Hazards and risk assessment of heavy metals from consumption of locally manufactured painkiller drugs in Nigeria

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ABSTRACT

In the informal sector of Nigeria’s economy, jobs are done manually as against automation resulting in body stress and pain, hence the need for painkiller drugs. Thirty different locally manufactured painkiller drugs, with analgesic, antipyretic and anti-inflammatory effects, were randomly sampled from pharmaceutical shops within Awka in October 2016. The drugs were pulverised, sieved and ashed before digestion using conc aquea regia HCl: HNO3 (3:1), carcinogenic heavy metals (arsenic, cadmium, chromium, mercury, nickled and lead) were assayed using Varian AA240 atomic absorption spectrophotometer (AAS). Risk assessment was carried out using US EPA model. The highest levels of arsenic (0.350 mg/kg) were found in samples with code 01, 03 and 020, cadmium (0.107 mg/kg and 0.144 mg/kg) were in samples code 013 and 028, and samples 03 and 011 had chromium levels as 6.637 mg/kg and 5.298 mg/kg. Highest value of mercury (0.470 mg/kg) was in sample code 01. All the painkiller drugs have nickel in the range of 0.046-0.448 mg/kg while highest values of lead were in sample code 05, 025 and 029 as 2.47 mg/kg, 1.11 mg/kg and 1.16 mg/kg. Non-cancer risk ranged as As (Nd-1.60×10-7), Cd (Nd-1.97×10-4), Cr (Nd-6.06×10-5), Hg (Nd-2.15×10-5), Ni (9.93×10-6-3.34×10-5) and Pb (Nd-4.36×10-4) while the cancer risk were As (Nd-1.63×10-7), Cd (Nd-4.45×10-6), Cr (Nd-1.56×10-4), Hg (Nd-1.53×10-6), Ni (1.50×10-10 -1.46×10-9) and Pb (Nd-8.82×10-6). The total cancer risk (TCR) and total non-cancer risk (TNCR) for all the heavy metals were in the range of 7.21×10^-4-1.51×10^-7 to 5.56×10^-5 respectively. The TCR was below 1 × 10^-6 -1 × 10^-4 range while TNCR for heavy metals was below 1; the values established by US EPA. In conclusion, continuous consumption of locally Nigerian made painkiller drugs may expose the subjects to heavy metal toxicity.

1. Introduction

Literacy statistics of 59.6 % cannot be regarded as a literate society in today’s modern world. Hence, it implies that higher population of Nigerians may not be aware of twin health hazards that may be caused on possible medical diagnostics result of ailments from painkiller drugs, heavy metal and other chemical constituents [1]. Rapidly growing and unregulated informal sector of the economy consisting of peasants, micro scale and several uncategorized occupation [2] is a sector of un-specialized skills where most jobs are at crude level and labour intensive, its intensity may result to body stress as most work place activities are still done manually against automation. The end result is somatic, neuropathic and dysfunctional pain, commonest amongst them are muscular pain and headache [3]. Treatment of pain is both physically and emotionally based but medications, have an overriding influence. The International Association for the Study of Pain defines it as encompassing damage to tissue and emotional fit associated with such damage [4]. A good number of pain tend to diminish on elimination of its cause while in some, it may persist despite removal of the inducer or more so when the cause is unknown [5]. Besides daily labourers on the lower rung of the economic indices, who are more prone to pain due to occupational and environmental hazard, most other citizens of different economic strata (professionals or semi-professionals) also experience pain. Pain is a form of medical condition with classification according to (a) “region of body involved- abdomen, lower limbs” (b) “system whose dysfunction may be causing the pain- nervous and gastrointestinal systems” (c) “duration and pattern of occurrence” (d) “intensity and time since onset and etiology” [6], though acceptance of this classification by

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medical professionals vary and were highly criticized [7]. Analgesics or painkillers are types of drugs used to soothe or eliminate pain [8]. They can in some conditions, through prolonged use or on addiction be a cause of attention or medical concern such as constipation [9], nausea, vomiting, drowsiness, itching, opioid-induced hyperalgesia [10], hormonal imbalance [11], work place disruption [12], erectile dysfunction, gastrointestinal effect, renal failure [13], increased proneness to accident [14], some of which has been ascribed to heavy metals. The six heavy metals - Arsenic (As), Cadmium (Cd), chromium (Cr), lead (Pb), mercury (Hg) and nickel (Ni) evaluated and found to be present, mimic and distort hormones and act as endocrine disruptors [15], thereby with ingestion of the locally made painkiller drugs and (c) establishment of contents may pose related risks as enumerated above. An often over looked health hazard is a possibility of association of pain drugs with disorders, liver failure, diabetes mellitus, cancer [17], cardiovascular disease (CVD), blood pressure (BP) and atherosclerosis [18], bronchiole phagia. The human body may also through trophic level and industrialization be increasingly subjected to heavy metal overload. Locally manufactured painkiller drugs possibly laden with heavy metals are veraciously consumed in Nigeria. Non adherence to good manufacturing practices and inadequate raw materials processing may be possible sources of heavy metals in drugs. The main objectives of the current study is (a) determination of carcinogenic heavy metals, (Hg, Cd, Ni, Cr, Pb and As) concentration in Nigerian locally made painkiller drugs, (b) evaluation of carcinogenic and non-carcinogenic health risk associated with ingestion of the locally made painkiller drugs and (c) establishment or evaluation of true metal intake.

2. Materials and method

2.1. Sampling and sample preparation

Thirty analgesics, one packet for each drug type, were purchased from retail medicine outlets in Awka, Anambra State, Nigeria in September 2016 and were utilized in the analysis. Information on product labels and packets were noted. Aliquot samples of painkiller drugs were ashed and digested using Teflon lab wares previously cleaned in a high-efficiency particulate air (HEPA) filtered (class 100) clean laboratory to ensure non-metal impurities contamination. Cleaning of experimental wares was carried out in solutions using baths followed by 6 NHCl (reagent grade) solution with distilled-deionized water rinses and finally 7.5 N HNO₃ and ultra-pure water rinses. The lab wares were then dried using air heated to dryness. 20 mL de-ionised water was added, stirred and digested by addition of 10 mL conc. aqua regia (3:1; HCl: HNO₃, heated to dryness. 20 mL de-ionised water was added, stirred and filtered [24].

2.2. Sample analysis

The filtrates were made up in standard volumetric flask. Cadmium, lead, mercury, arsenic, nickel and chromium were assayed using Varian AA240 atomic absorption spectrophotometer according to American Public Health Association [25] with a detection limit of 0.001. The background level of blank was 0.001 mg/L.

The true metal intake using simple linear arithmetic mean according to Parkhurst [26], was calculated by multiplying contaminant level i.e., heavy metal level in the painkiller drug by the amount of painkiller drug intake per day. In all, the estimated or calculated levels of cadmium, lead, mercury, arsenic, nickel and chromium in the drugs were determined in selected few. 3000 mg (3 g) was assumed to be the average intake amount per day for each of the painkiller drugs. 1.5 g sample gave value of metals as depicted in Table 1. A prescription of 2 tablets x 3 per day (2 tablets each in the morning, afternoon and night, a tablet is 500 mg 2 x 3 = 3000 mg/1000 = 3 g). Example of true metal intake was calculated using four painkiller drugs coded 001, 002, 003 and 005.

2.3. Human health risk assessment

(a) Chronic Daily Intake(Carcinogens) \[CDI_{CA} = \frac{CS \times IR \times EF \times ED \times CF}{BW \times AT}\] (1)

Where: CS depict exposure point concentration: mg/kg, IR is ingestion rate: 100 mg/d⁻¹, EF is exposure frequency: 350 d/a, ED is exposure duration: 30a [27,28], BW is Body Weight: 70 kg [29], AT is averaging time for carcinogens is 365 x 70d, CF is Units conversion factor (10⁻⁶ kg mg⁻¹) [30]

(b) Chronic Daily Intake(Non-carcinogens) \[CDI_{nca} = \frac{CS \times IR \times EF \times ED \times CF}{BW \times AT}\] (2)

Where: CS is exposure point concentration: mg/kg, IR is ingestion rate: 100 mg.d⁻¹, EF is exposure frequency: 350 d/a, ED is exposure duration: 30a [27,28], BW is Body Weight: 70 kg [29], AT is averaging time for non-carcinogens = 365 x EEd [27,28], CF is Units conversion factor: 10⁻⁶ kg mg⁻¹ [30]

(c) Non-cancer risk (hazard quotient) HQ = CDI/RFDₐ

CDI is chronic daily intake (non-carcinogens) (mg kg⁻¹ d⁻¹), RFDₐ is chronic reference dose of the toxicant (mg kg⁻¹ d⁻¹); [RFDₐ = Cd (0.0005); Cr (0.005); Ni (0.02); As (0.0003); Hg (0.003); Pb (0.0035)] [31]

Non-cancer risk (HQ) is the ratio of exposure to hazardous substances and translates into the total non-cancer risk (chronic hazard index) [HI] [32,33].

\[TTHQ = THQ_{As} + THQ_{Cd} + THQ_{Cr} + THQ_{Hg} + THQ_{Ni} + THQ_{Pb}\] (4)

Addition of hazard quotient of each of the metals in all the drugs

\[Hazard\ index\ due\ to\ heavy\ metals = \sum CDI_{k} / RFD_{h}\] (5)

HI is the sum of more than one HQ for multiple substances or addition of hazard quotient of all the heavy metals in each drug. The acceptable value for the HI set by US EPA is < 1 [31]

\[(d)\ Cancer\ Risk = CDI \times SF\]

CDI is chronic daily intake (carcinogens) (mg kg⁻¹ d⁻¹), SF is slope factor (mg kg⁻¹ d⁻¹), calculated using the equation [34]:

\[Cumulative\ cancer\ risk = CR_{As} + CR_{Cd} + CR_{Cr} + CR_{Hg} + CR_{Ni} + CR_{Pb}\] (7)

This is linear summation of cancer risk of each heavy metal present in
the 30 drug sample (if present) [1,28].

Slope factor (SF) = 1/6 (ED)  

But the total cumulative cancer risk can be calculated from [31]:

\[
\text{Total cancer risk due to heavy metal} = \sum_{i=1}^{n} C \text{DI}_i \times \text{SF}_k
\]

This is the totality of cancer risk of all the heavy metals present in each drug sample.

The acceptable standard cancer risk value set by the US EPA is \(1 \times 10^{-6} - 1 \times 10^{-4}\) [31].

3. Results

Table 1 contains information on 30 Nigerian locally manufactured painkiller drugs. 83.33 % of the samples contain arsenic, 80 % contain cadmium, 36.67 % contain chromium while 33.33 % contain mercury. 83.33 %, 80 %, 36.67 %, 33.33 %, 100 %, and 80 % of all the drug sample contain near toxic levels of As\(^{+3}\), Cd\(^{+2}\), Cr\(^{+6}\), Hg\(^{+2}\), Ni\(^{+2}\) and Pb\(^{+2}\), 19 (63.33 %) of the painkiller drugs contain nickel, arsenic and cadmium, while 100 % of the drugs contained nickel. 76.67 % of the drug samples contain lead (Nd-6.06E-6), and mercury (Nd-2.150E-4), lead (Nd-4.360E-4) and arsenic is in the range of Nd-1.600E-3, cadmium (Nd-1.973E-4), chromium (Nd-9.092E-6), mercury (Nd-6.438E-7), lead (Nd-.379 E-6) and nickel (6.301E-8 -2.753E-6). Arsenic is in the range of Nd-4.795E-7, cadmium (Nd-1.973E-7), chromium (Nd-3.897E-6); mercury (Nd-2.055E-7; Cd (Nd-8.454E-8; chromium (Nd-3.897E-6); mercury (Nd-2.055E-7) while nickel ranged from 9.511E-8 to 2.055E-7).

For arsenic, the range is Nd-2.759E-7 considering their carcinogenic health effect. For arsenic, the range is Nd-2.759E-7 while nickel ranged from 9.511E-8 to 2.055E-7.

Table 2 shows that chronic daily intake (CDI) of the metals when considering their carcinogenic health effect. For arsenic, the range is Nd-2.055E-7; Cd (Nd-8.454E-8; chromium (Nd-3.897E-6); mercury (Nd-2.759E-7) while nickel ranged from 9.511E-8 to 2.630E-7 but lead (Nd-1.448E-6).

Table 3 shows the chronic daily intake of non-carcinogenic effects. Arsenic is in the range of Nd-4.795E-7, cadmium (Nd-1.973E-7), chromium (Nd-9.092E-6), mercury (Nd-6.438E-7), lead (Nd-3.797E-6) and nickel (6.301E-8 - 2.753E-6).

Table 4 shows the non-cancer health risk of the heavy metals. That of arsenic is in the range of Nd-1.600E-3, cadmium (Nd-1.973E-4), chromium (Nd-6.06E-6), and mercury (Nd-2.150E-4), lead (Nd-4.360E-4) while nickel ranged from 9.930E-6 – 3.340E-5.
Table 5 shows cancer health risk values of the metals. Arsenic ranges from \( \text{Nd} - 1.631 \times 10^{-7} \), cadmium (\( \text{Nd} - 4.453 \times 10^{-9} \)), chromium (\( \text{Nd} - 1.562 \times 10^{-7} \)), lead (\( \text{Nd} - 8.823 \times 10^{-9} \)), mercury (\( \text{Nd} - 1.534 \times 10^{-9} \)) while nickel is in the range of \( 8.806 \times 10^{-10} – 1.416 \times 10^{-9} \).

Table 6 is a linear summation of each target quotient of each metal in all the drug and were in the range of \( 1.859 \times 10^{-5} \) (Cr) – \( 1.803 \times 10^{-2} \) (As) while the cumulative summation of cancer risk of each heavy metal in all the drugs ranged from \( 3.523 \times 10^{-9} \) (Hg) – \( 2.21 \times 10^{-7} \) (Cr).

Table 7 shows the total cancer and non-cancer health risk of five heavy metals in each drug. Total cancer risk ranged from \( 9.849 \times 10^{-15} – 1.251 \times 10^{-10} \).
while that of total non-cancer risk is in the range of 6.757E-7 – 3.602E-5.

### 4. Discussion

Impurity drug profile lies between organic and inorganics. Heavy metals are the main inorganic drug impurity which en-routes the bulk drugs and its intermediates via a number of processes [35]. Since drugs were not envisaged to contain toxic substances, safe levels of toxic As\(^{3+}\), Cd\(^{2+}\), Cr\(^{6+}\), Hg\(^{2+}\), Pb\(^{2+}\) and Ni\(^{2+}\) may not have been established [36], but a lot of data on toxic metals in pharmaceuticals abound [22,23].

### Table 4

Non-cancer risk (HQ) effect of heavy metals through painkiller drugs.

| S/N | Sample code | As       | Cd        | Cr        | Hg        | Ni        | Pb        |
|-----|-------------|----------|-----------|-----------|-----------|-----------|-----------|
| 1.  | 010         | 1.60E-3  | ND        | ND        | 2.15E-4   | 8.56E-6   | ND        |
| 2.  | 020         | 6.85E-4  | 1.718E-5  | ND        | 2.15E-4   | 6.85E-6   | ND        |
| 3.  | 030         | 1.598E-3 | 2.740E-5  | 6.06E-6   | ND        | 2.98E-6   | ND        |
| 4.  | 040         | 1.14E-3  | 2.12E-6   | 4.57E-5   | ND        | 1.37E-5   | ND        |
| 5.  | 050         | 2.28E-4  | ND        | 6.90E-5   | ND        | 1.19E-5   | 4.229E-04|
| 6.  | 060         | 6.85E-4  | 8.094E-5  | ND        | 3.15E-5   | 1.53E-5   | ND        |
| 7.  | 070         | 2.28E-4  | ND        | ND        | 1.85E-5   | ND        |
| 8.  | 080         | 1.14E-3  | 4.521E-5  | ND        | 3.34E-5   | 3.511E-04|

### Table 5

Cancer risk effect of heavy metals through painkiller drugs.

| S/N | Sample code | As       | Cd        | Cr        | Hg        | Ni        | Pb        |
|-----|-------------|----------|-----------|-----------|-----------|-----------|-----------|
| 1.  | 010         | 1.142E-9 | ND        | ND        | 1.534E-9  | 4.08E-10  | ND        |
| 2.  | 020         | 4.893E-10| 9.902E-11 | ND        | 3.55E-10  | 3.26E-10  | ND        |
| 3.  | 030         | 1.142E-9 | 1.52E-10  | 2.16E-8   | ND        | 1.41E-6   | ND        |
| 4.  | 040         | 8.156E-10| ND        | 7.56E-9   | 3.26E-10  | 6.52E-10  | ND        |
| 5.  | 050         | 1.631E-10| ND        | ND        | 4.92E-10  | 5.64E-10  | 8.04E-09  |
| 6.  | 060         | 1.631E-8 | 4.947E-10 | ND        | 3.75E-10  | 7.27E-10  | ND        |
| 7.  | 070         | 1.631E-7 | ND        | ND        | 8.80E-10  | 3.45E-09  | ND        |
| 8.  | 080         | 8.156E-10| 2.51E-10  | ND        | 1.46E-9   | 6.82E-09  | ND        |
| 9.  | 090         | 1.631E-10| 3.95E-9   | 6.32E-10  | 2.15E-10  | 6.45E-10  | 3.95E-09  |
| 10. | 010         | 1.631E-10| ND        | ND        | 5.90E-10  | 2.26E-09  | ND        |
| 11. | 011         | 8.156E-10| 2.28E-11  | ND        | ND        | 7.44E-10  | 4.45E-09  |
| 12. | 012         | 8.156E-10| 4.53E-9   | 1.72E-8   | ND        | 8.41E-10  | 3.48E-09  |
| 13. | 013         | 1.631E-10| 2.28E-11  | 4.23E-9   | ND        | 8.54E-10  | 1.45E-09  |
| 14. | 014         | 8.156E-10| 3.44E-9   | ND        | 1.63E-11  | 3.62E-10  | ND        |
| 15. | 015         | 1.631E-10| 8.37E-11  | ND        | 1.50E-10  | 3.41E-10  | ND        |
| 16. | 016         | 1.631E-10| 8.14E-10  | 6.70E-9   | ND        | 4.66E-10  | 1.11E-09  |
| 17. | 017         | ND        | ND        | ND        | 4.27E-10  | 6.15E-09  | ND        |
| 18. | 018         | 1.631E-10| 6.39E-10  | ND        | 5.90E-10  | 3.66E-09  | ND        |
| 19. | 019         | 1.631E-10| 5.48E-10  | ND        | 5.28E-10  | 3.07E-09  | ND        |
| 20. | 020         | 1.142E-10| 1.52E-10  | ND        | 6.48E-10  | 8.31E-09  | ND        |
| 21. | 021         | 4.893E-10| 1.82E-10  | ND        | 4.56E-10  | 4.95E-09  | ND        |
| 22. | 022         | ND        | 3.65E-10  | 1.46E-9   | ND        | 3.94E-09  | ND        |
| 23. | 023         | ND        | 2.81E-10  | 5.31E-10  | ND        | 2.26E-09  | ND        |
| 24. | 024         | 1.631E-10| 8.75E-10  | ND        | 4.73E-10  | 6.07E-10  | ND        |
| 25. | 025         | 2.935E-10| 6.62E-10  | 1.56E-7   | ND        | 1.10E-6   | 8.47E-09  |
| 26. | 026         | ND        | 4.33E-10  | ND        | 5.67E-10  | 6.95E-09  | ND        |
| 27. | 027         | 1.631E-10| 4.56E-10  | ND        | 8.40E-10  | 5.70E-09  | ND        |
| 28. | 028         | 1.631E-10| 1.599E-10 | 2.63E-9   | ND        | 5.25E-10  | 8.82E-09  |
| 29. | 029         | ND        | 7.15E-10  | ND        | 2.61E-11  | 1.09E-9   | 8.82E-09  |
| 30. | 030         | 1.631E-10| 6.01E-10  | 2.11E-9   | 1.73E-10  | 6.56E-10  | 7.59E-10  |

RfD\(_O\) = Cd (0.0005); Cr (0.005); Ni (0.02); As (0.0003); Hg (0.003); Pb (0.0035).
as both enjoy high patronage in Nigeria. The values of Cd in drugs may portend danger to public health but in conjunction with painkiller drugs. Total cancer risk and total non-cancer risk effect of heavy metals through exposure through intake of organic and inorganic air-driven suspensions [49–51], can add to the public heavy metal exposures, hence the human internal organs and systems may increasingly accumulate heavy metals. Chronic daily intake (CDI) for carcinogenic risk (Table 2) and non-carcinogenic health effects (Table 3) show similarity of values but with minor variations. The metals CDI values were in exponential range of $10^{-6} - 10^{-9}$, maximum values were $1.448 \times 10^{-6}, 3.897 \times 10^{-6}, 2.055 \times 10^{-7}, 8.454 \times 10^{-8}, 2.759 \times 10^{-7}$ and $2.630 \times 10^{-7}$ for Pb, Cr, As, Cd, Hg and Ni (carcinogens) (Table 2) while non-carcinogenic effect were in exponential range of $10^{-6} - 10^{-9}$ with maximum of $3.379 \times 10^{-6}, 9.092 \times 10^{-6}, 4.795 \times 10^{-7}, 1.973 \times 10^{-7}$, $6.438 \times 10^{-7}$ and $6.685 \times 10^{-7}$ values of Pb, Cr, As, Cd, Hg and Ni (Table 3). Total target hazard quotient (TTHQ) is a linear summation of target hazard quotient (Table 4) of each heavy metal in all the drug samples (Table 6), from Table 6, TTHQ As $>$ TTHQ Pb $>$ TTHQ Cd $>$ TTHQ Hg $>$ TTHQ Ni $>$ TTHQ Cr, while hazard indices (HI) is the summation of hazard quotient (HQ) of all the heavy metals (As, Cd, Cr, Hg, Ni, Pb) in each of the drug sample. TTHQ, TQH or HI values greater than 1 is a chance for non-carcinogenic effect - diabetes, blood disease (increased blood pressure (HBP), stroke, hypertension), skeletal defect, paralysis [17,18,20], but when HI $< 1$, shows non-likelihood of occurring or acceptable risk for chronic systemic effect [31–33]. The results of our study (Tables 4 and 6) are all below 1 (the tipping point value) established by the US EPA for non-cancer health issues, but the probability of other sources or additive effect of all the metals in this study may trigger public health crises [42,51]. The cancer risk as depicted in Table 5 were well below $1 \times 10^{-6}$ minimum value in a range of $1 \times 10^{-6} - 1 \times 10^{-9}$ US EPA standard value for cancer related issues as against $1 \times 10^{-12} - 1 \times 10^{-7}$ obtained in our study (Table 5). US EPA document states that cancer risk can be non-existent or insignificant when incremental life cancer risk (ILCR) value is lower than 1 $\times 10^{-6}$ but when ILCR equates to or surpasses $1 \times 10^{-6}$ are important in risk study [29]. An incremental lifetime cancer risk (ILCR) above one in ten, 0,000, meaning ILCR-$10^{-6}$ is a situation for enquiry but when it is one-thousandth (1/1000) or greater (ILCR $> 10^{-3}$) is a risk for further study. Linear addition of cancer risk or cumulative cancer risk (CCR) is a summation of cancer risk of each heavy metal in all the drug sample and it depicts CCR$_{Cr}$ ($2.210 \times 10^{-7}$) as highest risk while CCR$_{Hg}$ ($3.523 \times 10^{-6}$) as the lowest risk (Table 6) [34], but the total cancer risk is the addition of cancer risk of all metal per drug sample (Table 7). The total cancer and non-cancer risks depicted in Table 7 shows exponential range of $9.849 \times 10^{-13}-1.251 \times 10^{-10}$ for total cancer risk (TCR) and $6.757 \times 10^{-7}-5.560 \times 10^{-5}$ for total non-cancer risk (TNCR). All the heavy metals per drug sample (As, Cd, Cr, Hg, Ni, Pb) present in this study are studied to exhibit carcinogenic properties. Meanwhile, the values from Tables 2–7 were below comparative standards for carcinogenic and non-carcinogenic health effect of As$^{3+}, Cd^{2+}, Cr^{6+}, Hg^{2+}, Ni^{2+}, Pb^{2+}$. The values above may double or triple to a health crises emergency situation if the values of true or calculated metal intake were adopted in calculation of cancer and non-cancer risks (Table 8). The health hazards assumption from this work can be supported with the fact that tissues specimen of cancer patient showed As$^{3+}, Cd^{2+}, Cr^{6+}, Hg^{2+}, Pb^{2+}$ and Hg$^{2+}$ [52] with evidence of consumption of grains cultivated on heavy metal contaminated soil, it can therefore be correlated that the
skills. The product hidden ingredients in painkiller drugs and will improve their diagnostic when there is compliance with prescription but adverse effects have synergistically (Table 9). Drugs or excipients are, on the whole, safe (Table 9) and can exhibit twin negative health effect, as both can act

tered and properly documented by the food and drug regulatory au-
tority in Nigeria. It therefore, means that heavy metal monitoring may raise serious concern. Summation of these findings with the fact that ingestion of these painkiller drugs will expose an individual to the hazards of painkiller drugs and heavy metals, especially with the amount used for the analysis, we randomly used drugs samples coded 001, 002, 003 and 005 for true intake calculation).

same metals found in painkiller drugs may likely have the same effect, placing this side by side with the fact that exposing human tissues to analgesics hinders sperm and egg maturity [53]. Ovaries exposed to Ibuprofen experience two-ﬁfths drastic reduction in egg production and hastened menopause in female; a quartet reduction in sperm producing cells is observed when testicular tissue is subjected to either paracetamol or Ibuprofen [53,54]. Looking at the values of the true metal intake (Table 8), higher concentration or more of these metals can be ingested, most likely when they are abused, on prolonged usage or addiction. Estimated or the calculated true intake of As, Cd, Cr, Hg, Ni, and Pb shown in Table 8 was done by selecting the most frequently consumed painkiller drugs coded 001, 002, 003 and 005. The four most patronized painkiller drugs (coded 010, 02, 03, and 05) on exposure per day totalled -As (1.80 mg/kg), Cd (0.066 mg/kg), Cr (13.274 mg/kg), Hg (1.458 mg/kg), Ni (1.664 mg/kg), and Pb (4.940 mg/kg). These values raise serious concern. Summation of these ﬁndings with the fact that heavy metals, phthalates, parabens, phenols etc. and their precursors contained in some consumables-creams, lotions, toothpaste, fashion enhancers which are in high demand in Nigeria [1,46,54] cause early puberty in adolescents [55,56], assume hormonal action by manipu-

Table 8
Calculation of true metal intake.

| True metal intake | Calculation | Total intake of metal |
|-------------------|-------------|-----------------------|
| As 2 mg x 0.350 + 2 mg x 0.150 + 2 mg x 0.350 + 2 mg x 0.050 | 1.80 mg/kg, As | 2 mg x nd + 2 mg x 0.013 + 2 mg x 0.020 + 2 mg x nd | 0.066 mg/kg, Cd |
| Cr 2 mg x nd + 2 mg x nd + 2 mg x 6.637 + 2 mg x nd | 13.274 mg/kg, Cr | Hg 2 mg x 0.470 + 2 mg x 0.108 + 2 mg x nd + 2 mg x 0.151 | 1.458 mg/kg, Hg |
| Ni 2 mg x 0.125 + 2 mg x 0.100 + 2 mg x 0.434 + 2 mg x 0.171 | 1.664 mg/kg, Ni | Pb 2 mg x nd + 2 mg x nd + 2 mg x nd + 2 mg x 2.470 | 4.940 mg/kg, Pb |

( prized this side by side with the fact that exposing human tissues to analgesics hinders sperm and egg maturity [53]. Ovaries exposed to Ibuprofen experience two-ﬁfths drastic reduction in egg production and hastened menopause in female; a quartet reduction in sperm producing cells is observed when testicular tissue is subjected to either paracetamol or Ibuprofen [53,54]. Looking at the values of the true metal intake (Table 8), higher concentration or more of these metals can be ingested, most likely when they are abused, on prolonged usage or addiction. Estimated or the calculated true intake of As, Cd, Cr, Hg, Ni, and Pb shown in Table 8 was done by selecting the most frequently consumed painkiller drugs coded 001, 002, 003 and 005. The four most patronized painkiller drugs (coded 010, 02, 03, and 05) on exposure per day totalled -As (1.80 mg/kg), Cd (0.066 mg/kg), Cr (13.274 mg/kg), Hg (1.458 mg/kg), Ni (1.664 mg/kg), and Pb (4.940 mg/kg). These values raise serious concern. Summation of these ﬁndings with the fact that heavy metals, phthalates, parabens, phenols etc. and their precursors contained in some consumables-creams, lotions, toothpaste, fashion enhancers which are in high demand in Nigeria [1,46,54] cause early puberty in adolescents [55,56], assume hormonal action by manipu-

Table 9
Comparison of some hazardous effect of painkiller drugs with that of heavy metals.

| S/ No | Painkiller drug effect | References | Heavy metal effect | References |
|-------|------------------------|------------|--------------------|------------|
| 1     | Constipation            | 9          | Cd (abdominal cramps and vomiting) | 57         |
| 2     | Respiratory Depression  | 11         | As (Respiratory effect- laryngitis, bronchitis rhinitis and Bracheebronchitis) | 58         |
| 3     | Hyperalgiesia           | 10         | Ni (Alveolar congestion and alveolar cell hyperplasia) | 59         |
| 4     | Hormone imbalance       | 11         | Cd, Cr<sup>2+ </sup>, Ni, Hg (Endocrine disruptors and Metallolethromes), As (chromosomal aberrations in peripheral lymphocytes) | 17,18      |
| 5     | Gastrointestinal effect | 13         | As (Gastrointestinal effect) | 60         |
| 6     | Renal problems          | 6          | Cd (Renal effect) As (Renal effect) | 17,19      |
| 7     | Cardiovascular and congestive heart failure | 10 | As, Pb (Cardiovascular disease, myocardial infarction and arterial thickening, heart failure) | 18,61      |
| 8     | Fractures and Arthrities | 6          | Cd (Osteomalacia, osteopenia and spontaneous fractures) | 57         |
| 9     | Central nervous system disorder | 10 | Hg (Neurological disorders, total damage to the brain and central nervous system (CNS)) | 62         |

(Some health effects caused by painkiller drugs compared well with those of heavy metals and can act synergistically).

of the drug sample while Ni were contained in all of them. However, all the product’s labels contain regulatory agent’s numbers. This implies that ingestion of these painkiller drugs will expose an individual to the twin health effect of painkiller drugs and heavy metals, especially with cases of over dose, prolonged usage or on abuse. The chronic daily intake (CDI) values for metals ranged from 1 × 10<sup>-6</sup> – 1 × 10<sup>-9</sup> while carcinogenic and non-carcinogenic effect of the metals were below 1 × 10<sup>-6</sup> and one (1). Heavy metals and painkiller drugs can act singly or synergistically to mimic hormones and may impair human health by distorting DNA, thereby causing permanent negative health desirability. The regulatory body in Nigeria should be encouraged to step up its monitoring activities to include heavy metals so as to reduce public health burden that may result when they are consumed.

5. Conclusion

The results have shown that 26 (86.67 %) of the drug samples contain at least four of the six carcinogenic metals (As, Cd, Cr, Ni, Pb and Hg) evaluated. All the drug sample (100 %) contain nickel while sample 030 contain all (100 %) heavy metals. Cadmium was contained in 80 %

Author Statement

John Kanayocukwu Nduka, conceived, designed the work and carried out the laboratory work
Henrietta Ijeoma Kelle sourced the litratures
John Kanayocukwu Nduka and Henrietta Ijeoma Kelle did the calculations
Emeka Chima Ogoko reviewed the entire manuscript
All the author contributed financially for the work

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Declaration of Competing Interest

The authors declare no conﬂict of interest.
Appendix A. Supplementary data

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