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Research Idea

# Perspective and a proposed study to investigate the threat of hypertension and renal damage due to heavy metal pollution of rivers affected by illegal mining activities (*galamsey*) in Ghana

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## Abstract

Several water assessments of some rivers affected by illegal mining (locally known as *galamsey*) activities in Ghana have recorded high levels of heavy metals and metalloids (such as lead, cadmium, copper, arsenic, mercury, iron and zinc); this poses significant health threats to communities served by affected rivers. To the best of our knowledge, the haematological study by Armah and colleagues is the only one that revealed staggering folds of blood metal concentrations beyond the WHO-required levels in inhabitants of the Tarkwa Nsuaem Municipality and Prestea-Huni Valley District of Ghana. As inhabitants of communities near galamsey sites are constantly exposed to heavy metals since some individuals rely on polluted rivers for domestic purposes, it is necessary to investigate and understand the threat of hypertension and renal damage associated with this unfortunate situation. We share our perspective and a proposed study to elucidate the exact hypertensive and renal damage associated with heavy metal exposure in *galamsey*-polluted rivers in Ghana. Onsite/human studies should provide important information about blood metal concentrations and current hypertension, renal function and genetic status of individuals exposed to heavy metals in specific galamsey-infested

areas. Experimental studies using Sprague-Dawley rat models should determine the proportion of anthropogenic contribution to the levels of heavy metals in the bloodstream. Furthermore, the experimental studies should determine the extent (concentrations and time) and the possible mechanisms/pathways of galamsey-related heavy metals that trigger the pathogenesis and pathophysiology of hypertension and renal damage.

## Keywords

illegal mining, *galamsey*, heavy metals, hypertension, renal damage

## Background and Introduction

In Ghana, illegal mining (locally known as *galamsey*) activities pose direct and indirect threats to nearby communities and the nation as a whole (Eduful et al. 2020). Usually, these activities are carried out in rivers (freshwater bodies) that serve domestic and commercial purposes. These infamous, unfortunate *galamsey activities* have caused alarming pollution of rivers and threaten a drastic shortage of freshwater supply in the country (Yeleliere et al. 2018). Several studies have found that the muddy and turbid rivers resulting from *galamsey* pollution have high levels of heavy metals and metalloids [such as lead (Pb), cadmium (Cd), copper (Cu), arsenic (As), mercury (Hg), manganese (Mn) iron (Fe) and zinc (Zn) (Obiri et al. 2016, Yeleliere et al. 2018, Duncan et al. 2018, Duncan 2020, Bessah et al. 2021, Nti et al. 2023). In addition to their gross detrimental economic and environmental impacts, these levels of heavy metals pose alarming public health threats to consumers of *galamsey*-polluted rivers. This is because accumulations of the aforementioned heavy metals are known to be harmful to humans; their intake over a period may result in cardiovascular diseases, cancers (renal, prostate, ovarian), renal damage and abnormal growth in children (Sharma 2009, Garcia et al. 2017, Xu et al. 2021, Kwon et al. 2023). Previous water assessments to predict the health risk of miners exposed to these metals in the Prestea Huni Valley District of Ghana showed a hazard quotient above the guidance value of 1.0 and cancer health risk higher than the recommended $1 \times 10^{-4}$ to $1 \times 10^{-6}$ range of the USEPA (Obiri et al. 2016). Additionally, studies by Armah et. al. revealed staggering folds (18–20) of blood heavy metal (As, Cd, Pb, Hg and Mn) concentrations beyond the WHO-required levels in inhabitants of the Tarkwa Nsuaem Municipality and Prestea-Huni Valley District (Armah et al. 2012). Recent studies in Asia have shown that individuals exposed to elevated levels of these aforementioned heavy metals and metalloids in their blood are at risk of hypertension and other cardiovascular diseases (Xu et al. 2021, Kwon et al. 2023). Previous experimental studies demonstrated that chronic and limited exposure of SD rats to lead (via ingested water) triggers an elevation in blood pressure (Odigie et al. 2005) and may result in progressive renal insufficiency (Aviv et al. 1980). In addition, studies in Myanmar and Korea confirmed that prenatal maternal cadmium exposure was associated with an occurrence of low birth weight (Wai et al. 2017). Furthermore, Roy-Engel and colleagues demonstrated that exposures to cadmium, arsenic and nickel resulted in shifts in DNA repair pathways, thereby altering genetic products of double-stranded break (DSB) repair

(Morales et al. 2016). The inference from their study could be that alteration of DSB repair pathways may lead to disordered foetal development and severe birth defects. To the best of our knowledge, the haematological study by Armah and colleagues is the only study that successfully investigated blood metal concentrations of individuals exposed to *galamsey*-polluted rivers in Ghana. They suggest that the uncertainty surrounding the proportion of anthropogenic contribution to the levels of heavy metals in the blood has become a factor for the inaction of the government (Armah et al. 2012). Though these studies highlight the health risks posed by heavy metals exposures, no study has directly investigated the presence/incidence of hypertension, renal damage and birth defects in populations exposed to *galamsey*-related heavy metals in Ghana. As a result, there is a critical need for on-site and experimental research to investigate the presence, pathogenesis and pathophysiology of *galamsey* heavy metal-induced hypertension, renal damage and birth defects. We hypothesise that elevated accumulations of heavy metal concentrations in the bloodstream of exposed individuals trigger a cascade of haemodynamic, molecular, immunological and physiological events that result in hypertension and renal damage.

## Study Significance

As inhabitants of communities near *galamsey* sites are heavily exposed to heavy metals due to their reliance on polluted rivers for domestic purposes, it is necessary to investigate and understand the health risks associated with this unfortunate situation. This should be a holistic study that seeks to elucidate the exact disorders associated with exposure to heavy metals in *galamsey*-polluted rivers in Ghana. Onsite investigations must aim to provide significant medical information about current hypertension and renal functioning status, as well as the possible presence of mutations in individuals exposed to heavy metals in selected *galamsey*-infested areas. Experimental studies must aim to determine the proportion of anthropogenic contribution to the levels of heavy metals in the bloodstream. Furthermore, the experimental studies should determine the extent (concentrations and time), as well as the possible mechanisms/pathways through which *galamsey*-related heavy metals influence the pathogenesis and pathophysiology of hypertension, renal damage and birth defects. The findings from such a study will be beneficial to affected to individuals, as it will:

- Inform the scientific community and the public about the direct detrimental effects of *galamsey*-related heavy metals on the cardiovascular, renal, epigenetic and reproductive health of affected individuals;
- Contribute significant information to the biomedical inquiry of mechanisms responsible for hypertension, renal damage and birth defects.

## Proposed Study Objective

The primary objective of such a study should be to determine how heavy metals in *galamsey*-polluted rivers cause hypertension, renal damage and possible birth defects.

### Specific Research Questions

More specifically, the study should seek to answer the following questions (but not limited to only these);

- What are the concentrations of heavy metals (Pb, Hg, As, Cd, Fe, Mn, Cu and Zn) in the bloodstream of inhabitants of selected communities exposed to *galamsey* polluted rivers?
- What are the average heart rates, blood pressures, renal functioning and mutations in study participants?
    - Are they hypertensive, have renal dysfunction or have genetic mutation/ epigenetic modifications?
        - Are there sex differences in the disorders mentioned above?
- What extent (time) and concentration of heavy metals are required to trigger the pathogenesis of hypertension and renal damage in experimental animal models (preferably Sprague-Dawley [SD] rats)?
- What haemodynamic, immunological and molecular responses are elicited in Sprague-Dawley (SD) rats subjected to varying concentrations of heavy metals from *galamsey* water?
    - Are there sex differences in these responses?
- What are the exact hypertensive and renal pathologies heavy metals trigger in SD rats?
    - Are these pathologies similar to what is observed in humans?
- Could the ingestion of concentrations of heavy metals polluted water by pregnant SD rats affect foetal development and induce malformations/disorders?
    - Does it influence the occurrence of birth defects and epigenetic modifications?

## Proposed Research Methods

This should be a two-part study that will involve on-site and experimental investigations. The on-site study will involve human participants in selected communities affected by *galamsey* activities. On the other hand, experimental studies could be conducted in Sprague-Dawley rat models, due to their similar anatomy and physiology to humans.

### Design

**Onsite studies**: This part can include the following:

- *Study site identification*: Researchers must identify communities within districts most affected by *galamsey*. These communities should be near *galamsey*-polluted waterbodies where inhabitants depend on the water for domestic and/or commercial purposes. However, we propose the communities in the Prestea Huni Valley District of Ghana as preliminary study sites. This is because communities in this district meet the aforementioned criteria for the proposed study. Additionally,

previous studies have been conducted in the district to assess heavy metal concentrations in polluted rivers and blood metals in individuals exposed to *galamsey*-polluted waterbodies (Armah et al. 2012, Obiri et al. 2016). To add to this, researchers must identify and select a comparative control district with communities whose inhabitants are served by a river or waterbody not polluted by *galamsey* activities. We suggest that, in the selection of a control community, researchers must consider similarities in demographics, environmental parameters and history and prevalence of hypertension and renal diseases.

- Sample size: Based on the reported 13.3% CKD prevalence in Ghana (Adjei et al. 2018), we employed Cochran's formula to propose a minimum of 177 participants per study site (whether target or control). This would ensure that the study has enough power to detect the true effect of residents' exposure to heavy metals on the development of kidney diseases and hypertension.

- *Ethical Clearance*: As per the declaration of the Helsinki Protocols, researchers are required to seek ethical approval for studies involving human participants (Kapp 2006). For the proposed study, ethical approval could be sought from the following authorities: the Ghana Health Service Ethics Review Board (preferably), the Institutional Review Board of the Council for Scientific and Industrial Research (IRB-CSIR) Ghana and/or the Research Ethics Committee of the University of Ghana.

- *Recruitment of participants*: This should be a two-stage recruitment process. Firstly, the study objectives should be explained to prospective participants both verbally and with documented handouts. If an individual agrees to participate in the study, they should be given a consent form to sign and be subjected to a questionnaire to determine their medical history, demographics, lifestyle and habits that may expose them to *galamsey*-polluted rivers within the community. Only participants with a history of contact with *galamsey*-polluted water should be recruited for the study.

- *Data collection*: Using the ambulatory blood pressure monitor, 24-hour blood pressure, heart rate and pulse should be measured in all participants.

- *Sample collection*:

    - Urine samples should be collected from all participants for proteinuria and urine albumin-creatinine ratio (uACR) tests.

    - Intravenous blood samples should be collected from all study participants for the following tests:

        - Using biochemistry analysers to measure serum creatinine for glomerular filtration rates.

        - Blood cell counts and serum immunoglobulin (Ig) M level.

- Determination of blood metal concentrations using irradiation methods described by Armah et al. (2012). The confirmatory test can be carried out using mass spectrometry.
- Immunoassays in ELISA should be employed in measuring TNF-α, a biomarker and mediator of hypertension (Ramseyer and Garvin 2013).
- Molecular screening for polymorphisms and impairments in DSB DNA repair outcomes using methods described by Roy-Engel and colleagues (Morales et al. 2016). Additionally, research may investigate the presence of epigenetic modifications.

**Experimental Studies**: This is the second part of the proposed study that should investigate the pathophysiology of hypertension, renal damage and inherited renal defects due to *galamsey*-related heavy metal pollution in animal models. The Sprague-Dawley (SD) rat models should be the preferred choice for laboratory animals due to their predictable traits and their ability to develop similar physiological events that occur in human diseases (Lerman et al. 2005).

This part shall include:

- *Ethical Clearance*: The SD rats used in the study should be cared for and kept in humane conditions; standard operating procedures for appropriate care and use of laboratory animals could be obtained from the University of Ghana Institutional Animal Care and Use Committee (UG-IACUC). Ethical clearance could be sought from either the UG-IACUC or the IRB-CSIR.
- *Husbandry and grouping of SD rats*: A representative number of SD rats (per the discretion of researchers) should be used for this study. The SD rats (8–12 weeks old) could be obtained from colonies maintained at the Animal Experimentation Facility of the Noguchi Memorial Institute of Medical Research, University of Ghana. They should be housed and cared for in specialised breeding and experimentation rooms. All SD rats in the study should be housed in a temperature-controlled environment (20–23°C), maintained on standard rat chow and provided with clean water ad libitum.
- *Data Collection (Vitals: BP, heart rate, temperature, blood flow and pulse)*: After one (1) week of provision of clean water ad libitum, SD rats should be divided into two (2) experimental groups for data collection:
    - BP Radiotelemetry group (BPRG): Rats in this group should be anaesthetised and surgically instrumented with BP radiotelemetry catheters as described by Polichnowski and colleagues (Polichnowski et al. 2020, Potter et al. 2021). After surgery, SD rats should be allowed to heal for 7 days (1-week post-surgery), then baseline vitals should be recorded continuously, 24 hours per day (10 seconds every 10 minutes at

500 Hz) for 3 consecutive days, during which rats should be administered purified water ad libitum. SD rats should then be divided into separate sub-experimental groups (later described) for vitals recording up to 14 weeks post-surgery. We recommend radiotelemetry as the primary BP measurement technique as several researchers have confirmed its efficiency (Harrison et al. 2024).

- Tail Cuff Group (TCG): We propose non-invasive tail cuff BP measurement techniques to answer the specific research question "*Could the ingestion of concentrations of heavy metals polluted water by pregnant SD rats affect foetal development and induce malformations/disorders*?". Unlike the BPRG, the SD rats in TCG will be anatomically and physiologically fit for breeding and subsequent studies. Additionally, the TCG SD rats, free of extensive surgical instrumentation, will be ideal for longitudinal BP measurements throughout the entire study (baseline--heavy metal treatment--pregnancy--litter--post-weaning). In addition, another physiological activity that researchers may consider investigating is the levels of infiltration of immune cells into the kidneys of TCG rats vs. BPRG, since Harrison et al. (2024) stated that extensive surgical instrumentation may affect measures of inflammation. For the TCG, SD rats should first be trained for 2 to 3 days. Afterwards, rats should be restrained; and an inflatable cuff and a pulse sensor should then be fitted to the tail for BP measurements. As recommended by Harrison et al. (2024), multiple daily BP measurements should be recorded for 2 to 3 days weekly to improve the accuracy of the Tail cuff method. Baseline vitals should be recorded in week 1, during which rats will be administered purified water ad libitum. SD rats could be divided into separate sub-experimental groups (later described) for vitals recording up to 14 weeks post-baseline tail cuff measurements.

- *Sample collection (blood, urine, organs; kidney, liver and spleen)*: SD rats in the sample collection groups (BPRG and TCG) can be categorised into three (3) sub-experimental groups each. Therefore, two (2) data collection groups should further be divided into six (6) sample collection groups. It should be ensured that groupings are random and all groups have significant gender representation. The sample collection groups could be as follows;

  - *Galamsey* heavy metals polluted (GHMP) water group: After one (1) week post-surgery or post-baseline tail cuff measurements, SD rats in this group should be fed with *galamsey*-related heavy metals polluted water samples collected from sites of human studies. Before this, collected water samples may be assessed for heavy metal concentrations using standard methods to examine wastewater as outlined by the American Water Works Association.

- Laboratory-prepared heavy metals polluted (LPHMP) water group: After one (1) week post-surgery or post-baseline tail cuff measurements, SD rats in this group should be fed laboratory-prepared water induced with varying heavy metal concentrations. We propose this experimental group for the following reasons: **i.** to determine the concentrations of heavy metals required to trigger hypertension and renal damage in SD rats (since there are some difference in SD rat physiology as compared to humans). Separate groups of SD rats could be subjected to lower and/or higher concentrations of heavy metals as compared to the concentrations measured in GHMP water. Therefore, a positive control for the experimental study could be established from the LPHMP water group; **ii.** make up for physicochemical changes that may occur from the transportation and storage of *galamsey* heavy metals polluted water for the entirety of experimental studies; **iii.** additionally, the LPHMP water group will allow researchers to investigate the effects of singular or combinations of different heavy metals in triggering hypertension and renal damage (we believe this should be done, based on the discretion of the researchers).
- Control group; After one (1) week post-surgery or post-baseline tail cuff measurements, SD rats in this group should be continuously fed with purified water throughout the study.

Table 1 shows all six proposed data and sampling groupings.

Table 1.

The proposed cohort for heavy metal, hypertension and renal damage animal experimentation.

| | BP radiotelemetry group (BPRG) | | | Tail cuff group (TCG) | | |
|---|---|---|---|---|---|---|
| Cohort | GHMP-BPRG | LPHMP-BPRG | Control-BPRG | GHMP-TCG | LPHMP-TCG | Control-TCG |

The following samples should be collected and their corresponding tests should be conducted:

- Urine samples should be collected each week post-surgery and post-baseline tail cuff measurements till week 14. At each time point, rats should be placed in metabolic cages and 24-hour urine samples should be collected for the assessment of proteinuria and uACR. Protein concentrations in the urine samples could also be determined using the Bradford method.
- Blood samples should be collected each week post-surgery and post-baseline tail cuff measurements till week 14. The tail vein sampling and the cardiac puncture (for rats to be euthanised) procedures as described by Parasuraman and colleagues could be used in collecting blood from various SD rat groups (Parasuraman et al. 2010). SD rat blood samples should be subjected to the aforementioned tests conducted for human blood samples.

- Organ excision: At each weekly post-surgery and post-baseline tail cuff measurements, relatively equal percentages of SD rats in each sampling group should be euthanised and subjected to nephrectomy (frequency of nephrectomy could be at the reasonable discretion of researchers). Excised kidneys should then be weighed, appropriately stained and treated for histological, immunohistochemical (flow cytometric analysis) and microscopic assessments to identify sclerosis, fibrosis, vascular injuries, cell death (types; necrosis or apoptosis) and infiltrating immune cells (Shimada et al. 2020, Abdelbary et al. 2022). A portion of the excised kidneys could be homogenised and subjected to the aforementioned molecular assessments in humans. Emphasis should be placed on determining gene expression mutations, single nucleotide polymorphisms, biochemical pathways, telomere lengths, alteration in DSB repair pathways and epigenetic modifications.
- Investigating the effects of ingestion of heavy metals polluted water on foetal development and progeny malformations (birth defects and epigenetic modifications): After 14 weeks of experimentation, one male and one female SD rat in the tail-cuff group should be selected from each sampling group (GHMP, LPHMP and Control) for breeding and subsequent studies. Rats may then be placed in separate breeding cages based on their groups and allowed to mate to produce litters. Based on the initial sampling group, water should be provided to both parent rats and litter ad libitum. By analysing the BP recordings from pregnant SD rats, researchers could explore investigating the incidence of pre-eclampsia in the study group as studies by Wang et al. (2020) have associated exposures to chromium, mercury and arsenic to increased pre-eclampsia prevalence. After the litters are weaned, parent rats could be euthanised and subjected to the earlier described tests. Litters should be weighed before weaning. Weaned rats should be maintained in separate cages, based on gender and parent sampling group. All litters should be thoroughly observed for anatomical malformations and birth defects. At 5 weeks post-weaning, vitals should be measured using the tail-cuff method (however, researchers may employ telemetry in a select group of rats for efficiency in BP measurement). Urine and blood samples (tail venipuncture) should be collected at 5-, 6-, 7- and 8 weeks post-weaning for tests previously mentioned. At eight (8) weeks post-weaning, all surviving SD rats should be euthanised, nephrectomised and subjected to anatomical, histological, immunohistochemical (flow cytometric analysis) and microscopic assessments. Molecular analysis should be carried out to investigate alterations in DSB repair pathways. Furthermore, we propose that researchers investigate DNA methylation and alteration of DNA and chromatin structure, as Bitto et al. (2015) indicate that heavy metals may trigger epigenetic modifications in foetal development and early childhood, posing significant health risks.

## Limitations

Investigating the detrimental effect of galamsey requires a multifaceted approach and a longitudinal strategy to establish the short-term and long-term effects and explore other environmental factors. However, this study takes a cross-sectional approach, which limits its ability to examine the dynamics and changes in the health status of the participants over time.

In Ghana, studies that involve the collection of blood are met with the unwillingness of residents of the study area to participate, mainly due to superstitious beliefs. However, the researchers should conduct a thorough community entry to carefully explain the procedures and benefits of the study to the community and also employ the assistance of community health staff and a highly respected resident of the community to conduct successful data and sample collection on-site.

More so, issues connected to illegal mining are usually met with strong opposition from the illegal miners. Notwithstanding this, the residents and miners alike should be assured that their safety and privacy will be preserved without any repercussions from their participation in the study.

Additionally, we propose this study for the wider scientific community because, presently, we do not have the necessary funding and logistics required to successfully conduct this study.

## Ethics and security

The study should obtain ethical approval from the Institutional Review Board of the Council for Scientific and Industrial Research and the Ghana Health Service Ethics Review Board. Ethical clearance for the use of lab rats should be obtained from the University of Ghana Institutional Animal Care and Use Committee. To safeguard the well-being of the researchers and the study participants, the researchers should engage the traditional rulers and opinion leaders of the study area and explain the objectives and benefits of the study, while taking care not to implicate illegal miners. This is to create a harmonious and receptive environment for the researchers to conduct the study. More so, the district police service should be notified of the presence of the researchers in the study area. Subsequently, the appropriate written consent will be obtained from each participant prior to their involvement in the study. Study participants should be assured of the confidentiality of any data collected during the research activities and the data should solely be used for research and academic purposes only. Data collection should be done with assistance from an educated and well-respected resident of the study area and community health workers to create a familiar and comfortable environment for the study participants.

## Author contributions

The research idea was conceptualised by MKA, who also wrote the manuscript. FTA reviewed and revised the proposed study designs. All the authors helped with the final draft. All the authors have perused the work and given their approval.

## Conflicts of interest

The authors have declared that no competing interests exist.

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