Pattern of Arsenic Exposure to Children: New born to toddler Stages

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Abstract

Elevated levels of arsenic are found in several countries which exceed the World Health Organization (WHO) drinking water guideline (10μg/L), affecting 100 million people globally. Its prevalence varies in different countries among which Andean Argentina and South-East Asia are most severely affected. Bangladesh is considered a major As-contaminated zone and more than 10μg/L of As is present in the tube wells installed during the last decade. As-contaminated water poses serious threat to the population in general, and children in particular. School-age children exposed to As are found to be deficient in cognitive functions in several countries. Although As contamination is a global phenomenon reports on children's exposure to As, through breast milk pathway is limited. Findings of the few global studies show low level of As in breast milk even in populations exposed to high levels. Several reports indicate the potential counterbalancing the impact of exposures of chemicals through breast milk which outweigh the hazards of feeding contaminated breast milk. On the other hand, the presence of toxic elements in powdered and liquid infant milk is a cause of concern considering the probable health problems in infants. It is surmised from available data that although the lactating mothers resided in highly As-contaminated zones the concentration of the toxic metal is low in the breast milk and breast feeding infants are protected from the toxic effects of As. Therefore breast feeding is still the best way to protect the infants in As-contaminated zones as per WHO recommendations.

1. Introduction

Toxic chemicals present in the environment are accumulated in humans over time. Children also face such unintended risks throughout their growth phase. When risks of such contaminations are assessed during infancy it has to be recognized that children are not small adults; their early postnatal period is characterized by rapid growth and development and has unique metabolic and physiological pathways including a completely different exposure pattern as compared to the adult (Guzelian et al.,1992).The exposure of the mother to chemicals occurs mainly through food and the rate of transfer to breast milk depends on the concentration and pharmacological properties of the toxic chemicals in the serum of the mother (Somogyi and Beck, 1993). While nonpolar lipophilic compounds easily establish equilibrium between blood fat and milk fat (Somogyi and Beck, 1993), metals remain bound to transferrin in the serum (Pizarro et al., 2004). The following definitions have been recommended by WHO (IPCS, 2006) to categorize infants and young children. The neonatal period extends from birth to 4 weeks, infancy from 4 weeks to 1 year and young childhood from 1 year to 5 years. Zhongua et al. (2008) demonstrated that drinking high arsenic water over a long period of time is a risk factor of neonate development and Myers et al. (2010) reported that exposure to arsenic may have a   role in neonatal death in inner Mongolia, China. The focus of the present review is on exposure patterns of arsenic and risk evaluation of arsenic contamination in breast fed children. An attempt has also been made to compare the level of contamination of breast milk and infant formula to assess whether breast feeding is safe in arsenic contaminated zones.

The Pervasive Nature of Arsenic Contamination

Today millions of people are at risk of arsenic exposure and frank manifestation of arsenicosis. Natural contamination by arsenic has been the main source of environmental exposures in populations worldwide (Hopenhayn-Rich,2000). Approximately 15% of the U.S. population obtain their water from private wells (U.S. Geological Survey, 2004), and arsenic concentrations > 10 μg/L have been documented in private wells throughout the United States (Ayotte et al., 2003; Steinmaus et al., 2005). In certain areas people drinking well water may be exposed to arsenic levels ranging from 50 to 90 μg/L, well above the EPA's guideline of 10 μg/L (Mead, 2005). Globally about 100 million people are at risk of exposure to high levels of arsenic and countries where arsenic in drinking water exceeds the acceptable level include Argentina, Bangladesh, Bolivia, Chile, China, Hungary, India, Mexico, Nepal, Peru, Romania, Taiwan, USA and Vietnam (Ng, 2005).

Arsenic Toxicity

Inorganic arsenic compounds contain oxygen, chlorine and sulfur which can exist in trivalent or pentavalent forms. Various epidemiological studies have established a clear association of arsenic contamination with cancer in humans (Chiou et al., 1995).Trivalent forms of As, both inorganic (Hirano et al., 2003) and methylated   (Dopp et al., 2004) are   more toxic than the pentavalent forms. Owing to l6 years or more of latency period of As, it remains in the environment long enough to be absorbed by the biota (Zaldivar et al., 1981). Liver is the major organ for biotransformation and inorganic As at trivalent oxidation state is methylated through the involvement of S-adenosyl methionine. Two metabolized forms are produced which are a) monomethylarsonic acid or MMA and b) dimethyarsinic acid or DMA (Suzuki et al., 2002). Among these two compounds, MMA is found to be more toxic than DMA (Aposhian et al., 2003; Styblo et al., 2000).

Arsenic Exposures of Neonates and Children

Risks and Benefits of Breast Feeding

Studies in school-age children revealed deficiency in cognitive functions in Mexico (Calderon et al., 2001; Rosado et al., 2007), United States (Wright et al., 2006), Taiwan (Tsai et al., 2003) and India (von Ehrenstein et al., 2007). In Bangladesh, children of 6 and 10 years of age, consume high amounts of arsenic in their drinking water, which produces IQ performance deficits (Wasserman et al., 2007). During pregnancy, transplacental transfer of As occurs (Concha et al., 1998) and exposure to high levels during pregnancy results in reduced birth weight (Huyck et al., 2007) and increase in fetal loss (Rahman et al., 2007). Recently, however, Tofail et al. (2009) could not detect any significant effect of As exposure during pregnancy on infant development in Matlab, Bangladesh although Rahman et al. (2009) detected negative effect on birth size at low level of As exposure.

Breast feeding has substantial benefit and despite the concentrations of chemicals found in human milk, no major studies have demonstrated that these chemical concentrations lead to adverse health outcomes in breast fed children (Sonawane, 1995). Breast milk provides passive protection against infections during lactation and also stimulates the immune system of the infant with several long term positive effects (Hanson, 1998; Goldman, 2007) besides being an unsurpassed natural nutrition to the newborn and the infant (Jackson and Nazar, 2006). It is amply evidenced that colostrum and mature human milk have significant lethal effect on *Entamoeba histolytica* and protect from its infection in breast fed children (Akisu et al., 2004). The concept of the immune system in human milk emerged in the 1970s and later expanded to include not only antimicrobial but also anti-inflammatory and immunoregulatory agents (Goldman, 2007). There are reports on the absence of association of negative effects on exposure to organochlorine compounds (LaKind et al., 2000; Ribas-Fito et al., 2003) while several other reports indicate the potential counterbalancing the impact of exposures of these chemicals through breast milk (Boersma and Lanting, 2000; Hooper and She, 2003;   Ribas-Fito et al., 2003; Arendt, 2008). Evidences from studies of 32 mothers and their children in a province of Thailand establish that arsenic exposure during pregnancies harbored gene expression changes leading to cancer and other diseases later in life (Fry et al., 2007).

As the breast-feeding child grows up into a toddler typical "child-behaviors" are demonstrated such as hand-to-mouth movement, touching and tasting (Freeman et al., 2001). Yost et al. (2004) reported the mean dietary intake of 3.2μg of inorganic arsenic/ day in US children which came from milk, fruit and fruit juices, rice, grain, rice products and grain products.   In the living zone or micro environment of the child it is unable to sense or understand the danger of contamination. Moreover, owing to their rapid growth phase they have a dynamic developmental physiology demanding increased nutrient and energy requirements. One of the constituents of breast milk is fat which is derived from the mother's body. Adipose tissue is a natural repository of lipid soluble toxicants such as the organochlorines (Grandjean et al., 1995) thus the developing baby is exposed to such chemicals from their mother's body during pregnancy to weaning. Understandably, pregnant and breast feeding women are especially concerned, because the myriad chemicals present in the food can become concentrated in the breast milk.

Arsenic Residues in Human Milk - Monitoring Studies

Breast milk is the natural food containing the optimal balance of fats carbohydrates and proteins for infants meeting nutritional needs, and also provides a range of benefits for growth, immunity and development (Landrigan et al., 2002). Breast milk is also a unique pathway for the mother to child transfer of toxic heavy metals. The origin of metals in the breast milk is exogenous as evidenced by the reports on the environmental presence of arsenic. The level of metal contamination is expressed in terms of ppb or μg/L of breast milk instead of fat because metals are not lipophilic and remain bound to transferrin. There are only a few reports on arsenic contamination of human milk. In a study (Concha et al., 1998) with lactating mothers, exposed to arsenic through their drinking water (~ 200μg/L), low concentrations of arsenic in the range of 0.83-7.6 μg/kg (equivalent to 0.83-7.6 ppb) were recorded in 10 subjects. In a worldwide study conducted to assess the level of contamination of breast milk covering six countries (Guatemala, Hungary, Nigeria, Philippines, Sweden, Zaire)

various metals were detected at ppb concentrations (Table 1) where median arsenic value was found to be 0.3 ppb with a range of 0.1-0.8 ppb (WHO 1989), while Cd, Pb and Sb were reported in twenty six countries (Patriarca et al., 2000).

Besides the arsenic-high zones, such as Bangladesh and West Bengal, India, arsenic in the breast milk is found in various other countries. In Turkey, Izmir is a land of long extinct volcanoes, where Ulman et al. (1998) demonstrated arsenic concentration in the breast milk (4.219±0.079 µg/L/ ppb) not much different than what is present in the cow's milk (4.932±0.038 µg/L / ppb). Thus the children, either fed with breast or cow's milk, are equally exposed to arsenic contamination, although the level of contamination is not deleterious. In Munster, Lower Saxony, Germany, Sternowsky et al. (2002) conducted a study in a military training area where chemical weapons are dumped after the Second World War. More than hundred samples of breast milk collected from three different regions, Hamburg city, rural area of Soltau and Munster the potentially contaminated area, and analyzed for arsenic reveals that 156 out of 187 samples tested had arsenic contamination below 0.3µg/L (0.3 ppb) whereas the highest concentration of 2.8 µg/L (2.8 ppb) is in the breast milk sample collected from Soltau. From these findings the daily intake of arsenic by the breast fed infant is calculated and found to be 0.02-0.06 µg/kg body weight (bw) and even in the samples from women living in previously arsenic contaminated region, concentration of arsenic in breast milk is within the reported safety limits (WHO Permissible Limit 15µg/kg bw/week). In several other countries too breast milk samples tested positive for arsenic contamination (Table 2). Table 3 depicts the study of Concha et al. (1998) highlighting how arsenic was partitioned in blood, urine and breast milk. On analyzing the data it is abundantly clear that arsenic is present in the breast milk at very low concentrations as compared to both blood and urine. The data also indicate that arsenic is mainly cleared through the urine quite rapidly (Table 3) thus saving the breast fed infant from high arsenic exposures. Some toxic metals have been reported in breast milk (Concha et al., 1998). Since metals do not bind to fat the breast milk pathway was not considered to be significant in respect of metal accumulation (Golding, 1997). However, the presence of toxic metals in the breast milk suggests pathway exposure and also presents breast milk arsenic as a probable indicator of prenatal exposure (Oskarsson et al., 1995).

Very few breast milk monitoring studies are on record in the Indian subcontinent. One of the earliest studies was reported in Central India (Dang et al., 1985) where breast milk is analyzed for the presence of several metals in a group of 86 economically weak women who hailed from a tribal group residing either in rural or urban regions. Among the 86 samples of breast milk collected 0.73 ng As/g colostrums is found in the tribal group in contrast to 0.5 ng As/g in 19 urban women. Another study in a Steel Plant Township situated in Bhilai, Madhya Pradesh, India (Sharma and Pervez, 2005) revealed that in general, the concentration of toxic elements is higher in the blood than in the breast milk of the 120 subjects tested. Sharma and Pervez (2005) also noted higher levels of As in the blood samples as compared to breast milk samples in the study. From the above data it is obvious that Steel plant workers have higher presence of toxic metal in their breast milk; Mn, Pb, Hg have higher tendency to associate with blood and breast milk than As and Cd and the order of toxic metals in blood and breast milk is : Mn > Pb > Hg > As > Cd (Table 4). Watanabe et al. (2003) reported up to 38µg/L or 38 ppb arsenic in breast milk in a small group of seven women in Bangladesh. Among infants who are exclusively breastfed, urine levels did not exceed 19 µg/L inorganic arsenic and its metabolites, whereas infants who received infant formula prepared with local drinking water in addition to some breast milk had urine levels up to 1,100 µg/L or 1100 ppb. This clearly demonstrates that arsenic exposure through breast milk pathway is not as alarming as through other pathways.

Samanta et al. (2007) conducted a seminal survey on lactating women in arsenic affected areas of West Bengal, namely three blocks of North 24 –Parganas, one of the worst arsenic affected districts in West Bengal, India. The body burden is assessed in urine, hair and nail of the 226 lactating subjects and correlated with the load of arsenic in their drinking water. Ninety nine percent of the water samples had arsenic much above (220 µg/L) the WHO recommended level of 10µg/L. The normal rate of arsenic excretion through urine is 5-40 µg/day, through hair 0.08-0.25 mg/kg (1.0 mg/kg indicated toxicity) and through nail 0.43-1.08 mg/kg. In the breast milk samples of 39 subjects the mean arsenic concentration is 19.6 µg/L (19.6 ppb) as compared to the control levels of 2.5 µg/L (2.5 ppb). Infants are exposed to toxicants via breast milk, at the same time, they are exposed to arsenic through water and food.. In the Andean population exposed to arsenic through drinking water, 3µg/kg (3 ppb) is the median concentration in the breast milk sampled in 27 subjects with a range between 1.9-5.5 µg/kg or 1.9-5.5 ppb (Concha et al., 1998). Contrastingly in the Bangladesh study the range is higher. The various information gleaned from these monitoring studies suggest that mother's exposure to arsenic is owing to the contaminated food and water ingested and a fraction of it is reflected in the breast milk which is a major source of arsenic to the suckling infant. Moreover, it may be concluded from these studies that children are vulnerable to higher arsenic exposure, as evidenced by the arsenic concentration in the urine of the infants, when their mothers have a higher body load of arsenic (Watanabe et al., 2003).

Arsenic Metabolites in Breast Milk

It has been reported that the major form of the arsenic transferred via placenta is dimethylarsinic acid, although the mechanisms responsible are unknown (Concha et al., 1998). Human breast tissue contain entirely inorganic arsenic mainly in trivalent form   although in a very low dose and methylated arsenic metabolites in blood plasma are not known to   easily pass into the mammary gland. Fängström et al. (2008) analyzed inorganic arsenic and expressed as the sum total of the arsenic metabolites (iAs, MMA, DMA) in breast milk (1.0 µg/L or 1 ppb) and urine (1.2 µg/L or 1.2 ppb) from ninety eight three month-old infants. Moreover, the urine concentration of arsenic in the breast fed infants is significantly lower than those who are non-exclusively breast fed. There is also a significant association between infant urine and breast milk. It is concluded that a) breast milk contains, almost entirely, mainly trivalent form of   iAs; b) methylated arsenic metabolites in blood plasma do not easily enter the breast tissue and c) arsenic concentration in breast milk is negatively correlated with % DMA and positively correlated with % iAs in maternal urine. Highly efficient methylation of iAs thus leads to less arsenic excretion in human breast milk (Fängström et al., 2008)

Probable Pathway of Biotransformation of Arsenic
Liu et al. (2004) suggested that trivalent arsenic metabolite is protonated at physiological pH, passes via aquaglyceroporins, and the main transporters of As (III), to the mammary gland during lactation (Matsuzaki et al., 2005).Results also indicate that breast milk: plasma ratio is about one for iAs, corroborating other evidences (Gamble et al., 2007**)**. An efficient methylation is also found to occur in the infants (Fängström et al., 2008) with very high, 87-89% DMA, in the exclusively breast fed infants and MMA, which poses greater risk is only 2.3% compared to 10 % in the studied mothers (Vahter, 2002). A recent study brings to the fore that the mother's strong metabolism helps get rid of most of the harmful form of arsenic during breast feeding; furthermore during weaning the infants become more susceptible to the toxic effect of arsenic (Fängström et al., 2009).

Advantages of Breast Feeding against Infant Formulas
A declining rate of breast feeding and aggressive marketing of breast milk substitutes had blurred the distinction between breast milk and formula (Walker, 1993), although it was reported that infant formula may shorten the duration of breast-feeding and hasten the age at which solid foods are introduced (Bergevin et al., 1983). Moreover, infant formula may not be free from contamination of metals such as Cd (Jedrzejczak and Szteke, 1991), As (Krachler et al., 2000) Pb (Navarro-Blasco and Alvarez-Galindo, 2005), Al (Navarro Blasco et al., 2005a, b). Garg et al. (1993) compared the concentrations of various trace elements in human breast milk and infant formula and As, Cd and Hg were higher in the infant formula. The Joint Food Safety and Standards Group, Ministry of Agriculture Fisheries and Food, UK (1999) published relevant information on the level of elemental concentrations of several trace elements in infant foods including infant formula and breast milk (Table 5). An estimated daily intake further revealed (Table 6) dietary exposures of infants to metals from various types of infant formulae (Gregory et al., 1995). A series of milk samples were compared with infant formulae wherein several trace elements (Ag, Al, As, Au, Pt, Se, Ti, Co, Cr, Cu, Fe, Mn, Ni and V) levels were found to be significantly influenced by the quality of tap water used for preparation (Prohaska et al., 2000). Results of a study suggest that soy-based powder infant formulas generally have higher levels of toxic elements than milk based powder formulations (Ikem et al., 2002). More recently Ljung et al. (2011) have clearly demonstrated that concentrations of the essential elements were from ten to hundred times the intake of the breast fed infant, levels that may be associated with adverse health effects. They further found that one portion of infant food also provided more arsenic than one feeding of breast milk. Jackson et al. (2012) concluded from their analyses of 15 infant formulas of five main brands that although As is present in relatively low concentrations (1-23 ng/ g), these levels are of because As is present in more toxic inorganic form.

It has been documented earlier that a significant decline in mortality due to chronic arsenic exposure of late fetal, neonatal and post-neonatal occurred in Chile over a study period of 1950-1996 (Hopenhayn-Rich et al., 2000). Breast feeding is recommended by WHO in spite of several reports of breast milk contamination by toxicants and also infectious agents (Pronczuk et al., 2002). Devanathan et al. (2009) reported a decline in the levels of DDT and HCHs implying the effects of various bans and restrictions on their usage in Kolkata, Mumbai and New Delhi. Unlike the persistent organic pollutants (POPS) metals do not bind to fat and so do not usually accumulate to higher concentrations in breast milk than in blood (Golding, 1997); Arsenic as a water pollutant thus poses lesser risk to the breast fed infants. However, regional differences exist in levels of xenobiotics in breast milk owing to historical and current local use patterns (Solomon and Weiss, 2002). Even in high arsenic contaminated areas there are unquestionable advantages of breast feeding such as : i) breast fed babies have lower rates of some serious chronic diseases : asthma, diabetes and some childhood cancers ; ii) breast feeding reduces the risk and severity of communicable diseases : pneumonia, diarrhea, ear infections ; iii) women who breast feed have lower levels of ovarian and breast cancer; iv) breastfed daughters also have lower rates of breast cancer when they grow up; v) breast feeding may reverse some of the damage caused by chemical exposures in

the womb (IPCS, 2006). Targeting breast feeding to diminish chemical exposures is detrimental to the vulnerable developing organism, because it risks limiting acquisition of much needed nutrients and it deprives infants of breast feeding benefits essential to counteract neurotoxic effects arising from prenatal exposure (Dorea, 2007). Last but not the least, As is not excreted in breast milk to any significant extent. WHO's global public health recommendation of exclusive breast feeding of infants for six months to two years or even beyond should be made mandatory in all countries for the safety of the child, *in utero*, post-natal and also in the adult life of the girl child.

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Table 1: Metals present in human breast milk around the world *

Metal Type	Median value (ppb)	Concentration Range (ppb)
Arsenic	0.3	0.1-0.8
Cadmium	0.1	0.1-3.8
Lead	5.0	0.1-41.1
Manganese	18.0	7.0-102.0
Mercury	2.7	0.64-257.1

* WHO, 1989

Table 2: Arsenic levels found in human breast milk samples collected in several countries

Country	Number Samples	Median Level (µg/L)	Reference
Guatemala	26	0.29	Parr et al. 1999
Hungary	6	1.78	Parr et al. 1999
Philippines	14	18.9	Parr et al. 1999
Sweden	8	0.55	Parr et al. 1999
Zaire	20	0.26	Parr et al. 1999
Argentina	10	2.3	Concha et al. 1998
Bangladesh	14	12.0-38.0	Watanabe et al. 2003
Mumbai, India	25	0.8	Dang et al. 1983
N-24 Parganas, India	226	17.0	Samanta et al. 2007

Table 3: Arsenic partitioning in selected body fluids in an Andean population *

Condition	No. of Subjects	Blood-As (µg/L)	Urine-As (µg/L)	Breast Milk-As (µg/L)
Before delivery	11	11	35	.
2.8 weeks postpartum	10	11	234	3.4
2.5 weeks postpartum	8	15	255	2.8
4.4 weeks postpartum	9	16	301	3.4

* Concha et al. 1998

Table 4: Arsenic content in human breast milk (M) and blood (B) samples in a steel plant environment (India) (data expressed as ± Standard deviation; BDL- below detection limit)*

Sample source	Age group (years)	Number of Subjects	Blood - As (µg/L)	Milk-As (µg/L)	B/M ratio
Steel plant workers	20-25	5	1.6 ± 0.8	0.9 ± 0.2	1.9
	25-30	10	3.4 ± 2.3	1.7 ± 1.2	2.0
	30-35	9	6.2 ± 3.1	3.4 ± 2.3	1.8
	35-40	12	9.2 ± 4.8	4.5 ± 3.2	2.0
	40-45	4	10.8 ± 3.9	5.2 ± 3.8	2.1
Non-worker residents in the area of the steel plant	20-25	8	0.9 ± 0.3	0.4 ± 0.1	2.0
	25-30	7	2.4 ± 1.9	0.9 ± 0.7	2.8
	30-35	11	3.7 ± 3.0	1.8 ± 0.3	2.1
	35-4	9	4.5 ± 2.2	2.3 ± 1.0	1.9
	40-45	10	6.6 ± 1.6	3.2 ± 2.2	2.1
Subjects 100 km away from any industrial unit	20-25	5	0.1 ± 0.0	BDL	-
	25-30	6	BDL	BDL	-
	30-35	10	BDL	BDL	-
	35-40	9	0.2 ± 0.1	0.6 ± 0.1	0.3
	40-45	5	0.3 ± 0.1	0.9 ± 0.2	0.3

* Sharma and Pervez, 2005

Table 5: Mean Concentration of various elements analyzed in Milk formulae (MF) solids * (mg/kg)

MF	No of Samples	Al	As	Cd	Cr	Cu	Pb	Hg	Ni	Sb	Se	Sn	Zn
Dried all	21	1.3	**.006**	.003	.07	3.0	.006	.004	.07	.0025	.08	.03	43
Dried (excluding Soya)	18	0.7	**.005**	.002	.066	2.6	.005	.004	.04	.0013	.075	.027	41
Dried (Soya only)	3	4.5	**.01**	.012	.08	3.4	.012	.004	.23	.0097	.14	.034	52
Ready-to-feed	3	0.08	**.001**	.0004	.04	.36	.0015	.002	.02	.0008	.02	.004	6.4
All	24	1.1	**.005**	.003	.07	2.6	.005	.004	.06	.002	.08	.025	3.8

* Joint Food Safety and Standards Group, Ministry of Agriculture Fishers and Food, UK (1999)

Table 6: Estimated dietary exposure of infants to metals from cows' milk and soya-based formulae and commercially available infant foods *

Metal	Intake from cows' milk-based formula and commercially available infant foods (mean intake -µg/kg bodyweight (bw)/day)				Intake from soya-based formula and commercially available infant foods (mean intake -µg/kg bw/day)			
	0-3[a]	4-6[a]	7-9[a]	9-12[a]	0-3[a]	4-6[a]	7-9[a]	9-12[a]
Aluminium	14	142	175	177	82	242	222	218
Antimony	0.02	0.08	0.15	0.15	0.18	0.25	0.21	0.20
Arsenic	**0.09**	**1.3**	**1.8**	**1.8**	**0.18**	**1.6**	**2.0**	**1.9**
Cadmium	0.04	0.35	0.61	0.64	0.22	0.57	0.68	0.72
Chromium	1.2	2.9	3.6	3.6	1.5	3.3	3.7	3.7
Copper	41	72	78	76	62	98	82	81
Lead	0.08	0.37	0.51	0.52	0.22	0.56	0.59	0.61
Mercury	0.07	0.18	0.18	0.19	0.07	0.19	0.19	0.20
Nickel	0.7	4.2	5.8	5.9	4.2	8.4	7.6	7.9
Selenium	1.3	2.2	2.2	2.1	2.5	3.5	2.6	2.6
Tin	0.57	4.6	18.6	18.5	0.62	4.7	19.7	20.1
Zinc	756	1262	1089	1062	946	1503	1148	1128

a-Age range in months; *Gregory et al. 1995