ORIGINAL ARTICLE

Heavy Metal Content of a Polyherbal Drug: Any Exposure-associated Public Health Risks?

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Abstract

Background: Heavy metal contaminations of herbal formulations have constituted a public health challenge in the sub-Saharan Africa region and even in some developed nations. The study aimed to evaluate the public health concerns of chronic exposure to a polyherbal drug suspected to contain heavy metals.

Methods: This is an experimental study. Heavy metals were measured using Solaar-Thermo-Elemental Atomic Absorption Spectrophotometer. Human health risk assessment was estimated by calculating the estimated daily intake, target, hazard quotient (THQ), health index (HI), carcinogenic risk (CR) of exposure to the polyherbal drug.

Results: The results showed the presence of metals in this order: Cd<Hg<As<Pb<Zn<Mn<Cu<Ni<Cr<Fe. Cr, Pb, Ni, Mn, and Fe were above World Health Organization (WHO) and the United States Food and Drug Administration (USFDA) maximum permissible limits. THQ of Cr was > 1; HI for adolescents, adults, and geriatrics were >1. Ni and Cr had the highest cancer risk; total cancer risk was above the safe limit.

Conclusion: Since herbal medicines/dietary supplements are not under compulsory regulation by international, national, and local health regulatory authorities, these products must be manufactured using the highest manufacturing standards to ensure their safety among the end-users. Our findings suggest the likelihood of significant non-carcinogenic adverse health effects among adolescents, adults, and the geriatric population due to exposure to a mix of toxic metals, necessitating utmost caution on its chronic use. If policy formulations and implementations regarding the safety of herbal medicines and associated products prior to their circulation are ensured, public health will be protected and significantly improved.

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Introduction

Heavy metal contaminations of herbal formulations have constituted a public health challenge in the sub-Saharan African region and even in some developed nations. Herbal medicine is integral to the traditional medical practices of various ethnic groups. There is a trendy interest in herbal medicine primarily due to its aged-long history and a general belief that herbs are natural and intrinsically safe. The WHO reports that about 80% of the world population relies on traditional herbal medicine for their primary health care, especially in third-world countries.[1] The Nigerian state and other member states of the Sub-Saharan African region have witnessed an increased use of herbal remedies (both unfinished and finished/labeled products) to a manifold. Dr. Iguedo

Goko Cleanser® is one of such polyherbal formulations used traditionally and claimed to treat numerous diseases among native Nigerians. Primarily, poor manufacturing practices, accumulation, and uptake from agriculturally polluted sites are the primary sources of heavy metal contamination in medicinal products.

Heavy metals are ubiquitous, and the food web or chain is one of the important pathways of human exposure to these and other environmental contaminants. However, the importance of metals in health and diseases can never be underestimated because most of them are pivotal to the numerous biochemical and physiological processes in plants, animals, and human biology. For example, zinc is an important cofactor for several enzymatic or catalytic reactions in the human body. Also, cobalt is the core atom in vitamin B12, and elemental iron is the constituent of hemoglobin, whose role is well established in physiological and pathological conditions. Other trace elements such as manganese, copper, selenium, chromium, and molybdenum are all known to impact human physiology. However, there is an array of elements with no known benefit to human biology. Cadmium, lead, arsenic, and mercury are prime examples of such "toxic metals". On this premise, the term "heavy metal" is used to best describe those metals and semi-metals with the propensity to induce human and /or environmental toxicities.[2, 3] Metals may be contaminants in dietary supplements, labeled herbal drugs, and/or leech into food and drinks stored in metallic containers. Leeching usually occurs when such containers are exposed to higher temperatures (e.g., direct sunlight, microwave, or oven) for longer duration or repeatedly. Thus, in the management of metal poisoning, a complete dietary and lifestyle history may give helpful insight into metal exposure sources. Metal toxicity may complicate some forms of drug toxicity, especially as they may inhibit drug-metabolizing enzymes. For instance, during the 1970s, the addition of cobalt to beer was linked to cardiomyopathy diagnosed in Quebec and Minnesota among alcoholics. Wang et al.[4] reported that a parkinsonian syndrome among Latvian drug users of methcathinone was linked to manganese toxicity.

Presently, self-medication is a common practice in the sub-Saharan African region. Thus, there is an upsurge in the circulation of various drugs and quasi-drug formulations,[5] many of which are allegedly licensed or censored by local health regulatory authorities across the region. In Nigeria, for example, and to a greater extent, medicinal plants and their derivatives (here tagged 'herbal remedies') are copiously exploited for primary health care. However, since good manufacturing practices and quality assurance may not always be guaranteed in third-world countries, most of these herbal formulations may be subjected to heavy metal contamination vis-à-vis other chemicals and/or impurities either during plant collection (e.g., from agriculturally polluted sites), processing and packaging. Therefore, everyday exposures to these formulations are of serious concern to public health as they may induce an array of toxicities. For this reason, this research was designed to analyze the heavy metal content and the associated human health risks of repeated exposure to the polyherbal formulation – Dr. Iguedo Goko Cleanser®.

Methods

Experimental Design

This study is a health risk assessment conducted in two (2) phases: (1) measurement of the heavy metals content of the polyherbal product and (2) determination of exposure-associated health (carcinogenic and non-carcinogenic) risks using suitable mathematical paradigms. The polyherbal formulation (Dr. Iguedo Goko Cleanser®) was selected after a pilot survey and based on the assertion that it is easily accessed, the cheapest, most sold, and thus popularly consumed compared to other herbal remedies in the market.

Study Population

In tandem with the suggested dosage of this polyherbal mixture, three (3) age categories were selected for the health risk assessment based on their body weights. These were: adults (70 kg); adolescents (54.5 kg; 12 years and above); and geriatrics (62.5 kg).

Measurement of Heavy Metals

The concentration of heavy metals (Cr, Pb, Cd, Hg, As, Cu, Zn, Ni, Mn, and Fe) content of the herbal remedy was determined by Solaar Thermo Elemental Atomic Absorption Spectrophotometer (Model SG 71906, Australia), after digestion in a 20 mL tri-acid mixture of $HNO_3/H_2SO_4/HCLO_4$ (5:1:1, v/v/v) for 8 h at 80 °C until a transparent solution was obtained.[6] Digestion of sample was carried out according to the procedure reported by USEPA[7] and similar to the digestion of water. The well-digested solution was poured through Whatman filter paper No. 42, and the volume was made up to 25 mL with de-ionized water. All the analysis was done in triplicates. This determination was done at Jaros Inspection Services Limited, Port Harcourt, Rivers State, Nigeria.

Quality Assurance and Control

During the research, appropriate quality assurance precautions and procedures were implemented to ensure the results' reliability. Deionized water was used throughout the study. All the reagents were of analytical grade, and glassware was cleaned properly.

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.[8]

Health Risk Assessment

Due to the paucity of agreed limits for acceptable maximum carcinogenic and non-carcinogenic risk levels in Nigeria, the USEPA models and threshold values were employed to assess potential human health risks posed by heavy metal contamination . Specifically, the multi-phase and multi-component risk assessment model developed by USEPA was used to evaluate the heavy metal contamination/pollution hazard in urban residential areas.[9] The health risk assessment was estimated by calculating the estimated daily intake (EDI), target, hazard quotient (THQ), health index (HI), and carcinogenic risk (CR) of the exposure to the selected herbal remedy.

Estimated Daily Intake (EDI)

EDI (or CDI when exposure is chronic) is used to quantify the oral exposure dosage of substances for both carcinogenic and non-carcinogenic risk assessments during the exposure assessment stage.[10] The estimated daily intakes of the polyherbal formulation were determined by adopting the method in previous risk assessment studies.[11-13] This was determined using Equation 1.

$$EDI = \frac{Cmetal\ x\ Dfood\ intake}{BWaverage}$$ Equation 1

Where EDI=Estimated daily intake, C_{metal}=concentration of metal, $D_{food\ intake}$=food ingestion/intake rate in kg person^{-1}, while BW is the body weight average. The $D_{food\ intake}$ of the polyherbal mixture was determined to be 0.09 mL/kg/person/day for adults and 0.045 mL/kg/person/day for children (12 years and above). As earlier described by Igbiri *et al*.[14] and Udowelle *et al*.,[15] the body weights used were: adults (70 kg); adolescents (54.5 kg); and geriatrics (62.5 kg).

Target Hazard Quotient (THQ)

The THQ shows the probability that adverse health effects may occur following exposure to a toxicant and is unlikely to be proportional to the risk. It is calculated by determining the ratio of potential exposure to the dose of the substance (here referred to as toxicant) and the reference dose at which no adverse health effects are expected. When THQ>1, then adverse health effects are very likely to occur, and the reverse is the case when THQ<1. This method was used to estimate non-carcinogenic risk from consumption of heavy metals in the polyherbal mixture. This action was done by adopting the methods previously described in other risk assessment studies.[11-13] The THQ was calculated using Equations 2 or 3.

$$THQ = \frac{Efr\ x\ ED\ x\ FIR\ x\ C}{RfDo\ x\ BWaverage\ x\ ATN}\ x\ 10^{-3}$$ Equation 2

Or

$$THQ = \frac{EDI}{RfDo}$$ Equation 3

Where Efr is the exposure frequency assumed to be 365 days year−1, ED is the exposure duration in 55.8 years equivalent to an average life expectancy for Nigeria, FIR is the average daily consumption in mL/kg person^{-1}day^{-1}, C is the concentration of metal in the polyherbal mixture in mg/kg, and RfDo is the reference dose in mg/kg day^{-1}, ATn is the average exposure time for non-carcinogens in days and EDI is the estimated daily intake.[12] The reference doses adopted for this study were: Cd=0.0005 mg kg^{-1}, Pb=0.0036 mg kg^{-1}, Zn=0.30 mg kg^{-1}, As=0.0003 mg kg^{-1}, Cu=0.0370 mg kg^{-1}, Hg=0.0003 mg kg^{-1}, Ni=0.02 mg kg^{-1}, Fe=0.70 mg kg^{-1}, Cr=0.003 mg kg^{-1} and Mn=0.1400 mg kg^{-1}.[16-18]

Hazard Index

Hazard index quantifies the risk inherent in a mixture of different metals by combining the individual target quotients. Where and when HI>1, then there is an unacceptable level of risk of non-carcinogenic effect. However, HI<1 indicates an acceptable non-carcinogenic risk level.[13] It was calculated using the formula shown in Equation 4.

$$HI = \sum_{k=1}^{n} THQ \quad = HI = \sum_{k=1}^{n} CDIk/RFDk$$ Equation 4

Where HI is the hazard index – the summation of the THQ for all the metals found in the polyherbal mixture, CDI_k represents the metal daily intake, while RFD_k represents the value for the metal chronic reference dose.

Carcinogenic Risk (CR)

The risk of cancer associated with exposure to a carcinogen or potential carcinogen is best assessed and estimated using a slope factor. The cancer slope factor evaluates the probability of a person developing cancer from oral exposure to contaminant levels over a lifetime.[19] Furthermore, cancer slope factors are estimates of carcinogenic potency. They are used to relate the estimated daily intake of a substance over a lifetime exposure to the lifetime probability of excess tumors development. The estimation of cancer risk due to the heavy metals content of the polyherbal mixture was determined using the USEPA model as shown in Equation 5.

$$Cancer\ Risk = CDI\ x\ CSF$$ Equation 5

Where CDI is the chronic daily intake of potent carcinogenic agents (s) (mg kg^{-1} d^{-1}); CSF represents the ingestion cancer slope factor of hazardous substances (mg kg^{-1} d^{-1}). The cumulative or total cancer risk shows the probability of cancer due to lifetime exposure to two or more carcinogenic substances or due to multiple exposure routes to a potential carcinogen(s). In this study, the total cancer risk was calculated using Equation 6.

$$Total\ cancer\ risk\ (TCR) = \sum_{k=1}^{n} CDIkCSF_k$$

Equation 6

Where CDI_k is the chronic daily intake (mg kg^{-1} d^{-1}); of substance k, CSF_k is the ingestion cancer slope factor for substance k (mg kg^{-1} d^{-1}). As earlier adopted in previous risk assessment studies, $10^{-6} – 10^{-4}$ (i.e., 1 in 1,000,000 to 1 in 10,000) is the most acceptable safe range for cancer risk.[12, 13, 20] The ingestion cancer slope factors adopted in this study were 0.0085, 0.38, 0.50, 0.91, and 1.50 mg/$kg^{-1}day^{-1}$ for Pb, Cd, Cr, Ni and As, respectively.[20-22]

Assumptions for Risk Assessment

For the human health risk assessment, the following assumptions were made:

a. A tablespoon was assumed to be equivalent to 15 mL (US measurement).

b. The exposure frequency (Efr) for heavy metals was assumed to be 365 days per year.

c. The exposure duration (ED) for heavy metals was assumed to be equivalent to the average life expectancy for Nigeria (55.8 years).

d. The average body weights (BW) for the populations involved were assumed to be 70, 54.5, and 62.5 kg for adults, children (12 years and beyond), and senior citizens, respectively.

e. The United States Environmental Protection Agency (USEPA) and earlier risk assessment studies, oral reference doses for heavy metals, oral cancer slope, and conversion factor were adopted in this study.

Results

Heavy Metals Analysis

Table 1 presents the concentrations of the 10 heavy metals measured in the polyherbal mixture. From the result, the concentrations are in this order Cd<Hg<As<Pb<Zn<Mn<Cu<Ni<Cr<Fe. Comparing the available maximum permissible limit revealed that Cr, Pb, Ni, Mn, and Fe were all above the maximum permissible limits. Specifically, Cr was above this limit in all water types and plants. At the same time, Ni was above in mineral and/or drinking water only. Pb, Mn, and Fe were above the said limit in all water types (Table 1).

Health Risk Assessment

Tables 2 and 3 respectively present the estimated daily intake (EDI), Target hazard quotient (THQ), and

Table 1: Concentration (parts per million) of heavy metal in the polyherbal mixture (Dr Iguedo Goko Cleanser®) in comparison with maximum permissible limits (MPL)

Metal	Concentration (ppm)	MPL (NMW) ppm	MPL (IW) ppm**	MPL (PL) mg/kg[#]
Pb	0.092	0.010[a], 0.050[b]	0.065	2.00
Cd	<0.001	0.003[a], 0.005[b]	0.010	0.02
As	0.0034	0.010[a, b]	0.100	-
Cr	7.162	0.100	0.550	1.30
Hg	0.002	0.001[a], 0.002[b]	0.500	-
Cu	0.294	1.000 - 2.000[b]	0.017	10.00
Ni	1.043	0.200[**], 0.100[b]	1.400	10.00
Fe	8.470	0.300 – 1.000[b]	5.000	20.00[*]
Zn	0.096	5.000[b]	0.200	50.00
Mn	0.184	0.050[b]	0.020	-

*Shah et al.[23]; **WHO[24, 25] and WHO/FAO[26]; [a]WHO/FAO[27]; [b]USFDA[28]; [#]Hassan et al.[29]; PL: Plant; IW: Irrigation water; NMW: Natural mineral water; Source: Field Data (Nigeria, 2021)

Table 2: Estimated daily intake of heavy metals in the polyherbal mixture (Dr Iguedo Goko Cleanser®)

Metal*	Adolescents ($mLkg^{-1}day^{-1}$)	Adults ($mLkg^{-1}day^{-1}$)	Geriatrics ($mLkg^{-1}day^{-1}$)
Cd	8.2500E-7	1.2850E-6	1.4400E-6
Hg	1.6510E-6	2.5710E-6	2.8800E-6
As	2.8070E-6	4.3710E-6	4.8960E-6
Pb	7.5963E-5	1.1829E-4	1.3248E-4
Zn	7.9266E-5	1.2343E-4	1.3824E-4
Mn	1.5193E-4	2.3657E-4	2.6496E-4
Cu	2.4275E-4	3.7800E-4	4.2336E-4
Ni	8.6119E-4	1.3410E-3	1.5019E-3
Cr	5.9136E-3	9.2083E-3	1.0313E-2
Fe	6.9936E-3	1.0890E-2	1.2197E-2

* Metals presented in order of increasing concentration in the sample. Source: Field Data (Nigeria, 2021)

Table 3: Target hazard quotient and hazard indexes for heavy metals in the polyherbal mixture (Dr. Iguedo Goko Cleanser®)

Metal*	Adolescents	Adults	Geriatrics
Cd	1.6510E-3	2.5700E-3	2.8800E-3
Hg	5.5046E-3	8.5700E-3	9.6000E-3
As	9.3578E-3	1.4571E-2	1.6320E-2
Zn	2.6422E-4	4.1143E-4	4.6080E-4
Pb	2.1704E-2	3.3796E-2	3.7851E-2
Mn	1.0852E-3	1.6898E-3	1.8926E-3
Cu	6.5609E-3	1.0216E-2	1.1442E-2
Ni	4.3060E-2	6.7050E-2	7.5096E-2
Cr	1.9712E+0	3.0694E+0	3.4378E+0
Fe	9.9908E-3	1.5557E-2	1.7424E-2
HI	2.0704E+0	3.2234E+0	3.6108E+0

* Metals presented in order of increasing concentration in the sample. HI: Hazard index; Source: Field Data (Nigeria, 2021)

Table 4: Cancer risk for all carcinogenic metal congeners in the polyherbal mixture (Dr Iguedo Goko Cleanser®)

Metal*	CR	TCR
Cd	6.4200E-7	
As	6.5560E-6	
Pb	1.0050E-6	4.7276×10^{-3}
Ni	1.2203E-3	
Cr	3.4991E-3	

*Metals presented in order of increasing concentration in the sample. CR: Cancer risk; TCR: Total cancer risk; Source: Field Data (Nigeria, 2021)

Hazard index (HI) for children (adolescents), adults, and geriatrics exposed to the polyherbal mixture and contaminated with heavy metals. The EDI followed this order: Cd<Hg<As<Pb<Zn<Mn<Cu<Ni<Cr<Fe. The THQ of Cr was greater than one in the three age categories considered. Similarly, the hazard indexes for children (adolescents), adults, and geriatrics were 2.0704, 3.2234, and 3.6108, respectively. These values were all >1 in these age categories.

The cancer risk (CR) and total cancer risk (TCR) of all carcinogenic heavy metals present in the polyherbal mixture is presented in Table 4. Of the five carcinogenic heavy metals found in the polyherbal mixture, nickel and chromium had the highest cancer risk values (1.2203×10^{-3} and 3.4991×10^{-3} respectively). The TCR was calculated to be 4.7276×10^{-3}.

Discussion

In humans, exposure to toxic metals at a very tender age compromises key developmental processes potentiating a lifelong physical, cognitive, and behavioral impediment. Heavy metal exposure also poses risks to the environment and chiefly the living systems found therein. The health risks of heavy metal pollution are seen as individual vulnerability to chronic and degenerative diseases such as arthritis, diabetes, cardiovascular disorders, nephrotoxic and neurotoxic events.[30, 31] As earlier reported by Orisakwe,[32] heavy metals contributes to the aetiogenesis or pathogenesis of metabolic disorder chiefly by disrupting an array of metabolic pathways and processes, resulting in an increased incidence and prevalence of these disorders such as diabetes, hypertension, cancer, end-stage renal disease and complications, and male infertility in the Nigerian state.

Our findings recorded that Cr, Pb, Ni, Mn, and Fe were all above the maximum permissible limits. Logically, the presence of these heavy metals in the herbal formulation above the permissible limits increases the susceptibility and vulnerability of the end-users to the associated health risks of these ubiquitous substances. For instance, lead (Pb) is regarded as a human mutagen and probable carcinogen.[33] It induces renal tumors and disturbs the normal functioning of kidneys, joints, reproductive, and nervous systems.[34] Chromium (VI) is known to be mutagenic and carcinogenic. Thus, breathing high levels of chromium (VI) may cause asthma and shortness of breath. Moreover, long-term exposure may cause damage to the liver and kidneys.[35] Nickel, on the other hand, causes cancer, both oral and intestinal. It also causes depression, heart attacks, hemorrhages, and kidney problems.[36] Definitely, the effect of heavy metal toxicity is consequential even at low-level exposure. This issue is a major contributor to the onset and progression of chronic and degenerative diseases and impaired physiological processes than was previously thought.

The reported target hazard quotient (THQ) of Cr and the hazard indexes for the three (3) age categories [children (adolescents; 2.0704), adults (3.2234), and geriatrics (3.6108)] were all greater than one (>1). It indicates that children (adolescents), adults, and the elderly who consume the herbal mixture may be at high risk of heavy metals toxicity (non-carcinogenic) due to exposure to a mix of several toxic metals.[36] Of the five carcinogenic heavy metals found in the polyherbal mixture, nickel and chromium had the highest carcinogenic risk (CR) values (1.2203×10^{-3} and 3.4991×10^{-3}, respectively). The TCR was calculated to be 5.8325×10^{-3}. These values were above the safe limits and suggest the likelihood of significant adverse health effects, especially when exposure is persistent and chronic. Therefore, risks values exceeding 1×10^{-4} are regarded as intolerable, risks less than 1×10^{-6} are disregarded to cause significant health effects, and risks lying between 1×10^{-4} and 1×10^{-6} are regarded generally as the satisfactory range.[37] One in a million (1×10^{-6}) cancer risk means that one additional cancer case would be expected.

Since traditional medicine or herbalism is a common practice in Nigeria vis-à-vis other countries in the sub-Saharan Africa region, and medicinal plants cultivated in heavy metals laded environments serves as sources of contamination, it is therefore imperative that adequate public health policy for the protection of the local inhabitants, especially children, be implemented and enforced. This policy will include measures to remediate, reclaim and restore soils disrupted by persistent toxic metallic contaminants, which are known to bio-accumulate, bio-concentrate, and bio-magnify up the food web.[38]

Limitations

An epidemiological survey on the concurrent use of herbal remedies with conventional drugs by patients attending at least two (2) hospitals (secondary and tertiary) might provide insight on the possible interactions of these medications (herbal versus conventional) and the toxic outcome of such interactions. However, more studies on this issue and the exposure-associated effect of the polyherbal mixture on gene expressions and functions are recommended for further studies.

Implications of Findings

Effective communication of these findings among relevant stakeholders will aid policy formulations and implementation regarding the necessity for toxicological evaluations of herbal products and other quasi-drug formulations that freely circulate in the Nigerian market.

Conclusion

Since herbal drug formulations/dietary supplements are not under compulsory regulation by international, national, and local health regulatory authorities, these products must be manufactured using the highest manufacturing standards to ensure their safety among the end-users. Our findings suggest that the herbal formulation (Dr. Iguedo Goko Cleanser®) may have inherent abilities to induce varying degrees of toxicities, especially on long-term use. Contrary to the popular and general conception that herbal remedies due to their natural sources are entirely safe or devoid of toxicity, this study suggests the likelihood of exposure-associated non-carcinogenic adverse health effects. Therefore, the chronic and indiscriminate use of herbal formulation should be done with the utmost caution and be avoided wherever possible. If policy formulations and implementations regarding the safety of herbal medicines and associated products prior to their circulation are ensured, public health will be protected and significantly improved.

Disclaimer

It should be noted that the products used in this study are common products in our area of research and country. There is no conflict of interest whatsoever between the authors and producer of the product, especially as the authors do not intend to use these products as an avenue for any litigation but the advancement of scientific knowledge.

Conflicts of interest*:* None declared.

References

1 Akerele O. Nature's medicinal bounty: Don't throw it away. World Health Forum. 1993;14:390-395.

2 Saunders JE, Jastrzembski BG, Buckey JC, Enriquez D, MacKenzie TA, Karagas MR. Hearing loss and heavy metal toxicity in a Nicaraguan mining company: audiological results and case reports. Audiol Neurootolo. 2013;18(2):101-13. https://doi.org/10.1159/000345470.

3 Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ. Heavy metal toxicity and the environment. EXS. 2012;101:133-64. https://doi.org/10.1007/978-3-7643-8340_6.

4 Wang XL, Sato T, Xing BS, Tao S. Health risks of heavy metals to the general public in Tianjin, China via consumption of vegetables and fish. Sci. Total Environ. 2005;350:28-37. https://doi.org/10.1016/j.scitotenv.2004.09.044.

5 Solaade A. Assorted herbal mixtures: herbs or poison? [Internet] 2015 [Cited 2021 Aug 22]. Available from: https://parroteye.blogspot.com/2015/01/herbs-or-poison.html.

6 Säumel I, Kotsyuk I, Hölscher M, Lenkereit C, Weber F, Kowarik I. How healthy is urban horticulture in high traffic areas? Trace metal concentrations in vegetable crops from plantings within inner city neighbourhoods in Berlin, Germany. Environ Pollut. 2012;165:124-32. https://doi.org/10.1016/j.envpol.2012.02.019.

7 United States Environmental Protection Agency. Recommended protocols for measuring conventional water quality variables and metals in fresh water of the Puget Sound, 1200 6th Avenue Seattle, WA 98101. [Internet] 1900 [Cited 2021 Aug 22]. Available

from: https://www.psat.a.gov/Publications/protocols/protocol_pdfs.

8 Orisakwe OE, Dagur EA, Mbagwu HOC, Udowelle NA, Offor SJ. Levels of some heavy metals in vegetables from artisanal mining sites of Dilimi River, Bukuru and Barkin Ladi North Central Nigeria: any public health concern? Rocz Panstw Zakl Hig. 2018;69(4):335-45. https://doi.org/10.32394/rpzh.2018.0038.

9 United States Environmental Protection Agency. Risk Assessment Guidance for Superfund. Volume 1. Human Health Manual – Part E, Supplemental Guidance for Dermal Risk Assessment. Office of Superfund Remediation and Technology Innovation, Washington, D.C: United State Environmental Protection Agency; 2004.

10 Tripathi RM, Raghuanath R, Krishnamoorthy TM. Dietary intake of heavy metals in Bombay city, India J Sci Total Environ. 1997;208(3):149-59. https://doi.org/10.1016/s0048-9697(97)00290-8.

11 Orisakwe OE, Nduka JK, Amadi CN, Dike DO, Bede O. Heavy metals health risk assessment for population via consumption of food crops and fruits in Owerri, South Eastern Nigeria. Chem Century J. 2012;6:77.

12 Ekhator OC, Udowelle NA, Igbiri S, Asoumugha RN, Igweze ZN, Orisakwe OE. Safety evaluation of potential toxic metals exposure from street foods consumed in Mid-West Nigeria. J Environ Public Health. 2017;8458057. https://doi.org/10.1155/2017/8458057.

13 Igbiri S, Udowelle NA, Ekhator OC, Asoumugha RN, Igweze ZN, Orisakwe OE. Edible mushrooms from Niger Delta, Nigeria with heavy metal levels of public health concerns: a human health risk assessment. Recent Pat Food Nutr Agric. 2018;9(1):31-41. https://doi.org/10.2174/22122798409666171129173802.

14 Igbiri S, Udowelle NA, Ekhator OC, Asoumugha RN, Igweze ZN, Orisakwe OE. Polycyclic aromatic hydrocarbons in edible mushrooms from Niger Delta, Nigeria: carcinogenic and non-carcinogenic health risk assessment. Asian Pac J Cancer Prev. 2017;18(2):437-47. https://doi.org/10.22034/AJPCP.18.2.437

15 Udowelle NA, Igweze ZN, Asoumugha RN, Orisakwe OE. Health risk assessment and dietary exposure of polycyclic aromatic hydrocarbons (PAHs), lead and cadmium from bread consumed in Nigeria. Rocz Panstw Zakl Hig. 2017;68(3):269-80.

16 Harmanescu M, Alda LM, Bordean DM, Gogoasa I, Gergen I. Heavy metals health risk assessment for population via consumption of vegetables grown in old mining area; a case study: Banat County, Romania. Chem Cent J. 2011;5:64. https://doi.org/10.1186/1752-153X-5-64

17 Integrated Risk Information System. Regional screening level (RSL) summary table 2015 [Cited 2021 Aug 24] Available from: https://www.epa.gov/iris_pdf/.

18 Kamunda C, Mathuthu M, Madhuku M. Health risk assessment of heavy metals in soils from Witwaterssrand gold mining basin, South Africa. Int J Environ Res Public Health. 2016;13:633-44. https://doi.org/10.3390/ijerph3070663.

19 United States Environmental Protection Agency. Exposure Factors Handbook. [Internet] 2011a [Cited 2021 Aug 26]. Available from: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252

20 United States Environmental Protection Agency. USEPA regional screening level (RSL) summary table. [Internet] 2011b [Cited 2021 Aug 22]. Available from: https://www.epa.gov/regshwmd/risk/human/index.html

21 California Office of Environmental Health Hazard Assessment. Revised Draft: California Human Health Screening Level for Lead. [Internet] 2009 [Cited 2021 Aug 26]. Available from: https://oehha.ca.gov/risk/chhsl051809.html.

22 United States Department of Energy. The Risk Assessment Information System (RAIS). USDOE Oak Ridge Operations Office, Tennessee: United States Department of Energy; 2011.

23 Shah A, Niaz A, Ullah N, Rehman A, Akhlaq M, Zakir M et al. Comparative study of heavy metals in soil and selected medicinal plants. J Chem. 2013;2013:621265. https://doi.org/10.1155/2013/621265.

24 World Health Organization. Guidelines for the Safe Use of Waste Water, Excreta and Grey Water: Waste Water in Agriculture (Volume 2). Geneva: World Health Organization; 2006.

25 World Health Organization. Health Risks of Heavy Metals from Long-range Transboundary Air Pollution – Joint Task Force on the Health Aspects of Long-range Transboundary Air Pollution. Geneva: World Health Organization; 2007.

26 WHO/FAO. Guidelines for the Safe Use of Waste Water and Food Stuff: Waste Water in Agriculture (Volume 3). Geneva: World Health Organization; 2013.

27 WHO/FAO. General Standard for Contaminants and Toxins in Food and Feed (CODEX STAN 193 – 1995). Geneva: World Health Organization; 2015.

28 United States Food and Drug Administration. Code of Federal Regulations (CFR) Title 21: Food for Human Consumption – Requirements for Specific Standardized Beverages. [Internet] 2018 [Cited 2021 Aug 30]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=165.110

29 Hassan Z, Anwar Z, Khattak KU, Islam M, Khan RU, Khattak JZK. Civic pollution and its effects on water quality of River Toi at district Kohat, NWFP. Res J Environ Earth Sci. 2012;4(3):334-39.

30 Asomugha RN, Udowelle NA, Offor SJ, Njoku CJ, Ofoma IV, Chukwuogor CC et al. Heavy metals hazards from Nigerian spices. Rocz Panstw Zakl Hig. 2016;67:309-14.

31 Rehman K, Fatima F, Waheed I, Akash MSH. Prevalence of exposure of heavy metals and their impact on health consequences. J Cell Biochem. 2017;119(1):157-84.

https://doi.org/10.1002/jcb.26234.

32 Orisakwe OE. Lead and cadmium in public health in Nigeria: Physicians neglect and pitfall in patient management. New Am J Med Sci. 2014;6:61-70.

33 Podsiki C. Chart of heavy metals, their salts and other compounds. [Internet] 2008 [Cited 2021 Aug 30]. Available from: https://www.conservation-us.org/docs/default-source/resource-guides/chart-of-heavy-metals-theirsalts-and-other-compounds-nbsp-pdf.

34 Ogwuegbu MO, Muhanga W. Investigation of lead concentration in the blood of people in the copper belt province of Zambia. J Environ. 2005;11:66-75.

35 Agency for Toxic Substances and Disease Registry. Chromium toxicity: what are the physiologic effects of chromium exposure? [Internet] 2013 [Cited 2021 Aug 29]. Available from: https://www.atsdr.cdc.gov/csem/csem.asp?csem=10&po=10

36 Agency for Toxic Substances and Disease Registry. Toxicological Profiles, Toxic Substances Portal. Atlanta: Agency for Toxic Substances and Disease Registry; 2015.

37 Liu J, Zhang XH, Tran H, Wang DQ, Zhu YN. Heavy metal contamination and risk assessment in water, paddy soil, and rice around an electroplating plant. Environ Sci Pollut Res. 2011;18(9):1623-32. https://doi.org/10.1007/s11356-011-0523-3.

38 Liu X, Song Q, Tang Y, Li W, Xu J, Wu J et al. Human health risk assessment of heavy metals in soil-vegetable system: a multi medium analysis. Sci Total Environ. 2013;(463-464):530-40. https://doi.org/10.1016/j.scitotenv.2013.06.064.