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Review article

Mercury and lead during breast-feeding

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Hg and Pb are of public health concern due to their toxic effects on vulnerable fetuses, persistence in pregnant and breast-feeding mothers, and widespread occurrence in the environment. To diminish maternal and infant exposure to Hg and Pb, it is necessary to establish guidelines based on an understanding of the environmental occurrence of these metals and the manner in which they reach the developing human organism. In the present review, environmental exposure, acquisition and storage of these metals via maternal–infant interaction are systematically presented. Though Hg and Pb are dispersed throughout the environment, the risk of exposure to infants is primarily influenced by maternal dietary habits, metal speciation and interaction with nutritional status. Hg and Pb possess similar adverse effects on the central nervous system, but they have environmental and metabolic differences that modulate their toxicity and neurobehavioural outcome in infant exposure during fetal development. Hg is mainly found in protein matrices of animal flesh (especially fish and shellfish), whereas Pb is mainly found in osseous structures. The potential of maternal acquisition is higher and lasts longer for Pb than for Hg. Pb stored in bone has a longer half-life than monomethyl-mercury acquired from fish. Both metals appear in breast milk as a fraction of the levels found in maternal blood supplied to the fetus during gestation. Habitual diets consumed by lactating mothers pose no health hazard to breast-fed infants. Instead, cows' milk-based formulas pose a greater risk of infant exposure to neurotoxic substances.

Mercury: Lead: Pregnancy: Breast milk: Lactation

Most substances that persist in the environment and that meet the criteria for human-milk surveillance programmes are lipid soluble (Berlin *et al.* 2002). The exceptions are Hg and Pb. Both metals are of equal public health concern due to their widespread occurrence, persistence in the environment and toxic effects. Hg and Pb are ubiquitous in the environment and reach human populations through air, drinking water and the food chain. Naturally occurring background levels of Hg and Pb depend on geochemical conditions. However, human activities can substantially increase their release and dissemination into the environment. The widespread use of Hg and Pb results in large environmental discharges. Furthermore, the chemistry of these metals determines their occurrence, speciation, and environmental routes to maternal acquisition and transfer to vulnerable fetuses (*in utero*) and breast-fed infants (*ex utero*). The detrimental effects of Hg and Pb to the developing infant central nervous system (CNS) are well known (Mendola *et al.* 2002). Understanding how these toxic metals are released in the environment and how they are obtained and metabolised by the maternal organism is fundamental to establishing guidelines for diminishing exposure and toxicity during early human development.

Diet is the main source of maternal exposure to Hg and Pb, though a significant amount of Pb is also delivered by airborne particles (Chamberlain, 1985). Maternal acquisition of Hg is influenced by both its chemical form and dietary source. After absorption, Hg is either bound to metalothionein or cysteine residues of proteins, whereas Pb is preferentially taken up by bones. Pb acquisition and storage are modulated by maternal bone status, meal content of Pb, and accompanying osteoactive substances. The metabolism of these tissues determines the persistence of these metals in the maternal organism. Therefore, due to the dynamics of maternal body tissues (muscle and bone), the half-life of these metals is greatly different. And, in turn, it is the half-lives that determine their transfer rates from plasma to breast milk. The WHO considers concentration ranges of 1·4 to 1·7 ng Hg/g and 2 to 5 ng Pb/g as 'normal' in breast milk (World Health Organization, 1989). Concentrations of Hg and Pb in breast milk are important indicators of prenatal exposure, the period when most neurotoxic insults occur.

Early analyses of Pb contamination of breast milk may not be accurate. Gulson *et al.* (1998) discussed methodological problems related to Pb analysis in breast milk,

Abbreviations: CNS, central nervous system; DHA, docosahexaenoic acid; In-Hg, inorganic Hg; MMeHg, monomethyl-mercury; OCP, organochlorine pollutants.

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especially the difficulties and inaccuracies attributed to Pb contamination. Moreover, much of the old data and values above 3 parts per billion of Pb in breast milk reported in the last 15 years have been questioned.

The objective of the present study is to review the complex interactions between environmental exposure and maternal conditions (dietary practices, nutritional status and physiological factors) that affect mammary transfer of Hg and Pb to infants.

Mode of maternal acquisition of mercury and lead

Mercury

Clarkson (2002) has elegantly discussed the geochemistry of Hg and its acquisition by human populations. Briefly, Hg is released in the environment mainly as inorganic Hg (In-Hg). However, sulfate-reducing bacteria reduce metallic Hg to monomethyl-mercury (MMeHg). In this form, Hg is disseminated in the food web and is bioconcentrated at the top of the food chain. Mainly as MMeHg, it is taken up by aquatic organisms and is bioconcentrated in the trophic food chain where it is subsequently consumed by fish-eating populations. Although the consumption of MMeHg in fish is the primary means of human acquisition of organic Hg, dental fillings containing metallic Hg are the second most significant route of Hg acquisition and the primary source of human In-Hg contamination. These Hg species are differentially metabolised by the maternal organism.

After the accidental poisoning in Iraq, studies conducted on lactating mothers showed that the mean half-life of MMeHg in blood was 65 d (Bakir *et al.* 1973). The observation that blood-clearance half-life is faster (42 d) in lactating women than in non-lactating women (Greenwood *et al.* 1978) indicates that reproduction accelerates the maternal-Hg metabolism. Moreover, Hg transfer rates *in utero* (pregnancy) and *ex utero* (breast-feeding) differ depending on the chemical form of Hg (organic or inorganic). Both chemical forms (organic and inorganic) are equally efficiently transferred through milk (Mansour *et al.* 1973) but organic Hg is more readily transferred across the placenta than the inorganic form. In the Iraqi study, milk-Hg was 5 % of blood-Hg but the organic fraction of milk-Hg was only 3 % of blood-MMeHg (Bakir *et al.* 1973). Studies in fish-eating populations of the Amazonia region of Brazil (Barbosa & Dorea, 1998) show that Hg body burden (measured via hair-Hg) in infants was not significantly correlated with breast-milk Hg but with maternal hair-Hg. This indicates that the placenta plays a greater role in Hg transfer than milk, even in cases of prolonged breast-feeding (1·5 years). In addition, mean changes of 10 to 20 % of maternal Hg burden (hair-Hg) were observed during the second and third trimesters of pregnancy (Barbosa *et al.* 1998).

Experiments show that Hg acquisition in early life is more quantitatively significant during the prenatal period than during breast-feeding (Mansour *et al.* 1973; Nordenhall *et al.* 1995; Vimy *et al.* 1997; Sakamoto *et al.* 2002). Nordenhall *et al.* (1995) reported that when hamsters were injected with labelled Hg, 11 % of the dose appearing in the litter was transferred via the placenta while only 1·7 % was transferred via milk. Similar effects were observed in rats fed 5 parts per million MMeHg during gestation and lactation. In addition, brain-Hg of offspring was 1·4 times higher than in the dams. Brain-Hg decreased in the offspring during lactation, suggesting that Hg derived from milk was limited (Sakamoto *et al.* 2002).

Extrapolation of animal data to man should take into account, among other things, the high protein concentrations in milk of differing animal species. Based on total N measurements, protein concentrations are 3·4 times higher in cows', 11·8 times higher in rat and 13·9 times higher in rabbit milk than in human milk (Rossi & Wright, 1997). Furthermore, Sundberg *et al.* (1999) demonstrated differences between mice and man in protein Hg binding in milk and plasma. Moreover, specific protein fractions change during human lactation (Sanchez-Pozo *et al.* 1986).

Lead

Pb is widespread in the environment. Industrial pollution and exhaust fumes from leaded petrol are the primary sources of Pb contamination of water, food and air (Wade *et al.* 1993). The quantity of Pb in food and water is also attributed to: the use of pesticides containing Pb; soil uptake by plants and its subsequent consumption by grazing animals; contamination during industrial and domestic food processing, such as those used in food canning, water plumbing and food served in glazed pottery (Whanger, 1982; Needleman & Bellinger, 1991). An authoritative discussion of Pb-isotope studies and environmental sources was recently published (Gulson *et al.* 2003).

Few studies exist that address the dietary factors that regulate Pb metabolism, even though Ca influences Pb absorption and bone retention. Studies in adults have shown that Pb attachment to erythrocytes results in faster bone uptake of Ca (Heard & Chamberlain, 1984). Studies using ^{203}Pb have shown that both Ca and P reduce Pb absorption from 63 to 10·6 % (Heard & Chamberlain, 1982). Also, the addition of cows' milk to a low-Ca diet may cause a reduction in Pb absorption (Blake & Mann, 1983).

The maternal acquisition of Hg and Pb depends not only on the metal (and its chemical form) but also on environmental factors related to food and nutrition.

Environmental and breast-milk mercury and lead

Mercury speciation

Two outbreaks of Hg toxicity have been well documented. In Iraq, wheat laced with Hg-containing fungicide was used to make bread. And, in Japan, the cause of Minamata disease was attributed to the consumption of contaminated fish. Poisoning of Iraqi mothers resulted in high concentrations of Hg in breast milk, ranging from 10 to 200 ng Hg/g. Although there were no measurements of breast-milk Hg of Japanese mothers at the time of the Minamata disease outbreak, breast milk of healthy Minamata mothers was measured years later and displayed high total Hg (60 ng Hg/g) concentrations (Harada, 1968). In addition, in agricultural districts, breast-milk Hg concentrations were one order of magnitude higher (Wakatsuki, 1973).

Organic Hg poisoning, caused by the use of Hg-containing fungicide in Iraq and also by industrial pollution in Minamata Bay (Japan), constitutes isolated episodes of neurotoxic outbreaks due to Hg contamination of food (bread and fish). It is worth mentioning that, in Germany, accidental exposure to Hg-disinfectants did not affect breast-milk Hg concentrations (Muller *et al.* 1986).

More commonly, maternal environmental Hg exposure is directly related to fish consumption (MMeHg) or amalgam filling (In-Hg). Infant MMeHg exposure during fetal development and breast-feeding is strongly related to maternal Hg burden (Barbosa & Dorea, 1998). The transfer of Hg from the mother to the fetus is through the placenta (World Health Organization, 1996) and occurs at different rates, depending on the source of Hg (amalgam fillings or fish eating). These Hg sources influence total Hg concentrations in breast milk (Table 1). In mature milk, positive associations between breast-milk Hg and fish consumption (Oskarsson *et al.* 1995, 1996) and between breast-milk Hg and amalgam fillings (Oskarsson *et al.* 1995, 1996; Drasch *et al.* 1998) have been demonstrated. However, in transitional milk, such associations were not statistically significant (Klemann *et al.* 1990). Oskarsson *et al.* (1995) demonstrated that 51 % of total Hg in milk was In-Hg. And Westoo (1973) reported high levels of total Hg (0·3 to 1·6 μg/l) with proportions of MMeHg ranging from 8 to 100 %. Oskarsson *et al.* (1995) found that when freshwater fish (one to two meals) was consumed over the course of a 6-week study, it resulted in a significant increase in blood-Hg. Despite elevated blood-Hg in fish eaters, there was no significant difference in milk-Hg between fish eaters as compared with controls. Vimy *et al.* (1997) observed that total milk-Hg was not associated with fish consumption but with amalgam fillings. They noted that amalgam fillings might contribute up to 38 % of total milk-Hg, thereby indicating that a negligible amount of Hg (75 ng/d) is available for transfer to breast-fed (850 ml/d) infants. In only one instance has maternal occupational exposure to Hg (via vapour in lamp factories) been studied (Yang *et al.* 1997). Exposed mothers were found to possess a significantly higher mean Hg concentration (8·5 ng/ml) than controls (1·6 ng/ml), mostly due to higher proportions of In-Hg.

Table 1. Total mercury concentrations (ng/g or ng/ml) in breast milk according to country or according to those who may be affected by environmental factors

Reference	Country	Hg concentration	Comments
Al-Saleh *et al.* (2003)	Saudi Arabia	4·15	Riyadh residents
		2·19	Al-Ehssa residents
Bakir *et al.* (1973)*	Iraq	10–200	Poisoning by methyl-Hg fungicide in wheat
Baluja *et al.* (1982)	Spain	9·5	
Barbosa & Dorea (1998)	Brazil	5·8	High fish eaters
Drasch *et al.* (1998)	Germany	<0·2	No amalgam fillings
		0·57	One to four amalgam fillings
		0·50	Four to seven amalgam fillings
		2·11	Over seven amalgam fillings
Galster (1976)	Eskimos	7·6	Coastal
		3·2	Interior
Grandjean *et al.* (1995*a*)	Faroe Islands	2·45	Correlated with pilot-whale meals
Harada (1968)	Japan	63	Healthy mothers from Minamata
Juszkiewicz *et al.* (1975)	Poland	6·3	Rural area
		5·6	Urban area
Klemann *et al.* (1990)	Germany	1·9	5–10 d; no correlation with amalgam fillings
Muller *et al.* (1986)	German	NG	Hg-containing disinfectant did not affect breast-milk Hg
Nunes-Junior & Sotério (2000)	Brazil	3·3	Non-fish eaters living near gold fields
		ND	Control (non-fish eaters)
Oskarsson *et al.* (1995)	Sweden	NG	6 weeks of one to two meals freshwater fish
		NG	Control
Paccagnella & Riolfatti (1989)	Italy	13·9	
Ramirez *et al.* (2000)	Philippines	0–60	Only five samples above DL
Vimy *et al.* (1997)	Canada	0·24	Amalgam fillings
		0·15	Control
Wakatsuki (1973)*†	Japan	0·50–0·54	Range in agricultural district
Westoo (1973)	Sweden	0·8	
Winfield *et al.* (1994)	Canada	0·03–0·62	Range
World Health Organization (1989)	Guatemala	1·6	
	Hungary	1·4	
	Nigeria	2·5	
	Phillippines	1·7	
	Sweden	3·3	
	Zaire	2·7	
Yang *et al.* (1997)	China	8·5	Occupational exposure
		1·6	Control

NG, not given; ND, not detected (below detection limits); DL, detection limit (2 ng/ml).
* Data extrapolated from figure.
† Parts per million

In Swedish mothers, the estimated erythrocyte:plasma ratio of MMeHg is twenty times higher than that of In-Hg (Vahter *et al.* 2000). This result indicates that In-Hg is the favoured form of transfer from maternal plasma to milk. It has been estimated that 50 to 80 % of Hg in human milk is in the inorganic form (Skerfving, 1988; Oskarsson *et al.* 1996). Thus, recent exposure to MMeHg from fish consumption is reflected in Hg levels in maternal blood but not in milk. In milk, an average of 51 % of total Hg was found to be In-Hg, whereas in blood, only 26 % was present in the inorganic form (Oskarsson *et al.* 1995, 1996).

Fish consumption and amalgam fillings are the most important sources of MMeHg and In-Hg respectively. Despite the potentially higher toxicity of organic Hg, its transfer is attenuated by the mammary-gland barrier.

Environmental lead

Industrial and urban pollution can increase environmental levels of Pb, which, in turn, ultimately affect Pb concentration in milk. Environmental sources of Pb in breast milk are shown in Table 2. Mean Pb concentrations until 1973 ranged from 5 to 277 μg Pb/ml (Dillon *et al.* 1974). The World Health Organization's (1989) international study showed that industrialised countries (Sweden, Hungary) had higher breast-milk Pb concentrations than non-industrialised countries (Guatemala, Nigeria and Zaire). Also, studies comparing urban and rural areas showed that breast-milk Pb concentrations were significantly higher in some urban areas (Huat *et al.* 1983). In Egypt, large urban centres (Cairo, Alexandria, Assiut) had higher milk Pb concentrations than less populated areas (Saleh *et al.* 1996). However, this was not true in the Philippines and Zaire (Table 2). Unaccounted sources of environmental Pb or maternal constitutional factors may operate to promote differences in breast-milk Pb between rural and urban centres. Al-Saleh *et al.* (2003) also showed higher breast-milk concentrations in rural (Al-Ehssa) compared with Riyadh mothers.

Despite a wide range of Pb concentrations in human milk, there have been no reports of toxicity caused by breast-feeding. In electrical battery factories in China, occupational exposure to Pb caused a significant increase in breast-milk Pb (Li *et al.* 2000). In one case, a woman, who had worked in an electrical battery factory during her pregnancy (USA), had an infant who displayed no adverse neurological effects, even though the baby had received comparable levels (Table 2) of Pb in breast milk (Ryu *et al.* 1978).

Although airborne particles are the main source of maternal exposure, they are not direct modulators of breast-milk Pb.

Maternal constitutional factors related to mercury and lead in breast milk

Both Hg and Pb have low transfer coefficients (<1) from blood to breast milk (Tables 3 and 4). Due to the protein-binding properties of Hg, its transfer efficiency may be higher than that of Pb. However, the special affinity of Pb for bone appears to favour a higher bioaccumulation of Pb than Hg in soft tissues. Therefore, maternal transfer (*in utero* and *ex utero*) of these two metals is different. MMeHg in muscle is estimated to have a 72 d half-life (Sweet & Zelikoff, 2002) with a blood clearance half-life of 42 d (Greenwood *et al.* 1978). However, kinetic studies with ^{204}Pb have indicated a three-compartment model of Pb elimination with half-lives of 35 d in blood, 40 d in soft tissues, and an extremely slow half-life in skeletal tissue (Rabinowitz *et al.* 1976). In the tibia of adult smelter workers, the half-life of Pb is estimated to be between 9 and 15 years (Brito *et al.* 2001).

The estimated mean transfer efficiency from maternal blood to milk for Hg and Pb is shown in Tables 3 and 4, respectively. It appears that mammary glands exert an important barrier that restricts the transfer of Hg (organic and inorganic) and Pb. In the studies reporting the highest mean blood-Hg concentrations (Bakir *et al.* 1973; Yang *et al.* 1997; Klopov, 1998), the estimated milk:blood ratio was reported as the lowest of all other milk:blood comparisons (Table 3). It is reasoned that low milk-Hg concentrations are attributed to low protein concentrations in mature milk. Indeed, colostrum has significantly higher protein concentrations and, likewise, consistently higher mean milk-Hg concentrations (Table 3). This can be interpreted as a protective aspect of breast-feeding and also explains why prenatal exposure is initially high and then diminishes as lactation progresses. Yang *et al.* (1997) demonstrated that, in occupationally exposed mothers, the proportion of In-Hg was higher than in control mothers (Table 3). The mean milk:blood ratios were less variable and consistently low for Pb (Table 4). The only exception was found in Chinese (Shanghai) non-exposed mothers in whom there were higher Pb concentrations in milk than in maternal blood (Li *et al.* 2000).

There are maternal constitutional factors that affect Hg secretion into breast milk, such as maternal age (Juszkiewicz *et al.* 1975) and lactation stage (Drexler & Schaller, 1998). Both In-Hg and organic Hg are found to be associated with proteins in breast milk. In-Hg is mostly bound to caseins and, in low proportions, to albumin (Mata *et al.* 1997*)* and to the outer layer of fat globules (Sundberg *et al.* 1999). Differential protein binding may significantly alter both total Hg and MMeHg (fish-Hg) transfer from maternal serum to milk. Furthermore, total protein concentrations decrease during lactation, from colostrum to mature milk (Dorea *et al.* 1984), and protein composition differences in colostrum and mature milk may affect the distribution rates of organic Hg and In-Hg in milk. For example, the specific decrease in cysteine may reach 50 % (Davis *et al.* 1994). Likewise, there is a decline in Hg concentrations between colostrum and mature milk (Table 5). Vahter *et al.* (2000) demonstrated a decreased Hg concentration in blood (In-Hg) and urine (total Hg) during lactation.

The few studies that examined the effects of maternal constitutional variables on Pb concentrations in breast milk are shown in Table 6. A demonstrable, albeit slight, decline between colostrum and mature milk is seen in all studies. Such subtle changes appear to reflect bone turnover during lactation. Gulson *et al.* (2003) revised data

Table 2. Lead concentrations (ng/g or ng/ml) in breast milk according to country or according to those who may be affected by environmental factors

Reference	Country	Pb concentration	Comments
Abusamra (1995)	Sudan	2·6	
Al-Saleh *et al.* (2003)	Saudi Arabia	25·16	Riyadh residents
		37·3	Al-Ehssa residents
Altmann *et al.* (1981)	Austria	128	Treated with calcium phosphate and vitamin C
		148	Control
Casey (1977)	New Zealand	<10	
Counter *et al.* (2000)	Ecuador	17·4	Occupationally exposed in cottage ceramic industry
Dabeka *et al.* (1986)	Canada	1·0	Samples collected in 1981
Dillon *et al.* (1974)	USA	26	
Fong *et al.* (1998)	China	250	Exposed
		8·7	Control
Frkovic *et al.* (1997)	Croatia	10·6	Rijcka residents
		4·7	Non-residents, regional
		5·7	Smokers
		7·9	Non-smokers
Guidi *et al.* (1992)	Italy	126·5	Urban
		45·6	Rural
Hallen *et al.* (1995)	Sweden	0·9	Smelter area
		0·5	Control
Haschke & Steffan (1981)	Austria	50·2	
Huat *et al.* (1983)	Malaysia	25·3	Urban (air Pb 2·7–5·6 $\mu g/m^3$)
	Malaysia	21·1	Rural
Larsson *et al.* (1981)	Sweden	2	3–6 months
Lechner *et al.* (1980)	Austria	23·9	High traffic
		15	Low traffic
Li *et al.* (2000)	China	91·8	Occupationally exposed
		5·6	Control (Shanghai)
Rica & Kirkright (1982)*	NG	17·3	Poor urban residents
		14·7	High-standard urban residents
		20·0	Rural areas
	NG	18·7	Poor urban residents
		16·0	High-standard urban residents
		16·0	Rural areas
	NG	18·7	Poor urban residents
Rodriguez Rodriguez *et al.* (1999)	Spain	0·11	
Ryu *et al.* (1978)	USA	19–63	Range, 1–3 weeks, occupational exposure during pregnancy
		29	Control (four mothers)
Saleh *et al.* (1996)	Egypt	66	Cairo, urban
		101	Assiut, urban
		9	Minia, rural
		9	Matrouh, rural
Sternowsky & Wessolowski (1985)	Germany	15·5	Urban, colostrum
		12·5	Rural, colostrum
		9·1	Urban, mature
		8·0	Rural, mature
Tiran *et al.* (1994)	Austria	3·4	Median
Tripathi *et al.* (1999)	India	1·9	
VanderJagt *et al.* (2001)	Nigeria	67	Median; nomadic semi-pastoralists
Vavilis *et al.* (1997)	Greece	90	Urban (air 0·54 $\mu g/m^3$)
		84	Rural
Walker (1980)	USA	20	
World Health Organization (1989)	Guatemala	3·3	Urban
		2·8	Rural
	Hungary	14·9	All
	Nigeria	4·1	Rural
	Philippines	16	Urban
		17	Rural
	Sweden	16·8	All
	Zaire	3·1	Urban
		6·0	Rural
Zahradnicek *et al.* (1989)	Czechoslovakia	1·7	In 94·2 % of samples

NG, not given.

* Freeze-dried samples (3–9 months) comparing socioeconomic conditions of unidentified countries (NG). Original mean values (130, 110, 150, 140, 120, 120, 140) were converted to wet weight by applying the factor of 7·5 suggested by Yoshinaga *et al.* (1991). The same data were reported by Barnett *et al.* (1983).

Table 3. Mercury concentrations (ng/g or ng/ml) in samples of maternal blood and breast milk

Reference	Country	Blood	Milk	Estimated milk:blood	Comments
Bakir *et al.* (1973)	Iraq	870	29	0·03	Accidental poisoning
Drexler & Schaller (1998)	Germany	0·25	0·9	3·60	Colostrum
		0·59	0·40	0·68	Colostrum
		0·01	0·11	7·8	Colostrum
Fujita & Takabatake (1977)	Japan	25	3·6	0·14	
Klopov (1998)	Russia	12·7	2·7	0·21	Colostrum, Norilsk
		16·3	5·1	0·31	Colostrum, Salakhard
Negretti de Bratter *et al.* (1987)	Germany	1·0	2·6	2·6	Colostrum
Oskarsson *et al.* (1995)	Sweden	2·3	0·6	0·26	
Pitkin *et al.* (1976)	USA	1·0	0·9	0·9	Rural population
Plockinger *et al.* (1993)*	Austria	4·5	NG	$<$0·40	Detection limit of 1·8
Ramirez *et al.* (2000)*	Philippines	24	36	1·38	Colostrum (five of seventy-eight samples)
Schramel *et al.* (1988*a*)†	Germany	2·7	5·5	†	Colostrum
Skerfving (1988)	Germany	3·8	3·1	0·82	
Yang *et al.* (1997)	China	7·0	1·9	0·27	Organic Hg, occupational exposure
		10·8	6·5	0·60	Inorganic Hg, occupational exposure
		2·5	0·8	0·32	Organic Hg, control
		4·3	0·8	0·19	Inorganic Hg, control
		17·8	8·5	0·48	Total Hg, occupational exposure
		6·8	1·6	0·24	Total Hg, control

NG, not given.
* The ratio was estimated from the reported detection limit.
† Unequal number of observations (*n* 5 and *n* 4 respectively).

Table 4. Lead concentrations (ng/g or ng/ml) in samples of maternal blood and breast milk

Reference	Country	Blood	Milk	Estimated milk : blood	Comments
Baum & Shannon (1996)	USA	340	10	0·03	
		290	10	0·03	
Gulson *et al.* (1998)	Australia	29	0·73	0·02	
		24	0·73	0·03	
Hallen *et al.* (1995)	Sweden	32	0·9	0·03	Smelter area
		31·4	0·5	0·01	Control
Hanning *et al.* (2003)	Canada	22·9	2·01	0·09	
Huat *et al.* (1983)	Malaysia	173	25·3	0·14	Urban
	Malaysia	158	21·1	0·13	Rural
Klopov (1998)	Russia	161·7	26·7	0·17	Colostrum, Norilsk
		124·2	22·5	0·18	Colostrum, Salakhard
Kovar *et al.* (1984)	England	101	2	0·02	5 d
Kulkybaev *et al.* (2002)	Russia	0·51	0·27	0·54	Balkhash
		0·49	0·28	0·57	Karaganda
Li *et al.* (2000)	China	0·68	5·63	8·3	Non-exposed mothers
Moore *et al.* (1982)	Scotland	200	20	0·10	
Namihira *et al.* (1993)	Mexico	460	25	0·05	Vicinity of smelters
Nashashibi *et al.* (1999)	Greece	149	20	0·13	
Ong *et al.* (1985)	Malaysia	151	48	0·31	
Oskarsson *et al.* (1995)	Sweden	33	0·8	0·02	
Plockinger *et al.* (1993)	Austria	37	35·8	0·97	
Rabinowitz *et al.* (1985)	USA	72	17	0·23	
Rockway *et al.* (1984)	USA	119	3	0·02	
Ryu *et al.* (1983)	USA	96	26	0·26	
Sartorelli *et al.* (1986)	Italy	91	36	0·40	
Schramel *et al.* (1988*a*)*	Germany	39	2·6	0·06	Colostrum
		30	2·6	*	Unequal
Sowers *et al.* (2002)	USA	14	6·1	0·43	1·5 months
		16	5·6	0·35	3 months
		17	5·9	0·35	6 months
		14	4·3	0·31	12 months
Toth *et al.* (1989)	Hungary	213	64	0·30	
Yarushkin (1992)	Russia	234	209	0·89	

* Unequal number of observations (*n* 27 and *n* 34 respectively).

Table 5. Mercury concentrations (ng/g or ng/ml) in breast milk as a function of maternal constitutional variables

Reference	Country	Milk	Parameters
Drexler & Schaller (1998)	Germany	0·9	Colostrum
		0·25	Mature milk
		0·40	Mature milk
		0·17	Mature milk
		0·11	Mature milk
		0·04	Mature milk
Juszkiewicz *et al.* (1975)	Poland	8·1	Maternal age >30 years
		5·6	Maternal age <30 years
Negretti de Bratter *et al.* (1987)	Germany	2·6	Colostrum
		1·5	Mature milk, 10 d
Schramel *et al.* (1988*a*)	Germany	5·5	Colostrum
		2·0	Mature milk

Table 6. Lead concentrations (ng/g or ng/ml) in breast milk as a function of maternal constitutional variables

Reference	Country	Milk	Parameters
Friel *et al.* (1999)	Canada	0·50	Full-term, 2 weeks
		2·0	Full-term, 3 weeks
		1·0	Full-term, 4 weeks
		4·0	Full-term, 5 weeks
		3·0	Full-term, 6 weeks
		4·0	Full-term, 7 weeks
		3·0	Full-term, 8 weeks
		2·0	Full-term, 12 weeks
Frkovic *et al.* (1997)	Croatia	10·4	<25 years
		5·7	>25 years
		5·8	Primiparous
		8·7	Multiparous
Hurgoiu & Caseanu (1986)	Romania	ND	Preterm
Krachler *et al.* (1998*a*)	Austria	2·3	Colostrum, 1–3 d
		2·7	Transitory milk, 4–17 d
		2·4	Mature milk, 42–60 d
Nashashibi *et al.* (1999)	Greece	18	Caesarian delivery
		21	Vaginal delivery
Perrone *et al.* (1994)*	Italy	0·13	Term, 1 week
		0·16	Preterm, 1 week
		0·11	Term, 2 weeks
		0·13	Preterm, 2 weeks
		0·12	Term, 3 weeks
		0·12	Preterm, 3 weeks
		0·08	Term, >3 weeks
		0·6	Preterm, >3 weeks
Sowers *et al.* (2002)	USA	6·1	1·5 months
		5·6	3 months
		5·9	6 months
		4·3	12 months
Turan *et al.* (2001)	Turkey	14·6	Colostrum
Yarushkin (1992)	Russia	791	Colostrum
		209	Mature milk

ND, not detected.
* Original mean values of freeze-dried samples (1·0, 1·2, 0·82, 1·0, 0·9, 0·9,0·9, 0·6) were converted to wet weight by applying the factor of 7·5 suggested by Yoshinaga *et al.* (1991).

from their studies and estimated that the contribution of endogenous Pb to blood-Pb during pregnancy was about 33 %, increasing significantly during the postpartum period. The Pb transferred from the maternal skeleton via cord blood is about 79 % in women consuming 500 mg Ca/d (Gulson *et al.* 2003). A recent study by Manton *et al.* (2003) found that bone resorption, rather than dietary absorption, controls changes in blood-Pb. In some studies, although blood-Pb decreased from pregnancy to pregnancy, comparisons of parity status (Frkovic *et al.* 1997) and gestation age (Friel *et al.* 1999) showed no significant differences. Friel *et al.* (1999) suggested a median difference between preterm and full-term milk.

For Pb, body storage is higher and lasts longer. Despite that, the mammary-gland barrier is effective in maintaining a low milk:plasma ratio for both Hg and Pb.

Concurrent exposure to mercury, lead and other neurotoxic substances in breast milk

It is known that nursing infants and especially fetuses are most vulnerable to toxic substances. However, it is debatable whether Hg toxicity is attenuated when consumed as part of good-quality fish protein (Clarkson, 1995) or due to metabolic interactions with micronutrients (S-amino acids, Se, vitamin E), which are also present in fish (Peraza *et al.* 1998). Early experiments in cats showed that, although brain levels of MMeHg differed between cats fed fish containing intrinsic or added Hg (6 mg/kg), MMeHg was equally detrimental to the CNS (Albanus *et al.* 1972). Fish-Hg concentrations (6 mg Hg/kg) found in industrially polluted Swedish waters are high when compared with fish species of non-polluted waters of the Rio Negro (Amazon, Brazil). In predatory species of high-methylating tropical ecosystems, fish-Hg ranges from 0·45 to 1·06 mg Hg/kg (Barbosa *et al.* 2003).

Toxic metals (Pb, Cd, Hg) and organic substances in industrially polluted environments can occur concomitantly. Most often, persistent pollutants appear in the same food groups. In fish, in addition to lipophilic organochlorine pollutants (OCP), MMeHg is ubiquitously present, mostly due to the feeding behaviour of fish. In the case of maternal fish consumption, exposure to MMeHg and neurotoxic lipophilic OCP is certain (Muckle *et al.* 2001; Jacobson & Jacobson, 2002). Unfortunately, most of the maternal transfer of these toxic metals and other neurotoxic substances occurs during pregnancy, the most vulnerable period of the developing fetal CNS (Mendola *et al.* 2002). Faroese mothers who routinely consume pilot-whale meat containing high concentrations of MMeHg had relatively high blood concentrations of Hg, Pb and OCP (Grandjean *et al.* 1995*a*). Furthermore, while MMeHg and OCP are bioaccumulated by fish (or seafood), OCP are also accumulated in meats (especially poultry), eggs and dairy products (Sell *et al.* 1975; Schaum *et al.* 2003).

The consequence of multiple exposures to toxic substances is a complex issue in developmental toxicology. Studies relating infant neurological insults (*in utero* and *ex utero*) to maternal fish consumption are complicated to conduct and interpret. This is due to the difficulty of disentangling individual from cumulative effects of neurotoxic pollutants, which are often present in habitual diets (Risher *et al.* 2003). Concurrent exposure to neurotoxic substances (MMeHg and OCP) consumed in fish by Canadian autochthons was associated with subtle functional immune alterations (Belles-Isles *et al.* 2002). When comparing maternal smoking and blood-Hg concentrations, Bjerregaard & Hansen (1996) reported that smoking was significantly correlated with low birth weight, while cord-blood-Hg, attributed to the consumption of marine mammals, was not. Faroese children aged 18 months who had been exclusively breast-fed for at least 6 months weighed 0·59 kg less and were 15 mm shorter than those who were formula-fed (Grandjean *et al.* 2003). The transfer of contaminants (Hg and OCP) from human milk 'fully explained the attenuated growth', even though it was also found that doubling of the cord blood-Hg (*in utero* exposure) was associated with decreased weight and height (Grandjean *et al.* 2003). It should be noted that prenatal neurological insults may appear after breast-feeding age.

On a molar basis, the mean concentrations of Hg and Pb in fetus and infant brains are very close (Lutz *et al.* 1996). But, breast-milk concentrations of Hg and Pb vary greatly among populations. Breast milk of most urban populations contains both Hg and Pb. However, in studies measuring both metals in the same samples (Table 7), regardless of the country and environmental diversity, Pb concentrations were systematically higher than Hg with mean Pb:Hg ratios varying from 1 to >35. Therefore, it appears that, worldwide, the potential for milk concentrations exceeding the reference dose is higher for Pb than for Hg.

Environmental pollution from industry and human activities is not restricted to Hg and Pb. Other co-occurring neurotoxic xenobiotics have not yet been disentangled from Hg and Pb; collectively they are the determinants of health effects on infants mainly through maternal transfer during pregnancy.

Table 7. Concentrations (ng/g) of mercury and lead in the same samples of breast milk

Reference	Country	Hg concentration	Pb concentration	Pb:Hg	Comments
Ding *et al.* (1993)	China	1	27	27	
Durrand & Ward (1989)	England	113–358	12–139	–	Range of values
Gundacker *et al.* (2000)	Austria	4·1	1·5	0·36	
Gundacker *et al.* (2002)	Austria	1·59	1·63	1·0	
Lutter *et al.* (1997)	Kazakhstan	ND–0·08	ND–0·26	–	Range of means
Oskarsson *et al.* (1995)	Sweden	0·6	0·8	1·3	
Plockinger *et al.* (1993)	Germany	ND	35·8	>35	
Schramel *et al.* (1988*a*)	Germany	2·0–5·5	1·9–6·9	–	Range of means
Schramel *et al.* (1988*b*)	Germany	2·0	2·6	*	
Ursinyova & Hladikova (1997)	Slovakia	1·6	4·2	2·6	
World Health Organization (1989)	Guatemala	1·56	2·9	1·8	
	Hungary	1·43	14·9	10·4	
	Nigeria	2·15	4·9	2·3	
	Phillipines	1·71	16·6	9·7	
	Sweden	3·34	16·8	5·0	
	Zaire	2·65	5·0	1·9	

ND, not detected.
* Unequal number of observations for Hg (*n* 15) and Pb (*n* 34).

Intrinsic features of breast-feeding related to mercury and lead exposure

Counteractive nutrients of breast milk

Because of the known counteractive effects of Se and Ca on Hg and Pb metabolism, respectively, it is essential to examine these interactions in breast milk. Se and Ca concentrations in human milk have been thoroughly discussed and reviewed (Dorea, 1999, 2002). The mean Se concentration of breast milk varies greatly among studies (Dorea, 2002). Also, variations in breast-milk Ca concentrations are observed but, unlike Se, they neither depend on maternal constitutional variables nor on dietary Ca of natural foods or supplements (Dorea, 1999).

Due to the long duration of breast-feeding among population groups with high intakes of fish, the amount of Hg consumed by the breast-fed infant can be substantial. Barbosa & Dorea (1998) compared Amazonian riparian individuals with other population groups. They estimated that Hg exposure in 53 % (25/47) of the milk samples was greater than the WHO reference dose. Conservative estimates of breast-milk production (600 ml/d) and infant body weight at 3 months (5·46 kg) compute to a daily exposure of 0·64 μg Hg/kg body weight (Barbosa & Dorea, 1998). This level of exposure is greater than the 0·5 μg Hg/kg body weight recommended for adults (World Health Organization, 1996). Based on similar calculations using data from Swedish mothers, i.e. 1000 ml/d and infant intake of 150 g/kg body weight, Oskarsson *et al.* (1996) reported that the highest observed daily exposure of Hg was of the order of 0·3 μg Hg/kg body weight per d. Grandjean *et al.* (1995*a*) in the Faroe Islands reported only three cases with calculated daily exposure above the WHO recommended limits. And, in Italy, Paccagnella & Riolfatti (1989) found that 66 % of the milk samples would result in Hg exposure above recommended levels.

The wide range of breast-milk Se concentrations depends on Se consumed in food and supplements. In natural foods, Se concentrations reflect the Se content of the soils where the food is grown. Se prophylaxes, obtained through soil-Se fertilisation or maternal supplements, are effective in raising breast-milk Se concentrations. Though there is wide variation of Se concentrations, it has been reported that the median breast-milk Se concentrations in studies conducted worldwide are 26, 18, 15 and 17 μg Se/l in colostrum (0–5 d), transitional (6–21 d), mature (1–3 months) and late lactation (>5 months), respectively (Dorea, 2002). Studies that determined Hg and Se in the same breast-milk sample are shown in Table 8. In these studies, the mean Se:Hg ratios ranged from 18 to 49.

The reported averages of Ca concentrations range from 84 to 541 mg Ca/l (median 252 mg/l). For P, the average values range from 17 to 276 mg/l (median 143 mg P/l). Taken together, the median Ca:P ratio is 1·7 with a range of 0·8 to 6. Animal studies have shown that Pb

Table 8. Selenium:mercury and calcium:lead molar ratios in the same samples of breast milk

Reference	Country	Hg or Pb concentration	Se or Ca concentration	Se:Hg or Ca:Pb	Comment
Studies with Hg (nmol/l) and Se (nmol/l)					
Garg *et al.* (1993)	India	*	*	36	
Grandjean *et al.* (1995*a*)	Faroe Islands	12	241	20	
Schramel *et al.* (1988*a*)	Germany	27·4	544·6	19·9	Colostrum
Schramel *et al.* (1988*b*)	Germany	15·0	177·3	11·8	
		11·5	164·6	14·3	
		27·4	228	8·3	
		11·5	215·3	18·7	
		10	226	22·6	
World Health Organization (1989)	Guatemala	8·0	243·2	30	
	Hungary	7·0	176	25	
	Nigeria	12·5	304	24	
	Philippines	8·5	420·8	49	
	Sweden	16·7	166	10	
	Zaire	13·5	244·4	18	
Studies with Pb (nmol/l) and Ca (μmol/l)					
Gulson *et al.* (2001)	Australia	3·5	6013	1718×10^3	
Hurgoiu & Caseanu (1986)	Romania	ND	6337	$>6337 \times 10^3$	
Martino *et al.* (2001)	Spain	7·2	6262	869×10^3	
Richmond *et al.* (1993)	England	145	6287	$43·4 \times 10^3$	
Schramel *et al.* (1988*b*)	Germany	9·2	7·11	$775·4 \times 10^3$	
		33·3	7·18	$215·6 \times 10^3$	
		9·2	7·31	$797·2 \times 10^3$	
		11·1	7·41	$667·6 \times 10^3$	
		12·5	7·08	$564·6 \times 10^3$	
World Health Organization (1989)	Guatemala	13·9	2695	$193·9 \times 10^3$	
	Hungary	71·9	2535	$35·3 \times 10^3$	
	Nigeria	23·6	2010	$85·2 \times 10^3$	
	Philippines	80·1	2402	30×10^3	
	Sweden	81·1	2090	$25·8 \times 10^3$	
	Zaire	24·1	2438	$101·2 \times 10^3$	

ND, not detected.
* Powdered samples.

bioavailability varies in different milk diets (Pallinger-Hallen & Oskarsson, 1995). A decreased Pb bioavailability was seen for control (water, 47 %) > human milk (42 %) > infant formula (40 %) > cows' milk (31 %) > rat's own milk (11 %). Differences in Ca concentrations between human milk (300 mg Ca/l) and formulas (600 mg Ca/l) did not affect bone mineralisation or Ca homeostasis (Hillman, 1990). But, supplementation of human milk with P resulted in reduced urinary Ca excretion in 1-week-old term infants (Senterre *et al.* 1983). Low levels of vitamin D in human milk were found to affect bone mineralisation in breast-fed infants (Hillman, 1990).

The differences between Ca concentrations in breast milk and formulas are large (Dorea, 1999). It is not yet clear if the high Ca content of formulas protects infants against Pb acquisition since other milk constituents, such as lactose and fat, may enhance Pb absorption (Stephens & Waldron, 1975). However, experiments have shown that lactose at concentrations found in rat's milk does not enhance Pb absorption (Bushnell & DeLuca, 1983). There is an indication that an inverse relationship exists between dietary Ca (from sources other than human milk) and Pb absorption and retention in infants (Ziegler *et al.* 1978). In the case of breast-fed infants, the relationship between Ca nutrition and Pb exposure is more difficult to ascertain.

Fortunately for breast-fed infants, the occurrence of Se and Ca is much higher than Hg and Pb in human milk. A summary of studies that measured toxic metals (Hg and Pb) and their respective counteractive nutrients (Se and Ca) clearly shows that breast milk carries high Se:Hg ratios and even higher Ca:Pb ratios (Table 8).

Breast-feeding and neuromotor development

Breast-fed infant exposure to multiple substances with similar end-point effects, such as disturbance of neuromotor responses, awaits studies to differentiate their effects. The impact of the simultaneous occurrence of neurotoxic substances has not been adequately evaluated in studies comparing formula- *v.* breast-feeding. Furthermore, in most studies reporting an association of maternal body-Hg load with neurological disturbances in Amazonian infants, the disturbances were attributed to fetal exposure during gestation rather than exposure as a function of breast-feeding duration (Cordier *et al.* 2002). Studies in industrialised countries found no clear association between the duration of breast-feeding and motor development but did suggest that longer durations of breast-feeding benefit cognitive development (Paine *et al.* 1999; Angelsen *et al.* 2001). Additionally, one Danish study reported that breast-fed infants achieved motor milestones at earlier ages than formula-fed infants (Vestergaard *et al.* 1999) while Oddy *et al.* (2003) reported that the early introduction of milk other than breast milk was associated with a reduced verbal intelligence quotient. Indeed, in the meta-analysis study of Anderson *et al.* (1999), breast-feeding had a positive effect on cognitive development tests. Breast-feeding showed a small advantageous effect in neonates with defined neurological (hemisyndrome, hypotonia, or hypertonia) syndromes (Lanting *et al.* 1994). Collectively, the data support the hypothesis that a long duration of breast-feeding benefits cognitive development (Vestergaard *et al.* 1999). Furthermore, in Swedish infants, exposure to Hg (blood MMeHg) diminished as breast-feeding progressed (Sandborgh-Englund *et al.* 2001).

Protective factors in human milk can counteract the effects of prenatal neurotoxic exposure. Vreugdenhil *et al.* (2002) reported that the effects of prenatal exposure to polychlorinated biphenyls were more pronounced in formula-fed infants. Nutritional factors in breast milk that are essential to normal neuromotor development need to be evaluated with regard to maternal fish consumption. Rocquelin *et al.* (1998) reported that in communities with a dietary dominance of cassava and fish, a human milk rich in C_8–C_{14} and in PUFA is highly beneficial to breast-fed infants. Docosahexaenoic acid (DHA) derived from the essential *n*-3 fatty acids in the maternal diet is accumulated in the developing fetal brain and is critical for the infant's neural and visual functions (Innis & Elias, 2003). Additionally, Das (2003) suggested that the negative correlation between breast-feeding and insulin resistance and diabetes mellitus can be related to the presence of significant amounts of long-chain PUFA in breast milk. Concentrations of DHA in the milk of Canadian women have decreased in recent years (Innis & Elias, 2003). However, it has not yet been established if this decline is related to a decrease in fish consumption.

Some studies have shown negative neurobehavioural effects in infants, which were attributed to neurotoxic substances present in maternal fish consumption. However, the few studies that have examined harmful effects in older children and adults who were exposed early in life to neurotoxins showed no neurological outcome. Myers *et al.* (2000) summarised studies carried out in Samoa, Peru and the Seychelles, which showed no evidence that consuming large quantities of fish is associated with clinical adverse effects on adults or children. As for the long-term effects of consuming contaminated fatty fish, there was no lasting impact on medical or psychometric functions of Swedish boys in their conscript examinations (Rylander & Hagmar, 2000). But, the duration of breast-feeding has been found to be positively associated with intelligence in adults (Mortensen *et al.* 2002). Surprisingly, lifetime health effects due to fish consumption have been studied in association with cancer prevention (Vatten *et al.* 1990; Terry *et al.* 2003), the risk of Alzheimer's disease (Morris *et al.* 2003), CVD (Guallar *et al.* 2002), infertility (Choy *et al.* 2002) and, lately, in relation to the prevalence of infectious diseases (Silbergeld *et al.* 2002). Other substances found in fish that are neurotoxic to infants, such as OCP, have been studied in relation to breast cancer (Gammon *et al.* 2002).

Breast-feeding is essential to the behavioural and neuromotor development of infants. Because the mammary-gland barrier is effective in limiting the passage of Hg and Pb to milk and because mothers can have choices and select food (unlike dairy animals), breast-fed infants are probably safer than formula-fed infants.

Attenuation of infant exposure to mercury and lead during nursing

Maternal fish-mercury consumption

Reducing maternal MMeHg contamination may occur by removing Hg from foods or by avoiding the consumption of fish and seafood. There is limited research on Hg removal from foods. Roh *et al.* (1975) unsuccessfully attempted to use thiolated aminoethyl celluloses and reduced human hair to remove mercuric chloride added to milk. Detoxification of naturally occurring MMeHg in fish was proven ineffective by industrial (Aizpurua *et al.* 1997) and common cooking methods (Armbruster *et al.* 1988; Morgan *et al.* 1997; Chicourel *et al.* 2001). However, food preparation factors, such as increased cooling time and loss of moisture and fat, can increase Hg concentrations (Morgan *et al.* 1997). Burger *et al.* (2003) demonstrated that fish-Hg levels could increase from 45 to 75 % due to weight loss in deep-frying. Despite its lipid solubility, MMeHg is found in fish-muscle protein structures. As a consequence, the removal of fish skin and fat does not affect MMeHg but it will reduce total lipophilic OCP in this kind of food. Therefore, in most studies, reducing the consumption of fish is recommended to decrease maternal exposure to MMeHg (Oken *et al.* 2003).

Indeed, reduced fish consumption is effective in lowering its specific biomarker (hair-Hg). In Hong Kong, vegans who had not consumed fish, shellfish or meat for at least 5 years showed very low hair Hg concentrations when compared with other adults (Dickman *et al.* 1998). Also, switching to a vegetarian diet was effective in lowering hair-Hg in Sweden (Srikumar *et al.* 1992*a*,*b*). Therefore, health specialists have proposed the introduction of fish intake guidelines. The bioaccumulation of Hg at the top of the aquatic food chain is due to fish-feeding strategies, and aquatic organisms that reside at the top of the food chain, such as predatory fish or larger marine mammals, tend to have high Hg concentrations. Thus, the guidelines could recommend a reduced ingestion of these fish and mammals. Alternatively, the guidelines could suggest choosing to eat non-predatory aquatic species. In the case of farmed fish, the ultimate MMeHg concentration depends on the fish feed used. Farmed salmon has been shown to have higher Hg concentrations than wild salmon (Easton *et al.* 2002). Effective guidelines that aim to diminish Hg body load by decreasing fish consumption should also take into consideration that some protein sources may come from animals raised on fishmeal rations. Hg concentrations increase in products (dairy, eggs, pork and poultry) coming from animals raised on fishmeal rations (Sell *et al.* 1975). Farming practices of industrialised countries are increasingly using animal by-products as ingredients fed to animals used as food for human consumers (Dorea, 2004). Therefore, the consumption of such animal products may result in a higher exposure to organic Hg than eating fish (from the bottom of the food chain) twice weekly as recommended.

Reducing fish consumption may curb contamination by MMeHg and OCP, but it may also lead to the reduction of essential nutrients that are important for fetal and infant development. Indeed, for some native populations, curtailing fish consumption may disturb their balanced survival strategy (Dorea, 2003). There are population groups in tropical countries that depend heavily on cassava as an energy source. As a consequence, they are exposed to naturally occurring cyanogenic glucosides. In African populations, insufficient protein intake increases the toxicity of cyanide derived from incompletely processed cassava, thereby causing toxic ataxic neuropathy. Efficient cassava-processing methods and the abundance of game and fish protein in the Amazon have been credited with the absence of neurotoxic diseases associated with cassava consumption (Dorea, 2003).

Clarkson (1995) has suggested two mechanisms for the attenuation of naturally occurring MMeHg in consumed fish. Raised plasma amino acids from fish protein may increase levels of leucine, methionine, phenylalanine and other large neutral amino acids that might inhibit MMeHg entry into the brain. Also, defence mechanisms may operate in circumstances of chronic exposure to naturally occurring fish-MMeHg. For example, the enterohepatic cycle favours the conversion of MMeHg to In-Hg, thereby facilitating Hg depuration. Clarkson & Strain (2003) discussed nutrients (i.e. DHA, I, Fe, choline) in fish with potential roles to modify the toxicity of MMeHg in fish-eating populations. Recently, Passos *et al.* (2003) suggested that an increased consumption of fruits could decrease the Hg burden of the fish-eating populations of the Brazilian Amazon.

Conscientious mothers are capable of choosing balanced diets by selecting food items within food guidelines that help abate the exposure to Hg from predatory fish species. Such efforts, however, may be undermined by the consumption of products from animals raised on fishmeals.

Dental amalgam fillings

Amalgam placement and removal and Hg exposure during pre- and postnatal periods have been studied. Vimy *et al.* (1990, 1997) have suggested that the placement and removal of amalgam in pregnant and lactating mothers could subject fetuses and neonates to exposure risks. Lindow *et al.* (2003) reported that fetal hair-Hg was significantly higher in babies when their mothers had amalgam restoration procedures performed before or during pregnancy. Oskarsson *et al.* (1996) found that, in Swedish mothers, Hg from amalgam fillings was the main source of Hg in milk. Contrary to these results, several studies have concluded that amalgam work on pregnant and breast-feeding mothers poses no threat to fetuses and infants. Drasch *et al.* (1998) compared Hg in breast milk with that in formula and concluded that, even for mothers with large numbers of dental amalgam, these fillings should pose little danger to breast-feeding infants. It has been shown that the amount of Hg released from dental amalgam is minimal. Indeed, during the first 2 months, it is uncertain if any correlation between milk-Hg concentrations and maternal amalgam filling exists (Drexler & Schaller, 1998).

Studies have concluded that Hg exposure in breast-fed babies from maternal amalgam is of no significance to fetal and neonatal Hg in blood (Drexler & Schaller,

1998), and that newly made tooth fillings during pregnancy had no influence on Hg concentrations of newborns (Stoz *et al.* 1995). In addition, Jones (1999) estimated that 490 amalgam surfaces in an individual's mouth would be necessary to give off enough Hg vapour and ionic Hg to meet maximum exposure guidelines. The worldwide use of amalgam in dental practice for 150 years has not yet been associated with health effects in breast-fed infants.

Abatement of environmental sources of maternal exposure to lead

Contaminated air, water and food are major sources of Pb exposure that can be improved. In industrialised countries, the removal of Pb from petrol and from solder used in food cans has greatly reduced Pb exposure, which may be reflected in a decline in blood-Pb during the last two decades (Ducoffre *et al.* 1980; Annest *et al.* 1983). Although the abatement of environmental sources of contamination can be achieved, the removal of Pb from tap water depends on water composition and initial Pb content and speciation (Gulson *et al.* 1997). According to Gulson *et al.* (1997), control of the filtering efficiency of Pb depends on several factors. However, these may have no relevance when examined for practical use, especially when considering their impact on human health.

Pb has been found in various food and food-related items. A recent study associated elevated blood-Pb with traditional game consumption, reflecting a legacy of using Pb-containing ammunition (Hanning *et al.* 2003). In Sweden, a significant decrease of Pb concentrations in hair was reported in hypertensive (Srikumar *et al.* 1992*b*) and healthy (Srikumar *et al.* 1992*a*) subjects who switched from an omnivorous to a lacto-vegetarian diet. Food and utensils used in food preparation are notable sources of maternal Pb contamination. Belgaied *et al.* (2003) showed that Pb is leached from the glazes of some Tunisian earthenware in concentrations high enough to constitute a health hazard. A milk derivative that acts as a leaching agent could carry as much as 1·4 mg Pb in a drink from a mug. Studies in Mexico showed that the use of Pb-glazed ceramics is a positive predictor of maternal blood-Pb (Moline *et al.* 2000; Navarrete-Espinosa *et al.* 2000). Furthermore, Ca supplements may carry significant amounts of Pb (Kim *et al.* 2003).

The abatement of environmental sources of Pb is effective in decreasing human exposure. Observed maternal Pb contamination through Pb-glazed ceramics and Pb-contaminated nutritional supplements are special sources of exposure that can be controlled.

Modulating endogenous lead

In the human body, 90 % of Pb is stored in bone. And, according to Kalkwarf (1999), during lactation, part of the Ca used for milk production comes from bone, resulting in a 3 to 9 % decrease in bone density. Therefore, constitutional and environmental factors (such as hormones and diet) that affect bone turnover are critical to the endogenous availability of Pb during pregnancy and lactation.

Oestrogens play an important role in bone metabolism (Kitai *et al.* 1992) and women taking oral contraceptives benefit from decreased bone turnover (Garnero *et al.* 1995), conservation of bone mineral density (Goldsmith & Johnston, 1975) or even higher mean bone density (Wolman *et al.* 1992). However, the long-term use of oral contraceptives before gestation (Kirksey *et al.* 1979) and during lactation (Dorea & Myazaki, 1998) does not affect concentrations of Ca or P in milk. There is a significant correlation between the C-terminal parathyroid hormone-releasing protein and Ca concentration in milk (Seki *et al.* 1997; Uemura *et al.* 1997).

With the exception of teenage motherhood and conditions such as familial hypophosphataemia and hyperparathyroidism during lactation, environmental or constitutional variables do not consistently affect Ca and P concentrations in breast milk (Dorea, 1999). Nevertheless, constitutional and environmental modulators of bone metabolism (Pb storage and release) during lactation need proper consideration. Changes in breast-milk Ca can disturb Ca:Pb ratios. But, there are additional factors that can affect bone-Pb release and availability during lactation. Dietary options, such as vegetarianism, may (Dagnelie *et al.* 1992) or may not (Finley *et al.* 1985; Specker, 1994) affect milk Ca. In vegetarian mothers, dietary Ca intake (486 mg/d) and vitamin D status are low (Specker, 1994). Also, in situations of adverse Ca metabolism, bone mineral status decreases. Lactating adolescent mothers displayed decreased bone mineral status after 16 weeks of lactation (Chan *et al.* 1982). Lactating Nepalese mothers consuming a diet with 42 % less Ca than US mothers had greater bone turnover (urinary hydroxyproline) than their US counterparts (Moser *et al.* 1988). Temporal patterns of bone-Pb contribution to blood-Pb coincide with seasonal changes, suggesting that bone turnover could be higher in the winter months (Rothenberg *et al.* 2001; Oliveira *et al.* 2002). An annual variation in blood-Pb has been reported (Moore *et al.* 1982), but a seasonal influence on bone-Pb was seen only in prenatal blood-Pb (Rothenberg *et al.* 2001). Seasonal differences were shown to affect plasma vitamin D in mothers (Prentice *et al.* 1997) and infants (Dawodu *et al.* 2003). In addition, maternal vitamin D supplementation can affect both maternal and infant bone metabolism (Cancela *et al.* 1986).

Because breast-milk Pb concentrations are greatly influenced by maternal bone metabolism (Sowers *et al.* 2002), it may be possible to blunt 'endogenous' bone-Pb release by supplementing osteoactive nutrients (Pires *et al.* 2002). The consumption of milk products and use of Ca supplements have been associated with both reduced blood-Pb levels in pregnant women (Farias *et al.* 1996) and with lower patella-Pb content in lactating women (Hernandez-Avila *et al.* 1996). Mothers treated for Pb burden with calcium phosphate and ascorbic acid had a 65 % decrease in urine 5-aminolevulinic acid and a 15 % decrease in milk Pb concentration (Altmann *et al.* 1981). The interaction of dietary protein and bone metabolism has been further discussed by Massey (2003). Though it has been shown that an 'excess' of dietary protein affects bone metabolism while low-protein nutrition can affect toxicity outcome (Chapman &

Chan, 2000), the specific effect of protein on maternal blood-Pb availability has not yet been explored.

Modulation of infant Pb exposure during pregnancy (*in utero*) and lactation (*ex utero*) may be achieved by the supplementation of osteoactive nutrients that 'blunt' maternal bone-Pb release.

Formula use increases exposure risks

The advantages of breast-feeding outweigh the adverse effects of Hg in the breast milk of fish-eating mothers of developed societies (Grandjean *et al.* 1995*b*). Therefore, it is probably of even greater benefit to traditional communities or countries with limited resources (Dorea, 2003). Although adverse effects due to Pb in breast milk exist, it has been concluded that breast-feeding is a better alternative to formulas (Mushak, 1999; Sinks & Jackson, 1999). Moreover, shifting infant feeding from breast milk to formulas does not guarantee a reduced exposure to neurotoxic substances. It has been recognised that the heavy-metal burden is higher in formula-fed infants than in breast-fed infants (Niessen, 1986). Infant formulas may have higher concentrations of Hg and Pb than breast milk. This may be a reflection of the lack of quality control for Hg and Pb in manufacturing.

Cows' milk, the most utilised source of material in milk diets of non-breast-fed infants, can be a significant source of not only Hg and Pb but also of lipophilic OCP. Cattle feed, especially in affluent countries, often contains significant amounts of fishmeal, a source of bioaccumulated MMeHg and lipophilic neurotoxic substances, and bonemeal, a source of Pb contaminnation (Akayezu *et al.* 1997). Fishmeal is largely used in feeding dairy cows (Yeo *et al.* 2003) to increase milk production and to stimulate increases in DHA, EPA (Gulati *et al.* 2003), and conjugated linoleic acid (Abu-Ghazaleh *et al.* 2002). Dairy cows receiving marine oil supplements may have increased milk-fat conjugated linoleic acid up to more than 300 % above basal values (Chilliard *et al.* 2000). Indeed, Jorhem *et al.* (1991) reported a decrease in the levels of Hg in pig meat and attributed this to decreased fishmeal in the pigs' ration. Another important source of Pb contamination is the salt used in mineral-salt mixtures of cattle feed (Marcal *et al.* 2001). Metal poisoning in cows due to accidental food contamination is frequently reported.

If metal contamination is not high enough to clinically affect the herd, it may pass unnoticed even though it may result in elevated milk Hg and Pb concentrations. A Polish dairy herd, poisoned by Hg, continued to produce contaminated milk until metallic Hg was determined to be the cause of some of their deaths. Even after 4·5 months, milk-Hg concentrations remained high (23 ng/g) and yet the contaminated milk was still consumed by children (Chodorowski *et al.* 2001). Baars *et al.* (1992) found that, during an episode of Pb poisoning, dairy cows consuming about 60 g Pb did not show clinical signs of poisoning for 1 to 4 weeks. Such farming practices may channel Hg and/or fish bioaccumulated lipophilic substances into cows' milk at levels much higher than those found in the breast milk of health-conscious mothers. It is necessary to control the levels of Hg and Pb in dairy animal feed in order to abate both maternal and fetal exposure.

Oskarsson *et al.* (1996) reported higher Hg concentrations in formulas than in breast milk. Krelowska-Kulas (1990) showed that cows' milk in the proximity of a smelter (Krakow, Poland) had Pb concentrations up to ten times higher than in milk produced in agricultural areas distant from industry. Casey (1977) analysed cows' milk and cows' milk-derived infant formulas and found that Pb concentrations in these samples were consistently higher than those found in breast milk. Moreover, higher Pb concentrations in formulas than in breast milk were observed in New Zealand (Casey, 1977), Thailand (Chatranon *et al.* 1978), the UK (Kovar *et al.* 1984; Richmond *et al.* 1993), India (Tripathi *et al.* 1999), Spain (Rodriguez Rodriguez *et al.* 1999; Martino *et al.* 2001), Australia (Gulson *et al.* 2001) and Canada (Hanning *et al.* 2003). In industrial regions of Austria (Styria), the range of Pb concentration (0–20·4 ng Pb/g) in human milk was lower than in formulas (0–35·4 ng Pb/g) (Tiran *et al.* 1994). Furthermore, there was no significant difference in the concentrations of toxic Hg and Pb between vegetarian and non-vegetarian diets of children (Ursinyova & Hladikova, 1998).

It is important to note that during preparation, infant formulas end up over-concentrated (Dorea *et al.* 1988; Lucas *et al.* 1992), which can further elevate metal intake. In Germany, cows' milk-based formulas, already higher than human milk for Pb, sometimes were further contaminated by reconstitution of formula powder with the addition of water containing Hg and Pb (Schumann, 1990). For example, Schumann (1990) demonstrated a 10-fold higher concentration of Pb when using two different water samples. However, the increase in Hg was not of practical importance. Tap water in Graz (Austria) can increase Pb concentrations in formulas by 45 % (Krachler *et al.* 1998*b*). Baum & Shannon (1997) reported Pb concentrations above safety levels in infant formulas that were reconstituted in homes with plumbing over 20 years old. The preparation of infant formula in a Pb-soldered samovar resulted in Pb poisoning (Shannon, 1998). Moreover, if lactose promotes the absorption of Pb (Stephens & Waldron, 1975), then it is a cause for increased concern regarding Pb levels in infant foods prepared or derived from cows' milk.

Modern farming practices that use animal feeds with ingredients high in MMeHg and Pb, such as fish- and bonemeal, can result in dairy products and cows' milk-based infant formulas with higher concentrations than breast milk of health-conscious mothers on habitual diets.

Concluding remarks

It is of public health interest that not only should potentially hazardous substances be kept to a minimum, but also that the unquestionable benefits of breast-feeding (nutrition and psychological bonding) should be advocated. Long-lasting maternal exposure to metals such as Hg and Pb impacts the CNS during fetal development. But it should be noted that the translactational barrier is more effective than the transplacental barrier at preventing the

transfer of these toxic metals to infants. Most studies of fish-eating populations with high intakes of naturally occurring fish-MMeHg are certainly of legitimate concern for some population groups but, so far, no evidence shown has justified the suppression of breast-feeding. Neurological consequences of Hg or Pb in breast milk have been detected only by neurobehavioural tests. Such tests carry no prognostic value for neurological syndromes, at least for Hg. Also, they do not separate prenatal insults of either MMeHg (maternal fish consumption) or endogenous Pb (maternal bone) exposure from postnatal exposure in breast milk. The characterisation of foreign substances as hazardous to nursing infants must take into consideration potential nutritional risks from using alternatives (formula-feeding). Additionally, in the present-day environmental scenario, it is clear that changing breast milk for cows' milk-based formulas increases infant risk of exposure to neurotoxic substances.

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