy, which may increase the cadmium accumulation. The increase in cadmium body burden with increasing age is highly influenced by parity (Akesson et al., 2002). Multiple pregnancies was believed to be a contributing factor for development of the Itai-itai disease in heavily cadmium-exposed women in Japan (Kjellström, 1986). Animal data show increased toxicity (kidney and bone), increased hepatic transfer, and increased accumulation of cadmium in the kidney due to pregnancy (Bhattacharyya et al., 1988a, b; Chan and Cherian 1993).

In contrast to lead and mercury, the placenta acts as a barrier for cadmium and very little (~10%) is transferred to the fetus (Osman et al., 2000). Also, the transfer of cadmium to milk is low (Hallén et al., 1995). Thus the fetus and the newborn are fairly well protected against cadmium, while the mother may endure increased accumulation, due to a greater increase in dietary cadmium uptake than losses via placenta and milk.

The critical effect is renal tubular damage leading to increased excretion of low-molecular-weight proteins. The influence of menstruation on cadmium uptake and calcium (Jarup et al., 1998). If the exposure continues, the tubular dysfunction may progress and glomerular damage may lead to deterioration of kidney function and health. From recent data it is apparent that early signs of tubular damage are induced in the general population, including both men and women, already at present levels of environmental exposure, in many areas of the industrialized world (Jarup et al., 1998, 2000; Yamanaka et al., 1998; Oo et al., 2000; Ikeda et al., 2000; Noonan et al., 2002). Although a recent follow-up study concluded that tubular proteinuria in the general population was not associated with progressive renal dysfunction (Hotz et al., 1999), new alarming data showed that also the incidence of end-stage renal disease was increased at low to moderate cadmium exposure in people living within 10 km of a battery plant (Hellström et al., 2001). In addition, several Japanese studies have reported increased mortality in cadmium-exposed populations (Arisawa et al., 2001; Ishihara et al., 2001; Nishijo et al., 1999). Only a few studies have evaluated gender-related differences in the development of renal damage. There are indications of an increased risk for women compared to men (Hellström et al., 2001; Yamanaka et al., 1998; Oo et al., 2000; Kobayashi et al., 2002). Whether this is due to the generally higher body burden or represents increased susceptibility in women is not known. This is an urgent research task.

Cadmium may also affect the bone. Proposed mechanisms behind cadmium-induced bone damage include disturbed metabolism of vitamin D and calcium, secondary to renal tubular dysfunction, and direct effects on bone resorption and/or formation (Iwami and Moriyama, 1993; Wang and Bhattacharyya, 1993; Wilson et al., 1996; Uriu et al., 2000; Miyahara et al., 2001). Itai-itai disease, a combination of osteomalacia and osteoporosis and the most advanced form of cadmium-induced bone damage, was caused by consumption of heavily cadmium-contaminated rice (Kjellström, 1986). Itai-itai was characterized by multiple, spontaneous bone fractures in mainly elderly multiparous women. Recent data indicate that even rather low environmental cadmium exposure seems to affect bone Alfvén et al., 2000; Staaessen et al., 1999). Decreased bone density and increased risk of fractures were found to correlate with long-term cadmium exposure.
in postmenopausal women in Belgium (Staessen et al., 1999). Studies of people living in the vicinity of a former battery plant in Sweden showed a significant dose–response relationship between cadmium dose and osteoporosis in men, some of whom had been occupationally exposed, and close to significant for women (Alfvén et al., 2000). Associations between cadmium-induced kidney damage in polluted areas of Japan and lowered concentrations of 1,25-dihydroxyvitamin D, increased parathyroid hormone (PTH), and markers of bone formation have been reported (Kido et al., 1991; Tsuritani et al., 1992, 1994). The decrease in 1,25-dihydroxy vitamin D and increase in PTH was more marked in women than in men (Tsuritani et al., 1992). Taken together, available data strongly indicate that cadmium constitutes a greater health risk to women than to men.

NICKEL

A large number of metals and metal compounds cause adverse reactions upon exposure to the skin. Some are toxic, causing irritant contact dermatitis, ulceration, or granuloma, and several are contact allergens (Liden et al., 1995). Allergy to nickel and also to cobalt and chromate is prevalent in the general population and in some occupational groups. Nickel is the overall most common cause of contact allergy, and it is an important cause of hand eczema. Due to differences in exposure, nickel allergy is much more frequent in women than in men. Contact allergy to chromate has been much more frequent in men than in women, due to exposure to chromate in wet cement. The higher prevalence of nickel allergy in women is thus not genetically determined, but related to differences in exposure to nickel-releasing jewelry, buttons, accessories, etc., and to wet work. Nickel is present in the earth's crust, together with iron, cobalt, and copper. Nickel occurs naturally in drinking water and in food, and it is possibly an essential nutrient for humans. During the 19th century, white nickel-containing alloys were introduced in Europe as a substitute for silver and, around 1870, nickel was used in steels and platings. The production of nickel has, since 1940, increased considerably. Today, about half the nickel produced is used for stainless steel. Nickel is used in numerous alloys and coatings and in chemical compounds (Flint, 1998).

More than 3700 chemical substances are identified as contact allergens. Nickel is by far the most important contact allergen today, and nickel allergy affects approximately 15–20% of women and 2–5% of men (Fig. 2) (Nielsen and Menné, 1992; Lidén et al., 2001; Meding et al., 2001). The problem is not related to naturally occurring nickel, but to nickel used in industrial production. Skin exposure to bioavailable nickel that may cause sensitisation has increased dramatically during the 20th century due to the use of nickel in numerous alloys and coatings for everyday articles and for occupational use. Due to the corrosive effect of human sweat, nickel in several alloys is easily ionized when in contact with the skin (Flint, 1998). Nickel in stainless steel, however, is generally firmly bound and high-quality stainless steels are not regarded as a risk at skin contact. Release of nickel can be detected by extraction with artificial sweat, or directly by a screening test with dimethylglyoxime.

Nickel dermatitis was first described in 1889 in platers (Blaschko, 1889), and until 1930 nickel dermatitis was a frequent male occupational diseases in the plating industry. From 1930 it has become increasingly frequent in women, often related

![FIG. 2. Nickel allergy among men and women in different age groups in Sweden, according to a national inquiry in 1999 on environmental health (NBHW, 2001).](image-url)
to consumer items. In the 1970s it was recognized that nickel allergy affects large parts of the female general population, not only dermatology clinics’ patients and limited occupational groups, and the association with hand eczema was established (Lidén et al., 2001). Hand eczema implies itching, erythema, edema, vesicles, scaling, and fissures, and hand eczema in people with nickel allergy does often have far-reaching consequences such as chronic suffering, sick leave, change of jobs, and large costs for society.

Sensitization to nickel is generally caused by direct and prolonged skin contact with items that release nickel ions. The causes vary on fashion and other factors influencing exposure. Cheap jewelry, precious-metal jewelry, watches, spectacle frames, buckles, zippers, jeans buttons, and, previously, suspenders are items often associated with sensitization and elicitation of nickel dermatitis (Lidén et al., 1996; Lidén and Johnsson, 2001). Females of all ages—children, youths, and adults—are more exposed to nickel from such items than men are. Ear piercing is overrepresented among people with nickel allergy. Piercing of earlobes and other parts of the body, and subsequent wearing of jewelry, may facilitate sensitization, but the role of piercing should not be overemphasized with a disregard for other frequent causes of nickel allergy. Nickel allergy was very common long before this fashion became as popular as it is today.

Hand eczema affects approximately 10% of the adult population in Europe (one-year prevalence), and hand eczema is more frequent in women than in men (Meding, 2000). Nickel-sensitive people run a considerably increased risk of developing hand eczema. Other major risk factors for hand eczema are wet work and having had atopic dermatitis during childhood; 30–40% of nickel-sensitive persons report that they have experienced hand eczema. This relationship is equal for women and men. But, as much more women than men are affected by nickel allergy, hand eczema due to nickel is much more frequent among women. Handling of coins, tools, scissors, keys, handles, and other equipment may contribute to nickel exposure of the hands. Many of these items are used frequently and intensely, both in the occupational setting and in home and leisure. Nickel allergy and hand eczema is overrepresented in some occupations with nickel exposure, the risk being even larger in jobs with much wet work (Lidén, 2000). A typical example is hairdressing.

It took a long time for society and industry to recognize the problem and start to take some responsibility for this large dermatological problem, mainly affecting women. In 1989, Denmark and Sweden introduced regulations limiting the use of nickel in some applications, aiming at the prevention of nickel allergy. In 1994 the European Parliament and Council adopted the Nickel Directive, which entered into full force in 2001 (EU, 1994; Lidén, 2001). The Nickel Directive limits nickel content in items used during epithelization after piercing (limit 0.05%), and nickel release from objects intended for use in direct and prolonged contact with the skin (limit 0.5 µg/cm²/week). Indications on a decrease of new cases of nickel allergy have been reported from Denmark, 10 years after introduction of their national regulation (Duus Johansen et al., 2000). The Nickel Directive will, most probably, result in a decrease in Europe of the present large problems caused by nickel allergy, affecting women mainly.

LEAD

People in the general environment are exposed to lead via food, drinking water, ambient air, dust, and soil. Environmental exposure to lead has decreased considerably in countries that have banned leaded gasoline (Thomas et al., 1999). However, lead exposure is still a major health problem in many countries where former and present use of leaded gasoline, deteriorating lead paint used for indoor and outdoor household decoration, and lead-glazed ceramics used for storage and preparation of food are important sources. In many low-income countries, family-based workshops, processing, for example, car accumulators and lead-containing scraps, are sources of exposure to the whole family as well as neighbors (Vahter et al., 1997).

There is an enormous amount of data telling us that both occupational and environmental chronic lead exposure can damage the central nervous, renal, cardiovascular, reproductive, and hematological systems (WHO, 1995). Lead readily passes the placenta and the central nervous system is particularly sensitive during development. For that reason, the occupational standards for women of reproductive age are lower than for men in many countries. A number of cross-sectional and prospective epidemiological studies have shown impairment of cognitive behavioral development in children already at blood lead levels of about 100 µg/L or even less (for review, see WHO, 1995). Still, the existing occupational standards in, for example, the United States (300 µg/L for men and women who intend to have children), the United Kingdom (200 µg/L for
women of reproductive capacity), and Sweden (165 μg/L for women below 50 years of age) are well above that level and, therefore, do not prevent CNS effects in the fetus.

It is even doubtful if the existing occupational standards prevent health effects in workers. Recent studies of long-term low-level lead exposure suggest a weak association between relatively low exposure levels and development of hypertension in both men and women (Hu et al., 1996; Houston and Johnson, 1999; Korrick et al., 1999). Furthermore, past exposure to neurotoxicants such as lead may lead to decreased reserve capacity of the brain and detrimental effects on neuropsychological functions which may become apparent at old age (Payton et al., 1998/ men; Schwartz et al., 2000/ workers). In a cross-sectional study of nonoccupationally exposed older women, poorer cognitive function was demonstrated at blood lead levels as low as 80 μg/L (Muldoon et al., 1996). The role of lead exposure as a risk factor for hypertension and neuropsychological dysfunctions is less studied in women than in men.

Women generally have lower blood lead levels than men do, mainly because of lower exposure and lower hematocrit (WHO, 1995). The gastrointestinal absorption of lead is about 10–15% in adults. Some studies indicate that it is enhanced at low body iron stores but data are inconsistent (Goyer, 1997). Intake of milk (or adequate intake of Ca) seems to decrease gastrointestinal lead absorption and to prevent endogenous lead exposure from bone demineralization in pregnant and postmenopausal women (Hernandez-Avila et al., 1997; Weyermann and Brenner, 1998).

More than 90% of the body burden is localized in bone with an average half-life of about 10 years (WHO, 1995). Until recently lead in bone was thought of as immobilized with no adverse effects. However, it has been shown that bone lead accumulation and release of lead in bone follow the general physiology of bone calcium metabolism (Pounds et al., 1991). During both basal and increased bone turnover, especially during pregnancy, lactation (Gulson et al., 1997, 1998), and menopause (Silbergeld et al., 1988; Symanski and Hertz-Picciotto, 1995; Baekclund et al., 1999; Hernandez-Avila et al., 2000), skeletal lead stores can be mobilized, even long after cessation of external exposure (Nilsson et al., 1991; Gulson et al., 1995). This means that endogenous exposure may occur during critical periods of organ development in the fetus and the nursing child. Furthermore, the accelerated bone loss that occurs at menopause and the following years, mediated by decreased estrogen production, may constitute a potential threat to the woman at old age. Therefore, lead exposure should be brought to a minimum for all women.

Lead may also be a potential risk factor for osteoporosis, the incidence of which is increasing rapidly in most developed countries, and especially in women. Both in vivo and in vitro studies indicate that lead may exert both indirect and direct actions on bone turnover. Indirect effects of lead are via kidney dysfunction and inhibition of activation of 1,25-dihydroxyvitamin D, while direct effects are on osteoblast and osteoclast function by disturbance of the ability of bone cells to respond to hormonal regulation (Pounds et al., 1991; Silbergeld et al., 1988).

Lead exposure has also been associated with reduced bone growth in fetuses and children, resulting in reduced head circumference and stature (Schwartz et al., 1986; Ballew et al., 1999; Osman et al., 2000). However, there are not yet sufficient data to establish the role that lead plays in bone growth or development of bone diseases.

Genetic susceptibility to lead poisoning has been discussed. Candidate genes are those involved in regulation of absorption, accumulation, and kinetics of lead such as those coding for delta-aminolevulinic acid dehydratase (ALAD), the vitamin D receptor (VDR) gene, and the hemochromatosis gene (Onalaja and Claudio, 2000). In a study of subjects with hemochromatosis no differences in blood lead concentrations compared to matched controls were found (Åkesson et al., 2000). Studies of Swedish twins have shown that blood lead concentrations in middle-aged to older women, but not in men, reflect not only exposure but to a considerable extent hereditary factors (Figure 1; Björkman et al., 2000). The genetic influence on blood lead decreased with increasing age, possibly due to decreased bone turnover compared to that at menopause.

**MERCURY**

The health effects of mercury are highly dependent on the different chemical forms of mercury. Dental amalgam is the major source of mercury vapor (Hg⁰) exposure in the general population and an association between the number of amalgam fillings and the concentrations of inorganic mercury (I-Hg) in blood and urine has been reported (WHO, 1991; Vahter et al., 2000). The diet contains low concentrations of I-Hg, mainly as Hg²⁺. Occupational exposure occurs mainly in the chloralkali industries and in the gold mining industries. High levels of mercury exposure may occur via use of skin lightening beauty
creams and soaps (McRill et al., 2000) and herbal drugs (Li et al., 2000).

In the body, inhaled Hg⁰ is oxidized by catalase to Hg²⁺, which may cause neurotoxic and nephrotoxic effects (WHO, 1991). There are no reports on gender differences in the sensitivity toward mercury vapor. Experimental studies on mice indicated higher tissue retention of mercury, especially in the kidneys, in males than in females, but there were no major differences in the autoimmune effects studied (Hultman and Nielsen, 2001). On the contrary, analysis of mercury in biopsies of human kidney cortex showed three times as high concentrations in women as in men (Barregård et al., 1999). Kidney mercury is mainly inorganic with dental amalgam as the major source, but the reason for the observed gender differences is not known. Effects of Hg⁰ on the reproductive outcome have been demonstrated in experimental animals and women occupationally exposed to Hg⁰ (WHO, 1991; Yang et al., 1997; Fredriksson et al., 1996; Newland et al., 1996). Whether such effects are caused by mercury exposure from dental amalgam unknown. In some countries it is recommended that women refrain from dental restoration using amalgam during pregnancy.

Exposure to methylmercury (MeHg), a well-known neurotoxicant, occurs almost exclusively via consumption of seafood, especially predatory fish and marine mammals, which may contain mercury in the milligram per kilogram range (NRC, 2000). Fish consumption is highly influenced by cultural and socioeconomic factors. Although women seem to eat somewhat less wild-caught fish than men do, both male and female high consumers of fish tend to eat more wild-caught fish than bought fish or restaurant fish (Burger, 2000). In most instances, there are fewer data on MeHg concentrations in wild-caught fish than in commercial fish. Thus, there is no obvious reason for general gender differences in exposure to MeHg. Experimental studies indicate higher MeHg concentrations in blood and brain of female than male mice (Nielsen and Andersen, 1991), which would indicate gender differences in toxicokinetics. Human data are needed. The binding of MeHg to cysteine in the body renders it much less lipid soluble than the pure chemical (NRC, 2000). Obesity was found to increase both blood and brain concentrations of MeHg in chronically exposed female non-human primates (Vahter et al., 1994).

Gender-related susceptibility to MeHg neurotoxicity has not been extensively studied. Limited data, mainly from the Iraqi outbreak of MeHg intoxication due to consumption of pesticide-contaminated grain, together with experimental animal data, indicate that women are more affected than men following exposure at adult age (Magos et al., 1981). However, males seem to be more affected by exposure during early development, as indicated by both epidemiological studies and experimental animal studies (McKeown-Eyssen et al., 1983; Grandjean et al., 1998; Gimenez-Llort, 2001). It was recently reported that there was a declining male birth ratio associated with increased male fetal death due to MeHg in the Minmata City, Japan, in the 1950s, when severe MeHg pollution was experienced (Sakamoto et al., 2001).

Like Hg⁰, MeHg easily passes the placenta (NRC, 2000) and the concentration of MeHg in cord blood is often close to twice that in material blood (Vahter et al., 2000). Epidemiological studies have shown associations between prenatal exposure to MeHg and impaired psychomotor and cognitive function in children in some fish-eating populations (NRC, 2000). Recent data from the National Health and Nutrition Examination Survey indicate a narrow margin of safety (CDC, 2001). In some countries women are recommended to avoid intake of mercury-containing fish during pregnancy and lactation. As the half-time of MeHg in maternal blood is about 2 months, it is obvious that MeHg exposure before the onset of pregnancy will result in exposure of the fetus over a considerable part of early fetal development. As fish in many other respects is excellent food and beneficial for fetal development (Egeberg and Middaugh, 1997), women should be advised to eat fish with low MeHg content.

**ARSENIC**

Exposure to high levels of inorganic arsenic via drinking water is common in several countries. Gender-related exposure is probably mainly occurring in certain industries, e.g., electronic industries using gallium and indium arsenides. Arsenic exposure has been associated with cancer of the skin and various internal organs, as well as hyperkeratosis, pigmentation changes, and effects on the circulatory and nervous systems (NRC, 1999, 2001). Inorganic arsenic is metabolized in the body and the end-products methylarsonic acid (MMA) and dimethylarsinic acid (DMA) are readily excreted in urine. However, intermediate reduced forms of the methylated metabolites MMAII and DMAII have been detected in human urine. In particular MMAII is highly toxic (NRC, 2001). There are indications that subjects with higher fractions of MMA and inorganic arsenic in urine have slower overall elimination of the ingested arsenic and higher risk of adverse health
effects, compared to those with less of these metabolites and more DMA. It is probable that those with much MMA in urine also produce more MMA. III

Factors which have been shown to influence the methylation of arsenic include dose level, age, and to some extent gender (Vahter, 1999). In people exposed to inorganic arsenic via the drinking water in northern Chile, women had about 3% more DMA and less MMA in the urine than men (Hopenhayn-Rich, 1996). Similar gender differences were found in northeastern Taiwan (Hsu et al., 1997), but not in other studies (Kurtto et al., 1998). The discrepancies may partly be related to induced arsenic methylation in pregnancy, as was recently observed in Argentinean women (Concha et al., 1998a). The gender differences are mainly reported for cultures with many children per family, where it is more likely that pregnant women with elevated arsenic methylation are included in the study cohort than in cultures with few children per woman. Based on several epidemiological studies (see NRC, 1999, for review) there seem to be higher risks for arsenic-induced bladder and kidney cancer, but not arsenic-induced skin and lung cancers, in women compared to men. However, this has not been thoroughly evaluated.

Severe reproductive effects of arsenic have been observed in animal experiments (Golub et al., 1998; DeSesso et al., 1998). Despite the large number of people being exposed, there are very few studies on the reproductive effects of arsenic in humans (Hopenhayn-Rich et al., 2000; Ahmad et al., 2001; NRC, 2001). Such studies are warranted, as arsenic was recently shown to be readily transferred over the human placenta to the fetus, resulting in about as high concentrations of arsenic in cord blood as in maternal blood (Concha et al., 1998). In contrast, very little arsenic was excreted in breast milk (Concha et al., 1998b). Thus, it is essential to breast-feed infants in areas with elevated arsenic in drinking water.

CONCLUSIONS

We have discussed both obvious and possible factors that may result in gender differences in metal exposure and health effects. These are highly neglected research areas, which need considerable focus in the future. It is essential to identify risk groups in the population in order to achieve reliable risk assessment and cost-effective risk reduction.

REFERENCES


