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ORIGINAL ARTICLE

LEAD AND CADMIUM IN INFANT MILK AND CEREAL BASED FORMULAE MARKETED IN NIGERIA: A PROBABILISTIC NON-CARCINOGENIC HUMAN HEALTH RISK ASSESSMENT

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ABSTRACT

Background. There has been concern on the likelihood of contamination of infant formulae and consequent health risk in children.

Objective. This study has assessed and compared the lead and cadmium levels in infant formulae commonly consumed in Nigeria with international regulatory limits. It has also compared the estimated daily intake with Joint FAO/WHO Expert Committee on Food Additives (JECFA) and Proposition 65 Provisional Tolerable Daily Intake.

Material and Methods. Lead and cadmium levels in 26 different brands of infant formulae purchased from stores in Port-Harcourt, Rivers state, Nigeria in January 2018 were assayed by Atomic Absorption Spectrophotometry.

Results. The lead and cadmium levels in milk based infant formulae ranged from 0.61-3.50 mg/kg and 0.01-0.55 mg/kg respectively whereas the range of the lead and cadmium levels in the cereal and cereal mix based were 0.29-1.95 mg/kg and 0.02-0.37 mg/kg, and 0.47-2.34 mg/kg and 0.001-0.46 mg/kg respectively. The mean lead level in the milk-based formulae (1.49 0.89 mg/kg) was slightly higher than other groups of formulae but the difference was not significant ($p<0.05$). The mean level of cadmium (0.17 mg/kg) in milk-based infant formulae was higher than levels in cereal and cereal mix but there was no significant statistical difference ($p<0.05$) between the samples. The lead and cadmium level in milk, cereal and cereal mixed based infant formulae were above the food safe limits.

Conclusions. The consumption of infant formulae may add to the body burden of cadmium and lead of children with attendant public health implication. Regular monitoring and safety assessment of metals contamination of these infant formulae is advised.

Key words: *infant formulae, cadmium, lead, risk assessment, regulatory toxicology, child health, Nigeria*

INTRODUCTION

Lead is a known potent neurotoxin and reproductive toxin with permanent irreversible effects and the brain of infants and children are particularly vulnerable to its deleterious effect [7, 47]. Cadmium is a cumulative toxin and given its very long half life in the body, even very low exposure in children is associated with neurodevelopmental defects [11]. Cadmium is listed by the International Agency of Research on Cancer (IARC) as a category 1 carcinogen and has been shown to cross the placenta [4, 24]. Cadmium is primarily toxic to the kidney and can also cause bone mineralization [45]. Food contamination is a regular source of exposure to heavy metals like cadmium and lead [43] and health concern associated with this duo known for their multiorgan (neurotoxic, nephrotoxic, reprotoxic, etc.) in infant and children food was recently emphasized in French total diet study [24, 46]. The elevated blood lead levels among children in Nigeria are known to be multifactorial [32, 38, 54]. Infant formulae, candies and pediatric syrups sold in Nigeria have been reported to be contaminated with lead and cadmium [22, 35].

The California Office of Environmental Health Hazard Assessment [8] has set a new and stricter

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maximum allowable oral dose level of 0.5 µg/day for lead and 4.1 µg/day for cadmium (also called Proposition 65) with respect to the reproductive toxicity of lead and cadmium. So far, the maximum allowable limits of lead in foods are premised on its ubiquity and unavoidability due to its natural occurrence in soil. There is still a challenge to fine tune a realistic achievable limit given the emerging evidence of its deleterious cognitive effects even at much lower and commonly-observed exposure levels [7, 47]. The actual dietary intakes of these metals should be estimated and compared with corresponding toxicological reference intake such as the provisional tolerable daily intake (PTDI) and provisional tolerable weekly intake (PTWI) in order to assess the risk to children's health arising from the presence of these metals in food. The extent of exposure of children to contaminants in food is still patchy due to the scarcity of child-specific data on food consumption.

In the absence of Nigerian regulatory standards for lead and cadmium in baby foods and infant formulae, this study has examined the levels of lead and cadmium contamination in milk, cereal and cereal mixed based infant formulae sold in Nigeria and their comparisons with some international regulatory limits namely US FDA (CFR Title 21 – FDA) [50], International Diary Federation (IDF) [21], Joint FAO/WHO Food Standards Programme Codex Committee 2016 [17], US DA & China National Food Standard GB 2762-2012 [9]. This work has also compared the estimated daily intake (EDI) of lead and cadmium from these infant formulae with the California Office of Environmental Health Hazard (Proposition 65) and Joint FAO/WHO Expert Committee on Food Additives (JECFA).

MATERIALS AND METHOD

Sampling

Twenty-six samples of different brands of commonly consumed infant formulae (age range from birth up to first year of life and above) in Nigeria, were purchased from stores in Port-Harcourt, Rivers state, Nigeria in January 2018. These 26 different brands which represent about 65% of infant formulae in Nigerian market were divided into three types with group codes as milk based infant formula coded as: M1 to M9, Cereal based coded as: C1 to C7 and Cereal mix based coded as: CM1 to CM10. These included infant formulae and follow-on formulae samples; soy-based infant formulae; milk and rice-based products for infants; rice gruel, wheat gruel and mixed cereal for infant (all products sold as powder) vegetable meals and fruit-based desserts.

Infant formulae preparation and determination of metals

The infant formulae samples (1–2 g) were weighed with plastic materials to prevent contamination with metals and digested using the hot-block digestion as in our previous publication described [36]. Briefly, approximately 9 mL of 65% concentrated nitric acid (HNO_3) and 3 mL of perchloric acid was added in a ratio of 3:1 prior to heating and the solution was transferred to a hot plate and heated to a temperature of 120°C for about 5 h. The sample was introduced into an oven under a temperature that was gradually increased by 10°C every 60 min until the final temperature of 450°C was attained with white ashes obtained after 18 h. Afterwards the samples were left to cool, and the white ash was dissolved in 5 mL of 1.5% nitric acid (HNO_3) and a final volume of 25 mL was made by addition of deionized water. Metal concentrations were assayed with atomic absorption spectroscopy (Model 205, Buck Scientific, East Norwalk, CT, USA). Samples were analyzed in triplicates [36].

Quality control

The instrument was recalibrated after every ten runs. The analytical procedure was checked using the spike recovery method (SRM). A known standard of the metals was introduced into already-analyzed samples and re-analyzed. The results of the recovery studies for lead and cadmium were more than 97% [36]. The relative standard deviation between replicate analyses was less than 4%. The limit of detection (LOD) for lead and cadmium was 0.005 mg/kg, with blank values reading as 0.00 mg/kg in deionized water with an electrical conductivity value of less than 5 µS/cm. The limit of quantification (LOQ) for lead and cadmium was 0.04 mg/kg.

Estimation of risk of exposure to lead and cadmium from infant formulae

The non-carcinogenic health risks of a single metal via consumption of infant formulae were assessed based on the estimated daily intake (EDI) which can be calculated as the following from equation *(Bargellini* et al.) [5] :

$$EDI = C \times DIR / BW$$

where: EDI - is the estimated daily intake of lead and cadmium (mg/kg/day); *C* - is the mean concentration of lead or cadmium in infant formulae samples (mg/kg); DIR - is the daily intake rate of infant formulae per kg body weight per day; BW- is the body weight.

The estimated daily intake (EDI) of lead and cadmium in different infant formulae was calculated using the actual lead and cadmium levels from this study to multiply the recommended consumption/intake rate by manufacturers divided by body weight. The EDI was calculated for 0-12 months old of 3.5 - 10.5 kg body weight [45]. For the exposure assessment of lead and cadmium in infant formulae the percent of lead and cadmium of provisional tolerable daily intake (PTDI) and California Office of Environmental Health Hazard (Proposition 65) were calculated using the lowest and highest EDI of lead and cadmium as shown in Table 2. The estimated daily intake were compared with the California Office of Environmental Health Hazard (Proposition 65) [8] and WHO Provisional Tolerable Daily Intake (PTDI) of lead and cadmium. The highest and lowest value of EDI from all the three types of infant formula were used to calculate the percent lead and cadmium contribution to PTDI.

Percentage of lead and cadmium in infant formulae to California Office of Environmental Health Hazard (Proposition 65) [8] and WHO Provisional Tolerable Daily Intake (PTDI) were calculated by the following:

$$\% \text{ PTDI} = (\text{EDI} / \text{PTDI}) \times 100$$

$$\% \text{ Proposition 65} = (\text{EDI} / \text{Proposition 65}) \times 100$$

This study compared the percentage of estimated daily intake (EDI) with California Office of Environmental Health Hazard (Proposition 65) [8] and WHO Provisional Tolerable Daily Intake (PTDI) set by JECFA of lead and cadmium to characterize the extent of exposure.

Statistical analysis

Statistical analysis was carried out using the Graphpad prism version 6.5. All results were expressed as mean ± standard deviation (SD). The data were analyzed using one-way analysis of variance (ANOVA) and Turkey *post hoc* test at 95% confidence level. $P<0.05$ was considered as statistically significant.

RESULTS

Table 1 shows the brand names, types, manufacturers and packaging, of lead and infant formulae. Three types of infant formulae were used namely: milk, cereal and mixed cereal based with aluminum foil as the commonest packaging. Most of the infant formulae were manufactured in Nigeria with less than ten percent imported.

The comparisons of the Pb and Cd levels in the infant formulae with international regulatory limits namely US FDA (Pb 0.4 mg/kg, Cd 0.1 mg/kg),

Table 1. Types, brand names, manufacturers, packaging of infant formulae involved in this study

Sample code	Brand name of infant formulae	Type	Manufacturer	Packaging
M_1	Pre NAN	Milk based	Nestle	Aluminum
M_2	Sma	Milk based (starter powdered milk)	Wyeth nutritionals	Aluminum
M_3	Peak Baby	Milk based (starter powdered milk)	Friesland campina	Aluminum
M_4	Lactogen 1	Milk based (starter powdered milk)	Nestle	Aluminum
M_5	Nutristart	Milk based (follow-on milk)		Hard cardboard external with formulae in Al foil
M_6	Sma Pro	Milk based (follow-on milk)	Nestle	Aluminum
M_7	Sma Pro	Milk based (starter milk)	Wyeth nutritionals	Aluminum
M_8	Cowbell Tina	Milk based (follow-up milk)	Cowbell	Aluminum
M_9	My Boy Eldorin	Milk based		Aluminum
C_1	Nestle Cerelac	Cereal based	Nestle	
C_2	Nestum Baby Cereal	Cereal based	Nestle	Hard cardboard external with formulae in Al foil
C_3	Golden Country Baby Cereal	Cereal based	Sun mark Ltd.	Aluminum
C_4	Friso Gold	Cereal based	Friso Gold	Aluminum

C_5	Cerelac Infant Cereal	Cereal based		Aluminum
C_6	Pediasure: Grow And Gain	Cereal based		Hard cardboard external with formulae in Al foil
C_7	Aptamil: Organic Rice	Cereal based		Hard cardboard external with formulae in Al foil
Cm_1	Nutriban	Cereal based (Mix)	Nutrimental	Hard cardboard external with formulae in Al foil
Cm_2	Ridielac (Vina Milk)	Cereal based (Mix)	Vietnam dairy products	Hard cardboard external with formulae in Al foil
Cm_3	Nutriben	Cereal based (Mix)	Alter farmacia	Hard cardboard external with formulae in Al foil
Cm_4	Ninolac	Cereal based (Mix)	Ninolac maroc SARL	Hard cardboard external with formulae in Al foil
Cm_5	Gerber	Cereal based (Mix)	Nestle	Plastic
Cm_6	Heinz Dinners	Cereal based (Mix)	Heinz	Hard cardboard external with formulae in Al foil
Cm_7	Gerber Oatmeal	Cereal based (Mix)	Nestle	Plastic
Cm_8	Heinz Summer Fruits	Cereal based (Mix)	Heinz	Plastic with aluminum lining
Cm_9	Nutrilac Infant Cereal	Cereal based (Mix)		Hard cardboard external with formulae in Al foil
Cm_{10}	Cerelac Infant Cereal	Cereal based (Mix)		Aluminum

International Diary Federation (IDF) (Cd 0.026 mg/kg), Joint FAO/WHO Food Standards Programme Codex Committee (Pb 0.01 mg/kg), US FDA & China National Food Standard (0.02 mg/kg) [9] is shown in Figure 1.

The highest level of lead was found in formulae milk based M_9 (3.50 mg/kg) and the highest-level cadmium was in cereal based mix brand Cm_8 with a concentration of 0.46 mg/kg. The lead and cadmium levels in milk based infant formulae ranged from 0.61-3.50 and 0.01-0.55 mg/kg respectively whereas the range of the lead and cadmium levels in the cereal and cereal mix based were 0.29-1.95 and 0.02-0.37, and 0.47-2.34 and 0.001-0.46 mg/kg respectively. At least

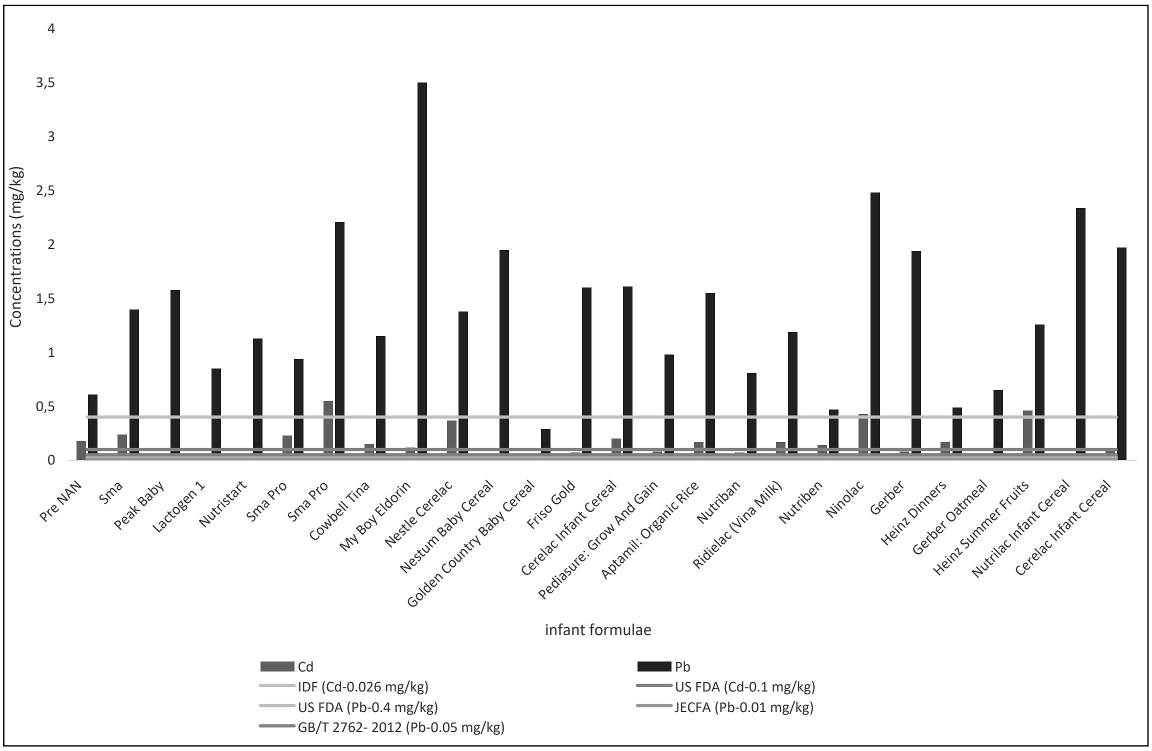

Figure 1. Comparison of mean concentrations (mg/kg) of lead and cadmium in infant formulae to international standard regulatory limits

96.15% of infant formulae violated the permissible limit of 0.4 mg/kg Pb set by US FDA, while 53.85% of infant formulae were above the US FDA maximum limit of 0.1 mg/kg Cd. International Dietary Federation (IDF) established a maximum limit of 0.026 mg/kg for Cd which was violated by 76.92% of infant formulae. One hundred percent of the infant formulae violated the limit set of 0.01 mg/kg and 0.05 mg/kg set by JECFA and GB/T2762-2012 for Pb respectively.

The mean levels of lead and cadmium in the three different groups of infant formulae is shown in Figure 2. The mean lead level in the milk-based formulae (1.49 0.89 mg/kg) was slightly higher than other kinds of formulae but the difference was not significant ($p<0.05$). The mean level of cadmium (0.17 mg/kg) in milk-based infant formulae was higher than levels in cereal and cereal mix but there was no significant statistical difference ($p<0.05$) between the samples.

The estimated daily intake EDI (mg/kg bw/day) of lead and cadmium in different groups of infant formulae in different age groups (0-12 months) of body weights 3.5 – 10 kg and daily intake rates (DIR) of 0.075 - 0.135 kg is shown on Table 2. The EDI of lead and cadmium in the milk-based infant formulae ranged from 0.02 to 0.035 mg/kg bw/day and 0.002 to 0.004 mg/kg bw/day respectively. The EDI of lead and cadmium in the cereal-based infant formulae ranged from 0.018 to 0.032 and 0.002 to 0.003 mg/kg bw/day

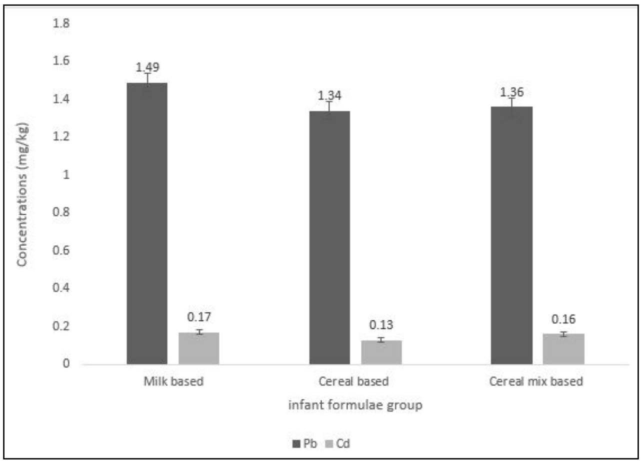

Figure 2. Mean concentrations of lead and cadmium (mg/kg) in different infant formulae groups

Table 2. Estimated daily intake (mg/kg bw/day) of lead and cadmium in different types of infant formulae

Age	DIR (kg)	Bw (kg)	Pb	Cd
Milk based				
0-2 weeks	0.075	3.5	0.032	0.004
2-4 weeks	0.1	4.2	0.035	0.004
2 months	0.11	4.7	0.035	0.004
4 months	0.145	6.5	0.033	0.004
6 months	0.135	7.5	0.027	0.003
6-12 months	0.135	10	0.020	0.002
Cereal based				
0-2 weeks	0.075	3.5	0.029	0.003
2-4 weeks	0.1	4.2	0.032	0.003
2 months	0.11	4.7	0.031	0.003
4 months	0.145	6.5	0.030	0.003
6 months	0.135	7.5	0.024	0.002
6-12 months	0.135	10	0.018	0.002
Cereal mix based				
0-2 weeks	0.075	3.5	0.029	0.003
2-4 weeks	0.1	4.2	0.032	0.004
2 months	0.11	4.7	0.032	0.004
4 months	0.145	6.5	0.030	0.004
6 months	0.135	7.5	0.024	0.003
6-12 months	0.135	10	0.018	0.002

DIR- daily intake rate, Bw - Body weight (*Sipahi* et al 2014)

Table 3. Percentage of lead and cadmium in infant formulae to California Office of Environmental Health Hazard (Proposition 65) and WHO Provisional Tolerable Daily Intake (PTDI)

	Pb	Cd		Pb	Cd
California Office of Environmental Health Hazard (Proposition 65) (µg/kg bw/day)	0.5	4.1	WHO Provisional Tolerable Daily Intake (PTDI) (µg/kg bw/day)	3.6	0.83
Age	% California Office of Environmental Health Hazard (Proposition 65) (µg/kg bw/day)		Age	% PTDI	
0-2 weeks	6385.7	88.85	0-2 weeks	886.9	438.9
2-4 weeks	7095.2	98.722	2-4 weeks	985.5	487.7
2 months	6974.5	97.042	2 months	968.7	479.4
4 months	6647.7	92.495	4 months	923.3	456.9
6 months	5364	74.634	6 months	745.0	368.7
6-12 months	4023	55.976	6-12 months	558.8	276.5

whereas in the cereal mix based, the EDI of lead and cadmium 0.018 to 0.032 and 0.002 and 0.004 mg/kg bw/day respectively.

Table 3 shows the percentage of lead and cadmium in infant formulae to California Office of Environmental Health Hazard (Proposition 65) [8] and WHO Provisional Tolerable Daily Intake (PTDI) in the different age group. The highest EDI of lead and cadmium across all age groups were used to calculate the percentage. For all the age groups, the percentage of lead and cadmium in infant formulae to California Office of Environmental Health Hazard (Proposition 65) was highest in age group 2-4 weeks. The EDI of lead and cadmium exceeded the PTWI set by JECFA across all age groups. The highest percentage contribution was in age group 2-4 weeks with a percentage value of 985.5% for lead while cadmium percentage contribution was highest in 2-4weeks with a value of 487.7%.

The mean levels of lead and cadmium in milk-based infant formulae were found to be highest of the three types of infant formulae considered in this study. Some workers have reported lead levels in various groups of infant formulae in the range of 1 ng/g to 10 ng/g [13]; 143 ng/g [18] and even 450 ng/g [52]. Lead and cadmium levels in the infant formulae in this present study were higher than the threshold values of Asian standards (0.05 mg/kg, 0.026 mg/kg) [9, 21]. The level of lead in all the infant formulae samples were higher than the limits in both China (0.05 mg/kg) and the EU (0.02 mg/kg). Similarly, the lead levels in this study were higher than those from Turkey, Ethiopia, Egypt, Pakistan and Canada [1, 12, 23, 28, 45]. Cadmium was observed in all our infant formulae samples to exceed the values reported in Pakistan (0.0042-0.0123 mg/kg), Iran (0.0403-0.058 mg/kg), and EU market [25, 29].

Table 4. Percentage of highest and lowest estimated daily intake (EDI) to California Office of Environmental Health Hazard (Proposition 65) and WHO Provisional Tolerable Daily Intake (PTDI) of lead and cadmium

	Pb	Cd		Pb	Cd
California Office of Environmental Health Hazard (Proposition 65) (μg/kg bw/day)	0.5	4.1	WHO Provisional Tolerable Daily Intake (PTDI) (μg/kg bw/day)	3.6	0.83
EDI Range (mg/kg bw/day)	% California Office of Environmental Health Hazard (Proposition 65) (μg/kg bw/day)		EDI Range (mg/kg bw/day)	% PTDI	
Highest EDI	0.035 (7000%)	0.004 (97.5%)	Highest EDI	0.035 (972%)	0.004 (481.9%)
Lowest EDI	0.018 (3600%)	0.002 (48.7%)	Lowest EDI	0.018 (500%)	0.002 (241%)

The percentage of highest and lowest estimated daily intake (EDI) to California Office of Environmental Health Hazard (Proposition 65) and WHO Provisional Tolerable Daily Intake (PTDI) of lead and cadmium are shown on Table 4. For the percent PTDI, highest and lowest EDI of lead and cadmium were 500 - 972% and 241 - 481% respectively.

DISCUSSION

Food is an important source of metal exposure in man. The poorly developed food surveillance system in sub-Saharan Africa does not have the capacity to monitor food sources to effectively safeguard public health. This study has revealed unacceptable levels of lead and cadmium in commonly consumed infant formulae sold in Nigeria with values exceeding the maximum permissible limits of various regulatory bodies.

Although exceeding the PTDI occasionally does not indicate a health risk per se; but in the present study the estimated daily intakes were more than the California Office of Environmental Health Hazard (Proposition 65) and JECFA PTDI. Infant formulae considered in this study may be adding to the body burden of lead and cadmium in children. The low body weights of infants and of course higher nutrient requirements predispose them to higher sensitivity to dietary contaminants because of the very efficient luminal absorption prior to full development of organs like liver and kidney tend to exaggerate the toxicity over a life time [37]. Higher blood lead levels have been seen in formula-fed children compared with the breast-fed counterparts [37].

Developing nations are particularly at high risk of lead poisoning and carry the highest burden of this hazard [6]. Childhood lead poisoning is a commonplace in Nigeria with long-term neurological impairment including blindness and deafness [14, 32, 40]. Infants and children are considered as a separate group in risk assessments due to their different consumption patterns and lower body weights.

Consequently, higher gastrointestinal absorption in combination with the consumption of infant formulae composed of ingredients with higher lead and cadmium levels than breast milk, may result in increased internal lead and cadmium exposure of these infants. One study in Nigeria, reported elevated blood lead levels in children with mean 8.974.8 µg/dL, the median 7.8 µg/dL, and the range 1–52 µg/dL [32]. Other studies based in Nigeria recorded mean BLL 11 µg/dL for children in Kaduna, a medium-size city in Northern Nigeria [33, 34] and 15±1.4 µg/dL for 218 children in Jos [38]. Blood lead level BLL may impair erythropoiesis by inhibiting protoporhyrin synthesis and impairing iron absorption thus increasing the risk of anaemia [19]. It is also a well-known neurotoxin and irreversibly affects the brain of infants [7]. Bioavailability plays a significant role in the assessment and management of risk posed by food contaminants. Although intestinal absorption of heavy metals is proportional to the concentration in the diet, there are other factors that may influence the rate of intestinal absorption and organ retention of heavy metals like lead and cadmium [42]. Since humans who have low iron status are likely to absorb more cadmium and lead than those with adequate iron status the consumption of infant formulae with high levels of lead and cadmium may have exaggerated health implications in anemic children.

The estimated daily intake of lead (for 6-12 months old infant weighing 10 kg) was calculated as 0.02 mg/kg bw/day which is 558% of PTDI in violation of the PTDI of lead recommended by JECFA. The percent PTDI of lead and cadmium from this study for infants aged 0-2 weeks to 6-12 months ranged from 558.8 to 985.5 and 276.5 to 487.7 respectively. Cadmium intake should not exceed 7 µg/kg of body weight over the course of one-week i.e. the PTWI [15]. The estimated daily intake and % PTDI of cadmium for different infant formulae at all age groups from 0-12 months were observed to be above the JECFA PTDI. Infant exposure to cadmium is very deleterious because cadmium elimination half-life from the blood is approximately 100 days and this accumulates in the proximal tubules of kidneys leading to kidney dysfunction [24]. The European Food Safety Authority (EFSA) in 2009 set for cadmium a Tolerable Weekly Intake (TWI) at 2.5 µg/kg body weight [24].

In addition to cadmium accumulation in the proximal tubules of kidneys, cadmium can also cause considerable changes in the renal cortical levels of many metals to constitute nephrotoxicity with early biomarkers as urinary beta-2-microglobulin which may be associated with enzymuria, aminoaciduria, glycosuria, hypercalciuria, hyperphosphaturia [39]. Hypercalciuria, hyperphosphaturia can ultimately lead to urolithiasis. Decline in bone mineral density is the main feature of cadmium toxicity in the skeleton [2, 31]. According to the International Agency of Research on Cancer cadmium is classified as a Category 1 carcinogen, and placental transfer has been demonstrated [3, 4].

In sub-Sahara Africa and many other places, infant formulae constitute vital source of food for infants and small children. It is of immense importance that the nutritional quality and status of infants and small children foods are not compromised. Raw materials especially agricultural produce, storage, packaging to tainted tap water constitute the likely sources of contamination of the infant formulae [26, 41].The risk assessment in this study has not considered the percentage of lead and cadmium that is bio-accessible in human body from infant formula and furthermore levels of lead and cadmium represent only the batch we studied.

CONCLUSION

Infant formulae sold in Nigeria may add to the body burden of lead and cadmium in children. Given the health implications of lead and cadmium, every effort should be made by manufacturers to reduce their levels to an achievable practical minimum and should be compelled to indicate the levels of these contaminants in the infant formulae labels stating the possible dangers particularly in nursing infants with renal insufficiency or other disorders that might favor accumulation of these metals.

Conflict of interest

The authors declare no conflict of interest.

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