EnvironmentAsia
The international journal by the Thai Society of Higher Education Institutes on Environment

EnvironmentAsia 13(3) 2020 26-35
DOI 10.14456/ea.2020.39
ISSN 1906-1714; ONLINE ISSN: 2586-8861

Effect of Copper Concentration on Lead and Cadmium Bioavailability in Children Age 9 to 15-Year-Old in Zinc Contaminated Areas

Tippawan Chaiwong[1], Pramote Loeskhampom[2], and Sanhawat Chaiwong[3*]

[1] *Emergency Room Department, Dok Kham Tai Hospital, Phayao, Thailand*
[2] *Tak Provincial Health Office, Tak, Thailand*
[3] *School of Public Health, Walailak University, Nakhon Si Thammarat, Thailand*

Corresponding: sanhawat.ch@wu.ac.th
Received: April 3, 2020; Revised: April 25, 2020; Accepted: June 24, 2020

Abstract

This study determined the levels of specific trace elements in the urine of children aged 9 – 15 years old in zinc-contaminated areas and studied the simultaneous presence of certain elements influenced the bioavailability of lead and cadmium. Urine samples of 736 children living in three sub-districts of Tak province, including Prathadpadeang, Mae Tao, and Mae Ku, were investigated with inductively coupled plasma mass spectrometry to determine levels of zinc (Zn), copper (Cu), iron (Fe), lead (Pb), and cadmium (Cd). The results showed that 43.0% of children lived in Mae Tao sub-district. The body weight of the subjects at birth was < 3,000 grams, and they were underweight as per body mass index. The difference in Cd level in urine (UCd) between 13-15 years old and 9-12 years old was statistically significant. Furthermore, statistically significant differences were observed in levels of Cu level in urine (UCu) and Pb level in urine (UPb) based on the gender of the subjects. UCd and UPb levels were higher compared to other trace elements in older children and female/male (SRM 2670:NIST). In contrast, UCu and UZn levels were low. Stepwise regression analyses indicated that Cu concentration was a dominant factor influencing the availability of Pb ($r^2 = 0.25$) and Cd ($r^2 = 0.16$) in human body as follows: Lead availability = 0.295 + 0.304 Cu + 0.256 Fe + 152 Zn, Cadmium availability = 0.050 - 0.079 Cu + 0.057 Fe + 0.395 Zn. Our study concluded that Cu levels were low in children aged 9-15 years old, which could have led to accumulation of Cd and Pb in their bodies.

Keywords: Trace elements; Lead and cadmium bioavailability; Age 9-15 years old; Tak; Zinc mining

1. Introduction

Mae Sot district is located in the Tak province, a mountainous area between northern Thailand and Myanmar (Padungtod *et al.,* 2006). Prathadpadeang is a sub-district where zinc mining and processing from sulphide ores potentially harms the environment (Ripley *et al.,* 1996). Many minerals are associated with complications and variations in chemical compositions due to the isomorphic substitution of chemical elements within their lattices. The same mineral can accordingly present different formulations, as in the case of sulphides. Its and their related minerals, such as pyrite (FeS_2), chalcopyrite ($CuFeS_2$), and sphalerite (ZnS) also contain lead (Pb) and cadmium (Cd). These have significant industrial value, contributing to the major ores such as copper (Cu), zinc (Zn), iron (Fe), lead (Pb), and cadmium (Cd) (Wenk and Bulakh, 2004). Non-essential toxic (Cd and Pb) and essential (Cu, Zn, and Fe) metals are trace elements and by-products obtained on refining sphalerite (Winiarska-Mieczan, 2014). These elements are released into the environment through irrigation via the Mae Tao creek, which is the source of water supply for the adjoining agricultural areas (Chaiwong *et al.,* 2009). In addition, human beings may also be exposed to these elements through the food chain: soil-plant-animal-man (Bradstreet *et al.,* 2003). This could be attributed to contamination of the soil, which is transferred to plants grown in the areas. Cd levels found in the soil from contaminated areas ranged from 1.13-94.00 mg Cd/kg. The permissible standard for Cd in the soil in Thailand is 0.15 mg Cd/kg soil (Padungtod *et al.,* 2006). Hellstrom *et al.* (2007) showed that consumption of locally grown vegetables, plant products, and root crops were an important pathway of exposure to heavy metals. A study by Suwatvitayakorn *et al.* (2019) explained that the level of Cd in locally grown rice was on an average 1.5 times higher than in rice grown in downstream areas. Trace elements can potentially cause diseases through deficiency, imbalance, or toxicity. Trace mineral deficits usually develop in cases of inadequate dietary intake or due to metabolic disturbances caused by antagonistic or synergistic activities between metals (Harraki *et al.,* 1995; Goldhaber *et al.,* 2003).

Among the essential elements (Fe,Cu and Zn) are involved in the functioning of several enzymes, and are essential for maintenance of health throughout life, whereas Pb and Cd are non-essential toxic metals (Delves, 1985; Papagiorgiou *et al.,* 2002; Wenk and Bulakh, 2004). Excessive intake of Zn can interact with other minerals and lead to imbalances in micronutrient status. Zn has been shown to interact with Cu and Fe (Reeves and DeMars, 2004). Zn and Cu demonstrate strong antagonism as they compete for the same site of absorption (Sandstead, 1994; Fosmire, 1990). These elements are related to metallothionein (MT) produced to response essential element and heavy metals but is not change the intracellular copper that result to inhibit to copper uptake to intestinal cell absorption (Sandstead, 1995; Cox and Moore, 2002).

The reduction in Cu level due to increased intake of Zn can also lead to Fe deficiency in humans (Arredondo *et al.,* 2006). It may be affected with copper deficiency through influencing the absorption, storage, and transportation of iron as copper helps intestinal iron absorption by acting through a copper dependent – ferroxidase, hephaestin (Hp), positioned in the duodenal enterocyte (Harvey and Harry, 2008; Wang *et al.,* 2010). Hegazy *et al.* (2010) reported that serum Fe and ferritin levels were considerably lower in individuals with high serum levels of Pb and anaemia than in individuals with low Pb level. In children, low serum levels of Zn and Cu could be considered as factors contributing to iron deficiency anaemia (IDA) due to known synergistic interactions of Fe and Zn in haemoglobin synthesis and erythropoiesis (Gibson *et al.,* 2008; Angelova *et al.,* 2014). In addition, the association should be considered due to inclusion of the Cu-containing enzymes ceruloplasmin, Hp, ferrochelatase, and cytochrome-c oxidase in Fe metabolism, formation of haemoglobin, and haematopoiesis (Olivares *et al.,* 2007). Meltzer *et al.* (2016) reported the presence of divalent metals, particularly Cd^{2+} and Pb^{2+}, in smoking and non-smoking women with low levels of Fe in their bodies. The quantity of these metals in women who smoked was significantly higher than in those who did not smoke. However, the difference in gender could be a factor associated with the higher occurrence of low levels of serum ferritin in women, causing higher uptake of Cd (Olsson *et al.,* 2002). Swaddiwudhipong *et al.* (2007) showed that urinary levels of Cd (UCd) were higher among women and increased with age. A similar study by Chaiwong *et al.* (2013) reported that the levels of UPb and UCd were higher in female than in male based on age.

Hence, this study examined Zn, Cu, Fe, Pb and Cd in urine of children aged 9-15 years old who living in three sub-district exposed to high concentration of zinc. Of particular interest is the relationship among Zn, Cu, Fe and effected on bioavailability of Pb and Cd

2. Materials and Methods

2.1 Study design and population

This cross-sectional study was performed in three sub-districts, namely Mae Tao (villages 1-6), Prathadpadeang (villages 1, 3, and 4), and Mae Ku (villages 6-8). Direct drainage of wastewater from the aforementioned villages into the Mae Tao creek have resulted in critical environmental pollution (high levels of Pb and Cd) and subsequent human health complications (Chaiwong *et al.,* 2009) (Figure 1).

Morning urine samples of 736 children were collected to investigate the levels of Zn, Cu, Fe, Pb, and Cd. The survey divided the children based on age into 2 groups as:

1) 9-12 years old (children born between 1 December 2006 and 1 January 2009) and

2) 13-15 years old (children born between 1 December 2003 and 1 January 2005).

The inclusion criterion was children living in zinc-contaminated areas since birth or those residing in the area for > 10 years.

2.2 Determination of metals

Village health volunteers (VHVs) collected the urine samples. The target population was briefed and guided regarding the procedure of urine collection by the VHVs. Urine was collected in a polypropylene container and immediately preserved in 65% concentration of double distilled nitric acid in a ratio of 10:1 (urine sample: nitric acid) for extraction of Cd and Pb. Heavy metals were converted from their organic to inorganic forms. Samples were immediately transported to a laboratory and stored at –20 °C until analyses. The diluents were prepared as follows: 5 ppb of Rhodium (Rh) and Iridium (Ir) was prepared by pipetting 0.50 µL of 1,000 ppm dilution; to which 30 mL of 2% double distilled HNO_3 was added diluted by 18 MΩ DI water to 1,000 mL. This was stored at 4-8 °C. Sample preparation was done by adding 9,000 µL of the diluent, 900 µL of 18 MΩ deionised water, and 100 µL of urine into 20 mL polypropylene tubes, followed by then centrifuging this solution at 3,500 rpm for 10 minutes.

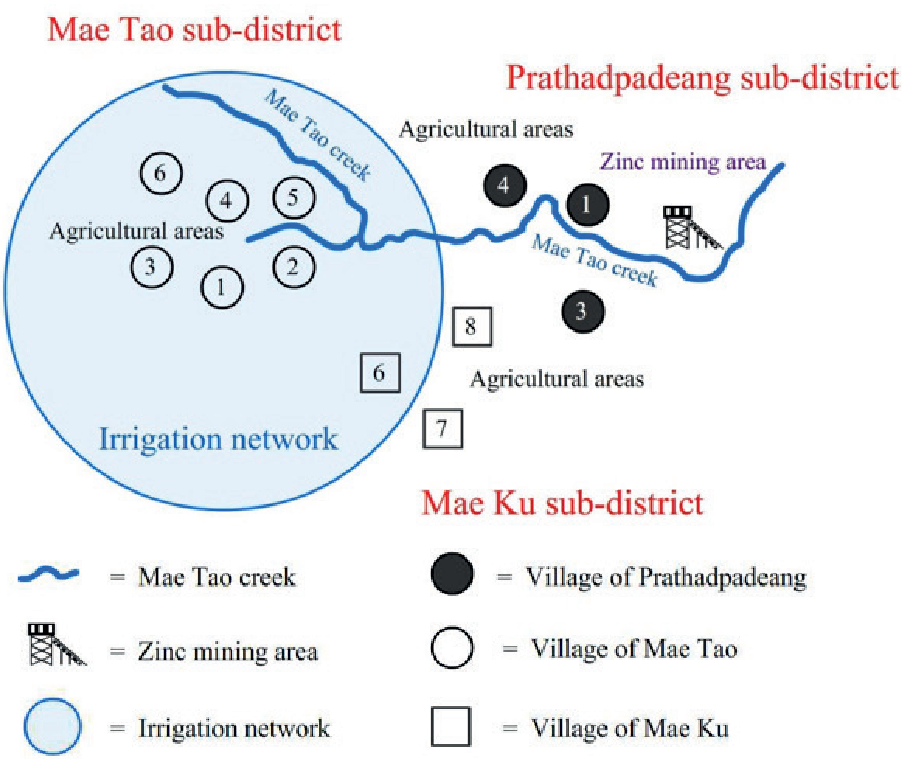

Figure 1. Overview of studied areas with cadmium contamination

The final solution was aspirated into a 20 mL sample cup. The quality control was carried out using a standard material (c.f.a.s., Cat. No.759350) before the samples were analysed. Presence of heavy metals in urine was determined by inductively coupled plasma mass spectrometry (ICP-MS) (Agilent 7500 series). Recovery experiments were also conducted using a blank concentration volume (CCV) after every 10 samples that showed satisfactory results with relative percentage difference (%RPD) ranging from 85% - 115% (Munkhuamdee, 2007). The credibility of the method to accurately assess Cd, Cu, Fe, Pb, and Zn levels was investigated based on the National Institute of Standard and Technology (NIST).

2.3 Data analysis

1) Descriptive statistics: frequency, percentage, mean, and standard deviation

2) Analytical statistics were divided into two parts:

2.1) Independent t-tests were used to compare UZn, UCu, UFe, UPb and UCd levels between genders and age groups ($p < 0.05$).

2.2) Multiple regression analysis (MRA) were used, with UZn, UCu, and UFe as the independent variables, to predict the bioavailability of Pb and Cd ($p < 0.05$).

Table 1. Demographic details of the subjects aged 9-15 years old (N = 736)

	Prathadpadeang		Mae Tao		Mae Ku		Total	
	N	%	N	%	N	%	N	%
1. Subjects								
Total	177	24.0	316	43.0	243	33.0	736	100.0
2. Gender								
Male	90	12.2	156	21.2	121	16.5	367	49.9
Female	87	11.8	160	21.8	122	16.5	369	50.1
3. Age								
9-12 years old	86	48.6	177	56.0	137	56.4	400	54.3
13-15 years old	91	51.4	139	44.0	106	43.6	336	45.7
4. Body weight at birth								
<3,000 grams	104	14.0	156	21.3	134	18.2	394	53.5
>3,000 grams	73	10.0	160	21.7	109	14.8	342	46.5
5. Body Mass Index								
Underweight (<18.50)	98	55.3	192	60.7	147	60.5	437	59.3
Normal weight (18.60-24.90)	75	42.4	101	32.0	85	35.0	261	35.5
Overweight (25.00-29.90)	4	2.3	18	5.7	8	3.3	30	4.1
Obesity (>30.00)	0	0.0	5	1.6	3	1.2	8	1.1
6. Location								
Born and lived in the polluted area	159	89.8	282	89.2	230	94.6	671	91.2
Migration	18	10.1	34	10.8	13	5.4	65	8.8

3. Results and Discussion

3.1 Results

Table 1 showed that 43.0% of children samples live in Mae Tao sub-district. In terms of gender, 50.1% of the subjects were female. The majority of the subjects were 9 - 12 years of age (54.3%). Birth weight of < 3,000 grams was reported in 53.5% of the total subjects included in this study. Analysis of body mass index (BMI) showed that 59.3% of the subjects were underweight (BMI < 18.5). Most of the subjects from the three included sub-districts were born and lived in the Zn-contaminated areas (91.2%), whereas the proportion of those born outside the polluted area was 8.8 %.

As illustrated in Table 2, the concentration of UCd was higher in subjects aged 13 - 15 years old (mean = 0.131 µg/L) than in those aged 9-12 years old (mean = 0.114 µg/L), and the difference was statistically significant at a level of 0.05 ($p < 0.05$). Levels of both UCd and UPb were higher than the normal range compared with the standard of trace elements in urine. In contrast, levels of UCu and UZn were lower than the normal range compared with the standard of trace elements in urine.

The normal ranges of UCd are 0.056 - 0.062 µg/L, UPb are 0.474 - 0.506 µg/L, UCu are 106.000 - 114.000 µg/L, and UZn =100.000 - 130.000 µg/L (Willie and Rumble, 2003). There is no reference value for Fe concentration in urine.

Table 2 showed that the levels of Zn and Cu in urine were significantly different between the two groups. The two elements are related to the structural and catalytic components of metallothionein (MT) and are required for growth and development (Vasak and Meloni, 2011).

Increase in the intake of Zn may cause an inherited disorder of metabolism (Cox and Moore, 2002). Both essential and toxic elements, including Zn, Fe, Mo, Pb, and Cd are factors that contribute to successfully and compete absorption of Cu. Zn and Cd are the most potent inhibitors of Cu absorption (Choi and Kim, 2005). A study conducted by Chaiwong *et al.* (2018) reported that female aged 13-15 years old had higher absorption of Cd than male of the same age group, based on quantification of Cd level in urine, it may be considered that Cu is lost through blood during menstruation in female, and this results in increased absorption of both Cd and Pb in their bodies.

Table 3 illustrates the averages of trace elements in the urine of 9 - 15 years olds based on gender. Levels of both UCu and UPb were higher in female than in male, with a statistically significant difference at the level of $p < 0.05$. However, levels of UCu and UZn were low, whereas levels of UCd and UPb were high, compared to the normal ranges of heavy metals in urine.

Table 2. The amount of trace elements in urine (µg/L) of 9 - 12 years old and 13 - 15 years old.

Trace element	9-12 years old (N=400)	SD.	Interpretation	13-15 years old (N=336)	SD.	Interpretation
Cd	0.114*	0.10	High	0.131*	0.12	High
Cu	34.525	56.50	Low	31.097	52.36	Low
Fe	20.867	22.48	Not available	21.723	22.88	Not available
Pb	0.835	0.76	High	0.891	0.76	High
Zn	75.504	49.81	Low	75.565	44.36	Low

*Difference significant at the .05 level; SD: standard deviation

Low = the amount of trace elements in urine was lower than certified concentration values and/or reference concentration values.

High = the amount of trace elements in urine was higher than certified concentration values and/or reference concentration values.

Table 3. Trace elements in urine (µg/L) based on gender in Mae Sot district (N = 736)

Trace element	Males (N = 367)	SD	Interpretation	Females (N = 369)	SD	Interpretation
Cadmium	0.119	0.11	High	0.124	0.11	High
Copper	29.874*	50.34	Low	35.145*	56.69	Low
Iron	19.576	21.52	Not available	23.090	23.63	Not available
Lead	0.771*	0.53	High	0.941*	0.92	High
Zinc	74.415	45.25	Low	77.022	50.15	Low

* Difference significant at the .05 level; SD: standard deviation

UCu levels were significantly different between females and males; however, the levels were lower than the normal range. UPb levels were significantly different between females and males. Therefore, Cu insufficiency in females may be associated with the overall health status. It is possible that the Fe and Cu lost in blood during menstruation leads to an increase in the absorption of Pb in their bodies (Ahameda *et al.,* 2007). Cu plays a role in the metabolism and transport of Fe as well as in the formation of erythrocytes.Cu also enables attachment between Fe and transferrin by participating in the enzyme oxidation reaction of Fe^{2+} and Fe^{3+} (Crichton and Pierre, 2001). Furthermore, living in high Zn-contaminated areas induces MT, a cytosolic protein, which leads to Cu deficiency and accumulation of Pb in females. Both Zn and Cu combine with MT and form Zn-MT and Cu-MT, respectively in the body of girls.However, the intestinal uptake of Zn-MT is higher, which leads to Cu deficiency. These results suggest that adolescent girls are at a higher risk of Pb absorption due to loss of Cu during menstruation leading to increased bioavailability of Pb.

Multiple linear regression analyses were used to investigate and confirm these associations, underlining the effects of Cu, Fe, and Zn on the bioavailability of Pb and Cd. All essential elements such as Cu, Fe, and Zn were present in minor quantities to induce heavy metals in the bodies of the subjects living in Zn-contaminated areas. The following equation can be used to predict the availability of Pb and Cd, which were approximately 25% and 16%, respectively. The relationships showed the influence of Cu on the bioavailability of Pb (Equation 1) ($r^2 = 0.25$) and Zn on the bioavailability of Cd (Equation 2) ($r^2 = 0.16$). These data provide an insight into the mechanism of elevated heavy metal accumulation through Cu deficiency. Finally, Cu was the most essential element to evaluate the availability of Pb and Cd in the body. The focus should be on prevention of Cu deficiency in girls aged 13 - 15 years old (as shown in Table 2 and 3).

$$\text{Lead availability} = 0.295 + 0.304\text{Cu} + 0.256\text{Fe} + 152\text{Zn}\ (r^2 = 0.25) \quad (1)$$

$$\text{Cadmium availability} = 0.050 - 0.079\text{Cu} + 0.057\text{Fe} + 0.395\text{Zn}\ (r^2 = 0.16) \quad (2)$$

3.2 Discussion

3.2.1 Effect of high Zn on Cu and Fe

It is possible that high Zn levels inhibited Cu and Fe in 13-15 years old due to rapid growth compared to children aged 9 - 12 years old. Both Zn and Cu are trace elements that contribute to the structural and catalytic components of metalloenzymes and are vital for growth and advancement (Iskandar *et al.,* 2005), possibly by competing with Cu for transport and/or by increasing the intestinal concentrations of MT. Zn interferes with Cu due to induction of MT synthesis in the intestine (ATSDR, 2004). Sandstead (1995) reported that high Zn:Cu ratio leads to Cu deficiency in humans.Prolonged and high dietary Zn consumption may cause mild Cu deficiency and lead to anaemia and other abnormalities (Arsenault and Brown, 2003; Bialostosky *et al.,* 2002). Zn reduces the absorption of Cu through its antagonistic action and also affects the absorption of Fe.

Studies have shown that low levels of Fe stored in the body correlated with the bioavailability of Cd. Absorption of Cd intensifies when Fe stores in the body are diminished (Berglund *et al.,* 1994; Vahter *et al.,* 1996; Meltzer *et al.,* 2010). The consequences of long-term burden on the body are unrecognized.As the absorption of Fe is notably elevated in late pregnancy, particularly among Fe-deficient female, there is reason to believe that the uptake of Cd could also be affected.

3.2.2 Effect of Cu deficiency on heavy metal bioavailability

In both genders and age groups, bioavailability of both Cd and Pb correlated with the levels of Cu. Rapid growth may be an influencing factor in the bioavailability of Cd and Pb. Growth can cause Fe deficiency, which induces the expression of divalent metal transporter 1 (DMT1), thereby increasing the absorption of Cd. Fe is a component of both myoglobin and hemoglobin (Friberg *et al.,* 1986; Somsuan *et al.,* 2019). Berglund *et al.,* (1994) indicated that increasing absorption of Cd inversely correlated with low Fe storage in the body because low levels of Fe induced the expression of DMT1. A previous study reported negative whole-body retention of serum ferritin in humans after consumption of a single dose of radio-labeled Cd mixed with rolled oats and milk. High dietary intake of Zn can affect the absorption of Cu and Fe. Thus, the synthesis of heme is indirectly interrupted by Zn (Sandstead, 1995).The principal/chief mechanism involves induction of MT by Zn in the mucosa of the gastrointestinal tract.

The rate of affinity of Cu is higher than Zn, which is bound to MT (ATSDR, 2004). Cu is an essential element of ceruloplasmin, which oxidises ferrous to ferric form. IDA results due to Zn overload and deficiency of Cu and Fe (Friberg *et al.,* 1986). Children aged 9-15 years old living in the three sub-districts were continually exposed to an overload of Zn. Increasing the uptake of Zn without concomitant increase in the uptake of Cu would cause negative health effects. Zn is transferred to the environment and accumulates in the human body through the food chain. Zn overload interferes with heme synthesis by interfering with the absorption of Cu. The ratio of Cu to Zn is clinically more important than the individual concentrations of either of these trace elements. Zn interferes with the absorption of Cu (Sandstead, 1995).

A diet high in Zn can result in Cu deficiency (ATSDR, 2004). Flanagan *et al.* (1978) demonstrated an 8.9% increase in $CdCl_2$ levels in cases of decrease in Fe stores in the body, which could be up to four times higher than in cases with normal Fe stores. These observations were supported by Turgut *et al.* (2007) who reported that BCd and BPb were remarkably higher in children with IDA than in controls. The main pathway for heavy metals exposure is therefore the daily food diet (Moon *et al.,* 1999), with drinking water a minor pathway (Wright, 2003; Satarug and Moore, 2004). Hellstrom *et al.* (2007) reported the consumption of locally grown vegetables and root crops. It was an important exposure pathway and that a statistically significant relationship exists between concentrations of heavy metals in urine and eating home grown products. From study of Juwa (2008) found that the local plants and meats contained high Cd level in contaminated areas. Hence, by consumption that plants and meats can intake the Cd into the body. Supported by Krissanakriangkrai *et al.* (2009) human health risk assessment the hazard quotient (HQ) from eating Swamp eel is higher than 1. In addition, children with low levels of serum ferritin had statistically higher levels of BCd and BPb, indicating increased gastrointestinal absorption of these metals due to diminished Fe stores (Osman *et al.,* 1998). It has been shown that increased Cu absorption was due to the known antagonism between Cu and Fe at the level of DMT1 (Turgut *et al.,* 2007; Wajeunnesa *et al.,* 2009; Angelova *et al.,* 2014; Ranganathan *et al.,* 2011).

4. Conclusions

Cu levels affected the bioavailability of heavy metals, such as Pb and Cd in people living in polluted areas. High levels of Zn suppress the absorption of Cu. Subsequently, Cu deficiency led to reduced absorption of Fe. Consumption of large quantities of Zn for extended periods caused severe deficiency of Cu. Prolonged Zn intake via the food chain may also cause Cu deficiency, as Zn induces MT, which may combine with Cu. Furthermore, Zn and Cu compete for intestinal uptake. Deficiency, as well as excess of Cu has deleterious effects on Fe metabolism. Fe levels in the body may be affected by Cu deficiency through its influence on absorption. Cu deficiency leading to deficiency of Fe can affect the bioavailability of Cd and Pb in the human body. Fe deficiency related to growth and blood loss can increase the bioavailability of heavy metals in the body.

Acknowledgments

The researchers would like to express their gratitude to the National Research Council of Thailand (NRCT) for financial support for specimen collection.

References

ATSDR. Interaction profile for arsenic, cadmium, chromium and lead. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service; 2004.

Ahameda M, Singha S, Beharib JR, Kumarc A, Siddiquia MKJ. Interaction of lead with some essential trace metals in the blood of anemic children from Lucknow, India. Clinica Chimica Acta 2007; 377(1-2): 92-97.

Angelova MG, Petkova-Marinova TV, Pogorielov MV, Loboda AN, Nedkova-Kolarova VN, Bozhinova AN. Trace element status (Iron, Zinc, Copper, Chromium, Cobalt, and Nickel) in iron-deficiency anaemia of children under 3 Years. Anemia 2014; 2014: 718089.

Arredondo M, Martinez R, Nunez MT, Ruz M and Olivares M. Inhibition of iron and copper uptake by iron, copper and zinc. Biological Research 2006; 39: 95-102.

Arsenault JE, Brown KH. Zinc intake of US preschool children exceeds new dietary reference intakes. The American Journal of Clinical Nutrition 2003; 78: 1011-1017.

Berglund M, Akesson A, Nermell B, Vahter M. Intestinal absorption of dietary cadmium in women depends on body iron stores and fiber intake. Environmental Health Perspectives 1994; 102: 1058-1066.

Bialostosky K, Wright JD, Kennedy-Stephenson J, McDowell MA, Johnson CL. Dietary intakes of macronutrients, micronutrients, and other dietary constituents: United States, 1988-1994. Vital Health Statistics 2002; 11(245): 1-168.

Bradstreet J, Geier DA, Kartzinel JJ, Adams JB, Geier MR. A case-control study of mercury burden in children with autistic spectrum disorders. Journal of American Physicians and Surgeons 2003; 3: 76-79.

Chaiwong S, Sthiannopkao S, Kim KW, Chuenchoojit S, Poopatpiboon S, Poodendean C, Supanpaiboon W. Urinary cadmium level in children between nine to fifteen years old in three Sub-districts of Tak Province in Thailand. Physics Procedia 2009; 2: 121-125.

Chaiwong S, Sthiannopkao S, Supanpaiboon W, Chuenchoojit S, Pupatwibul K and Poodendaen C. Urinary cadmium concentrations in a population downstream from a zinc mining area in Mae Sot District, Tak Province. Thailand. Environmental Geochemistry and Health 2013; 35: 69-78

Chaiwong S, Chanthanao W, Loeskhampom P, Wiwatanadate P, Sthiannopkao S. The comparison of urinary cadmium (UCd) and urinary lead (UPb) between 2007 and 2015 in a population living in a zinc contaminated area. Environment and Natural Resources Journal 2018; 17(2): 54-61.

Choi JW, Kim SK. Relationships of lead, copper, zinc, and cadmium levels versus hematopoiesis and iron parameters in healthy adolescents. Annals of clinical laboratory science 2005;35:428-434.

Crichton RR, Pierre JL. Old iron, young copper: from Mars to Venus. Biometals 2001; 2: 99-112.

Cox DW, Moore SD. Copper transporting P-type ATPases and human disease. Journal of Bioenergetics and Biomembranes 2002; 34: 333-338.

Delves HT. Assessment of trace element status. Clinics in Endocrinology and Metabolism 1985; 14: 725-760.

Flanagan PR, McLellan JS, Haist J, Cherian G, Chamberlain MJ, Valberg LS. Increased dietary cadmium absorption in mice and human subjects with iron deficiency. Gastroenterology 1978; 74: 841-846.

Fosmire GJ. Zinc toxicity. The American Journal of Clinical Nutrition 1990; 51: 225-227.

Friberg L, Kjellstrom T, Nordberg GF. Cadmium. New York: Elsevier Science Amsterdam; 1986.

Gibson RS, Abebe Y, Stabler S, Allen RH, Westcott JE, Stoecker BJ, Krebs NF. Zinc, gravida, infection, and Iron, but not vitamin B-12 or folate status, predict hemoglobin during pregnancy in Southern Ethiopia. Journal of Nutrition 2008; 138: 581-586.

Goldhaber SB. Trace element risk assessment: Essentiality vs toxicity. Regulatory Toxicology and Pharmacology 2003; 38: 232-242.

Harraki B, Guiraud P, Rochat MH, Alary J, Favier A. Interactions related to trace elements in parenteral nutrition. Pharmaceutica Acta Helvetiae 1995; 70: 269-278.

Harvey LJ, Harry JM. Biomarkers of copper status: A brief update. British Journal of Nutrition 2008; 99: S10-S13

Hegazy AA, Zaher MM, El-Salam MA, Morsy AA. Relation between anemia and blood levels of lead, copper, zinc and iron among children. BMC Research Notes 2010; 3(1): 133.

Hellstrom L, Persson B, Brudin L, Petersson GK, Oborn I, Jarup L. Cadmium exposure pathways in a population living near a battery plant. Science of the Total Environment 2007; 15: 447-455.

Iskandar M, Eleonora SE, Trick KD, Wang BL, Abbe MR, Bertinato J. Copper chaperone for Cu/Zn superoxide dismutase is a sensitive biomarker of mild copper deficiency induced by moderately high intakes of zinc. Nutrition Journal 2005; 4: 35-45.

Juwa S. Environmental impact and health risk assessment from foods consumption in cadmium contaminated areas Mae Sot District, Tak Province. Ph.D. Dissertation, Naresuan University, Phitsanulok, Thailand (2008).

Krissanakriangkrai1 O, Supanpaiboon W, Juwa S, Chaiwong S, Swaddiwudhipong W, Anderson KA. Bioavailable cadmium in water, sediment, and fish, in a highly contaminated area on the Thai-Myanmay Border. Thammasat International Journal of Science and Technology 2009; 14: 60 - 68.

Meltzer HM, Brantsaeter AL, Borch-Iohnsen B, Ellingsen DG, Alexander J, Thomassen Y, Stigum H, Ydersbond TA. Low iron stores are related to higher blood concentrations of manganese, cobalt and cadmium in non-smoking, Norwegian women in the HUNT 2 study. Environmental Research 2010; 110, 497-504.

Meltzer HM, Alexander J, Brantsaeter, AL, Borch-Iohnsen B, Ellingsen DG, Thomassen Y, Holmen J, Ydersbond TA. The impact of iron status and smoking on blood divalent metal concentrations in Norwegian women in the HUNT2 Study. Journal of trace elementsin medicine and biology 2016; 38; 165-173.

Moon CS, Zhang ZW, Shimbo S, Watanabe T, Lee CU, Lee BK, Ikeda M. Evaluation of urinary cadmium and lead as markers of background exposure of middle-age women in Korea: Dietary intake as an influential factor. Toxicology Letters 1999; 108: 173–178.

Munkhuamdee D. Guide. Bangkok: Bureau of Laboratory Personnel Development Analytical AAS. 2007.

Olivares ME, Hertramp F, Uauy R. Copper and zinc interactions in anemia: A public health perspective. In: Kraemer K and Zimmermann MB, editors. Nutritional Anemia: Sight and Life Press. Switzerland: Basel. 2007, p. 99-109.

Olsson IM, Bensryd I, Lundh T, Ottosson H, Skerfving S, Oskarsson A. Cadmium in blood and urine - impact of sex, age, dietary intake, iron status, and former smoking - association of renal effects. Environ Health Perspective 2002; 110: 1185-1190.

Osman K, Schutz A, Akesson B, Maciag A, Vahter M. Interactions between essential and toxic elements in lead exposed children in Katowice, Poland. Clinical Biochemistry 1998; 31: 657-665.

Padungtod C, Swaddiwudhipong W, Nishijo M, Ruangyuttikarn W, Inud T. Health risk management for cadmium contamination in Thailand forum v-side events on heavy metals. Intergovernmental forum on chemistry safety Budapest, Hungary. Available from: http://www.who.int/ifcs/documents/forums/forum5/thai_padungtod.pdf; 2006.

Papagiorgiou T, Zacharoulis D, Xenos D and Androulakis G. Determination of trace elements (Cu, Zn, Mn, Pb) and magnesium by atomical absorption in patients receiving total parenteral nutrition. Nutrition 2002; 18: 32-34.

Ranganathan PN, Lu Y, Jiang L, Kim C and Collins JF. Serum ceruloplasm in protein expression and activity increases in Iron-deficient rats and is further enhanced by higher dietary copper intake. Blood 2011; 118: 3146-3153.

Reeves PG, DeMars LC. Copper deficiency reduces iron absorption and biological half-life in male rats. Journal of Nutrition 2004; 134(8): 1953-1957.

Ripley EA, Redmann RE, Crowder AA. Environmental effects of mining. Florida, St. Lucie Press. 1996.

Sandstead HH. Understanding zinc: Recentobservations and interpretations. The Journal of Laboratory and Clinical Medicine 1994; 124: 322-327.

Sandstead HH. Requirements and toxicity of essential trace elements, illustrated by zinc and copper. The American Journal of Clinical Nutrition 1995; 61: 21S-24S.

Satarug S, Moore, MR. Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. Environmental Health Perspectives 2004; 112: 1099–1103.

Swaddiwudhipong W, Limpatanachote P, Pranee Mahasakpan P, Krintratun S, Padungtod C. Cadmium-exposed population in Mae Sot district, Tak province: 1. Prevalence of high urinary cadmium levels in the adults. Journal of the Medical Association of Thailand 2007; 90: 143-148.

Somsuan K, Phuapittayalert L, Srithongchai Y, Sonthi P, Supanpaiboon W, Hipkaeo W, Sakulsak N. Increased DMT-1 expression in placentas of women living in high-Cd-contaminated areas of Thailand. Environmental Science and Pollution Research 2019; 26(1): 141-151.

Suwatvitayakorn P, Ko MS, Kim KW, Chanpiwat P. Human health risk assessment of cadmium exposure through rice consumption in cadmium-contaminated areas of the Mae Tao sub-district, Tak, Thailand. Environmental Geochemistry and Health 2019. doi:10.1007/s10653-019-00410-7.

Turgut S, Polat A, Inanetal M. Interaction between anemia and blood levels of Iron, Zinc, Copper, Cadmium and Lead in children. The Indian Journal of Pediatrics 2007; 74: 827-830.

Vahter M, Berglund M, Nermell B, Akesson A. Bioavailability of cadmium from shellfish and mixed diet in women. Toxicology and Applied Pharmacology 1996: 136, 332-341.

Vasak M, Meloni G. Chemistry and biology of mammalian metallothioneins. Journal of Biological Inorganic Chemistry 2011; 16: 1067-1078.

Wajeunnesa MN, Begum S, Ferdousi SA, Quarishi SB. Serum Zinc and Copperin Iron deficient adolescents. Journal of Bangladesh Society of Physiologist 2009; 4: 77-80.

Wang K, Wang C, Liu B, Jiang S. Effect of copper deficiency on iron metabolism in rats. Wei Sheng Yan Jiu 2010; 39: 426-429.

Wenk HR, Bulakh A. Minerals: Their constitution and origin. Cambridge, The PressSyndicate of the University of Cambridge. 2004.

Willie EM, Rumble JJr. Certificate of analysis;standard reference material (2670a). National Institute of Standards &Technology 2003; 1-5.

Winiarska-Mieczan A. Cadmium, Lead, Copper and Zinc in breast milk in Poland. Biological Trace Element Research 2014; 157: 36-44.

Wright J. Environmental Chemistry. New York, NY: Routledge. 2003.