



RESEARCH ARTICLE

REVISED Assessment of Arsenic, Vanadium, Mercury, and Cadmium in Food and Drug Packaging [version 3; peer review: 2 approved, 1 not approved]

Previously titled: Assessment of heavy metals in food and drug packaging materials

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Abstract

Background

Food and drug packaging materials are an integral part of our everyday life. Noxious elements can inadvertently be included in packaging materials in various stages of their production. Adulterants, adhesives, colorants and heavy metal interference are the common sources of contamination in food packaging materials. Heavy metal toxicity has far-reaching ill effects on living organisms. The present study aimed at qualitatively and quantitatively analysing heavy metal content of various materials that are used for food and drug packaging in India.

Methods

The qualitative detection was done by rapid assay and heavy metals were quantified with the help of inductively coupled plasma-optical emission spectrometry (ICP-OES). A total of thirteen types of food and drug packaging materials were procured from local market and analysed for four heavy metals *viz.* arsenic (As), vanadium (V), mercury (Hg) and cadmium (Cd). The concentration of each heavy metal in the samples was compared with the permissible values published by the European Council.

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Approval Status

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Any reports and responses or comments on the article can be found at the end of the article.

Results

Heavy metals were qualitatively detected in ten out of thirteen samples. Among the ten samples mercury and arsenic were detected the most followed by cadmium and vanadium. Quantitative estimation by ICP-OES showed presence of vanadium and cadmium in ten samples and arsenic and mercury in all the thirteen samples above the permissible range.

Conclusions

The notable elevation in mercury concentration, followed by cadmium, arsenic and vanadium registering the least, presents a potential health hazard to consumers and compromises the food quality.

Keywords

Drug, Food, Heavy Metal, ICP-OES, Packaging Material



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REVISED Amendments from Version 2

In response to reviewer's suggestions, significant enhancements have been incorporated into the manuscript, with reference to arsenic, vanadium, mercury, and cadmium in food and drug packaging materials. One notable modification is in the title of the manuscript focusing four heavy metals considered in the study. The updated guidelines issued by the European Council for Food Packaging Association, specifically the Nordic guidance for authorities, have been included in the manuscript to explain the permissible limits of the select heavy metals found in food and drug packaging materials. These guidelines provide essential insights and regulations regarding the permissible levels of heavy metals in food contact materials, serving as a crucial reference point for evaluating the safety and compliance of packaging materials. Moreover, the inclusion of calibration graphs and detailed specifications on the detection limits for each heavy metal analysed enhances the methodological accuracy and rigor of the study. By presenting this information, the manuscript offers readers an inclusive understanding of the analytical techniques employed and the precision of the measurements obtained, reinforcing the credibility and reliability of the research outcomes. In addition, the discussion section has been elaborated to provide more inclusive consistent analysis of the findings, drawing upon relevant studies to emphasize the significance of heavy metal content in food and drug packaging materials. These corroborative evidences have led to the addition of five more references in the manuscript that elucidates the multifaceted implications of heavy metal exposure on public health and environmental sustainability, fostering a more comprehensive understanding of the issue among readers and stakeholders. The improvements made to the manuscript not only enhance its scholarly credibility and scientific understanding, but also stress upon the need for development of evidence-based policies and regulatory frameworks to assess the heavy metal content within the permissible limits in food and drug packaging materials.

Any further responses from the reviewers can be found at the end of the article

Introduction

Packaging materials are defined as any substance or item that comes in contact with food and drug including containers, cans, bottles, cartons, boxes, cases and covering material such as foil, film, metal, paper, wax paper or cloth.¹ The main objective of packaging is to provide protection from foreign materials while in-transit and help in maintaining the shelf life of food products. Packaging is a field, combining science and technology used for protecting products during distribution, storage, sale and use. It can also be applied to the procedure of evaluating, designing and manufacturing a packed item. Storage and preservation instructions, directions for use, expiry or use by date, and design of packaging materials among others are crucial information which give cognoscibility to the brand and increase the visibility on the shelf.^{2,3}

All the above processes result in migration of additives, adulterants and toxins such as colourants and adhesives from packaging material into the food, as shown by previous research.⁴⁻⁶ Leaching can be explained as any process that allows transfer from surface to the core particles.⁷ With reference to food packaging, the term "leaching" can be defined as the movement of undesirable particles from packaging materials to the packaged particle. The European Council Standard requires that various contaminants like aromatic amines, benzophenones, polyaromatic hydrocarbons, plasticizers and heavy metals be controlled and analyzed in food packages.⁸ Heavy metals are a huge source of environmental pollution.⁹ The toxicity of heavy metals has harmful effects on biological systems as they do not undergo biodegradation. They accumulate in living organisms, causing several diseases and disorders even when present in very low concentrations.¹⁰

The toxic effects of vanadium are particularly seen in lung and stomach tissues, resulting in pneumonia, bronchitis and breach in the gastric mucosal lining.¹¹ Increased concentration of arsenic in humans can induce epigenetic changes and genetic mutations causing cancer.¹² Cadmium has been used in industries for a long time. Toxicity due to cadmium can affect kidneys, and the reproductive, skeletal, and respiratory systems, causing proteinuria, kidney stones, loss of bone density and mineralisation, destruction of mucous membranes, pneumonitis, testicular necrosis, and affects steroid hormone synthesis.¹³ Mercury pollution impacts human health leading to developmental flaws in children and Minamata disease.¹⁴ Metals like vanadium and mercury may be added as additives as a part of manufacturing process or may be an unintentional adulterant released from the moulds used specifically in the plastic industry.¹⁵

In this study locally procured food and drug packaging materials were used. The study started with digestion of packaging materials followed by preliminary qualitative analysis. All the samples were analysed for four heavy metals using spot test for vanadium, senSafe Boris's mercury detection strips, swab test for cadmium and aquasol arsenic detector kit. After analysing the presence or absence of heavy metals all the samples were quantified using ICP-OES (Inductively coupled plasma optical emission spectrometry). The use of ICP-OES is advantageous for sample preparation since it eliminates the need for several dilutions because it can identify multiple components from an analysis. When plasma energy is applied externally to a sample, the constituent elements are stimulated and excited atoms return to their low energy positions leading to emission of rays and the spectrometer captures these to calculate the photon wavelength. The position of the photon rays determines the element type and the strength of the rays establishes the component of each element.¹⁶

The detection for arsenic (As), vanadium (V), mercury (Hg) and cadmium (Cd) was quantified in ppm (parts per million). The detection limits are stated in the standard curves (Figure 10) viz., V – 0.000011 ppm, As – 0.000156 ppm, Cd – 0.000442 ppm, Hg – <0.001ppm.¹⁷

Considering the wide applications of the packaging material, stringent regulation is necessary due to elevated concentration of heavy metals in them. The Environmental Defence Fund¹⁸ states that these heavy metals can be toxic and the route of ingestion can be packaging materials.¹⁹ Sometimes, odorous compounds from the food packaging may get transferred to the food items and affect the foods' flavour. This results in considerable nutritional loss and consumer dissatisfaction. Although food and drug packaging are a multi-billion industry, studies on the presence of heavy metal in these packaging materials in India are lacking. The assessment of heavy metals vanadium, cadmium, arsenic and mercury in thirteen types of locally procured food and drug packaging materials was done by qualitative analysis showcasing presence or absence of heavy metals in them and then confirming their presence using quantitative technique of ICP-OES (Inductively coupled plasma optical emission spectrometry).

Methods

This study was conducted at the Department of Biochemistry, Kasturba Medical College, Mangalore, Karnataka and Department of Chemical Engineering, National Institute of Technology, Suratkal, Karnataka. The Institutional Ethics Committee (IEC) approval was obtained prior to the conduct of the study.

A total of eleven food packaging samples and two drug packaging materials were bought from the local market. The samples included aluminium cans, leak-proof bags, cardboard, tetrapaks, cellophane, tissues, sachets, aluminium bags and boxes, plastic bags and containers, as well as medicinal blister packets and medicinal closures. The packaging materials were collected, cleaned with distilled water and dried in a hot air oven. The samples were cut into small pieces using scissors and metal cutters, and 10 grams each of the sample were weighed using a calibrated electronic weighing scale.

Analysis of toxins in the samples

Packaging material was collected and cleaned as mentioned above. A total of 10 grams of weighed samples were digested using standard acid digestion technique as described by USEPA 305 (United States Environmental Protection Agency amendment no 3050(B)).²⁰ Operating conditions for microwave-assisted digestion were followed as per the USEPA 3051.²¹ The operating conditions were followed as per original protocol. Digestion of the complete sample takes place in the process leaving the heavy metals in solution form. Digested solutions were cooled at room temperature and filtered through 0.45- μ m microfilters. Prior to inductively coupled plasma-optical emission spectrometry (ICP-OES) analysis, the samples were again filtered using 0.25- μ m filters ensuring a clear filtrate. Analytical grade reagents such as concentrated hydrochloric acid (36%), sulphuric acid (98%) and nitric acid (68%) procured from Sigma Aldrich Chemicals Private Ltd, Bangalore, India were used. Double distilled water was procured from the Chemical Engineering lab at the National Institute of Technology, Karnataka using Accumax Distillation Unit for the extraction of the probable toxins from the samples.

Qualitative analysis

Post digestion of the sample, preliminary tests were performed to qualitatively confirm the presence of heavy metals. The following tests were performed in triplicates.

Spot test for vanadium: The digested solution was treated with 0.1% sodium salicylate solution in a medium of 20 ml syrupy phosphoric acid. A turquoise blue colour obtained indicated a positive result.²² The blue colour is spotted when vanadium forms vanadium hydroxyamide naphthol ternary complex with the hydrogen-free radical.²²

SenSafe Boris's mercury detection strips were used for the quick and easy detection of low levels of mercury procured by Industrial Test Systems Ltd, U.S.A. Dithizone in the digested fluid acts as a sensitive reagent for the determination of mercury in acidic media. Dithizone forms coloured primary and secondary dithizonates complexes with mercury.²³ The presence of a yellow to ochre colour indicates a positive result for presence of mercury.

Swab test for cadmium: a clean cotton swab was dipped in 70% alcohol and dried, after which it was immersed in the digest and air-dried. The indicator was prepared in a small cup containing 1,5- diphenylcarbazon and alcohol (70%) in a concentration of 70:30. The cotton swab dipped in the indicator turns violet-blue colour confirming the presence of cadmium. The coloured complex is formed when cadmium reacts with diphenylcarbazon.²⁴

Aquasol arsenic detector kit was used following the manufacturer's instructions. Briefly, (i) an arsenic silica reagent (ASR) test paper was placed on the black lid of the test bottle, using a forceps provided and making sure that the hole in the lid was covered by the test paper. (ii) The blue disc on the black lid was fixed gently. (iii) Precaution was taken not to touch the test zone. (iv) A 5 ml sample digest was taken in the test bottle with the syringe provided. (v) Three demitasse spoons of ASR-1 were added and gently swirled for a minute. (vi) Six demitasse spoons of ASR-2 were added to the above and immediately tightly screw-capped with the blue disc as prepared above. (vii) The test bottle was allowed to stand for 15 minutes, with intermittent swirling. (viii) The ASR test paper was removed from the lid and dipped in water for two seconds and excess water shaken off. The colour obtained on the test paper was compared with the colour comparison chart provided, at the end of five and eight minutes. A yellow tint indicated a positive test.

Quantitative analysis

All thirteen samples were digested as described above, labelled and subjected to ICP-OES to quantify the chosen heavy metals. Multi-element standard (REICPCAL29A) was used to standardize and calibrate the metal concentration.²⁵ Standards of all four metals were run in triplicates using an inductively coupled optical plasma emission spectrometer (ICP-OES) from Agilent Technologies (U.S.A) with Expert software version of 7.100.6821.61355 and firmware version of 2994.

Results

All tests were run in triplicates to ensure consistency in results. The average of the three readings was taken for computation and analyses.

Digestion

Microwave-assisted digestion was carried out using hydrochloric acid and sulphuric acid in a concentration of 80:20²⁶ used for samples like aluminium can and leak-proof bag. Dehydrator aid proof digestion used a combination of sulfuric acid and nitric acid in the ratio of 80:20 was used for medicinal blister packets, tetrapak, sachets, plastic containers and medicinal closures. Acid digestion with a combination of hydrochloric acid and nitric acid in ratio of 80:20 respectively was employed for the digestion of cellophane, tissue cardboard, aluminium bags, box and plastic container. The time taken for digestion ranged from 210 minutes to 34 minutes (Table 1).

Table 1. Digestion of heavy metals from the samples.

Packaging material	Type of digestion	Time taken for digestion (in minutes)
Leak proof bags	Microwave assisted digestion HCl and H ₂ SO ₄	210
Plastic container	Dehydrator aid proof digestion H ₂ SO ₄	190
Aluminium can	Microwave assisted digestion HCl and H ₂ SO ₄	140
Cellophane	Acid digestion 80:20 HCl and HNO ₃	140
Tetrapak	Dehydrator aid proof digestion H ₂ SO ₄	130
Sachet	Dehydrator aid proof digestion H ₂ SO ₄ and HNO ₃	80
Plastic bag	Acid digestion 80:20 HCl and HNO ₃	60
Cardboard	Acid digestion 80:20 HCl and HNO ₃	60
Medicinal closure	Dehydrator aid proof digestion H ₂ SO ₄ and HNO ₃	46
Medicinal blister packet	Dehydrator aid proof digestion H ₂ SO ₄ and HNO ₃	46
Aluminium bag	Acid digestion 80:20 HCl and HNO ₃	45

Table 1. Continued

Packaging material	Type of digestion	Time taken for digestion (in minutes)
Aluminium box	Acid digestion 80:20 HCl and HNO ₃	42
Tissue	Acid digestion 80:20 HCl and HNO ₃	34

A) Qualitative analysis

Cardboard, medicinal blister packets and closures were positive for the presence for vanadium. Mercury was qualitatively identified in eight samples *viz.* aluminum can and bag, leak-proof bags, sachet, plastic bag, cellophane, medicinal blister packets and closure. Arsenic was present in samples: aluminum bag and box, sachet, cellophane and leak-proof bags. Cadmium was detected in plastic bag, aluminum bag, sachet, cardboard and leakproof bag (Table 2). The qualitative analysis assay images are presented as Figures 1–9 below.

Table 2. Presence of heavy metals using qualitative analysis.

SI No	Packaging material	Vanadium	Mercury	Arsenic	Cadmium
1	Leak proof bags	-	+	+	+
2	Plastic container	-	-	-	-
3	Aluminium can	-	+	-	-
4	Cellophane	-	+	+	-
5	Tetrapak	-	-	-	-
6	Sachet	-	+	+	+
7	Plastic bag	-	+	-	+
8	Cardboard	+	-	+	+
9	Medicinal closure	+	+	-	-
10	Medicinal blister packet	+	+	-	-
11	Aluminium bag	-	+	+	+
12	Aluminium box	-	-	+	-
13	Tissue	-	-	-	-

“+” - presence of heavy metal , “-” - absence of heavy metal.

**Figure 1.** Spot test for vanadium.

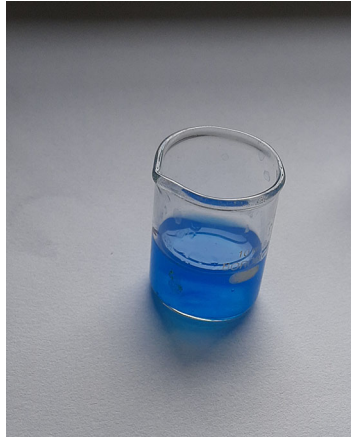


Figure 2. Turquoise colour indicating positive test for vanadium.



Figure 3. Mercury Boris's SenSafe strips tested for presence of mercury.

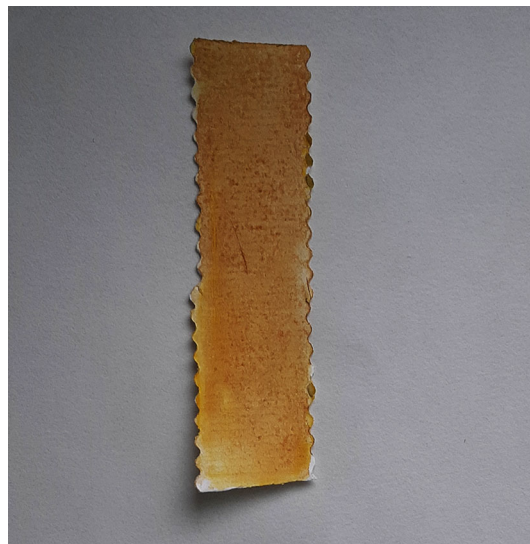


Figure 4. Ochre colour indicates positive test for mercury.

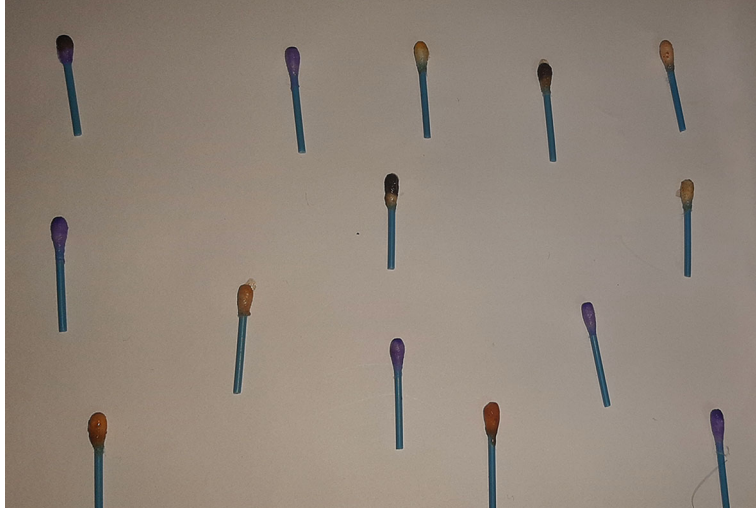


Figure 5. Cotton swab test for cadmium.

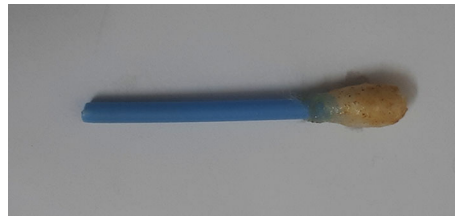


Figure 6. Negative test for cadmium.



Figure 7. Violet colour indicates positive test for cadmium.

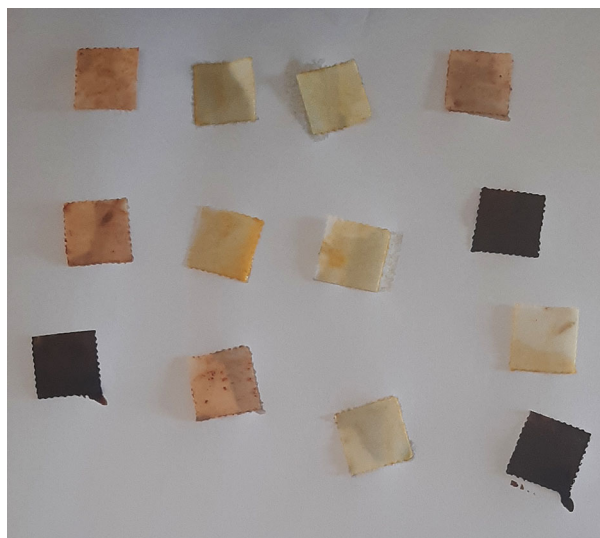


Figure 8. Aquasol arsenic detector test.

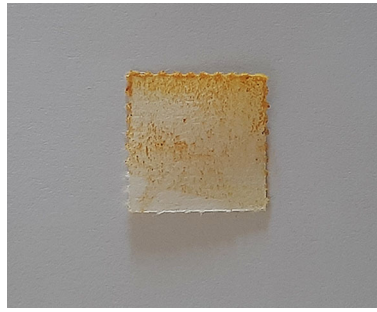


Figure 9. Yellow to ochre indicates positive test for arsenic.

Figure 10 - Calibration curves

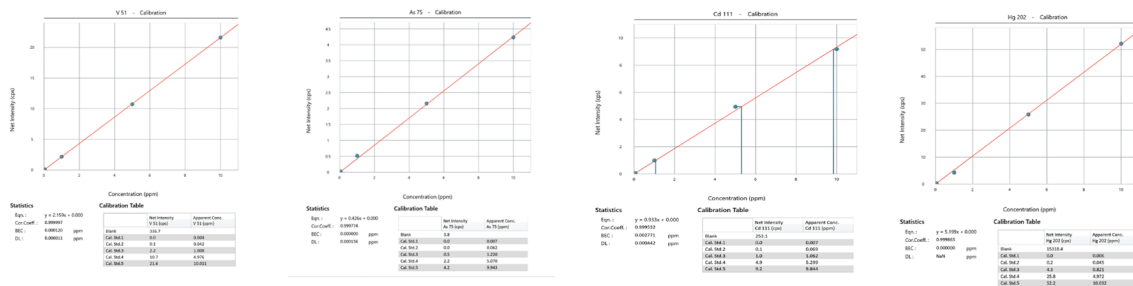


Figure 10.1- Vanadium

Figure 10.2- Arsenic

Figure 10.3 - Cadmium

Figure 10.4 - Mercury

*DL – Detection limit
NaN – value lesser than 0.001

Figure 10. Calibration curves for select heavy metals.

Quantitative analysis

Heavy metals were detected in the all the thirteen samples. The levels of heavy metals ranged from 0.29 – 40.8 ppm for vanadium, 1.7 – 236.2 ppm for arsenic, 1.53 – 546 ppm for mercury and 2.2 – 337 ppm for cadmium. The maximum permitted quantity (ppm) as suggested by the European Council for Food Packaging Association (Nordic guidance for authorities) is; As – 0.002 ppm, V – 0.01 ppm, Hg – 0.003 ppm, Cd – 0.005 ppm.²⁷ Vanadium was found within the permissible limits in three samples (tissue, sachet, cellophane). Arsenic, mercury and cadmium were above the permissible limit in all the studied samples. Arsenic and mercury were the most common heavy metal contaminants and cadmium and vanadium were the least (Table 3).

Table 3. Concentrations in parts per million (ppm) of heavy metals detected in study materials. Bold values indicate values of heavy metals in packaging materials below the or under acceptable amount that is within the given range and not higher than the prescribed limit.

Label	Vanadium (V) (ppm)	Arsenic (As) (ppm)	Mercury (Hg) (ppm)	Cadmium (Cd) (ppm)
Permitted concentration	≤0.01	≤0.002	≤0.03	≤0.05
Packaging material				
Aluminium can	0.59	3.3	3.2	ND
Leak proof bags	0.49	86	5.6	3.50
Cardboard	40.8	0.83	17.5	35.6
Tetrapak	0.92	1.5	9.75	10.0
Cellophane	ND	2.61	2.03	0.65
Tissue	0.097	94.3	1.72	1.5

Table 3. *Continued*

Label	Vanadium (V) (ppm)	Arsenic (As) (ppm)	Mercury (Hg) (ppm)	Cadmium (Cd) (ppm)
Sachet	ND	1.7	546	337
Aluminium bag	0.29	29.5	3.00	16.6
Aluminium box	0.84	123	1.53	2.20
Plastic bag	35.6	62.2	174	34.4
Plastic container	0.88	2.80	9.10	ND
Medicinal closure	19.6	236.2	19.6	0.28
Medicinal blister packet	0.98	0.54	4.50	ND

ND = not detected.

Table 4. Nomenclature.

Symbol	Meaning
V	Vanadium
As	Arsenic
Hg	Mercury
Cd	Cadmium
ppm	Parts per million
ml	Milliliter
%	Percentage
ICP-OES	Inductively coupled plasma optical emission spectrometry
USEPA	United States Environmental Protection Agency
ASR	Arsenic silica reagent
IARC	International Agency for Research on Cancer
WHO	World Health Organization
NTP	The National Toxicology Programme
NIH	National Institute of Health
FDA	Food and drug administration
CDC	Center for Disease Control and Prevention

Discussion

In the current study, eleven commercially available food packaging materials and two drug packages were analysed for the presence of four heavy metals, namely vanadium, arsenic, mercury and cadmium. Packaging materials constitute the mainstay of the modern food industry. Hence, it is important to study their interference with food/drug present within the packaging material. As research has shown leaching of toxins from packaging materials, monitoring the heavy metal leaching is essential to prevent harmful effects to the human body.⁶

Vanadium is a heavy metal which is used as an additive in stainless steel as well as a catalyst for manufacturing sulfuric acid. It is also used in glass coating and lacquering in aluminum cans to give strength to the material. Vanadium is used as an amalgam in manufacturing cans with stainless steel to give it tensile strength. Vanadium toxicity is known to cause abdominal discomfort by interfering with mucosal lining leading to nausea, bloating, diarrhoea and vomiting in the initial stages. Prolonged exposure can result in renal and neural damage.²⁸ Qualitative tests detected the presence of vanadium in only three samples. However, ICP-OES values showed presence of vanadium higher than permissible amounts in 10 samples. The study by Imtiaz *et al.*²⁹ stated that vanadium causes oxidative stress in human cells and alteration in human metabolism, reduces enzymatic activities and disturbs membrane integrity in humans.²⁹ This oxidative stress leads to the formation of pentavalate vanadium which is its most toxic and mobile form.

Arsenic, found in higher concentration in all the study materials (detected by six samples qualitatively), is a heavy metal that can act as a toxin due to its high presence in water which is used for material cleaning and lacquering processes.³⁰ Arsenic is also known to be present as one of the food packaging colorants used in the packaging industry.³¹ Arsenic could enter the food packaging material during the cleaning process or as an adulterant of iron source. Arsenic has been used as a common ingredient in many pesticides and herbicides in the past. It is known to cause skin lesions and cancer in humans.³² The International Agency for Research on Cancer (IARC), a part of the World Health Organisation (WHO) has stated that exposure to arsenic is the leading cause of lung, bladder and skin cancer.³³ The National Toxicology Programme (NTP) is composed of several different government agencies, including the National Institute of Health (NIH), the Center for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA). In its most recent *Report on Carcinogens*, the NTP classifies arsenic and inorganic arsenic compounds as known to be human carcinogens. The study by Park *et al.* stated that arsenic is present in paper in contact with food such as any kind of wrapping, and paper board, and presents a risk to consumer safety as increased ingestion in humans can cause skin lesions and gastric cancers.³⁴

Mercury dissolves in aluminum at room temperature and is added as an additive in aluminum cans and foils to enhance the shelf-life of the seafood packed inside.³⁵ Ingestion of mercury is the leading cause of Minamata disease. Mercury was detected qualitatively in eight samples and quantitatively in amounts greater than those permissible in sachet and plastic bag only. The mercury absorbed in the body mainly concentrates in the kidneys and brain.³⁶ The half-life of mercury in the body is about 70 days. Inorganic mercury is mainly absorbed through the respiratory tract, but is also absorbed through the skin to a small extent (3-4%) or gastrointestinal (GI) tract (2-10%). Methylmercury is easily absorbed into the GI tract ($\geq 95\%$) and into the respiratory tract ($\approx 80\%$). About 90% of methylmercury is excreted through the faeces via bile, and less than 10% through urine. The absorbed mercury is distributed throughout all tissues within 30 hours. Its half-life ranges from 45 to 70 days.³⁷ Higher concentrations (more than 100 ppm) of mercury have been known to cross the placenta and result in foetal defects.¹⁴ Toxic effects of mercury have been reported even at lower concentrations in humans.³⁸⁻⁴⁰ Therefore, it would be worthwhile to study the leaching from the packaging material and reconsider the permissible limit if proven.

Ingestion of cadmium in higher concentration creates oxidative stress in the cells and increases the level of antioxidant uptake to protect against macromolecular cell damage, thus leading to prolonged exposure to cadmium, causing depletion of antioxidant levels in the body. Cadmium is generally a contaminant present as residues of the recycling and manufacturing processes, and hence determining their suitability in packaging materials coming in direct contact with foodstuffs is imperative. During the recycling process and cooling of cans, cadmium enters the food production system due to changes in temperature or as an additive used in the metal and glass industry. Cadmium can cause respiratory illnesses, lung fibrosis and cancer.⁴¹ Huff *et al.*, found cadmium to be the major causative agent of lung cancer, and possibly prostate cancer. Studies in experimental animals have demonstrated that cadmium concentrations higher than those set by regulations (100 ppm) cause tumours at multiple tissue sites, by various routes of exposure, and in several species and strains.⁴²

Further, these studies offer important context for our findings and support the urgent need for remedial action to mitigate heavy metal exposure through packaging materials. Studies by Sood *et al.*, and Marcelo Enrique Conti, have reported similar trends in heavy metal presence, emphasizing the need for improved quality control measures and regulatory oversight in the packaging industry.^{43,44} Muhammad *et al.* conducted research on heavy metals in food-contact papers in 2019. This study looked at the levels of heavy metals in papers that come into touch with food, including paperboard and wrapping paper used in packaging.⁴⁵ Concerns over consumer exposure to these contaminants were raised by the researchers' discovery that a sizable portion of the samples tested had increased levels of heavy metals, including cadmium and arsenic. A thorough investigation of heavy metal contamination in plastic materials used to package food and pharmaceutical goods was carried out by Khan *et al.* in 2015.⁴⁶ Their research showed that heavy metals, such as lead and mercury, were widely present in a variety of plastic packaging types, raising the possibility of health risks related to these substances. The amounts of heavy metals in glass packaging materials that are often used for food and medicine goods were assessed by Turner and Andrew (2016).⁴⁷ Their study brought attention to the prevalence of heavy metals in glass packaging, specifically lead and cadmium, and emphasized the necessity of regulation and oversight to protect consumers.⁴⁷ A thorough assessment of research examining the effects of heavy metal pollution on food and medication packaging materials was carried out by Scutarasu and Trinca in 2023. Their findings emphasized that in order to reduce the dangers associated with heavy metal exposure through packing materials, more stringent quality control procedures and regulatory oversight are required.⁴⁸ Together, these investigations offer insightful information about the frequency of heavy metal contamination in food and medicine packaging materials, emphasizing the necessity of regulatory action to safeguard the health and safety of consumers.

It is alarming to find high concentrations of toxic metals in several of the packaging materials studied. While cadmium seemed to be the least abundant contaminant, arsenic was the most prevalent heavy metal contaminant. Of all the types of packaging materials studied, sachets, which are manufactured using a plastic and aluminium amalgam, had the highest concentration of all the heavy metals.

Conclusions

In summary, a wide variety of food and drug packaging materials from an Indian market were tested for the presence of heavy metal, namely vanadium, arsenic, cadmium and mercury. Our study shows the presence of heavy metals in routinely used food packaging materials, measured quantitatively and qualitatively. All samples, irrespective of the results of qualitative analysis, were subjected to quantitative analysis, as ICP-OES is a sensitive technique for the detection of heavy metals. Of the thirteen samples analysed, arsenic, mercury and cadmium were found in all samples at concentrations above the regulated limits. Vanadium was present in lower concentration in tissue, cellophane and sachets. Leaching of these heavy metals into the packaged food/drug may be potential health hazard that severely compromise the well-being of humans and the environment. This study calls for stringent regulatory guidelines and strict monitoring of packaging materials at all stages, starting from raw material selection, storage and production until it reaches the consumer. The post-packaging handling, transport, storage and conservation of the supply chain requirements further add to prospective leaching, which may be the scope of future studies.

Data availability

Underlying data

Mendeley data: ICP-OES data for “Assessment of toxins in food and drug packaging materials”, <https://data.mendeley.com/datasets/gnwy7nzpnt/1>.⁴⁹

This project contains the following underlying data:

- SENNA As KMC 6.12.21.docx (Arsenic ICP-OES data)
- SENNA Hg KMC 6.12.21.docx (Mercury ICP-OES data)
- SENNA KMC Cd 6.12.21.docx (Cadmium ICP-OES data)
- SENNA kmc V 6.12.21.docx (Vanadium ICP-OES data)
- Table 1. docx

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

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Open Peer Review

Current Peer Review Status:   

Version 3

Reviewer Report 18 March 2024

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Marin Senila 

National Institute for Research and Development of Optoelectronics INOE 2000 INCD Bucharest, Research Institute for Analytical Instrumentation, Cluj-Napoca, Romania

Editorial note (15th May 2024): the reviewer's report for Version 3 of this article was originally published on 18th March 2024, but the reviewer had not yet been able to view the authors' direct response to their previous comments due to a delay with processing this response from the editorial side. The reviewer has since been notified of the authors' direct response and after reading this response the reviewer has now updated their report status and comments to "Approved".

Approved.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Atomic spectrometry, metals determination, ICP-OES

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 19 February 2024

<https://doi.org/10.5256/f1000research.152481.r229064>

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Marin Senila 

National Institute for Research and Development of Optoelectronics INOE 2000 INCD Bucharest, Research Institute for Analytical Instrumentation, Cluj-Napoca, Romania

In the manuscript entitled "Assessment of heavy metals in food and drug packaging materials", authors tried to assess the concentration of some heavy metals in several food and drug packaging materials. There are many necessary improvements, the most important:

1. The title is too general and should be rewritten to be more specific for the conducted research.
2. The correct name of the ICP-OES technique is inductively coupled plasma-optical emission spectrometry (as it is written in the Abstract), not Inductively coupled plasma optical emission spectrophotometry (as it is written in the Introduction). It is not necessary to give the principle of functioning of this technique; it is well-known.
3. Arsenic is a metalloid; it is not a metal; please mention that.
4. No quality control is provided for the digestion method and for instrumental determination. How do you check that the results are correct?
5. The authors state that the ICP-OES can detect heavy metals from 0.0002 ppm to 1000 ppm range. It depends on the metal. For mercury, a studied analyte in this research, the range of concentrations is much limited. The authors should provide the range of calibration curves used in their own study, working ranges for each analyte, limits of detection and limits of quantification. For quantitative analysis, the LOQ is necessary; the authors reported in Table 3 ND as not detected, but below LOQ should be given.
6. For Table 3, the cited reference for the permitted concentration of metals in packaging materials should be provided. Strangely, the permitted concentration of Hg and Cd (known as very toxic elements) is 50000 times higher than for As, and 10000 times higher than for V. Please check the reference and measurement units.
7. Generally, the Discussion is too general and contains well-known literature information about metal toxicity. Please discuss your results in relation to measured concentration and maximum admitted values and compare your data with previous reports.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Atomic spectrometry, metals determination, ICP-OES

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 21 Feb 2024

SENNA Mukhi

Query 1 - The title is too general and should be rewritten to be more specific for the conducted research.

Response 1 - The title is changed to - Assessment of Arsenic, Vanadium, Mercury, and Cadmium in Food and Drug Packaging

Query 2 - The correct name of the ICP-OES technique is inductively coupled plasma-optical emission spectrometry (as it is written in the Abstract), not Inductively coupled plasma optical emission spectrophotometry (as it is written in the Introduction). It is not necessary to give the principle of functioning of this technique; it is well-known.

Response 2 - The changes are made in the manuscript.

Query 3 - Arsenic is a metalloid; it is not a metal; please mention that.

Response 3- Arsenic is classified chemically as a metalloid, having both properties of a metal and a nonmetal; however, it is frequently referred to as a metal. It is referred to as a metal at ATSD website, and therefore we have mentioned the same in the entire manuscript

Reference - Agency of toxic substances and diseases. <https://www.atsdr.cdc.gov/>

Query 4 - No quality control is provided for the digestion method and for instrumental determination. How do you check that the results are correct?

Response 4 - At first, calibration of each heavy metal is conducted only then samples are run in the machine for detection of heavy metal. Calibration curves in Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES) are crucial for accurately quantifying element concentrations in samples. They establish a relationship between signal intensity and concentration, ensuring precise measurements in unknown samples. Calibration curves also demonstrate the instrument's linear response to varying concentrations, ensuring accurate measurements across a wide range. They also serve as quality control measures, verifying instrument performance and providing a standardized method for consistent results across different analyses and laboratories. Calibration curves (Figure 10) enclosed in the manuscript.

Query 5 - The authors state that the ICP-OES can detect heavy metals from 0.0002 ppm to 1000 ppm range. It depends on the metal. For mercury, a studied analyte in this research, the range of concentrations is much limited. The authors should provide the range of

calibration curves used in their own study, working ranges for each analyte, limits of detection and limits of quantification. For quantitative analysis, the LOQ is necessary; the authors reported in Table 3 ND as not detected, but below LOQ should be given.

Response 5 - The detection limits are stated in the standard curves provided viz., V- 0.000011 ppm, As- 0.000156 ppm, Cd- 0.000442 ppm, Hg- <0.001.

Query 6 - For Table 3, the cited reference for the permitted concentration of metals in packaging materials should be provided. Strangely, the permitted concentration of Hg and Cd (known as very toxic elements) is 50000 times higher than for As, and 10000 times higher than for V. Please check the reference and measurement units.

Response 6 - The maximum permitted quantity (ppm) as suggested by the European Council for Food Packaging Association (Nordic guidance for authorities) is; As-0.002 ppm, V-0.01 ppm, Hg - 0.003 ppm, Cd, 0.005 ppm. This change has been incorporated. The updated reference no is 27 in the manuscript and is also stated below.

Reference - Cederberg, D.L., Christiansen, M., Ekroth, S., Engman, J., Fabech, B., Guðjónsdóttir, K., Mikkelsen, B., et al. (2015) Food Contact Materials—Metals and Alloys. Vol. 2015522, Nordic Guidance for Authorities, Industry and Trade, Nordic Council of Ministers. <https://doi.org/10.6027/TN2015-522>

Query 7 - Generally, the Discussion is too general and contains well-known literature information about metal toxicity. Please discuss your results in relation to measured concentration and maximum admitted values and compare your data with previous reports.

Response 7 - The discussion section has been elaborated in relation to measured concentration and maximum admitted values and in comparison, with previous reports. The additional references (Ref 43 – 48) have been incorporated.

Competing Interests: There are no competing interests

Reviewer Report 24 July 2023

<https://doi.org/10.5256/f1000research.152481.r185018>

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Mahesh Ganesapillai

School of Chemical Engineering, Vellore Institute of Technology, Vellore, India

The queries are addressed. The article can be accepted for indexing.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Solid Waste Management; Closed loop, Nutrient recovery, Separation Technology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 29 June 2023

<https://doi.org/10.5256/f1000research.133336.r178554>

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Xin-Yuan Huang

Nanjing Agricultural University, Nanjing, China

In this manuscript, authors quantified four heavy metals in 13 types of food and drug packaging materials, including arsenic (As), vanadium (V), mercury (Hg) and cadmium (Cd). They found that 10 of 13 samples are above the permissible range for vanadium, all samples for arsenic, two samples for mercury and one sample for cadmium. This manuscript was well written but I have the following concerns.

1. Concentrations of the 4 heavy metals shown in Table 3 are presented as parts per million (ppm), which represent the concentrations of these 4 heavy metals in the extract buffer (probably after dilution but not mentioned in the methods). The concentrations of heavy metals in the extract buffer depends on the amount of the food and drug packaging materials used for extraction. So the concentrations must be normalized to the weight of

the materials.

2. The same extraction method was used for all eleven food packaging samples and two drug packaging materials. How to make sure they have the same extraction efficiency?
3. Quantitative analysis of 4 heavy metals were determined by ICP-OES. What are detection limits for arsenic (As), vanadium (V), mercury (Hg) and cadmium (Cd) in this instrument?
4. Blank control samples must be included when run samples on ICP-OES. Without blank controls, it is hard to rule out the presence of heavy metal coming from the samples or simply from reagents for extraction or the contamination during the extraction.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Plant ionomics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 01 Jul 2023

Rukmini M S

1. As per standard deduction method it represents the digestion of each packaging material having concentration of vanadium, arsenic, mercury and cadmium, when 10 gram of sample was digested. Accordingly, the experiment is performed and analysed and the concentration of heavy metal is determined in ppm.

2. The word used in place of extraction is digestion, the same correction would be made in the updated version of the manuscript. Digestion of complete sample takes places in the process leaving the heavy metal in solution form and therefore the accuracy was 100%.

3. The detection for arsenic (As), vanadium (V), mercury (Hg) and cadmium (Cd) for our study was carried out in ppm (parts per million). The machine is highly sensitive and detects these heavy metals in ppm (parts per million), ppb (parts per billion) and ppq (parts per quadrillion). For heavy metal samples ICP -OES can detect heavy metals from 0.0002ppm to 1000ppm range. This information would be added in the updated version of the manuscript.

4. The analysis was done with standards of heavy metals namely vanadium, cadmium, mercury and arsenic. For all these heavy metals, calibration curve was developed using standard solution and then the concentration was determined. Thus, no control was required as same solution was used for digestion.

Competing Interests: No competing interests were disclosed.

Reviewer Report 11 November 2022

<https://doi.org/10.5256/f1000research.133336.r154512>

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Mahesh Ganesapillai

School of Chemical Engineering, Vellore Institute of Technology, Vellore, India

The study conducted is well aligned with the scope of the journal and boasts considerable novelty in its approach. However, there are a few possible revisions which may alleviate the overall quality of the work:

1. The objective of the study needs to be clearly outlined in the last paragraph of introduction. Please refer the following articles for a proper understanding of the expected phrasing^{1,2,3}.
2. **Introduction:** Information on the various quantitative analyses conducted must be mentioned in this section. Such details provide readers with valuable context for the study and improves the logical flow of the manuscript.
3. **Extraction:** "...a concentration of 80:20 used..." Why was this composition chosen? Please provide valid reference for the same.
4. **Table 2:** The data represented lacks clarity. Consider incorporating a legend representing the symbols.

5. There are several abbreviations in the manuscript – please include a nomenclature table for the convenience of readers.
6. **Conclusions:** The section needs further improvement and inclusion of better inferences. The mere mention of the presence of heavy mental entities does not conclude the study adequately.

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Solid Waste Management; Closed loop, Nutrient recovery, Separation Technology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 18 Nov 2022

Rukmini M S

1. The objective of the study will be clearly stated and suggestions will be incorporated.
2. The changes suggested in the introduction will be made.
3. Regarding the extraction procedure: 'The Aqua Regia is a standard acid mixture of HCl:HNO₃ (*volume* ratio is usually 4 parts concentrated hydrochloric acid to 1 part concentrated nitric acid) prepared to digest most of the samples for the metal analysis.'
4. **Table 2:** The legends have been inadvertently omitted while editing. We will make the changes as per the suggestion.
5. We will include a nomenclature table for abbreviations or incorporate the complete metal name, wherever applicable.

Competing Interests: No competing interests were disclosed.

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