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# Arsenic, cadmium, and lead exposition: a risk factor for breast and prostate cancers? – Protocol for a systematic review

## Exposição à arsênio, cádmio e chumbo: fator de risco para cânceres de mama e de próstata? – Protocolo de revisão sistemática

## Exposición a arsénico, cadmio y plomo: ¿factor de riesgo para cáncer de mama y de próstata? – Protocolo de revisión sistemática

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**Abstract**
Objective: This study aims to develop a protocol for a systematic review of the literature published until April/2021 related to exposure to heavy metals and the development of breast and prostate cancer, to understand the relationship between metals such as arsenic, cadmium, and lead and these types of cancer, considering the characteristics of bioaccumulation of these elements and the intensification of their use in contemporary society. Methodology: The mnemonic PECOS (Population, Exposure, Control, Outcome, and Study Design) will guide the search strategy that will be carried out in eight databases (Pubmed, Pubmed PMC, BVS, Embase, Scopus, Web of Science, Cochrane, and ProQuest). The selection process and data extraction will be conducted by two authors independently. Articles that meet the pre-established inclusion criteria (age over 18 years, exposed metals, type of cancer, case-control, and cohort studies) will be included in the review and, after reading the complete text, will have the data and characteristics extracted and organized in a table containing the bibliometric data and characteristics of the studies (population, data obtained, conclusions and results). Results: They will be presented in a descriptive synthesis followed by tables and diagrams.
**Keywords:** Heavy metals; Breast neoplasms; Prostatic neoplasms; Environmental exposure.

**Resumo**
Objetivo: Este estudo visa desenvolver um protocolo para uma revisão sistemática da literatura publicada até abril/2021 relacionada à exposição a metais pesados e o desenvolvimento de câncer de mama e de próstata, a fim de compreender a relação existente entre metais como arsênio, cádmio e chumbo e esses tipos de câncer, dadas as características de bioacumulação desses elementos e a intensificação de seu uso na sociedade contemporânea. Metodologia: O mnemônico PECOS (População, Exposição, Controle, Desfecho e desenho dos estudos) norteará a estratégia de busca que será realizada em oito bases de dados (Pubmed, PubMed Central, BVS, Embase, Scopus, Web of Science, Cochrane e ProQuest). Os processos de seleção e a extração de dados serão conduzidos por dois autores de maneira independente e cega. Os artigos que obedecerem aos critérios de inclusão pré-estabelecidos (público-alvo acima de 18 anos, metais expostos, tipo de câncer, estudos caso-controle e de coorte) serão incluídos na revisão e, após a leitura na íntegra de seu conteúdo, terão os dados e características extraídos e organizados em um formulário

específico contendo os dados bibliométricos e características dos estudos (população, dados obtidos, conclusões e resultados). Resultados: Serão apresentados em síntese descritiva acompanhada de tabelas e diagramas.
**Palavras-chave:** Metais pesados; Neoplasias da mama; Neoplasias da próstata; Exposição ambiental.

**Resumen**
Objetivo: Este estudio tiene como objetivo desarrollar un protocolo para una revisión sistemática de la literatura publicada hasta abril/2021 relacionada con la exposición a metales pesados y el desarrollo de cáncer de mama y próstata, con el fin de comprender la relación entre metales como el arsénico, el cadmio y el plomo y estos tipos de cáncer, dadas las características de bioacumulación. de estos elementos y la intensificación de su uso en la sociedad contemporánea. Metodología: La nemónica PECOS (Population, Exposure, Control, Outcome and Study Design) guiará la estrategia de búsqueda que se realizará en ocho bases de datos (Pubmed, Pubmed PMC, BVS, Embase, Scopus, Web of Science, Cochrane y ProQuest). El proceso de selección y extracción de datos será realizado por dos autores de forma independiente. Los artículos que cumplan con los criterios de inclusión preestablecidos (público objetivo mayor de 18 años, metales expuestos, tipo de cáncer, estudios de casos y controles y cohortes) serán incluidos en la revisión y, luego de la lectura completa de su contenido, tendrán la datos y características extraídos y organizados en un formulario específico que contiene los datos bibliométricos y características de los estudios (población, datos obtenidos, conclusiones y resultados). Resultados: Se presentarán en una síntesis descriptiva acompañada de tablas y diagramas.
**Palabras clave:** Metales pesados; Neoplasias de la mama; Neoplasias de la próstata; Exposición a riesgos ambientales.

## 1. Introduction

Cancer is a complex and multifactorial disease caused by metabolic imbalances, exogenous factors (diet, lifestyle, exposure to radiation and contaminants), heredity, and other elements. The disease formation is called carcinogenesis, which is triggered by inherited or acquired genetic mutations, and by the action of chemical, hormonal, radioactive, and viral agents. These agents are called carcinogens (Shibamoto & Bjeldanes, 2014).

In 112 countries of the world, cancer is the main cause of death before 70 years old and this is an obstacle to increasing life expectancy. In 2020, among the 19.3 million new cases (excluding melanomas), the highest incidence of the disease was represented by breast cancer, with 11.7% of new cases. Breast cancer was the most common cancer among women (24.5% of new cases) in 159 countries and the most lethal in 113 countries (Sung et al., 2021).

The highest rates of cancer mortality are due to lung cancer, leading to the world's mortality rates for the disease. However, the detected cases of prostate cancer are attracting attention: in 2020, 14.1% of new cases were due to prostate cancer. The exception to this is Asia, where lung cancer cases are still predominant in males. On the other hand, in some continent prostate cancer is already the most frequent among men. In addition, the incidence of prostate cancer presents geographic variations that are drawing attention to the role of behavioral factors and environmental exposure in the development of the disease. This fact is supported by studies in populations that move to countries with high rates of the disease, and the number of cases in these populations then approaches the rates of the country that they migrate to (moving away from their home country rates), providing evidence that exogenous factors can play an important role in carcinogenesis (Brito-Marcelino et al., 2021; Sung et al., 2021).

The discussions about the causes of cancer emerged in the discovery of the disease and persist to the current day; going through theories that point from fluid imbalance as one of the causes (Hippocrates' Humoral Theory) to the conclusion that tumors were made up of cells and their indiscriminate propagation (Maciel-Silva et al., 2018).

An example of a contaminant in contemporary society are pesticides and some of these elements - such as DDT (dichlorodiphenyl-trichoroethane) – have their use controlled and even forbidden, the bioaccumulation property of these elements means that they are found at different trophic levels of the food chain, as well as in human adipose tissue, blood, and milk (Beard & Collaboration, 2006).

The relationship between environmental exposure to contaminants and carcinogenesis is because some of these

elements can act as endocrine disruptors, playing an important role, especially in hormone-dependent cancers. Such elements have the ability to mimic the action of hormones, due to the similarity of their chemical structure to natural hormones, or even to neutralize the action of elements that, under natural conditions, would act as protectors against abnormal cell proliferation (Beard & Collaboration, 2006).

Endocrine disruptors are chemical substances or mixtures that interfere with normal hormonal activity and can occur naturally (food) or artificially (synthetic products, pesticides, etc.). The harmful effects resulting from exposure to these elements may not be perceived during the period of exposure, but manifest themselves throughout life, intensifying in adulthood or aging (Kabir et al., 2015).

Among the environmental contaminants, we find heavy metals, which refer to the group of elements that occur naturally in small concentrations and have a density ≥ 5 g/cm3. The association of the term "heavy metal" with pollutants and contaminants has become common, but in this classification are found some essential metals for living beings, such as cobalt (Co), iron (Fe), copper (Cu), manganese (Mn), molybdenum (Mo), vanadium (V), strontium (Sr) and zinc (Zn) (Alloway, 1990; Duarte & Pasqual, 2000).

Thereby, contact with heavy metals is inevitable, as sources can be both natural and anthropogenic. Some may be essential to the functioning of organisms (zinc, selenium, magnesium, etc.), iron is essential for oxygen transport, and selenium and manganese in antioxidant defense; however, metals such as lead, cadmium, and arsenic may be harmful when in high amounts or prolonged exposure, and they can neutralize the anticarcinogenic action of essential elements, like as the interaction between cadmium and selenium (Alatise & Schrauzer, 2010; Perrelli et al., 2022).

The heavy metals can cause epigenetic disorders, including DNA methylation, responsible for inhibiting the expression of tumor suppressor genes, altering the cell division process, and facilitating the proliferation of malignant cells. Another important factor is that metals, such as lead and cadmium, tend to decrease the action of metalloproteins that act as antioxidants and help in the detoxification process of free radicals (Balali-Mood et al., 2021).

Among environmental carcinogens, arsenic is the most widespread. According to the International Agency for Research on Cancer, arsenic and its inorganic compounds are recognized as carcinogens for the skin, lung, and bladder and, despite limited evidence in humans, it is also noted in the carcinogenesis of the liver, prostate, and kidneys. In addition, exposure to arsenic is associated with other chronic diseases such as type 2 diabetes and cardiovascular problems (Sung et al., 2021).

Although arsenic is a metalloid, it has properties similar to that of a metal and occurs naturally in the environment in geological formations. As such, the contamination of waterways by arsenic is a matter of great concern in certain regions; especially in rural areas that use groundwater to supply and irrigate crops. Cases of mass contamination have already been observed in the regions of Taiwan and Bangladesh and in some places in the United States (Davey et al., 2007).

Even without a consensus on the role of arsenic in carcinogenesis, the main mechanisms of action of this metal that contribute to neoplasms are related to oxidative stress, genotoxicity, and chromosomal aberrations, also present in other elements covered by this classification (Zhou & Xi, 2018).

Another metal that has attracted the attention of researchers regarding breast and prostate carcinogenesis is lead since it can function as an endocrine disruptor and promote imbalances in relation to essential metals. Lead contamination is geographically unequal and can be through different routes: soil, air, water, or anthropogenic actions (water pipes, paints, and fuels), the amount of lead present in the blood can be a good indicator of the presence of this metal, both in humans and animals (Levin et al., 2021).

Lead is a metalloestrogen, acting in a similar way to estrogen can stimulate cell proliferation in breast cancer. Lead is also associated with infertility in both men and women. In prostate carcinogenesis, for example, one of the most consistent

pieces of evidence is that high levels of exposure to lead affect the levels of zinc in humans. Zinc is an essential metal with an important role in the healthy development of the prostate (Neslund-Dudas et al., 2018). The toxic effects of lead on human health can differ according to age group. While in children the attention turns to the effects on the nervous system; among adults changes in the cardiovascular system, involvement in cases of hypertension, and chronic kidney dysfunction are the center of attention (Moreira & Moreira, 2004; Perrelli et al., 2022).

Another non-essential element that occurs naturally in the environment is cadmium, which has food and smoking as its main source of contact with humans. Furthermore, it is present in soil fertilizers and pesticides (Järup, 2003; Van Maele-Fabry et al., 2016). Cadmium has bioaccumulative characteristics and may have its amount increased due to age. It is usually present in greater quantities in women and its absorption is related to the presence of essential metals such as zinc, magnesium, selenium, calcium, and iron. Thus, the deficiency of these elements can result in greater absorption of cadmium. Cadmium toxicity may cause changes in the homeostasis of essential metals, inhibition of DNA repair mechanisms, and increased oxidative stress by weakening the enzymatic and non-enzymatic antioxidant barrier. The main role of cadmium in carcinogenesis is its influence on gene expression, inducing mutations in proto-oncogenes and interrupting cell death signaling pathways, as well as interrupting DNA repair mechanisms (Aalami et al., 2022; Adams et al., 2011; Mezynska & Brzóska, 2018).

Cadmium, arsenic, and lead are endocrine disruptors, playing an important role in estrogen receptors and in hormone-dependent tumors. The oxidative damage caused by them constitutes the main mechanism for promoting carcinogenesis (Davey et al., 2007). In both breast cancer and prostate cancer, endocrine disruption can be fundamental, it can have a direct action or by binding to hormone receptors, blocking or mimicking such pathways (Corti et al., 2022; Florea & Büsselberg, 2011).

In this way, the knowledge and recognition of substances that contribute to carcinogenesis become relevant in the face of the use of various elements in a more pronounced way, due to the industrialization processes, the disposal of waste, and the accumulation of pollutants in water courses, soil, and the atmosphere. Therefore, the question that guides this research arises: is there an association between exposure to heavy metals (cadmium, arsenic, and lead) and the development of breast and prostate cancer in adults?

## 2. Methodology

### *2.1 Design and protocol register*

This is a systematic review protocol, following the method defined by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols – PRISMA-P (Moher et al., 2015; Shamseer et al., 2015). This guideline was created to have accurate and transparent reports, guaranteeing the quality of the reviews; for this, a systematic review must follow some steps: formulation of the research question, elaboration of a research protocol, construction of a search strategy, establishment of inclusion and exclusion criteria, selection and evaluation of studies for inclusion(Dermeval et al., 2020; Page et al., 2021).

The systematic review protocol was registered in the Prospective International Register of Systematic Reviews (PROSPERO - http://www.crd.york.ac.uk/PROSPERO ) under the registration number CRD42020150720.

### *2.2 Eligibility Criteria*

The review was structured from the acronym PECOS (Population, Exposure, Control, Outcome, Study Design), as detailed in the Table 01, and the following research question was formulated: Is there an association between exposure to arsenic, cadmium, and lead and the development of breast and prostate cancer in adults?

**Table 1** - Structuring of the research question according to the PECOS acronym.

| Acronym | | Inclusion Criteria | Exclusion Criteria |
|---|---|---|---|
| **P** | Population | Studies conducted in adults (over 18 years old) | Under 18 years old |
| **E** | Exposure | Arsenic, Cadmium, Lead | Other metals |
| **C** | Control | Exposed | Not exposed |
| **O** | Outcome | Breast cancer<br>Prostate cancer | Outcomes related to other types of carcinomas and related to endocrine receptors |
| **S** | Study Design | Cohort studies<br>Case-control studies | Case Reports<br>Case Study<br>Reviews |

Source: Prepared by the authors.

### *2.3 Search Strategy*

According to the research question, searches will be carried out in the following databases: Pubmed, Pubmed PMC, BVS, Embase, Scopus, Web of Science, Cochrane, and ProQuest until April 2021. An initial date was not established in the research, with the objective of outlining the beginning and evolution of studies related to the theme. Studies in English, Spanish, and Portuguese will be considered for inclusion in this review. Information on grey literature, websites, expert opinion, unpublished research, hand-searching of journals, reference lists of studies, and conference proceedings will not be consulted. The strategies will use specific descriptors for each of the databases, with their respective translation into English and combinations with boolean operators (AND, OR, NOT), according to the example in Table 2. When there are no specific descriptors for the respective database, keywords defined in the structure of the research question and their variants, combined by Boolean operators, will be used.

**Table 2** – Example of search terms selected for the PubMed – Lead Exposure.

| Descriptors and free terms used | Search | Search Strategy |
|---|---|---|
| Breast Neoplasms (Mesh Term 1)<br>Prostate Neoplasms (Mesh Term 2)<br>Lead Exposure (Free term) | Title/Title or Abstract | (((Breast Neoplasms[MeSH Terms]) OR ("Breast Neoplasms"[Title/Abstract] OR "Breast Neoplasm"[Title/Abstract] OR "Neoplasm, Breast"[Title/Abstract] OR "Breast Tumors"[Title/Abstract] OR "Breast Tumor"[Title/Abstract] OR "Tumor, Breast"[Title/Abstract] OR "Tumors, Breast"[Title/Abstract] OR "Neoplasms, Breast"[Title/Abstract] OR "Breast Cancer"[Title/Abstract] OR "Cancer, Breast"[Title/Abstract] OR "Mammary Cancer"[Title/Abstract] OR "Cancer, Mammary"[Title/Abstract] OR "Cancers, Mammary"[Title/Abstract] OR "Mammary Cancers"[Title/Abstract] OR "Malignant Neoplasm of Breast"[Title/Abstract] OR "Breast Malignant Neoplasm"[Title/Abstract] OR "Breast Malignant Neoplasms"[Title/Abstract] OR "Malignant Tumor of Breast"[Title/Abstract] OR "Breast Malignant Tumor"[Title/Abstract] OR "Breast Malignant Tumors"[Title/Abstract] OR "Cancer of Breast"[Title/Abstract] OR "Cancer of the Breast"[Title/Abstract] OR "Mammary Carcinoma, Human"[Title/Abstract] OR "Carcinoma, Human Mammary"[Title/Abstract] OR "Carcinomas, Human Mammary"[Title/Abstract] OR "Human Mammary Carcinomas"[Title/Abstract] OR "Mammary Carcinomas, Human"[Title/Abstract] OR "Human Mammary Carcinoma"[Title/Abstract] OR "Mammary Neoplasms, Human"[Title/Abstract] OR "Human Mammary Neoplasm"[Title/Abstract] OR "Human Mammary Neoplasms"[Title/Abstract] OR "Neoplasm, Human Mammary"[Title/Abstract] OR "Neoplasms, Human Mammary"[Title/Abstract] OR "Mammary Neoplasm, Human"[Title/Abstract] OR "Breast Carcinoma"[Title/Abstract] OR "Breast Carcinomas"[Title/Abstract] OR "Carcinoma, Breast"[Title/Abstract] OR "Carcinomas, Breast"[Title/Abstract])) OR ((Prostatic Neoplasms[MeSH Terms]) OR ("Prostatic Neoplasms"[Title/Abstract] OR "Prostate Neoplasms"[Title/Abstract] OR "Neoplasms, Prostate"[Title/Abstract] OR "Neoplasm, Prostate"[Title/Abstract] OR "Prostate Neoplasm"[Title/Abstract] OR "Neoplasms, Prostatic"[Title/Abstract] OR "Neoplasm, Prostatic"[Title/Abstract] OR "Prostatic Neoplasm"[Title/Abstract] OR "Prostate Cancer"[Title/Abstract] OR "Cancer, Prostate"[Title/Abstract] OR "Cancers, Prostate"[Title/Abstract] OR "Prostate Cancers"[Title/Abstract] OR "Cancer of the Prostate"[Title/Abstract] OR "Prostatic Cancer"[Title/Abstract] OR "Cancer, Prostatic"[Title/Abstract] OR "Cancers, Prostatic"[Title/Abstract] OR "Prostatic Cancers"[Title/Abstract] OR "Cancer of Prostate"[Title/Abstract]))) AND ("lead exposure") |

Source: Prepared by the authors.

### *2.4 Data Extraction*

After searching the databases, the results will be transferred to the reference manager (EndNote-Web), from which duplicate results will be removed. Subsequently, these files will be transferred to the Rayyan software — a web and mobile app for systematic reviews – Systematic Reviews (Ouzzani et al., 2016). The titles and abstracts will be screened and selected by three independent reviewers to assess eligibility according to the inclusion criteria defined for this review. If any eventually occur disagreements between the reviewers will be solved by a fourth reviewer.

When reading titles and abstracts, the following inclusion criteria will be applied:

a) Does the target population fit into the pre-established age group (from 18 years old)?

b) Is the study related to breast and/or prostate cancer?

c) Is the study related to the metals studied: arsenic, cadmium, and/or lead?

d) Is the publication available in English, Spanish or Portuguese?

e) Is it a cohort or case-control study?

After reading the titles and abstracts, eligible studies will be read in full and relevant data for the systematic review will be extracted (author, title, DOI, country, University/Institution of the main author, study type and design, country of data collection, collection period, date of publication, language, metals studied, type of cancer, nature of exposure, characteristics of the population and form of measurement – if any). This data will be organized in a summary table.

### *2.5 Quality assessment and narrative synthesis*

For eligible studies, the risk of bias will be assessed using the New Castle Ottawa Scale (NOS), which presents this assessment in three domains: selection bias, comparability, and results (Stang, 2010).

After this analysis, a narrative synthesis of the included studies will be carried out. If there is quantitative data, these will be extracted in a summary table, and tables, graphs, or figures will be designed in order to present the results.

## 3. Results and Discussion

The results of the systematic review protocol will be presented in a PRISMA flow diagram and described in the final systematic review report (Page et al., 2021). From this systematic review, it is expected to gather cohort studies (prospective and retrospective) and case-control studies that relate exposure (occupational and non-occupational) to arsenic, cadmium, and lead to breast and prostate carcinogenesis; verifying established associations; as well as the most used methods for determining the concentration of these metals in humans.

## 4. Final Considerations

We believe that the standardized approach outlined in this systematic review protocol offers a transparent and accurate method to conduct the systematic review.

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## References

Aalami, A. H., Hoseinzadeh, M., Hosseini Manesh, P., Jiryai Sharahi, A., & Kargar Aliabadi, E. (2022). Carcinogenic effects of heavy metals by inducing dysregulation of microRNAs: A review. *Mol Biol Rep*, *49*(12), 12227-12238. https://doi.org/10.1007/s11033-022-07897-x

Adams, S. V., Newcomb, P. A., Shafer, M. M., Atkinson, C., Bowles, E. J., Newton, K. M., & Lampe, J. W. (2011). Urinary cadmium and mammographic density in premenopausal women. *Breast Cancer Res Treat*, *128*(3), 837-844. https://doi.org/10.1007/s10549-011-1383-8

Alatise, O. I., & Schrauzer, G. N. (2010). Lead exposure: a contributing cause of the current breast cancer epidemic in Nigerian women. *Biol Trace Elem Res*, *136*(2), 127-139. https://doi.org/10.1007/s12011-010-8608-2

Alloway, B. J. (1990). ***Heavy metals in soils***. Springer, Dordrecht. https://doi.org/https://doi.org/10.1007/978-94-007-4470-7

Balali-Mood, M., Naseri, K., Tahergorabi, Z., Khazdair, M. R., & Sadeghi, M. (2021). Toxic Mechanisms of Five Heavy Metals: Mercury, Lead, Chromium, Cadmium, and Arsenic. *Front Pharmacol*, *12*, 643972. https://doi.org/10.3389/fphar.2021.643972

Beard, J., & Collaboration, A. R. H. R. (2006). DDT and human health. *Sci Total Environ*, *355*(1-3), 78-89. https://doi.org/10.1016/j.scitotenv.2005.02.022

Brito-Marcelino, A., Duarte-Tavares, R. J., Marcelino, K. B., & Silva-Neto, J. A. (2021). Breast cancer and occupational exposures: an integrative review of the literature. *Rev Bras Med Trab*, *18*(4), 488-496. https://doi.org/10.47626/1679-4435-2020-595

Corti, M., Lorenzetti, S., Ubaldi, A., Zilli, R., & Marcoccia, D. (2022). Endocrine Disruptors and Prostate Cancer. *Int J Mol Sci*, *23*(3). https://doi.org/10.3390/ijms23031216

Davey, J. C., Bodwell, J. E., Gosse, J. A., & Hamilton, J. W. (2007). Arsenic as an endocrine disruptor: effects of arsenic on estrogen receptor-mediated gene expression in vivo and in cell culture. *Toxicol Sci*, *98*(1), 75-86. https://doi.org/10.1093/toxsci/kfm013

Dermeval, D., Coelho, J., & Bittencourt, I. I. (2020). Mapeamento sistemático e revisão sistemática da literatura em informática na educação. *Jaques, Patrícia Augustin; Siqueira; Sean; Bittencourt, Ig; Pimentel, Mariano.(Org.) Metodologia de Pesquisa Científica em Informática na Educação: Abordagem Quantitativa. Porto Alegre: SBC*.

Duarte, R. P. S., & Pasqual, A. (2000). Avaliação do cádmio (Cd), chumbo (Pb), níquel (Ni) e zinco (Zn) em solos, plantas e cabelos humanos. *Energia na Agricultura*, *15*(1), 46.

Florea, A. M., & Büsselberg, D. (2011). Metals and breast cancer: risk factors or healing agents? *J Toxicol*, *2011*, 159619. https://doi.org/10.1155/2011/159619

Järup, L. (2003). Hazards of heavy metal contamination. *Br Med Bull*, *68*, 167-182. https://doi.org/10.1093/bmb/ldg032

Kabir, E. R., Rahman, M. S., & Rahman, I. (2015). A review on endocrine disruptors and their possible impacts on human health. *Environ Toxicol Pharmacol*, *40*(1), 241-258. https://doi.org/10.1016/j.etap.2015.06.009

Levin, R., Zilli Vieira, C. L., Rosenbaum, M. H., Bischoff, K., Mordarski, D. C., & Brown, M. J. (2021). The urban lead (Pb) burden in humans, animals and the natural environment. *Environ Res*, *193*, 110377. https://doi.org/10.1016/j.envres.2020.110377

Maciel-Silva, P., Caldeira, I., de Assis Santos, I., Carreira, A. C. O., Siqueira, F. R., Antonioli, E., . . . Garay-Malpartida, H. M. (2018). FAM3B/PANDER inhibits cell death and increases prostate tumor growth by modulating the expression of Bcl-2 and Bcl-X. *BMC Cancer*, *18*(1), 90. https://doi.org/10.1186/s12885-017-3950-9

Mezynska, M., & Brzóska, M. M. (2018). Environmental exposure to cadmium-a risk for health of the general population in industrialized countries and preventive strategies. *Environ Sci Pollut Res Int*, *25*(4), 3211-3232. https://doi.org/10.1007/s11356-017-0827-z

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., . . . Group, P.-P. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*, *4*(1), 1. https://doi.org/10.1186/2046-4053-4-1

Moreira, F. R., & Moreira, J. C. (2004). A cinética do chumbo no organismo humano e sua importância para a saúde. *Ciência & Saúde Coletiva*, *9*(1).

Neslund-Dudas, C. M., McBride, R. B., Kandegedara, A., Rybicki, B. A., Kryvenko, O. N., Chitale, D., . . . Mitra, B. (2018). Association between cadmium and androgen receptor protein expression differs in prostate tumors of African American and European American men [Article]. *Journal of Trace Elements in Medicine and Biology*, *48*, 233-238. https://doi.org/10.1016/j.jtemb.2018.04.006

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Syst Rev*, *5*(1), 210. https://doi.org/10.1186/s13643-016-0384-4

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., . . . Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, *372*, n71. https://doi.org/10.1136/bmj.n71

Perrelli, M., Wu, R., Liu, D. J., Lucchini, R. G., Del Bosque-Plata, L., Vergare, M. J., . . . Gragnoli, C. (2022). Heavy metals as risk factors for human diseases - a Bayesian network approach. *Eur Rev Med Pharmacol Sci*, *26*(24), 9275-9310. https://doi.org/10.26355/eurrev_202212_30681

Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., . . . Group, P.-P. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*, *350*, g7647. https://doi.org/10.1136/bmj.g7647

Shibamoto, T., & Bjeldanes, L. F. (2014). *Introdução à toxicologia de alimentos* (2 ed.). Elsevier.

Stang, A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*, *25*(9), 603-605. https://doi.org/10.1007/s10654-010-9491-z

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*, *71*(3), 209-249. https://doi.org/10.3322/caac.21660

Van Maele-Fabry, G., Lombaert, N., & Lison, D. (2016). Dietary exposure to cadmium and risk of breast cancer in postmenopausal women: A systematic review and meta-analysis. *Environ Int*, *86*, 1-13. https://doi.org/10.1016/j.envint.2015.10.003

Zhou, Q., & Xi, S. (2018). A review on arsenic carcinogenesis: Epidemiology, metabolism, genotoxicity and epigenetic changes. *Regul Toxicol Pharmacol*, *99*, 78-88. https://doi.org/10.1016/j.yrtph.2018.09.010