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Single and Combined Aluminium and Cadmium Exposure during Pregnancy Mediate Changes in Cardio Metabolic Indices in Mice

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ABSTRACT: The potential risk of Aluminium and Cadmium co-exposure is high owing to evidence of their co-contamination of several food products. Therefore, the present study investigated effect of single and combined exposures of aluminium and cadmium during pregnancy on cardio metabolic changes in mice. Following delivery and at the end of 78 days postnatal development, it was observed that exposure to Al and Cd during pregnancy altered indices of cardiac function via pathways related to angiotensin, cardiac troponin and oxidative stress signalling which may have impacted directly on the histoarchitectural features of the heart. Comparatively, prenatal exposure to Cd alone impacted more negatively to the heart in relation to exposure to either Al only or co-exposure to Al and Cd.

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Heavy metals are non-biodegradable in nature; thus, they have an extended biological half-life (Gupta and Joia, 2016; Asagba *et al.*, 2019). Exposure to these metals occurs through diverse human activities which include application of pesticides and fertilizers to the soil, sewage sludges, electroplating, mining and manufacturing, burning of fossil fuels, and the use of metallic cookware (Tasrina *et al*., 2015; Orisakwe *et al*. 2017; Quinteros *et al*. 2017; Olufemi *et al.,* 2018; Obasi *et al*., 2019). When harmful metals seep into bodily tissues, other metals may be depleted as a result. These metals can then bioaccumulate and cause a variety of health problems, such as kidney damage, cancer, cardiovascular disease, mental retardation, growth retardation, lowered immune system, anaemia, abdominal pain, lipid peroxidation, and DNA damage, among other conditions. (Javed and Usman 2013; Asagba *et al*. 2019; Bazir *et al*. 2023; Khalaf *et al*. 2023). Although there are several heavy metals found in nature, Aluminium is very abundant and is ranked as the third most abundant element within the earth crust (Exley 2013; Gerard and Gray 2015). Pure aluminium is soft in nature and can combine with other metals and elements to form alloys which are harder. Such metals and elements include copper, silicon, manganese, zinc, magnesium and lithium. Aluminium metal and its alloys can be used in the production of cookware, doors, windows, roofing sheets, electrical equipment, including antacids, body care products, storage and packaging materials due to its affordability, light weight, high heat conductivity, malleability, and availability (Mohammad *et al*., 2011; Odularu *et al*., 2013; Alabi *et al*., 2020). In most developing countries, the recycling of aluminium-based materials is used for the production of forged aluminium cook wares from scrap metals like

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computer parts, bicycles, lead batteries, old and broken spoons, cans and containers thrown in gutters. This singular process thus increases the exposure risk potential of aluminium as this often increases the propensity of aluminium leachates together with other toxic metals and metalloids into food (Yang *et al.* 2019; Ghobakhloo *et al*. 2024). There is increased evidence that the highest form of aluminium exposure comes through the food chain as the metal is primarily sourced from diets which include nuts, herbs, tea, spices, salt, grain products and processed cheese (Alabi and Yetunde, 2020). Also, the rampant usage of aluminium foils for the packaging of various meat and poultry products sauced with tomato sauce, salt, citric acid, vinegar and cooked in the oven at different temperatures, leads to the increase in aluminium exposure and its toxicity (Dordevic *et al*. 2019; Fermo et al. 2020, Covaliov *et al*. 2021). Nestled between zinc (Zn) and mercury (Hg) in the periodic table of elements, cadmium (Cd) is a naturally occurring metal that exhibits chemical behaviour akin to that of zinc. It commonly exists as a cation with a divalent charge, attached with other elements (e.g., $CdCl_2$). Ingestion or inhalation are the main ways that humans are exposed to Cd. Based on particle size, 10–50% of cadmium dust inhaled is absorbed (Ichipi-Ifukor *et al.* 2013; Ezdom and Asagba, 2016; Asagba, 2019). In work environments, breathing in particulates from industrial exposure can be harmful. Soldering or welding, for instance, can result in a serious case of chemical pneumonitis. Consumption of tainted food (such as crabs, fish, organ meats, rice, leafy vegetables, etc.) or water (from outdated zinc/cadmium sealed water lines or industrial pollutants) might result in long-term health consequences from cadmium exposure (Horiguchi**,** 2020; Lien *et al*. 2021; Gao *et al*., 2022). Another possible cause of pollution is drugs and dietary supplement contamination. Adults who are exposed to Cd experience harm to numerous organ systems, including the nervous system (Zhao *et al*., 2015). Studies have demonstrated Cd to cross the placental barrier and affect foetal development (Dharmadasa *et al*., 2017). Reduced birth weights have occasionally been connected to prenatal blood lead levels (Luo *et al*., 2017). Previous studies have connected Cd to cerebral palsy (Hong *et al*., 2016). As a result, exposure to cadmium during lactation or pregnancy may be harmful to the baby, especially to the nervous system. The toxicity of Cd has been connected to numerous reasons, such as oxidative stress, cellular death, and inflammation that affects the kidney, testis, and brain (Rinaldi *et al*., 2017). Cd and Al have also been implicated in the remodelling of the heart structures and shape. Both metals are said to contribute to uncontrolled rise to hypertensive symptoms, clogged arteries, DNA oxidation and cardio mineral redistribution (Schmidt *et al*., 2016; Martins *et al.,* 2021; Zhang *et al.,* 2022; Ranke et al. 2023). While serum aluminium levels have been widely implicated in cardiac anomalies in patients undergoing dialysis, serum cadmium and cord blood cadmium levels is said to be significantly correlated with birth weight outcomes, cognitive development indices and risk of cardiac diseases (Oritsemuelebi *et al*., 2021) It is important to state therefore, that with the ubiquitous nature of these metals there exist risk potentials of their co-exposures among several inhabitants as research evidence reveals that these metals often occur side by side either in metal ores or as metalloids during recycling of different metallic products. Therefore, the objective of this study was to investigate the effect of single and combined exposures of aluminium and cadmium during pregnancy on cardio metabolic changes in mice offsprings.

MATERIALS AND METHODS

Chemicals and Reagents: $CdCl_2$ and $AlCl_3$ was purchased from sigma Aldrich UK while all other reagents were of analytical grade.

Ethical Approval: Ethical approval (REL/FOS/2023/05) for the study was granted by the Delta State University Faculty of Science Ethical committee in agreement with previously published guidelines by the World Medical Association (2000).

Acquisition of Animals for the Study: 40 neonate mice were used in this investigation. They were produced by breeding 20 adult non-pregnant female and 20 adult male mice at the age of 8–10 weeks. The animals were acquired from Delta State University's College of Medicine's animal facility in Abraka. The mice were given two weeks to acclimate in the Department of Biochemistry. They were housed in well-constructed plastic mouse cages, with free access to food (hybrid growers' mash feed), water, and other supplies during the experiment similar to those reported by Mordi *et al*. (2021). The adult female mice's oestrous cycle and vaginal cyclic period were discovered towards the conclusion of the acclimation stage before one female and one male were placed in a mating cage, and a predetermined mating procedure was carried out.

Animal Treatment and Experimental Design: Day 1 following the mating process was determined to be the first day of pregnancy through the presence of spermatozoa following a vaginal smear. Different groups of pregnant mice were subjected to different treatments from gestation day 7 to 20. Group 1 was the control group (CTR) and received no treatment other than normal saline (0.9% NaCl) (10 ml/kg, PO). Group

2 consisted of the aluminium (Al) group that was given $AlCl_3$ (10 mg/Kg) exclusively, Group 3 was given $CdCl_2$ (1.5 mg/Kg PO) exclusively and was labelled as (Cd), and Group 4 was given a combination of both treatments from Groups 2 and 3 labelled (Al+Cd). After parturition, the animals remained with their mothers until day 21 post-delivery before the male animals were divided into four groups, with no more than three individuals from a single birth. The mice were given the opportunity to reach adulthood, and on postnatal day 78, a timeframe that is analogous to adult human development (Anderson 2003), they were sacrificed. The heart tissue and blood were extracted from the animals, and conventional biochemical and histological analyses were conducted on them.

Collection and Preparation of Samples for Biochemical Assays: For the purpose of biochemical testing, six animals had their cervical discs removed. Blood was drawn via the aorta vein, and samples were centrifuged for 10 minutes at 4 °C at 10,000 rpm. After being separated into sterile, non-heparinized bottles, the serum samples were stored at -20 °C until they were needed to measure cardiac troponin I, angiotensin, and creatinine kinase. Intermittently, the harvested cardiac tissues were homogenised at 3,500 rpm for three minutes in test tubes with 4 mL of 0.05M phosphate buffer (pH 7.4). Additionally, homogenates were spun in a cold centrifuge set to 10,000 rpm for 10 minutes at 4^{o}C. Supernatants were collected and maintained at -20 ^{o}C until required for biochemical assays (alanine and aspartate transferases, alkaline phosphatase activity and oxidative stress indices) within 48 hours.

Estimation of Serum cardiac functional Indices: According to the manufacturer's instructions (Monobind Inc. USA), the levels of serum creatine kinase, angiotensin converting enzyme and cardiac troponin I (CTPI) was measured using enzyme-linked immunosorbent assay (ELISA) techniques (Acculiteclia microwells). All reagents were reconstituted and brought to room temperature (20–27 °C) as instructed and tests carried out entirely in accordance with instructions.

Estimation of cardiac amino transferases and alkaline phosphatase activity: Alanine and aspartate amino transferase and alkaline phosphatase activities were assayed using a commercial diagnostic Kit Produced by Randox Laboratories Limited, England. The assay protocol adhered strictly to the manufacturer's instruction.

Estimation of antioxidant and oxidative stress parameters: Oxidative stress indices in the heart were estimated following already existing standard protocols as described by the following authors; Gutteridge and Wilkins (1982) (lipid peroxidation); Misra and Fredorich (1959) (superoxide dismutase (SOD)); Cohen et al. (1972) (catalase (CAT); Elman (1959) (reduced glutathione (GSH)).

Histopathological evaluation of the Heart: Before receiving a transcardial infusion of normal saline and 10% buffered formaldehyde for a histological examination of the heart, the mice in each treatment group from the four groups were given ketamine anaesthesia. The heart was excised after perfusion and put into a 10% formaldehyde solution. It was then left for 24 hours before being moved to a 30% sucrose solution, and it was processed further within 48 hours as previously mentioned (Okhue *et al*. 2024). An automatic tissue processor was used to treat the excised heart tissue for paraffin wax embedding. This involved dehydrating the tissue through 70%, 90%, and 95% ethanol changes, each lasting 90 minutes. Two xylene changes lasting two hours each were used to achieve clearing, and two paraffin wax changes lasting two hours each were used to infiltrate. Using a rotary microtome, a transverse piece of the heart was cut at 5 µm and Haematoxylin and eosin (H and E) staining technique was done according to Zhang *et al*. (2017), evaluated, and captured on camera with a light microscope.

Statistical and Data Analysis: Graph pad Prism software, Inc., Lajolla, USA, version 9.5.1 was used to analyse the data using one-way (ANOVA) analysis of variance and the Bonferroni post-hoc test for comparison across experimental groups. At level $p<0.05$, statistical differences were deemed significant and the Mean ±SEM (standard error of the mean) used for data presentation.

RESULT AND DISCUSSION

The heart is an important organ that controls several significant activities in the body. The heart is primarily concerned with the pumping of blood which aids in the circulation of hormones, nutrients and other vital substances round the body (Suárez *et al.,* 2020). An impact on this organ by exposure to harmful metals like aluminium and cadmium would cause an alteration to these biological processes which could cause deleterious effects that may lead to death. Findings in the current study indicates that there was a significantly reduced activity of creatine kinase in all metal treated groups compared to control however, no significant difference was observed when the metal groups were compared. Creatinine kinase is known as an essential enzyme in the energy coupling system of

the heart and muscles. Phosphocreatine (PCr) and adenosine diphosphate are produced by the reversible transformation of creatinine and adenosine triphosphate by the enzyme. The enzyme catalyses the reversible conversion of creatinine and adenosine triphosphate to phosphocreatine (PCr) and adenosine diphosphate (Del franco *et al*. 2022). The observed reduction of CK levels in the groups exposed to the metals indicates an interference of the metals on the functionality of the enzyme through either inhibition of the enzyme or alteration in one of the creatinine metabolic intermediates such as the creatinine transporter (Zervous *et al*. 2016; Cao *et al*. 2018). Earlier low serum creatinine kinase has been associated with rheumatoid arthritis an autoimmune and inflammatory condition were the body's immune set up is programmed to attack healthy cells (Stucki *et al.* 1996) arising from very weak muscles. This is linkable to a possible high-level weakness of the cardiomyocytes which plays a significant role in the pathological process of heart failure. It also further substantiates the reports of Nascimben *et al.,* (1996) who validated the correlation between a decrease in creatine levels to heart failure and the left ventricular ejection fraction hence the stabilization of creatinine metabolism and signalling functions essentially in heart contraction and imperative in managing heart morbidities. (Balestrino, 2021). Angiotensin converting enzyme is an important enzyme that functions in the regulation of blood pressure by controlling the rate of fluid cum blood flow from the arteries to the body (Danilzyk *et al*. 2004; Ahmad *et al.* 2023). A significantly elevated activity of ACE in the Al group may be linked to early onset of sarcoidosis by the prenatal aluminium exposed to the mice. Aluminium and other metals such as silica, barium, cobalt and gold have earlier been implicated in the development of granulomatous lung disease that mimics sarcoidosis (Newman, 1998; Fireman *et al*. 2016; Bajer *et al*. 2020; Judson 2020). Though the Cd group had a non-significantly elevated ACE activity, the findings in this study are in contrast to that reported by Broseghini-Filho *et al.,* (2015) which noted a reduction in the serum concentration of ACE after acute cadmium exposure but agrees with Júnior *et al.,* (2020) that reported a similar result stating an increase in serum ACE levels in mice exposed to Cd only. The increases signifies that the renin-angiotensin system plays an important role in the toxicity of the cardiovascular system and therefore may also promote the progression of hypertension. Also, its reduction in the coadministration group may signify possible negative response factors from other organs such as the liver and may be significant for the determination of the liver's health in the co-exposed animals (Lim *et al*. 2020; Laitselart *et al*. 2022; Pan *et al*. 2023). The significant elevation of CTP1 by cadmium signifies the possible induction of heart attack (myocardial infarction) in the group prenatally exposed to cadmium. This assertion is so because the CTP1 has been identified as a superior marker for the left ventricular malfunction (Buiten *et al.* 2015) and that in most cases, wherever there is a rise in CTP, it is indicative of heart damage or a very recent myocardial infarction. Our findings therefore agree with previous studies of Salah and Hafez (2016), which reported increased CTPI levels in rats exposed to $CdCl_2$ in an oxidative cardiac toxicity model. It also further supports Liu *et al.,* (2021) which observed an elevation of cardiac troponin in mice exposed to cadmium. It is also of great importance to state that in an earlier study from our lab (Ichipi-Ifukor *et al*. 2019) we had postulated the possible involvement of Cd in the induction of myocardial infarction owing to elevated serum and cardiac AST and alteration in cardiac myofibers. Thus, in line with these conclusions, it can suffix to submit that cadmium causes myocardial damage and leads to the intensification of cardiac injury.

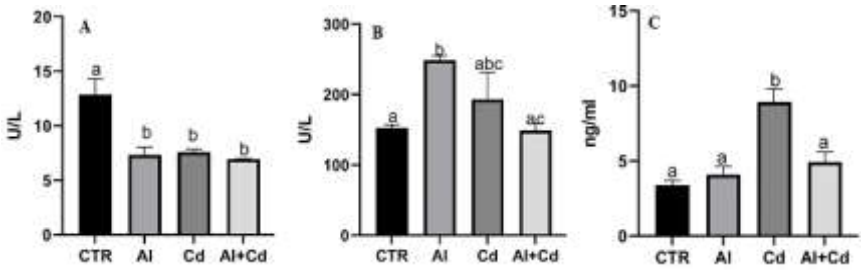

Fig. 1: Effect of Aluminium and Cd co-exposures on serum cardiac functional markers
Bars with varying alphabet superscripts are significantly different ($p<0.05$).
Key; A: Creatinine Kinase; B: Angiotensin Converting Enzyme; C: Cardiac troponin I (CTP-I)

Fig. 2 shows that there was no significant difference on ALT, AST and ALP activities in the heart of mice prenatally exposed to only Al compared to control and the Al+Cd group. Significant elevation of cardiac ALT, AST and ALP were observed in the group exposed to Cd only compared to control, and Al groups

while only AST was significantly increased when comparing the Cd and the Al+Cd groups. Findings in this study are similar to those reported by Ichipi-Ifukor *et al.* (2019). The overall increase in aminotransferase concentrations in the groups exposed to the metals can be attributed to the stress induced on the cells. It has been earlier postulated that in a dysfunctional heart tissue, that there is usually a metabolic shift from fatty acid utilization as major energy pool of the myocardium to the utilization of glucose as the increased hypoxic condition of the heart necessitates an upsurge of oxygen supply for glucose breakdown and utilization (Bertero and Maack, 2018; Nabben *et al.*, 2018; Shi and Qiu 2022). Based on this therefore, it will suffix to say that the cardiac cells in this study resorted to alternative means of energy sources by channelling amino acids towards energy generation via gluconeogenesis (Cetica *et al.* 2003; Sanchz and Raja 2023).

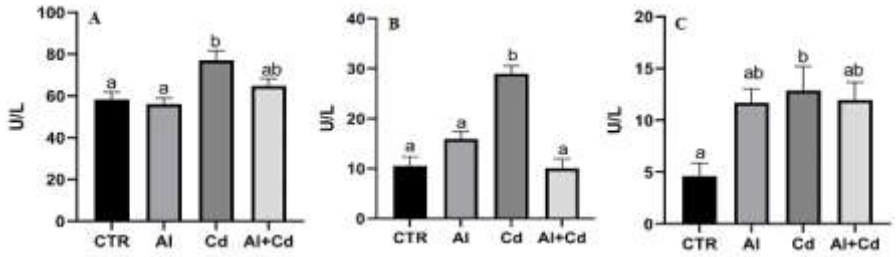

Fig 2: Effect of Al and Cd co-exposures on cardiac amino transferases and alkaline phosphatase
Bars with varying alphabet superscripts are significantly different ($p<0.05$).
Key; A: Alanine transferase (ALT), B: Aspartate transferase (AST) C: Alkaline phosphatase (ALP)

Fig. 3 shows that there was a significantly reduced levels of lipid peroxidation in the Al group compared to control and the Cd group. The reported significant reduction in the MDA of the Al group is not in consonance with the ability of Al to elevate MDA levels as reported by Hegazi and Elebshany (2019). Likewise, the non-significant change mediated by Cd is contrary to that reported by Ichipi-Ifukor *et al.* (2022) as Cd mediated rise in cardiac MDA within a 72h period. The reported variation in these studies as compared to the current study may be as a result of the exposure route and duration of exposure. SOD being a second messenger enzyme that functions in the dismutation of super oxides to less harmful products were reported to be non-significant across all treatment groups compared to control. This observation may also be related to dose, route and exposure timelines. It is of great importance to note that similar results have earlier been reported for the testes and liver by our lab (Okhue *et al*. 2024; Irehievwie *et al.* 2024) in a related co-exposure regimen and supports in entirety the submission that the handling of the toxic malignancies of Al and Cd co-exposures in the current study did not depend fully on SOD activities. While the reported significant reduction on catalase enzymes and the GSH in the Al, Cd and co-exposure group for GSH only is in tandem to earlier reports implicating Al and Cd in the inhibition of the activities of catalase as well as modification of the GSH function by attaching to its sulfhydryl group along its sulfhydryl homocysteine moiety which further promotes its depletion along the metabolic pool (Asagba *et al*. 2008; Ameri *et al*. 2020; Ding *et al.* 2017; Ichipi-Ifukor *et al*. 2022).

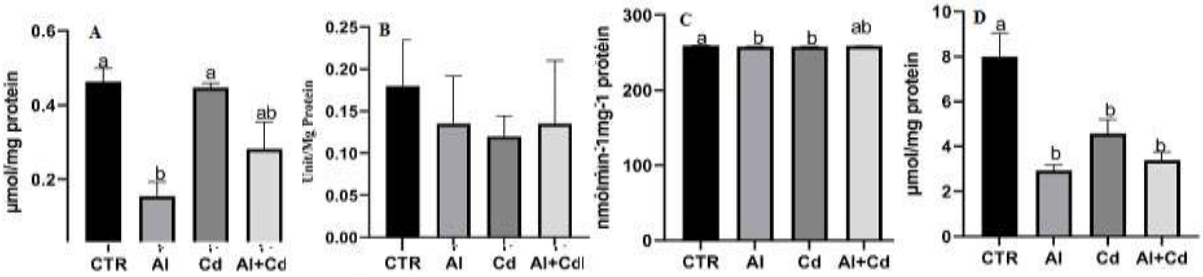

Fig 3: Effect of Al and Cd co-exposures on cardiac Oxidative stress markers
Bars with varying alphabet superscripts are significantly different ($p<0.05$).
Key; A: Malondialdehye (MDA), B: Superoxide dismutase (SOD) C: Catalase (CAT); D: Reduced Glutathione (GSH)

Fig. 4 shows a representative histological feature of the heart of mice exposed to prenatal Al and Cd. The control mice (A) show there was no observable lesion in the heart indicating an intact myofibers and cardiomyocytes and normal heart histology (blue arrows). The group exposed to prenatal Al (B)

displayed intact cardiomyocytes with an early onset of myofiber weakening and necrosis (green arrows). The Cd group (C) and the group exposed to Al+Cd prenatally however shows random disintegration of cardiomyocytes (black arrows), patchy and early onset of myofiber degeneration and necrosis (green arrows) and multiple congestion of blood vessels (white arrows). The features of the heart in these groups are indicative of an abnormal heart histology and development of varying levels of heart disease and malfunction confirming earlier claims in this study of a possible weakness of the cardiomyocytes and pathological heart failure induced by prenatal Cd exposure. The Alterations observed in the histology of the heart in the Cd and Al +Cd groups are similar to those reported in earlier studies relative to Cd toxicity (Kushalf 2009; Arbi *et al*. 2021; Chou *et al*. 2023).

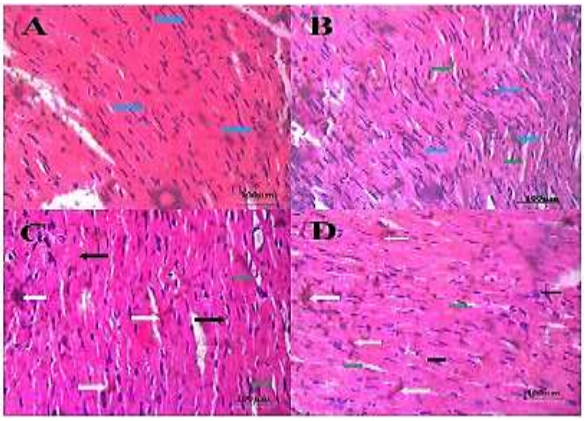

Fig 4 A-D: Effect of Aluminium and Cadmium co-exposures on cardiac Histoarchitectural features
Key: A = Control (CTR); B = Al, C= Cd, D= Al + Cd

Conclusion: Our findings revealed that exposure to aluminium and cadmium during pregnancy altered indices of cardiac function via pathways related to angiotensin, cardiac troponin and oxidative stress signalling which may have impacted directly on the histoarchitectural features of the heart. Comparatively, prenatal exposure to Cd alone impacted more negatively to the heart in relation to exposure to either Al only or co-exposure to Al and Cd.

REFERENCES

Ahmad, H; Khan, H; Haque, S; Ahmad, S; Srivastava, N; Khan, A (2023). Angiotensin-Converting Enzyme and Hypertension: A Systemic Analysis of Various ACE Inhibitors, Their Side Effects, and Bioactive Peptides as a Putative Therapy for Hypertension, *J. Renin-Angiot-Aldoster Sys.*, 2023: 7890188,

Alabi, OA; Adeoluwa, YM (2020). Production usage, and potential public health effects of aluminium cookware: a review. *Ann. Sci. Tech. 5*(1):20-30.

Ameri, M; Baron-Sola, A; Khavari-Nejad, RA; Soltani, N; Najafi, F; Bagheri, A; ... Hernández, LE (2020). Aluminium triggers oxidative stress and antioxidant response in the microalgae Scenedesmus sp. *J. plant physiol.* 246*:*153114.

Arbi, S; Bester, MJ; Pretorius, L; Oberholzer, HM (2021). Adverse cardiovascular effects of exposure to cadmium and mercury alone and in combination on the cardiac tissue and aorta of Sprague–Dawley rats. *J. Environ, Sci. Health, Part A*, 56(6):609-624.

Asagba, S.O; Eriyamremu, GE; Igberaese, M.E (2008). Bioaccumulation of cadmium and its biochemical effect on selected tissues of the catfish (Clarias gariepinus). *Fish Physiol Biochem.* 34:61-69.

Asagba, SO (2019). Cadmium in our food and drinking water - should we be worried? 70th in the series of inaugural lectures of the Delta State University, Abraka. 14th February, Delsu Press.

Asagba, SO; Ichipi-Ifukor, PC; Ichipi-Ifukor, RN; Oyem, JC. (2019). Palm Oil Fractions Alter Acute Cadmium Mediated Haematotoxicity. *GMJ*. 26(3): E201933.

Bazir, H; Hassou, N; Benchekroun, MN; Bessi, H; Ennaji, MM (2023). Risk of the development of cancers induced by the consumption of mussels accumulating metallic trace elements. In Ennaji, MM (Ed). Oncogenic Viruses Academic Press, pp. 39-59.

Beijer, E; Meek, B; Bossuyt, X; Peters, S; Vermeulen, RC; Kromhout, H; Veltkamp, M. (2020). Immunoreactivity to metal and silica associates with sarcoidosis in Dutch patients. *Resp. Res.* 21(1):1-8.

Bertero, E; Maack, C (2018). Metabolic remodelling in heart failure. *Nat Rev Cardiol.* 15(8): 457-470.

Broseghini-Filho, G. B., Almenara, C. C., Vescovi, M. V., Faria, T.deO., Vassallo, D. V., Angeli, J. K., and Padilha, A. S. (2015). Acute Cadmium Exposure Reduces the Local Angiotensin I Converting Enzyme Activity and Increases the Tissue Metal Content. *Biol. Trace* Elem Res. 166(2):149-156.

Buiten, MS; de Bie, MK; Rotmans, JI; Dekker, FW; van Buren, M; Rabelink, TJ; Cobbaert, CM; Schalij, MJ; van der Laarse, A; Jukema, JW (2015). Serum cardiac troponin-I is superior to troponin-T as a marker for left ventricular dysfunction in clinically stable patients with end-stage renal disease. PloS *one*, 10(8): e0134245.

Cao, F; Zervou, S; Lygate, CA (2018). The creatine kinase system as a therapeutic target for myocardial ischaemia-reperfusion injury. *Biochem Soc Transact* 46(5): 1119-1127.

Cetica, P; Pintos, L; Dalvit, G; Beconi, M. (2003). Involvement of enzymes of amino acid metabolism and tricarboxylic acid cycle in bovine oocyte maturation in vitro. *Reproduction*, 126(6):753-763.

Chen, S; Shen, R; Shen J; Lyu, L; Wei, T (2023). Association of blood cadmium with all-cause and cause-specific mortality in patients with hypertension. *Front. Public Health*. 11:1106732

Chou, SH; Lin, HC; Chen, SW; Tai, YT; Jung, SM; Ko, FH; Chu, PH. (2023). Cadmium exposure induces histological damage and cytotoxicity in the cardiovascular system of mice. *Food and Chem. Toxicol.* 175:113740.

Cohen, H.J; Betcher-Lange, S; Kessler, DL; Rajagopalan, KV (1972). Hepatic sulphite oxidase congruency in mitochondria of prosthetic groups and activity. J. Biol. Chem. 247(2):7759-7766

Covaliov, E; Gutium, O; Cazac, V; Babcenco, C (2021). Traditional Preparation of Baba Neagra, a Moldovan Culinary Treasure. *Glob. J. Hum-Soc. Sci.: C Soc and Cult.* 21(5): 59-62 https://doi.org/10.34257/GJHSSCVOL21IS5PG59

Danilczyk, U; Eriksson, U; Oudit, G.Y; Penninger, JM. (2004). Physiological roles of angiotensin-converting enzyme 2. *CMLS*, 61(21): 2714-2719.

Del Franco, A; Ambrosio, G; Baroncelli, L; Pizzorusso, T; Barison, A; Olivotto, I; Recchia, FA; Lombardi, CM; Metra, M; Ferrari Chen, YF; Passino, C; Emdin, M; Vergaro, G. (2022). Creatine deficiency and heart failure. *Heart Failure Rev*. 27(5):1605–1616.

Dharmadasa, P; Kim, N; Thunders, M. (2017). Maternal cadmium exposure and impact on foetal gene expression through methylation changes. Food Chem Toxicol, 109:714-720.

Ding, S; Ma, C; Shi, W; Liu, W., Lu, Y; Liu, Q; Luo, ZB. (2017). Exogenous glutathione enhances cadmium accumulation and alleviates its toxicity in Populus × canescens. *Tree Physiol.*, 37(12)*:*1697–1712.

Dordevic, D; Buchtova, H; Jancikova, S; Macharackova, B; Jarosova, M; Vitez, T; Kushkevych, I. (2019). Aluminium contamination of food during culinary preparation: Case study with aluminium foil and consumers' preferences. *Food Sci. Nutr. 7*(10):3349-3360.

Ellman, G.C; (1959). Tissue sulflydryl groups. Arch. Biochem. Biophy. 82:70-77

Exley, C (2013). Human exposure to aluminium. *Environ. Sci. Proc. Impts*, 15(10): 1807-1816.

Ezedom, T; Asagba, SO (2016). Effect of a controlled food-chain mediated exposure to cadmium and arsenic on oxidative enzymes in the tissues of rats. *Tox. Reports*, 3:708-715.

Fermo, P; Soddu, G; Miani, A; Comite, V. (2020). Quantification of the aluminium content leached into foods baked using aluminium foil. *Intl J Environ Res. Pub. Health, 17*(22), 8357.

Fireman, E; Shai, AB; Alcalay, Y; Ophir, N; Kivity, S; Stejskal, V (2016). Identification of metal sensitization in sarcoid-like metal-exposed patients by the MELISA® lymphocyte proliferation test - a pilot study. *J. Occupational Med toxicol.* 11:18.

Gao, Y; Duan, Z; Zhang, L; Sun, D; Li, X. (2022). The status and research progress of cadmium pollution in rice- (*Oryza sativa* L.) and wheat- (*Triticum aestivum* L.) cropping systems in China: A critical Review. *Toxics*, 10(12):794.

Gérard, D; Gray, SK (2015). Special issue on aluminium plasmonics. *J. Physics and Appl. Physics*, 48(18).

Ghobakhloo, S; Mostafaii, GR; Khoshakhlagh, AH; Moda, HM; Gruszecka-Kosowska, A (2024). Health risk assessment of heavy metals in exposed workers of municipal waste recycling facility in Iran. *Chemosphere*, *346*, 140627.

Gupta, A; Joia, J; Sood, A; Sood, R; Sidhu, C; Kaur, G (2016). Microbes as potential tool for remediation of heavy metals: a review. *J Microb Biochem Technol*, 8(4):364-372.

Gutteridge, JMC; Wilkins, C (1982). Copper dependent hydroxyl radical damage to ascorbic acid. Formation of a thiobarbiturie acid reactive products. *Febs letter* 137:327–340

Horiguchi, H; Oguma, E; Sasaki, S; Miyamoto, K; Hosoi, Y; Ono, A; Kayama, F. (2020). Exposure assessment of cadmium in female farmers in cadmium-polluted areas in Northern Japan. *Toxics*, *8*(2), 44.

Ichipi-Ifukor, PC; Evwhre, OL; Eferobohwo, A. (2013). A comparative study of the effect of cadmium and arsenic On the Activities of brain sulphite oxidase and aldehyde oxidase in the african cat fish (*Clarias gariepienus*). J Res Biosci, 9(1): 68-71

Ichipi-Ifukor, PC; Asagba, SO; Nwose, C (2019). Potentiating role of palm oil (Elaeis guineensis) and its extracts in cadmium-induced alteration of aminotransferases in albino rats. *Trop. J. Pharmaceut. Sci*. 43(1):36-48.

Ichipi-Ifukor, PC; Asagba, SO; Nwose, C; Mordi, JC; Oyem, JC (2022). Palm oil extracts protected against cadmium chloride poisoning via inhibition of oxidative stress in rats. Bull. *Natl Res Centre* 46(1):1-11.

Irerhievwie, O; Ichipi-Ifukor, PC; Asagba, SO (2024). Hepatocellular degeneration in mice co-exposed to in-utero aluminium and cadmium: Implication of a disordered antioxidant and energy homeostatic response in the liver. Environ toxicol Pharmacol, 106:104375. https://doi.org/10.1016/j.etap.2024.104375

Javed, M; Usmani, N (2013). Assessment of heavy metal (Cu, Ni, Fe, Co, Mn, Cr, Zn) pollution in effluent dominated rivulet water and their effect on glycogen metabolism and histology of Mastacembelus armatus. *SpringerPlus*, 2:390 https://doi.org/10.1186/2193-1801-2-390

Judson MA (2020) Environmental Risk Factors for Sarcoidosis. *Front. Immunol.* 11:1340.

Khalaf, EM; Taherian, M; Almalki, SG; Asban, P; Kareem, AK; Alhachami, FR; ... Mohammadi, MJ. (2023). Relationship between exposure to heavy metals on the increased health risk and carcinogenicity of urinary tract (kidney and bladder). *Rev. Environ. Health*, https://doi.org/10.1515/reveh-2022-0245

Kushlaf, HA. (2009). Toxic myopathies. In *Clinical Neurotoxicology*. WB Saunders.

Laitselart, P; Derely, J; Daban, JL; De Rudnicki, S; Libert, N. (2022). Relationship between creatine kinase and liver enzymes in war wounded with rhabdomyolysis. *Injury* 53(1):166-170.

Lim, AKH; Arumugananthan, C; Lau Hing Yim, C; Jellie, LJ; Wong, EWW; Junckerstorff, RK (2020). A Cross-sectional study of the relationship between serum creatine kinase and liver biochemistry in Patients with Rhabdomyolysis. *J. Clin. Med.* **2020**, *9*, 81.

Liu, X; Wang, S; Li, M; Li, J; Sheng, Z. (2021). Chronic Cadmium Exposure Aggravates the Cardiac Dysfunction in Type 2 Diabetic Mice by Promoting Inflammation and Fibrosis. Res Sq. Preprint https://doi.org/10.21203/rs.3.rs-639901/v1

Martins, AC; Lopes, ACBA; Urbano, MR; Maria de Fatima, HC; Silva, AMR; Tinkov, AA; ... Paoliello, MM (2021). An updated systematic review on the association between Cd exposure, blood pressure and hypertension. *Ecotox. Environ. Safety*, *208*, 111636.

Misra, HP; Fridovich, I (1972). The Role of Superoxide ion in the auto-oxidation of epinephrine and a simple assay for superoxide dismutase. *J. Biol. Chem.* 247:3170–3175

Mohammed, AS; Kapri, A; Goel, R (2011). Heavy Metal Pollution: Source, Impact, and Remedies. In: Khan, M; Zaidi, A; Goel, R; Musarrat, J (Eds) Biomanagement of metal-contaminated soils. *Environ. Pollut.* 20. Springer, Dordrecht. https://doi.org/10.1007/978-94-007-1914-9_1

Mordi, JC; Ichipi-Ifukor, PC; Kweki, GR; Ichipi-Ifukor, RN; Oyem, JC; Dennis-Eboh, U (2021). Preliminary toxicology profile of *Dennettia tripetala* (Pepper Fruit) methanolic leaves extract. *Clin. Phytosci.* 7(1):1-15. https://doi.org/10.1186/s40816-021-00298-w

Nabben, M; Luiken, JJFP; Glatz, JFC (2018). Metabolic remodelling in heart failure revisited. *Nat Rev. Cardiol*, 15(12):780.

Newman, LS (1998). Metals that cause sarcoidosis. *Sem. Resp. Infect*. 13(3):212–220.

Obasi, PN; Akudinobi, BEB (2019). Heavy metals occurrence, assessment and distribution in water resources of the lead–zinc mining areas of Abakaliki, Southeastern Nigeria. *Intl. J. Environ. Sci. Technol.* 16:8617-8638.

Odularu, AT; Ajibade, PA; Onianwa, PC (2013). Comparative Study of Leaching of Aluminium from Aluminium, Clay, Stainless Steel, and Steel Cooking Pots. *Public Health*, 3(13):1-4.

Okhue, E; Kadiri, HE; Ichipi-Ifukor, P.C; Ben-Azu, B; Asagba, SO; Achuba, FI; Oyem, JC (2023). Prenatal double-hit with aluminium and cadmium mediate testicular atrophy and hypothalamic hypoplasia: the role of oxido-nitrergic stress and endocrine perturbations. *Biometals*, https://doi.org/10.1007/s10534-023-00563-0

Olufemi, AC; Bello, PO; Mji, A (2018). Conflict implications of coal mining and environmental pollution in South Africa: Lessons from Niger Delta, Nigeria. *Afr. J. Conflict Resol.* 18(1):7-35.

Orisakwe, OE; Oladipo, OO; Ajaezi, GC; Udowelle, NA (2017). Horizontal and vertical distribution of heavy metals in farm produce and livestock around lead-contaminated goldmine in Dareta and Abare, Zamfara State, Northern Nigeria. *J. Environ. Pub. Health*. 2017:3506949

Oritsemuelebi, B; Frazzoli, C; Eze, EC; Ilo, CE; Nwaogazie, IL; Orisakwe OE (2021). Levels of toxic and essential metals in maternal cord blood and anthropometry at birth: a pilot study. *J. Global Health Rep*. 5: e2021104.

Pan, N; Wu, Y; Yang, B; Zhang, M; He, Y; Wang, Z; Tan, L; Zhang, L. (2023). The liver and blood cells are responsible for creatine kinase clearance in blood Circulation: A retrospective study among different human diseases. *Clinica Chimica Acta*, 544:117335.

Quinteros, E; Ribó, A; Mejía, R; López, A; Belteton, W; Comandari, A; ... López, DL (2017). Heavy metals and pesticide exposure from agricultural activities and former agrochemical factory in a Salvadoran rural community. *Environ. Sci. Pollut. Res* 24:1662-1676.

Renke, G; Almeida, VBP; Souza, EA; Lessa, S; Teixeira, RL; Rocha, L; ... Starling-Soares, B. (2023). Clinical outcomes of the deleterious effects of aluminium on neuro-cognition, inflammation, and health: a review. *Nutrients* 15(9):2221.

Salah, EH: Hafez, R (2016). The protective role of curcumin and melatonin in amelioration of cadmium-induced cardiac toxicity in adult albino rats. Ain Shams *J. Foren Med Clin Toxicol* 26(1):161–170.

Sánchez López, de NA; Raja, A (2023). Physiology, metabolism. In: StatPearls Internet Treasure Island (FL): StatPearls Publishing, Available from: https://www.ncbi.nlm.nih.gov/books/NBK546690/

Schmidt, PM; Escobar, AG; Torres, JGD; Martinez, CS; Rizzetti, DA; Kunz, SN; ... Wiggers, GA. (2016). Aluminium exposure for one hour decreases vascular reactivity in conductance and resistance arteries in rats. *Toxicol. Appl. Pharmacol*. 313:109-118.

Shi, X; Qiu, H. (2022). New Insights into energy substrate utilization and metabolic remodelling in cardiac physiological adaption. *Front. Physiol*. 13:831829.

Stucki, G; Brühlmann, P; Stoll, T; Stucki, S; Willer, B; Michel, BA (1996). Low serum creatine kinase activity is associated with muscle weakness in patients with rheumatoid arthritis. *J. Rheumatol*. 23(4): 603–608.

Tasrina, RC; Rowshon, AAMR; Mustafizur, AMR; Rafiqul, I; Ali, MP (2015). Heavy metals contamination in vegetables and its growing soil. *J Environ Ana Chem*, 2(142):2-6.

Yang, S; He, M; Zhi, Y; Chang, SX; Gu, B; Liu, X; Xu, J (2019) An integrated analysis on source-exposure risk of heavy metals in agricultural soils near intense electronic waste recycling activities. *Environ Intl.* 133:105239.

Zervou, S; Whittington, HJ; Russell, AJ; Lygate, CA (2016). Augmentation of Creatine in the Heart. *Mini Rev in Medici Chem*., *16*(1):19–28.

Zhang, Y; Huan, J; Gao, D; Xu, S; Han, X; Song, J; ... Lu, X (2022). Blood pressure mediated the effects of cognitive function impairment related to aluminium exposure in Chinese aluminium smelting workers. *Neurotoxicol.* 91:269-281.

Zhao, X; Cheng, Z; Zhu, YI; Li, S; Zhang, L; Luo, Y (2015). Effects of paternal cadmium exposure on the sperm quality of male rats and the neurobehavioral system of their offspring. *Exper. Therap. Med* 10(6): 2356-2360.